Robert Yarchoan *Editor*

Cancers in People with HIV and AIDS

Progress and Challenges

Springer

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This book is an expansion of the section,
Opportunistic Malignancies, in the Encyclopedia of AIDS,
editors-in-chief Thomas J. Hope, Douglas D. Richman,
and Mario Stevenson.

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Editor
Robert Yarchoan
HIV and AIDS Malignancy Branch and
Office of HIV and AIDS Malignancy
National Cancer Institute
National Institutes of Health
Bethesda, MD, USA

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Preface

The field of HIV-associated cancer has undergone a number of changes and advances in the past several years, and this book was conceived to fill the need for a resource that summarizes this new information. The 28 chapters describe the current state of knowledge in this area. These chapters were written by some of the most renowned experts in this field, and they cover a wide array of topics, including epidemiology, pathogenesis, clinical manifestations, and treatment.

From the earliest days of the AIDS epidemic, it was evident that cancer was a major part of this new disease—many of the patients had Kaposi sarcoma or aggressive lymphomas, which along with cervical cancer were called "AIDS-defining." For reasons that were not well understood, only certain tumors seemed associated with AIDS, and most developed in patients who were profoundly immunosuppressed. Since that time, our understanding of HIV-associated cancers has increased dramatically. With the discovery of Kaposi sarcoma-associated herpesvirus and its identification as the cause of Kaposi sarcoma, it became apparent that many AIDS-associated cancers are caused by other viruses. In addition, we have seen dramatic changes in the AIDS epidemic itself. The development of highly active antiretroviral therapy (HAART), also called combination antiretroviral therapy (cART), around 1996 profoundly changed AIDS from a death sentence to a treatable disease. Patients had dramatic improvements in their immune function, and the incidence of AIDS-associated tumors decreased. In fact, there was a sense that HIV-associated cancer was no longer a major problem. Nothing could be further from the truth. With the introduction of HAART, people with AIDS started living longer. Along with this, the number of persons living with AIDS has increased, and this population in general has gotten older. With these changes in the epidemic, the scope of HIV-associated tumors has changed. In addition to the more classic AIDS-defining tumors, patients with HIV infection are now developing more HIV-associated tumors, such as lung cancer, anal cancer, Hodgkin disease, and liver cancer. The factors causing the increase in these tumors vary, and each cancer is its own unique story. Also, as HIV-infected patients are less likely to die of AIDS-associated opportunistic infections or AIDS, cancer is now becoming a leading cause of death in this population. The story of HIV-associated cancers is somewhat different in the

developing world, and especially in sub-Saharan Africa. Many of the cancers associated with AIDS, such as Kaposi sarcoma, were common in sub-Saharan Africa even before the AIDS epidemic, and fueled by HIV, several of these cancers are among the most common in this region and pose substantial public health challenges. Also, patients in this region are susceptible to a number of uncommon HIV-associated cancers not often seen in the USA or other more developed countries.

Along with this evolution of the epidemic and increased awareness of HIV-associated cancers in sub-Saharan Africa, there has been a dramatic increase in our knowledge about and understanding of these tumors. Even so, a number of challenges remain, and better means to prevent, diagnose, and treat these tumors are urgently needed. With this backdrop, it is timely to present a book summarizing the current state of information about HIV-associated tumors. This project grew out the *Springer Encyclopedia of AIDS*, in which I edited the section on Opportunistic Malignancies. As I organized this section, it soon became apparent that a separate book covering this material would be of value and that the authors who contributed to the Encyclopedia were the best to pull this effort together. The space in the *Encyclopedia* was limited, and for the book, each contributor was given the opportunity to expand and update their contribution and to increase the number of references as they saw fit. This book is the result of that effort.

Bethesda, MD, USA Robert Yarchoan

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Contents

Contributors

David M. Aboulafia Division of Hematology and Oncology, Virginia Mason Medical Center, Seattle, WA, USA; Division of Hematology, University of Washington, Seattle, WA, USA

Richard Ambinder Division of Hematologic Malignancies, Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Accursio Augello Division of Medical Oncology A, National Cancer Institute, Aviano (PN), Italy

Massimiliano Berretta Department of Medical Oncology A, National Cancer Institute, Aviano (PN), Italy

Kishor Bhatia AIDS Malignancy Program, Office of HIV and AIDS Malignancy & Infections and Immunoepidemiology Branch, National Cancer Institute, Bethesda, MD, USA

William A. Blattner Division of Epidemiology and Prevention, Institute of Human Virology, University of Maryland School of Medicine, Baltimore, MD, USA

Bruno Cacopardo Division of Infectious Diseases, Department of Clinical and Molecular Biomedicine, University of Catania, Catania, Italy

Corey Casper Vaccine and Infectious Disease, Public Health Sciences and Clinical Research Divisions, Departments of Medicine, Epidemiology and Global Health, Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, USA

Rosanna Ciancia Division of Medical Oncology A, National Cancer Institute, Aviano (PN), Italy

Kristina R. Dahlstrom Department of Head and Neck Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; Department of Epidemiology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Blossom Damania Program in Global Oncology, Department of Microbiology and Immunology, Lineberger Comprehensive Cancer Center, Center for AIDS Research, University of North Carolina, Chapel Hill, NC, USA

Jan Davidson-Moncada Medical Oncology Branch, Center for Cancer Research, NCI, Bethesda, MD, USA

Paolo De Paoli Scientific Directorate, National Cancer Institute, Aviano, Italy

Dirk P. Dittmer Program in Global Oncology, Department of Microbiology and Immunology, Lineberger Comprehensive Cancer Center, Center for AIDS Research, University of North Carolina, Chapel Hill, NC, USA

Kieron Dunleavy Lymphoid Malignancy Branch, CCR, NCI, Bethesda, MD, USA

Christine Durand Division of Infectious Diseases, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Nicole Fischer Institute for Medical Microbiology, Virology and Hygiene, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Andrew E. Grulich HIV Epidemiology and Prevention Program, The Kirby Institute, University of New South Wales, Sydney, NSW, Australia

Adam Grundhoff Heinrich Pette Institute, Leibniz Institute for Experimental Virology, Hamburg, Germany

Neel K. Gupta Division of Hematology/Oncology, Department of Medicine, University of California, San Francisco, CA, USA

Lindsey Hutt-Fletcher Department of Microbiology and Immunology, Center for Molecular and Tumor Virology and Feist-Weiller Cancer Center, Louisiana State University Health Sciences Center, Shreveport, LA, USA

Lawrence D. Kaplan Division of Hematology/Oncology, Department of Medicine, University of California, San Francisco, CA, USA

Susan E. Krown AIDS Malignancy Consortium, New York, NY, USA

Bethany Lema Department of Dermatology, Roswell Park Cancer Institute, Buffalo, NY, USA

Richard F. Little Clinical Investigations Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI), Bethesda, MD, USA

Deepthi Mani Division of Internal Medicine, Multicare Good Samaritan Hospital, Puyallup, WA, USA

Sam M. Mbulaiteye Infections and Immunoepidemiology Branch, Division of Cancer Epidemiology and Genetics, Department of Health and Human Services, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

Ronald T. Mitsuyasu UCLA Center for Clinical AIDS Research and Education (CARE Center), University of California, Los Angeles, CA, USA

Rebecca G. Nowak Division of Epidemiology and Prevention, Institute of Human Virology, University of Maryland School of Medicine, Baltimore, MD, USA

Joel M. Palefsky University of California, San Francisco, CA, USA

Stefania Pittaluga Laboratory of Pathology, Center for Cancer Research (CCR), Bethesda, MD, USA

Mark N. Polizzotto HIV and AIDS Malignancy Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

Erin Reid Division of Hematology/Oncology, Department of Internal Medicine, University of California San Diego Moores Cancer Center, La Jolla, CA, USA

Erle S. Robertson Department of Microbiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Kenneth O. Simbiri Department of Microbiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Michele Spina Division of Medical Oncology A, National Cancer Institute, Aviano (PN), Italy

D. Cristina Stefan Department of Paediatrics and Child Health, Tygerberg Hospital, Stellenbosch University, Cape Town, South Africa

Elizabeth A. Stier Boston University Medical Center, Boston, MA, USA

Erich M. Sturgis Department of Head and Neck Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; Department of Epidemiology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Umberto Tirelli Division of Medical Oncology A, National Cancer Institute, Aviano (PN), Italy

Giovanna Tosato Laboratory of Cellular Oncology, Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA

Thomas S. Uldrick HIV and AIDS Malignancy Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

Huan-You Wang Department of Pathology, University of California San Diego Moores Cancer Center, La Jolla, CA, USA

Ida Wong-Sefidan Division of Hematology/Oncology, Department of Internal Medicine, University of California San Diego Moores Cancer Center, La Jolla, CA, USA

Robert Yarchoan HIV and AIDS Malignancy Branch and Office of HIV and AIDS Malignancy, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

Nathalie C. Zeitouni University of Arizona Cancer Center, Tucson, AZ, USA

Zhi-Ming Zheng Tumor Virus RNA Biology Section, Gene Regulation and Chromosome Biology Laboratory, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

Part I
Overview and Epidemiology

Chapter 1
HIV-Associated Cancers

Robert Yarchoan, Thomas S. Uldrick, and Mark N. Polizzotto

Abstract HIV-associated cancers are cancers whose incidence is increased in patients with HIV infection, and especially those in which the increased incidence is a result of the HIV infection. These include both AIDS-defining cancers (cancers that confer a diagnosis of AIDS when they occur in HIV-infected persons) and non-AIDS-defining cancers (other cancers whose incidence is increased in HIV infection). The AIDS-defining cancers are Kaposi sarcoma, certain high grade B cell lymphomas, and cervical cancer.

1.1 Introduction

On June 5, 1981, the Centers for Disease Control (CDC) reported in *Morbidity and Mortality Weekly Report* a cluster of five cases of *Pneumocystis* pneumonia in young homosexual men (1981). A month later, on July 3, they reported on both *Pneumocystis* pneumonia and Kaposi's sarcoma (KS) (see Chap. 9) occurring among homosexual men in New York and California (Centers for Disease Control 1981). These were the first reports of the disease we now call acquired immunodeficiency syndrome (AIDS). KS had previously been a very rare skin cancer reported primarily in elderly men in Mediterranean regions, and its occurrence in young men who had sex with men (MSM) and the severity of many of these cases was a distinct departure from previous epidemiologic patterns.

R. Yarchoan (✉)
HIV and AIDS Malignancy Branch and Office of HIV and AIDS Malignancy, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA
e-mail: robert.yarchoan@nih.gov

T.S. Uldrick • M.N. Polizzotto
HIV and AIDS Malignancy Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA
e-mail: uldrickts@mail.nih.gov; polizzottomn@mail.nih.gov

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1.2 AIDS-Defining and Non-AIDS-Defining Tumors in the AIDS Epidemic

As the AIDS epidemic unfolded over the next several years, it became apparent that AIDS was a complex disease characterized by profound immunodeficiency, especially of CD4+ T cells; immune dysregulation; and unusual opportunistic infections. Also, it became apparent that this syndrome was associated with certain cancers, especially KS, central nervous system lymphoma (see Chap. 15), and certain other high grade B cell lymphomas (see Chap. 11) (Ziegler et al. 1982, 1984). As we now know, HIV/AIDS is associated with an increased risk of a number of tumors, some like KS that are rare outside the setting of profound immunodeficiency (Fig. 1.1) and others that develop in immunologically intact individuals but occur at a higher rate in patients with HIV/AIDS.

As the CDC established criteria for this new and complex syndrome, they considered Kaposi's sarcoma and certain B cell lymphomas (Burkitt or equivalent term (see Chap. 13), immunoblastic or equivalent term (see Chap. 12), or primary brain lymphoma (see Chap. 2)) as "AIDS-defining" (Table 1.1) (Centers for Disease Control 1985). This meant that the development of these tumors in an HIV-infected individual conferred a diagnosis of AIDS. These tumors tended to occur particularly in patients with low CD4 counts. It should be noted that the AIDS-defining lymphomas included in the 1985 CDC criteria are based on the classification of lymphomas in use at that time, which has since been superseded. There is some uncertainty as whether certain lymphomas in the current terminology should be considered AIDS-defining. Primary effusion lymphoma (PEL) (see Chap. 14), for example, was not

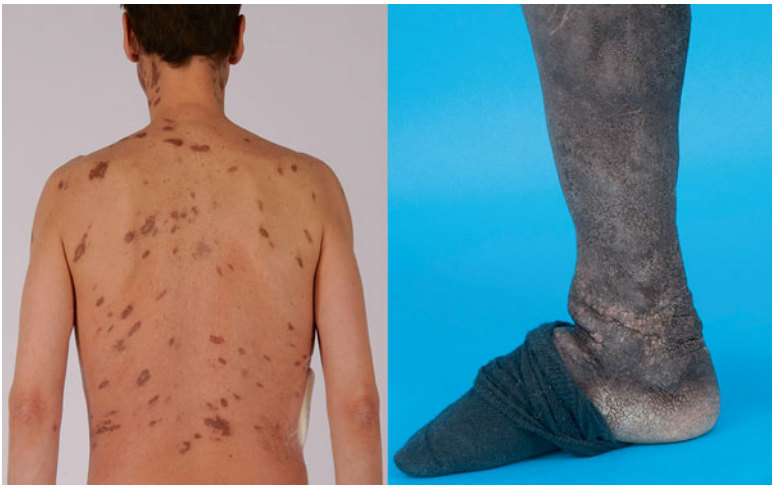

Fig. 1.1 Two patients with AIDS-associated KS. *Left*: Patient with multiple lesions of cutaneous KS on the back. *Right*: Lower limb, showing extensive involvement with confluent KS and lymphedema

Table 1.1 Selected malignancies that are more frequent in HIV patients and their associated viruses

Malignancy	AIDS-defining	Principal associated virus or viruses	Comment
Kaposi sarcoma	Yes	KSHV	
Primary central nervous system lymphoma	Yes	EBV	
Diffuse large B cell lymphomas (germinal center or activated B-cell subtypes)	Yes	EBV	A substantial percentage of cases are EBV negative
Burkitt lymphoma	Yes	EBV	A substantial percentage of cases are EBV negative
Primary effusion lymphoma	Yes	KSHV	Often also EBV
Hodgkin lymphoma	No	EBV	Sometimes EBV negative in HIV patients
Multicentric Castleman's disease	No	KSHV	
Anal cancer	No	HPV	
Pharyngeal cancer	No	HPV	
Primary hepatocellular carcinoma	No	HBV or HCV	
Plasmablastic lymphoma (oral-cavity associated)[a]	No	EBV	Occasionally EBV negative in HIV patients
Merkel cell tumor	No	Merkel cell polyomavirus	Some are negative for Merkel cell polyomavirus.
Leiomyosarcoma in children[b]	No	EBV	
Conjunctival carcinoma	No	Unclear; possibly HPV	Reported almost only in Africa
Lung cancer	No	None yet identified	Much of increased risk due to high prevalence of smoking

KSHV Kaposi sarcoma-associated herpesvirus, *EBV* Epstein–Barr virus, *HPV* human papilloma virus, *HBV* hepatitis B virus, *HCV* hepatitis C virus

[a] See Chap. 16

[b] See Chap. 26

described as a separate entity in 1992 but is generally considered an AIDS-defining lymphoma. Subsequently, in 1992, invasive cervical carcinoma (see Chap. 19) was added to the list of "AIDS-defining tumors," although it did not have as clear an association with profound immunodeficiency (Centers for Disease Control 1992).

These were not the only tumors that are increased in patients with AIDS (or infected with HIV). Epidemiological studies identified a number of other tumors with increased incidence, such as anal carcinoma (see Chap. 20), lung cancer (see Chap. 22), and Hodgkin's lymphoma (see Chap. 17). These additional HIV-associated are now called "non-AIDS-defining tumors" (see Chap. 3) (Engels et al. 2006a; Herida 2003). This term is sometimes also used to refer to any cancer that arises in an HIV-infected patient (even if it is not HIV-associated) and that is not one of the AIDS-defining tumors.

For a number of years, the fact that some tumors were markedly increased in incidence in HIV-infected patients, while others were not, was a puzzle to scientists. Some clues came from epidemiology. For example, KS was particularly common in HIV-infected patients who had had sex with men, while the incidence of lymphoma

was relatively equal in all HIV risk groups. The epidemiology of KS suggested that another infectious agent besides HIV was responsible for its pathogenesis (Beral et al. 1990), but attempts to identify such an agent failed until 1994, when the husband and wife team of Patrick Moore and Yuan Chang reported sequences of a novel gammaherpesvirus in the KS lesions of AIDS patients using the technique of representational difference analysis (Chang et al. 1994). This virus, which is called Kaposi's sarcoma-associated herpesvirus (KSHV) (see Chap. 5) or human herpesvirus-8 (HHV-8), is now known to be the cause of KS (Moore and Chang 1995; Whitby et al. 1995). It has also been identified as the etiologic agent of a rare lymphoma called PEL (Cesarman et al. 1995), and of most cases of multicentric Castleman's disease (MCD) (see Chap. 18) that arise in HIV-infected individuals (Soulier 1995; Uldrick et al. 2012). With the discovery of KSHV, it became evident that most (but not all) HIV-associated tumors were caused by another oncogenic virus (Table 1.1).

The development of several effective anti-HIV drugs (Mitsuya et al. 1990; Yarchoan et al. 1986a; Yarchoan et al. 1991) enabled the use of highly active combination regimens, often called highly active antiretroviral therapy (HAART) (Hammer et al. 1997). The use of HAART in the USA and other resource-rich countries started around 1996. In addition to markedly reducing the mortality of HIV, the widespread use of HAART led to a decrease in the incidence of some AIDS-defining cancers, especially those (such as KS or central nervous system lymphoma) that occur in patients with very low CD4 counts and immunologic impairment (Engels et al. 2006a, b; Herida 2003; International Collaboration on HIV and Cancer 2000; Shiels et al. 2011a). There was initially optimism that these tumors would largely become a thing of the past. However, because of several factors, after an initial decrease, the number of cases of AIDS-defining malignancies has remained fairly constant in the USA since about 2002 (Shiels et al. 2011a, b). One reason is that there has been more than a doubling of the number of individuals living with AIDS in the USA, because the rate of new HIV infection has not changed and HIV-infected patients are living longer (Shiels et al. 2011b; Yarchoan et al. 2005). Another factor is that some HIV-infected patients do not realize they are infected, or do not engage with medical care, until they become substantially immunosuppressed and develop an AIDS-defining tumor. A third is that some AIDS-defining tumors, such as cervical cancer, develop in patients with relatively high CD4 counts. Finally, the population of HIV-infected patients is becoming older, and age is an additional major risk factor for many tumors (Shiels et al. 2011b).

As noted above, in addition to the AIDS-defining tumors, a number of other tumors develop more often in HIV-infected individuals than the general (age-matched) population (Clifford 2005; Engels et al. 2006a, b; Mbulaiteye et al. 2003; Silverberg et al. 2007). These include anal carcinoma, Hodgkin lymphoma, lung cancer, pharyngeal carcinoma (see Chap. 21), and Merkel cell tumor (see Chap. 24). In addition, as HIV-infected patients live longer and this population is increasing in age, they are increasingly developing the wide range of tumors seen in the general population (Shiels et al. 2011b). The best evidence is that many of these tumors arise independent of HIV infection, although it is possible that HIV will be found to be a contributory factor as we learn more about the epidemiology and factors contributing to their pathogenesis.

Recent studies have shown that unlike the AIDS-defining tumors, the number of cases of non-AIDS-defining tumors has increased substantially since the introduction of HAART in 1996, and in fact, there are now more non-AIDS-defining tumors than AIDS-defining tumors in HIV patients in the USA (Shiels et al. 2011b). Also, with the widespread use of HAART, there are now fewer deaths from uncontrolled HIV infection, complications of profound AIDS immunosuppression, or opportunistic infections, and in some studies, cancer has now become the most common cause of death in patients with HIV/AIDS (Bonnet et al. 2004, 2009).

1.3 Pathogenesis of Tumors in HIV/AIDS

As noted above, the discovery of KSHV (Moore and Chang 1995) and its identification as the cause of KS (and several other tumors) was crucial, not just for its understanding of KS, but also because it led to an appreciation that most (but not all) tumors that are associated with HIV infection are caused by other oncogenic viruses (Table 1.1). Our current understanding is that the immune system plays an important role in suppressing infection with these viruses and also suppressing malignant cells that express foreign epitopes from the viruses. Thus, in the setting of AIDS, the profound immunodeficiency permits an outgrowth of these viruses and cells transformed by them. In some cases, such as KS or KSHV-associated MCD, the tumor is really a hyperproliferative state although there can be clonality in some cases (Gill et al. 1997; Rabkin et al. 1995; Uldrick et al. 2012). In other cases, such as lymphomas caused by Epstein–Barr virus (EBV) (see Chap. 6), our understanding is that a proliferation of virus-infected cells increases the likelihood of mutations that eventually lead to clonal tumors (Martinez-Maza and Breen 2002). Even HIV patients who are treated with HAART and have relatively normal CD4 counts have defects in their immune repertoire that over time can enhance the risk of various tumors. An increased incidence of a tumor in the setting of HIV infection is a clue that this tumor may be caused by a virus. As an example, Merkel cell carcinoma, a rare skin cancer, is more likely to develop in HIV-infected patients, and an investigation of this relationship let to the discovery of Merkel cell polyomavirus (see Chap. 8) as a new oncogenic virus (Feng et al. 2008).

Interestingly, not all tumors are more frequent in HIV-infected patients, and in particular, the incidence of some common tumors such as colon cancer, breast cancer, or cancer of the prostate is not increased (Engels et al. 2006a, b; Goedert et al. 1998). This observation suggests that either the immune system does not play an important role in keeping such tumors in check, or time for such tumors to arise is longer than the survival of AIDS patients, at least until HAART was developed. It will be of interest to see if these tumors also become more common in the setting of HIV infection than in the general population as HIV-infected patients live for decades on HAART.

HIV can promote tumorigenesis in other ways as well. HIV infection is associated with immune dysregulation and B cell hyperactivation (Lane et al. 1983; Yarchoan et al. 1986b), and this can promote the development of B cell lymphoma

and other tumors (such as KS) that respond to cytokine excess. Also, specific proteins of HIV may promote tumor development; for example, the Tat protein can penetrate cells and has been shown to enhance infection of cells with KSHV (Aoki and Tosato 2004). Another possible factor is long-term exposure to antiretroviral drugs. Nucleoside reverse transcriptase inhibitors such as zidovudine act as chain terminators, and administration of high doses of certain of these drugs, including azidothymidine (AZT) to pregnant mice has been reported to lead to an increased incidence of tumors in the offspring (Olivero et al. 1997). However, it is important to note that epidemiologic studies of these drugs in humans have not yielded evidence that they contribute to tumorigenesis.

For some of the tumors whose incidence is increased in HIV-infected patients, the cause of the increased incidence may be in part or whole because of increased exposure to other cancer risk factors. For example, such patients have an increased risk of lung cancer that is due, at least in part, to increased cigarette use in the HIV-infected population. Studies trying to determine if immunodeficiency or HIV infection independently contributes to the increased incidence of lung cancer have yielded conflicting results (Engels et al. 2006a, b). Also, HIV-infected patients often have co-infection with hepatitis B virus (HBV) or hepatitis C viruses (HCV), as these viruses, like HIV, are spread through injection drug use, and hepatitis B can be spread sexually. Infection with these viruses can lead to hepatocellular carcinoma, which is also increased in incidence in HIV-infected patients (Mbulaiteye et al. 2003). It appears that most of this increased incidence is due to the increased co-infection with HBV and/or HBC. However, there is reasonable evidence that immunosuppression also plays a role in the increased incidence of hepatocellular carcinoma (see Chap. 23). Similarly, HIV-infected patients have higher exposure to human papillomavirus (see Chap. 7) than the general population, and this can work in conjunction with immunosuppression to lead to a higher incidence of cancer of the cervix, anus, penis, and oral pharynx. Thus, each HIV-associated cancer has its own complex story, and while there are some common themes, the pathogenesis of each has to be considered separately.

As the rate of HIV infection does not appear to be changing, at least in the USA, and as HIV-infected patients live for years with HAART, the HIV-infected population overall is increasing in age and we are seeing an increasing population of HIV-infected patients over the age of 50 or 60 years. Cancer is in general a disease of aging, and some AIDS-defining tumors, such as KS can occur in elderly patients outside the setting of HIV infection (Mitsuyasu 2000). It is not known exactly how the combination of aging, chronic mild immune defects of HIV and aging, co-infection with other oncogenic viruses, prolonged exposure to antiretroviral drugs, and enhanced exposure to other cancer risk factors such as cigarettes will interact to affect the development of tumors as we see a "graying" of the HIV-infected population. As HIV-infected patients age, they are increasing susceptible to develop tumors on that basis alone. It is not known at this time how this process may be affected by long-term HIV infection. It will be important to monitor the development of various tumors in the population living with long-term HIV infection to understand these issues and develop appropriate screening, preventive, and therapeutic strategies.

1.4 HIV-Associated Tumors in Resource-Limited Countries

Special attention must be given to HIV-associated cancers in resource-limited countries (see Chap. 4). In these regions, a higher proportion of cancers overall are due to infectious agents than in the more developed world, and many of these areas have a high prevalence of viruses that cause HIV-associated cancers. In particular, there is a high prevalence of KSHV infection in sub-Saharan Africa (Chokunonga et al. 1999; Mbulaiteye et al. 2003; Wabinga et al. 1993, 2000), and in this region, KS is among the most common cancers; in some sub-Saharan countries, it is the most common tumor in males. Even before the spread of HIV, KS was a relatively common tumor in Africa, and KSHV-infected patients in Africa are more likely to develop KS than in other regions. The reasons for this are not clear. Possible explanations include exposure to other diseases, such as malaria, that cause inflammation; an earlier age of infection with KSHV; genetic factors that predispose to KS; or exposure to certain plants or other environmental factors that promote KS. Also, Burkitt lymphoma is relatively common in regions of sub-Saharan Africa even in HIV-uninfected patients (Parkin et al. 1999). Most endemic cases of Burkitt lymphoma are caused by EBV, and epidemiologic studies show that co-infection with malaria is an important contributor to tumorigenesis (Ziegler et al. 1972). There are certain HIV-associated tumors reported in Africa, such as carcinoma of the conjunctiva (see Chap. 25), that are not reported elsewhere, and there is much we need to learn about these unusual tumors.

Research on the epidemiology and pathogenesis of HIV-associated tumors in the developing world, and especially Africa, is hampered by the relatively undeveloped state of the medical and research infrastructure in these regions. Patients with suspected tumors are often treated without biopsy or in setting with limited pathological expertise, and lymphoma, for example, can be confused with tuberculosis or other common diseases. As an example of this, while KSHV-associated MCD has been diagnosed in a number of African immigrants to the USA, there are only few reports of this condition in Africa in spite of a very high prevalence of both KSHV and HIV. It is almost certain that many cases of this disease in Africa go unrecognized and are thought to be tuberculosis or a related illness.

The President's Emergency Plan for AIDS relief (PEPFAR) is an ambitious program of the USA to provide effective therapy to HIV-infected patients in resource-limited settings. This program started in 2003, and has brought AIDS treatment to a substantial number of patients in Africa and other regions. As a result of this, we are starting to see a drop in AIDS-related tumors, especially KS. However, there is some evidence that, like in the resource-rich world, there is now the beginning of an increase in non-AIDS-defining tumors in these areas.

1.5 Treatment of Tumors in HIV-Infected Patients

The treatment of specific HIV-associated tumors is discussed in the specific sections on these tumors. However, it is worth presenting some broad principals. While KS has been, until recently, the most common tumor arising in AIDS patients in the USA,

it was relatively rare in the USA prior to the AIDS epidemic and relatively little was known about how to treat it. Thus, treatments for KS (see Chap. 10), including the use of interferon alpha, the identification of effective cancer chemotherapeutic drugs such as vincristine or paclitaxel, and the development of liposomal anthracyclines, were largely developed in the setting of AIDS (Gill et al. 1995; Krown et al. 1983; Mitsuyasu et al. 1997; Stewart et al. 1998; Welles et al. 1998). As we have learned more about the pathogenesis of this tumor, novel treatments aimed at blocking specific steps in its pathogenesis are now being developed (Yarchoan et al. 2007).

With regard to systemic AIDS lymphomas, a challenge was that while these tumors were often curable outside the setting of AIDS with combination chemotherapy regimens, such regimens were initially viewed at too toxic to administer to AIDS patients. As a result, before the widespread use of HAART, low dose chemotherapy regimens were developed specifically for HIV-associated lymphomas (Kaplan et al. 1997). An additional challenge at that time was that patients often died of their AIDS even if the lymphoma could be effectively treated. This was a problem with essentially all tumors developing in AIDS patients, and in fact, AIDS patients were almost universally excluded from experimental protocols to treat cancers except for studies of specific AIDS-related tumors.

With the development of HAART, this whole picture changed. The immune system of many AIDS patients could be restored to a large degree, they were not as frail, they had a better life expectancy, and they could tolerate toxic regimens better than before HAART. As a result, in a series of incremental clinical studies, it was shown that such patients could generally tolerate full-dose lymphoma regimens (Little et al. 2003; Ratner et al. 2001; Sparano et al. 2004, 2010). There is recent information that HIV-infected patients can even tolerate allogeneic stem cell transplantation (see Chap. 28), and this approach is being explored as a means of eradicating HIV in infected patients. At the same time, a number of advances (such as rituximab and infusional regimens) were made in the therapy of various lymphomas (Dunleavy et al. 2010; Little et al. 2003; Sparano et al. 2010), and the expected survival of patients with certain types of AIDS lymphoma now approaches that of lymphoma patients without HIV.

While AIDS patients on HAART could often tolerate cancer chemotherapy, physicians treating such patients have often been reluctant to use full-dose therapy because of their experience with AIDS patients before the widespread use of HAART, and such patients have often been undertreated. Contributing to this problem has been the relative paucity of published information on the treatment of various tumors in HIV-infected patients as a result of their exclusion from cancer trials. Another concern for physicians is that many HIV drugs, and especially the protease inhibitors that interact with cytochrome P450, can have substantial pharmacokinetic interactions with other drugs including cancer drugs (see Chap. 27). In many cases, there was little published information on these interactions, and this was another cause for caution. In 2008, the United States National Cancer Institute determined that in most instances, there was no good reason to exclude HIV-infected patients from cancer trials, and they have made a concerted effort to open trials to such patients when feasible (Persad et al. 2008). Other cancer research agencies have

also made an effort to study the treatment of cancer in HIV-infected patients, and as a result, there is an emerging body of information on the optimal treatment of a variety of cancers in the setting of HIV infection. This is an important development, as we see a shift from a few AIDS-defining tumors to a wide variety of AIDS-non-defining tumors arising in patients with HIV/AIDS.

1.6 Prevention of Tumors in HIV-Infected Patients

As noted above, a number of HIV-associated tumors are caused by oncogenic infectious agents, and they may thus be amenable to preventive strategies aimed at the underlying virus. Moreover, HIV itself plays an important role in the pathogenesis of the tumors, and strategies to prevent or treat HIV infection can therefore affect the development of these tumors. In fact, the development and widespread use of HAART caused a dramatic decrease in the incidence of AIDS-defining tumors, especially those that are associated with very low CD4 counts (Clifford et al. 2005; Engels et al. 2006a, b; Jones et al. 1998; Mbulaiteye et al. 2003; Shiels et al. 2011a, b). It goes without saying that successful prevention of HIV infection, for example by public health measures or, if developed, an HIV vaccine, will prevent HIV-associated cancers.

A number of approaches can also be used to prevent or reduce the extent of infection with the viruses responsible for causing many of these tumors. A vaccine against HBV has been in use for several decades, and vaccines have recently been developed against strains of HPV responsible for the majority of cases of cervical, anal, and other HPV-associated cancers (Lowy and Schiller 2006; Schiller and Lowy 2001). These vaccines must be given prior to infection with HPV, usually before the time of sexual activity. As a result, the population of adults today will generally not be protected by this vaccine, and its effects will be largely seen over the next several decades. Another concern is that, at least in the USA, the uptake of the vaccine in boys is very low, and MSM may remain an unprotected population for some time.

There are currently no vaccines developed against HCV or KSHV. Antiviral drugs have been developed or shown to be active against both of those viruses, and the use of ganciclovir (for cytomegalovirus retinitis) has been shown to reduce the development of KS (Martin et al. 1999). The spread of HCV, as well as HBV, has been reduced by the development of tests to screen the blood supply, and can also be impacted by public health measures. KSHV is known to be secreted in saliva, although there is still much we do not know about the main causes of transmission (Butler et al. 2009; Martin 2011). Unlike EBV, KSHV appears to only be effectively transmitted in certain populations, and as we learn more about this, it may be possible to institute public health recommendations to reduce its spread. Strategies to prevent tumors in HIV-infected patients will be an important area of research and development as we move forward.

1.7 Conclusion

While HIV does not appear to be directly oncogenic, HIV infection and its associated immunodeficiency enhance the development of a variety of tumors. Some of these tumors, called "AIDS-defining," confer a diagnosis of AIDS when they arise in an HIV-infected individual. The widespread use of HAART has dramatically reduced the incidence of several of these AIDS-defining tumors, especially those associated with very low CD4 counts. A number of other "non-AIDS-defining" tumors are also more frequent in the setting of HIV infection. In some cases, HIV or HIV-associated immunodeficiency has directly contributed to their development. HIV-infected patients also often have increased exposure to a variety of oncogenic agents, such as HCV or cigarette smoke, and this may contribute or even be the cause of the increased frequency of certain tumors. As HIV-infected patients live longer on HAART and as this population becomes older, we are seeing a decrease in AIDS-associated tumors and an increase in others. It is possible that new trends may emerge as patients live for decades with suppressed HIV infection, chronic subtle immune defects, and chronic exposure to antiretroviral drugs.

Most of the AIDS-defining or HIV-associated tumors are caused by oncogenic viruses, and it may be possible to effectively screen, prevent, or treat these tumors by strategies directed at the underlying virus. Substantial progress has already been made in this area, and it promises to be a fruitful area for future progress. At the same time, the trend towards development of a wider range of tumors in HIV patients is increasing the complexity of this field and will require teasing out and understanding the trends as they emerge.

Whether or not it is HIV-associated, the treatment cancer in an HIV-infected individual is often quite complex, as patients have two life-threatening conditions. Immunodeficiency and other manifestations of HIV may complicate treatment of the tumor, and there are the potential for substantial drug interactions. It will be important to continue to develop improved therapy for those tumors that principally develop in HIV patients. At the same time, it will be important to learn how to optimally manage other cancers, whether or not they are HIV-associated, that develop in the setting in HIV infection.

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Chapter 2
Epidemiology of AIDS-Defining Malignancies

William A. Blattner and Rebecca G. Nowak

Abstract AIDS-defining malignancies are a subset of HIV-associated malignancies that include Kaposi sarcoma, some forms of non-Hodgkin lymphoma (NHL), and invasive cervical cancer (see also Chap. 3). Kaposi sarcoma along with *Pneumocystis carinii* pneumonia was among the first diseases that comprised the original surveillance definition of AIDS in the USA. Subsequently NHL (1985) and invasive cervical cancer were added (CDC 1992). Compared to non-AIDS-defining malignancies, Kaposi sarcoma and NHL demonstrated the highest incidence in the early AIDS epidemic. As shown in the first figure of this chapter, with the introduction of highly active antiretroviral therapy (HAART) in 1996, the incidence patterns of these cancers with the exception of cervical cancer dropped significantly. It is hypothesized that HAART restores immune function and delays progression to AIDS. However, even with improved clinical outcomes, HAART has not eliminated the risk of AIDS-defining malignancies. HIV-positive persons still remain at a substantially increased risk of developing these cancers as compared to the general population and AIDS-related and non-AIDS-related cancers combined are the most frequent underlying causes of death in AIDS in the USA.

2.1 Epidemiology of Kaposi Sarcoma Before HAART

Prior to the AIDS epidemic Kaposi sarcoma (KS) was a cancer with an incidence in white males of 0.3 per 100,000 in the USA (1973–1978) (Mbulaiteye et al. 2003). With the advent of the AIDS epidemic in 1981, a new form of KS, classified as "epidemic" or AIDS-associated KS, was identified. In the initial definition of AIDS, it was considered

W.A. Blattner, M.D. (✉) • R.G. Nowak, Ph.D., M.P.H.
Division of Epidemiology and Prevention, Institute of Human Virology,
University of Maryland School of Medicine, Baltimore, MD, USA
e-mail: wblattner@ihv.umaryland.edu; rnowak@ihv.umaryland.edu

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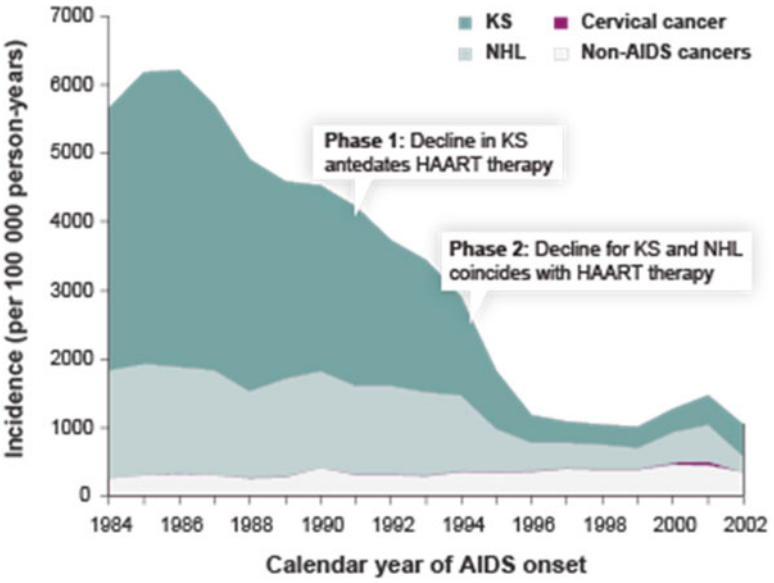

Fig. 2.1 Cancer incidence among people with AIDS in the USA (1984–2002). Incidence is shown as a function of calendar year of AIDS onset for Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL), cervical cancer, and non-AIDS-defining cancers. Incidence estimates for each cancer are stacked on top of each other to depict the proportion of total cancer incidence contributed by each cancer type. Analysis was restricted to the 2-year period 4–27 months after AIDS onset. Engels EA, et al., Trends in cancer risk among people with AIDS in the United States 1980–2002. AIDS 2006;20:1645–54, by permission of Wolters Kluwer Health

an AIDS-defining illness because epidemiologically these cases [characterized by young age at onset, high prevalence among men who have sex with men (MSM), and association with unexplained immunodeficiency] were distinct from the other three recognized patterns of KS (classic KS—elderly Mediterranean men, endemic KS—sub-Saharan Africa, and iatrogenic KS—associated with therapeutic immunosuppression) and they tended to occur in individuals with other manifestations of this new syndrome. Beginning with the first report of KS among MSM in 1981, incidence rapidly increased and peaked in 1985–1986. By 1989–1991, incidence was 8.9 per 100,000 with nearly 40–50 % of men who have sex with men (MSM) presenting with KS as their AIDS-defining illness (Fig. 2.1) (Mbulaiteye et al. 2003). KS became the most common AIDS-associated cancer in the USA in 1990–1995 and it was associated with a 53,000-fold higher risk compared to the general population (Engels et al. 2006). AIDS-associated KS generally presented not only with purple or black cutaneous lesions but also frequently with organ involvement, especially among those with advanced immunodeficiency. Survival prior to antiretroviral treatment was at most 12–18 months (Bower et al. 2006) and for the cases with extensive involvement of internal organs and concurrent opportunistic infections, prognosis was particularly poor.

Epidemiological studies documented an association of epidemic KS with high rates of sexual partner exchange, co-incident sexually transmitted infections (particularly oral gonorrhea), anal intercourse, fecal-oral exposure [particularly oral anal insertive sex (rimming)], fisting (insertion of the hand into the partner's rectum), usage of nitrite (a smooth muscle relaxant used to facilitate anal sex), and contact of KS cases with a sex partner from the New York and San Francisco epicenter. These associations, plus a discordance in KS rates between MSM compared to those who acquired AIDS through parenteral [transfusion (4 %) and injection drug use (10 %)] and perinatally (3 %) (Mbulaiteye et al. 2003), supported the hypothesis that a sexually transmitted factor independent of HIV was responsible.

Human herpesvirus 8 (HHV-8), also known as Kaposi sarcoma-associated herpesvirus (KSHV), was discovered by Chang and Moore in KS lesions, and this virus is now established as the causative agent of KS. Epidemiological analyses established that HHV-8 is a necessary but not sufficient cause of KS, based on cross-sectional and longitudinal studies of MSM that documented that all AIDS-associated KS cases were HHV-8 positive. Also, these studies revealed that a substantial fraction of MSM, especially in the New York and San Francisco epicenters, were carriers of the virus. Seroepidemiological studies further documented that not only was HHV-8 linked to AIDS-associated KS, but that HHV-8 is also detected in cases with classic, endemic, and iatrogenic KS. By contrast, the prevalence of HHV-8 infection was low in blood donors in the USA. To better understand the complex epidemiological relationship between HIV and HHV-8, several epidemiological studies documented that anal-related sexual activities were independent risk factors for acquisition of both viruses, confirming the hypothesis that co-epidemics of HIV and HHV-8 accounted for the emergence of AIDS-associated KS. These co-epidemics were most prominent in the New York and San Francisco epicenters and this pattern explained the association with sexual contact with someone from New York or San Francisco as a risk factor for KS in populations outside of the New York and San Francisco areas. In summary both HIV and HHV-8 share some overlapping risk factors, particularly fecal-oral exposure for HHV-8 and the closely related penile-anal exposure for HIV.

The AIDS-associated KS epidemic in Africa has a different epidemiological pattern, essentially reflecting the super-imposition of HIV upon an existing endemic pattern of HHV-8 infection that drives the occurrence of endemic KS. Epidemiological data suggest that in this setting, HHV-8 was highly prevalent before the AIDS epidemic and like other herpesviruses is associated with oral exposure resulting from poor hygiene and practices such as pre-mastication of food during infant feeding common in the African setting. The sexual risk factors detected in the African KS setting (e.g., high rates of sexual partner exchange, commercial sex worker exposure, etc.) are associated with acquisition of HIV infection rather than with the acquisition of HHV-8. This super-infection with HIV in an HHV-8 infected person and its attendant HIV-induced immunosuppression accelerates and amplifies the imposition of epidemic KS on a background of endemic KS.

2.2 Epidemiology of Kaposi Sarcoma After HAART

As shown in Fig. 2.1 the phase 1 decline in KS incidence commencing in 1986 likely represented the rapid expansion of AIDS beyond the original epicenters with high rates of HHV-8, changes in sexual behaviors, and modest impacts of early mono and dual antiretroviral HIV therapy. A more dramatic declination occurred in 1994–1996 (Fig. 2.1) in the USA coincident with the introduction of highly active antiretroviral therapy (HAART), a pattern observed in other populations when effective treatment was implemented. In the Multicenter AIDS Cohort Study (MACS) of MSM, the incidence of KS declined by 87 % in the post-HAART era (1996–2007) as compared to the pre-HAART era (1984–1995) (Seaberg et al. 2010). In the Swiss HIV Cohort study, the standardized incidence rates of KS declined from 1,375 to 67 per 100,000 in 1985–1996 and 2002–2006 periods, respectively (Franceschi et al. 2010). Similarly, the incidence rate of KS declined significantly from 15.2 to 4.9 per 1,000 person-years in the 1992–1996 and 1997–1999 periods, in a collaborative study of 23 prospective studies from North America, Europe, and Australia (International Collaboration on HIV and Cancer 2000). HAART was also associated with improved survival of KS. The mortality rate from KS decreased fourfold for persons with AIDS and nearly 70 % of persons survived up to 3 years (Simard et al. 2010; Spagnuolo et al. 2012).

Regardless of these improvements, individuals continue to present with AIDS-associated KS (Fig. 2.2). KS is currently associated with a 3,640-fold higher risk in HIV-infected individuals compared to the general population (Engels et al. 2006). KS has been documented in individuals with failing HAART, individuals with immune reconstitution inflammatory syndrome (IRIS) after initiating HAART for the first time, and those who have steady suppressed HIV viral loads and relatively high CD4+ T cells. Children diagnosed with AIDS before the age of 14 years have significantly elevated risk of developing KS in the post-HAART era as compared to the general population. The current risk of AIDS-associated KS remains elevated, even though the risk has decreased significantly since the pre-HAART era.

Risk factors associated with KS in the post-HAART era primarily include low CD4 cell counts and high plasma HIV RNA levels. In particular, low CD4+ T cell counts (<50 cells/μl) were associated with an increased risk of KS for those taking HAART in the Swiss HIV Cohort (Franceschi 2008). Additional risk factors specific to the post-HAART era include older age and IRIS. HIV-infected individuals may be surviving longer and becoming at risk of KS independent of restored immunity from HAART. With IRIS, there is a transient increased incidence of KS after initiation of therapy independent of current CD4 counts. Starting HAART in a proportion of treatment naïve individuals may stimulate a heightened inflammatory response that induces KS, perhaps in part by provoking HHV-8 activation from latent to active gene expression. The relationship between HIV-related immune suppression and HHV-8 activation is dynamic and understanding the relevance of the current risk factors, such as age and IRIS, may be better understood at a molecular rather than population level.

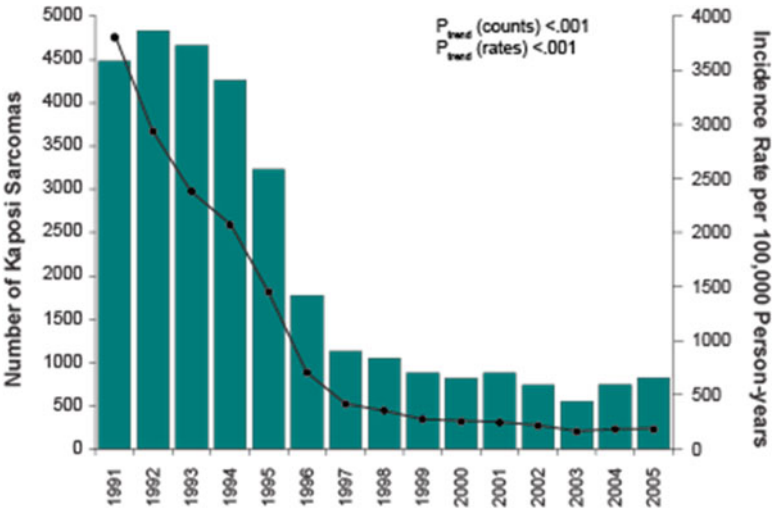

Fig. 2.2 Cancer burden of Kaposi sarcoma among people living with AIDS in the USA during 1991–2005. *Bars* depict estimated counts (i.e., number of cancers) and *points connected by lines* depict the incidence rates standardized to the 2,000 US AIDS population by age group, race, and sex. Trends in cancer counts and rates were estimated with linear regression. Two-sided *P* values were calculated using the χ^2 test. Shiels MS, et al., Cancer Burden in the HIV-Infected Population in the United States. J Natl Cancer Inst. 2011;103(9):753–62, by permission of Oxford University Press

More recently, host and viral cofactors are emerging as recognized factors in the development of KS. Molecular epidemiologic studies suggest that polymorphisms in host genes involved with inflammation or immune responses are associated with a slightly increased risk of KS. Host factors include a positive association between KS and substitution of phenylalanine for glycine at position 13 in the HLA-DRB1 locus, suggesting a role for immunogenetic factors. Also, a specific polymorphism in the IL-8 promoter (TT is protective versus AT) is associated with both the occurrence and severity of KS. Additional host factors include a decrease in NK cells and immune activation measured by elevated cytokine levels.

A number of HHV-8 genes have functions that can promote tumoragenesis. Like other herpesviruses, HHV-8 has "picked up" host genes that encode for key cell cycle regulatory genes [e.g., human complement-binding protein, IL-6, BCL-2, cyclin-D, Flice inhibitory protein (FLIP)] and some DNA altering genes (e.g., dihydrofolate reductase, thymidine kinase, thymidylate synthetase, and DNA polymerase). These "accessory" genes are thought to be integral to KS oncogenesis on the molecular level. HIV-1 itself has a viral protein, Tat (trans-activating factor) that may synergize with HHV-8 to foster angiogenesis, disease progression, and promote tumor survival. The potential synergistic effect of host and viral cofactors on KS progression may further disrupt immune control of HHV-8 and explain the more advanced clinical state of KS among HIV-1 infected individuals as compared to immunosuppressed organ transplant recipients.

An emerging risk factor in the post-HAART era is ineffective treatment. Ineffective HAART may be the result of poor adherence resulting in insufficient immune restoration and the development of drug-resistant strains. Ineffective therapy may also be associated with interrupted treatment. In the Swiss HIV cohort study, absence of antiretroviral therapy (ART) for 3 months was associated with an eightfold increased risk of KS (Franceschi 2008). In a randomized clinical trial, KS incidence was higher among those with intermittent therapy as compared to those on continuous therapy (Silverberg et al. 2007). These relapses in HIV viremia may have a direct effect on viral and host interactions, ultimately altering host susceptibility to KS disease progression.

2.3 Epidemiology of Non-Hodgkin Lymphoma Before HAART

Non-Hodgkin lymphoma (NHL) was the second most common cancer early in the AIDS epidemic and it was included as an AIDS-defining illness by the Centers of Disease Control (CDC) in 1985. The background prevalence of NHL in the USA prior to the AIDS epidemic was much higher than KS, so incidence trends were not as striking. In a period analysis, the incidence of NHL from 11 regions in the USA in the Surveillance Epidemiology and End Results (SEER) Program was 21.1 per 100,000 white men in 1995 as compared to 10.4 per 100,000 white men in 1973 (Mbulaiteye et al. 2003). For those with HIV infection, the incidence of NHL was 60–200 times higher as compared to HIV-negative individuals (Bower et al. 2006). Five to ten percent of all HIV-infected individuals were expected to develop lymphoma as either the first or subsequent AIDS-defining malignancy (Hamilton-Dutoit et al. 1991). Overall survival from NHL was worse than KS, less than a year (Bower et al. 2006).

AIDS-related lymphomas (ARL) are cancers of the lymphatic system. These NHL are predominantly of B-cell origin, intermediate to high-grade malignancies, and often have extensive extranodal involvement, such as the central nervous system. The prevalence of high-grade malignancy is much higher among AIDS patients (80–90 %) as compared to HIV-uninfected individuals (10–15 %) (Levine 1993). They occur late in HIV infection, and in general, their incidence is not affected by transmission group or geographic region in the USA. Women have a slightly lower incidence of ARL, but that is similar to the gender distributions of lymphomas in HIV-uninfected individuals. The strongest risk factors are duration of HIV infection, low CD4+ T cell counts at lymphoma diagnosis, and having a prior AIDS-defining illness. Of the 35 different histological types of NHL, four are associated with AIDS-defining malignancies by the 1985 definition of the Centers for Disease Control: diffuse large B-cell lymphoma (DLBCL) with centroblastic features; DLBCL with immunoblastic features; primary central nervous system lymphoma (PCNS); and Burkitt's lymphoma (BL). The nomenclature for lymphomas has changed since then, and while it is hard to map the DLBCL in the 1985 nomenclature to current lymphoma types, it is generally accepted that DLBCL of either the

germinal center subtype or activated B-cell subtype can be considered AIDS-defining. Three additional lymphomas that rarely occur in immunocompetent patients, but are more specific to HIV infection are primary effusion lymphoma (PEL), plasmablastic lymphoma (often of the oral cavity), and large B-cell lymphoma arising in HHV-8-associated multicentric Castleman's disease. About 70 % of the ARL are of the DLBCL histologic type which also includes variants or subtypes such as PCNS, PEL, and plasmablastic lymphoma.

Epstein-Barr virus (EBV), which had previously been identified as an etiologic agent of certain lymphomas, is a major contributor to AIDS-related lymphoma. EBV is ubiquitous in the general population and it has been associated with transplant-related lymphomas and primary immunodeficiency-associated lymphoma. Another oncogenic virus more recently linked to NHL is HHV-8, which like EBV is specifically associated with a subset of AIDS-associated lymphomas. EBV occurs in 30 % of centroblastic-DLBCL, 90 % of immunoblastic-DLBCL, 100 % of PCNS, 30–50 % of Burkitt-like lymphoma, and 50 % of plasmablastic lymphoma (Carbone 2003). PEL is associated with both EBV (about 80 %) and HHV-8 (100 %) (Carbone 2003). With varying prevalence of oncogenic viruses, no clear transmission patterns, and a multitude of host and viral risk factors, the only common risk among the ARL is HIV-related immunosuppression. Fortunately for those who were most susceptible to NHL, HAART significantly changed the incidence of the disease.

2.4 Epidemiology of NHL After HAART

Upon the introduction of HAART the incidence of NHL declined in the USA, but not as dramatically as KS (Fig. 2.1). Further unlike KS, which showed a biphasic decline, the decline for ARL was only observed during the 1994–1996 period when HAART was introduced (Fig. 2.3). In the MACS of MSM, the incidence of NHL declined by 77 % in the post-HAART era (1996–2007) as compared to the pre-HAART era (1984–1995) (Seaberg et al. 2010). In the Swiss HIV Cohort study, the standardized incidence rates of NHL declined from 952 to 98.4 per 100,000 in the 1985–1996 and 2002–2006 periods, respectively (Franceschi et al. 2010). Similarly, the incidence rate of NHL declined from 6.2 to 3.6 per 1,000 person-years in the 1992–1996 and 1997–1999 periods, respectively based on a collaborative study of 23 prospective studies from North America, Europe, and Australia (International Collaboration on HIV and Cancer 2000). In looking more specifically at the histologic types that comprise ARL, HAART has been particularly effective at reducing the incidence of PCNS and immunoblastic DLBCL, but it appears to have less impact on the incidence of Burkitt's lymphoma. Both mortality and survival improved for NHL in the post-HAART era, but the changes were more gradual. NHL mortality rate decreased twofold for persons with AIDS and about 56 % had an overall survival of 3 years with HAART and improved lymphoma therapies (Simard et al. 2010; Spagnuolo et al. 2012). HIV-positive individuals continue to present with NHL (Fig. 2.3) and are at a 23-fold increased risk compared to the general

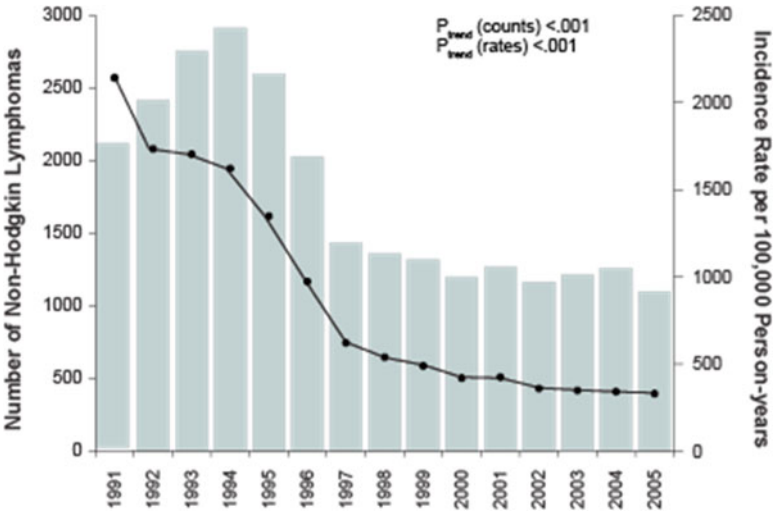

Fig. 2.3 Cancer burden of non-Hodgkin lymphoma among people living with AIDS in the USA during 1991–2005. *Bars* depict estimated counts (i.e., number of cancers) and *points connected by lines* depict the incidence rates standardized to the 2,000 US AIDS population by age group, race, and sex. Trends in cancer counts and rates were estimated with linear regression. Two-sided *P* values were calculated using the χ^2 test. Shiels MS, et al., Cancer Burden in the HIV-Infected Population in the United States. J Natl Cancer Inst. 2011;103(9):753–62, by permission of Oxford University Press

population (Engels et al. 2006). In several recent studies in the USA and Europe, NHL has emerged as the most common AIDS-associated malignancy. For example, in a record linkage study that evaluated the cumulative incidence of all cancers across the pre- and post-HAART eras, NHL surpassed KS as the most prevalent cancer in the post-HAART era (Simard et al. 2011). One risk factor in the post-HAART era driving this increase is a larger and aging AIDS population. The AIDS population has grown fourfold and is comprised of a higher proportion of individuals aged 40 years or older (Shiels et al. 2011). For those on HAART, older age (45 years+) is independently associated with a threefold increased risk of NHL (Polesel et al. 2008). Cases currently present with the same stages of disease as seen early in the epidemic, but they are older, less likely to have a prior AIDS diagnosis, and have a higher CD4+ T cell count at NHL diagnosis. As a result, current epidemiologic studies have focused less on markers of immune suppression and more on the molecular markers of pathogenesis to better understand risk factors in the post-HAART era.

Studies of archived pre-lymphoma samples from the MACS document that several markers of immune function are altered years before AIDS-associated lymphoma development. CXCL13 (a chemokine promoting B-cell chemotaxis) is significantly elevated particularly among EBV-negative compared to EBV-positive cases (Husain et al. 2010). CD23 (a B-cell stimulatory factor), IgE, IL6, CD27, and IL10 as well as the IL10 promoter 592C/C genotype are all elevated a year or more before lymphoma development compared to age and immune status matched

controls, demonstrating underlying markers of immune activation associated with future risk for HIV-associated lymphoma (Breen et al. 2011). An emerging risk factor in the post-HAART era is HIV viral replication as measured by cumulative or intermittent viremia (linked to treatment interruption) (Silverberg et al. 2007; Zoufaly 2009). Recent epidemiologic studies have found that HIV may upregulate activation-induced cytidine deaminase (AID) prior to NHL diagnosis. AID's normal function is to promote hypermutation of immunoglobulin genes associated with increasing affinity of the antibody during normal development of memory B cells and to promote class switching of antibody isotypes (i.e., IgM to IgG). The genetic modifications induced by AID sometimes lead to mistakes, such as chromosomal translocations or point mutations in immunoglobulin and/or oncogenes. The chromosomal translocations of the c-MYC gene common in HIV-associated Burkitt's lymphoma may be related to this upregulation of AID. Other early genetic modifications in HIV-related lymphomas include alterations of the BCL-6, a transcription repressor gene and point mutations or deletions in proto-oncogenes (Ras) and tumor suppressor genes (P53) (Carbone 2003). The decreased functionality of EBV-specific CD4+ and CD8+ T lymphocyte cells affects the cell-mediated responses necessary to control reactivation and replication of EBV-associated lymphomas. Any combination of these risk factors may have a multiplicative effect on developing NHL. While the pattern of HIV-associated lymphomas has changed in the post-HAART era (Fig. 2.3), there remains the paradox of emerging lymphoma risk particularly for some histological types not previously linked to HIV, such as certain T-cell lymphomas. In summary, lymphoma remains a major cause of mortality among HIV-infected patients even in the HARRT era.

2.5 Epidemiology of Cervical Cancer Before and After HAART

Invasive cervical cancer occurring in HIV-infected women was added as an AIDS-defining condition in 1993. Its inclusion at the time was somewhat controversial, as the incidence of cervical cancer was not substantially increased in AIDS patients. However, the increase in cervical cancer in HIV-infected patients has since become more apparent. It takes approximately 10–15 years for a cervical abnormality to become invasive and during those years it progresses through stages of cervical intraepithelial neoplasia (CIN 1,2,3). The benefit of HAART in delaying the progression of HPV disease in HIV-infected women remains unclear. As seen in Fig. 2.4, the pattern of HIV-associated cervical cancer differs from the patterns for KS and NHL where in the pre-HAART era, rates were exceptionally high and declined after the introduction of HAART. In the case of HIV-associated cervical cancer the initially high incidence rate in the early 1990s may be attributed to a lack of regular screening and management of abnormal pap smears in HIV-infected women. As screening and treatment of precursor lesions improved, the incidence rate stabilized. HIV-infected women compared to the general population maintained

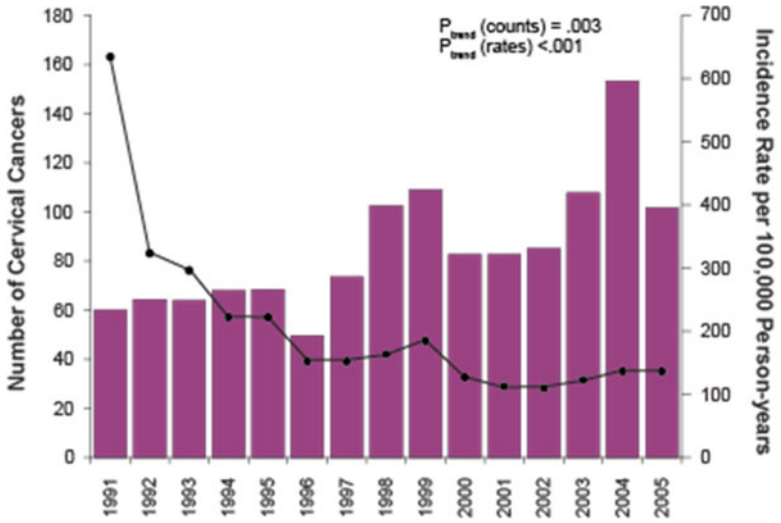

Fig. 2.4 Cancer burden of cervical cancer among people living with AIDS in the USA during 1991–2005. *Bars* depict estimated counts (i.e., number of cancers) and *points connected by lines* depict the incidence rates standardized to the 2,000 US AIDS population by age group, race, and sex. Trends in cancer counts and rates were estimated with linear regression. Two-sided *P* values were calculated using the χ^2 test. Shiels MS, et al., Cancer Burden in the HIV-Infected Population in the United States. J Natl Cancer Inst. 2011;103(9):753–62, by permission of Oxford University Press

a similar risk of cervical cancer through the introduction of HAART (1990–1995, SIR:4.2; 1996–2002, SIR:5.3) (Engels et al. 2006). The 5-year cumulative incidence of cervical cancer in the post-HAART era (0.64 %, 1996–2006) is similar to the pre-HAART era (0.63 %, 1980–1989; 0.73 %, 1990–1995) among those living with AIDS (Simard et al. 2011). Additionally, a collaborative study of 23 prospective studies from North America, Europe, and Australia found no change in the incidence of cervical cancer in the post-HAART era (International Collaboration on HIV and Cancer 2000). HAART appears to have had little or no impact on the incidence of cervical cancer so far and HIV-infected women remain at an elevated risk of developing the disease. However, it is possible that HAART may in the future be found to have effects on cervical cancer after a number of years.

For HIV-infected women who do develop cervical cancer, the disease is more aggressive, develops at younger age with more advanced disease that relapses after treatment (Pantanowitz and Michelow 2010). AIDS-defining cervical cancer progresses more rapidly and has a worse median survival compared to cervical cancers among HIV-negative women (Bower et al. 2006). The aggressive nature of cervical cancer in HIV-infected individuals would suggest that HIV-related immunosuppression may play a role in disease progression. However, HAART has had little impact on the incidence or progression rates of cervical lesions (Bratcher et al. 2010). Declining levels of CD4+ counts have not been shown to be a strong risk factor for disease progression. This is further supported by the observation that there is no difference in severity of neoplasia in women with asymptomatic HIV as com-

pared to women with AIDS (Clarke and Chetty 2002). It is possible that oncogenic changes that result in genetically unstable precancerous lesions determine progression rates independent of any restored immunity from HAART. There is also the possibility that the inconsistent findings in the prior research have been biased by the variability in cervical detection methods, follow-up time, duration of HAART, and small numbers of incident cases of cervical cancer.

The strongest risk factor for cervical cancer is persistent infection of high-risk types of the sexually transmitted virus, human papillomavirus (HPV). HPV is comprised of at least 40 different genotypes that infect the genital tract, 15 of which are considered high oncogenic risk. Genotypes HPV 16 and HPV 18 carry the highest risk and account for nearly 70 % of cervical cancers in the USA. HPV is highly transmissible particularly among younger women at sexual debut where an immunologically naïve host first experiences viral exposure. Risk factors associated with HPV acquisition include lifetime number of sexual partners, frequency of sex, partner's sexual history and behavior, parity, hormonal contraception, smoking, HIV, and other sexually transmitted infections. For most women, nearly 90 % of the infections are cleared by cell-mediated immunity within 2 years. For those coinfected with HIV, the course of HPV disease differs significantly.

HIV-infected women have a higher incidence, prevalence and number of concurrent HPV infections than HIV-negative women, and this is compounded by the sexual risk factors shared between HIV and HPV. Cervical HPV infection persists longer in HIV-infected women and has a higher probability of progressing from low to high-grade lesions. The regression rates of low grade cervical lesions decrease from 60 % in uninfected women to 27 % in HIV-infected women (Clarke and Chetty 2002). The burden of HPV infections increases as CD4 counts decline and HIV-1 viral loads increase. It is believed that selective depletion of effective CD4+ T cells results in poor responses by local CD8+ T cells in promoting clearance or regression of HPV (Clarke and Chetty 2002). A decrease in Langerhans cells in the cervical epithelium where HPV resides results in fewer numbers of antigen presenting cells needed to activate a cell-mediated response (Clarke and Chetty 2002). HIV may also release viral proteins, such as Tat, in the local environment that can enter cells and interfere with repair of DNA double strand breaks resulting in mutations and genetic instability (Nunnari et al. 2008). Tat may also activate gene transcription which may not be specific to the host or virus. Tat has been found to increase expression of early HPV genes that promote cell cycle progression (Clarke and Chetty 2002). Further studies of novel cofactors, such as HIV viral proteins, are needed to understand malignant transformation and development of cervical cancer. Any restored immunity from HAART may be too late depending on when therapy is initiated relative to the oncogenic events occurring with HPV.

Central to HPV's oncogenic potential are two viral gene products viral proteins termed E6 and E7 that increase cell proliferation, immortalization, and transformation. The E6 protein, particularly from HPV 16 and HPV 18, is efficient at binding the tumor suppressor protein, p53 leading to degradation. Loss of p53 prevents DNA repair and apoptosis and allows cell cycle progression regardless of any DNA damage. The E6 protein also increases telomerase activity and promotes cell immortalization. The E7 protein binds and inactivates another tumor suppressor,

retinoblastoma gene protein (pRB), resulting in activation of gene transcription and cell cycle progression. Unlike low risk HPV types that are not associated with precancerous lesions, high-risk types are more likely to integrate HPV's episomal chromosome into the host DNA. This disrupts a regulatory gene, viral E2, resulting in over expression of E6 and E7 proteins. Viral integration confers an advantage of cell cycle progression, but it is not in itself sufficient for malignant transformation. The majority of invasive cancers, particularly for HPV 18, have integrated HPV genomes, but there are still a proportion of invasive cervical cancers with episomal genomes. Recently, HPV DNA methylation has been described as a potential biomarker that may be able to distinguish the HPV infections that will progress to precancerous lesions (Clarke et al. 2012). HPV has conserved sites of CpG that when methylated by the host cell's DNA methyltransferase may, by mechanisms that are not completely understood, promote pathogenesis. Increased methylation in the capsid genes, L1 and L2, has been associated with increased risk of CIN2+ lesions (Clarke et al. 2012). However, methylation of the promoter and enhancer regions upstream of E6 are mixed and further studies are needed (Clarke et al. 2012). As more studies explore the epigenetic changes in precancerous lesions, the role of HIV and the host's genetic background in enhancing HPV infection will be better understood. In summary, HIV is a strong risk factor for more aggressive cases of cervical cancer, but widespread use of HAART so far appears to have little effect on the incidence, progression, or mortality rates of cervical cancer.

2.6 Conclusion

Most studies evaluating the changes in morbidity and mortality of AIDS-defining malignancies across calendar time rely on record linkage studies. This is an effective way to evaluate the cumulative effect of changing treatment strategies on cancer risk, given the power of the large sample sizes. A number of studies have shown that HAART on a population level has significantly decreased the rates of KS and NHL but has had little impact on cervical cancer. However, in part because the AIDS population is increasing and ageing, and fewer patients are dying of other manifestations of AIDS, cancer is increasing as a cause of death in the USA among HIV-infected individuals. Further studies that evaluate HAART on the level of the individual are needed to identify molecular factors involved with the pathogenesis of these different malignancies. More specifically, studies need to evaluate the role of HIV and its viral proteins in driving lytic replication in KS, somatic hypermutations and chromosomal translocations in NHL, or early gene expression in cervical cancer. A common theme across all these malignancies is that they often present with more aggressive cases during HIV infection. Therefore, cohort studies that dive deeper into the molecular interactions will offer new insights into the continued burden of AIDS-defining malignancies and potentially lead to new therapies and prevention measures in the current era of HAART.

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Chapter 3
The Epidemiology of Non-AIDS-Defining Malignancies

Andrew E. Grulich

Abstract AIDS-defining malignancies are those which are included in the case definition of AIDS, namely Kaposi Sarcoma, non-Hodgkin Lymphoma, and cervical cancer. *Non-AIDS-defining malignancies* are those other malignancies whose incidence is increased in individuals with HIV infection. In some instances, the term can also refer to any malignancy occurring in an individual with HIV infection. More recently, as the incidence of AIDS has declined in people with access to antiretroviral therapy, the term "HIV-associated malignancy" has become more widely used to describe the same group of malignancies.

3.1 Introduction

In the early 1980s, a rare form of skin cancer, Kaposi sarcoma (KS), occurring at greatly increased rates among homosexual men, was a harbinger of the AIDS epidemic. Over the subsequent decade, when it became apparent that non-Hodgkin lymphoma (NHL) and cervical cancer occurred at increased rates in people with HIV, these two cancers were added to the case definition of AIDS when they occurred in an HIV infected person. Collectively, KS, NHL, and cervical cancer are called AIDS-defining cancers and are separately considered in the section *AIDS-defining malignancies*.

Even early in the AIDS epidemic, it was recognized that other cancers also occurred with increased rates. In the mid-1990s, the introduction of highly active anti-retroviral therapy (HAART) changed the clinical face of HIV disease. In particular, it led to immune recovery and the much longer survival of people with HIV.

A.E. Grulich (✉)
HIV Epidemiology and Prevention Program, The Kirby Institute,
University of New South Wales, Sydney, NSW 2052, Australia
e-mail: agrulich@kirby.unsw.edu.au

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In general, immune recovery was only partial, and subtle effects of long-term mild immune deficiency, including the occurrence of certain cancers, began to emerge.

In this chapter, the spectrum of non-AIDS-malignancies is defined, and then individual cancer types are examined in detail. These cancers are grouped as (1) cancers with a known infectious cause that occur at increased incidence in people with HIV; (2) other cancers occurring at increased incidence in people with HIV and (3) cancer types that do not occur at increased incidence in people with HIV.

3.2 The Spectrum of Non-AIDS-Defining Malignancies

In the late 1990s, as the survival of people with HIV began to increase, it became more apparent that people with HIV were experiencing higher rates of a number of types of cancer than in the general population. This was identified within large-scale studies which linked population-based AIDS and/or HIV registers with cancer registries in several countries including the USA, Italy, and Australia. Increased rates of a wide range of cancers were identified. Initially, there was considerable debate about whether these cancers occurred at increased rates because of HIV-associated immune deficiency. The alternate explanation was confounding, because people with HIV also experience increased exposure to a number of other common carcinogens including tobacco smoke, and sexually transmitted and blood-borne oncogenic viral infections. The answer to whether cancer was truly caused by HIV came in part from studying cancer patterns in solid organ transplant recipients. Solid organ transplant recipients are required to take lifelong immune suppressive medications, and so share long-term immune deficiency with people with HIV. In other respects, they do not share similar carcinogenic exposures. A study published in 2007 conclusively demonstrated that these two populations have a broadly similar pattern of cancer occurrence, with increased rates of about 20 mostly infection-related cancer types (Grulich et al. 2007). The pattern of increased risk of cancer types is summarized in Fig. 3.1. More recently, cohort studies of people with HIV, which have included data on CD4-positive lymphocyte count and HIV viral load have demonstrated that many of these cancers are associated with impaired immune function.

In the remainder of this chapter, I will review the epidemiology of specific types of cancer in people with HIV, focussing in particular on the association with level of immune function.

3.3 Infection-Related Cancers

Cancers Related to Epstein–Barr Virus

The World Health Organization's International Agency for Research on Cancer (IARC) classifies Epstein–Barr virus (EBV) as carcinogenic in humans with respect to certain types of NHL (including Burkitt lymphoma, immunosuppression-related

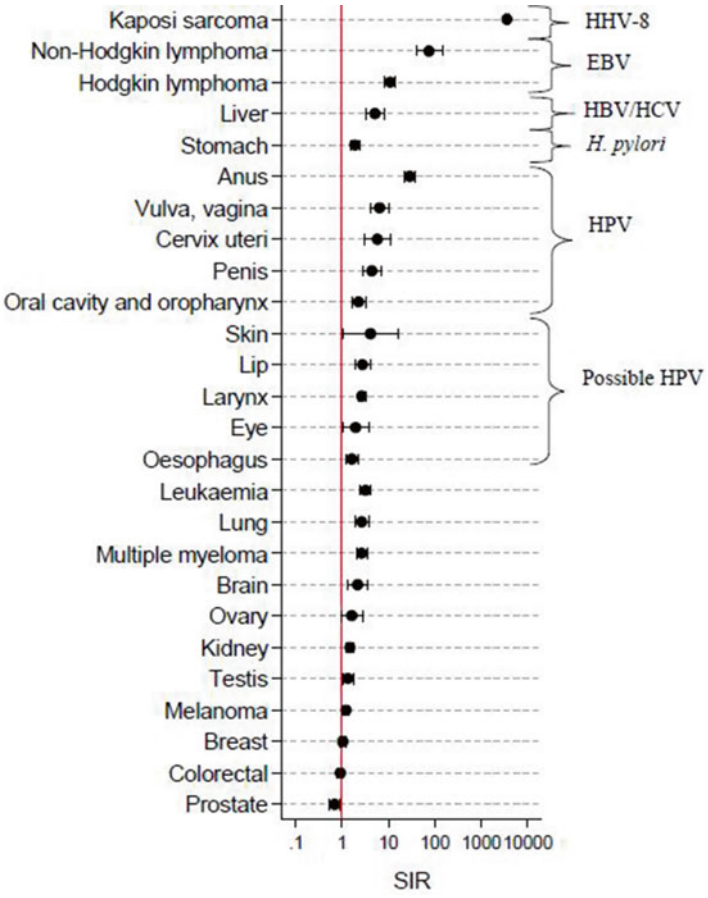

Fig. 3.1 Standardized incidence ratios of cancer types in people with HIV, grouped by infectious cause (figure based on data presented in Grulich et al. 2007)

NHL, extranodal NK/T cell lymphoma of nasal type), Hodgkin lymphoma, and cancer of the nasopharynx (IARC 2009). Data on NHL are summarized in *AIDS-defining malignancies* and are not further considered here.

EBV can be detected in 40–50 % of cases of Hodgkin lymphoma in developed countries, and is even more commonly detected in people with HIV (IARC 2009). Hodgkin lymphoma occurs about 11-fold more commonly in people with HIV than in the general population, and is raised about fourfold in organ transplant recipients (Grulich et al. 2007). The increase in risk in people with HIV is not consistent across Hodgkin lymphoma subtypes, and is confined to the mixed cellularity and lymphocyte-depleted subtypes. In recent years, rates of Hodgkin lymphoma in people with HIV have been relatively constant, and despite improvements in antiretroviral therapy and immune function they have not declined. Three cohort studies with longitudinal measurements of CD4 lymphocyte count have described an asso-

ciation between increasing rates of Hodgkin lymphoma and declining CD4 count (Guiguet et al. 2009; Reekie et al. 2010; Silverberg et al. 2011). At least part of the reason why rates of Hodgkin lymphoma have not declined in people with HIV in recent years is that the association with immune deficiency is much weaker than with NHL and Kaposi sarcoma.

Prospective studies have identified a strong relationship between serological markers of EBV infection and future risk of nasopharyngeal carcinoma (IARC 2009). As nasopharyngeal carcinoma is a rare cancer except in people originating from certain areas of South-East Asia, there are relatively few data on the association with HIV infection. A US-based linkage study of AIDS and cancer registers described a twofold increase in risk, based on only 39 cases, and a sixfold increase in risk was reported in a Chinese cohort of people with HIV.

Cancers Related to Human Papillomavirus

The IARC classifies certain types of human papillomavirus (HPV) infection as carcinogenic in humans with respect to cancers of the cervix, vulva, vagina, penis, anus, oral cavity, oropharynx, and tonsils (IARC 2009). There is weaker evidence that HPV may be associated with cancer at some other sites, including cancer of the larynx (IARC 2009).

Globally, the most common HPV-associated tumor is cervical cancer. Cervical cancer is an AIDS-defining cancer and is reviewed in AIDS-defining malignancies.

HPV can be detected in over 80 % of cases of anal cancer (IARC 2009). Anal cancer occurs at approximately 30-fold increased rates in people with HIV, and is also raised about fivefold in organ transplant recipients (Grulich et al. 2007). Risk is greatest in homosexual men with HIV, but substantial elevations in risk (greater than tenfold) are also seen in men with other risk factors for HIV, and in women with HIV (Chaturvedi et al. 2009). Some cohort studies have described an increase in anal cancer incidence in the HAART era, although a plateau in rates appears to have emerged in recent years. In some settings where homosexual men comprise a majority of people with HIV, anal cancer has become the most commonly occurring non-AIDS-defining malignancy (van Leeuwen et al. 2009). Anal cancer is not strongly related to current immune function, although a more moderate association with declining CD4 count has been described in two recent cohort studies (Reekie et al. 2010; Silverberg et al. 2012). Associations with prolonged duration below a CD4 cell count of 200 cells per microliter (Guiguet et al. 2009) and lower CD4 cell count nadir have also been described. The high incidence of this cancer in people with HIV, and the lack of a decline in incidence in recent years has led to anal cancer becoming a substantial health issue in people with HIV. Preventive interventions, including the possibility of a screening test for early detection of anal cancer and its precursors, have received considerable research attention in recent years. However, introduction of screening at a population level has been impeded by the lack of evidence of the efficacy of treatment of the pre-invasive lesion, and concerns about the accuracy and the complexity of the screening test.

Fewer data have been published on other HPV-related cancers and only small numbers have been described in cohort studies of people with HIV (IARC 2009), making a description of the relationship with immune function impossible. For cancer of the vulva and vagina, HPV can be detected in about 40 and 70 % of cases, respectively (IARC 2009). The cancers are increased about 6- and 23-fold in people with HIV and in organ transplant recipients, respectively (Grulich et al. 2007). HPV can be detected in about 50 % of cases of penile cancer (IARC 2009), and incidence rates are increased 4- and 16-fold in people with HIV and in organ transplant recipients, respectively (Grulich et al. 2007). Within the oral cavity, there is substantial variation in the association of cancer types with HPV. The strongest association is with cancer of the oropharynx and tonsils. In recent series 60 % or more of cases have detectable HPV (IARC 2009). For oral cavity cancer overall, incidence rates are increased two and threefold in people with HIV and in organ transplant recipients, respectively (Grulich et al. 2007). A US-based AIDS-cancer linkage study reported a modest 1.6-fold increase in oropharyngeal cancer in people with AIDS (Chaturvedi et al. 2009).

Cancers Related to Hepatitis B Virus and Hepatitis C Virus

The IARC classifies Hepatitis B virus (HBV) and Hepatitis C virus (HCV) as carcinogenic in humans with respect to hepatocellular carcinoma (liver cancer), and, for HCV only, for certain subtypes of NHL. There is weaker evidence that HBV may be related to NHL, and that both viruses may be related to cholangiocarcinoma (IARC 2009).

Liver cancer is increased about five and twofold in people with HIV and organ transplant recipients, respectively (Grulich et al. 2007). Risk of liver cancer is greatly increased in people with HIV who are co-infected with HBV and/or HCV (Guiguet et al. 2009), and thus incidence is particularly high in injection drug users and hemophiliacs with HIV. Two cohort studies have reported a moderate association of increased liver cancer risk with impaired immune function (Clifford et al. 2008; Guiguet et al. 2009).

A US-based AIDS-cancer linkage study has recently reported that risk of cholangiocarcinoma was increased by about 40 % in people with AIDS, but this did not reach statistical significance (Sahasrabuddhe et al. 2012).

Cancers Related to Helicobacter pylori

The IARC classifies *H. pylori* as carcinogenic in humans with respect to gastric carcinoma and low grade B cell mucosa-associated lymphoid tissue (MALT) gastric lymphoma (IARC 2009).

The incidence of stomach cancer is increased about twofold in people with HIV and in organ transplant recipients (Grulich et al. 2007). When examined by sub-site

within the stomach, increased risk does occur at non-cardia sites, where *H. pylori* has been casually associated with cancer (Persson et al. 2012). There is some evidence that EBV may cause a proportion of cases of gastric cancer (IARC 2009), and this is another potential reason why the incidence of gastric cancer is increased in people with HIV.

In the US AIDS-cancer match, gastric MALT lymphoma occurred about sixfold more commonly in people with AIDS than in the general population (Persson et al. 2012). *H. pylori* eradication is frequently associated with complete remission of the MALT lymphoma (IARC 2009).

Merkel Cell Carcinoma

Merkel cell carcinoma (MCC) is a rare but very aggressive skin cancer. In people with HIV, MCC occurs about 13-fold more commonly than in the general population, and it also occurs at greatly increased rates in organ transplant recipients and other immunosuppressed states including chronic lymphocytic leukemia. In 2008, it was discovered that a polyomavirus, now termed Merkel cell polyomavirus, is clonally integrated in Merkel cell carcinoma tissue (Feng et al. 2008). It is now recognized that Merkel cell polyomavirus is the cause of about 80 % of cases of Merkel cell carcinoma.

3.4 Cancers Occurring at Increased Rates in People with HIV with No Accepted Infectious Cause

In this section, cancers that have been documented to occur at increased rates in people with HIV, but do not have a well-accepted infectious cause, are discussed.

Lung Cancer

The incidence of lung cancer is increased about 2.7- and 2.2-fold in people with HIV and in transplant recipients, respectively (Grulich et al. 2007). Lung cancer is a common cancer in the general population of developed countries, and in many developed countries, lung cancer is the most common non-AIDS-defining carcinoma as assessed by the number of cases year. It is thus a very important cause of morbidity. Assessing the cause of this excess risk is made complex by the fact that people with HIV have a substantially raised prevalence of tobacco smoking. While tobacco smoking has been controlled for using multivariate techniques in several studies, it is difficult to confidently exclude the possibility of residual confounding by dose or timing of tobacco exposure (IARC 2009).

Another possible cause of the increased lung cancer incidence in people with HIV is an unknown pulmonary infection. In favor of this hypothesis is the fact that several cohort studies have found an association between lower CD4 count and increased lung cancer risk (Guiguet et al. 2009; Reekie et al. 2010; Silverberg et al. 2011), although one well-conducted cohort reported no association with immune function (Clifford et al. 2012). One study reported an association of lung cancer risk in people with HIV with recurrent pneumonia (Shebl et al. 2010), but another found no association of lung cancer with AIDS-related pulmonary disease. Irrespective of the cause, lung cancer is a major public health issue in people with HIV.

Conjunctival Cancer

Squamous cell cancer of the conjunctiva is a rare cancer that has been described as occurring at approximately 12-fold increase in people with AIDS in the USA, and also occurs at increased risk in kidney transplant recipients. A marked increased in risk of this cancer has been described in African settings (IARC 2009). Both solar ultraviolet radiation and HPV have been hypothesized to contribute to the etiology of this cancer (Chaturvedi et al. 2009).

Non-Melanoma Skin Cancer

In most parts of the world, data on basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of the skin are not recorded by cancer registries, and hence there are relatively few data on their occurrence in people with HIV. In solid organ transplant recipients, SCCs occur about 50 times more commonly than in the general population. In that population, SCC also behaves much more aggressively than in the general population, and is a substantial clinical management issue. It is clear that people with HIV are less predisposed towards SCC than are solid organ transplant recipients. Nevertheless, a recent cohort study in California reported that rates of SCC were increased about twofold, which was a similar increase to the incidence of BCC (Silverberg et al. 2013). In that study, SCC but not BCC was related to lower recent CD4 count. The association with immune deficiency is suggestive evidence that an infective agent may be related to SCC. There is suggestive but not definitive evidence that HPV may play a role.

Melanoma

The incidence of melanoma is increased marginally, by about 24 %, in people with HIV, and by 2.3-fold in organ transplant recipients (Grulich et al. 2007). In kidney transplant recipients, the current receipt and intensity of immune suppression

increase melanoma risk, suggesting that impaired immunity is related to melanoma risk. The absence of a substantially increased risk in people with HIV suggests that HIV-induced immune deficiency may be less closely linked to melanoma risk than the pharmacological immune suppression in transplant recipients.

Lip Cancer

The incidence of lip cancer is increased by 2.8-fold in people with HIV, and is increased very markedly, by about 30-fold, in organ transplant recipients (Grulich et al. 2007). In organ transplant recipients, the increase in lip cancer probably reflects the very large increase in risk of SCC of the skin. In this population, increased risk is associated with current immune suppression, and risk rapidly returns to normal in kidney transplant recipients who stop receiving immune suppression because of kidney graft failure.

Esophageal Cancer

The incidence of esophageal cancer is increased by 1.6-fold in people with HIV, and is increased about threefold in organ transplant recipients (Grulich et al. 2007). The increase in incidence in people with HIV appears to be similar for adenocarcinoma and SCC of the esophagus (Persson et al. 2012). The increased alcohol and tobacco exposure of people with HIV is a potential explanation for these increased rates.

Laryngeal Cancer

The incidence of laryngeal cancer is increased by 2.7-fold in people with HIV, and is increased about twofold in organ transplant recipients (Grulich et al. 2007). Based on a small case-series, HPV does not appear to be associated with this cancer in people with HIV. Increased tobacco is a likely cause of the increased occurrence in HIV disease.

3.5 Cancers That Do Not Occur at Increased Rates in People with HIV Infection

Given the large range of cancer types that occur at increased rates in people with HIV, it is notable that for several of the cancer types that occur commonly in the general population, incidence is not increased. These cancers include breast cancer, prostate cancer, and colorectal carcinoma.

Breast Cancer

In a meta-analysis of prospective research, breast cancer incidence was neither increased in people with HIV (meta-analysis SIR 1·03, 95 % CI 0·89–1·20) nor in transplant recipients (meta SIR 1·15, 95 % CI 0·98–1·36) (Grulich et al. 2007). Studies from earlier in the HIV epidemic described a decreased incidence of breast cancer compared to the general population. Incidence increased towards that of the general population in more recent years. A potential explanation for that pattern is that prior to effective anti-retroviral therapy, women with AIDS received less breast cancer screening, and that with prolonged survival screening rates are likely to have increased.

Prostate Cancer

In the meta-analysis described above, prostate cancer incidence was decreased about 30 % in men with HIV. In transplant recipients incidence was not significantly different to 1 (meta-SIR 0·97, 95 % CI 0·78–1·19) (Grulich et al. 2007). In the USA, the decreased incidence of prostate cancer in people with AIDS was confined to the era when prostate-specific antigen was being used as a screening test. The deficit in incidence was confined to early stage-cancers and not present for advanced cancer. These findings suggest that decreased prostate cancer incidence is related to decreased cancer screening in men with AIDS.

Colorectal Cancer

In the meta-analysis described above, colorectal cancer incidence was not increased in people with HIV (meta-SIR 0·92, 95 % CI 0·78–1·08). In transplant recipients incidence was increased by about 70 % (Grulich et al. 2007). The reason for the increased incidence in organ transplant recipients is unclear.

3.6 Conclusion

As the HIV epidemic unfolds, the pattern of cancer occurrence in people with HIV has continued to change. A constant theme has been that people with HIV experience increased oncogenic exposure compared to the general population, and this has led to patterns of cancer that are often very distinct. Over the years, these increased exposures have changed, but in most populations have included immune deficiency, tobacco and alcohol, and oncogenic blood-borne and sexually transmitted infectious agents. The occurrence of immune deficiency in millions of people has given

us a unique opportunity to examine the role of infection in carcinogenesis. For many types of cancer, this has helped us delineate the role of infection in causing cancer. For a few others, most particularly for prostate and breast cancer, the absence of any increased risk in either people with HIV or organ transplant recipients has provided strong evidence that infection appears not to be an important cause.

The HIV epidemic is over 30 years old, and most people with HIV have acquired infection in early adulthood. With effective anti-retroviral therapy, these individuals are living substantially longer and a substantial ageing of the HIV-infected population is occurring. As a result, the large-scale interaction of the carcinogenic effects of mild immune deficiency with the much higher cancer incidence that is experienced in old age will occur. If people with HIV carry the relative risks of HIV-related cancer into older age, that will lead to a very large increase in the burden of HIV-related cancer. Such increases are already beginning to happen. However, to the extent that effective anti-retroviral therapies can completely or nearly completely remove the oncogenic effect of immune deficiency, then such increases may be lessened. Further follow-up of large cohorts of people with treated HIV is required to clarify these issues.

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Chapter 4
HIV Cancers in Resource-Limited Regions

Sam M. Mbulaiteye

Abstract About 29 of 33 million persons living with human immunodeficiency virus (HIV) or the acquired immunodeficiency syndrome (AIDS) (PLHA) worldwide in 2009 reside in resource-limited countries. The burden of cancer in this population is substantial, although there is much we still do not know about the epidemiology of various HIV-associated tumors in these regions. Access to life-extending combination antiretroviral therapy (cART), which has been rapidly expanding since 2000, has improved survival to nearly normal life expectancy, including in resource-limited countries where about 30 % of PLHA are receiving cART. The improvements in survival with HIV, however, are occurring at the expense of increased incidence of chronic co-morbidities including cancer in PLHA on cART. Sparse data about risk of cancer in PLHA in resource-limited countries complicates efforts to evaluate this concern. Cancer is diagnosed in about 30 % of PLHA in developed countries. Cancers in PLHA are historically categorized as "AIDS-defining" cancer (ADC) or "non-AIDS-defining" cancers (NADC). ADCs include Kaposi sarcoma (KS), aggressive non-Hodgkin lymphoma (NHL), including Burkitt lymphoma (BL), and invasive cervical cancer. These cancers have a viral etiology and are more likely to be associated with degree or duration of immunosuppression. NADCs include Hodgkin lymphoma, anogenital, liver, and lung cancer. Most of these cancers have a viral etiology or are associated with lifestyle factors, e.g., cigarette smoking or injection drug use, which are more prevalent in PLHA. These cancers often occur in spite of sustained immune-restoration. Thus, NADCs have assumed greater importance as PLHA survive longer and ADCs proportionately decrease. Cancer is diagnosed in fewer than 5 % of PLHA in resource-limited countries. This rate is likely a gross underestimate, and is also affected by

S.M. Mbulaiteye, M.B.Ch.B., M.Phil., M.Med. (✉)
Infections and Immunoepidemiology Branch, Division of Cancer Epidemiology and Genetics, Department of Health and Human Services, National Cancer Institute, National Institutes of Health, 9609 Medical Center Dr, Rm. 6E118 MSC 9706, Bethesda, MD 20892-9704, USA
e-mail: mbulaits@mail.nih.gov

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competing mortality from endemic infectious diseases such as malaria and tuberculosis. The low access to diagnostic services in low resource settings may also mean that a notable fraction of cancers remain undiagnosed in PLHA. Increasing access to affordable cART in resource-limited settings is likely to rapidly reduce infectious co-morbidities such as tuberculosis and thus amplify the importance of cancer in PLHA. Studies of PLHA in resource-limited countries are needed to characterize the additional cancer burden in PLHA to inform public health policy and knowledge about cancer etiology in different populations.

4.1 Introduction

In 2009, 28.8 million PLHA were living in resource-limited countries, including 22.5 in sub-Saharan Africa and 6.3 million in countries in South Asia, South-East Asia, East Asia, and Central and South America (Fig. 4.1) (2009) The risk for cancer in PLHA in resource-limited countries has not been well described, with fewer than 5 % of PLHA in resource-limited countries being diagnosed with cancer [Cancers related to HIV, essay 00369]. This low rate is most likely a gross underestimate because of competing mortality due to common infections like malaria and tuberculosis and because of lack of specialized hospitals that can diagnose and treat cancer and cancer registries that can collect and analyze incidence data on various cancers that are seen in the region (Parkin 2006). For example, only four countries in sub-Saharan Africa had registries of high quality sufficient for inclusion in the *Cancer Incidence in Five Continents* monograph published by IARC in 2002. Thus, the relationship between HIV and cancer in the resource-limited countries remains poorly described.

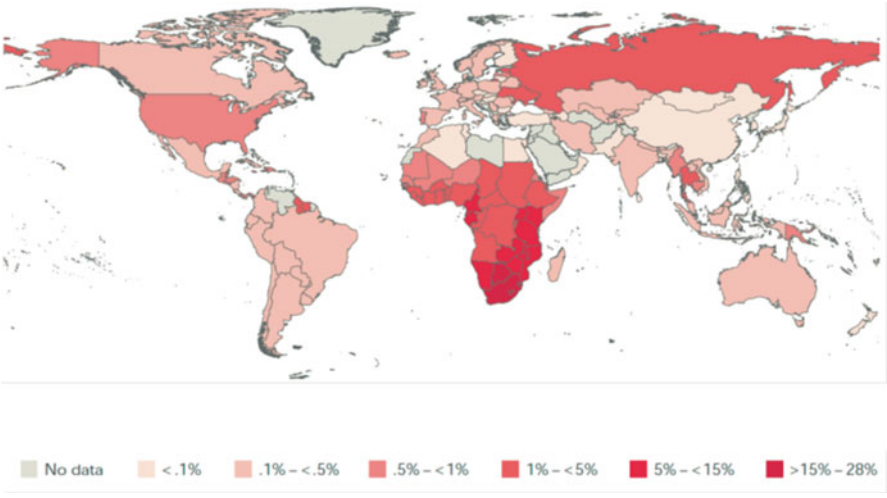

Fig. 4.1 Global prevalence of HIV in 2009 (UNAIDS Report)

Understanding the impact of HIV on cancer in populations residing resource-limited countries is important for public health and science (Chap. 1). In 2008, the International Agency for Research on Cancer (IARC) estimated that 12.7 million new cancers were diagnosed worldwide, 56 %—or 7 million new cases—were in resource-limited countries and about 23 % of those cancers could be attributed to infections (de Martel et al. 2012). Also, the profile of cancers occurring in resource-limited countries varies considerably from region to region, because they span a broad range of prevalent infections, lifestyle factors, genetic, environmental and dietary backgrounds, and the demographic distributions are different. No prospective studies have been conducted to investigate cancer risk in PLHA in resource-limited countries. In developed countries, the evaluation of cancer burden in PLHA has been facilitated by linking the records of population-based HIV/AIDS registers [AIDS service organizations, essay 00038] to population-based cancer registers (Chaps. 2 and 3), but this is difficult to implement in most resource-limited countries because of lack of electronic registries. Some data has accumulated from case series reports and a few case–control studies that have been published (Sasco et al. 2010). The case series suggest an increase in the number of cases or a change in the clinical pattern of disease, but they are not useful for quantifying risk or identifying co-factors associated with cancer in PLHA. Case–control studies have provided some insights into risk, but they are few and often have been small. The results from the studies are described in detail below. For these reasons, more quantitative and accurate studies of HIV-associated cancers in resource-limited regions are urgently needed.

4.2 AIDS-Defining Cancers

Kaposi Sarcoma

KS was endemic in sub-Saharan Africa before the onset of the AIDS epidemic (Hutt and Burkitt 1965; Hutt 1983). The epicenter of KS was around the Congo-Nile watershed in equatorial Africa, and the incidence fell with distance away from this epicenter (Ziegler 1993). In the early 1980s, clinicians working in Uganda and Zambia noted an increase in the number of KS cases attending their clinics and a change in clinical course of the disease (Ziegler 1988). The changes in the clinical picture and epidemiology resembled the pattern of epidemic KS cases that had recently been described in men who have sex with men in the USA and Europe (Chap. 2). Subsequent studies on site in Africa confirmed that epidemic, but not endemic, KS in Africa was associated with AIDS (Bayley 1984; Downing et al. 1984). In contrast to patients with endemic KS, whose clinical course was indolent and who developed lesions mostly on the feet or hands, patients with epidemic KS often developed widely disseminated lesions almost anywhere on the body, including internal body organs and mucosal surfaces, and often had a rapidly fatal course (Chap. 9). The median age of patients with epidemic KS was also lower,

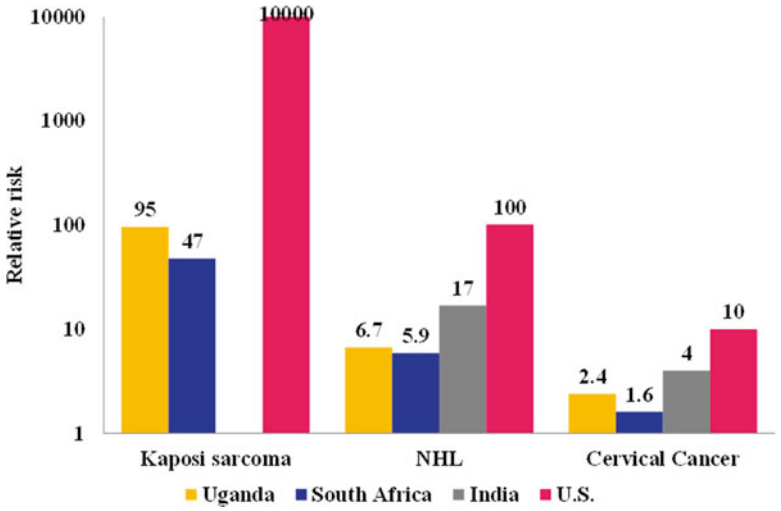

Fig. 4.2 Relative risk of AIDS-defining cancers (Kaposi sarcoma, non-Hodgkin lymphoma, and cervical cancer) in people living with HIV in three different resource-limited countries and the USA as compared to unaffected populations in the same countries (Mbulaiteye 2011)

corresponding the median age of patients with AIDS, and the male-to-female sex ratio was close to 3:1, in contrast to 10:1 reported for endemic KS.

The incidence of KS has increased in the general population of countries in sub-Saharan Africa with a substantial HIV epidemic. For example, in Uganda, one of the first countries to be touched by the HIV epidemic, KS incidence rate per 100,000 increased 12-fold in men and 218-fold in women during 1995–1997 as compared with 1960–1966 (Wabinga et al. 2000; Mbulaiteye et al. 2011). It is currently the first or the second commonest cancer in men, women, and children in Uganda. Similar changes have been reported in other countries in equatorial Africa, including Zimbabwe (Chokunonga et al. 2013), Zambia (Bayley 1991), and Tanzania (Amir et al. 2001), although precise estimates of the change in the incidence are not available. The risk of KS is increased 22–95 times in persons with HIV compared to unaffected persons (Fig. 4.2) (Mbulaiteye et al. 2011). For example, in Rwanda, close to the epicenter of endemic KS, the risk of KS is increased 35 times in persons with HIV compared to unaffected persons (Newton et al. 1996). Similarly, elevated risks have been reported in South Africa (22–47 increased risk with HIV) (Sitas et al. 2000). The impact of HIV on KS risk appears to be higher in children. One study conducted in Uganda reported that the risk of KS was 95 times higher in children ($\leq$ 15 years) with HIV compared to unaffected children (Newton et al. 2001). While the fold increases in risk of KS in Africa are lower in PLHA than in the USA, these estimates probably grossly underestimate the impact of HIV because of premature mortality due from more common illnesses, such as malaria and tuberculosis, due to underdiagnosis, and higher background incidence rate of KS in the general population in Africa.

An essential risk factor for KS is infection with Kaposi sarcoma-associated herpesvirus (KSHV) (Chap. 5), which was discovered by Moore and Change in 1994 (Boshoff 2000). Serological studies conducted in Africa, where KS is endemic, have confirmed, as expected, that KSHV is common, with antibodies detected in 20–80 % of persons tested. The highest prevalence is found in populations residing in the Congo-Nile watershed, the epicenter of endemic KS, where 50–90 % of adults have KSHV antibodies (Dedicoat and Newton 2003). The risk of KS is associated with presence of KSHV antibodies or DNA in peripheral blood, and with severe T-cell immunosuppression. In resource-limited countries, the use of cART is associated with a substantial reduction in risk of KS [Management of Kaposi's sarcoma, essay 00224]. The globally coordinated efforts aimed at interrupting the spread of HIV/AIDS and reducing mortality from AIDS in sub-Saharan Africa have dramatically increased access to cART, from a few hundreds a few years ago to close to four million PLHA in 2009 (2009), mostly using the more affordable regimens based on non-nucleoside reverse transcriptase inhibitors (NNRTIs). Significant increase in life expectancy has already been reported among PLHA using cART in sub-Saharan Africa and the incidence of KS is falling, although less precipitously than was observed in developed countries. The reasons for the apparent lower protection of cART against KS in patients in Africa are unclear, but they may include poor adherence, the effects of co-infections on immunosuppression, or other unknown factors. There is some evidence suggesting that anti-HIV regimens containing NNRTI may provide less protection against KS than regimens containing protease inhibitors, although some retrospective studies suggest there is no difference and this remains a controversial area. KS has also been reported to develop shortly after initiation cART, suggesting that KS may occur as a complication of the immune reconstitution syndrome (Jaffe et al. 2011). These observations suggest that unlike in developed countries, where KS has become less of a concern with the introduction of cART, KS is likely to continue to be a major problem of PLHA in sub-Saharan Africa because of the significant overlap of KSHV and HIV infections in the population. Thus, public health messages in Africa should stress the link between HIV and KSHV and highlight the opportunity for screening and early detection of KS and linkage to HIV care (Mbulaiteye and Goedert 2008).

While KS can occur in Asian PLHA, it is distinctly uncommon. Only a handful of cases have been reported in India, although the country has more than 1.5 million PLHA, including a substantial proportion of men who have sex with men. KS was not observed among 137 HIV-positive patients with cancer treated from 2001 to 2005 at the Tata Memorial Hospital in Mumbai, the largest tertiary cancer referral medical center in India (Biggar et al. 2009). The reasons for the low rate of KS in India are unclear. KS also is uncommon in Thailand. Since KSHV infection is required for KS to develop, the low rate of KS suggests low prevalence of KSHV. However there is little known about KSHV seroprevalence; in one study, the seroprevalence was about 7 % in India (Ablashi et al. 1999). Why KSHV would be uncommon in India is unclear. In Africa, KSHV infection occurs in early childhood and prevalence increases rapidly with age in both sexes, particularly in poorer households without access to clean water. Transmission is probably via saliva

exchange. Why KSHV has not spread in India or other areas of Asia, despite a large population living in poor socioeconomic conditions and lacking access to clean water raises interesting questions about the biology of the virus versus human hosts in Asia. KSHV infection can occur among Asians because infection and KS has been reported in populations on the west coast areas of India, which have had many centuries of immigration and trade interaction with east and central Africa. Although data are sparse, there is evidence that half or more of adults in those regions are KSHV-infected and KS is also endemic. Studies conducted in PLHA and in the general population to confirm the low prevalence of KSHV and KS in Asia could provide insights about viral-host pathobiology. These studies might reveal, for example, pockets of KSHV infection in remote rural areas of India or Asia, which when they overlap with HIV might be associated with increased risk of KS.

In contrast to India, KS is diagnosed frequently in men who have had sex with men in Latin American countries, including Brazil, Columbia, and Argentina. In these countries, one-quarter of KS cases are AIDS-defining, and three-quarters are diagnosed after AIDS onset (Yoshioka et al. 2004). The risk of KS has been linked to infection with KSHV, which can be transmitted through male–male sexual contact (Boshoff 2000).

4.3 Non-Hodgkin Lymphoma

The risk for non-Hodgkin lymphoma (NHL) in resource-limited countries is considered to be lower than in resource-replete countries, with notable exceptions. For example, Burkitt lymphoma (BL), which was first described by Denis Burkitt in 1958 in African children and linked to Epstein–Barr virus (EBV) [Epstein–Barr virus, essay 00008], is endemic in sub-Saharan Africa (Chap. 13). In 1982, BL was one of the aggressive lymphomas that heralded the AIDS epidemic (Chaps. 2 and 3). Not surprisingly, scientists wondered whether all or some of endemic BL cases might also be AIDS associated (Wright 1999). Studies conducted on site in Africa dispelled this notion. Those studies demonstrated, as has been shown by studies conducted since, that most instances of BL in sub-Saharan Africa are HIV negative (Parkin et al. 1999; Mutalima et al. 2010). The prevalence of NHL was 2.8 % (compared to 6 % in developed countries) in a necropsy study of among 247 persons aged 14 years or older who died of HIV-related disease and underwent post-mortem diagnosis at a hospital in Abidjan Cote d'Ivoire during 1991–1992 (Lucas et al. 1994). This included 1.6 % with visceral NHL and 1.2 % with primary cerebral lymphoma. Childhood BL was not observed among 78 autopsies performed on children in the same study. In the absence of well-conducted prospective studies, the results from this autopsy study provide the best data about the impact of HIV on NHL in Africa, where underdiagnosis may contribute to the low rates of NHL. A study of 26 NHL cases among persons aged 16 years or older diagnosed between 1992 and 1996 in Kenya found that 19 of the cases were diagnosed in HIV-positive persons (Mwanda et al. 2005). This number was higher than the investigators had

expected, based on historical patterns before the HIV epidemic. The median age of the HIV-positive BL cases was 35 years, which is higher than the peak age 5–9 years observed in endemic BL.

Data from population-based cancer registries comparing the incidence of NHL before and after onset of the AIDS epidemic support the notion that the NHL incidence may be increasing during the AIDS era. The incidence increased about three times for all NHL, and about four times for pediatric BL, in the general population covered by the Kampala Cancer Registry between 1961 and 1971 and 1997 (Wabinga et al. 2000; Mbulaiteye et al. 2011). While these results support the notion of a positive impact of HIV on NHL, the lack of HIV status results on the NHL cases in registry studies prevents firm conclusions.

Data from case–control studies conducted at large tertiary hospitals have provided a mixed picture. The results are compatible with a null or a modest impact of HIV with the estimates of increased risk ranging from 2.2 to 46.2 times compared to unaffected populations (Fig. 4.2). The largest study conducted in South Africa that looked at 154 histologically confirmed adult NHL cases and compared them to 4,399 adult hospital controls drawn from cancers unrelated to HIV among the men or vascular conditions among the women (Stein et al. 2008). This study reported a fivefold increase in HIV infection in the NHL cases (95 % CI 2.7–9.5) (Mbulaiteye et al. 2011). The results from an HIV/AIDS-cancer record-linkage study conducted in Uganda observed that NHL incidence was increased seven times in persons with HIV compared to the general population (SIR 6.7, 95 % CI 1.8–17) (Mbulaiteye et al. 2006), but no independent histological verification of NHL was done. The impact of HIV on BL varies from 2.1 to 46. The uncertainty about the degree of impact of HIV on BL is due to inclusion of cases diagnosed clinically or with local histopathology without confirmation by expert hematopathologists (Ogwang et al. 2011). The possible exception is the result from a study conducted in South Africa, where the BL subtype observed is sporadic. Compared to other children with other cancers, children with BL were 46 times more likely to be HIV positive, based on finding 13 of 33 cases who were HIV positive (Stefan et al. 2011). The impact of HIV on BL in South Africa is more similar to the impacts reported in developed countries than in Africa (Mbulaiteye et al. 2011). The contrasting impacts of HIV on BL according to the subtype of BL are intriguing and prompt the question whether the association with HIV is different between endemic and sporadic BL (Chap. 13). Some of the reasons for the relatively low impact of HIV on BL include premature mortality from competing causes like malaria or tuberculosis or due to underdiagnosis of BL. If HIV increases the risk of BL, then the success in reducing mortality from preventable infections like tuberculosis and malaria may more clearly reveal the impact of HIV on BL. If the risk for BL is increased, approaches to increasing surveillance may have to be considered. In addition, questions about the proper treatment of HIV-positive children with BL will have to be considered.

Studies in Asia and Latin America also suggest that NHL risk is increased in persons with HIV. In India, the proportional incidence of NHL in persons infected with HIV was increased 17 times in men and 10 times in women, based on a study conducted at Tata Memorial Hospital (Dhir et al. 2008). NHL was the most common

type of cancer reported in this study, accounting for 38 % of the cancers seen in HIV-infected males and 16 % of all cancers in HIV-infected women. The apparently lower risk of NHL in women than men is due to a large proportionate contribution from cervical cancer. Data from population-based cancer registries in Thailand suggest that the incidence of NHL has almost tripled from 1989–1991 to 1999–2001 (Sriplung and Parkin 2004). The incidence increased most steeply (11 % per year) for diffuse/high-grade lymphoma, which is an ADC (Sriplung and Parkin 2004). The risk of NHL was elevated 34 times among 3,554 PLHA in Hubei Province in China followed from 2004 to 2007 compared to the general population.

Data from Latin America are scanty, but NHLs have been reported in persons with HIV and show a strong association with EBV in different countries, including Brazil (Sampaio et al. 2007). The low rates of NHL in PLHA from resource-limited countries are likely due to gross underestimate of the real risk due to competing mortality [Access to care, essay 00035]. Under-ascertainment and/or misclassification of cases likely contribute. Conclusions about the impact of HIV on NHL await results from studies using sound epidemiological and laboratory design.

4.4 Cervical Cancer

Cervical cancer is the leading cancer and cause of cancer death in women in the resource-limited countries (Chap. 19) (Sylla and Wild 2012). The principal cause is infection with carcinogenic human papillomavirus (HPV) via sexual contact (Chap. 19). Thus, an association between HIV and invasive cervical cancer might be expected in populations where there is significant overlap of both infections because of shared routes of transmission (Chap. 2). An additional biological association might be expected because immunosuppression by HIV would impair the women's ability to clear their HPV infection, and it might act synergistically with HPV oncoproteins E6 and E7 to facilitate progression to invasive cervical cancer in HIV/HPV-co-infected women. Consistent with this expectation, the prevalence of cervical intraepithelial neoplasia (CIN), which reflects infection of cervical epithelium with HPV, with or without cellular abnormalities, is increased with HIV infection, and the prevalence or incidence of HPV or CIN is inversely associated with CD4 counts. However, the evidence for association between invasive cervical cancer with HIV infection in resource-limited countries is controversial. The incidence of invasive cervical cancer in the general population in Uganda increased about threefold from 1960–1966 to 1991–2006 (Wabinga et al. 2000; Mbulaiteye et al. 2011), based on data from the Kampala Cancer Registry, but this magnitude of increase is small and could be due to effects of temporal changes, e.g., urbanization, better access to medical care, or improved case reporting. In Zimbabwe, which has also been severely affected by the HIV epidemic, no significant change in the incidence of invasive cancer in the general population was seen between 1990–1992 and 1993–1995 despite a sharp increase in the HIV prevalence among women during the same period (Chokunonga et al. 2013). Moreover, the clinical presentation of invasive

cancer has not dramatically changed during the AIDS era. The null or small increase (1.6–8 fold) in risk of invasive cervical cancer in HIV-infected women has been confirmed by findings from case–control studies. In Uganda, HIV was associated with a non-significant 1.6-fold increase in invasive cervical cancer in a hospital-based case–control study conducted in 5 hospitals in Kampala, the capital city of Uganda (Newton et al. 2001) (Fig. 4.2). The risk was similar, but statistically significant, in a hospital-based study on Johannesburg in South Africa (Stein et al. 2008). A record linkage study of the women registered in The AIDS Support Organization in Uganda with a local cancer registry reported a 2.4-fold increase in invasive cervical cancer incidence in HIV-infected women compared to women in the general population (Mbulaiteye et al. 2006). The highest risk of invasive cancer was reported in a case-referent study conducted in referral hospitals in Côte d'Ivoire and Benin from October 2009 to October 2011 (Tanon et al. 2012). The prevalence of HIV was 8 times higher in women with invasive cervical cancers compared to other cancers.

Because African countries have only begun implementing cervical screening programs, the small impact of HIV on the risk of invasive cancer in sub-Saharan Africa may be largely due to competing causes of mortality in HIV-infected women. This explanation would be consistent with reports of elevated risk of CIN in HIV-infected women, but small impact with invasive cervical cancer, which takes up to 10 years to progress from initial lesion to invasive cancer. Despite the small impact, the prevention of invasive cervical cancer must remain a priority in many African countries. Recently established HIV treatment cohorts provide suitable opportunities to not only gather information about cancer risks but also introduce innovative approaches that link HIV services to cancer screening, early detection and treatment services (Chap. 27).

The impact of HIV on cervical cancer in India, the country with the world's highest number of cervical cancer cases, was slightly stronger (Biggar et al. 2009). The prevalence of HIV was four times higher in women with invasive cervical cancers compared to other cancers. The impact might be as high as 68-times higher in HIV-positive women compared to unaffected women in other countries, based on results from one study in Hubei Province in China during 2004–2008 (Mbulaiteye et al. 2011). These results, while not confirmed yet, justify continued concern about the potential association between invasive cervical cancer and HIV in resource-limited countries.

4.5 Non-AIDS-Defining Cancers

Squamous Cell Carcinoma of the Conjunctiva

The diagnosis of squamous cell carcinoma of the conjunctiva (SCCC), a rare cancer of the ocular surface linked to exposure to ultraviolet light, has been linked to HIV infection in African countries close to the equator (Chap. 25). This association was first reported in Uganda, where a curious doctor noticed an increase in the number

of cases presenting with SCCC at eye clinics in Kampala. A formal study of 48 patients with SCCC and matched to 48 patients with benign conditions attending the eye clinics at Mulago Hospital revealed HIV infection in 75 % of the cases compared to 19 % among the controls (Ateenyi-Agaba 1995; Mbulaiteye et al. 2011). Studies conducted subsequently in Uganda and Malawi have confirmed the association of a tenfold higher risk of SCCC in HIV-infected individuals than in the unaffected individuals (Mbulaiteye et al. 2011). Consistent with this high risk, the SCCC incidence rates have increased 15 times in the general population in between 1960 and 1997 (Mbulaiteye et al. 2011). This increase corresponds to the increase in the fraction of eye tumors that are due to SCCC, which increased from 23.5 to 71 % among the men and from 0 to 85 % among the women between 1960 and 1997 (Wabinga et al. 2000). The strong association between SCCC and HIV has prompted a search for infectious etiology, focusing on mucosal high-risk and cutaneous HPV. However, in spite of the initial excitement about the possibility of discovering a novel infection or association, no clear etiologic agent has yet emerged.

An increase in the risk of SCCC has not been observed in South Africa (Mbulaiteye et al. 2011), despite a substantial HIV epidemic in that region and advanced medical services. The absence of impact in South Africa, which lies in the southern hemisphere far away from the equator, suggests that the HIV impact may be mediated by ultraviolet light-mediated damage to the surface of the eye.

The risk for SCCC in other resource-limited countries has not been quantified, but reports of cases in HIV-infected people in India suggests that it occurs (Biggar et al. 2009).

4.6 Hodgkin Lymphoma

While studies conducted in developed countries suggest an excess risk of Hodgkin lymphoma in HIV-infected persons (Chap. 17), the association with HIV in sub-Saharan Africa is less clear (Mbulaiteye et al. 2011). In Uganda, Newton et al. found that two of the four adults with HL (50 %) were HIV-seropositive compared to the (21 %) HIV seropositivity observed among other cancers not known to be related to an infectious etiology. The risk of Hodgkin lymphoma was increased 1.4-fold in a case-referent study conducted in Johannesburg in South Africa (OR 1.4, 95 % CI 1.0–2.7), and it was 1.6-fold when follow-up analysis was conducted with larger numbers (95 % CI 1.0–2.7). The risk was increased 5.7-fold in a record-linkage study conducted in Kampala in Uganda (OR 5.7, 95 % CI 1.2–17) (Mbulaiteye et al. 2006), which is compatible with an adverse impact of HIV on Hodgkin lymphoma risk. Similar to other cancers, the risk of Hodgkin lymphoma may be grossly underestimated because of lack of pathology diagnosis in most countries in sub-Saharan Africa. It is interesting that some studies, but not all, conducted in resource-limited countries suggest that the risk of Hodgkin lymphoma may be increasing in patients who are started in cART. If this pattern is confirmed, then studies conducted in sub-Saharan Africa patients who are initiated on cART may reveal an increase in risk in patients started on cART.

In India, a study of cancer patients at the TATA Memorial Hospital observed a fourfold increase in the proportional incidence of Hodgkin lymphoma among HIV-positive men and twofold increase in women (Dhir et al. 2008), which was not statistically significant.

4.7 Liver Cancer

Hepatocellular carcinoma (HCC) is one of the most common cancers in sub-Saharan Africa (Sylla and Wild 2012), with most cases attributed to hepatitis B and/or C virus infections. Studies conducted in sub-Saharan Africa have confirmed the expected high frequency of co-infection between HIV and chronic HBV and HCV infections in many countries in sub-Saharan Africa (Sutcliffe et al. 2002). However, an impact of HIV on liver cancer has not been demonstrated (Mbulaiteye et al. 2011) in the studies conducted in South Africa (OR 0.8, 95 % CI 0.4–1.7) (Stein et al. 2008) or Uganda (OR 1.2, 95 % CI 0.3–4.2) (Newton et al. 2001; Mbulaiteye et al. 2011). Data from population-based cancer registries have demonstrated continuing stable rates during the HIV epidemic, consistent with lack of an impact from HIV. Recently, a case-referent study conducted in referral hospitals in Côte d'Ivoire and Benin has reported an increased risk of liver cancer in their series including 1,017 cancers (OR 2.7, 95 % CI 1.1–7.7) (Tanon et al. 2012). Liver cancer has a long induction period, and the observed risk may be low because of competing causes of mortality in HIV-infected patients in Africa. Thus, conclusions about the associations with HIV will have to wait for better data coming from the new consortia established to provide treatment in sub-Saharan Africa, and may also increase as more HIV-infected patients get access to anti-HIV therapy.

A study of cancers in a cohort of HIV patients at the Zhongnan Hospital Wuhan University in Hubei Province in China observed an elevated risk of liver cancer (SIR 6.0, 95 % CI 2.6–12.2) (Zhang et al. 2011; Mbulaiteye et al. 2011). While these results must be confirmed, they suggest that the risk of liver cancer may be significantly increased in HIV-positive patients in China, perhaps because of co-infection with HBV and/or HCV (Mbulaiteye et al. 2011).

4.8 The Role of Infections as Drivers of Cancer in PLHA

The onset of the HIV epidemic, heralded by cancers with suspected infectious etiology, focused attention on the role of infections and immunity on cancer risk. Although it was initially suspected that HIV might directly influence the risk of some cancers, it is now well established that HIV lacks oncogenes, which are needed to directly influence the risk of cancer in PLHA. The consensus is that HIV primarily influences the risk of cancer indirectly via suppression of T-cell immunity [CD4 T cell depletion, essay 00150], which then permits reactivation of latent oncogenic infections such as KSHV and EBV. This indirect mechanism has been

Table 4.1 Summary of associations with selected cancers among people living with HIV/AIDS (PLHA) in resource-replete and resource-limited countries

Cancer sites with increased risk	Relative risks in resource-replete countries	Correlated with duration or degree of CD4 loss in PLHA	Tumor-associated co-viral infections	Incidence in resource-limited relative to resource-replete countries	Fold increase in PLHA in resource-limited countries	Additional comments
AIDS-defining cancers						
Kaposi sarcoma	>1,000	++++	KSHV	Varies by region; very high in Africa	20–600 in Africa	Reported occasional in Asia
Non-Hodgkin lymphoma	20–350	+++	EBV	Low	2–46	
Cervical cancer	2–20	–	HPV	Very high	2–68	
Non-AIDS-defining cancers						
Squamous carcinoma of the conjunctiva	10–15	–+	?HPV	Very high	10	Reported in Africa, rare elsewhere
Hodgkin lymphoma	3–18	Inverse	EBV	Low	2–7	
Liver					<1	
Anus	20–50	–	HPV	Low	?	Little information
Vulva and vagina	4–8	–	HPV	High	?	

supported by studies showing both the degree and the duration of immunosuppression measured by deficit in CD4 T cells correlates with risk of KS and aggressive NHLs. However, not all cancers associated with infection show this expected pattern, suggesting that the relationship between HIV and cancer risk is multifactorial. The studies are limited in number and duration and have few outcomes, precluding any confident comment on risk factors, which might affect cancer risks in PLHA. The patterns of diagnosed cancer in resource-limited countries differ from those in the developed countries. Thus, the cancer profile and the risk factors for cancer in PLHA in resource-limited countries will differ from those in developed countries (Tables 4.1). More than 50 % of the 12 million cancers diagnosed globally are in resource-limited countries and about 30 % are attributable to infection (de Martel et al. 2012). The overlap between cancer and the 29 million PLHA in resource-limited countries is unknown, but a even small relative risk increase in risk of cancer among PLHA has important public health consequences. Study of PLHA in the resource-limited countries could lead to discovery of novel infections or novel associations with cancer. The discovery of KSHV and of a polyomavirus associated with Merkel cell carcinoma in patients with HIV/AIDS demonstrates the potential for such discoveries [Merkel cell virus, essay 00010].

4.9 Conclusions

While cancer is not currently a considered a common clinical problem in PLHA in resource-limited countries, this is likely to change as access to affordable cART improves and premature mortality from other causes is reduced (Chap. 27). In resource-replete, cancer is responsible for up to one-third of deaths in PLHA. The burden of cancer has increased in spite of the reduction in risk of ADCs in PLHA principally because of a shift from ADC to NADCs. Projecting the future impact of HIV on cancer in resource-limited countries is fraught with difficulty given the lack of reliable data on cancer and HIV, but the negative aspect of increasing risk of cancer in PLHA is a real concern. Linkage of cancer care to HIV services may provide new opportunities to quantify the risk and to identify creative ways to implement early cancer detection and treatment programs.

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Part II
Oncogenic Viruses Causing HIV-Associated Cancers

Chapter 5
Kaposi Sarcoma-Associated Herpesvirus (KSHV) or Human Herpesvirus 8 (HHV-8)

Blossom Damania and Dirk P. Dittmer

Abstract Kaposi sarcoma-associated herpesvirus (KSHV) or Human herpesvirus 8 (HHV-8) is a virus that is associated with the original AIDS-defining tumor, Kaposi sarcoma (KS). This virus is necessary for the development of KS. Expression of the viral protein, LANA, represents the definitive diagnostic marker for KS. In addition to KS, KSHV is also associated with primary effusion lymphoma and a plasmablastic variant of multicentric Castleman disease.

KSHV is a double-stranded DNA virus. There exists no vaccine against this virus. Viral DNA replication is sensitive to gancyclovir. The virus establishes life-long latency in the infected host.

5.1 Introduction

The development of Kaposi sarcoma (KS) is linked to infection with Kaposi sarcoma-associated herpesvirus (KSHV, also known as human herpesvirus 8). This association was established when Drs. Yuan Chang and Patrick Moore discovered viral DNA in KS biopsies, but not in the skin from healthy controls. KSHV is present in essentially every tumor cell within a KS lesion (Chang et al. 1994). Within each tumor cell, the viral latent proteins, as well as the viral microRNAs are expressed (Dittmer 2003, 2011; Gottwein et al. 2011). Other viral proteins may be expressed as well depending on tumor subtype and the particular signals that emanate from the tumor microenvironment, e.g., hypoxia can activate lytic replication and gene expression of specific KSHV genes (Davis et al. 2001). In addition to KS,

B. Damania (✉) • D.P. Dittmer
Program in Global Oncology, Department of Microbiology and Immunology,
Lineberger Comprehensive Cancer Center, Center for AIDS Research,
University of North Carolina, CB#7295, Chapel Hill, NC 27599, USA
e-mail: damania@med.unc.edu

R. Yarchoan (ed.), *Cancers in People with HIV and AIDS: Progress and Challenges*,
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KSHV also drives the pathology of primary effusion lymphoma (PEL) (Cesarman et al. 1995) and a plasmablastic variant of multicentric Castleman disease (MCD) (Carbone et al. 2009; Soulier et al. 1995). In KS and PEL, the virus predominantly exists in its latent form and does not replicate to high levels. MCD may be an exception, since it is associated with high-level expression of the viral IL6 homolog and other lytic proteins. Primary infection or reactivation from tumor cells and latently infected $CD20^+$ B cells in MCD lead to systemic viremia, salivary shedding, and person-to-person transmission. In extremely severe cases, high-level viremia may also lead to KS-associated inflammatory cytokine syndrome (KICS) (Polizzotto et al. 2012).

5.2 Transmission

KSHV is transmitted orally, by sexual routes, blood transfusion, or by the transplantation of infected organs (reviewed in Bagni and Whitby 2009). In endemic areas such as sub-Saharan Africa and the Mediterranean region, the prevalence of KSHV is high. KSHV is detected in breast milk and maternal saliva suggesting an oral route of transmission in children. There exists the exciting possibility that KSHV shedding in saliva is modified by HLA polymorphisms (Alkharsah et al. 2007; Guech-Ongey et al. 2010). Close family relatives are positive for viral DNA in their saliva, also suggesting an oral transmission route (Koelle et al. 1997; Vieira et al. 1997). By comparison to endemic and epidemic regions, Western Europe and the US have a low prevalence of KSHV. Here the virus is thought to be transmitted sexually, particularly in men who have sex with men (MSM) (Gao et al. 1996; Martin et al. 1998). The mechanism of transmission here may be largely through the use of saliva as a lubricant. The reason for this apparent geographic difference in transmission pattern is unknown. Blood-borne transmission, as well as transmission by a transplanted organ can also occur (Barozzi et al. 2003). At present the blood supply even in endemic areas or for high-risk donors is not routinely screened for KSHV.

5.3 Kaposi Sarcoma

The incidence of KS reflects the prevalence of KSHV. In certain high prevalence regions, such as sub-Saharan Africa, KS is not uncommonly seen in children, the elderly, and transplant recipients independent of HIV infection. Whether there exists a genetic susceptibility locus for KSHV infection, or for the development of KS, is currently unknown. KS is the most common cancer in men in many regions of sub-Saharan Africa where it causes significant morbidity and mortality (Jemal et al. 2012). HIV co-infection substantially increases the risk for developing KS. In Western Europe and the US, the number of KS cases has declined since the introduction of combination antiretroviral treatment (cART), but KS still occurs even in the presence of high CD4 counts and low HIV viral load (Krown et al. 2008).

For example, KS rates in the San Francisco area for white men were ~30 per 100,000 during 1987–1991 (pre-cART era) and declined to 2.8 in 1998 (post-cART era). A further decline however is unlikely (Shiels et al. 2011). There are multiple epidemiological forms of KS:

1. "Classic" KS afflicts elderly men of Mediterranean or eastern European origin. Classic KS occurs in the absence of HIV co-infection.
2. "Endemic" KS occurs in Central and Eastern Africa in the absence of HIV co-infection. It is often a disease of children or young adults.
3. "Transplant-associated" or iatrogenic KS develops in immunosuppressed individuals, e.g., organ transplant patients. This also occurs in the absence of HIV co-infection.
4. "Epidemic" KS also known as AIDS-KS is the most common AIDS-defining cancer, which predominantly afflicts HIV-infected MSM, although HIV-infected women can also develop KS.

In addition KS has been noted to flare up shortly after the start of cART, a phenomenon that is called KS immune reconstitution inflammatory syndrome (KS-IRIS). KS is also seen in some cases of KSHV-associated herpesvirus-inflammatory syndrome (KICS), which is a recently described clinical entity that is associated with high-level KSHV replication (Polizzotto et al. 2012).

Systemic KSHV viral load is associated with KS development and often precedes it. It is important to consider, however, that KSHV levels in the plasma of KS patients are low (200–30,000 copies) compared to other herpesviruses. There is no direct correlation between the severity of disease, or number of lesions and KSHV viral load. This suggests that KS lesions result from seeding of infected cells (analogous to traditional metastasis) as well as de novo infection of peripheral, lymphatic endothelial cells (reviewed in Ganem 2010). In addition, local seeding and autocrine stimulation may help local KS lesions grow once they begin.

5.4 Kaposi Sarcoma-Associated Herpesvirus (KSHV): Genetic Structure

KSHV is a double-stranded DNA virus. Its genome is approximately 130,000 bp in length. A long unique region encodes all known viral proteins and is flanked on either end by a varying number of terminal repeat sequences. Upon circularization the terminal repeat sequences fuse and serve as the latent origin of replication, and as the anchor point by which the viral extrachromosomal plasmid is tethered to the host chromosome. During latency the host cell DNA-dependent DNA polymerase is used to replicate the latent episomes. By contrast, lytic viral replication initiates at two conserved regions (oriLyt) and is dependent on the viral DNA-dependent DNA polymerase, as well as a complex of core replication proteins. The viral DNA polymerase is sensitive to gancyclovir, azidothymidine, foscarnet, and cidofovir, but not acyclovir (Casper et al. 2008; Kedes and Ganem 1997). Two viral kinases (Orf36 and Orf21) mediate susceptibility to gancyclovir and azidothymidine.

KSHV encodes approximately 84 open reading frames. These can be categorized in multiple ways. Blocks of co-regulated proteins exhibit homology to other herpesviruses and mediate viral DNA replication, entry, capsid, envelope, and tegument formation. A second set of genes (K genes) are unique to KSHV, or only present in the lymphotropic lineage of herpesviruses, which includes Epstein–Barr-Virus (EBV), as well as the monkey and mouse homologs of KSHV (reviewed in Chang and Moore 1996; Damania 2004). Several KSHV genes are homologs of human cellular genes and appear to have been originally pirated from the human genome.

5.5 KSHV Structure

KSHV virions exhibit an electron-dense capsid surrounded by a lipid bilayer envelope. In between the capsid and the envelope is a morphologically amorphous, but highly organized proteinaceous layer called the tegument. The envelope is studded with viral glycoproteins, which engage host cell surface receptors and participate in viral entry. KSHV encodes seven glycoproteins: ORF22 (gH), ORF39 (gM), ORF47 (gL), ORF53 (gN), ORF68, gB, and K8.1. Three of these, gB, gH, and gL, are required to mediate membrane fusion. The tegument contains multiple proteins and RNA transcripts. The herpesvirus tegument proteins are important as they are delivered into the target cell upon primary infection, and may thus contribute to early reprogramming events before the synthesis of immediate-early proteins (Zhu and Yuan 2003). The KSHV capsid architecture and polypeptide composition has been determined. Cryo-EM reconstruction has revealed that the icosahedral capsid is symmetric (T = 16) with 20 triangular faces (Trus et al. 2001; Wu et al. 2000). The building blocks are composed of hexamers and pentamers of the major capsid protein (MCP/ORF25) and interconnected by heterotrimer structures comprised of the minor capsid proteins ORF62 and ORF26.

5.6 KSHV Entry

The virus enters target cells through multiple receptors and co-receptors (reviewed in Chandran 2010). The αVβ3 and αVβ5 integrins serve as receptors for KSHV (Akula et al. 2001). The viral gB protein contains the signature integrin-binding RGD motif. Antibodies to either integrins or RGB peptides block entry. xCT is another receptor for KSHV (Kaleeba and Berger 2006). It is part of the cell surface CD98 (4F2 antigen) complex. Expression of xCT restores permissivity for KSHV and antibodies against xCT block infection. DC-SIGN (CD209) is also a receptor for KSHV. KSHV infection can be blocked by an anti-DC-SIGN monoclonal antibody and soluble DC-SIGN. Most recently, Ephrin receptor A2 has been shown to act as a co-receptor of KSHV by binding to the viral gH and gL proteins (Chakraborty et al. 2012; Hahn et al. 2012). This feature is conserved in the related primate virus, rhesus monkey rhadinovirus (RRV) (Hahn and Desrosiers 2013) Lastly, heparin

sulfate increases the efficiency of infection. Since this virus enters multiple cell types (B lymphocytes, monocytes, endothelial cells, epithelial cells) different receptors may be utilized in different cell lineages; they may be essential for some cells, but only serve auxiliary roles in others.

Upon entry, the virus immediately triggers an innate host response and induces interferon. In monocytes, KSHV activates TLR3 resulting in its upregulation and induction of downstream mediators, including IFN-β1 and the chemokine CXCL10 (also called IP-10) (West and Damania 2008). In plasmacytoid dendritic cells (pDCs), which are the chief IFN producing cells in the body, KSHV activates TLR9 (reviewed in West et al. 2012). In endothelial cells KSHV downregulates TLR4 (Lagos et al. 2008).

5.7 KSHV Gene Regulation

Many of the studies of KSHV gene regulation have been done in PEL cell lines. These studies have shown that viral reactivation, replication, egress, and infectious virion production can be triggered by a variety of signaling pathways (reviewed in Mesri et al. 2010). The initial trigger event leads to the coordinated transcription of three kinetic classes of transcripts: those encoding immediate-early proteins (RTA/Orf50, K-bZIP), those encoding early proteins (MTA/Orf57, polymerase and its associated factors, vGPCR/Orf74), and those encoding late genes (capsid and tegument proteins) (Dresang et al. 2011; Fakhari and Dittmer 2002; Jenner et al. 2001).

The viral immediate-early transactivator RTA is necessary and sufficient to initiate KSHV viral replication (reviewed in Deng et al. 2007; Staudt and Dittmer 2007). The KSHV *Rta* gene encodes a 691 amino acid protein that is highly phosphorylated and localizes to the nucleus of mammalian cells. Deletion of 160 amino acids in the C-terminal activation domain of the KSHV Rta/ORF50 results in production of a truncated, but stable, Rta/ORF50 protein. This truncated Rta/ORF50 protein forms multimers with wild-type Rta/ORF50 in PEL cells, and functions as a dominant negative inhibitor of Rta/ORF50 (Lukac et al. 1999). A KSHV deletion mutant missing the Rta gene is unable to reactivate upon chemical treatment. Rta/ORF50 is present in KSHV virions, i.e., it can be considered a virion transactivator and thus ensures lytic replication upon primary infection. Rta/ORF50-responsive promoters fall into one of two subgroups: those where Rta/ORF50 directly binds promoter DNA and those where Rta/OrRF50 does not directly bind promoter DNA, but rather transactivates the promoter by establishing protein–protein interactions with cellular transcription factors that mediate sequence-specific DNA binding. Most important among these interactions is the binding of Rta/ORF50 to cellular RBP-Jκ to modulate KSHV transcription (Liang et al. 2002; Palmeri et al. 2011). RBP-Jκ is a sequence-specific DNA binding protein that is a downstream effector of cellular Notch signal transduction. KSHV can usurp the function of cellular RBP-Jκ without the requirement for Notch–ligand interaction, as the binding of KSHV Rta/ORF50 protein to RBP-Jκ converts RBP-Jκ from a transcriptional repressor to a transactivator.

Of note, the pattern of KSHV gene transcription is not as rigid as for other herpesviruses. Specific signaling stimuli and cellular environments can induce specific and sporadic transcription patterns. Stimuli that sporadically activate transcription of oncogenic viral proteins, such as K1, viral interleukin-6 (vIL-6)(Chatterjee et al. 2002), or vGPCR in the absence of complete replication (which would destroy the infected cell) are thought to contribute to oncogenesis in a paracrine fashion (Bais et al. 1998; Ma et al. 2010; Montaner et al. 2003; Mutlu et al. 2007). Periodic reactivation and re-infection cycles are also thought to contribute to viral persistence in endothelial lineage cells.

Histone-deacetylase inhibitors (vorinostat, valproic acid, sodium butyrate) (Shin et al. 2014), signaling inducers such as TPA (Renne et al. 1996), ligands for Toll-like receptor (TLRs) such as TLR7/8 agonists (Gregory et al. 2009), and depletion of the TLK cellular kinase (Dillon et al. 2013) can induce KSHV reactivation from latency in culture. Interferon-alpha does not induce KSHV in its entirety, but only the expression of specific viral genes, e.g., the vIL-6 protein (Chatterjee et al. 2002).

5.8 KSHV Carcinogenesis

All KS and PEL cells consistently express the viral latent proteins LANA/Orf73, vCyclin/Orf72, vFLIP/Orf71, Kaposin, the viral microRNAs, and one or more of the viral interferon regulatory factor (vIRF) homologs (Dittmer et al. 1998; Dittmer 2011). These exhibit transforming activities in specialized assays or specialized cells. Other viral proteins like K1, vIL6, and vGPCR are strongly transforming in multiple assays in culture (Bhatt et al. 2013). They are expressed at low and varying levels in latent KSHV-infected cells but are highly upregulated during the lytic replication cycle. Abrogation either of latent proteins, latent-protein-induced signaling, receptor-induced signaling, or purging of the viral episome is incompatible with tumor growth, demonstrating that KSHV is required for KS (Damania and Cesarman 2013).

LANA is the major latency protein involved in latent viral replication and maintenance of the latent genome. LANA tethers the viral episome to histones on the host chromosome. During normal cell division, viral genomic DNA is replicated and segregated along with host chromosomes, thereby ensuring that each of the daughter cells also contains viral genomes. LANA also functions to augment cell proliferation and survival. LANA has been shown to bind the tumor suppressors, p53 and Rb (reviewed in Ballestas and Kaye 2011; Damania and Pipas 2009).

LANA, vCyclin, and vFLIP are expressed on a polycistronic transcript. vFLIP is a viral homolog of cellular FLIP [FLICE (protein FADD-like interleukin-1 beta-converting enzyme, now called caspase-8) inhibitory protein]. vFLIP strongly activates the NFκB signaling pathway and is thought to contribute to KSHV-associated oncogenesis (reviewed in Mesri et al. 2010). Another latency-associated protein is vCyclin, vCyclin is a homolog of cellular cyclin D. vCyclin binds and activates cdk6 and is thought to promote S-phase entry. vCyclin transgenic mice develop lymphomas only in the context of p53 deficiency (reviewed in Damania and Pipas 2009; Dittmer 2009).

A working model of how the different molecular effectors that are encoded by KSHV work together to bring about the molecular phenotypes that are associated with KSHV infection can be constructed based on our knowledge of homologous viruses. The related gammaherpesvirus, herpesvirus samiri (HVS), only requires two proteins, STP and TIP, to transform human T cells in culture, yet it encodes homologs of many of the genes of KSHV, which function primarily in modulating host interactions, in vivo persistence, and pathogenesis. The KSHV K1 protein can functionally substitute for STP and engages signaling pathways, principally PI3K/AKT/mTOR, through its ITAM motif (Lee et al. 1998; Tomlinson and Damania 2004). Whereas K1 is located on the left end of the KSHV genome, K15 another viral receptor signaling protein is located on the right side. K15 engages TRAFs 1, 2, and 3, which leads to the activation of NFkB and NFkB-regulated cytokines. It also triggers mitogen activated protein kinase (MAPK) signaling. The KSHV K1 and K15 proteins appear to phenocopy the two principal EBV transforming genes LMP1 and LMP2A (reviewed in Damania 2004), thus establishing a receptor-initiated signaling environment as a common theme for all lymphotropic herpesviruses.

KS is arguably one of the most angiogenic tumors that arises in the human population. It is thought that KSHV viral proteins expressed in endothelial (and surrounding epithelial cells) induce the overexpression of angiogenic factors like vascular endothelial growth factor (VEGF). vGPCR, K1, and vIL-6 have been shown to induce VEGF and function to stimulate angiogenesis in a paracrine fashion (reviewed in Mesri et al. 2010). KSHV infection can also reprogram endothelial cells creating a gene expression phenotype that is intermediate between blood and lymphatic endothelium (reviewed in Dimaio and Lagunoff 2012; Hong et al. 2004).

Finally, KSHV has also been shown to modulate glycolysis and fatty acid synthesis in KSHV-infected endothelial cells as well as B cells (Bhatt et al. 2012; Delgado et al. 2010, 2012). Modulation of these metabolic pathways may also contribute to KSHV-associated oncogenesis.

Please note that the clinical and systemic manifestations of KSHV infection and KSHV-associated cancers are discussed elsewhere (Ablashi et al. 2002; Dittmer and Krown 2010).

5.9 KSHV MicroRNAs

The most recent addition to our understanding of KSHV biology has been the discovery of the KSHV microRNAs (miRNA). KSHV encodes 12–20 mature miRNAs (reviewed in Cullen 2011; Skalsky and Cullen 2010). Each mature miRNA is made from a looped, double-stranded pre-miRNA. Depending on cell type and the exact RNA sequence, one or the other strands are preferentially processed and incorporated into the active RISC complex. Hence, there exists extensive variation in the count of mature miRNAs. KSHV miRNAs are expressed in KS and PEL and together with the cellular miRNA profile can be used to distinguish stages of KSHV infection (O'Hara et al. 2009). At present the function of all the miRNAs is not completely known. Thrombospondin 1, TGF-beta, xCT1, and Bach1 are examples

of some proteins known to be targeted by the KSHV miRNAs (Gottwein et al. 2011; Haecker et al. 2012). Analogous to viral proteins, which mimic functions of host proteins, some viral miRNAs also share seed sequence (and therefore the same target range) as cellular miRNAs, most notably miR-K12-11 and miR-155 (Gottwein et al. 2007; Skalsky et al. 2007). Down-regulation of cellular miR-155 has been implicated in terminal plasma cell differentiation and it can be reasoned that by ectopically expressing an ortholog, KSHV can stall this process. In fact, KSHV microRNAs are transforming and can complement miR-155 deficiency in mice (Boss et al. 2011; Dahlke et al. 2012; Sin et al. 2013). Because KSHV miRNAs, like many host miRNAs, is also incorporated into systemically circulating vesicles (Chugh et al. 2013), so-called exosomes, they may through this process mediate some of the paracrine effects that define KS.

5.10 KSHV Immune System Interactions

Equally important to carcinogenesis is the means by which KSHV proteins modulate the immune system (reviewed in Lee et al. 2010; Moore and Chang 2003). These events may have systemic effects long before the development of clinically apparent lymphoma and KS. For instance, KSHV encodes a homolog to CD200/Ox2 (Foster-Cuevas et al. 2004; Misstear et al. 2012). Cellular CD200 is a negative regulator of inflammation. CD200 knockout mice exhibit increased susceptibility to experimentally induced autoimmune disease. The viral homolog of CD200, K14, is soluble and can bind to the CD200 receptor. How exactly this event modulates target cell function is not currently known.

KSHV is detected by the innate immune system upon viral infection of naïve cells (Gregory et al. 2011; West and Damania 2008; West et al. 2011, 2012). The virus encodes different viral proteins to subvert immune responses. The KSHV K3 and K5 proteins are viral ubiquitin E3 ligases that target a number of cell surface receptors for ubiquitin-mediated receptor endocytosis and degradation in order to prevent presentation of viral antigen on the surface of infected cells (Boname and Lehner 2011; Coscoy and Ganem 2001; Ishido et al. 2000a, b; Lang et al. 2013).

KSHV encodes homologs to cellular interferon regulatory factors (IRFs). The cellular IRFs transmit the activating signals from IFN alpha/beta receptors to the nucleus. This initiates and subsequently increases interferon production in a positive feedback loop. KSHV encodes four viral IRFs, vIRF-1,2,3,4. The vIRF3 protein is constitutively expressed in latently infected PEL; vIRF1 is expressed in latent KS cells, whereas vIRF2 and vIRF4 have thus far only been seen upon lytic infection. vIRF-1, -2, and -3 interfere with IFN signaling (reviewed in Jacobs and Damania 2011). The molecular mechanism by which these proteins function is quite varied. For example, vIRF1 binds to cellular IRF-1 and -2 and inhibits these proteins in a classical dominant negative mechanism. However, vIRF1 also binds to CBP/p300, p53, and Bim. The vIRFs can downregulate IFN activation from TLR receptors as well (Jacobs et al. 2013). For a more detailed review of the function of the four vIRFs please see review article (Jacobs and Damania 2011).

As mentioned above, KSHV encodes for a viral IL6 homolog, vIL-6 (reviewed in Sin and Dittmer 2012). Unlike human IL-6, vIL-6 does not need to bind to the gp80 subunit of the IL-6 receptor complex to activate signal transduction. vIL-6 has been shown to activate cell signaling in an intracrine, autocrine, and paracrine fashion (Aoki et al. 2001). vIL-6 can augment cell survival, prevent apoptosis, and activate angiogenesis through the upregulation of the pro-angiogenic factors, VEGF, and angiopoietin 2. Depletion of vIL-6 in PEL has also been shown to inhibit their ability to proliferate.

In addition to coding for a viral IL6 homolog as described above, KSHV also encodes homologs to cellular inflammatory cytokines. These are vCCL1/v-MIP-I/ ORFK6), vCCL-2/vMIP-II/ORFK4), and vCCL-3/v-MIP-III/ ORF K4.1). KSHV vCCL-1 signals through CCR8; vCCL-2 signals through CCR8 and CCR3; and vCCL-3 signals through CCR4. Thus, these KSHV chemokines activate chemokine receptors that are present on CD4+ Th2 cells. vCCL-2 can also bind to multiple other chemokine receptors, but this binding is non-productive and therefore diminishes signaling through the cognate, cellular ligand.

5.11 Conclusion

KSHV encodes an arsenal of viral proteins that control cell proliferation, cell survival, and angiogenesis. Moreover, KSHV viral proteins help the virus evade both adaptive and innate immune responses in the infected host. Several KSHV proteins are homologs of cellular proteins, while others are uniquely encoded by KSHV. By modulating cellular signaling, apoptotic, and immune pathways in the infected cell, KSHV creates an environment that maintains virus survival and allows for virus dissemination and spread within the infected individual, as well as viral transmission from person to person. By commandeering the host environment in the aforementioned ways, KSHV infection may inadvertently result in cellular transformation and subsequent malignancy in some infected and susceptible hosts.

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Chapter 6
Epstein–Barr Virus

Lindsey Hutt-Fletcher

Abstract There are more than one hundred viruses in the herpesvirus family, which is divided into three subfamilies, alpha, beta, and gamma, based on the genome structure and biological behavior of the viruses. Epstein–Barr virus (EBV) is one of the eight herpesviruses currently known to infect humans and is a member of the gammaherpesvirus subfamily, genus lymphocrytovirus. Like all herpesviruses it can establish latent infections and persist for the lifetime of the host. In some individuals it behaves more as a commensal than a pathogen, while in others it can cause significant and even life-threatening disease. EBV is the cause of or contributing factor to the development of a number of HIV-associated cancers, including nearly all cases of central nervous system lymphoma and plasmablastic lymphoma, as well as a high percentage of other non-Hodgkin lymphomas and Hodgkin lymphomas.

6.1 Introduction

All viruses are problematic for those who are infected with the human immunodeficiency virus (HIV), but the herpesviruses, which are often carried by the vast majority of individuals worldwide and are typically fairly well controlled by a functioning immune system, pose a particular concern. EBV, like its fellow oncogenic gammaherpesvirus, Kaposi's sarcoma-associated herpesvirus, can contribute significantly to the morbidity and mortality of HIV. In the developing world primary infection with EBV, which is orally transmitted in saliva, usually occurs in the first few years

L. Hutt-Fletcher (✉)
Department of Microbiology and Immunology, Center for Molecular and Tumor Virology and Feist-Weiller Cancer Center, Louisiana State University Health Sciences Center, Shreveport, LA, USA
e-mail: lhuttf@lsuhsc.edu

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of life. In the developed world infection generally occurs somewhat later in the second decade or beyond. Few individuals anywhere, however, escape infection by mid-life and in none has elimination of the virus been documented.

6.2 Biology of the Virus and Colonization of the Host

EBV shares the structural characteristics of all herpesviruses. It has a relatively large linear double stranded DNA genome of approximately 175 kb, which encodes more than 80 genes. The genome is tightly housed in a proteinaceous icosahedral capsid and is wrapped in a lipid envelope carrying multiple copies of eleven different membrane glycoproteins (Johannsen et al. 2004; Gore and Hutt-Fletcher 2008). An additional space between the envelope and the capsid includes proteins and RNAs capable of modifying virus and host cell function. These are collectively known as the tegument (Kieff and Rickinson 2007).

EBV has two major target cells, B lymphocytes and epithelial cells and it appears to behave very differently in each. The prevailing dogma in the field is that, in vivo, virus primarily establishes long-term latency in B cells and primarily replicates in epithelial cells.

In an uncomplicated, asymptomatic, primary infection, incoming virus, either cell free or associated with lymphocytes found in saliva, accesses B cells in the lymphoid tissue of Waldeyer's ring, the tonsils and adenoids that surround the pharynx (Thorley-Lawson and Gross 2004; Hislop et al. 2007). This occurs perhaps directly, or perhaps subsequent to an initial round of replication in a mucosal epithelial cell. B cell infection does not immediately lead to productive replication, but instead the virus genome circularizes, remains extra-chromosomal and all initial transcripts are devoted to maintaining the episome and changing the behavior of the cell.

This type of latent infection is easily modeled in vitro by infection of peripheral B cells and their immortalization into the lymphoblastoid cell lines that are so frequently used for study of human tissue. It involves expression of a full panoply of latency proteins, the latency III phenotype or growth program, including six EB nuclear antigens or EBNAs, EBNA 1, EBNA2, EBNA3A, EBNA3B, EBNA3C, EBNA-LP, the latent membrane proteins, latent membrane protein 1 (LMP1) and latent membrane protein 2 (LMP2), two sets of small, abundant untranslated RNAs, EBER1 and EBER2, and some miRNAs. These collectively drive the cell to become a proliferating blast cell in which the latent virus episome is replicated by host polymerases (Kieff and Rickinson 2007). In one prevalent model of colonization of the host (Thorley-Lawson and Gross 2004), they are considered responsible for initiating the passage of the infected cell down a pathway that parallels that of an antigen stimulated B cell during a normal immune response. Unlike in the lymphoblastoid cell line in vitro, where continued expression of the latency III phenotype maintains the cell in a proliferative state, a switch in promoter usage is then thought to limit expression to the latency II phenotype in which a subset of latency proteins including EBNA1, LMP1 and LPM2 are expressed. This mimics positive selection by antigen

stimulation, rescues the cell from the default of apoptosis, and enables it to emerge as a long-lived virus-carrying memory B cell. Memory B cells can circulate in the periphery and seed distant sites. Protein expression in the memory B cells can then be further limited to the latency I phenotype (Hochberg et al. 2004), in which only EBNA1 and some miRNA are expressed. EBNA1 tethers the genome to the chromosome, which is required for its maintenance in dividing cells (Frappier 2012). In addition to these phenotypes, a resting cell may express no virus proteins at all. This means that while an emerging immune response, primarily a CD8+ T cell response (Long et al. 2011), can control cells that express EBV encoded proteins, resting memory cells remain invisible to the immune system and persist as the long-term reservoir of virus in the infected host. Sporadic terminal differentiation into plasmablasts in Waldeyer's ring triggers reactivation of virus into the lytic cycle, leading to the ultimate death of the cell and production of virus (Laichalk and Thorley-Lawson 2005). At this point virus can reenter an epithelial cell and undergo amplification for transmission in saliva to a new host or for reinfection of a B cell and replenishment of the latent reservoir, completing the ongoing cycle of persistence; infectious virus is thus continually found in saliva in healthy carriers (Jiang et al. 2006; Hadinoto et al. 2009). In individuals treated over very long periods with valacyclovir, which inhibits lytic virus DNA replication mediated by the viral DNA polymerase but does not affect the latent episome, the frequency of latently infected memory cells is reduced. It has, however, been estimated that it would take at least 11 years of daily therapy to eliminate the latent reservoir entirely (Hoshino et al. 2009).

Despite its assumed occurrence in vivo, full lytic replication resulting in production of new virions has not yet been achieved in vitro in epithelial cells. In these cells, if EBV persists at all, which it frequently does not, the virus becomes latent. Because of this experimental limitation, lytic replication of EBV has primarily been studied by reactivating virus in latently infected B cell lines. A variety of stimuli including cross-linking of surface immunoglobulin (Takada 1984), which may mimic events leading to terminal differentiation triggered by antigen cross-linking, or addition of transforming growth factor beta 1, phorbol esters or histone deacetylase inhibitors, can be used to induce virus reactivation in a variable proportion of cells (Israel and Kenney 2005). Thus a picture of the entire life cycle of the virus at the cellular level comes not from a continuum, but from piecing together early events involving virus entry, which can be studied in both cell types, and reactivation from latency.

Infection of a B cell is initiated by attachment of the virus through the binding of one of the envelope glycoproteins, gp350, to the cellular complement receptor type 2, CR2/CD21 (Hutt-Fletcher 2007). The virus is then endocytosed into what becomes a thin-walled vesicle or endosome and its envelope fuses with the endosomal membrane to deliver tegument and capsid into the cytosol. Fusion of virus and cell is triggered by an interaction between envelope glycoprotein gp42 and cellular Human Leukocyte Antigen (HLA) class II. Glycoprotein gp42 exists as part of a trimeric complex with glycoproteins gH and gL (gHgL) to which it is thought to transmit the activating trigger. Current models (Connolly et al. 2011) propose that activation of gHgL via gp42 in turns in activates the core virus fusion machinery

comprised of gHgL and glycoprotein gB. Glycoprotein gB is thought to be the ultimate fusogen, but it requires gHgL for function.

As on a B cell, epithelial cell infection may be initiated by binding of glycoprotein gp350 to CR2, which is expressed on some, though not all epithelial cells (Yoshiyama et al. 1997; Fingeroth et al. 1999; Jiang et al. 2008). Infection of a CR2-negative epithelial cell in vitro can be more efficient if cells are overlaid with virus producing B cells (Imai et al. 1998), or if virus is presented to an epithelial cell on the surface of a B cell (Shannon-Lowe et al. 2006) than if cell-free virus is used, but the major players in attachment and fusion are probably the same. In addition to gp350 binding, attachment can also occur as result of binding of the dimeric complex of gHgL to one of three integrins, αvβ5, αvβ6, or αvβ8 (Chesnokova and Hutt-Fletcher 2011). These same integrins then directly trigger the core machinery of gHgL and gB to mediate fusion with epithelial cells, which lack constitutive HLA class II expression (Chesnokova et al. 2009). The use of two different triggers of fusion has allowed the virus to evolve an ingenious strategy for trafficking alternately between B cells and epithelial cells during the cycle of persistence. The virion contains both dimeric gHgL complexes and trimeric gHgLgp42 complexes. Only the trimeric complexes can support fusion with B cells because of the required interaction between gp42 and HLA class II. Only dimeric complexes can support fusion with an epithelial cell because of the required interaction between gHgL and an integrin, which is blocked by the presence of gp42. In a B cell with replicating EBV, some trimeric complexes interact with HLA class II in the endoplasmic reticulum and are lost to the HLA class II trafficking pathway. Virus emerges rich in dimeric complexes and is about fivefold more infectious for an epithelial cell than a B cell. Conversely, virus emerges from an HLA class II-negative epithelial cell with more trimeric complexes and can be as much as 100 fold more infectious for a B cell than an epithelial cell (Borza and Hutt-Fletcher 2002).

Once in the cytoplasm of the cell the virus ultimately travels to the nucleus where the genome and some virus proteins enter through the nucleopore and the episome is established. The events that follow initiation of lytic reactivation then follow a pattern similar to those of other herpesviruses that enter a productive lytic cycle directly. Gene expression is divisible into three general classes, immediately-early, early and late. The immediate-early proteins Zta and Rta, encoded by the BZLF1 and BRLF1 genes, are transactivators. Expression of these immediate-early proteins is followed by activation of expression of early proteins, which include enzymes required for DNA synthesis, and finally late proteins, which are principally the structural components of the new virion (Kieff and Rickinson 2007). Assembly of the DNA-containing capsid occurs in the nucleus and it is assumed, primarily by analogy with work done with other herpesviruses, to follow an envelopment–deenvelopment pathway of egress (Mettenleiter 2002). It is believed that the capsid first acquires a primary envelope as it buds through the inner nuclear membrane, loses it as it fuses with the outer nuclear membrane, acquires tegument proteins and a secondary envelope as it buds into a compartment of the secretory pathway, possibly the trans-golgi, and is released from the cell by exocytosis.

The latently infected resting memory B cell can evade immune recognition by virtue of expressing few or no EBV proteins. The virus has also, however, evolved a series of approaches to blunting both innate and adaptive immune responses to lytic cycle proteins. Three early proteins, pBNLF2A, pBILF1 and pBGLF5, have been identified as variously binding to the TAP transporter and interfering with peptide delivery to HLA class I, binding to HLA class I itself and blocking its export, and effecting a general shut off of host protein synthesis, which limits the expression of new HLA proteins. Perhaps to compensate for loss of HLA protein, which could activate natural killer (NK) cell recognition, one of the EBV miRNAs can in turn reduce expression of the NK activating ligand MicB. The immediate-early protein, Zta down-regulates HLA class II by targeting inhibiting transcription of the class II transactivating protein and the glycoprotein gp42 can interfere with HLA class II recognition by CD4+ T cells (Ressing et al. 2003; Long et al. 2011).

6.3 Disease Associated with Primary Infection

Primary infections with EBV, particularly those occurring before adolescence, are almost always asymptomatic or at least unrecognized. However, as many as 70 % of those in whom infection first occurs during adolescence or later in life develop infectious mononucleosis (Luzuriaga and Sullivan 2010; Balfour et al. 2012). This syndrome is generally thought to be an immunopathology and to reflect a more intense version of what occurs during an asymptomatic infection, though why it occurs more frequently in adolescence than in infancy remains unclear. The incubation period is estimated at about 6 weeks, which, together with the fact that mononucleosis does not occur epidemically, has made the early events difficult to document. Once the classic symptoms of fever, sore throat, fatigue and cervical lymphadenopathy appear, sometimes accompanied by eye-lid edema, splenomegaly and liver abnormalities, one of the pathognomonic features is a lymphocytosis including large atypical lymphocytes. These atypical cells are activated CD8+ T cells and in mononucleosis caused by EBV, they are directed at controlling latent and lytically infected cells. Responses to epitopes derived from lytic cycle proteins dominate. The onset of symptoms coincides with the activation and proliferation of the CD8+ T cells and they, with attendant cytokines and perhaps an increase in the number of NK cells in the periphery, are thought to be primarily responsible for the clinical symptoms (Hislop et al. 2007; Odumade et al. 2011; Balfour et al. 2012). Diagnosis is then typically based on these clinical symptoms, on the presence of a lymphocytosis, and also on the production of heterophile antibodies, which appear transiently during the acute phase. These antibodies are measured by the monospot test in which agglutination of the red blood cells of sheep or other species is assessed. Heterophile-negative infectious mononucleosis does, however, occur and diagnosis may need to be further refined by examining specific antibody responses. Acute infection is typically associated with high levels of antibodies to early lytic (EA)

and late lytic antigens (VCA), in particular immunoglobulin M (IgM) antibodies, and absence of antibodies to EBNA1, which become more readily detectable in months following acute disease (Odumade et al. 2011).

Uncomplicated infectious mononucleosis resolves as cells expressing EBV antigens decline in number, with an accompanying decrease in the number of reactive activated CD8+ T cells. There are, however, two extremely rare disorders that can follow primary infection (Hislop et al. 2007). One occurs in patients with a genetic disorder, X-linked lymphoproliferative disease (XLP), in which there is a mutation in the SH2D1A gene encoding SLAM-associated protein (SAP). SAP deficiency produces multiple immunologic abnormalities including defects in NK and T cell effector functions. Following EBV infection there is an exaggerated NK and CD8+ T cell response, but one which fails to control infected cells. High levels of cytokines are produced, macrophages become activated and a hemophagocytic syndrome can develop and prove fatal. The second disorder is not familial, but occurs more commonly in children in Southeast Asian children than elsewhere. It appears to result from an unusual entry of EBV into T cells and NK cells. High levels of cytokines are again produced and virus loads remain very high in peripheral blood. A potentially fatal viral-associated hemophagocytic syndrome may develop or the disease may rather present with chronic or recurrent mononucleosis symptoms accompanied by large expansions of EBV-positive NK and T cell clones. In vitro studies of infected T cell lines have demonstrated the down-regulation of SAP by LMP1, suggesting that the underlying pathogenesis of the disorder may resemble that of XLP (Chuang et al. 2005).

6.4 Diseases Associated with Long-Term Carriage of Virus

For the vast majority of infected individuals, long-term carriage of EBV has little apparent consequence. EBV-induced infectious mononucleosis does not recur and although virus shedding continues indefinitely it is controlled and has no deleterious effects. The virus is, however, potentially oncogenic. It has after all evolved to profoundly change the behavior of latently infected cells and has been implicated in development of long list of cancers (Rickinson and Kieff 2007). Some of these, including plasmablastic lymphoma and leiomyosarcoma, which are almost exclusively seen HIV-infected individuals, AIDS-associated-Burkitt's lymphoma, AIDS-associated Hodgkin's lymphoma and immunoblastic lymphoma, are linked in some way to immune suppression. Others, such as endemic and sporadic Burkitt's lymphoma, Hodgkin's lymphoma, NK/T cell lymphoma, undifferentiated nasopharyngeal carcinoma, gastric carcinoma are not. Some are always EBV-associated, some have only a partial association.

The role that the virus plays in immunoblastic lymphomas in the context of iatrogenic immunosuppression is possibly the most straightforwardly etiologic. Post-transplant lymphoproliferative disorders occurring early after transplant-related immunosuppression, most of which are immunoblastic lymphomas, can begin as

polyclonal expansions of EBV-infected B cells in uncontrolled latency III and may respond to reduction in immunosuppression, suggesting that they are driven by EBV gene expression (Cohen 2005). They are most common in EBV-seronegative recipients, consistent with the assumption that it represents failure to control initial infection of a B cell and a failure of the infected cell to transition into the resting memory B cell compartment (Thorley-Lawson and Gross 2004). Many such tumors, however, particularly those that arise several years after transplantation, are monoclonal and may carry mutations and chromosomal abnormalities. The vast majority are still EBV-positive, but the role of the virus is less certain. This is also the case for the systemic EBV-associated AIDS-associated lymphomas, which, although they are associated with immune deregulation, can arise in patients with relatively high CD4 counts. In general, their incidence has not dropped as profoundly as certain other tumors, such as Kaposi sarcoma, with the advent of highly active antiretroviral therapy (HAART) (Appleby et al. 2000; Matthews et al. 2000). However, some EBV-associated lymphomas, such as primary central nervous system lymphoma, are generally associated with profound immunosuppression and are rarely seen in HIV patients receiving HAART.

Endemic Burkitt's lymphoma is the tumor in which EBV was originally identified (Epstein 2005). It is a tumor typically seen in children in East Africa in areas of holoendemic malaria, essentially always carries latent virus, and generally expresses a latency I phenotype. Sporadic and AIDS-associated Burkitt's lymphomas, found elsewhere, are less consistently associated with EBV. The principal underlying cause of all Burkitt's tumors is believed to be the c-myc translocation that they all carry. They are typically B cells that have undergone somatic hypermutation, a process during which any B cell is more vulnerable to the occurrence of inappropriate translocations. EBV upregulates the activation-induced deaminase required for hypermutation and translocation and can counterbalance the apoptotic effects of c-myc overexpression (Gromminger et al. 2012; Heath et al. 2012). EBV, HIV, and malaria are also all potent B cell drivers and this is one possible contribution that each may make to the development of the tumor (Magrath 2012).

About 50 % of non-AIDS-associated Hodgkin's lymphomas are EBV-positive and the risk for development of Hodgkin's lymphoma is increased about fourfold following infectious mononucleosis. Many Hodgkin's lymphomas and most EBV-positive lymphomas, which typically expressed the latency II phenotype, have nonproductively rearranged immunoglobulin genes and it has been suggested that the role of EBV may be to rescue such a cell, which otherwise would be lost to apoptosis because of the absence of antigen stimulation (Thorley-Lawson and Gross 2004).

Extranodal nasal NK/T cell lymphomas and undifferentiated lymphoma are relatively rare tumors, most common in East Asia and are typically also associated with EBV (Nava and Jaffe 2005). As noted above infection of NK and T cells is not typically seen in uncomplicated infection with EBV and these cells are not known to harbor virus in generally healthy individuals. However, just as infection of NK and T cells in the context of viral-associated hemophagocytic syndrome has potentially life-threatening outcomes, the EBV-positive NK/T cell lymphomas are particularly aggressive. It is perhaps of interest that both are most common in the same part of the world.

Essentially all undifferentiated nasopharyngeal carcinomas (NPC) carry latent EBV, often with a latency II phenotype. It is generally agreed that EBV is an essential risk factor for the disease, but the view that is developing is that it may play the role of a tumor promoter rather than a tumor initiator (Shah and Young 2009; Lo et al. 2012). Although the cancer occurs worldwide, it is most common in ethnic Southern Chinese, in Eskimos of Alaska and Greenland, and in some populations in North Africa. In Southern China, the annual incidence rate in men, in whom the disease is more prevalent, is more than 20 per 100,000. NPC also shows a familial distribution which has facilitated studies of its etiology. The current model of tumor development is that genetic abnormalities, perhaps exacerbated by exposure to carcinogens, facilitate infection and latency of EBV. EBV then contributes further to disease as a result of expression of RNAs and proteins that influence the cell environment, perhaps effect epigenetic changes, and lead to outgrowth of a faster growing clone (Lo et al. 2012). High titers of antibodies to lytic cycle proteins presumably reflective of a burst of lytic replication precede development of disease by several years and are prognostic (Henle and Henle 1976; Zeng 1985; Zeng et al. 1985).

The association of EBV with gastric cancer is less strong with only about 10 % of cases being positive, but on a global scale this amounts to possibly the largest tumor burden associated with the virus. Again, it is generally believed that EBV is playing some role in development of the cancer and emphasis has been put on the epigenetic changes that it can induce, particularly CpG island methylation (Fukayama 2010).

Finally, it should be noted that there is one, and currently only one disease associated with lytic replication of EBV, namely oral hairy leukoplakia (OHL). OHL was first recognized at the beginning of the AIDS epidemic (Greenspan et al. 1985). It is a feature of substantial immunosuppression and is infrequently seen outside the context of full-blown AIDS. It is an epithelial lesion, resembling thrush in appearance and is typically seen on the lateral borders of the tongue. In patients receiving HAART, it is rarely seen (Nokta 2008).

6.5 Vaccines and Therapeutics

To date there is no licensed vaccine for EBV, although there is a general consensus that there is a need for both a preventive and a therapeutic vaccine (Cohen et al. 2011). One phase 2 trial of a soluble form of the glycoprotein gp350 has been performed (Sokal et al. 2007). It failed to prevent infection, but did significantly reduce the incidence of infectious mononucleosis in those who were infected. It has been suggested that T cell epitopes should be included in any improved vaccine to eliminate B cell infections (Long et al. 2011), although a recent study of the efficacy of a combination of gp350 and EBNA3 proteins from the very closely related rhesus monkey lymphocryptovirus in rhesus monkeys did not support this (Sashihara et al. 2011). Use of gp350 alone was the most effective approach in this model, and it significantly reduced virus load. Clearly more work is needed to explore additional candidate proteins.

EBV replication is sensitive to valacyclovir and related drugs, but no EBV-associated disease, beyond OHL has been shown to be amenable to treatment with them. Considerable progress, however, has been made towards generating EBV-specific T cells for therapy of post-transplant lymphoproliferative disease (Heslop et al. 2010) and efforts are ongoing to extend the approach to treatment of other tumors expressing EBV antigens. The main challenge has been to overcome the potentially immunosuppressive environment of the tumor and the fact that there are fewer CD8+ epitopes in those tumors that express the latency II phenotype (Long et al. 2011).

6.6 Conclusion

Like many of its herpesvirus brethren, EBV is a very successful virus that has evolved primarily for peaceful coexistence with its host. Even the best of relationships can go wrong, however, and, given the vast numbers of people who carry EBV, even relatively rare outcomes can have significant consequence. The ever growing list of diseases associated with long-term carriage gives pause for concern. Several of the tumors arising in individuals at known risk, transplant recipients or populations at risk for NPC, are potentially amenable to early diagnosis by monitoring for increased DNA loads in blood or, in the case of NPC, altered antibody profiles and these kinds of preemptive measures are ongoing. There has been no big effort to this point to interfere with infection ab initio, but this may be changing. Prevention of infection with any virus capable of establishing latency is extremely challenging, as experience with HIV vaccines has shown us. Unlike HIV, EBV is, however, antigenically very stable, so the prospects for success are brighter.

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Chapter 7
Human Papillomaviruses

Zhi-Ming Zheng

Abstract Human papillomaviruses (HPV) are a family of small DNA tumor viruses with a size of ~52–55. The family consists of ~200 different genotypes; many of the types cause benign warts or papilloma, while a small fraction of oncogenic or "high-risk" types can cause invasive cervical cancer or other tumors. HPV infects keratinocytes in the basal layer of stratified squamous epithelia and replicates in the nucleus of infected keratinocytes along with keratinocyte differentiation. The viral genome in size of ~7.9 kb encodes six early, non-structural regulatory proteins (E1, E2, E4, E5, E6, and E7) and two late structural proteins (L1 and L2). E6 and E7 are two oncoproteins responsible for the viral oncogenesis of high-risk HPVs, including HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82. L1 is a major structural component of viral capsid and its self-assembly in vitro into a viral-like particle (VLP) provides the basis of prophylactic vaccines against infections of several HPV types. In addition to cervical cancer, high-risk HPVs are associated with the development of various anogenital cancers and certain head and neck cancers.

7.1 A Brief History and Classification of Human Papillomaviruses

Human papillomaviruses (HPV) are a family of small DNA tumor viruses in size of ~52–55 nm in diameter measured initially under electron microscope from skin papillomas by Joseph Melnick at Yale in 1950 (Strauss et al. 1950). Since discovery of the first two genotypes of HPV, HPV1 and HPV2, in 1977 (Orth et al. 1977) and

Z.-M. Zheng (✉)
Tumor Virus RNA Biology Section, Gene Regulation and Chromosome Biology Laboratory, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Frederick, MD 21702, USA
e-mail: zhengt@exchange.nih.gov

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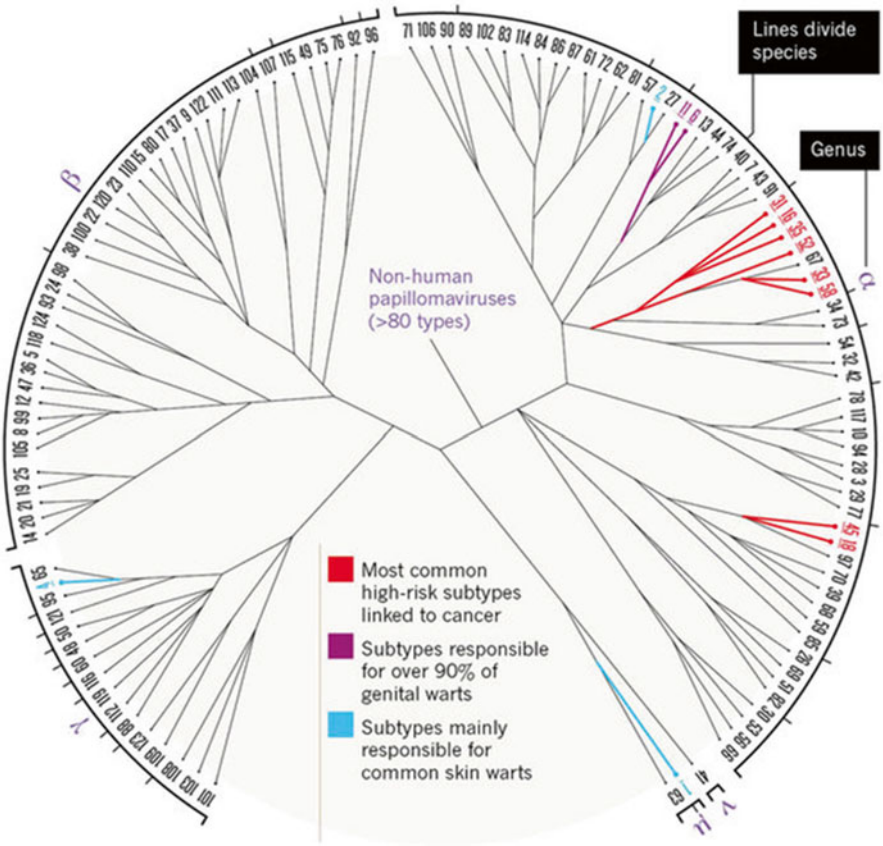

Fig. 7.1 Classification of papillomaviruses, adapted with permission from Nature (Crow 2012)

first completion of HPV1a genome sequence in 1982 (Danos et al. 1982), the family has grown to consist of ~200 different genotypes, with 185 genotypes being completely sequenced and deposited in GenBank (www.pave.niaid.nih.gov).

Papillomaviruses were initially classified as a subfamily of the family *Papovaviridae* in 1962 (Melnick 1962), but reclassified in 2002 as an independent family, *Papillomaviridae*, in the seventh Report of the International Committee on Taxonomy of Viruses (ICTV). The family *Papillomaviridae* currently contains at least 29 genera and human papillomaviruses are classified into five (alpha, beta, gamma, mu, and nu) genera (Fig. 7.1). The classification of papillomaviruses depends on the most conserved L1 ORF by genotyping. Different genera share less than 60 % nucleotide sequence identity in the L1 ORF. A new type of papillomavirus is given when its DNA sequence of L1 ORF differs by more than 10 % from the closest known HPV type. Otherwise, a subtype indicates the difference between 2 and 10 % and a variant less than 2 %. HPV types are numbered in the order by their discovery. HPVs in the alpha genus cause mucosal and a fraction of cutaneous HPV

lesions, while HPVs in the beta, gamma, mu, and nu genera cause cutaneous lesions (de Villiers et al. 2004; Bernard et al. 2010).

HPVs are also grouped clinically as high-risk (oncogenic) types, which are frequently associated with invasive cervical cancer, and low-risk (non-oncogenic) types, which are found mainly in genital warts. Epidemiologic studies of HPV types associated with cervical cancer indicate that 15 HPV types (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82) are high-risk, and 12 HPV types (types 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, and 89) are low-risk. Among the high-risk HPVs, HPV16 and HPV18 are the principal causes of cervical cancer, with a combined, worldwide relative contribution of ~70 % of invasive cervical cancer (Munoz et al. 2003; de Sanjose et al. 2010).

7.2 General Properties of Human Papillomaviruses

HPV Virions and Genome Structure

A mature HPV particle or virion contains a double-stranded, circular genome in size of ~7.9 kb covered by an icosahedral shell or capsid. Unlike many other viruses, HPV particles do not have an envelope or a lipid membrane outside of its capsid and thus is resistant to ether treatment. An HPV capsid is composed of 72 pentamers, of which 60 are hexavalent and 12 are pentavalent (Fig. 7.2a). These pentamers are made up by two viral structural proteins, L1 and L2. Viral L1 (~55 kDa) is the major capsid protein and represents approximately 80 % of the total viral protein. Viral L2

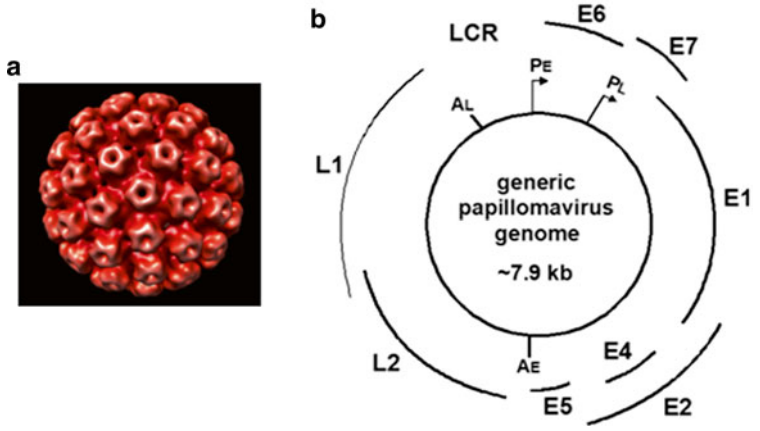

Fig. 7.2 HPV genome structure and virion particles. (**a**) HPV11 VLP visualization of cryoEM reconstruction (http://nramm.scripps.edu/?p=1042). (**b**) HPV genome in a circular episomal form, with relative positions of viral early (PE) and late (PL) promoters and early (AE) and late (AL) polyadenylation signals

(~70 kDa) is a minor capsid protein. Each viral pentamer is comprised of five copies of L1 attached by one L2 from the inside of the pentamer (Bishop et al. 2007; Chen et al. 2000). This is particularly true for the pentamers on the 12 vertices of icosahedral capsid shell. HPV virions are extremely stable and tolerate high temperature, low pH, proteases, and desiccation.

The HPV genome can be divided into three major regions: early, late, and a long control (LCR), also called the non-coding region (NCR). The three regions are separated by two polyadenylation (pA) sites: early pA (AE) and late pA (AL) sites (Fig. 7.2b). The early region encodes six ORFs (E1, E2, E1^E4, E5, E6, and E7) and this region of HPV16, HPV18, and HPV-31 also encodes an E8^E2. The late region lies downstream of the early region and encodes L1 and L2 ORFs. The LCR region (~850 bp) has no protein-coding function, but bears the origin of DNA replication and transcription factor binding sites important for viral RNA transcription (Zheng and Baker 2006).

HPV Life Cycle

HPV depends on keratinocyte differentiation for completion of its life cycle (Fig. 7.3). HPV infection is cell type-specific and requires access of virion particles to human basal cells on the basal lamina through micro-wounding induced by scratching, sexual intercourse, etc. Initial attachment of HPV virions to the host cells takes place by the interaction of viral major capsid protein L1 with the host receptor, heparan sulfate proteoglycan (Dasgupta et al. 2011). This interaction leads to a conformational change and exposes viral minor capsid protein L2 for furin/proprotein convertase digestion (Richards et al. 2006). Subsequently, exposed L2 (amino acid (aa) 108–120) interacts with the S100A10 subunit of annexin A2, a secondary cell receptor (Woodham et al. 2012; Dziduszko and Ozbun 2013), followed by viral entry of the infected cells by endocytosis. L1 dissociation from L2-viral genome, which is facilitated by cyclophilin B (Bienkowska-Haba et al. 2012), results in viral particle uncoating and leaves L2-associated viral genome in the endosome to interact with the retromer complex to be transported to the nucleus via the trans-Golgi network (Lipovsky et al. 2013). Once in the nucleus, L2 localizes the viral genome to PML bodies for transcription of early genes and establishment of infection (Day et al. 2004).

HPV DNA replication requires the A+T-rich origin of DNA replication in the LCR and two viral DNA-binding proteins, E1 as a DNA helicase and E2 as an accessory factor to E1. It occurs bidirectionally in the nuclear replication foci (Swindle et al. 1999) during two different stages of the viral life cycle. The initial DNA replication takes place in an average of once per cell cycle in the G2 phase in the infected basal cells that have already completed S phase. This replication allows the cells to maintain approximately 50–100 copies per cell. DNA repair plays a role in promotion of HPV DNA amplification (Moody and Laimins 2009; Hoskins et al. 2012; Reinson et al. 2013). The interaction of E1 with a cellular protein p80/UAF1

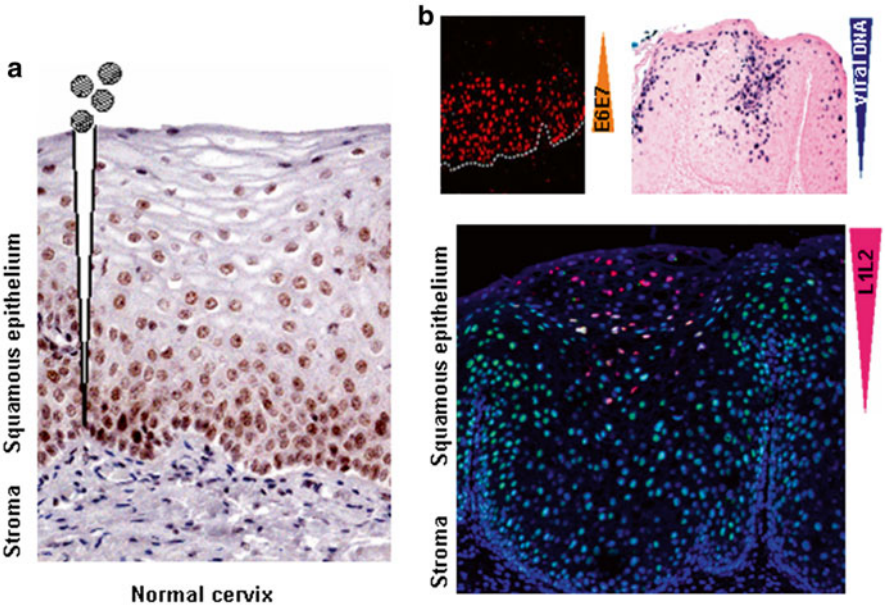

Fig. 7.3 Keratinocyte differentiation-dependent HPV life cycle. (**a**) Infection of the cervical basal keratinocytes by viruses (*circles*, *top left*) is initiated through a microtrauma usually during sexual intercourse. The panel is modified with permission (Jia et al. 2009). (**b**) Expression of viral E6 and E7 is initiated in the infected basal cells (*orange color* on the *top left* for MCM7 as a surrogate for viral E6 and E7). Viral DNA replication takes place in the spinous and granular keratinocytes under intermediate or high differentiation (*navy blue color* on the *top right* for viral DNA). However, viral L1 and L2 (*red color* for L1 in the *bottom*) become detectable only in the granular and cornified keratinocytes under terminal differentiation. This panel is used with permission (Zheng and Wang 2011)

is required for efficient maintenance of the viral episome in undifferentiated keratinocytes (Lehoux et al. 2012; Cote-Martin et al. 2008). E2 binds to the viral genome and tethers it to mitotic chromosomes through mitosis by interaction with Brd4 on mitotic chromosomes to ensure replicated viral episomes to the nuclei of both daughter cells (You et al. 2004; Abbate et al. 2006; Wang et al. 2013).

Viral vegetative DNA replication differs from its initial replication and takes place in highly differentiated, upper layer spinous keratinocytes no longer undergoing cellular DNA synthesis. This stage of viral DNA replication is robust and presumably undertaken by a rolling circle replication mechanism (Flores and Lambert 1997; Kusumoto-Matsuo et al. 2011; Geimanen et al. 2011), leading to amplify from a low, stable copy number to several thousands of the viral genome copies per cell to be packaged into progeny virions. Viral DNA amplification is required for HPV late gene expression. Virions assemble into paracrystalline arrays in the granular layer and egress from the cornified layers of the epithelium. DNA repair also play a role in promotion of HPV DNA amplification (Moody and Laimins 2009; Hoskins et al. 2012; Reinson et al. 2013).

HPV Genome Expression

HPV transcribes its RNA from one strand of its genome in one direction and starts from two major promoters named by their transcription start site position in the virus genome. A viral early promoter upstream of E6 ORF and a viral late promoter resided in E7 ORF are responsible for the expression of viral early and late ORFs, respectively. The viral early promoter P97 in HPV-16, P99 in HPV31, and P55/P102 (previously named as P105) in HPV18 are three most studied early promoters. Their activities are tightly controlled by cis-elements in the LCR. These cis-elements, including consensus E2-binding sites, interact with cellular transcription factors and the viral transactivator/repressor E2 protein and regulate the transcription from each viral early promoter in undifferentiated keratinocytes. The resulting early primary transcripts (pre-mRNAs) carry all early ORFs, which span three exons and two introns and undergo alternative RNA splicing and polyadenylation using an early pA signal. Viral late promoter P670 in HPV16, P811 in HPV18 (Wang et al. 2011a), and P742 in HPV31 are three studied late promoters. Their activities can be induced only in differentiated keratinocytes during vegetative virus replication. Because a viral late promoter is positioned in the E7 coding region (Fig. 7.4), transcription from the late promoter has to bypass the early pA site to allow expression of the late region. As a result, a true late pre-mRNA is a chimeric transcript of the early and late regions, with the early region in its 5′ half and the late region in its 3′ half. This late pre-mRNA can be processed either into an early region transcript which is cleaved and polyadenylated at the early pA site (transcript K) or a late region transcript which is cleaved and polyadenylated at the late pA site (transcript L–O) (Fig. 7.4). Alternative RNA splicing of HPV early and late transcripts produces various species and sizes of mRNA transcripts with multiple coding potentials (Fig. 7.4 transcripts A–O). Thus, any given HPV transcript, no matter whether it is an early or late transcript, could be bicistronic, tricistronic, or even polycistronic and contains two or more ORFs. Conversely, a particular ORF can be a part of multiple mRNA species. Thus, to determine which transcript encodes which viral protein has been a challenge and we know very little about which protein is translated from which transcript. Because E6, E1, and L2 ORFs span over an intron region, the expression of these three proteins requires the retention of its corresponding intron. RNA splicing promotes expression of E7 from viral early transcripts in high-risk HPVs and E4 from viral late transcripts (Tang et al. 2006; Doorbar et al. 1990).

Viral Proteins

HPV genome encodes eight major viral proteins: E1, E2, E4, E5, E6, E7, L1, and L2. L1 and L2 are viral structure proteins for virus capsid formation. The other six viral proteins are non-structural and are responsible for virus replication and pathogenesis. Viral E6 and E7 are two viral oncoproteins responsible for cell transformation and tumorigenesis.

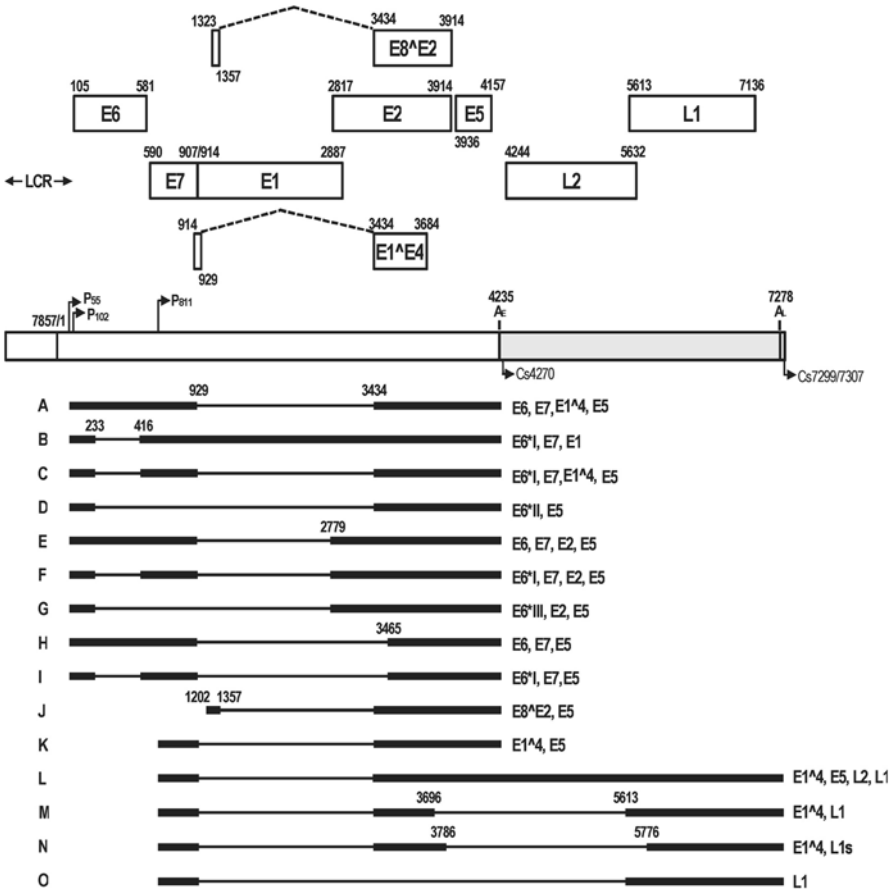

Fig. 7.4 Genome structure and transcription map of HPV18 (Wang et al. 2011a). The *bracket line* in the middle of the panel represents a linear form of the virus genome for better presentation of head-to-tail junctions, promoters (*arrows*), early (AE) and late (AL) pA sites, and mapped cleavage sites (CS). The ORFs (*open boxes*) are diagramed above the bracket, and the numbers above each ORF (E6, E7, E1, E2, E5, L2, and L1) are the positions of the first nucleotide (nt) of the start codon and the last nt of the stop codon assigned to the HPV18 genome. The E1^E4 and E8^E2 ORFs span two exons with the nt positions indicated. Because the first AUG of E1^E4 and E8^E2 is positioned in the first exon, formation of an intact E1^E4 or E8^E2 ORF requires RNA splicing (*dashed lines*). LCR indicates a long control region. Below the *bracket line* are the RNA species derived from alternative promoter usage and alternative RNA splicing. Exons (*heavy lines*) and introns (*thin lines*) are illustrated for each species of RNA, with the mapped splice site positions being numbered by nt positions in the virus genome. Coding potentials for each RNA species are shown on the *right*. Adapted with permission (Wang et al. 2011a)

E1

E1 protein (~68 kDa, 649 aa residues) is a site-specific DNA-binding protein for the viral origin of DNA replication. Although relatively little is known about how E1 protein is produced in HPV-infected tissues, E1 is biochemically a well-studied

protein. E1 can be subdivided into three functional regions: a C-terminal helicase/ATPase domain, a central origin-binding domain, and an N-terminal regulatory region. E1 serves as a DNA helicase and opens the DNA duplex to initiate viral DNA replication. E1 by itself has low affinity for the viral origin of replication, which contains specific, palindromic E1 binding sites. However, binding of E2 protein to specific sites adjacent to the E1 binding sites helps recruit E1 in a cooperative manner. When loaded onto the origin of DNA replication, the E1/E2 protein complex recruits host replication factors such as topoisomerase I, DNA polymerase alpha/primase, replication protein A, and Brd4 to initiate viral DNA replication (Wang et al. 2013; McBride 2008). E1 is dispensable for maintenance replication, but is essential for initial and productive replication of HPV16 DNA (Egawa et al. 2012). Overexpression of E1 blocks S-phase progression and triggers an ATM-dependent DNA damage response in viral DNA replication foci during the initial viral DNA amplification (Reinson et al. 2013; Sakakibara et al. 2011; Fradet-Turcotte et al. 2011).

E2

E2 protein (~42 kDa, 365 aa residues) is a viral transcription factor in addition to its role in viral DNA replication. E2 contains two defined functional domains. The N-terminal domain is crucial for transcriptional activation, whereas the C-terminal domain possesses the DNA/RNA binding and dimerization properties of the protein. These two domains are linked by a hinge region. E2 interacts with E1 and enhances the binding affinity of E1 to the replication origin (Abbate et al. 2004). E2 functions as a transcriptional activator or repressor to regulate viral early promoter activity through consensus E2-binding sites (Androphy et al. 1987; Hawley-Nelson et al. 1988; Sousa et al. 1990; Romanczuk et al. 1990), upstream of the viral early promoter. However, E2's transcriptional repression occurs only in cells harboring integrated, but not episomal HPV16 DNA (Bechtold et al. 2003). E2 binding to the viral genome is important for tethering viral genome to mitotic chromosomes throughout mitosis (McBride 2008). E2 also plays roles in apoptosis (Parish et al. 2006; Blachon et al. 2005), ubiquitination, and intracellular trafficking (Muller et al. 2012). E2 binds RNA and interacts with RNA processing factors to regulate RNA splicing (Bodaghi et al. 2009; Lai et al. 1999) and RNA polyadenylation (Johansson et al. 2012).

E4

E4 (~10 kDa, 92 aa residues) is the most abundantly expressed HPV late protein and accumulates in the cytoplasm of differentiating cells in the upper epithelial layers (Griffin et al. 2012). E4 is expressed as an E1^E4 protein in which the N-terminal 5 aa residues are derived from the E1 ORF spliced to the E4 ORF. HPV16 E4 expression and cleavage of its N-terminal 17 amino residues by calpain lead E4 to

multimerization, formation of amyloid-like fibers, and disruption of the normal dynamics of the cytokeratin networks (Doorbar et al. 1991; Khan et al. 2011). E4 mediates cell cycle arrest in G2 by sequestering Cdk1/cyclin B1 onto the cytokeratin network to prevent the accumulation of active Cdk1/cyclin B1 complexes in the nucleus (Davy et al. 2002; Nakahara et al. 2002). The E1^E4 protein of HPV16 might also regulate gene expression at the post-transcriptional level by interacting with a DEAD-box containing RNA helicase (Doorbar et al. 2000) and SR protein kinase 1 (SRPK1) (Bell et al. 2007).

E5

E5 (~10 kDa, 83 aa residues) is a small hydrophobic and oligomeric channel-forming membrane protein, which is localized in the endoplasmic reticulum (ER) and the nuclear envelope. Assembled hexameric E5 channels in membranous environments have a defined luminal diameter and stoichiometry (Wetherill et al. 2012). The N-terminus of E5 is restricted to the ER lumen, while its C terminus is exposed to the cytoplasm to mediate interactions with cytoplasmic and ER proteins (Krawczyk et al. 2010). The C terminus of E5 also induces koilocytosis, structural cellular changes that are characteristic of papillomavirus infection (Krawczyk et al. 2008). HPV16 E5 is an oncoprotein. High levels of E5 expression in the mouse skin in the presence of persistently provided exogenous estrogen induce epithelial hyperproliferation, resulting in spontaneous tumor formation and increased dysplastic disease in the cervical epithelium (Maufort et al. 2010). E5 induces anchorage-independent growth of murine fibroblasts, enhances the immortalization of human primary keritonocytes by E6 and E7, and causes cell–cell fusion (Ganguly 2012). E5 activates epidermal growth factor receptor (EGFR) signaling pathways and enhances mitogen-activated protein kinase (MAPK) activity (Zhang et al. 2005; Straight et al. 1993; Kim et al. 2006), but attenuates the TGFbeta1/Smad signaling (French et al. 2013) and down-regulates the expression of MHC class I (Campo et al. 2010).

E6

E6 (~18 kDa, 151 aa residues) is a nuclear oncoprotein that interacts with hundreds of cellular proteins (White et al. 2012a). E6 inactivates cellular p53 family proteins (p53, p63, and p73) essential for cell cycle control, DNA repair, and cell adhesion (Ben et al. 2011; Moody and Laimins 2010). The complex of E6 and E6-associated protein (E6-AP) functions as an ubiquitin-protein ligase in the ubiquitination of p53 (Huibregtse et al. 1993). E6 contains two hypothetical zinc fingers involved in zinc binding and three nuclear localization signals (NLS) (Tao et al. 2003) as well as a PDZ-binding site in the N-terminus (Kiyono et al. 1997; Lee et al. 1997). E6 dimerizes through its N-terminal domain and this self-association promotes the polyubiquitination of p53 by E6AP (Zanier et al. 2012). The basic-hydrophobic pocket of E6, which composes of two zinc domains and a linker helix, interacts with an acidic

LxxLL motif of host proteins to exercise E6 transformation and degradation activities (Zanier et al. 2013). Besides its ability to immortalize and transform cells, E6 regulates gene expression at transcriptional and post-transcriptional levels (Desaintes et al. 1992; Klingelhutz et al. 1996) through interaction with other transcription factors/coactivators (Patel et al. 1999; Ronco et al. 1998; Kumar et al. 2002; Veldman et al. 2001, 2003; Thomas and Chiang 2005) and splicing factors, as well as its direct interaction with DNA and RNA (Bodaghi et al. 2009; Imai et al. 1989; Ristriani et al. 2000, 2001; Nomine et al. 2003). High-risk E6 enhances telomerase activity and activates several signal pathways including Akt, Wnt, Notch, and mTOC1 (Rampias et al. 2010; Lichtig et al. 2010; Weijzen et al. 2003; Spangle and Munger 2010, 2013), but inhibits apoptosis, keratinocyte differentiation, and interferon response (Ronco et al. 1998; Jackson et al. 2000; DeFilippis et al. 2003; Li et al. 1999). High-risk E6 regulates expression of a subset of cellular miRNAs (Zheng and Wang 2011; Wang et al. 2009, 2014). In E6 transgenic mice, E6 oncoprotein, in the absence of E7, synergizes with estrogen to induce cervical cancer after 9 months (Shai et al. 2007, 2010).

E7

E7 (~16 kDa, 98 aa residues) is a nuclear oncoprotein. The N-terminus of E7 contains conserved regions (CR) that have sequence similarity to other viruses. These conserved regions have sequence similarity to a portion of CR1 and the entire CR2 in adenovirus E1A and SV40 T antigen. E7 contributes to the binding and degradation of pRB and its related pocket proteins p107 and p130 through cullin 2 ubiquitin ligase complex associated with ZER1 (McLaughlin-Drubin and Munger 2009; Huh et al. 2007; White et al. 2012b). A conserved Leu-X-Cys-X-Glu (LXCXE) motif in the CR2 is sufficient for the association of E7 protein with pRB (Munger et al. 1989; Lee et al. 1998). A CK2 phosphorylation site is adjacent to the LXCXE motif. The C-terminal half of E7 contains a CR3 region with a zinc-binding domain and contributes to degradation of pRB and to E7 dimerization and transformation activities (Todorovic et al. 2011, 2012). E7 interacts with many cellular transcription factors/coactivators (Massimi et al. 1997; Avvakumov et al. 2003; Bernat et al. 2003; Huang and McCance 2002; Pim and Banks 2010; Zheng 2010) and participates epigenetic reprogramming (McLaughlin-Drubin et al. 2011). In addition to its cellular transformation activities, oncogenic E7 also plays a role in the viral life cycle and deregulates the cell cycle by stabilizing p21 and upregulating p16 expression. Oncogenic E7 interacts with the centrosomal regulator gamma-tubulin and induces mitotic defects and aneuploidy, leading to centrosome abnormalities and chromosomal instability (Duensing et al. 2000). High-risk E7 regulates expression of a subset of cellular miRNAs (Zheng and Wang 2011; Wang et al. 2014). In transgenic mice, the continuous expression of E7 is required for the maintenance of cervical cancers and precancerous lesions even in the presence of viral E6 (Jabbar et al. 2012; Shin et al. 2012). E7 down-regulates the expression of MHC class I (Bottley et al. 2008; Li et al. 2006) and prevents recognition of HPV-induced lesions by cytotoxic CD8 T cells.

L1

L1 (~55 kDa) is a major structural component of viral capsid. Both HPV16 and HPV18 L1 mRNAs initiate their translation from an initiation codon right at the splice junction of exon 2 and exon 3 of the viral late mRNA and encode a corresponding 506-aa HPV16 L1 and a 508-aa HPV18 L1 (Fig. 7.4), both of which are shorter than the one originally predicted in GenBank database (Zheng and Baker 2006; Wang et al. 2011a). L1 self-assembles into pentameric capsomers with a hollow channel at the center through a fivefold central axis when five L1 monomers come together and assemble in a symmetrical manner (Bishop et al. 2007; Chen et al. 2000). Thus, its tendency to form a pentavalent structure is directly reflected in the star-shape motif visible as a result of each capsomere. Purified capsomers can form capsids, which are stabilized by disulfide bonds between neighboring L1 molecules through their C-termini. The C-terminal half of L1 also contains activities for HPV DNA-binding and nuclear localization (Schafer et al. 2002; Nelson et al. 2002; Li et al. 1997). The N-terminal half of L1 interacts with L2. L1 capsids assembled in vitro are the basis of prophylactic vaccines against several HPV types (Schiller et al. 2012). Although most portions of L1 are well-conserved between types, the surface loops of L1 can differ substantially, probably reflecting a mechanism for evasion of neutralizing antibody responses elicited by previous papillomavirus infections.

L2

L2 (~70 kDa) is a minor capsid protein bearing 474 aa residues for HPV16 and 463 aa residues for HPV18. L2 exists in an oxidized state within the papillomavirus virion, with the two conserved cysteine residues forming an intramolecular disulfide bond. A single molecule of L2 interacts with an L1 pentamer via a C-terminal L1-binding domain (Finnen et al. 2003). L2 is not required for capsid formation, but participates in encapsidation of the viral genome. Up to 72 molecules of L2 can be incorporated per capsid, one beneath the axial lumen of each L1 capsomer (Buck et al. 2008). Both C- and N- terminal NLSs of L2 bind viral DNA during capsid formation and are important for nuclear localization of the DNA particle (Zhou et al. 1994; Bousarghin et al. 2003). L2 interacts with cellular proteins during the infectious entry process. After the initial binding of the virion to the cell, the N-terminus of L2 containing a consensus furin cleavage site (RxKR) is cleaved by the cellular protease, furin (Richards et al. 2006). The N-terminal L2 has a conserved transmembrane domain with three GxxxG motifs to facilitate homotypic and heterotypic interactions between transmembrane helices for vDNA translocation across the endo-/lysosomal membrane. Disruption of some of these GxxxG motifs has been shown to result in noninfectious viruses (Bronnimann et al. 2013). L2 interacts with members of T-box family, TBX2 and TBX3, and represses transcription from the long control region of HPVs (Schneider et al. 2013). A small N-terminal portion of L2 is well-conserved between different papillomavirus types. Experimental vaccines targeting these regions may offer protection against a broad range of HPV types (Jagu et al. 2013a, b).

7.3 HPV Infections and Transmission

HPVs can cause benign and malignant tumors in persistently infected skin and mucosal tissues anywhere in the human body. Benign tumors induced by low-risk HPVs are also called papilloma or warts, and these are in general harmless. However, when such a papilloma occurs in the larynx or upper airway, it could be life-threatening as exemplified by recurrent respiratory papillomatosis (RRP), a juvenile disease predominantly caused by HPV6 and HPV11 infection. RRP tends to recur and has the potential to spread throughout the respiratory tract (Bonagura et al. 2010). Benign tumors in the genital area are called condyloma acuminatum or genital (venereal) warts, of which around 96–100 % are caused by low-risk HPV6 and HPV11 infection. Although sexual contact as a risk factor in the development of cervical cancer was described in 1842 by Domenio Rigoni-Stern and the infectious nature of human warts was established in 1907 by Giuseppe Ciuffo's self-inoculation experiments with a cell-free extract of common warts, a landmark breakthrough on HPV cervical infection as a cause of cervical cancer was not achieved until 1983 when HPV16 DNA was discovered in ~60 % of cervical cancer samples by Herald zur Hausen and colleagues in Germany (Durst et al. 1983). Since then, the role of various HPV genotypes in invasive cervical cancer has been extensively studied, with HPV16, 18, 31, 33, 35, 45, 52, and 58 contributing to 91 % of invasive cervical cancer, and HPV16, 18, and 45 contributing to 94 % of cervical adenocarcinomas (de Sanjose et al. 2010). Cervical cancer (Cervical Cancer Essay 00021 40/40) is the second most common cancer among women worldwide. Approximately 500,000 incident cases and 320,000 cases of attributable deaths are predicted each year. More than 80 % of cases arise in developing countries.

In addition to the cervix, high-risk HPVs also infect other anogenital areas and can lead to development of anal, vaginal, vulvar, and penile cancers. Most anal cancers (~84 %) are caused by HPV infection (Frisch et al. 1997) (Anal Cancer Essay 00022 10/10). High-risk HPV infection of oropharynx (tonsils and the back of the tongue) may lead to the development of oropharyngeal cancer (Other HPV-associated Cancer Essay 00234 262/262). Oropharyngeal cancer is more common in men than women. The prevalence of HPV in oropharyngeal cancer is increasing from 16.3 % during 1984–1989 to 71.7 % during 2000–2004 (Chaturvedi et al. 2011; Gillison et al. 2012). Epidermodysplasia verruciformis (EV) is an extremely rare autosomal recessive genetic hereditary skin disorder associated with a high risk of skin carcinoma and is characterized by high susceptibility to HPV5 and HPV8 of the skin (Orth 1986). The role of HPVs in cutaneous squamous cell carcinoma (SCC) is elusive (Iannacone et al. 2013).

HPV infection is transmitted through skin abrasions (skin warts), by sexual intercourse, during passage through an infected birth canal (juvenile RRP), and probably in other ways. Women with multiple sex partners or a history of prostitution have an increased risk of infection with HPVs and an increased risk of cervical cancer. Women with history of cervical cancer (or pre-cancer) also have an increased risk of anal cancer (Anal Cancer Essay 00022 10/10). Receptive anal intercourse increases the risk of anal cancer in both men and women. Oral HPV infection is

related to oral sex behavior. Most HPV infections are transient and have either no viremia or only a minimal viremic phase. Thus, HPVs are not disseminated in general to other sites by blood in the course of HPV infections. However, detection of HPV DNA in human peripheral blood mononuclear cells and the findings of papillomavirus productive infection in lymphocytes, placenta, and bovine fetal tissues indicate that hematogeneous and vertical spread of HPVs should be carefully investigated (Freitas et al. 2013; Roperto et al. 2011).

7.4 Pathogenesis and Immune Responses of HPV Infections

After HPVs enter epithelial cells in the wound basal layer, virus infection is established by initiation of viral gene expression and then DNA replication. HPV life cycle is tightly linked to cell differentiation, and the time from infection to release virus can be approximately 3 weeks. Viral early gene expression and initial viral DNA replication occur in undifferentiated cells in the lower layers of the infected skin or cervix, while late gene expression and vegetative DNA replication occur in highly differentiated cells in the upper layers of the infected skin or cervix (Fig. 7.3). Although HPVs do not induce a lytic virus infection or cytolysis/cell death, viral early gene expression causes cell cycle interruption, apoptosis, keratin network collapse, DNA damage, genome instability, viral genome integration into host genome, and cell immortalization and transformation. The viral late gene expression leads to maturation of virus particles which appear as aggregates in the infected cell nuclei.

Even though most HPV infections are asymptomatic and cause no clinical problems, chronic or persistent cervical or anal HPV infection may result in histologic changes, with the infected cells displaying koilocytosis and nuclear inclusion bodies. The presence of koilocytes is a characteristic of HPV infection in all precancerous lesions and can be found in cervical smears. The period between infection and first appearance of lesions is highly variable and can range from weeks to months. HPV-induced histologic changes are classified as cervical intraepithelial neoplasias (CIN) grades 1, 2, or 3 on the basis of increasing degree of abnormality of cell growth in the cervical epithelium (Massad et al. 2013) (Cervical Cancer Essay 00021 40/40). The likelihood of spontaneous clearance versus progression to cancer in the absence of treatment varies for CIN1, CIN2, and CIN3. Histology CIN1 or cytology low-grade squamous intraepithelial lesion (LSIL) indicates abnormal cell growth that is confined to the basal 1/3 of the epithelium, usually clears spontaneously (80 % of cases) and rarely (<1 %) progresses to cancer. About 10–20 % of women with CINl progress to CIN2 and CIN3, which correspond to cytology high-grade squamous intraepithelial lesion (HSIL). CIN2 and CIN3 have a lower percentage (~40 %) of spontaneous clearance and a higher (~10 %) percentage rate of progression to cancer if not treated (Schiffman et al. 2007). CIN2 and CIN3 are distinguished by the extent of neoplasia, which is confined to the basal 2/3 of the epithelium in CIN2 or more than 2/3 in CIN3. CIN3 may involve the full thickness of the epithelium and is sometimes referred to as "cervical carcinoma in situ." Expression of viral E6 and E7 in the infected epithelial cells inhibits cell differentiation and induces cell immortalization

and transformation, resulting in disruption of virus productive life cycle and leading to viral genome integration into host genome. Although the integration of host genome is random in general, the circular HPV genome is commonly disrupted at E1 or E2 region for the integration. Thus, the degree of E1 or E2 integrity would reflect HPV genome status in cervical cancer tissues.

Because HPVs cause infection that is largely if not exclusively limited to the epithelium, they are largely shielded from the host immune response. To date, the correlates of immunity to HPV infection remain elusive. The majority of HPV infections are transient and cause no clinical problems. Most of new HPV infections clear within 1–2 years. The median duration of new infections is 6–18 months (Schiffman et al. 2007). However, the women with HIV/AIDS or immunosuppressed transplant patients take longer time to clear their HPV infection (Koshiol et al. 2006; Moscicki et al. 2004). Not all infected persons have antibodies. Approximately 60 % of women with incident HPV infections may have antibodies. The median time to seroconversion after a new infection is approximately 8 months (Ho et al. 2004). Among serum antibodies against many different viral products, the best characterized and most type-specific antibodies are those directed against conformational epitopes of the L1 protein.

HPV inhibits innate immunity and evades the host immune system. HPV infection suppresses interferon (IFN) synthesis and signaling (Ronco et al. 1998) and the expression of MHC class I in the infected cells (Bottley et al. 2008), resulting in reduced recognition of the infected cells by $CD8^+$ T cells (Campo et al. 2010) or exclusion of $CD8^+$ T cells from the dysplastic epithelium of HPV16-associated cervical lesions (Trimble et al. 2010). HPV-specific CD4 T cells isolated from lymph node biopsies of cervical cancer patients also suppress proliferation and cytokine (IFN-gamma , IL-2) production by responder T cells (van der Burg et al. 2007). However, T cells do play a role in preventing persistent HPV infection and inducing wart regression (Coleman et al. 1994; Nicholls et al. 2001). Healthy individuals with HPV infections display E6-specific memory T-helper cells in their blood. The majority of subjects clearing HPV16 display an HPV16 E6-specific cytotoxic T-lymphocyte (CTL) response. Failure of this response is associated with the development of cervical cancer. A significant $CD8^+$ T-cell tumor infiltration with a higher $CD8^+/CD4^+$ and/or $CD8^+$/regulatory T-cell ratio prevents the tumor cells from metastasizing to the tumor-draining lymph node. Moreover, T-cell defects due to a mutation in a *ras* homolog gene family member H (RHOH) gene and MST1, EVER1, and EVER2 deficiencies also lead to persistent EV-HPV infections (Crequer et al. 2012a, b).

7.5 Diagnosis of HPV Infections

Exfoliated Cell Cytology and Tissue Biopsy

Pap smear, also called a cervical smear or smear test, is a screening test to check for changes in the cervical cells from the outer opening of the cervix; it is done to identify individuals who can benefit from procedures to prevent progress to cervical

cancer (Cervical Cancer Essay 00021 40/40). The test was invented by and named after Georgios Papanikolaou. Cervical lavages are performed by a colposcopist by rinsing the opening of the ectocervix with 10 mL of sterile physiologic saline for the cervical cytology. The cytological changes that can be observed include atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells—cannot exclude HSIL (ASC-H), low-grade squamous intraepithelial lesion (LGSIL or LSIL), high-grade squamous intraepithelial lesion (HGSIL or HSIL), squamous cell carcinoma, and atypical glandular cells not otherwise specified (AGC or AGC-NOS) (Nayar and Solomon 2004).

Dysplasia seen on a biopsy of the cervix is grouped histologically into three categories: CIN I—mild dysplasia; CIN II—moderate to marked dysplasia; CIN III—severe dysplasia to carcinoma in situ (Massad et al. 2013; Wright et al. 2007).

Electron Microscopy

HPVs cannot be grown by conventional tissue culture methods. HPV infection can be diagnosed by electron microscopy, in which virus particles in clinical specimens can be visualized either by negative staining or thin-sectioning techniques. In thin sections of human skin warts, papillomavirus particles can be found in aggregates in an infected nucleus.

Viral Antigen Detection

HPV infection can also be diagnosed by detection of HPV proteins in infected tissues or exfoliated cells. In general, HPV L1 is detectable in cervical smears in most high-risk HPV-associated LSIL, but becomes undetectable in most of HSIL cases (Rauber et al. 2008).

Viral E2, E4, and E7 proteins have been detected from formalin-fixed paraffin-embedded cervical cancer tissues or cervical smears. Type-specific HPV E4 and E7 antibodies are particularly useful in distinguishing HPV type-specific infection of HPV16, HPV18, HPV58, and other genotypes by immunohistochemistry, ELISA, or Western blot (Griffin et al. 2012; Lidqvist et al. 2012; Xue et al. 2010; Ehehalt et al. 2012).

Viral DNA and RNA detection

Qualitative or semi-quantitative DNA or RNA tests for diagnosis of high-risk HPV infection have been developed that are based on the sequence conservation and variation of viral L1 coding regions. To date, four FDA-approved HPV DNA tests, one FDA-approved RNA test, and two Europe-approved HPV DNA tests are

commercially available. These include (1) Hybrid Capture 2 (HC2) HPV DNA test (Digene Corp., Gaithersburg, MD), (2) Cervista HPV HR test (Hologic, Bedford, MA), (3) Cervista HPV 16/18 test (Hologic, Bedford, MA), (4) Cobas 4800 HPV test (Roche, Pleasanton, CA), (5) Aptima HPV assay (Gen-Probe, San Diego, CA), (6) Linear Array HPV Genotyping Test (Roche Molecular Systems Inc, Alameda, CA), and (7) INNO-LiPA HPV Genotyping Extra (Innogenetics, Ghent, Belgium) (Poljak et al. 2012).

The HC2 HPV DNA test is an in vitro nucleic acid hybridization assay with signal amplification using microplate chemiluminescence for the qualitative detection of 13 high-risk types of HPV (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) and 5 low-risk types of HPV (6, 11, 42–44). This DNA assay was the first FDA-approved HPV DNA test and has become the standard in many countries widely used in clinical studies. The HC2 distinguishes between the low-risk and high-risk groups, with the detection limits of ~5,000 genome copies, but can't determine the specific HPV genotype

The Cervista HPV HR test and Cervista HPV16/18 test are two HPV DNA tests for high-risk HPV infections, but have no genotyping capability. The Cervista HPV HR test is an in vitro diagnostic test for detection of 14 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) in cervical specimens. The Cervista HPV HR test uses the invader chemistry and is a signal amplification method for detecting specific nucleic acid sequences.

The Cobas 4800 high-risk HPV test uses fluorescence signal to detect nucleic acids amplified by using real-time PCR methodology and detects 14 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68). The Cobas 4800 system, consisting of two separate instruments (Cobas z 480 and Cobas x 480 analyzers), integrates sample preparation, amplification and detection, and result management. It has high throughput (designed to process up to 280 samples per day) and is automated.

The Aptima HPV assay detects viral E6/E7 mRNA transcripts of 14 high-risk HPVs (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68), but has no genotyping capability. The Aptima HPV assay uses the Gen-Probe's Tigris DTS System, a fully automated testing system, and is a transcription-mediated amplification-based assay. The amplicons are then detected by hybridization protection with chemiluminescent-labeled single-stranded nucleic acid probes that are complementary to the amplicons.

The Linear Array HPV Genotyping Test is used in the European Union for detection and genotyping of 37 high- and low-risk HPVs (6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 58, 59, 61, 62, 64, 66, 67, 68, 69, 70, 71, 72, 73 (MM9), 81, 82 (MM4), 83 (MM7), 84 (MM8), IS39, and CP6108). The test utilizes amplification of target DNA by PCR with PGMY09/11 primers and then hybridizes the amplicons to multiple HPV genotype-specific probes fixed on a membrane strip.

INNO-LiPA HPV Genotyping Extra uses the principles of reverse line blot hybridization. The test amplifies HPV DNA with SPF10 primers at the L1 region and then hybridizes the amplicons to the probes fixed on membrane strips in

sequence-specific lines. The INNO-LiPA test detects and distinguishes 28 low- and high-risk HPVs including 18 high-risk HPVs (16, 18, 26, 31, 33, 35, 39, 45, 51–53, 56, 58, 59, 66, 68, 73, 82), 7 low-risk HPVs (6, 11, 40, 43, 44, 54, 70), and 3 additional genotypes (69, 71, 74).

Serology

HPV serology is a valuable tool to study immune status prior to and after HPV vaccination. Although most HPV infections are cleared spontaneously within 2 years, the majority of infected subjects develop and maintain serum antibodies to viral L1 for up to five subsequent years. Serology is not commonly used for clinical diagnosis because more than 40 % of women do not seroconverted after HPV infection. The standard methods are VLP ELISA and pseudovirion neutralization assays (http://home.ccr.cancer.gov/lco/NeutralizationAssay.htm). Both methods have similar sensitivity and specificity in the detection of serum L1 antibodies in the majority of infected subjects. There is recent evidence that antibody to HPV16 E6 can be predictive of subsequent development of oropharyngeal or anal cancer with a high degree of specificity, and this will be an important area for future research (Kreimer et al. 2013).

Detection of Cellular Surrogates of High-risk E6 and E7 in Infected Tissues

A few cellular biomarkers of high-risk HPV E6 and E7 expression have been widely used to indicate viral oncoprotein expression in pre-cancer lesions or cancers. These include cell cycle inhibitors (p16Ink4a and p18Ink4c), MCM7 (minichromosome maintenance protein 7), cyclin E2, and a subset of miRNAs (Zheng and Wang 2011; Wang et al. 2011b, 2014; Klaes et al. 2001; Middleton et al. 2003).

7.6 Epidemiology and Prevention of HPV Infections

The global prevalence of HPV infection among women with normal cytology is around 11–12 %, with a higher rate in Africa, Caribbean, and South America and a lower rate in Asia, Europe and Northern America. The prevalence of any HPV is about 26.8 % in females aged 14–59 and 44.8 % among women aged 20–24 years in the United States (Dunne et al. 2007). The majority of HPV infections are transient and asymptomatic; 70 % of new HPV infections clear within 1 year, and approximately 90 % clear within 2 years. The median duration of new infections is 8 months. Up to 50 % of young women with one type of HPV infection may acquire another type of HPV infection within a few years. Although co-infections with multiple

high-risk HPVs may lead to an increased risk of CIN2/3, persistent infection with any high-risk HPV is the most important risk factor for cervical lesions and cervical cancer. The risk of cancer development varies by HPV type, with HPV16 being more oncogenic than other high-risk HPV types. Factors associated with cervical cancer (Cervical Cancer Essay 00021 40/40) also include an increased number of life-time sexual partners, increased age, other sexually transmitted infections, immune suppression, and other host factors. There are also epidemiology reports of smoking being associated with increased cervical cancer, although it isn't clear if this may be due to association with other risk factor (Haverkos et al. 2003). The time between initial HPV infection and development of cervical cancer is usually decades. Many aspects of the natural history of HPV remain to be understood, including the role and duration of naturally acquired immunity after HPV infection.

Because HPV is the most common sexually transmitted infectious agent, condom use and circumcision are two common practices to prevent sexual partners from HPV transmission. Pap smear screening is widely used in developed world to check for changes in the cervical cells from the outer opening of the cervix and to prevent progress to cervical cancer by treatment of these lesions. While likely, it is not known if screening for and treatment of anal HSIL will similarly prevent anal cancer; the United States National Cancer Institute has recently initiated a large randomized clinical trial to study this issue. Two FDA-licensed prophylactic HPV vaccines, Gardasil from Merck (USA) and Cervarix from GlaxoSmithKline (UK), are very safe and effective in preventing new or persistent HPV infections and reducing HPV infection-induced cervical, vulvar, vaginal, anal, and penile lesions. Their use will be an important public health measure to prevent HPV-associated cancers (Schiller et al. 2012). Both vaccines are comprised of viral DNA-free, L1 VLP. Cervarix contains L1 VLP from HPV16 and 18 produced in insect cells, while Gardasil is comprised of L1 VLP from HPV6, 11, 16 and 18 produced in yeast. Because it contains L1 VLP from HPV6 and HPV11, Gardasil immunization also provides protection against genital warts (Donovan et al. 2011). In the presence of adjuvant aluminates, both the quadrivalent Gardasil and the bivalent Cervarix are highly immunogenic and excellent HPV type-specific protection is provided to girls and boys at age 11 or 12 years who receive all three vaccine doses (0, 1, and 6 month). Catch-up vaccination with either one of HPV vaccines is approved by the US FDA for young women through age 26 or young men through age 21 (Cervical Cancer Essay 00021 40/40).

Due to the limited inclusion of HPV types, the current vaccines do not provide cross-immune protection against other high-risk mucosal HPVs. However, there is evidence to suggest that HPV L2 might work as a pan-HPV vaccine against different HPVs. A small N-terminal portion of L2 is well-conserved among different HPVs, and experimental vaccines targeting these conserved domains offer protection against a broad range of HPV types (Jagu et al. 2013b).

Most of therapeutic vaccine approaches target high-risk HPV E6, E7 or both to control disease progression in preexisting HPV infections and lesions. To date, these studies have provided only a gleam of success. An experimental HPV16 E6 and E7 synthetic long peptide vaccine can increase the number and activity of

HPV16-specific $CD4^+$ and $CD8^+$ T cells in patients with vulvar intraepithelial neoplasia or cervical cancer (Welters et al. 2008; Kenter et al. 2009). HPV VLP entry into NK cells triggers cytotoxic activity and cytokine secretion (Renoux et al. 2011), although VLP does not activate Langerhans cells (Fausch et al. 2002). A therapeutic HPV16/18 DNA vaccine with optimized E6 and E7 codons stimulate high titers of anti-E6/E7 antibodies and high levels of cellular immunity by both $CD8^+$ and $CD4^+$ T cells (Bagarazzi et al. 2012).

7.7 Conclusion

HPVs have been well recognized as a group of small DNA tumor viruses that are highly transmissible through sexual or close contact. In the past decades, HPV infection has been found in association with development of various human cancers, including cervical, anogenital, oropharyngeal, and even some skin cancers. Although there is more to be learned about the basic biology of HPV, the translational research on HPVs has remarkably advanced our understanding of HPV epidemiology, disease progression, clinical diagnosis, and cervical cancer prevention. Today, L1-based HPV vaccination has become a general practice and has been mandated in many countries to protect girls and boys from HPV infections and HPV-related precancerous lesions and cancer.

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Chapter 8
Merkel Cell Polyomavirus

Nicole Fischer and Adam Grundhoff

Abstract Merkel cell polyomavirus (MCV) is a recently discovered member of the polyomaviridae, a family of small DNA viruses that replicate in the nucleus of their host cell. MCV is one of at least 12 polyomaviruses that naturally infect humans, and furthermore one of four polyomaviruses that are known to cause severe human disease, predominantly in immunosuppressed or deficient individuals (DeCaprio and Garcea, Nat Rev Microbiol 2013;11(4):264–76; Korup et al., PLoS One 2013;8(3):e58021). Of these, MCV is of particular interest since it presently is the only human polyomavirus known to be involved in tumorigenesis. The virus was first identified in 2008 in tissue from Merkel cell carcinoma (MCC) by high throughput sequencing (Feng et al., Science 2008;319(5866):1096–100). Considerable evidence suggests that MCV is causally linked to MCC pathogenesis: Viral DNA is monoclonally integrated into the genome of the tumor cells in up to 90 % of all MCV cases, and the integrated MCV genomes furthermore harbor signature mutations that selectively abrogate viral replication while preserving cell cycle deregulating functions of the virus (Chang and Moore, Annu Rev Pathol 2012;7:123–44). Nonetheless, the development of MCC is doubtlessly a very rare complication of MCV infection, given that MCV is highly prevalent in the general population, with 44–80 % of adults displaying serum reactivity against viral antigens. What cells represent the natural reservoir of MCV infection in healthy individuals, whether the virus is potentially linked to human diseases other than MCC, and how precisely MCV infection contributes to cellular transformation during MCC pathogenesis are unresolved issues that are the subject of current research efforts.

N. Fischer (✉)
Institute for Medical Microbiology, Virology and Hygiene, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
e-mail: nfischer@uke.de

A. Grundhoff
Heinrich Pette Institute, Leibniz Institute for Experimental Virology, Hamburg, Germany
e-mail: adam.grundhoff@hpi.uni-hamburg.de

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8.1 Introduction

Merkel cell carcinoma (MCC) is a rare but highly aggressive skin cancer which predominantly arises in elderly and immunosuppressed patients. The risk to develop MCC is 10–15 fold increase in patients undergoing solid organ transplantation (SOT) and HIV patients. This, together with occasional reports of spontaneous regression of MCC after reconstitution of the immune system, strongly suggests an infectious etiology of the disease (Schrama et al. 2012). In 2008, high throughput sequencing of RNA derived from MCC tissue successfully identified a novel human polyomavirus (Feng et al. 2008). Subsequent studies from different laboratories worldwide confirmed the frequent detection of viral DNA in MCC; hence, the virus was named Merkel cell polyomavirus (MCV) (Chang and Moore 2012). Due to the considerable molecular and serological evidence that argues for a causative link between MCV and MCC pathogenesis (see Sect. 8.6), MCV has been classified by the WHO International Agency for research on Cancer (IARC) as a group 2A carcinogen (Chang and Moore 2012).

Polyomaviruses and other small DNA viruses (adenoviruses and papillomaviruses) have long been known to induce malignant transformation of cells in vitro or in vivo. This ability is closely linked to the replication strategy of these viruses: Upon entry in the host cell nucleus, they rapidly express early genes that mediate aberrant S-phase entry and inhibit apoptosis, e.g. by inhibiting pRb and p53. These manipulations serve to create an environment supportive of massive replication of viral DNA and subsequent production of viral progeny, a process that usually results in the death of the host cell, or its clearance by the immune system. However, if viral DNA replication is blocked (e.g., due to the infection of a non-permissive species or cell type), and if the viral genome additionally integrates in the cellular genome and hence is stably propagated upon host cell division, constitutive low-level expression of early viral gene products may promote cellular transformation. Many polyomaviruses can cause tumors under experimental conditions, e.g. when introduced into tissues or animal species in which the virus normally does not replicate. However, in their natural host, polyomaviruses only very rarely induce tumors. Indeed, MCV is one of only two members of the family (the other being African green monkey polyomavirus) that has been reported to contribute to neoplastic disease of its natural host.

8.2 MCV Genome Organization

MCV is a non-enveloped virus with a circular DNA of 5,386 bp. Its genome shows the typical organization of polyomaviruses and can be divided into three regions (Fig. 8.1): (1) The non-coding control region (NCCR) encompassing the origin of replication as well as the promoters for early and late gene expression, (2) the early gene region that produces alternatively spliced early transcripts encoding large T-Antigen (LT), small T-Antigen (ST), a 57 kDa antigen and an alternative open

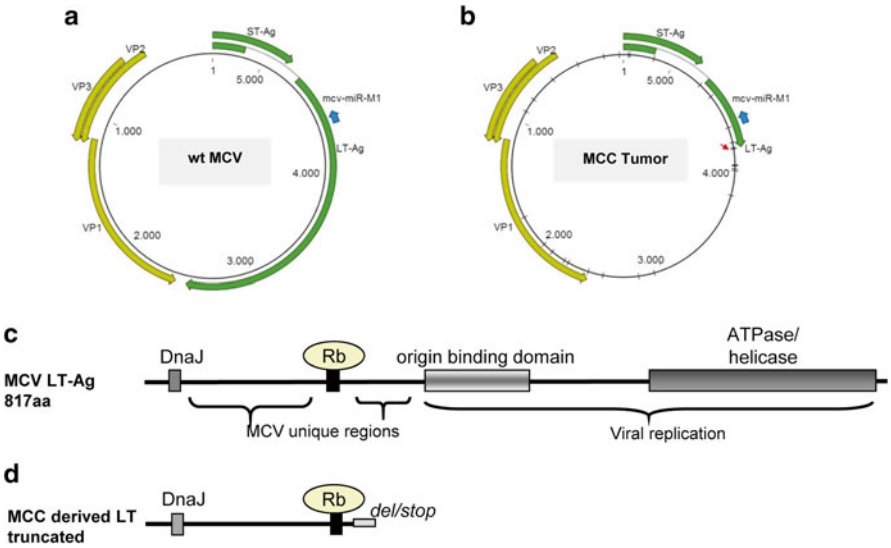

Fig. 8.1 MCV genome organization. (**a**) The genome is divided in three regions: the early gene region illustrated in green, the late gene region, counterclockwise to the early transcripts; pictured in yellow and the non-coding control region. MCV is one out of few polyomaviruses encoding for a viral micro RNA (MCV mIR-M1), located antisense to the LT transcripts (shown in blue). (**b**) Sequences identified in MCC tissue. LT sequences carry point mutations, frameshift mutations or small deletions all resulting in premature STOP codon. In the MCC tumor only the N-terminal region encompassing the Retinoblastomprotein (Rb) binding region of LT is expressed. The C-terminus containing the origin binding domain as well as the helicase is not expressed. (C+D) Schematic drawing of MCV LT protein domains. (**c**) MCV LT full length protein as identified in wild type strains isolated from healthy skin and (**d**) MCC derived truncated LT protein

reading frame called ALTO (Carter et al. 2013), and (3) in reverse orientation relative to the early transcripts the late genes that encode the structural proteins VP1, VP2, and probably VP3. Whether MCV indeed expresses a VP3 structural protein is still under discussion, given that the amino acid motif Met-Ala-Leu that initiates VP3 translation in other polyomaviruses is not present (An et al. 2012; Chang and Moore 2012; Schowalter and Buck 2013). Like certain other polyomaviruses, the MCV genome also harbors a viral microRNA located antisense to the early transcripts. However, it lacks middle T-Antigen (MT) as seen in mouse polyomavirus, and also does not encode an agnoprotein as in SV40.

Phylogenetically, the MCV LT-Ag possesses closest homology to chimpanzee polyomavirus (ChPyV) (Fig. 8.2). Among the human polyomaviruses (hPyV), MCV is most closely related to trichodysplasia spinulosa-associated virus (TSV), a virus that causes a rare (non-neoplastic) skin disease in immunocompromised individuals (DeCaprio and Garcea, 2013). The two remaining polyomaviruses associated with major diseases in humans, JC virus and BK virus. These two viruses cause a usually fatal demyelinating or severe renal disease, respectively, and are more closely related

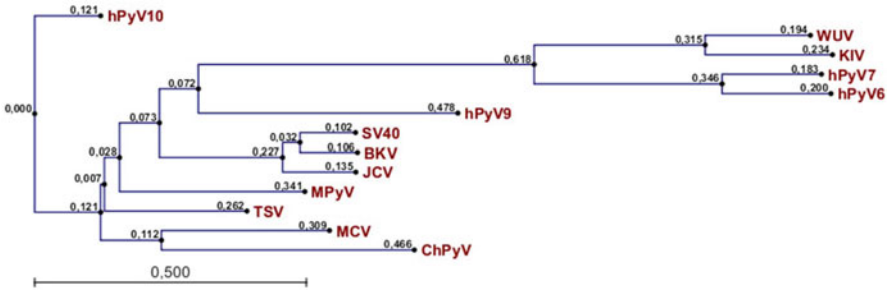

Fig. 8.2 Phylogenetic analysis of Large T-Antigen aa sequence from hPyV, SV40, mouse polyomavirus (MPyV) and chimpanzee PyV (ChPyV). Large T-Antigen sequences from ten hPyV (BKV, NC_001538.1; JCV, NC_001699.1; WUV, NC_009539.1; KIV, NC_009238.1; hPyV6, NC_014406.1; hPyV7, NC_014407.1; MCV, JN707599.1; TSV, NC_014361.1; hPyV9, HQ696593.1; hPyV10, JX262162.1; MPyV, NC_001515.1; ChPyV, NC_014743.1; SV40, NC_001669.1) were aligned using CLC workbench 6.6.1; the phylogenetic tree was generated using neighbor-joining method

to the simian virus 40 (SV40), the prototypical member of the polyomavirus family, than to MCV. BKV and SV40 LT-Ag share more than 75 % amino acid (aa) sequence similarity, whereas the LT-Ags of BKV and MCV are only 55 % homologous.

8.3 MCV Replication and Persistence

A fully permissive in vitro replication system for MCV does not yet exist, a fact which severely hampers studies of the viral life cycle. The absence of such a system may be explained by the fact that polyomaviruses often exhibit a highly restricted tissue tropism and only replicate in specific cell types. At present, the authentic cell type in which MCV replicates in vivo is unknown. This is true for most human polyomavirus; in fact, the full viral lifecycle can so far be only studied for two human polyomaviruses, and in both cases a particular cell system is required (primary human renal proximal tubule epithelial cells (RPTE) for BK virus, and human glial cells for JC virus). In contrast, simian virus 40 can successfully be cultured in monkey cell lines (Vero, CV1). Consequently, most information about the polyomavirus life cycle is derived from the study of SV40 replication (An et al. 2012).

Attempts to recapitulate the MCV lifecycle by transfection of episomal DNA into cultured cells have so far not identified a cell type that allows the efficient production infectious virions. However, the initial phase of the life cycle (receptor binding, entry and viral DNA replication) can be studied in some established cell lines (Chang and Moore 2012; Neumann et al. 2011; Schowalter et al. 2011). Viral entry is a sequential process that involves attachment of MCV particles to large linear polysaccharides (glycosaminoglycans), and a subsequent post attachment step that requires the presence of sialic acid (Schowalter et al. 2011).

Although not studied in authentic MCV infection, the subsequent steps are likely to be similar to those observed during SV40 infection: after virion uptake by endocytosis, the viral genome is delivered to the nucleus where early gene transcription immediately starts. Polyomaviruses infect quiescent cells and do not encode their own DNA polymerase; they thus need to induce the cell cycle to be able to replicate their DNA. Induction of S-phase is achieved by LT-Ag binding to the Rb protein and subsequent inactivation of p53. Late gene transcription is concomitantly initiated with viral DNA replication, and translation of the structural antigens is followed by virion assembly and egress of viral particles.

Upon transfection of MCV genomes, expression of T antigens and efficient replication of viral episomes has been observed in some, but not all of the tested cell types (Chang and Moore 2012; Neumann et al. 2011), indicating that cell type-dependent post-entry blocks to early gene expression or DNA replication may exist. Another block that limits the MCV lifecycle appears to be on the level of late gene expression and/or virion assembly, as all cell systems studied so far (including those that permit DNA replication) fail to efficiently produce viral particles. The molecular nature of the mechanisms that hinder viral replication in above models is unknown. Likewise, it remains an open question whether similar mechanisms contribute to a replication block that may precede integration and mutagenesis of MCV genomes during MCC pathogenesis.

8.4 MCV and MCC Pathogenesis

Several observations support the notion that MCV infection plays a causative role in MCC tumorigenesis. Firstly, MCV genomes can be detected with high frequency in MCC, with 80–90 % of all MCC tumors being positive for MCV DNA. Secondly, the tumor cells express early viral gene products and contain the viral DNA monoclonally integrated in the host genome. The fact that integration sites are always identical within a given tumor and its metastases strongly suggests that viral infection must precede tumorigenesis. At the same time, integration sites vary among tumors from different patients, indicating that integration is likely to reflect a selection pressure to maintain viral DNA and expression of early antigens, rather than a proliferative advantage gained by changes in expression or structure of flanking cellular chromatin. Thirdly, all integrated viral genomes harbor signature mutations that are absent from viral episomes residing in tissues in which the virus is thought to replicate (Chang and Moore 2012; Schrama et al. 2012). Strikingly, although these mutations are diverse among different tumors, they unequivocally occur in the form of point mutations or small deletions that lead to the disruption of the LT-Ag coding region between the sequences that code for the Rb-binding motif and those that encode the origin binding and ATPase/helicase domains (see Fig. 8.1c, d). Hence, the resulting truncated LT-Ags are unable to support viral DNA replication, but retain their ability to bind to and sequester Rb. It is therefore likely that the mutations represent the result of a dual selection pressure: the need to prevent the

untimely firing of integrated viral replication origins outside of S-phase (which would result in the death of the host cell), while simultaneously preserving cell cycle deregulatory functions of early antigens.

Besides of LT-Ag, sT-Ag may also play a critical role during MCC pathogenesis. Indeed, the sT-Ag (which is expressed in MCC tumors and is not affected by the LT-Ag mutations) was found to induce loss of contact inhibition and permit anchorage independent growth of rodent fibroblasts. In contrast to other polyomaviruses (SV40, MPyV), the mechanism by which sT-Ag influences proliferation does not involve PP2A inhibition, but appears to act downstream within the Akt-mTOR pathway, ultimately resulting in 4E-BP1 inhibition and stimulation of cap-dependent mRNA translation (Chang and Moore 2012). Experiments using siRNAs to either selectively inhibit sT-Ag expression alone, or sT- together with LT-Ag expression in MCV-positive MCC cell lines have indeed shown that both early antigens contribute to cell survival (Chang and Moore 2012; Schrama et al. 2012), making them attractive targets for potential future therapeutic approaches.

8.5 MCV Epidemiology

Capsid epitope immunoassays demonstrate a high prevalence of MCV (up to 80 %) in healthy adults, similar to rates that have been previously described for other human polyomaviruses (Chang and Moore 2012). Fifty percent of children younger than 15 years are seropositive for MCV antibodies, indicating a common infection that already occurs at young age, and that only in very rare cases leads to the development of a tumor. Although antibody titers against viral capsid protein can be detected in the majority of adults, MCC patients with MCV-positive tumors demonstrate higher antibody titers compared to patients with MCV-negative tumors (Chang and Moore 2012). This observation suggests that such patients may be unable to efficiently control MCV replication and supports the notion of a causative role of MCV in MCC. In contrast to seroreactivity against viral capsid proteins, antibodies against the early T antigens are only sparsely detectable in the general population or are only detected at very low titers. However, patients with MCV-positive MCC demonstrate high LT antibody titers. Interestingly, LT antibody titers fluctuate during disease progression with high titers in patients with recurring disease and progressing metastasis and decreased titers in patients in which the tumor did not recur.

In addition to seroprevalence studies, the presence of MCV DNA on the skin of healthy patients has also been analyzed, using swab samples from different body sites and subsequent qualitative as well as quantitative PCR (Wieland et al. 2009). Wild-type MCV genomes that carry no premature stop codons in the early region were successfully isolated from healthy persons, again supporting the hypothesis that MCV is part of the normal skin flora (Schowalter et al. 2010; Wieland et al. 2009). Furthermore, a recent study demonstrated that the amount of viral DNA shedded correlates with serum antibody responsiveness, suggesting that the skin is a major site of MCV replication (Pastrana et al. 2012). Nonetheless, as indicated

above, the specific cell type in which MCV may replicate has not been identified yet. MCV may also reside in other tissues, as viral sequences can be detected by PCR in respiratory tract, saliva, gut, urine, lymphoid tissue, and whole blood from healthy patients. However, compared to skin viral copy numbers are much lower in these tissues (Chang and Moore 2012). Whether they only represent secondary sites of replication or play other important roles during MCV infection, for example as long-term reservoirs of infection, is currently unknown.

8.6 MCV Infection in HIV Patients

HIV patients show an increased rate of neoplastic diseases, with Kaposi sarcoma (KS) and large B cell non-Hodgkin lymphomas representing the most common virally induced AIDS defining cancers. With the widespread use of HAART for more than a decade, the population of HIV-infected patients is increasing and this population is becoming older. Along with these changes, the number of HIV-infected patients developing non-AIDS defining cancers is increasing, and the repertoire of these cancers is expanding. MCC is increasingly being appreciated as an HIV-associated cancer. In addition, the sites at which MCC occurs are more diverse in location in AIDS patients compared to HIV-negative patients and in HIV-infected patients, it frequently develops on non-sun-exposed body parts. This observation suggests that UV-mutagenesis might be of lesser important in MCC development in AIDS patients as compared to other patients (Wieland and Kreuter 2011).

Although MCC occurrence in AIDS patients is increased up to 15 fold, studies evaluating the seroprevalence of antibodies against MCV capsid protein have not found a correlation between MCV infection and HIV status or AIDS progression (Tolstov et al. 2011). However, MCV-specific PCR performed with forehead skin swaps of 210 HIV-positive men demonstrated that individuals with poorly controlled HIV infection are more than twice as frequently positive for MCV DNA, and also exhibit significantly higher viral loads than a control cohort (Wieland and Kreuter 2011).

8.7 MCV in Diseases Other Than MCC

The potential association of MCV with neoplasia other than MCC has been extensively studied in the years since the identification of the virus. Mostly PCR, but to some extent also LT immunohistochemistry techniques have been used to detect MCV sequences and/or Ag expression in tumor tissues. So far, MCV has only rarely been detected (and if so, only in low copy numbers) in, e.g., neuroendocrine tumors from different anatomical sites, mesotheliomas, different skin cancers (BCC, SCC, melanoma, and Kaposi Sarcoma), breast cancer, prostate cancer and ovarian cancer, suggesting no direct association of MCV with these diseases (Chang and Moore 2012).

Since patients with MCC have an increased risk of developing chronic lymphocytic leukemia (CLL) and vice versa, the association of MCV and CLL was analyzed in particular detail. Two independent studies lead to contradictory results (Chang and Moore 2012): one study detected MCV DNA in 27 % of CLL samples and 13 % of control samples by PCR, FISH as well as IHC, whereas another study investigated CLL cases with and without concurrent MCC and not find MCV sequences or LT-Ag expression in CLL tissues. Based on these findings, it may be reasonable to conclude, at least for the moment, that MCV represents a passenger virus in CLL, perhaps being a result of increased viral replication rates due to decreased immunity. However, at present a contribution of MCV infection to CLL disease cannot be categorically ruled out.

8.8 Diagnostic and Prognostic Value of MCV Detection in MCC

Immunohistochemistry (IHC) of MCV antigen expression (LT and sT) is useful to discriminate between virus-positive and virus-negative tumors. IHC staining of MCC tissue with a monoclonal antibody against LT (Cm2B4) has been applied by several studies, and reliable IHC protocols for the diagnostic use have been established. Staining of viral antigens is generally restricted to MCC tumor cells and has not been described for healthy tissue surrounding or interspersed within the tumor. However, some MCV-positive MCC cases that are negative for IHC staining with the Cm2B4 antibody directed against LT-Ag, but positive when tested with an antibody that detects sT-Ag have been reported. As sT-Ag expression is detectable in all MCV-positive MCC tumors tested so far, IHC for this viral antigen would be superior to LT-Ag staining. Unfortunately, no antibody against sT antigen is commercially available thus far. Therefore, LT-Ag IHC is routinely employed to complement the panel of non-viral marker proteins (CK20, CK18, neuron-specific enolase, chromogranin A, synaptophysin) used to diagnose MCC.

The use of LT antigen IHC staining (and/or MCV DNA load) as a prognostic marker is still under discussion, with conflicting reports about MCV status and MCC recurrence. While a Finnish study reported a correlation of LT antigen expression and MCV DNA load with survival rates, with patients with MCV-positive tumors having prolonged survival rates (Sihto et al. 2011), a German study that included MCC cases from Germany and Australia found no direct association between MCV status and MCC recurrence (Schrama et al. 2011).

More recent studies are encouraging with regard to using the immune status of MCC patients as a potential prognostic marker. Several reports indicate that an increased number of CD8+ T-cells in MCC tumors are associated with longer disease-free survival. MCV-positive tumors often contain high numbers of infiltrating immune cells. Interestingly, MCV-negative tumors with high numbers of immune cells also have a better disease outcome, so the relationship of these immune cells to a viral antigen is unclear (Paulson et al. 2011; Sihto et al. 2012).

8.9 Conclusion

MCV is the first polyomavirus with convincing evidence of an etiological role in human cancer formation. This evidence includes high association (up to 90 %) of MCV with the tumor in which the virus was identified, monoclonal genomic integration of viral DNA carrying signature mutations in the cells of primary tumors and subsequent metastases, expression of viral oncoproteins in the tumor tissue, and significantly increased viral titers in patients with disease.

Since the discovery of MCV, significant progress has been made with regard to the understanding of MCV biology and its role in MCC pathogenesis. However, the precise mechanism that lead to virally induced transformation in vivo remain to be unraveled. It is to be expected that future studies of the viral life cycle and its role in cellular transformation will provide not only important information for the diagnosis and prognosis of MCC, but may also allow novel therapeutic approaches that directly target viral antigens required for the survival and continued proliferation of the tumor cells.

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Part III
Kaposi Sarcoma

Chapter 9
Presentation and Pathogenesis of Kaposi Sarcoma

Corey Casper

Abstract Kaposi sarcoma (KS) is a vascular neoplasm caused by infection with human herpesvirus 8 (HHV-8). Epidemic KS is found among persons with HIV infection; it is the most common malignancy in persons with HIV worldwide. Two decades after HHV-8 was first identified, much is now known about how chronic infection leads to the development of KS. HHV-8 is likely transmitted via saliva in most cases. The virus, host, and possibly environmental factors all contribute to the risk of developing KS. Heterogeneous clinical manifestations of the disease feature skin and mucous membrane involvement in adults, with advanced disease involving the thoracic or abdominal viscera. Pediatric KS is unusual outside of sub-Saharan Africa, but is typically characterized by lymph node and cutaneous disease. KS also may be the presenting manifestation of an immune reconstitution inflammatory syndrome after HIV-infected patients initiate antiretroviral therapy, and can be co-morbid with other HHV-8-associated diseases including multicentric Castleman disease and primary effusion lymphoma. For patients with access to ART and/or chemotherapy, survival after a diagnosis of KS is excellent, but clinical responses to therapy are often incomplete and new therapies for the disease are needed.

9.1 Introduction

Kaposi sarcoma (KS) remains among the most common cancers seen in persons with human immunodeficiency virus (HIV) infection more than three decades after it was initially described as a key presenting manifestation of the Acquired

C. Casper, M.D., M.P.H. (✉)
Vaccine and Infectious Disease, Public Health Sciences and Clinical Research Divisions, Departments of Medicine, Epidemiology and Global Health, Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, USA
e-mail: ccasper@fhcrc.org

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Immunodeficiency Syndrome (AIDS) in 1981 (Center for Disease Control 1981; Hymes et al. 1981). While new cases of KS have decreased dramatically in the USA with the widespread availability of combination antiretroviral therapy (cART), the incidence remains threefold higher than prior to the HIV pandemic (Shiels et al. 2011) and the cancer is the most common in the entire male population of several countries in sub-Saharan Africa (Ferlay et al. 2013). Much has been learned about the pathogenesis of KS and its clinical manifestations in HIV-infected persons, and many of these discoveries have led to effective therapies for the disease. However, KS remains a cancer that infrequently responds completely to therapy, and continued research into the biology of the malignancy will likely lead to more effective, safer, and less expensive therapies that may be used in the coming years.

9.2 Pathogenesis

The dramatically increased incidence of KS among persons with severe CD4 T-cell deficiencies led investigators to seek an infectious etiology of the tumor. In 1994, a novel human herpesvirus (human herpesvirus 8, HHV-8 or Kaposi sarcoma-associated herpesvirus) was shown to be the cause of KS (Chang et al. 1994). Subsequently, it has been observed that infection with HHV-8 is necessary, but not sufficient, for the development of KS. In the pre-cART era, only half of severely immunosuppressed individuals with HHV-8 infection developed KS (Martin et al. 1998), and in some regions of sub-Saharan Africa the majority of the general population is infected with HHV-8 but few go on to develop KS (Dollard et al. 2010). Although many aspects of the pathway to tumorigenesis have been worked out for KS, a number of gaps in the understanding of the pathogenesis remain.

Several epidemiologic patterns of KS have been recognized; these include classic KS (arising in elderly men in regions surrounding the Mediterranean Sea), endemic KS (arising in individuals in Africa before the AIDS epidemic or who are not infected with HIV), epidemic KS (associated with HIV infection), and transplantation-associated KS. It is now recognized that these are all forms of the same disease.

Acquisition and Dissemination of HHV-8

Behavioral, seroepidemiologic, and virologic studies have consistently underscored the importance of salivary transmission and acquisition of HHV-8 (Pauk et al. 2000; Casper et al. 2006). In areas where KS is not endemic, HHV-8 is most often acquired as a sexually transmitted infection after the time of sexual debut (Martin et al. 1998). In regions of the world where KS is endemic, HHV-8 is most often acquired in childhood with persistent acquisition into adulthood (Dollard et al. 2010). The timing of primary acquisition of HHV-8 may play an important role in determining

whether the infection will remain asymptomatic or progress to KS. Precedent with other viral infections, such as hepatitis B virus, shows that infection earlier in life may be associated with immune tolerance that is permissive of viral replication. HHV-8 replication is associated with a higher risk of developing KS (Engels et al. 2003), and therefore may explain why one of the two peaks in KS incidence in endemic regions occurs shortly after the time that HHV-8 is acquired.

Primary infection with HHV-8 likely occurs in oral epithelial cells (Pauk et al. 2000), and dissemination to other anatomic sites is thought to be an important next step in the progression to KS (Duus et al. 2004). Infection of circulating B lymphocytes may then lead to wider anatomic dissemination, which may in turn allow for infection of circulating endothelial cells (Browning et al. 1994; Della Bella et al. 2008; Taddeo et al. 2008). Endothelial cells are almost certainly the primary origin of the pathognomonic cell of KS tumor, the "spindle cell" (Carroll et al. 2004), though the absence of an animal model which completely recapitulates all of the features of the progression from primary viral infection to tumorigenesis makes definitive conclusions about the process challenging.

KS is an unusual tumor, in that it does not share some of the key characteristics of almost all other malignant tumors. First, while the spindle cell is central to the pathogenesis of the malignancy, it comprises the minority of many KS lesions and the neoplasm is always a heterogeneous mix of cell types. Inflammatory cells (B and T lymphocytes as well as monocytes) and vascular proliferations predominate. Spindle cells tend not to be clonal, cannot proliferate in culture in the absence of growth factors or in nude mice, and KS tumors are dependent on persistent HHV-8 replication for survival.

The development and maintenance of KS tumors is clearly therefore reliant on host, viral and environmental factors, as summarized below.

Viral Factors

Like all herpesviruses, HHV-8 has two genetic programs: the lytic stage, in which viral replication occurs, and the latent stage, in which the virus persists with expression of an extremely restricted number of gene programs (Paulose-Murphy et al. 2001). Latency is maintained through a tethering of the HHV-8 episome to the host chromosomes by the latency-associated nuclear antigen (LANA, or ORF73) (Renne et al. 1996). In addition to maintaining the viral genome through cell division, LANA and other viral latency genes play a clear role in carcinogenesis. LANA also inhibits traditional tumor suppressors (p53 and Rb) and up-regulates the expression of proto-oncogenes (Radkov et al. 2000). The viral FLICE-like inhibitory protein (v-FLIP) is anti-apoptotic (Djerbi et al. 1999), and v-Cyclin (Lundquist et al. 2003) and the Kaposins (Muralidhar et al. 1998) may contribute to neovascularization, disruption of the cell cycle, and inflammation. During lytic infection a larger number of viral genes are expressed. Key among the lytic viral genes for the initiation and propagation of the KS tumor includes the viral interleukin 6 analogue (v-IL6)

(Chatterjee et al. 2002) and the viral G-protein coupled receptor (v-GPCR) (Schwarz and Murphy 2001) which each increases angiogenesis in a number of different ways, and the viral ORFK15 that incites a pro-inflammatory cytokine and chemokine response permissive to KS tumors.

Genomic Heterogeneity

Human herpesviruses exact efficient and accurate replication of their DNA genome due in part to the presence of a proofreading DNA polymerase. However, the large size of the genome and the number of viruses produced in some portions of the lytic life cycle can lead to genomic heterogeneity (Zong et al. 2002). Distinct "strains" of HHV-8 can be detected between individuals that tend to cluster by geographic region, though within an individual are stable over time. These strains are determined based on sequencing small regions of one or a limited number of genes that are thought to be hypervariable. It is unclear as to how these genetic variations affect the clinical manifestations of disease, and this will be an interesting area for future research.

Co-infection

In the field of cancer biology, increasing attention is being paid to the microbial community in a given anatomic compartment and how that may alter the susceptibility to cancer within an individual. Both in vitro models and data from clinical cohorts support a role for co-infections to potentiate HHV-8 replication, which may in turn increase the odds of developing KS from asymptomatic infection. The HIV *Tat* protein increases the production of HHV-8 in culture (Aoki and Tosato 2004), and relationships have been established between the detection of HIV in the plasma and both the frequency of detection of HHV-8 at mucosal sites (Johnston et al. 2009) and the risk for development of KS over time. Taken together with epidemiologic evidence that HIV infection increases the risk of developing KS over that seen in immunocompromised transplant recipients (Grulich et al. 2007), the data are compelling that HIV co-infection strongly potentiates the development of KS. Similarly, cytomegalovirus co-infection increases HHV-8 replication (Vieira et al. 2001), though the clinical relevance of this interaction has not been established. Observations that HHV-8 lytic replication may be triggered by the engagement of toll-like receptors 7 and 8 (TLR 7/8) (Gregory et al. 2009), whose ligands are typically single or double-stranded RNA, raise the possibility that RNA viruses inhabiting the human virome could also play a role in KS tumorigenesis. No data to date has evaluated the role of the gut microbiome and predisposition to KS, but with the understood importance of the oral cavity in HHV-8 acquisition and dissemination, the preliminary evidence that oral inflammation is associated with HHV-8 oral replication, and increasing appreciation of the role of the oral microbiome in oral inflammation, further research is necessary to determine if there is an association between the microbiome and the susceptibility to KS.

Host Factors

Cellular Immunity

The inverse association between the incidence of KS and the quantity of CD4 T-lymphocytes in HIV-infected individuals highlights the importance of T cells in the biology of KS (Biggar et al. 2007), but to date the exact mechanisms by which T-cell deficiencies predispose to KS are not clear. Early studies were mixed, but overall found either a weak or no association between the absolute number of T lymphocytes and the risk of classic or endemic KS (Kestens et al. 1985; Touloumi et al. 1999). In the setting of HIV infection, weak CD4 T-cell responses to latent HHV-8 antigens can be detected, but have not been correlated with risk of developing KS (Sabbah et al. 2012). CD8 T-cell responses have been identified to both latent and lytic (Ribechini et al. 2006) HHV-8 antigens, with a suggestion that the LANA protein is immunodominant. Observations from small numbers of patients with KS show that cytotoxic T-cell responses in patients with KS are most robust after immune reconstitution with cART, and that an inverse relationship exists between robustness of cytotoxic T-cell response and the presence of HHV-8 in the peripheral blood (Bihl et al. 2009). Taken together, it is clear that while T-cell immunity is important in the pathogenesis of KS, other immunologic factors must also contribute.

Fewer studies have examined the role of B lymphocytes or NK cells in the development of KS. Reduced numbers of NK cells and impaired function has been observed with classic KS (Weltfriend et al. 1990), and deficits in NK cell function are restored after cART (Sirianni et al. 2002).

Humoral Immunity

Given the importance of HHV-8 replication in the development of KS, it is possible that control of viral replication with neutralizing antibodies could reduce the progression to KS. Reduced levels of neutralizing antibodies to HHV-8 are found in the peripheral blood of persons with KS compared with asymptomatically infected controls (Kimball et al. 2004). Neutralizing epitopes have not been identified.

Inflammation

The development of KS at sites of surgical incisions or trauma (the "Koebner phenomenon") has been held out as an example of the importance of inflammation in the development of KS (Niedt and Prioleau 1988). Worsening or newly emergent KS lesions have been described as a complication cART initiation, often attributed to "immune reconstitution inflammatory syndrome" (Achenbach et al. 2012). The detection of higher quantities of leukocyte esterase in the oral mucosa (traditionally a marker for the presence of inflammatory white blood cells from clinical specimens) was associated with high quantities of HHV-8 detected in that compartment (Casper et al. 2004).

While no studies to date have definitively characterized the inflammatory cytokines or "milieu" that may predispose to KS in vivo, careful study of HHV-8 has allowed a greater understanding of how inflammation may lead to KS. While the virus acts aggressively to down-regulate certain specific immune responses that could result in its elimination (i.e., Th1 responses), several viral proteins act to increase the Th2 response (chemokine ligands), recruit T lymphocytes to areas of HHV-8 replication, and subsequently produce inflammatory cytokines such as TNF-alpha, IL-6, etc. which may allow for the rapid development of the KS tumor (Weber et al. 2001). Additional research is needed to understand how differences in the inflammatory response to HHV-8 may lead to differential rates of progression to KS.

Environmental Factors

Given the widespread geographic and demographic variations in KS incidence, it is tempting to speculate that environmental factors may also modify the risk of developing KS from HHV-8 infection. However, epidemiologic studies to investigate these associations are challenging due to the relative rarity of the disease, the difficulty in finding comparable controls for cases in case–control studies, and even the absence of biologically plausible environmental factors to examine in such studies. There are few similarities in the environments of the diverse populations where KS is endemic, such as East Africa, Southern Italy, and Western China. However, exposure to iron-rich soil (Ziegler 1993; Iscovich et al. 2000), plants which produce phorbol esters, or arthropods (Coluzzi et al. 2003) have all been proposed as environmental risk factors for KS in at least one study. Perhaps more consistent is the strong association between the use of amyl nitrates ("poppers") and the risk of KS among the community of men who have sex with men in resource-rich regions (Beral et al. 1992; Armenian et al. 1993; Pauk et al. 2000). Again the biologic plausibility of this association has not been established and it remains possible that the use of amyl nitrates is a surrogate for another exposure that is the true cause of increased risk for KS.

Exploiting Knowledge of KS Pathogenesis for Clinical Therapeutics

The mainstay of treatment for KS currently is cytoreductive chemotherapy. While this treatment in many is highly effective, even in resource-rich settings the combination of chemotherapy and cART may leave residual disease in more than half of patients treated (Nguyen et al. 2008). Thus the knowledge gained from understanding the pathogenesis of KS can inform more effective and less toxic therapies for the disease. Strategies aimed at inhibiting HHV-8 replication have been ineffective in treating classic KS (Little et al. 2003; Krown et al. 2011), likely because current

antiviral drugs are only moderately effective in reducing HHV-8 replication (Casper et al. 2008; Cattamanchi et al. 2011), the possibility that these DNA synthesis inhibitors may still allow production of early viral gene products (Lu et al. 2004), and the fact that only the minority of cells in KS tumors contain lytically replicating virus (Grundhoff and Ganem 2004). Inhibition of angiogenesis was thought to be a promising target for these extremely vascular tumors, but results to date have been disappointing (Levine et al. 2006; Uldrick et al. 2012). Modulation of the inflammatory response has shown some evidence of success; interferon administration results in modest tumor response (Krown et al. 2006), interleukin-12 has shown activity in pilot studies, and more promise has been seen with the immunomodulatory drugs thalidomide and lenalidomide (Soler et al. 1996; Fife et al. 1998; Little et al. 2000; Martinez et al. 2011). Finally, drugs that inhibit specific pathways important for tumorigenesis such as matrix metalloproteinases (Cianfrocca et al. 2002; Dezube et al. 2006) and tyrosine kinases (Koon et al. 2005, 2014) have limited activity in small clinical trials. It is clear that due to the complexity of the disease process, the optimal therapy for KS will likely entail drugs that inhibit multiple targets and future studies will need to define optimal treatment strategies.

9.3 Presentation

KS is a disease with diverse clinical manifestations. An HHV-8 "primary infection syndrome" has been described in African children (Andreoni et al. 2002), transplant recipients (Luppi et al. 2000), and HIV-negative men who have sex with men (Wang et al. 2000), typically consisting of fever, cytopenias, and cutaneous manifestations (rash or even KS), but it is thought that the majority of cases of incident KS occur some time after primary infection. In resource-rich regions where the HIV epidemic has matured, KS often presents in patients who have either been marginalized from HIV care or who are not able to adhere to HIV therapy, though occasionally is identified as the AIDS-defining illness. In resource-poor areas, KS often is the diagnosis which prompts HIV testing, but may also be identified among patients participating in HIV care programs. In resource-rich regions, KS most commonly presents at low CD4 T-cell counts (Biggar et al. 2007), though the disease is increasingly being identified in persons with higher CD4 counts and suppressed HIV replication (Maurer et al. 2007). In places where the tumor was endemic prior to the HIV pandemic, the range of CD4 counts for persons presenting for care appears to be wider than what has been reported in the USA and Europe (Phipps et al. 2010; Mosam et al. 2012). In the USA, Europe, and Australia, epidemic KS is predominantly a disease of men, whereas in sub-Saharan Africa epidemic KS cases in women are beginning to approximate the number seen in men (Mbulaiteye et al. 2006; Parkin et al. 2010).

Patients typically present with mucocutaneous disease, though many may have co-existing visceral disease, most typically involving the lungs or gastrointestinal tract. cART has modified the presenting manifestations of KS from what was initially described in the early HIV epidemic (Nasti et al. 2003).

Mucocutaneous KS

The morphotypes and distribution of mucocutaneous KS appear to vary by demographic and geographic populations. In the USA, Europe, and Australia, epidemic KS classically presents as an erythematous patch, progressing to a violaceous plaque or macule, and often on to a larger nodule. These lesions can be distributed virtually anywhere on the body. The oropharynx is the most common mucosal surface involved, and the tumor typically involves the hard palate and less commonly the soft palate, gingiva, and tongue. Especially in sub-Saharan Africa, additional morphotypes of KS are seen, including fungating and infiltrative disease. Perhaps due to the tendency to present with more advanced disease or the challenges of diagnosing the disease among persons with darkly pigmented skin, the patch morphology is infrequently observed as a presenting manifestation of KS in the region, but may come to predominate following treatment. Also of note in sub-Saharan Africa are the differences in clinical presentations between women and men, with women more often having disease which involves the face and less commonly involving the lower extremities (Phipps et al. 2010).

Although the diagnosis of mucocutaneous KS is often made clinically, even astute clinicians may incorrectly ascribe a different disease process to KS. Definitive diagnosis is rendered through biopsy, where histopathology reveals the classic spindle cells and, where available, in resource-rich regions in situ hybridization for HHV-8 proteins (most often LANA) can provide confirmation to the visual histology.

Visceral KS

Up to 40 % of HIV patients presenting with KS had visceral disease identified in the early HIV pandemic in the USA, but this number has decreased substantially in the era of cART (Nasti et al. 2003). Visceral disease is not routinely or exhaustively sought in the workup of patients with cutaneous KS in either resource-rich or resource-poor regions, so the true prevalence of disease is not known. Presenting manifestations of visceral KS are most commonly hemoptysis or hematochezia, representing pulmonary and gastrointestinal disease, respectively. Early staging systems for KS, which were subsequently validated later in the HIV pandemic, confirm that visceral disease portends a poorer prognosis (Krown et al. 1997). Diagnosis of pulmonary KS is established by bronchoscopy—because biopsy of lesions may be associated with hemorrhage, the detection of HHV-8 by polymerase chain reaction has been proposed as both a sensitive and specific alternative (Tamm et al. 1998). Conversely, diagnosis of gastrointestinal KS is best established through biopsy or reliance on morphologic appearance in the appropriate clinical setting. Involvement of lymph nodes is also common, and KS in inguinal lymph nodes is often associated with substantial edema of the lower extremities.

Pediatric KS

Epidemic KS among children is uniquely described in sub-Saharan Africa. Interestingly, disease in HIV-positive children most commonly presents with lymphadenopathic involvement and mucosal disease is less common (Gantt et al. 2010). The median presenting CD4 T-cell count is substantially higher than what has been reported in adults, and outcomes tend to be poor.

KS as a Manifestation of IRIS

The exacerbation or novel presentation of KS among persons initiating cART has now been well described in both the USA and sub-Saharan Africa, with the incidence ranging from ~4 % of persons in the USA (Achenbach et al. 2012) to one-third of persons in Uganda (Martin et al. 2009). The predictors of developing KS-IRIS and the complete clinical manifestations are still being identified, though cases of fatal KS-IRIS complicated by systemic inflammatory syndrome, multiorgan system failure, and death have been reported (Crane et al. 2005).

Associated Co-morbidities

KS represents one of several HHV-8-associated diseases, including multicentric Castleman disease (MCD), primary effusion lymphoma (PEL) and the recently described Kaposi sarcoma-associated herpesvirus inflammatory cytokine syndrome (KICS) (Uldrick et al. 2010). Not surprisingly, immunocompromised patients with HIV may present with more than one of these illnesses. KS accompanies up to 1/3rd of cases of MCD, and although PEL and KICS are too rare to develop accurate estimates of the frequency of co-presentation with KS, clinical reports suggest it commonly occurs.

Outcomes After Diagnosis of KS

KS is a disease that when treated early and aggressively is infrequently fatal, but as noted above responses to therapy are uncommonly complete and advanced disease still is associated with a poor prognosis. In the current cART era in the USA, a diagnosis of mucocutaneous KS is associated with a 2-year overall survival of 85 %, but visceral disease reduces the 2-year overall survival to 64 % (Achenbach et al. 2011). In the pre-cART era in Uganda, less than 10 % of patients with HIV-associated KS survived 5 years (Gondos et al. 2005), though more recent data suggests that survival approximates what has been described in the USA.

9.4 Conclusions

More than three decades after the resurgence of KS accompanied the HIV pandemic, the disease remains a common complication of HIV infection worldwide. Years of steady research have led to great leaps in the understanding of KS pathobiology and facilitated better treatments for the disease, but significant gaps in knowledge preclude the development of highly effective and implementable prevention and treatment strategies. Continued efforts are needed to comprehensively reduce the morbidity of KS.

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Chapter 10
Management of AIDS-Related Kaposi Sarcoma

Susan E. Krown

Abstract Kaposi sarcoma (KS) is a multifocal angiogenic neoplasm whose development requires systemic infection with a human herpesvirus, known as human herpesvirus-8 (HHV-8) or the KS-associated herpesvirus (KSHV). KSHV infection is required for development of this neoplasm, but KS occurs in only a fraction of KSHV-infected individuals. Although KS lesions may arise in the absence of overt immunodeficiency, defects in endogenous viral control mechanisms increase the likelihood that KS will develop. KS is thus more frequently observed among individuals with underlying conditions, such as HIV infection, that impair antiviral immune responses, and is considered an AIDS-defining condition when it occurs in an HIV-infected person. In formulating a management strategy for KS in HIV-infected individuals, two main aspects of the disease need to be considered: (1) The extent of dissemination of KS and the extent to which it impairs the functional status and quality of life of the affected individual; and (2) The degree to which HIV infection is suppressed and the options available for improving HIV control and immune function.

10.1 Introduction

Kaposi's sarcoma-associated herpesvirus (KSHV), like other human herpesviruses, persists in host cells in a latent form (Klass and Offermann 2005). Available treatments are not able to eradicate human herpesvirus reservoirs, so any therapeutic approaches—either directed at KSHV or at the resulting KS lesions—must currently be considered palliative. There are, however, treatments that can be successfully utilized to control KS tumors either via direct effects on tumor cell growth or indirectly, by stimulating host antitumor and antiviral defenses, and in some

S.E. Krown, M.D. (✉)
AIDS Malignancy Consortium, New York, NY, USA
e-mail: krowns@mskcc.org

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instances it is possible to eradicate all discernable disease. In AIDS-associated KS, combining both therapeutic approaches is often the best way to manage tumor-associated morbidity.

10.2 Evaluation of the Patient

Diagnostic Tests

A definitive diagnosis of KS requires biopsy and pathological examination of a suspected lesion. Although an experienced clinician may diagnose KS presumptively based on the appearance of typical red or violaceous skin or mucous membrane plaques, patches or nodules, other pigmented vascular lesions (e.g., bacillary angiomatosis; pyogenic granuloma) may look similar to KS, particularly in darker-skinned individuals, so biopsy is indicated in all cases of suspected KS. Immunohistochemistry using antibodies to KSHV-associated proteins (e.g., latency-associated nuclear antigen, LANA-1) and/or antibodies to endothelial cell proteins (e.g., CD-31) can help confirm the diagnosis of KS, and is particularly useful for determining the nature of vascular lesions showing atypical histopathology (O'Donnell et al. 2010).

Documenting the extent of disease is required for KS staging and monitoring the response to treatment. The extent of KS varies widely; some individuals may present with a few, inconspicuous skin lesions and show minimal or no progression over time, whereas others may show widespread skin and/or visceral disease and rapid development of new lesions. Evaluation includes a medical history, review of systems (including functional impairments related to the presence of edema, oral lesions, ulcerated skin lesions, pulmonary and/or gastrointestinal lesions) and careful examination of the entire skin surface, including the feet, the external genitalia, the scalp and ears, documentation of lesional ulceration, examination of the oral cavity, assessment of lymph node enlargement and edema, and a rectal examination, including testing of a stool specimen for the presence of occult blood. KS-associated edema is typically non-pitting; edema is most common on the lower extremities, but may involve the genitals, the periorbital area (with resulting visual impairment), the upper extremities, and the trunk. A chest X-ray should be performed in all patients to evaluate for parenchymal lesions or effusions. Computerized tomography (CT) or magnetic resonance imaging (MRI) of the chest may provide better definition of parenchymal KS lesions (Restrepo et al. 2006). In some cases where pulmonary symptoms are prominent but the results of radiographic studies are normal or equivocal, bronchoscopy may disclose endobronchial KS lesions. Bronchoscopy may also be helpful in diagnostically challenging situations where pulmonary KS and opportunistic infections co-exist or when imaging of the lung is suggestive of KS in a patient who does not have other evidence for KS. Patients should be questioned about the presence of gastrointestinal symptoms (pain, dysphagia, symptoms of

Table 10.1 Kaposi sarcoma staging classification

	Good risk (0) (all of the Following)	Poor risk (1) (any of the following)
Tumor (T)	Confined to skin and/or lymph nodes and/or minimal oral disease[a]	Tumor-associated edema or ulceration Extensive oral KS Gastrointestinal KS KS in other non-nodal viscera
Immune system (I)	CD4 cells ≥200/μL	CD4 cells <200/μL
Systemic illness (S)	No history of opportunistic infection (OI) or thrush No "B" symptoms[b] Performance status ≥70 (Karnofsky)	History of OI and/or thrush "B" symptoms present Performance status <70 Other HIV-related illness (e.g., neurological disease, lymphoma)

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[a]Minimal oral disease is non-nodular KS confined to the palate

[b]"B" symptoms are unexplained fever, night sweats, >10 % involuntary weight loss, or diarrhea persisting more than 2 weeks

obstruction or bleeding). If positive, or if the stool shows the presence of occult blood, upper and/or lower gastrointestinal endoscopy may demonstrate typical KS lesions. Such lesions may be submucosal and difficult to biopsy, but some lesions, particularly superficial or ulcerated lesions, may show KS on histopathologic examination. Routine gastrointestinal endoscopy in the absence of gastrointestinal signs or symptoms is not indicated. As a rule, contrast-enhanced plain radiographs or scans are not useful in evaluating and managing gastrointestinal KS.

Unless lymph node enlargement is particularly prominent or asymmetric, biopsy of lymph nodes to diagnose KS is not indicated, as the finding of incidental KS in lymph nodes has no bearing on prognosis (Myskowski et al. 1988). Even in the presence of proven lymph node KS, regional lymph node dissection is not indicated. Similarly, wide surgical excision of cutaneous KS lesions is not indicated as it does not prevent local or distant KS spread, and surgical excision should be reserved for diagnostic purposes or for the rare isolated lesion that is either cosmetically disfiguring or causing local symptoms (e.g., an isolated, pedunculated lesion of the foot that is bleeding).

Staging

Several staging classifications have been proposed for KS in the presence and absence of HIV infection. The classification used most commonly to describe HIV-infected individuals was described by the AIDS Clinical Trials Group in 1989 (Table 10.1) (Krown et al. 1989) and subsequently validated as a predictor of survival based on data obtained in the "pre-HAART" era between 1989 and 1995

(Krown et al. 1997). The staging system, often referred to as the TIS (for Tumor/Immune System/Systemic Illness) or ACTG classification, categorizes the disease as "good risk" (denoted by subscript 0) or "poor risk" (denoted by subscript 1) based on tumor extent, CD4 count as a measure of immune system function, and the presence or absence of systemic manifestations of HIV infection. A subsequent analysis of the utility of the TIS classification in predicting survival in the "post-HAART" era (Nasti et al. 2003) showed that the presence of poor-risk tumor features, particularly the presence of pulmonary KS, in combination with poor-risk HIV-related symptoms (i.e., low performance status, history of other AIDS-defining illness, unexplained night sweats, fever, weight loss, diarrhea) (T_1S_1), defined an especially poor-risk group of patients with a significantly shorter survival than those patients with good-risk tumor features and/or absence of poor-risk HIV-related symptoms (T_0S_0, T_1S_0, or T_0S_1).

Response Assessment

Evaluating the efficacy of treatments for KS presents unique challenges. Cutaneous KS lesions are often multiple, closely spaced or confluent, irregularly shaped, and show varying degrees of nodularity, making accurate assessments of tumor size difficult. Lung lesions are often irregular and poorly defined. Gastrointestinal lesions often require invasive procedures, such as endoscopy, for detection and evaluation, and assessments of lesion numbers and size are only semi-quantitative. Tools that attempt to assess patient benefit with respect to relief of KS-related symptoms (e.g., pain, edema, respiratory symptoms) have been developed, but thus far have not been validated as surrogates for objective response or survival. In fact, the results of some studies have suggested that even among individuals not meeting the criteria for objective tumor response, chemotherapy may provide clinical benefits with respect to KS-related symptoms, although symptomatic improvement may also reflect the long-term benefits of co-administered cART (Cianfrocca et al. 2010).

10.3 Therapeutic Options

Developing an Overall Treatment Strategy

The extent and rate of progression of KS lesions is quite variable, as is the severity of tumor-related symptoms, organ dysfunction, and quality of life. The presence of KS may, by itself, be life-threatening (e.g., when there is extensive lung involvement or gastrointestinal bleeding). More commonly, however, KS contributes to morbidity by way of physical manifestations (e.g., by causing pain, difficulty walking, or predisposing to cellulitis of edematous extremities) or by the emotional

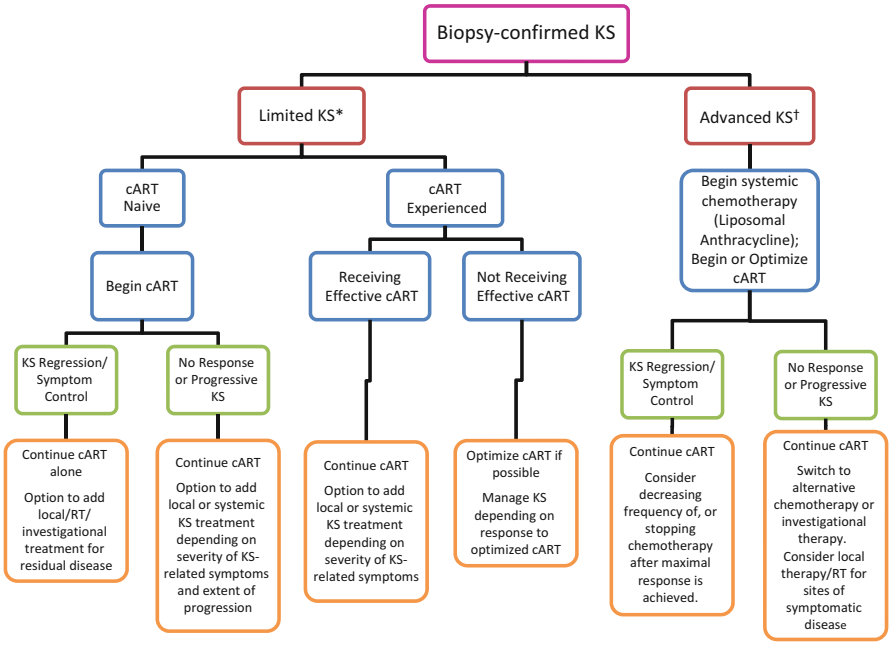

Fig. 10.1 KS therapeutic strategy decision tree. *Limited KS is KS confined to the skin and/or lymph nodes and/or non-nodular palatal KS, not causing significant disfigurement or interfering with function, and without symptomatic tumor-associated lymphedema, tumor ulceration, pulmonary KS, or other symptomatic visceral KS. †Advanced KS includes cutaneous KS that is ulcerated, disfiguring, or rapidly progressive; oral KS that is nodular or involves structures other than the palate; symptomatic tumor-associated lymphedema; any pulmonary KS; symptomatic or bulky KS in other visceral sites

distress and social stigma occasioned by the presence of highly visible or disfiguring lesions. In some cases, KS may be an incidental finding that contributes to neither mortality nor morbidity. In individuals with HIV-associated KS, there is also variation in the severity of immunosuppression, the degree to which HIV replication is controlled, and the presence and severity of HIV-related symptoms and other comorbid conditions, including opportunistic infections, wasting, cytopenias, HIV-related or HIV-unrelated organ (e.g., heart, kidney, liver, pulmonary) dysfunction that may influence the available therapeutic options and overall prognosis. Thus, treatment for AIDS-associated KS must be individualized according to the specific disease features in a given individual. In addition, because there is no treatment for KS that can be said to be curative, and because a variety of potential management options with different side effects and therapeutic potential may be available for a given patient, the patient's personal goals must be considered in devising a course of treatment. A basic overall schema for developing a therapeutic approach for AIDS-associated KS is outlined in Fig. 10.1.

HIV Management

The widespread introduction in 1996 of combination antiretroviral therapy (cART) capable of inducing long-term suppression of HIV replication and restoration of immune function was associated with a marked reduction in the incidence of opportunistic diseases including KS. In addition to its well-established role in KS prevention, cART, often referred to as highly active antiretroviral therapy (HAART), is considered a critical component of the effective management of HIV-infected patients with an established KS diagnosis. In some cases, particularly when KS is diagnosed in antiretroviral-naïve patients or when it occurs in the setting of suboptimal HIV suppression and immune reconstitution by ART, initiating effective cART or optimizing the cART regimen may, by itself, lead to KS regression (Cattelan et al. 1999; Lebbé et al. 1998; Krown 2004). The decision of whether to attempt to treat KS in such individuals with cART alone, or to use cART together with other KS-directed treatments (e.g., chemotherapy), depends on how widely disseminated the KS lesions are and the degree to which they impair function and quality of life. HIV-infected patients diagnosed with or suspected to have KS should be evaluated by an oncologist, preferably one familiar with KS evaluation and management options, very early in the course of the disease, to facilitate treatment planning and follow-up. There is general consensus that attempts to manage KS with cART alone should be confined to individuals with limited, asymptomatic, or minimally symptomatic KS that does not involve visceral organs. Among patients with advanced KS, there is evidence that the combination of cART with cytotoxic chemotherapy results in a higher rate of KS regression and a longer response duration than that afforded by cytotoxic chemotherapy alone (Bower et al. 1999).

Several mechanisms may be involved in cART-induced KS control, but their relative contributions are unknown. These include overall improvements in immune function leading to generation of specific anti-KS responses, and inhibition of HIV-1 proteins, angiogenic growth factors and cytokines that are thought to be important in KS development and progression (Bihl et al. 2007; Bourboulia et al. 2004; Stebbing et al. 2003). In addition, there is in vitro evidence that several HIV protease inhibitors may interfere with tumor growth and angiogenesis through mechanisms that are independent of their effects on HIV infection. One protease inhibitor, nelfinavir, has also been shown to directly inhibit KSHV replication in vitro (Gantt et al. 2011). However, the extent, if any, to which HIV protease inhibitors provide benefit to KS patients over and beyond their effects on HIV is not yet known.

Local Treatments

Several methods that aim to control individual KS lesions by the topical application or intralesional injection of antineoplastic agents may be considered for management of selected patients with limited, non-bulky, slowly progressive cutaneous KS.

Local treatments avoid many of the side effects associated with systemically administered therapy and often provide acceptable cosmetic results, sometimes after single or short-term treatment courses. However, these approaches may be associated with local inflammatory skin reactions, pain, and changes in skin pigmentation, prolonged treatment or re-treatment may be required, and there is no expectation that local lesion control will impede the development of new KS lesions in untreated areas.

Of the available local treatment options for KS, only alitretinoin 0.1 % gel, applied to cutaneous KS lesions two to four times daily has been specifically approved by the U.S. Food and Drug Administration (FDA) for this purpose (Walmsley et al. 1999; Duvic et al. 2000; Bodsworth et al. 2001). Although improvement of treated lesions has been observed as early as 2 weeks after starting alitretinoin, much longer treatment courses may be required and treatment durations of up to 96 weeks have been described. Other commonly used local approaches include liquid nitrogen cryotherapy (Tappero et al. 1991) and intralesional injections of vinblastine (Boudreaux et al. 1993). The results of several other intralesional treatments have been described in small clinical trials, including recombinant interferon alfa (Depuy et al. 1993), granulocyte-macrophage colony-stimulating factor (Boente et al. 1993), platelet factor 4 (Staddon et al. 1994), and human chorionic gonadotropin (Gill et al. 1996a), but none of these has been widely adopted in clinical practice. Photodynamic therapy, in which photosensitization of KS lesions is achieved using topical or systemically administered photosensitizers and tumor cell killing is achieved by subsequent irradiation with light from a laser, has also been reported to induce local KS lesion regression (Bernstein et al. 1999), as has the topical administration of imiquimod 5 % cream.

Radiation Therapy

KS lesions are highly radiosensitive. Radiation therapy (RT) has most often been used to treat cutaneous or oral KS lesions, but has also been used rarely in the past to palliate complications of advanced, visceral KS, including bleeding gastrointestinal lesions and extensive pulmonary lesions (Berson et al. 1990; Meyer 1993). Although small-field, single-fraction or multi-fraction irradiation with superficial electron beams has been used as a local approach to treat individual KS skin lesions (Stelzer and Griffin 1993), photon beam RT is more commonly used in the management of more widespread disease such as extensively involved lower extremities, with or without associated lymphedema (Berson et al. 1990). Although often effective in achieving local lesion control, patients frequently develop long-term cutaneous changes including a woody appearance and pigmentation changes and, as with other local approaches to therapy, there is no expectation that control of individual treated lesions impedes the development of new KS lesions in untreated areas. An increased risk of mucosal radiation toxicity was described in the era before the introduction of cART, but there is scant data recent data on the subject.

With the introduction of cART and the subsequently reduced incidence of advanced KS, the need for RT has declined. In addition, since other systemic treatments, including chemotherapy, are well tolerated and highly effective for treating widespread KS, RT is now generally used only as palliative treatment in individuals with KS that is limited in extent but causing local symptoms (Housri et al. 2010) or in those in whom other treatment alternatives have failed or are not appropriate because of poor performance status or co-morbidities.

Systemic Chemotherapy

Systemic chemotherapy is indicated for the management of advanced KS. Advanced KS can be broadly defined as encompassing widespread, symptomatic, and/or rapidly progressive cutaneous KS, including (but not limited to) fungating and/or ulcerated lesions and lesions that cause pain or disfigurement; extensive, nodular oral KS; symptomatic KS-associated lymphedema; pulmonary KS, including endobronchial or parenchymal lesions, and tumor-associated pleural effusion; and symptomatic gastrointestinal KS, causing pain, obstruction and/or bleeding. The successful and safe treatment of KS in the HIV-infected patient requires cognizance of and careful monitoring for the multiple overlapping toxicities and potential drug–drug interactions between chemotherapy drugs, antiretroviral agents, and drugs used to treat other HIV-related complications, and close cooperation between the primary HIV care provider and the oncologist (Rudek et al. 2011).

KS is highly sensitive to multiple chemotherapeutic agents, many of which were shown to induce regression of classic KS and/or African endemic KS long before AIDS-associated KS was first described. However, only three chemotherapeutic agents have been approved by the United States FDA specifically for use in AIDS-associated KS. These include two liposomal anthracyclines (pegylated liposomal doxorubicin and liposomal daunorubicin) and paclitaxel (Gill et al. 1996b; Stewart et al. 1998; Northfelt et al. 1998; Welles et al. 1998; Gill et al. 1999; Krown 2008). Most oncologists experienced with treating AIDS-associated KS have favored pegylated liposomal doxorubicin as first-line chemotherapy based on observed rates of tumor regression and symptom palliation, good tolerance over long treatment courses and convenient treatment schedule (one dose every 3 weeks). Paclitaxel is also highly effective (Welles et al. 1998; Gill et al. 1999), but is more frequently associated with peripheral neuropathy, asthenia, and alopecia than liposomal anthracyclines and is primarily used as second-line therapy after anthracycline failure or anthracycline-related toxicity.

Although not specifically FDA approved for KS treatment, activity against AIDS-associated KS has been reported for various other chemotherapy drugs used alone (bleomycin, docetaxel, doxorubicin, epirubicin, etoposide, gemcitabine, vinblastine, vincristine, and vinorelbine) or in combination (e.g., the ABV regimen in which doxorubicin (Adriamycin) is combined with bleomycin and vincristine; bleomycin

and vincristine without doxorubicin; alternating cycles of vincristine and vinblastine) (Kaplan et al. 1986; Krown 2008). Of these agents, only etoposide has shown anti-KS activity when administered by the oral route (Paredes et al. 1995; Evans et al. 2002). The relative efficacy of these drugs in KS is difficult to estimate because they were studied primarily in the pre-cART era in uncontrolled, non-randomized trials that employed different methods to document extent of disease and in which response definitions were sometimes ambiguous and inconsistently applied.

The optimal duration of chemotherapy has not been well defined. In advanced KS, durable tumor control usually is dependent not only on the achievement of cytoreduction with chemotherapy, but also on the extent to which immunocompetence is restored with antiretroviral therapy. Prior to the availability of cART, significant tumor regression was often observed after chemotherapy for AIDS-associated KS, but the duration of remission was usually short after chemotherapy was stopped. Once effective cART became available, however, it was often possible to discontinue chemotherapy after achieving KS regression without the rapid re-growth of the KS lesions. In some cases, tumor regression continues after chemotherapy is discontinued. These observations support the concept that cytotoxic chemotherapy is not expected, by itself, to cure KS, and support the practice of stopping or decreasing the frequency of chemotherapy after stabilization of the lesions, control of tumor-related symptoms and improvement in quality of life, rather than continuing cytotoxic treatment indefinitely and on a predefined schedule until complete tumor regression is achieved. Although KS may subsequently progress after stopping chemotherapy, it is not uncommon for tumors to regress again when chemotherapy (often with the same drug that initially induced tumor regression) is reinstituted; this suggests that tumor progression does not result from the acquisition of mutations that confer chemotherapy resistance.

Interferon Alfa

Recombinant interferon alfa (IFN-α) preparations were the first agents specifically tested and FDA approved for treatment of AIDS-associated KS in the 1980s, on the basis of studies performed prior to the availability of cART (Krown 2007). Although infrequently used to treat KS for the past decade or more, primarily because of its side effects, the need for frequent parenteral administration, and the introduction of other, easier to administer and more highly effective agents like liposomal doxorubicin, the sometimes remarkable activity of IFN-α against KS is noteworthy, and probably reflects the net result of its multiple potential effects on this neoplasm, which include inhibitory effects on viruses (including HIV and KSHV) and on cell growth and function, including abnormal angiogenesis. Many of these potential mechanisms of IFN action are being investigated in studies of investigational agents that more narrowly target proteins and signaling pathways that are overexpressed or activated in KS.

Investigational Approaches

The growing knowledge of KS pathobiology has provided multiple opportunities to evaluate rational targeted therapies using novel agents. Several preliminary studies have shown the potential promise of this approach. Among the agents for which there is preliminary evidence for anti-KS activity are: drugs such as imatinib, that interfere with tyrosine kinase-mediated transmembrane receptor signals for angiogenic growth factors that are overexpressed in KS lesions (Koon et al. 2005); mTOR inhibitors, such as rapamycin (sirolimus), that target the constitutively activated Akt/mTOR signaling pathway in KS (Krown et al. 2012); and interleukin-12, a cytokine that enhances type 1 immunity, mediates antiangiogenic effects, and can downregulate a constitutively active G-protein coupled receptor that is encoded by KSHV (Yarchoan et al. 2007). These and other agents, such as those that can reverse KSHV latency (Lechowicz et al. 2009) and induce apoptosis of infected cells, and immunomodulators such as thalidomide and its derivatives (Fife et al. 1998; Little et al. 2000), require further formal testing.

Diagnosis and Management of KS-IRIS

Starting cART in the setting of advanced HIV infection has been associated, in some cases, with an apparently paradoxical appearance or worsening of various opportunistic diseases, including KS, during immune system recovery. This process, known as immune reconstitution inflammatory syndrome (IRIS), has been reported to occur in a variable proportion of patients with KS. The frequency with which KS-IRIS develops is the subject of some debate, and may vary in different patient populations. Estimates for the frequency of KS-IRIS have been much higher, for example, in sub-Saharan Africa than in the USA. One difficulty in interpreting the literature on the frequency of KS-IRIS is the lack of a consistent, predefined case definition (Letang et al. 2012). Reports of KS-IRIS have not used standard, rigorously defined criteria for KS progression, and the time interval after initiation of cART during which progression occurred and the degree to which CD4 counts must have increased and to which HIV viral load must have been suppressed has not been uniform.

The optimal management of patients suspected to have KS-IRIS has not been well studied. As a general rule, cART should be continued, and the patient should be evaluated for the presence of opportunistic infections that may have precipitated worsening of KS. Institution of nonsteroidal anti-inflammatory agents may be considered, but there is general consensus that the use of corticosteroids should be avoided whenever possible because they may exacerbate KS progression. The decision to institute or modify systemic chemotherapy in patients with suspected KS-IRIS needs to be individualized. In some cases, KS has been reported to stabilize and eventually regress with continued cART treatment, without addition or modification of KS-specific therapy. In other cases, however, KS may rapidly progress with

symptomatic edema and life-threatening involvement of vital visceral organs. In such individuals, prompt institution of systemic chemotherapy may be life-saving.

KS Management in Resource-Limited Settings: Special Considerations

The foregoing remarks on KS management apply to the experience in well-resourced settings where both cART and large numbers of cancer therapeutic agents have been widely available for many years, rates of KSHV infection and KS tumors are relatively low, and many patients present with KS of limited extent. By contrast, the vast majority of AIDS-associated KS cases worldwide occur in low-resource settings, primarily in sub-Saharan Africa, where rates of KSHV infection are much higher than in the USA and Europe, access to cART is more restricted, the diagnostic and therapeutic armamentaria and the options for supportive care for treatment-related complications are constrained, and co-morbid conditions, such as tuberculosis, are common. These factors may affect the choice and tolerance of KS therapy. Moreover, in such settings, KS often is diagnosed at an advanced tumor stage.

Although much has been published on the epidemiology of KS in HIV-infected adults and children in sub-Saharan Africa, there have been few prospective studies to assess KS management strategies in this setting. Some initial reports suggest that chemotherapy with agents commonly available in this setting (i.e., bleomycin and vincristine, with or without concomitant, non-liposomal doxorubicin) provides benefit to patients receiving concomitant cART (Borok et al. 2010; Mosam et al. 2012). Studies to compare the ability of different treatments to induce KS regression, the impact of therapy on survival and quality of life (including effects on KS-associated signs and symptoms, the frequency of drug-related toxicities, and effects on HIV control), prognostic factors, ease of administration of therapy (which may have an impact on therapeutic adherence), and cost effectiveness are needed to address these important management issues.

10.4 Conclusion

KS is the most common HIV-associated malignancy worldwide. In high-resource settings, its incidence has declined since the widespread availability of cART, but KS still represents a therapeutic challenge in a subset of individuals, including some with well-controlled HIV infection. A variety of strategies that include cART, either alone or in combination with other therapeutic modalities, are available for management of such patients, and in many cases can control lesion growth and KS-related symptoms. However, currently available treatments must be considered palliative, as none have been shown to eradicate KSHV, the causal virus required for KS development. In lower resource settings, in particular sub-Saharan Africa, the incidence

of HIV-associated KS remains high. Although many of the same considerations that figure in developing an approach to management of KS in well-resourced settings apply to management decisions in lower resource areas, the availability of therapeutic agents and supportive care is more limited, the incidence of other co-morbid illnesses is higher, and the tumor itself may be intrinsically more aggressive in African patients, so the optimal therapeutic approach may be different in this setting.

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Part IV
HIV-Associated Lymphomas and Lymphoproliferative Diseases

Chapter 11
Presentation and Pathogenesis of B-Cell Lymphoid Cancers Associated with HIV Infection

Richard F. Little, Stefania Pittaluga, and Kieron Dunleavy

Abstract B-cell lymphomas associated with HIV infection refer to a spectrum of lymphoid neoplasms whose incidence is increased in patients with HIV infection. These include AIDS-defining lymphomas, which confer a diagnosis of AIDS when they occur in an HIV-infected individual, as well as other lymphomas that are associated with HIV infection but do not confer an AIDS diagnosis. There is evidence that the immunologic milieu and the inflammatory state induced by HIV proteins are integral to the pathogenesis of these neoplasms. Effective combination antiretroviral therapy modulates these pathophysiologic features and effects changes in both tumor epidemiology and biology. Improved outcomes in patients with these tumors are based not only on improved prospects for HIV disease control but also due in part to more treatment-sensitive tumors that are more likely to develop when there is better preserved immune function. This chapter reviews the epidemiology and tumor pathology supporting this thesis. An additional and essential concept forwarded by this chapter is that AIDS-related lymphoma is no longer a clinically meaningful term, and the importance of modern lymphoid tumor classification is highlighted.

R.F. Little, M.D. (✉)
Clinical Investigations Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI), Bethesda, MD, USA
e-mail: littler@mail.nih.gov

S. Pittaluga, M.D.
Laboratory of Pathology, Center for Cancer Research (CCR), Bethesda, MD, USA
e-mail: stefpitt@mail.nih.gov

K. Dunleavy, M.D.
Lymphoid Malignancy Branch, CCR, NCI, Bethesda, MD, USA
e-mail: DunleavK@mail.nih.gov

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11.1 Introduction and Overview

During the late 1970s and early 1980s, marked changes in the typical occurrence and clinical behavior of aggressive B-cell lymphomas were among the initial manifestation of the new epidemic disease that ultimately became known as the acquired immunodeficiency syndrome, AIDS. The original Centers for Disease Control and Prevention case definition expanding the definition in 1982 of AIDS to include lymphoma specified that a patient with HIV and an aggressive B-cell lymphoma would carry an AIDS diagnosis. Several years later this definition was expanded to include intermediate grade B-cell lymphomas. The study and treatment of AIDS-related lymphoma (ARL) consequently suffered from a poorly structured case definition terminology that failed to classify distinct lymphoma types. Instead, ARL was almost thought of as a single disease. ARL were designated as AIDS indicator conditions, meaning that ARL conferred an AIDS diagnosis when it was the initial manifestation of the syndrome. As the case definition of AIDS evolved over time, the percentage of lymphoma indicator cases shifted downward somewhat as other indicator conditions were more likely to occur before ARL. For example, if another antecedent AIDS indicator condition, such as CD4 cell count falling below 200/mm^3, had already been documented, ARL would likely go unreported. The total burden of lymphoma cases in those who already have an AIDS diagnoses is estimated to be up to 25 %. About 3 % of those with HIV come by their AIDS diagnosis due to ARL.

Early in the AIDS epidemic, prior to the discovery of HIV, immunologic derangement was recognized as the common pathophysiologic event leading to both infectious and neoplastic disease complications. In the ensuing 30-plus years, the epidemiology of the common AIDS complications has evolved dynamically, owing largely to the availability of effective combination antiretroviral therapy (cART). At the same time, the approaches to lymphoid tumor biology and lymphoma classification have been revolutionized as the science has advanced. The epidemiologic patterns of ARL in the pre-cART and cART eras and the improved lymphoid tumor classification schema provide important clues to ARL presentation and pathology. This chapter will review the highlights of HIV-related lymphoid tumor epidemiology and pathophysiology that have been described in the context of the still evolving AIDS epidemic. Although the formal AIDS case definition does not include all the lymphoma types discussed in this chapter, the broader range of lymphoid tumors occurring in those with HIV infection will be presented under the designation of ARL.

A critical concept to appreciate is that ARL is not a clinically or biologically specific term. There are specific ARL entities each of which requires clinical management approaches specific to the ARL type. Expert hematopathology consultation is thus required to ensure accurate diagnosis and enable the delivery of optimal therapy. Owing to substantially improved prospects for near normal lifespan with effective management of HIV infection, curative treatment for ARL should be considered in most cases.

Mounting evidence suggests the immune status plays a substantial role in the type of ARL that develops. This evidence is comprised of studies of the epidemiology, pathobiology, and clinical studies in ARL. As immunodepletion advances, the risk of ARL increases. Moreover, the type of ARL likely to manifest is related to the degree and duration of HIV replication and immunosuppression. Highlighting this is the marked shift in the occurrence of certain lymphoid tumor types that has been observed in populations where cART is widely used. The ARL epidemiology in such populations diverges markedly from that of pre-cART historic controls and from those populations without widespread access to cART. Cataloging the specific ARL entities thus becomes important not only to individual patient management but also for understanding these tumors in AIDS. Table 11.1 summarizes the clinicopathological HIV-lymphoma types according to the WHO classification of lymphoid tumors and also incorporates other ARL-specific data (Little 2003; Swerdlow 2008).

ARL are nearly all B-cell lymphomas. B-cell neoplasms to some extent resemble normal B-cells at a particular stage of differentiation. This similarity between the neoplasm and the normal or postulated normal counterpart forms in large part the classification and nomenclature of lymphoid tumors. An advantage to this organizational system is that it aids in correlating the tumor cell morphology, its immunophenotype, and provides insights into clinical behavior by relating tumors back to their cells of postulated origin. It is beyond the scope of this chapter to review normal B-cell development, but there are several important aspects in relation to ARL that should be mentioned.

Normal B-cells begin from common lymphoid progenitor cells in the bone marrow and develop into mature B-cells expressing surface immunoglobulins. During this process, immunoglobulin heavy-chain (IgH) and light chain (IgL) genes are formed through a process where the V, D, and J gene segments are recombined to create a vast immunologic repertoire. Until the B cells encounter an antigen with a specific fit for their surface immunoglobulin receptor, they are considered mature naïve B-cells. When they encounter antigen, the B-cell is activated to proliferate, and this begins a process wherein the cells differentiate into centroblasts or plasma cells. This is accomplished via interactions within peripheral lymphoid tissues. A process of immunoglobulin somatic hypermutation (SHM) of the immunoglobulin heavy chain variable (IGHV) region genes occurs, and class switch recombination is the end result (Klein and Dalla-Favera 2008). In HIV disease, the lymph node normal architecture, including a derangement in the proportion of follicular T-helper cells involved in regulating B-cell responses, is disrupted (Lindqvist 2012). The degree of lymph node derangement is correlated with the HIV disease status and may influence the processes of normal B-cell differentiation. It may also influence both the risk and type of B-cell neoplastic disease that occurs. Consistent with this hypothesis is the differential risk of the specific lymphoma types that occur in association with the duration and magnitude of HIV replication and the degree of T-cell depletion in HIV disease (Little 2003; Shiels and Engels 2012).

Table 11.1 Human immunodeficiency virus (HIV)-associated lymphomas: viral, genetic, and clinical feature

Histologic subtype	Percent association						CD4 cells	Prospects for chemosensitivity	Prognosis in cART era
	EBV	KSHV	BCL-2	BCL-6	TP53	MYC			
Burkitt	<50	0	0	100	40–60	100	Usually relatively well preserved	Excellent	Excellent
DLBCL-GC	<30	0	0	>75	Rare	0–50	Variable but rarely depleted	Favorable	Excellent
DLBCL-ABC	>50	Rare	30	0	0	0–20	Usually low	Intermediate	Intermediate
PCNSL	100	0	90	<50	0	0	<50	Good (limited data)	Intermediate/good if CD4 recovery can be achieved
Hodgkin lymphoma	>70	0					Generally preserved	Good	Intermediate (relapse common)
Primary effusion lymphoma[a]	>80	100	0	0	0	0	Variable	Poor	Poor
Plasmablastic lymphoma[a]	50–90	0	20	<10		40	Variable	Intermediate	Poor
Large B-cell lymphoma arising in HHV-8 multicentric Castleman disease[a]	0	100					Variable	Intermediate	Poor

[a]Occur more specifically in HIV

Aggressive B-cell neoplasms, such as those typically found in association with AIDS, broadly correspond to later stages of B-lymphocyte development (beyond the stem cell and lymphoblast stages). If naïve to antigen, such a cell will undergo a blast transformation when it is exposed to antigen. These are large proliferating cells that give rise to progeny cells that have activity against the specific inciting antigen. HIV-related antigenic stimulation results in this type of activation and is thought to be an important initiator of lymphomagenesis. The effect is related to the degree and duration of immune depletion, which can be modified by effective cART. In addition to the CD4 cell counts and HIV viral loads, several other biomarkers appear to be related to the lymphomagenic immunologic interface. For example, HIV induces cytokine dysregulation and polyclonal B-cell expansion (Breen 2006). Biomarkers that correlate with B-cell expansion, such as elevated serum CD30 and CD23 and serum free light chains, appear to be associated with increased risk of ARL. The gammaherpesviruses EBV and HHV-8 are associated with ARL that occur at low CD4 cells, and could reflect derangements in immune control of the viruses in association with chronic antigenic stimulation (Gloghini 2013). These viruses, along with other infections, can perturb the cytokine profile in patients, potentially making them useful as diagnostic or risk biomarkers. However, dysregulation of cytokines such as IL-6, IL-7, IL-8, IL-10, and IL-15 are found to be perturbed in HIV cases without lymphoid neoplastic disease. These cytokines are not at present reliable markers for lymphoma, either diagnostically or prognostically, most likely owing to a variety of features including host immune genetics such as HLA type. Yet, these features suggest that early therapeutic intervention for HIV could have a beneficial effect on lymphoma prevention. Indeed, preservation of higher CD4 cells has reduced the incidence of ARL overall by around 50 % (Besson 2001). Although overall ARL risk is reduced with cART, there is not absolute risk normalization. In addition to reduced overall ARL risk, cART appears to shift the ARL types that occur toward those with a more favorable biology and prognosis (Fig. 11.1) (Dunleavy and Wilson 2012). The positive effects of cART on lymph node preservation, reduction in antigenic stimulation, and gammaherpesvirus control are features that underlie the changing ARL epidemiology in the cART era.

The clinical presentation of lymphomas can be understood in terms of these immunologic and cytokine effects as well. The systemic symptoms that are associated with frank lymphoma, such as fever, fatigue, and weight loss, are partly related to abnormal cytokine production. Likewise, cytopenias, and even psychiatric symptoms may be explained in part by cytokine derangements, though these can also be due to the presence of tumor in the affected organ systems. However, some cases present with no symptoms at all, other than lymphadenopathy. The mass effect from enlarged nodes can mechanically compress nerves and other organs with specific related pain or vague discomfort in some cases. Thus, given the elevated risk of NHL in HIV-infected persons, vigilance and recognition of such symptoms merit consideration for ARL in the differential diagnosis for patients presenting with any of these symptoms. Even with well-preserved CD4 cell counts in patients on cART, lymphoid tumors have a markedly excess incidence relative to the background population, and so the possibility of lymphoid malignancy should always be a consideration in the HIV-infected patient.

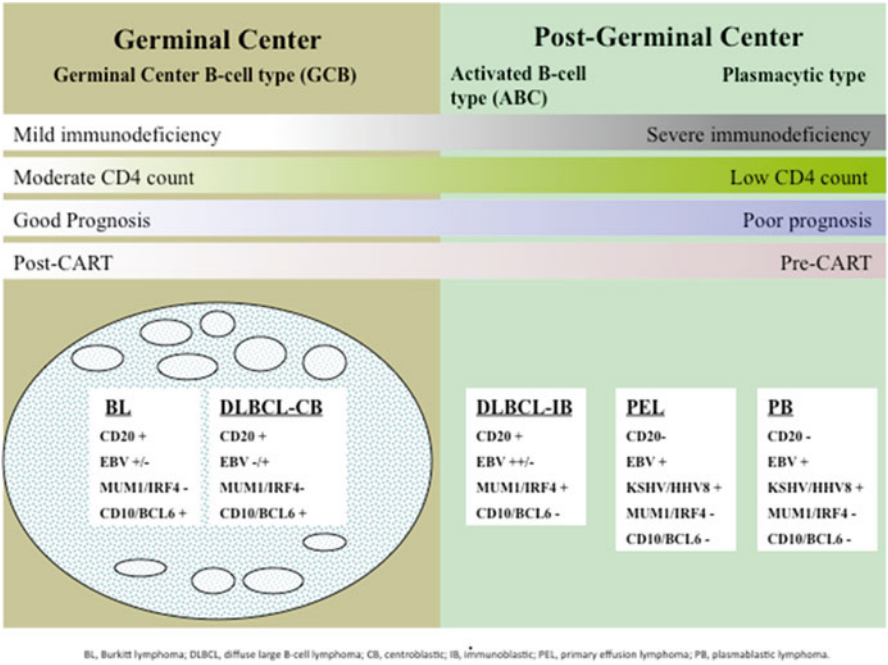

Fig. 11.1 A model for the histogenesis of human immunodeficiency virus (HIV)-associated lymphomas showing molecular and viral pathogenesis, diffuse large B-cell lymphoma taxonomy. From Dunleavy and Wilson (2012)

11.2 Specific AIDS-Related Lymphomas

ARL can broadly be viewed as (a) those lymphoid tumors that also occur in immunocompetent hosts; and (b) those that occur more specifically in persons with HIV infection (Table 11.1) (Swerdlow 2008). The following section reviews the specific lymphoma types in that context. A common theme among the histologic types is that the more advanced the immune dysregulation, the greater the propensity for an oncogenic virus to be associated with the tumor and for other biologic features that may confer relative treatment resistance to be present.

11.3 Burkitt Lymphoma

Burkitt lymphoma accounts for approximately 30 % of lymphomas in HIV-infected persons. Burkitt typically occurs early in the course of HIV disease before the CD4+ cells are greatly depleted, and this is true for patients treated with cART as

well as those who are cART naïve (Guech-Ongey 2010). This likely accounts for the relatively little change in Burkitt incidence comparing pre-cART and cART treatment eras. It is not yet clear whether these tumors continue to occur at a constant risk over the duration of HIV infection, or whether with time, the lymphoma risk largely shifts to another histologic type, even though the CD4 cells counts are preserved. After all, non-AIDS Burkitt occurs mainly in children and younger adults, so as those with HIV infection age, the age-pattern of NHL may parallel that observed in the HIV-unrelated setting. If this turns out to be the case, over time, a person's risk of Burkitt lymphoma may decline, and the risk for diffuse large B-cell lymphoma (DLBCL) may increase, similar to the background population epidemiological patterns. However, in the developing world, Burkitt incidence may have increased to some extent since the introduction of cART (Abayomi 2011). As yet these findings are not fully understood, but may reflect differences in guidelines for cART including timing of treatment initiation and definitions for viral suppression. The role of EBV in African Burkitt may also influence the emerging epidemiologic patterns there.

There are three epidemiologic forms of BL: sporadic (sBL), seen in developed Western countries; EBV-associated endemic BL (eBL), seen in Africa; and HIV-associated BL (HIV-BL). The three forms are clinically and biologically distinct, but share major similarities. Burkitt lymphoma is an aggressive mature B-cell neoplasm that histologically appears as sheets of medium-sized cells with a growth fraction of essentially 100 %, and this in part accounts for the treatment failure seen with standard CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) therapy. The proliferation rate is essentially 100 % and the cells rapidly undergo apoptosis and are phagocytosed by macrophages leading to an appearance commonly called the "starry sky" pattern. Burkitt express CD10 and BCL6, along with mutated immunoglobulin genes suggesting a germinal center origin. CD20 and CD79a (both B-cell markers) are essentially always present. The cells are generally negative for BCL2. Constitutive MYC protein expression is characteristic owing to the translocation of the MYC gene to one of the immunoglobulin gene loci, causing deregulated cell cycle control. The most common translocation is t(8;14) (q24;q32), which occurs in 70–80 % of patients. MYC activation can also be caused by variant translocations: t(2;8) (p12;q24) and t(8;22) (q24;q11) occur in 10–15 % of patients. MYC overexpression induces apoptosis through a p53-dependent pathway in normal B cells. TP53 mutations occur in Burkitt and could override this effect. However, this may be negated by BIM (Bcl-2 interacting mediator of cell death) down-regulation through a variety of mechanisms including EBV, thus in balance promoting cell survival.

Clinically, eBL, which is nearly always EBV associated, occurs mainly in children and involves the abdomen and jaw most frequently. Its geographic distribution overlaps areas where malaria and parvovirus infections are high, and these appear to be not only epidemiological features but also possibly biological cofactors. The incidence of eBL is up to 200 times greater than other BL forms. Indeed, there appear to be molecular interactions between malaria and EBV resulting in viral reactivation that may in part explain the epidemiologic findings.

The sBL form typically occurs in a wide range of ages, but the median is in the young adult years. EBV is seen in 30 % or less of cases. HIV-BL is similar to sBL in terms of EBV association and is often the first AIDS complication and initial manifestation of HIV disease. However, in areas of Africa where HIV and eBL overlap, it is not as yet fully clear what the epidemiological dynamics are. This may be in part due to patterns of diagnosis and treatment. The increase in HIV-BL is only partially explained by the various cofactors for sBL and eBL. As mentioned above, immunosuppression is generally relatively mild. However, there is ongoing immune activation in the presence of HIV, even when well treated. This can result in deregulated cytokine profiles affecting B cell proliferation and survival involving activation-induced cytidine deaminase (AID), which can lead to c-MYC translocation (Greisman 2012). Duration of HIV viremia, independent of CD4 cell counts, appears to be associated with risk of NHL development (Engels 2010). If HIV viremia is key, then it would seem a potent effect at low replication levels. Apparently, early cART initiation after HIV diagnosis has no effect on Burkitt incidence, but it will be important to see whether this observation holds over time (Abayomi 2011).

An emerging appreciation for the biological differences in the three BL forms suggests that the eBL and sBL have distinct molecular characteristics, and that the HIV-BL shares some characteristics of both (Schmitz 2012). The eBL and HIV-BL have higher rates of immunoglobulin heavy chain mutations than sBL, and they show signs of antigen selection, in contrast to the sBL form. When the tumors are segregated on the basis of EBV association (regardless of which epidemiologic form), the differences segregate more pronouncedly by EBV status. Overall, the molecular findings suggest that EBV-negative BL derive from early centroblasts, whereas the EBV-positive BL might derive from late GC B-cells that have already started to differentiate into memory B-cells.

The clinical presentation for AIDS-related Burkitt lymphoma is variable. Unexplained fever and night sweats may be the initial symptoms leading to the suspicion of an infection. Bone marrow infiltration can lead to bone pain and cytopenias with consequent easy fatigability, bruising, and bleeding. Abdominal pain or distention, nausea, vomiting, or gastrointestinal bleeding is relatively common owing to a predilection for intraabdominal involvement by BL. Head and neck presentation is also common, with involvement of the sinuses, oropharnyx, and tonsils accounting for symptoms referable to those sites. Involvement of the CNS is common, and the CSF of patients with Burkitt lymphoma should be checked by cytology and flow cytometry for the presence of leptomeningeal disease. Owing to the rapid proliferation rate, Burkitt lymphoma is highly aggressive and often presents with rapid clinical decline. Elevated lactate dehydrogenase, renal and hepatic abnormalities, uric acid elevations, and electrolyte abnormalities are common. Coagulation proteins may also be abnormal with frank bleeding. It is essential to recognize that these derangements are due to the lymphoma, and prompt lymphoma therapy is mandatory. Delays in lymphoma therapy can adversely affect survival prospects in this disease, and as such, the cancer therapy and supportive care for the lymphoma complications should take priority in clinical management over any concerns for HIV therapy. The hepatic and renal abnormalities may render cART infeasible to

administer until improvement is achieved from lymphoma therapy. It is important to recognize that CHOP is not appropriate therapy for Burkitt, although earlier in the AIDS epidemic it was often utilized for HIV-BL. The current standard of care for HIV-BL is to use Burkitt lymphoma regimens that are effective in the HIV-negative setting. In the USA, a National Cancer Institute sponsored nationwide clinical trial of rituximab with infusional dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) chemotherapy is underway. The infusional regimen appears to overcome resistance related to high proliferation providing evidence for a rational and less toxic effective therapy for Burkitt lymphoma relative to other regimens (Dunleavy 2013).

11.4 Diffuse Large B-Cell Lymphoma

The clinical presentation for DLBCL has been reviewed in the introductory comments. Where there are special considerations, these will be mentioned for each of the following DLBCL types.

11.5 DLBCL, Not Otherwise Specified

Patients often present with advanced stage disease, including extranodal involvement. The bone marrow should always be examined. The cerebrospinal fluid (CSF) should be sampled for cytological and flow cytometric evidence of leptomeningeal involvement in all cases with extranodal or marrow involvement. Some experts suggest sampling the CSF regardless. Constitutional symptoms include unexplained fevers, drenching night sweats, fatigue, and unexplained weight loss.

DLBCL NOS is a diagnosis of exclusion, not corresponding to other more specific diagnostic categories within the DLBCL category. It is termed “not otherwise specified (NOS)” because there are no clear and accepted criteria for further subdivision, although it is clear that within this category there are biologically heterogeneous entities. DLBCL NOS is the most commonly occurring NHL among persons with HIV infection. Within this DLBCL NOS group, there are three common morphological variants, two of which account for the majority of HIV-DLBCL: the centroblastic and the immunoblastic variants. These also occur in the immunocompetent host. In the immunocompetent setting, DLBCL NOS comprises about 30 % of adult NHL and the median age is 70 years. In the setting of HIV, they comprise over 70 % of lymphomas and the median age is reported to be less than 40 years.

The immunoblastic variant of DLBCL shows a preponderance of cells with pronounced basophilic cytoplasm and plasmacytoid differentiation. Up to 90 % are EBV associated. These tend to occur with more advanced immune depletion. In contrast, the centroblastic variant occur at higher CD4 cell counts, and histologically appear as medium to large lymphoid cells with oval to round vesicular nuclei.

They have a monomorphic cellular appearance with scanty cytoplasm that stains with either basic or acidic dyes. EBV association is found in less than 30 % of cases. Some cases do include immunoblasts admixed with the predominant centroblasts.

Gene expression profiling (GEP) of DLBCL of HIV-unrelated cases has identified distinct molecular subtypes that correspond to different stages of normal B-cell differentiation and are prognostically distinct, following standard therapy. The two major subtypes identified are of germinal center B-cell (GCB) or activated B-cell (ABC) origin—a third, less commonly encountered type is derived from a thymic B-cell [primary mediastinal B-cell lymphoma (PMBL)] (Alizadeh 2000; Rosenwald 2002). The GCB subtype is associated with a better prognosis than the ABC type, when various prognostic clinical features are controlled for, it is now recognized that all three subtypes of DLBCL are characterized by distinct mechanisms of oncogenic activation that can be individually targeted. For example, in the ABC type, the NF-κB pathway is constitutively active and this can be activated by mechanisms that include mutated CARD11 or chronic active B-cell receptor signaling. Recently, Bruton's tyrosine kinase (BTK) has been shown to be a critical step in the activation of NF-κB by B-cell receptor signaling and inhibitors of it, such as ibrutinib, are under clinical development in DLBCL. Approximately 30 % of ABC-DLBCL cases have mutations in the MYD88 gene that lead to NF-kappa B activation and strategies to target this pathway are also under development. Although GEP-defined molecular subtyping and prognostic validity have not been well studied in HIV DLBCL, studies suggest that tumor histogenesis also predicts outcome in these patients and molecular therapeutic advancements should mirror the HIV negative setting (Dunleavy 2010).

Attempts to use immunohistochemical (IHC) algorithms to replicate GEP results and/or stratify patients according to survival have been pursued, in part because they are technologically more straightforward. However, while IHC can accurately identify the majority of cases as GCB, the various algorithms have not been universally successful in maintaining the prognostic value of GEP (Chadburn 2009; Castillo 2012). For ARL cases treated across a spectrum of backbone regimens, IHC designation of GCB and non-GCB DLBCL subtypes did not segregate the subtypes by overall survival (Chadburn 2009). Also, CD4 count at cancer presentation did not segregate according to DLBCL subtype. A drawback to the various IHC algorithms is that while they identify the GCB type fairly well, they poorly separate the unclassifiable and the ABC type, and this blurs the outcome measures (when unclassifiable and ABC type are combined, the grouped outcome is less bad). In addition, if the treatment administered is not optimal, any potential outcome differences may be further obscured. Since ARL-DLBCL tend to be highly proliferative, they may have relative chemoresistance to standard CHOP chemotherapy thus making outcome differences by histogenic subtype less obvious. Additionally, if there is death due to non-lymphoma causes, it is difficult to ascribe outcomes according to lymphoma subtype. There is nevertheless data supporting the parallel in HIV and non-HIV DLBCL outcomes by histogenic subtype. A number of studies have suggested that dose-adjusted infusional EPOCH-R overcomes resistance due

to high tumor proliferation. In a phase II study using IHC to identify the DLBCL subtypes, there was marked segregation in outcome by subtype, again highlighting the critical interrelationship with tumor biology and specific treatment (Dunleavy 2010). Because ARL is a rare disease, each case should be approached as a vital opportunity to better define the tumor biology. Utilization of gold standard biomarker technology should be used in order to avoid pitfalls of conflating inadequate biomarker technology with conclusions regarding biological differences and clinical behavior in ARL. RNA extraction from formalin-fixed, paraffin-embedded provides accurate GEP-based classification of DLBCL and has potential for use in stratified trials designs.

Epidemiological dynamics over the period of the AIDS epidemic provide important clues toward integrating the knowledge gained from HIV-unrelated cases to the AIDS lymphomas. The incidence of AIDS-defining cases of DLBCL peaked in the early 1990s and then substantially declined in areas where widespread use of effective cART became available. The risk of DLBCL in HIV is inversely associated with CD4 cell count. Since cART increases and/or maintains higher CD4 cell counts, the prevalence of those low CD4 AIDS cases has decreased by over 50 %, and consequently a 50 % decrease in DLBCL incidence has been observed (Besson 2001). This is due to cART keeping the majority of patients in a CD4 cell range where the lymphoma risk is somewhat reduced compared to the higher lymphoma risk seen when the CD4 cells are low. It is instructive to note that within any given CD4 strata, the risk on ARL is unchanged when comparing pre-cART and ART treatment eras. Also, high CD4 cell levels do not fully normalize the risk of HIV-DLBCL, which remains elevated over the background population by over 50-fold.

In addition to the CD4-related overall risk of ARL risk, there appears to be an association between the CD4 cell count and the specific biologic and clinical characteristics of the ARL type most likely to occur (Dunleavy 2010; Dunleavy and Wilson 2012) (Fig. 11.1). Patients with advanced immune depletion are more likely to develop EVB-associated immunoblastic tumors with ABC characteristics, known to have a poor outcome in the background population because of the inferior curative potential of this subtype. In contrast, those who develop DLBCL at relatively high CD4 cell counts are more likely to develop GCB DLBCL. Thus, the observation that survival has improved for ARL in the cART era is likely to be explained in part by the improved curability of the GCB-DLBCL subtype and its rise as the predominant DLBCL type owing to less advanced immune suppression (Little 2003). Further advances in ARL outcomes will depend on accurate biologic identification of cases and will most likely involve relevant targeting of molecular pathways with rational novel therapeutic agents (Wilson 2010). Moreover, it is essential to recognize the differences in prognosis on the basis of tumor biology. The GCB DLBCL in HIV may already have excellent outcome for which further improvement will be difficult to measure. However, ABC DLBCL clearly has a poor prognosis and outcome improvements can be meaningfully targeted in reasonably sized clinical trial designs (Fig. 11.2).

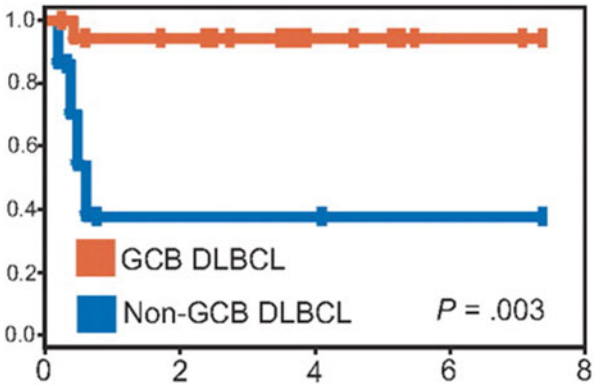

Fig. 11.2 PFS for GCB and non-GCB DLBCL. From Dunleavy (2010)

Primary DLBCL of the Central Nervous System

AIDS-related primary central nervous system lymphoma (AR-PCNSL) is a CD20+ immunoblastic DLBCL. It is almost always restricted to patients with severe T-cell depletion to less than 50 CD4+ cells/mm^3 and is essentially always associated with EBV in the malignant cells. The risk of AR-PCNSL is several thousand-fold greater than in the background population. Thus, while PCNSL also occurs in the immunocompetent population, in those with HIV-infection, its singular relationship with severe immune depletion and the fact that each cell harbors latent EBV infection suggest substantial pathobiological differences relative to PCNSL occurring in the immunocompetent host. AR-PCNSL is truly an opportunistic cancer. This is highlighted by the marked decrease in incidence of AR-PCNSL in areas where there is widespread use of cART. Occasionally PCNSL develops in an HIV-infected person with no prior AIDS complications and with CD4 cells counts in the normal range. Such cases may be EBV unrelated, and likely represent a qualitatively separate process more akin to those PCNSL occurring in the background population. It is questionable whether these cases are truly AR-PCNSL, and it is more likely that they represent primary brain lymphoma coincidentally occurring in a substantially non-immune suppressed HIV-infected person. It is worth recognizing that HIV-infected persons get cancers seen in the background population with similar presenting features and risks. Discussed here are those PCNSL occurring at very low CD4 cell counts.

The pathogenesis of AR-PCNSL remains unclear. The finding of sentinel white matter lesions in the brain suggests that normal B-lymphocytes may undergo clonal proliferation as the basis for lymphomagenesis. The EBV latent membrane protein LMP1 likely contributes to malignant transformation through upregulation of the anti-apoptotic protein BCL2. Alternative explanations involve the trafficking of peripheral lymphocytes into the brain. Toll-like receptor (TLR) activation from HIV-nef and other proteins may lead to immune activation and dysregulation of cytokines (Sasakawa 2012). TLR polymorphisms (e.g., TLR9) may predispose to AR-PCNSL through effects of EBV. Pre-clinical models of PCNSL suggest higher

expression of certain-adhesions molecules (such as LFA-1 and ICAM-1) mediated by dysregulated cytokines such as IL-8 in HIV compared to non-HIV-derived specimens, and that these can be interrupted with agents such as zidvoudine. Interestingly, AR-PCNSL responses have been reported with the use of high-dose zidvoudine (Raez 1999). In patients with advanced HIV infection, poor immunosurveillance enables EBV-related lymphoma cells to escape detection and then to disseminate and lodge through interactions between chemokine receptors on lymphocytes and brain vascular endothelium owing to HIV-induced aberrant cell adhesion- and chemokine- receptor expression. These factors likely create a unique microenvironment for the development and growth of opportunistic tumors. Though no studies have performed molecular profiling on AR-PCSNL, the few studies that have done so in HIV negative PCNSL suggest that these tumors are of late or post germinal center origin and may be susceptible to strategies that target NF-kappa B.

The clinical presentation for AR-PCNSL varies considerably. Patients can be symptomatic in a very subtle sense, showing only vague personality changes such as poor attentiveness or memory loss, or mild lethargy. Neurological deficits such as cranial nerve paralysis, visual impairment, aphasia, and seizures can be seen. Headache is less common than one might suspect, but can be the only presenting feature. Rapid clinical deterioration over days or weeks is typical.

Radiological findings are nonspecific but very sensitive. There can be considerable overlap with toxoplasmosis or other CNS abscess. On brain imaging, there can be unifocal or multifocal lesions that are variably radiodense on non-contrast CT scan. MRI typically shows a hypointense or isointense T1-weighted image. Gadolinium-enhanced MRI can appear as ring enhancing or a variety of other forms and even non-enhancing at all.

The near universal association with EBV in AR-PCNSL and the fluorodeoxyglucose (^{18}F) positron emission tomography (FDG-PET) avidity of the tumor provides the basis for an important diagnostic biomarker. In cases where CSF is collected and found to be positive for EBV by polymerase chain reaction (PCR), and where the FDG-PET is also positive, the positive predictive value for AR-PCNSL approaches 100 %. If both the tests are negative, the negative predictive value approaches 100 % (Antinori 1999). Though a definitive biopsy for diagnosis is optimal and should be performed, in very rare cases where this is not feasible, definitive therapy for lymphoma can be considered. The standard approach in the era prior to cART was to first treat for presumptive infectious toxoplasmosis; if the patient did not respond, it was then thought likely that the diagnosis was lymphoma. This approach is no longer justifiable, at least for many cases. Understanding the rationale that distinguishes past and current practice is critical. Prior to cART, patients with AR-PCNSL had a dismal prognosis based on both the brain tumor and the advanced irreversible HIV disease. In contrast, a patient in the current area may have highly reversible HIV disease, particularly if cART naïve. Thus, a patient who presents with AR-PCNSL may have a rapid immune reconstitution (including specific EBV immune surveillance) and rapid tumor resolution if therapy is promptly initiated for both the HIV and the brain tumor. Therefore, urgent initiation and completion of definitive diagnostic workup and treatment initiation for the identified pathology should be the standard of care in

the current era. In the HIV unrelated setting, a trial of antibiotics for undiagnosed intracranial processes would be an egregious and indefensible approach. In the cART era, if the HIV is highly treatable, the approach to those with AIDS should be just as urgent as in the HIV unrelated setting.

Unfortunately, use of a biomarker driven diagnostic approach and its potential lifesaving application is difficult to study well owing to the rarity of the disease. The irony is that with improved therapy and improved diagnostics available, the condition has become even more rare, and producing a high level of evidence to inform practice is increasingly elusive. Nevertheless, there is little justification for adhering to the clinical approach established in the early 1980s. Administering a trial of antitoxoplasmosis therapy and waiting for that to fail before commencing with definitive lymphoma only increases the permanent morbidity and lethality of the tumor. Though the evidence is limited, AR-PCNSL may be particularly responsive to therapy, and the approach to care should consider the prospects for long-term control of the underlying HIV.

It is important to reiterate that more typical PCNSL may occur in those with well-treated HIV-disease without advanced immune suppression. These cases are likely to be like those in the elderly background population. The diagnostic approach should be the same as in the background population, as the association with EBV is likely to be much less than then AR-PCNSL as categorized here.

Hodgkin Lymphoma

Hodgkin lymphoma clinical presentation is similar to that for DLBCL, with the exception that the central nervous system is not involved. Patients may present with minimal symptoms, or with the constellation of systemic symptoms mentioned as above in the DLBCL section.

Although not designated as an AIDS-defining condition, the risk of classical Hodgkin lymphoma (CHL) is elevated eightfold or more in HIV-infected persons relative to the background population. CHL is distinguished from nodular lymphocyte predominant Hodgkin lymphoma (NLPDHL) owing to distinct clinical, epidemiological, and biological features. NLPDHL is not elevated in HIV. There are four histological subtypes of CHL: lymphocyte-rich CHL, nodular sclerosis CHL (NSCHL), mixed cellularity CHK (MCCHL), and lymphocyte-depleted CHL (LDCHL). In HIV, MCCHL and LDCHL are the predominant forms seen. In the background population, NSCHL is the most common form.

The risk of CHL appears to have increased during the cART era, though whether this is mainly due to changes in diagnostic accuracy, the increasing prevalence of persons with HIV in the cART era, or to ageing over the period of the AIDS epidemic is somewhat unsettled. Also, the risk of CHL appears greatest during the first few months after initiation of cART, and then decreases or stabilizes with chronic therapy, and this may contribute to the apparent increase in CHL in the cART era. Patients with 50–99 CD4 cells/mm^3 appear to be most affected by cART initiation, suggesting that CHL could be related to immune recovery. Most cases present with

advanced stage and nearly 50 % have extranodal sites or marrow involvement. This may reflect in part that MCCHL has a propensity for disseminated presentation with abdominal and splenic involvement, in contrast to NSCHL, which typically spreads in an orderly fashion among contiguous lymph node groups. Also, in HIV infection, 80 % of cases are EBV associated. Interestingly MCCHL is more likely to EBV associated than NSCHL regardless of HIV status. The EBV-associated cases express the latent membrane protein 1 (LMP1) and are EBER-positive. An interesting finding in CHL is that while the immunophenotype of the tumor cells are similar among the subtypes, there are marked difference in other features including the sites of involvement, clinical features, growth pattern, presence of fibrosis, and the composition of the cellular background. It has been postulated that cART enables the cellular background to thrive and promote CHL (Biggar 2006).

CHL is characterized by the presence of Reed-Sternberg (HRS) cells that are multinucleated monoclonal B-cells residing in a background of non-neoplastic reactive cellular infiltrate (Swerdlow 2008). It is the appearance of this infiltrative process that defines the CHL subtype. HRS variants that have only one nucleus are called Hodgkin cells. The HRS or variant usually are the minority of cells comprising the affected tumor tissue, making up less than 10 % of the total cellularity. They are CD30+ in nearly all cases and this feature is being exploited in clinical trials of the conjugated monoclonal antibody brentuximab vedotin in HIV CHL. CD15 is found in about 85 % of cases. If CD20 expression is detected, it is generally variable in its intensity on the neoplastic cells, with many of them not expressing it at all. Other markers of B-cell specificity include PAX5/BSAP seen in ABCs, though its comparatively weaker intensity in HRS cells distinguishes them from the former. There is overexpression of cytokines and chemokines and/or their receptors in CHL, and this feature is consistent with the inflammatory CHL tumor appearance. Clonal immunoglobulin gene rearrangement is found in the HRS cells in nearly all cases. Along with the finding that these show SHM and other features, HRS cells appear to be derived from a germinal center B cell. In cases associated with HIV, this is consistent with the finding that many cases occur when the CD4 cells are relatively intact, or improving during cART initiation as mentioned above. Nevertheless, HRS appear to have lost much of the typical B-cell gene expression pattern. Deregulated NKκB, JAK/STAT and other transcription factors are found by gene expression in HIV unrelated cases. These features require further study in HIV-related cases.

Therapeutically, classical HL in the setting of HIV should be approached in the same way as HIV-negative HL, and regimens such as ABVD should be the standard approach. Recent data shows HIV status does not influence outcome in patients with cHL treated with ABVD chemotherapy in the cART era (Montoto 2012).

Primary Effusion Lymphoma

Primary effusion lymphoma (PEL) is a large B-cell lymphoma with variable morphology (Swerdlow 2008). It can appear as plasmablastic, immunoblastic, or frankly anaplastic. It almost always presents as a serous effusion, hence its synonym body

cavity lymphoma. Generally it is asymptomatic until the effusion has accumulated sufficiently to cause mechanical effect, such as pain or a feeling of fullness. If the effusion is in the pleural space, shortness of breath may occur. If the effusion is in the pericardial space, fatigue, dizziness, and signs of heart failure can occur as cardiac function becomes compromised. Patients presenting with PEL may have concomitant Kaposi's sarcoma and/or multicentric Castleman disease (MCD), or a history of these.

Diagnosis is confirmed by examination of the cellular component of the effusion, which can sometimes be aspirated in large quantities. PEL are always positive for the human herpes virus-8 (HHV-8, also known as the Kaposi sarcoma-associated herpes virus, KSHV). In upwards of 70 % of cases, the tumor cells are dually coinfected with HHV-8 and EBV. If HHV-8 is not present, but EBV is found in a lymphomatous effusion, the likely diagnosis is pyothorax-associated DLBCL, not PEL.

B-cell immunophenotypic markers can be lost in PEL, though some are weakly CD20 positive. Non-lineage antigens including CD30 can be present, possibly suggesting a role for the use of brentuximab vedotin therapeutically. B-cell histology can be confirmed by molecular analysis and the finding that immunoglobulin genes are clonally rearranged and hypermutated. GEP shows a distinct profile with features of both plasma cells and EBV transformed lymphoblastoid cell lines (Fan 2005).

It is reported that PEL occurs mainly with depleted CD4 cell counts, though cases clearly do occur when the CD4 cell count is near normal. The HHV-8 gene expression program includes a number of human gene analogues that can affect immune surveillance and immune evasion. The prognosis is generally not favorable and the response to chemotherapy is poor. Targeted therapies based on the virology and tumor pathobiology will likely be critical to improving the therapeutic outcomes.

Plasmablastic Lymphoma

Plasmablastic lymphoma (PBL) is an uncommon B-cell tumor occurring predominantly in HIV-positive middle-aged males (Swerdlow 2008). It can also occur in other immunodeficiency states. Among the elderly, it can occur without evident immunodeficiency. In nearly all cases the tumor is EBV-infected. PBL frequently involves the oral cavity, and originally was termed PBL of the oral cavity prior to the realization that it does involve other anatomic sites as well. Most patients have stage III-IV disease at presentation and a high-risk international prognostics index score, a clinical rating system of lymphoma prognosis.

There is a spectrum of morphologic appearances in PBL. PBL can resemble immunoblasts, or have a more plasmacytic differentiation appearing similar to plasmablastic plasma cell myeloma. They often have a high proliferation fraction with a monomorphic plasmablastic cytology, particularly when presentation involves the

oral, nasal and paranasal areas in those with HIV infection. The immunophenotype shows expression of CD138, CD38, Vs38c and IRF4/MUM1, with week or no expression of CD45, CD20. CD79a (a B-cell marker) is present in the majority of cases. Cytoplasmic immunoglobulins are expressed and most are IgG with restriction to either kappa or lambda light chain. Clonal immunoglobulin heavy chain rearrangement is found even when immunoglobulin expression is not detectable. CD30 is frequently expressed, and may suggest a role for brentuximab vedotin. Ki67 index is usually over 90 %, so the tumor is highly proliferative. EBV EBER in situ hybridization is positive in most cases but LMP1 is rarely expressed. HHV-8 is absent. The clinical course is very aggressive with median survival less than 1 year. Cases with limited involvement may respond well to chemotherapy followed by involved field radiotherapy.

HHV-8 Multicentric Castleman Disease

HHV-8 MCD is a syndrome of constitutional symptoms with variable organ and hematopoietic dyspoiesis. Histopathologically it is characterized by an involution and hyalinization of germinal centers of B-cell follicles in the lymph nodes and spleen. The mantle zone can be prominent and intrude into the germinal center. In the mantle zone are found larger plasmablastic cells that are positive by immunohistochemistry for HHV-8 latent nuclear antigen-1 (LANA). The syndrome is mediated in part by aberrant interleukin-6 (IL-6) production (Uldrick 2011). HHV-8 encodes for a viral form of IL-6, and can also serve to promote human IL-6. Immunoglobulin M lambda is expressed without evidence of monoclonality. Consideration for HHV-8 MCD should be raised in a patient with intermittent constitutional symptoms, fevers, and cytopenias. HHV-8 serology and viral loads can be determined in support of the diagnosis. Though splenomegaly may be impressive, there may be only moderate adenopathy. FDG-PET may be useful to identify metabolically active nodes and help to identify the most likely lymph node to biopsy in order to confirm the histopathologic diagnosis. Needle aspiration yields inadequate architecturally intact material for diagnostic utility.

11.6 Conclusions/Future Directions

The availability of cART has significantly changed the landscape of HIV-associated lymphoma. Both BL and DLBCL, in the setting of HIV infection, are now highly curable with current strategies. For these lymphomas, future directions should focus on identifying driver pathways and novel targets and improving strategies particularly for the treatment of non-germinal center tumors.

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Chapter 12
Diffuse Large B-Cell Lymphoma

Neel K. Gupta and Lawrence D. Kaplan

Abstract Diffuse large B-cell lymphoma (DLBCL) is an AIDS-defining, aggressive lymphoid neoplasm in which normal lymph node architecture is replaced by sheets of large, atypical lymphoid cells. It is thought to arise from mature B-cells and is comprised of large, non-cleaved centroblasts and immunoblasts with abundant cytoplasm and prominent nucleoli. As the most common form of non-Hodgkin lymphoma (NHL) in both HIV-positive and HIV-negative individuals, there is an increasing appreciation of its morphologic, genetic, and biologic heterogeneity.

12.1 Epidemiology and Risk Factors

Diffuse large B-cell lymphoma (DLBCL) accounts for roughly 30 % of all non-Hodgkin lymphomas (NHLs) in the HIV-negative population. By comparison, up to 75 % of systemic NHL subtypes in HIV seropositive individuals are comprised of DLBCL or variants thereof (Cote et al. 1997). As a whole, standardized incident ratios for NHL in HIV-positive individuals have decreased over the last two decades from over 1,000 in the early 1990s to below 200 in the mid-2000s due to the advent and widespread use of combination antiretroviral therapy, or cART (Patel et al. 2008). Primary central nervous system (PCNS) lymphomas account for approximately 15 % of AIDS-related lymphomas (ARL) and are morphologically classified as DLBCL; however, given recent insights into the tumor microenvironment and unique biology of this disease, PCNS lymphoma likely represents a distinct ARL entity and will not be further addressed in this section.

N.K. Gupta • L.D. Kaplan (✉)
Division of Hematology/Oncology, Department of Medicine, University of California, San Francisco, CA, USA
e-mail: neel.gupta@ucsf.edu

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Risk factors for DLBCL and ARLs in general are linked to the degree of host immune-suppression and viral activity. In the pre-cART era, a CD4 count less than 50 and plasma HIV RNA levels greater than 100,000 were strongly linked to the development of ARL; however, in the era of cART most patients with newly diagnosed ARLs will have CD4 counts greater than 200 (Kaplan 2012).

12.2 Pathogenesis

The mechanisms by which HIV exerts its oncogenic effects in human lymphoid tissue are complex and not yet fully elucidated. While B-cells are not considered a direct target of HIV, it has been proposed that immune dysregulation as a consequence of HIV viremia results in aberrant somatic hypermutation and loss of T-cell immunity against pathogenic viruses such as Epstein–Barr (EBV) or human herpesvirus 8 (HHV8, also known as Kaposi's sarcoma herpesvirus, or KSHV) (Kaplan 2012). The loss of regulation leads to hypergammaglobulinemia and polyclonal B-cell hyperplasia in milieu of constant antigenic stimulation. In addition, myeloid dendritic cells (mDC) play a pivotal role in propagating HIV-related B-cell disease states via increased expression of B lymphocyte stimulator (BLyS) surface expression, which is in turn correlated with disease progression (Fontaine et al. 2011).

12.3 Presentation, Diagnosis, and Staging

Patients with ARLs typically present with advanced-stage disease, constitutional symptoms, marrow involvement, and extranodal distribution in unusual sites such as the gingiva, rectum, and biliary tree. DLBCL in particular involves the gastrointestinal tract in many cases, with patients reporting abdominal pain, bleeding, diarrhea, or severe nausea.

Definitive diagnosis requires tissue biopsy with sufficient material to correlate morphologic, immunohistochemical, and immunophenotypic characteristics. Excisional biopsy is the preferred method for obtaining tissue for subtype classification. Core needle biopsy may be utilized for sampling otherwise inaccessible or high-risk areas, although fine-needle aspiration should be avoided due to the potential for sampling error and lack of cytological architecture. Biopsy material should be processed for standard B-cell immunohistochemical and flow cytometric markers in addition to a comprehensive morphologic assessment by an experience hematopathologist. Evaluation of the proliferative index using Ki-67 or MIB-1 staining helps to distinguish aggressive from very aggressive subtypes, which in turn may influence the choice of chemotherapeutic regimens. In addition to adequate peripheral tissue sampling, unilateral bone marrow aspirate and core biopsy should be obtained to evaluate for lymphomatous involvement. Central nervous system (CNS)

evaluation is not routinely indicated unless there are greater than two areas of extranodal involvement in the context of elevated LDH, marrow involvement, epidural disease, paranasal sinus disease, or testicular involvement.

Along with pre-treatment assessment of renal and hepatic function, serum lactate dehydrogenase (LDH), phosphorous, and calcium should be obtained to evaluate potential tumor lysis, especially in the presence of bulky or rapidly progressive disease. If not already known, hepatitis B serologies should be obtained, and in patients with a positive core antibody, positive surface antigen, or circulating levels of hepatitis B DNA, appropriate anti-viral therapy should be initiated due to the risk of re-activation or exacerbation with rituximab-containing regimens.

Contrast computed tomography (CT) of the chest, abdomen, and pelvis is recommended as a baseline assessment of disease distribution as per the Cotswold-modified Ann Arbor staging system. In contrast to the HIV-negative population, interpretation of positron emission tomography with [18F] fluoro-deoxyglucose (FDG-PET, or PET hereafter) in HIV-positive individuals can be confounded by persistent generalized lymphadenopathy related to viral load and opportunistic infections secondary to immune suppression. As such, its role in staging, interim scanning, and risk-adapted therapy for HIV-related DLBCL remains an area of active investigation. However, end of treatment response assessment carries a similarly high negative predictive value (NPV) as seen in the HIV-negative population, suggesting a possible role for response assessment in individuals with limited disease without suspected co-infection (Hentrich et al. 2011).

12.4 Prognosis

The previously poor prognosis of patients with HIV-associated DLBCL in the pre-cART era stemmed from a variety of factors including the presence of concomitant opportunistic infections, aggressive and advanced-stage disease at presentation, and toxicities associated with the use of multi-agent chemotherapy in a severely immunocompromised population. By contrast, prognosis in the era of cART has improved to the point that outcomes now approach those of the HIV-negative population. In one study relatively early in the cART era, improvement was limited to individuals demonstrating a virological response to cART (Antinori et al. 2001), highlighting the importance of a functional or recovering immune system through the course of therapy. This improved immuno-competency of HIV-positive patients has resulted in lymphoma-specific factors playing a more important role in predicting clinical outcome than was previously the case. The International Prognostic Index (IPI) is a well-validated model incorporating disease stage, patient age, presence of extranodal involvement in two or greater areas, performance status, and serum LDH into a prognostic index with high discriminatory power in HIV-negative individuals. Several studies have examined its utility in ARLs and HIV-associated DLBCL specifically, demonstrating a similar ability to risk-stratify patients at diagnosis.

The lowest-risk individuals with either none or one of the aforementioned risk factors appear to maintain an overall survival approaching 70 % at 5 years, nearly identical to the comparable HIV-negative population (Lim et al. 2005; Bower et al. 2005). In addition, multivariate analyses have shown a CD4-positive lymphocyte count less than 100 as being associated with significantly worse outcomes, though it is unclear if this has retained prognostic significance in the era of cART.

The use of gene expression profiling (GEP) has identified distinct cell of origin (COO) signatures in DLBCL. Lymphomas with a post-germinal center (non-GC), also called activated B cell (ABC), subtype are associated with a markedly worse prognosis compared to lymphomas with a germinal center (GC) signature in HIV-negative lymphomas. The data in HIV-associated DLBCL are less clear. Retrospective data from two trials of the US AIDS Malignancy Consortium (AMC) suggest no difference in lymphoma-specific nor overall survival. Conversely, a planned subset analysis of patients with HIV-associated DLBCL receiving dose-dense rituximab and the infusional regimen EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) at the National Cancer Institute (NCI) reported a substantial difference in PFS between GC and non-GC subtypes (95 vs 44 %).

The true prognostic relevance of COO in HIV-related DLBCL notwithstanding, routine incorporation of GEP into clinical decision making remains a work in progress due to the expense and limited availability of testing outside academic centers. Attempts at correlating GEP with immunohistochemistry have been complicated by a lack of reproducibility or standardization of diagnostic algorithms. Despite these challenges, however, the unique biology and disparate prognosis of non-GC subtypes in the HIV-negative population has spurred investigation into targeted agents and novel multi-agent regimens. For example, constitutive activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB) in these tumors is a potential target for proteosome inhibition, and this is supported by preliminary studies indicating increased activity of the drug bortezomib in relapsed non-GC DLBCL compared with GC DLBCL in HIV-negative patients. Recently, inhibitors of Bruton's tyrosine kinase (BTK) have been shown to induce responses in relapsed HIV-negative non-GC DLBCL and are currently undergoing further testing in clinical trials.

12.5 Clinical Management and Initial Treatment

Early attempts at treatment of ARL in general were limited by the baseline immunodeficiency and cytopenias commonly found in HIV-positive individuals at presentation. Administration of cytotoxic therapy compounded these deficiencies, thereby increasing the risk of opportunistic infections that further compromised delivery of adequate treatment. Through the bolstering immunologic effects of cART and improved supportive care, clinicians are now able to administer even high dose therapy with a manageable side effect profile.

The standard of care treatment for DLBCL in HIV-negative individuals combines the anti-CD20 monoclonal antibody rituximab (R) with a multi-agent chemotherapy regimen including cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) administered every 21 days for six to eight cycles. This regimen has produced 5-year OS rates of approximately 60 % in randomized phase III trials, averaged over all risk groups. Historically, CHOP and CHOP-like regimens had not achieved anywhere near this degree of success in HIV-positive individuals treated in the pre-cART era, with 2-year OS no better than 20 % (Kaplan 2012). Given these dismal outcomes and concern for hypo-gammaglobulinemia in already immunocompromised hosts, prospective trials sought to evaluate the role of rituximab in combination with chemotherapy in the HIV-positive population.

A prospective multicenter German trial evaluated 72 patients, risk-stratified by World Health Organization (WHO) performance status >3, CD4 count less than 50, and prior opportunistic infection. The 48 patients with zero or one risk factor were considered "standard risk" and achieved a CR rate of 79 % with median survival not reached at 47 months follow-up. This was in contrast to the 29 % CR rate obtained in the 24 "high-risk" patients with 2 or more risk factors. A phase II trial of 61 patients with one or no risk factors including CD4 <100, prior AIDS, or Eastern Cooperative Oncology Group (ECOG) performance score >2 produced 2-year OS rates of 75 %.

The AMC conducted the only randomized, phase III prospective trial comparing standard dose CHOP with R-CHOP in patients with HIV-related DLBCL. One hundred fifty patients were administered CHOP or R-CHOP in a 2:1 fashion while receiving cART, growth factor support, and prophylaxis against pneumocystis jorvecii. Patients randomized to rituximab had a statistically nonsignificant improvement in CR rate from 47 to 58 %, and median OS of 2.6 years compared to 2.1 years in the CHOP cohort. However, 14 % of the patients in the R-CHOP group suffered infection-related deaths compared to 2 % in the CHOP group. While majority of these deaths occurred in patients with a CD4 count less than 50/μl, and neutropenic antibiotic prophylaxis was not administered in the study, these findings initially raised concerns over the use of rituximab in HIV-positive individuals with severe immunodeficiency (Kaplan et al. 2005).

Subsequent studies evaluating the combination of rituximab and infusional chemotherapy firmly established rituximab as not only safe given the proper supportive care, but also highly effective in the treatment of HIV-related DLBCL. The infusional regimen EPOCH was developed intramurally at the NCI on the basis of in-vitro studies suggesting greater tumor kill as a result of continuous—rather than bolus or episodic—exposure to multi-agent cytotoxic therapy. Importantly, this regimen adapted a pharmacodynamic approach to dosing, with subsequent dose increases or reductions based on nadir CD4 counts in preceding cycles. A modified, dose-adjusted (da) EPOCH regimen was employed in another multicenter AMC phase II trial whereby patients were randomized to receive rituximab either concurrently with chemotherapy or sequentially after each cycle. Although the study was not designed to evaluate overall survival, 73 % of patients receiving rituximab concurrently achieved a CR, compared with 55 % in the sequential arm. Deaths related to sepsis were uncommon due to the routine use of neutropenic antibiotic prophylaxis with flouroquinolones.

A phase II intramural NCI trial evaluating daEPOCH with dose-dense rituximab delivered one cycle of chemotherapy beyond documentation of complete response for a minimum of three cycles. The 5-year PFS and OS were 84 and 68 %, respectively, and there were no treatment-related deaths. As stated above, along with CD4 count, COO was an independent predictor of outcome (Dunleavy and Wilson 2012).

In summary, several trials have demonstrated both efficacy and safety of this infusional approach. An ongoing phase III, multicenter randomized controlled trial comparing R-CHOP with daEPOCH-R for the treatment of DLBCL in HIV-negative patients may further inform the choice of treatment for DLBCL in HIV-positive individuals.

12.6 Treatment of Relapsed/Refractory Disease

As is the case for HIV-negative individuals, the goal of treatment for relapsed/refractory HIV-associated DLBCL is to achieve a response sufficient enough to proceed with high-dose chemotherapy followed by autologous stem cell rescue (ASCT). The PARMA study was the first multicenter randomized trial to establish the superior event-free and overall survival benefit of this approach for chemo-sensitive relapsed/refractory DLBCL in HIV-negative patients. Though such an approach would have been impractical in the pre-cART era, it is now considered the standard of care for fit HIV-positive patients with chemo-sensitive disease at relapse.

The largest prospective trial evaluating the efficacy of ASCT in HIV-positive lymphomas looked at a total of 50 patients, 22 of whom had DLBCL. Thirteen of the 22 patients received transplant, with 11 of those (42 %) in continuous CR at the data cutoff time point. For the DLBCL subset, the overall and progression-free survival post-transplant was 81.5 and 83 %, respectively, at 44 months (Re et al. 2009). Importantly, there were no treatment-related deaths, and median time to neutrophil and platelet engraftment was 10 and 12 days, respectively, similar to that observed in the HIV-negative population. Although somewhat smaller in sample size, other prospective and retrospective studies have confirmed the efficacy and safety of ASCT in HIV-associated, relapsed/refractory DLBCL with chemo-sensitive disease (Krishnan et al. 2005). Predictably, long-term survival seen in these studies was largely confined to patients with well-controlled viral loads. As this is a population with significant pre-transplant treatment exposure, CD4 counts are generally low prior to ASCT and therefore not a reliable index of for prediction of outcomes or toxicities.

The role of allogeneic stem cell transplantation remains an area of active investigation. An ongoing multicenter trial conducted by the United States Bone Marrow Transplant Clinical Trials Network and the AMC is intended to provide the first prospective data on efficacy and transplant-related toxicities; however, until completion of this study with sufficient follow-up, it is recommended that allogeneic transplantation for HIV-positive patients occur within the context of a clinical trial at an academic institution.

12.7 Management of cART and Supportive Care

The optimal point at which cART should be incorporated during treatment has been evaluated in several studies but remains an unresolved issue. Given the previously discussed importance of sustained virological suppression on outcomes, the prospect of uncontrolled HIV replication during cytotoxic and lymphocyte-depleting therapy argues for the continuation of cART during treatment. Conversely, potential pharmacokinetic and pharmacodynamic interactions may lead to lower effective chemotherapeutic drug exposure or, importantly, increased toxicities. In particular the CYP 3A inhibition associated with protease inhibitors (PIs) has been associated with increased myelosuppression without an increased rate of infectious complications. As shown by the NCI EPOCH study, high response rates can be seen without the concomitant use of cART. At the same time, concerns over cART noncompliance—and therefore suboptimal viral control and subsequent emergence of viral resistance—due to nausea or vomiting are increasingly unfounded given the highly effective anti-emetics and supportive care currently available. If there are concerns over excess toxicity or specific drug interactions, consideration may be given to raltegravir-based regimens, which are less frequently associated with these potential interactions. Ultimately, in the absence of prospective, randomized controlled data, the decision to incorporate cART during chemotherapy must be made on a case-by-case basis, taking into account the above considerations and individual risk/benefit ratio. However, in general, most physicians with expertise in this field now feel that it is preferable to continue antiretroviral therapy through the course of chemotherapy when possible. Should toxicities necessitate discontinuation of cART, it is best to continue to hold these agents until after the completion of all chemotherapy.

Use of pegylated granulocyte-colony stimulating factor (G-CSF) ameliorates chemotherapy-induced neutropenia, and infectious complications are minimized by the use of prophylactic fluroquinolone antibiotics and azoles during periods of protracted neutropenia. All patients should receive Pneumocystitis *jiroveci* prophylaxis (e.g., dapsone, inhaled pentamidine, atovaquone) regardless of initial CD4+ cell count. Caution should be exercised when using trimethoprim-sulfamethoxazole given its potential to exacerbate myelosuppression with concurrent chemotherapy.

12.8 Conclusion

The prognosis and treatment of DLBCL in HIV-positive individuals has improved dramatically in the era of cART. As a result of improved immuno-competency secondary to anti-viral therapy, supportive care, and evolving treatment strategies, remission rates for individuals with at least certain types of DLBCL rival those of the HIV-negative population, and patients with good-risk features can reasonably expect to be cured of their disease. Results of ongoing trials examining the role of GEP, allogeneic stem cell transplantation, and novel targeted therapies will clarify the optimal strategy for treatment of relapsed or otherwise poor-prognosis disease.

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Chapter 13
Burkitt and Burkitt-Like Lymphoma

Kishor Bhatia and Sam M. Mbulaiteye

Abstract Burkitt lymphoma (BL) is a rare tumor of mature B lymphocytes. Clinically, it develops rapidly and runs an aggressive course. Tumor can develop in any body organ, but most often involves sites other than lymph nodes, especially in the abdomen, pharynx, or the jaw. BL is relatively more common in sub-Saharan Africa, where it is endemic. Patients with HIV infection are also at increased risk of BL, and in this setting it is called epidemic BL. Endemic and epidemic BL are both associated with Epstein–Barr virus, a common virus that infects 90 % of the global population. Although the tumor is highly aggressive, being the most rapidly growing cancer known and doubling every 24 h, it is also very responsive to modern chemotherapy. With currently available regimens, 90 % of patients can expect to be cured when properly treated.

13.1 Introduction

In 1982, reports of Kaposi sarcoma and *Pneumocystis carinii* infections in *men who have sex with men* (*MSM*) heralded the advent of the AIDS epidemic in the USA. Soon afterward, a cluster of cases of aggressive B-cell non-Hodgkin lymphoma (NHL) was noted in the same population. As the epidemic unfolded, it was noted that these AIDS-associated lymphomas included cases of Burkitt lymphoma (BL)

K. Bhatia (✉)
AIDS Malignancy Program, Office of HIV and AIDS Malignancy & Infections and Immunoepidemiology Branch, National Cancer Institute, Bethesda, MD, USA
e-mail: bhatiak@mail.nih.gov

S. M. Mbulaiteye
Infections and Immunoepidemiology Branch, Division of Cancer Epidemiology and Genetics, Department of Health and Human Services, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA
e-mail: mbulaits@mail.nih.gov

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or Burkitt-like lymphomas (BLL). Burkitt lymphoma (BL), a rapidly growing B-cell NHL, was known prior to the HIV epidemic. The pathology of BL was described as small non-cleaved cell lymphoma in the Lukes and Collin's classification system of lymphomas, and prior to the AIDS epidemic, it was relatively rare outside sub-Saharan Africa, where it was known to be endemic. First described by Denis Burkitt in 1958, the tumor was known to affect mostly children who developed tumors in the jaw or in the abdomen. Shortly after, the pathology of the tumors was described, allowing sporadic cases to be described worldwide, and leading to the disease to be named after Burkitt as a specific clinical and pathologic entity.

Three epidemiological variants of BL are now recognized: endemic, sporadic, and immunodeficiency-related (or epidemic). These variants differ with respect to their incidence, geographic areas, and associated factors, but they are currently not distinguishable by routine histopathological, immunohistochemical, or molecular criteria. All three variants of BL share the starry-sky pattern under the microscope, and a morphology of uniform medium sized cells with cytoplasmic vacuoles, small nucleoli and a non-cleaved nucleus. The immunophenotype typically shows positivity for monotypic surface IgM, B-cell antigens (CD20, CD10, CD79a), and a high proliferation index. Cytogenetic studies show the presence of a rearranged *c-myc* gene. The rearrangement is often the result of translocation of *c-myc* on chromosome 8 into the vicinity of heavy chain immunoglobulin (IgH) sequences on chromosome 14, or light-chain immunoglobulin genes on chromosomes 2 and 22 as well. The cell of origin for BL is a germinal center B-cell, and BL thus expresses bcl-6 but not bcl-2, CD-138 or TdT (Swerdlow et al. 2008).

13.2 Epidemiology

The two major variants of BL described prior to the HIV epidemic mainly differ by geography and incidence rates. Endemic BL occurs in sub-Saharan Africa and Papua New Guinea, in regions that are also holoendemic for *Plasmodium falciparum* malaria. In sub-Saharan Africa, patients with endemic BL frequently present with a rapidly growing tumor involving the jaw or abdomen. The peak age is 5–9 years, in part because of early acquisition of *Epstein–Barr virus* (*EBV*) infection in sub-Saharan Africa coupled with repeated infection with *Plasmodium falciparum*, the two generally accepted key risk factors. EBV is detected in more than 95 % of endemic BL cases. In regions of sub-Saharan Africa that have holoendemic malaria, BL constitutes the majority of pediatric lymphomas and accounts for as many as half of all childhood cancers. Accurate estimates of the incidence of endemic BL are lacking, but the annual incidence is between 40 and 50 cases per million children (Molyneux et al. 2012). Boys are affected more than girls, particularly for tumors involving the jaw where the male-to-female ratio may be higher than 10:1. BL occurring outside the malarial regions of Africa and Papua New Guinea and outside the setting of HIV infection is referred to as sporadic BL.

The clinical presentation of sporadic BL differs from that of endemic BL by more frequently involving the lymph nodes, abdomen, and the bone marrow. In addition, sporadic cases generally occur later during adolescence and young adult age, although cases have been reported in the elderly. The incidence of sporadic BL is at least ten times lower than endemic BL—about two per million in the USA, Europe, and some parts of Asia. Unlike endemic BL, no specific risk factors have been identified for sporadic BL. The association of EBV in sporadic BL varies considerably from country to country. In the USA and Western Europe, only about 20–30 % of BL are EBV-positive. However, in Brazil, Argentina, Turkey, and Egypt, where the cases are considered to be sporadic, EBV positivity ranges from 50 to 70 % (Magrath et al. 1992). It is not clear whether EBV-positive BL in the USA differs by race.

Risk for BL is very high in individuals with immunodeficiency, either as a result of infection with human immunodeficiency virus (HIV) or following solid organ transplantation. Patients with AIDS have about a 50–60-fold greater risk of developing BL than people without AIDS of a similar age and sex. The burden of AIDS-associated BL in the USA from 1980 to 2007 has been estimated to be about 3,452 cases (Shiels et al. 2011a, b), and these cases account for one-fifth of all BL cases diagnosed in the USA during the same period. A distinct age-associated peak of BL at age 40 has been identified in persons with HIV infection, perhaps influenced by the fact that most HIV-infected individuals are less than 50 years of age. More recent analyses of cancer registry datasets now suggest that the age-specific pattern of BL in most countries (except Africa, for which data are sparse and/or incomplete) is trimodal. Separate incidence peaks near ages 10, 40, and 70 are clearly apparent. While the middle peak overlaps with cases of AIDS BL, this trimodal age-specific incidence of BL is also apparent in the general population. The multiple incidence peaks of BL raises the possibility that conditions currently diagnosed and classified as BL comprise a mixture of entities with distinct biology or etiology and distinct age peaks. It remains to be seen if variation in BL immunophenotype, molecular and viral profiles corresponds with the distinct age peaks identified and/or with the immune status of tumors.

How immunodeficiency increases the risk for BL is not entirely clear. It is likely that immunocompromised patients are unable to control EBV infection, which might increase the risk of EBV-associated BL. EBV is indeed found in a 40–60 % of HIV-associated BL from the USA and Western Europe, but changes in control of EBV alone may not explain all of the observed increase in HIV-associated BL because a substantial proportion of cases are not EBV-positive. Although HIV has been associated with dramatically increased BL incidence in the USA and Western Europe, data are conflicting about the impact of HIV on BL in sub-Saharan Africa, where the HIV epidemic is substantial and BL was previously endemic. For example, comparison of rates of incidence of BL in Uganda, between pre-HIV (1960–1971) and HIV era (1991–1997) suggests only slight increase in BL incidence, and while some of the increase might be attributable to HIV, it is not possible to be certain because cancer registry studies do not collect HIV status on their patients. Two case–control studies conducted in Uganda showed a modest but statistically

significant increase in BL risk with HIV, with the odds ratio in one study of 7.5 and the other 2.2, raising doubt about the significance of the overall association. Similarly conflicting results were reported in two analyses from a study conducted in Malawi, with significant results reported in one analysis (OR = 12.4) and a non-significant result in the other (OR = 2.2). There are sparse data on the association between HIV and BL in adults in Africa. A study from Kenya (Otieno et al. 2001) showed the median age of BL was 35 years, suggesting an impact HIV on the age of BL diagnosis, but this study was small and it did not estimate the fold increase. Therefore, it is quite unlikely that a substantial effect of HIV on AIDS-associated BL in sub-Saharan African BL belt has been missed. Why this difference? One reason is that competing mortality—death from other, more common, conditions—contributes. This may be supported by one study that has reported a stronger impact in South Africa, where survival rates for children with HIV may be better than in Uganda and Malawi, although this has not been shown. In that study, the BL risk in children with HIV was increased nearly 46-fold. However, since BL in South Africa is more likely the sporadic type, i.e., not associated with holoendemic malaria, the substantially higher risk of BL with HIV infection may simply indicate that the impact of HIV on BL is greater for sporadic than endemic BL. Following the widespread availability of combination antiretroviral therapy (cART), the overall incidence of AIDS-related NHLs has significantly decreased with the largest decrease seen for primary central nervous system (CNS) lymphomas (Shiels et al. 2011a, b). There are conflicting data on the incidence of BL in particular during the cART era. A large meta-analysis of 23 cohort studies did not support a decline in BL (International Collaboration on HIV and Cancer 2000).

BL accounts for a substantial proportion of AIDS-associated NHL in the cART era. The relationship between degree of immunosuppression and risk to BL contrasts with that of the correlation between degree of immunosuppression and risk for primary CNS lymphoma. While the latter occurs at very low CD4 counts, there is a clear deficit of BL cases in people with very low CD4, suggesting a requirement of a threshold of CD4 for BL pathogenesis (Guech-Ongey et al. 2010). Although access to antiretroviral therapy has expanded significantly in recent periods in sub-Saharan Africa, there are sparse data to understand whether cART has impacted incidence of BL in these regions.

13.3 Molecular Features of BL

Irrespective of the epidemiological variant, almost all BL are characterized by a signature translocation that juxtaposes and thereby deregulates the c-myc gene, bringing it under the regulatory control of the B-cell-specific immunoglobulin locus. Most frequently this translocation is between c-myc on chromosome 8 and the IgH gene on chromosome 14 [t(8:14)]. Variant translocations involving c-myc and antibody light chain genes, either IgK [t(2:8)] or IgL [t(8:22)], occur in about one fifth of BL cases. Some reports of lymphomas that otherwise are immunophenotypically identical to BL but do not carry these translocations have also been

described. Such myc-negative cases occur both in adults and in children. It is likely that alternate pathways with the end result similar to a deregulated myc might be in play in these lymphomas. The proportion of AIDS-related BL that similarly show absence of a c-myc translocation is not known. Molecular translocations of chromosomes 8 and 14 differ with respect to their breakpoints between sporadic and endemic BL and also differ between sporadic BL from different regions. In endemic BL the breakpoint often leaves the transcriptional unit of c-myc intact and occurs several hundred kilobases upstream or downstream of the c-myc gene. On the other hand, in sporadic BL cases in the USA, the translocation often involves breaks between exons 1 and 2 of the c-myc gene. Sporadic BL and AIDS-associated BL from the USA do not appear to be different at the molecular level of the translocations. The breakpoints in sporadic BL cases from other world regions such as Argentina and Brazil differ and often cluster immediately upstream of c-myc gene (Magrath et al. 1992). There is insufficient data on breakpoints from AIDS-associated BL from countries outside the USA. The significance of these regional differences in breakpoints is unclear. However with the exception of BL from Algeria (where the breakpoints are often within the c-myc transcriptional unit), there appears to be a gradient of association between the proportion of EBV positivity and breakpoint location among BL from other regions. Patients with EBV-negative BL are relatively more likely to have breaks occurring within the transcriptional structure of c-myc gene, suggesting the possibility that EBV may contribute to deregulation of translocated c-myc with breakpoints far upstream or far downstream of c-myc.

There is considerable evidence that the Ig-myc translocations lead functionally to myc deregulation, although this in itself is insufficient to trigger onset of clinical BL. Some data suggest that proliferation in normal germinal center cells is not myc driven and thus a forced expression of c-myc in germinal center B cells is the most likely central component of the pathway to B-cell lymphomagenesis in BL. In addition to the translocation, a contribution to the deregulation of c-myc is also provided in AIDS-associated BL by mutations that are present in a small 500 base pair regulatory region in the junction of the first exon and first intron of the c-myc gene. Most BL, including AIDS-associated BL, carry no or only a few other cytogenetic abnormalities. Abnormalities involving chromosome 1q, 7q21 and 12p13 have been reported in sporadic BL.

However, like other cancers, additional genetic alterations are required to circumvent the homeostatic feedback loops triggered by deregulated c-myc to prevent progression to malignancy. Among the additional molecular lesions described in BL, those that incapacitate apoptotic pathways are prominent. Inactivation of p53 is frequently found in BL including AIDS-associated BL. Other molecular abnormalities include mutations in proapoptotic proteins such as Bak and diminished expression of proteins that inhibit apoptosis such as cIAP-1 and cIAP-2. Presence of inactivating mutations of RBL2 has been reported in endemic and some sporadic BL, while HIV-positive BL cases have been found to demonstrate an overexpression of wild-type RBL2. The tumor suppressor functions of RBL2 have been shown to be neutralized by physical interactions with HIV-1 Tat protein suggesting that HIV-1 may directly interact in the pathogenesis of BL. In addition to mediating

proliferation, constitutional expression of c-myc also blocks cell differentiation and induces apoptosis. The oncogenic conversion of c-myc in HIV-associated BL often incorporates mutations within the c-myc coding regions (Bhatia et al. 1993). Mutations affecting c-myc are most likely a result of abnormal somatic hypermutations (SHMs). Aberrant SHM also results in a wide range of mutations in other oncogenes including BCL6. Epigenetic alterations are also frequently associated with both HIV and non-HIV BL and target expression of MGMT, DAPK, and P73.

Phosphoinositide-3-kinase (PI3K) signaling plays a critical role downstream of B-cell receptor signaling in B cells. More recent data implicate activation of PI3K pathway as an important pathogenic event in BL that might synergize with deregulated c-myc (Schmitz et al. 2012). Aberrations in this pathway result from somatic mutations that deregulate the activity of E2A or inactivate its negative regulator ID3 and also as a result of mutations in cyclin D3 a gene that is the direct target of E2A and is intricately involved in the control of germinal center B-cell proliferation. It is not yet clear whether there are differences in the proportion of HIV and non-HIV BL with respect to the synergistic involvement of the PI3K pathway in conjunction with a deregulated c-myc.

13.4 Role of EBV

Most of the cancers associated with HIV infection have a viral etiology. *Hodgkin lymphoma* and primary CNS lymphomas arising in the context of immunodeficiency are almost always associated with EBV, and approximately 30–50 % of *diffuse large B-cell lymphomas* (*DLBCL*) in people with HIV are EBV-positive compared to less than 5 % of EBV-positive DLBCL in the HIV-negative setting. Also, approximately 30–60 % of cases of HIV-associated Burkitt lymphoma are EBV-associated. This is more than observed in sporadic BL, but less than found in endemic BL, in which 95 % or so of cases are EBV-associated.

As in other lymphomas, EBV is generally latent in BL tumor cells. In latent EBV infection, a very restricted pattern of gene expression is observed. There are three programs of EBV latency, ranging from latency I, in which only EBV nuclear antigen 1 (EBNA-1) and EBV-encoded RNAs (EBERs) are expressed, to latency III in which all the latent genes are expressed. Many latently expressed EBV proteins are immunogenic. Latency III is only found in tumors in immunodeficient hosts such as in HIV-associated DLBCL and the polymorphic post transplant lymphoproliferations. Interestingly, in BL that occur in the context of immunodeficiency, the pattern of latency expression is latency I, in which only EBNA-1 and EBERs are expressed. This is similar to the latency pattern in non-HIV BL. Also similar to the non-HIV BL, EBV is monoclonal in BL that arise in AIDS patients. Both these observations are consistent with the hypothesis that EBV is not merely an opportunistic passenger as a result of diminished immunosurveillance but plays a pathogenic role in HIV-associated BL.

Several possible roles for EBV in the pathogenesis of BL have been suggested. The expression of EBERs might support survival by inducing the expression of IL-10. Both EBNA-1 and EBERS also confer antiapoptotic activity and thereby promote survival of clones with a deregulated c-myc. The restriction of expression of latency genes to latency pattern I in immunodeficiency associated BL is nonetheless intriguing and suggests that even in the context of reduced immune pressures, there is a need for downregulating the expression of the majority of EBV latent genes. It is possible that the expressions of certain latent EBV genes, such as EBNA-2, are incompatible with pathways that support BL lymphomagenesis. A scenario that emerges therefore is that HIV-positive BL cells are derived from an amplified pool of EBV-transformed B cells that initially expressed the full repertoire of latent genes. It might be that some of these genes such as latent membrane protein-1 (LMP-1) helped orchestrate immunoglobulin class switching and SHM through the induction of activation-induced deaminase (AID) pathways, as will be discussed below.

The contribution of EBV to antiapoptotic mechanisms in BL along with the incompatibility of EBNA-2 with BL lymphomagenesis is also supported by recent observations of a variant latency pattern in a small proportion of BL. This latency pattern, called Wp-restricted latency, results from the use of the Wp promoter in mutant EBV genomes and is associated with about 15 % of BL. The mutant EBV genomes carry a deletion of the EBNA-2 region and allow expression of EBNA 3A, 3B, 3C and the EBV antiapoptotic gene BHRF1 (Bornkamm 2009). It is yet not known how often mutated EBV genomes are associated with HIV-positive BL in comparison with non-HIV BLs. There is a greater genomic diversity associated with EBV in HIV-infected individuals, and HIV-positive BL are more often associated with type B EBV. The theoretical possibility therefore exists that a wider genomic diversity of EBV strains and subtypes prevalent in the context of a reduced EBV immunosurveillance in people with HIV infection allows for more "oncogenic" variants of EBV to enhance likelihood of lymphomagenesis including the development of Burkitt's lymphomas.

13.5 Role of HIV

HIV does not directly infect BL clones and thus its influence in enhancing risk for BL in people with HIV infection is mediated indirectly. T-cell immunodeficiency resulting from HIV infection plays a central role in increasing the risk of certain cancers, particularly those caused by oncogenic viruses. Thus both the degree and the duration of immunosuppression measured by deficit in CD4 T cells correlate with risk of lymphomas. A decrease in incidence of some lymphomas such as primary CNS lymphomas in the cART era supports the importance of such immune surveillance, directed against the virus and/or viral antigens expressed on the tumor cells. By contrast with primary CNS lymphoma, the correlation between the degree of immunosuppression and the risk for BL is more complex. The incidence of BL is only modestly affected in the cART era, and BL arises even in the context of a

relatively recovered immune status in patients receiving cART therapy. A deficit of BL has been documented in patients with extremely low CD4, such as those with CD4 counts between 100 and 50/μl, suggesting a threshold requirement of T cells in BL lymphomagenesis. In addition to decrease and dysfunction of T-lymphocyte as a result of HIV infection, there is a parallel increase in B-cell activation and an overproduction of B-cell stimulatory cytokines combining to allow chronic B-cell hyperactivation, contributing indirectly to risk for lymphomas. As noted above, one postulated mechanism of HIV-driven lymphomagenesis is the activation and expression of the DNA editing enzyme-induced cytidine deaminase (AID). AID expression has been shown to be elevated in B cells of HIV-positive individuals prior to the diagnosis of NHL. It is possible thus that this overexpression of AID, which is known to promote *c-MYC*/*IgH* translocations, induces aberrant (*Ig*) class-switch recombination (CSR) and SHM contributing to increased frequency of B cells with lymphoma-specific translocations (Epeldegui et al. 2006).

Other mechanisms whereby HIV-related proteins may directly influence BL development also need to be considered. HIV-infected cells secrete *tat* protein which is present in sera and thus is capable of exerting biological effects when taken up by other cells including B cells. *Tat* has potential oncogenic activity and can inactivate tumor suppressor genes including RB2, which has been shown to play a contributory role in development of some BL.

13.6 Presentation and Pathology

Endemic BL often presents with localized disease, frequently affecting the jaw or the abdomen. In some cases, other extranodal sites including breasts, ovaries, and kidneys may be involved. Bone marrow involvement and nodal involvement is rare in endemic BL. Sporadic BL particularly in children also frequently involves the abdomen, while facial involvement is rare. A greater proportion of sporadic BL than endemic BL involves the bone marrow. By contrast to endemic BL, AIDS-BL often presents with lymphadenopathy. CNS involvement and advanced stage at presentation is also seen more frequently with AIDS-BL than in other types of BL, both in children and adults.

Most cases of endemic and pediatric BL present a classical cytologic appearance. The tumor is comprised of monomorphic, uniform cells of medium size with round nuclei, moderately clumped chromatin, and multiple basophilic nucleoli. The cytoplasm is abundant and basophilic and contains many lipid vacuoles. The characteristic "starry sky" pattern of BL results from multiple infiltrating macrophages that ingested apoptotic tumor cells. Compared to classic BL, AIDS-associated BL and a proportion of adult BL have a variant appearance and depict less uniformity. In AIDS-associated BL there is a tendency for plasmacytoid differentiation. Irrespective of the type of BL several important immunophenotypic characteristics are common. These include positivity for surface IgM, CD10, CD79a, a high score

of proliferation identified by Ki67 staining of all or nearly all (>95 %) of tumor cells, and an absence of BCL-2 and TdT staining.

In patients with HIV and particularly in adults, distinguishing between cases that are true BL from morphologically similar other aggressive B cell lymphomas such as those that are DLCBL is prognostically important. A fraction of BL cases remain difficult to classify because they have features intermediate between DLCBL and BL. Recent data using molecular gene expression profiles have provided a characteristic molecular signature of BL. Therefore application of such molecular diagnostics might provide added diagnostic tools in the future. In the more recent WHO classification of lymphomas a category of B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL (B-UNC/BL/DLBCL) has been introduced to characterize the lymphomas that are difficult to distinguish between BL and DLCBL (Jaffe and Pittaluga 2011).

13.7 Treatment

Endemic BL was one of the first malignancies that was shown to respond to chemotherapy. Since then, chemotherapy has remained the mainstay for therapeutic management of all forms of BL. Surgery and radiotherapy have little to offer to BL treatment. Early studies demonstrated a high degree of chemosensitivity of endemic BL, which responds particularly well to cyclophosphamide, methotrexate and vincristine. Long durations of remissions were noted with these drugs, and late relapsing tumors were found to retain chemosensitivity to the initial treatment, and to respond fully to second line treatment. The use of simultaneous and upfront combination chemotherapy, particularly using drugs that were not cross-reactive, along with intrathecal chemotherapy, improved long-term outcomes and reduced relapse of BL in the CNS. The experience gained from these early treatment protocols continues to influence the management of BL in Africa.

The recommended first line treatment of BL is intravenous treatment with cyclophosphamide, vincristine, and methotrexate (COM) and intrathecal methotrexate and cytarabine. At least three cycles, given every 2–3 weeks, are recommended for early stage disease and six cycles late stage disease. The second line regimen, for patients who fail the first line, is a four-drug intravenous regimen including etoposide, ifosfamide, mesna, and cytarabine, along with intrathecal methotrexate and cytarabine. While these treatments are likely very efficacious (80 % response in African settings), many patients with endemic BL die soon after diagnosis from tumor lysis syndrome, late presentation, and the patients choosing to stop receiving treatment.

Treatment of sporadic BL in the USA and other western countries was informed by the experience treating endemic BL. Cyclophosphamide, vincristine, and methotrexate formed the backbone of initial treatment regimens, which over time became increasingly intensive. An important step to optimal treatment of both adult and pediatric BL was the design of the CODOX-M/IVAC regimen, sometimes called the Magrath regimen, which achieves remission rates of up to 100 and 92 % event-free

survival at 5 years in children and adolescents (relapses in BL are very rare after 1 year). Subsequent clinical studies have evaluated this protocol in multi-institutional settings, and some modifications of the protocol have been introduced to preserve efficacy while decreasing neurotoxicity. These modifications include a reduction in the dose of methotrexate, limiting the dose vincristine, and increasing the dose of doxorubicin. Utilizing data from pre-clinical studies that suggested diminished tumor resistance when sustained concentrations of doxorubicin, vincristine, and etoposide are used, Wyndham Wilson and colleagues in the National Cancer Institute intramural program introduced infusion dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (DA-EPOCH) for the treatment of adult lymphomas, and this regimen was found to have utility in the treatment of sporadic BL.

Early in the AIDS epidemic, most AIDS-associated lymphomas, irrespective of histological subtype and stage were treated with less aggressive therapy as compared to standard regimens, and the general outcomes of these initial approaches in HIV-associated BL were inferior compared to non-HIV BL. With the introduction of cART, there was an appreciation that HIV patients were better able to tolerate standard chemotherapeutic regimens, generally along with cART. The AIDS Malignancy Consortium has studied modified CODOX/IMVAC regimen for AIDS-related BL. DA-EPOCH is another option that has been shown to be effective for treating AIDS-BL and AIDS BL-like lymphomas. Because BL and BL-like lymphomas, both in HIV-positive and HIV-negative patients, frequently express CD20, the use of rituximab, a monoclonal anti CD20 antibody, has also been tested and found to have activity. Rituximab has been incorporated into a modified Magrath regimen as well as with the infusion dose-adjusted EPOCH regimens (Mwamba and Remick 2012). In a more recent study, a short course of low dose intensity EPOCH regimen with added double dose of rituximab (Dunleavy et al. 2013) provided 90 % overall survival in the subset of adults with HIV-associated BL. Concurrent HAART was not included and a modest decline in the mean CD4 counts before and immediately after treatment was observed in the treated patients. If further confirmation of these studies in controlled trials is achieved, it would suggest that high rates of cure are possible in HIV-associated BL even with low intensity regimens.

The treatment of HIV-related BL in sub-Saharan Africa poses special challenges. In general, the use of highly intensive therapy is difficult in Africa because of limited drug supply, as well as a lack of high-quality supportive care. Modified regimens that are practical in the loco-regional setting, including oral-based regimens and modified CHOP-like regimens, are being studied in Africa, similarly incorporating cART to standard regimens used to treat BL in sub-Saharan Africa such as the COM regimen are possible alternatives for use in sub-Saharan HIV-related BL (Magrath 2012).

13.8 Summary and Future Directions

The discovery of the entity now known as Burkitt's lymphoma was first made by Dr. Dennis Burkitt in equatorial Africa. The study of what is now called endemic BL proved to be immensely important and established several landmarks in biology and treatment of cancers worldwide. These included the discovery of the first human virus associated with cancers—EBV—and the first demonstration of the use of chemotherapy in the treatment of solid tumors. The risk for BL is increased about 50–60-fold in people with AIDS in the USA; however, the magnitude of increase of BL is only about tenfold in HIV-infected children and adults in areas where BL is endemic. BL is a lymphoma derived from germinal center B-cell and is variably associated with EBV. A defining feature of BL is the presence of a simple translocation involving the c-myc locus with an IgH, IgK, or IgL locus. It is a highly proliferating tumor with more than 95 % of tumor cells staining for Ki67. Molecular analysis of gene expression studies has defined a BL signature, which distinguishes it from other aggressive B-cell lymphomas such as DLBCLs. However, some tumors are intermediate between BL and DLBCL and are now considered a separate category of tumor. A diagnosis of BL is clinically relevant since BL-specific therapy is essential for optimal outcome. The treatment of HIV-associated BL now yields a comparable response rate and outcome as compared to BL in the HIV-negative setting. Recent laboratory-based studies have identified new genetic lesions in BL which may provide novel targets for the development of small molecules capable of interfering with genetic circuits that sustain proliferation of BL cells.

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Chapter 14
Primary Effusion Lymphoma

Giovanna Tosato

Abstract Primary effusion lymphoma (PEL) is a rare non-Hodgkin's lymphoma that characteristically presents as a malignant effusion in the body cavities of patients with AIDS and occasionally in other patients with an underlying immunodeficiency. The malignant PEL cells are infected with Kaposi's sarcoma herpes virus (KSHV, also known as human herpesvirus-8, HHV8) and are often co-infected with Epstein–Barr virus (EBV). PEL cells display morphologic features of large-cell lymphomas and are of B-cell lineage. The diagnosis of PEL is characteristically made in AIDS patients presenting with a malignant effusion in the pleural, pericardial, or peritoneal cavity characterized by the presence of KSHV-infected cells with characteristic morphology and phenotype. The clinical course of PEL is generally aggressive, with a mean survival of less than 1 year, despite chemotherapy.

14.1 Introduction

Primary effusion lymphoma (PEL) was recognized as a distinct clinical entity when it was discovered that certain non-Hodgkin's lymphomas arising in the pleural, pericardial, or peritoneal cavity of HIV-infected patients (Knowles et al. 1989a) were infected with KSHV, often in conjunction with the related herpes virus EBV (link to chapter 6) (Cesarman et al. 1995). By definition, PEL cells are infected with KSHV. In 70–90 % of cases, PEL cells are co-infected with EBV. KSHV viral sequences were first identified in Kaposi's sarcoma (link to chapter 9) (KS) tissues (Chang et al. 1994), and were subsequently detected in a proportion of lymphoid tissues affected by multicentric Castleman's disease (MCD) (Soulier et al. 1995), and in

G. Tosato (✉)
Laboratory of Cellular Oncology, Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA
e-mail: tosatog@mail.nih.gov

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PEL cells (Cesarman et al. 1995). KS, MCD, and PEL are the three principal malignancies caused by KSHV that arise in AIDS patients. Clinical descriptions of PEL in patients with AIDS preceded by about 5 years the discovery of KSHV, and since then it was suspected that these lymphomas might constitute a distinct entity because of their unusual presentation in body cavities, histology, and phenotypic characteristics (Knowles et al. 1989b; Nador et al. 1995; Subar et al. 1988; Walts et al. 1990). PEL may give rise to solid tumor masses inside the body cavities by adhesion to the mesothelial layer and may infiltrate surrounding tissues; these forms are referred to as "solid PEL" (Huang et al. 2002; Menon et al. 2012). More infrequently, KSHV-infected large-cell lymphomas resembling PEL have been observed in HIV-infected individuals without malignant effusions (Carbone et al. 2005; Hasegawa et al. 2004; Mylona et al. 2008; Pan et al. 2012). Because these KSHV-infected lymphomas resemble PEL in morphology, phenotypic and genetic characteristics and are often co-infected with EBV, the 2008 World Health Organization classification described them under the category of PEL as they may represent part of a spectrum of PEL types (Menon et al. 2012).

14.2 Epidemiology and Pathogenesis

PEL comprises only about 4 % of all HIV-associated non-Hodgkin lymphomas (link to chapters 12, 13, 15, 16) (Simonelli et al. 2003), which are estimated to develop in 5–20 % of HIV-positive patients, with a relative risk 60–200-fold higher than that of the general population (Little et al. 2001; Yarchoan et al. 2005). The development of high-grade B-cell non-Hodgkin's lymphoma in an HIV-positive individual is considered an AIDS-defining illness; this occurs in 3–4 % of HIV-infected individuals (Little et al. 2001). The introduction of highly active antiretroviral therapy (HAART) (link to chapter 27) has decreased the incidence of HIV-associated non-Hodgkin's lymphomas, particularly the incidence of primary central nervous system lymphomas (link to chapter 15) (Navarro and Kaplan 2006; Yarchoan et al. 2005).

Studies of PEL pathogenesis have focused on KSHV, since infection with this herpesvirus defines the illness, but the mechanisms by which KSHV promotes tumorigenesis are currently incompletely understood, and are likely complex. KSHV is a gammaherpesvirus, which is endemic in sub-Saharan Africa (where the seroprevalence ranges between 50 and 70 % of the population) and in the Mediterranean basin (where the seroprevalence ranges between 20 and 30 % of the population); in North America KSHV infection among blood donors is believed to range between 1 and 3 % but is higher in certain risk groups (e.g. men who have sex with men) (Dukers and Rezza 2003). Some aspects of the natural history of KSHV are incompletely understood, including how the virus is transmitted to humans, in which cells it replicates, where it establishes latency and how the immune system controls primary and latent infection. The strong association of KSHV malignancies with HIV infection has prompted investigation into the role of HIV infection. HIV does not infect PEL cells, but T-cell immunodeficiency associated

with AIDS is believed to contribute to KSHV tumorigenesis by reducing immunity to the virus and to virus-infected cells, and by promoting expression of growth-promoting cytokines and growth factors (Ganem 2006). In addition, one of the HIV-1 proteins, the TAT protein may facilitate KSHV infection of target cells (Aoki and Tosato 2004). The observation that the majority of PEL are co-infected with EBV has suggested a contribution by EBV, a herpesvirus that infects most adult individuals worldwide. Unlike KSHV, which has not been shown to immortalize any cell type in culture, EBV is a potent B-cell immortalizing herpesvirus. However, EBV is not always present in PEL cells suggesting that it is not necessary. Nonetheless, EBV may contribute to PEL tumorigenesis (Horenstein et al. 1997; Xu et al. 2007). Comparative biochemical profiling of PEL cells infected with KSHV alone or co-infected with KSHV and EBV has failed to identify major differences, except for increased activation of the MAPK (Mitogen-Activated Protein Kinase) pathway in cells infected with KSHV alone (Carbone et al. 2005; Fan et al. 2005). In spite of its inability to immortalize normal cells of B-cell lineage in culture, KSHV is required for the survival and growth in culture of established PEL cell lines (Godfrey et al. 2005; Guasparri et al. 2004; Kliche et al. 1998).

KSHV exists in PEL cells as an oligoclonal or monoclonal episome, and in PEL usually does not undergo complete lytic replication resulting in the production of infectious viral particles (Judde et al. 2000). Rather, PEL cells are generally latently infected with KSHV, expressing only a few viral gene products. Thus, attention has focused on these KSHV latency genes (Speck and Ganem 2010). LANA (latency-associated nuclear antigen-1) is one such gene product, which tethers the viral DNA to the host-cell DNA, and this ensures viral DNA persistence during PEL cell replication (Ballestas et al. 1999). LANA also binds to the tumor-suppressor genes p53 (Friborg et al. 1999) and Rb (Radkov et al. 2000), thereby promoting cell survival and sustained growth. Viral cyclin (vCYC), which is closely related to cellular cyclin D2, can inhibit the cell cycle inhibitor p27 KIP1 promoting cell cycle progression (Ellis et al. 1999; Swanton et al. 1997). Viral FLICE inhibitory protein (vFLIP) is required for the continuous growth and survival of PEL cells in vitro (Guasparri et al. 2004), and v-FLIP activates the NFκB pathway thereby promoting the expression of many cellular genes that can contribute to PEL survival and growth (Matta and Chaudhary 2004; Sakakibara et al. 2011; Speck and Ganem 2010). Viral IL-6 (vIL-6), which shares similarity with cellular IL-6, is an autocrine growth factor for PEL cells in culture (Jones et al. 1999; Sakakibara and Tosato 2011). The viral G-protein-coupled receptor stimulates cell proliferation and promotes the expression of the pro-angiogenic and vascular permeability factor VEGF (Bais et al. 1998; Speck and Ganem 2010). The viral Bcl2 homolog, vBcl-2, blocks cell apoptosis (Cheng et al. 1997; Speck and Ganem 2010), and a viral homologue of the interferon regulatory factor (IRF) family of proteins, vIRF, inhibits interferon signaling (Gao et al. 1997). All these KSHV latency genes have the potential to contribute to PEL malignant phenotype as they promote cell progression through the cell cycle resulting in uncontrolled cell growth, and prevent cell death (Speck and Ganem 2010). In spite of this pattern of viral gene expression and gene function, and in contrast to their sustained and progressive growth in the body cavities,

PEL are not easily propagated in culture once removed from the patients' body cavities, whether or not PEL cells are infected with KSHV alone or are co-infected with EBV (Ganem 2006). This situation differs drastically from the ease with which B cells naturally infected with EBV can be propagated in vitro as immortalized cell lines, suggesting an important contribution of the tumor microenvironment in supporting PEL cell growth. As a consequence, only few PEL cell lines are currently available, which provide the only cells naturally infected with KSHV that can be propagated in vitro.

PEL cells resemble a post-germinal center B cell because they display immunoglobulin gene rearrangement and somatic hyper-mutation; gene expression profile analysis suggests that PEL cells are plasmablastic (Klein et al. 2003; Menon et al. 2012). Consistent with this, PEL cells express the plasma cell-associated CD138/syndecan-1 marker and CD45 but lack expression of common B-cell-associated antigens (including surface immunoglobulin, CD19 and CD20). They also generally lack the T-cell markers CD4 and CD8, although they may express cytoplasmic CD3. A number of activation markers, including CD30, CD38, CD71, and HLA-DR are usually detected in PEL (Carbone et al. 1998; Gaidano et al. 1997). Cytogenetic analysis has revealed no common chromosomal aberration in PEL, but Myc is often amplified (Boulanger et al. 2001; Bubman et al. 2007). Morphologically, PEL cells appear plasmablastic, immunoblastic, or anaplastic lymphoid cells.

14.3 Clinical Presentation, Diagnosis, and Treatment

Patients with PEL are usually HIV-positive men, often with AIDS, presenting with symptoms resulting from accumulation of the malignant effusion in the pleural, pericardial, or peritoneal cavity, including dyspnea (pleural and pericardial PEL) and abdominal distension (peritoneal PEL). In cases of extra-cavitary PEL localized to the gastrointestinal tract, soft tissue or other extra-nodal sites, patients may present with symptoms reflecting PEL tissue location (Costes et al. 2002). A proportion of patients with PEL have preexisting or concomitant KS and/or MCD, the principal other malignancies associated with KSHV infection (Yarchoan et al. 2005). Occasionally, PEL arises in pharmacologically immunosuppressed HIV-negative patients who have received a solid organ transplant (Dotti et al. 1999; Jones et al. 1998) and in elderly patients of Mediterranean origin who are also at risk for developing HIV-negative, classical KS (Klepfish et al. 2001). The diagnosis of PEL is based on histological, virological, immunophenotypic, and molecular characteristics of the cells or tissue. Typically, PEL cells are derived from the effusions as cell suspensions, and are processed as cytospin preparations or embedded as a cell block. In cases of solid PEL, the diagnostic sample is a tissue fragment. Histologically, PEL cells are large, resembling plasmablastic (eccentric nuclei and abundant cytoplasm), immunoblastic (round central nuclei with prominent nucleoli), or anaplastic (very large cells with pleomorphic nuclei) lymphoid cells (Fig. 14.1). All these features can be simultaneously present, resulting in PEL having pleomorphic

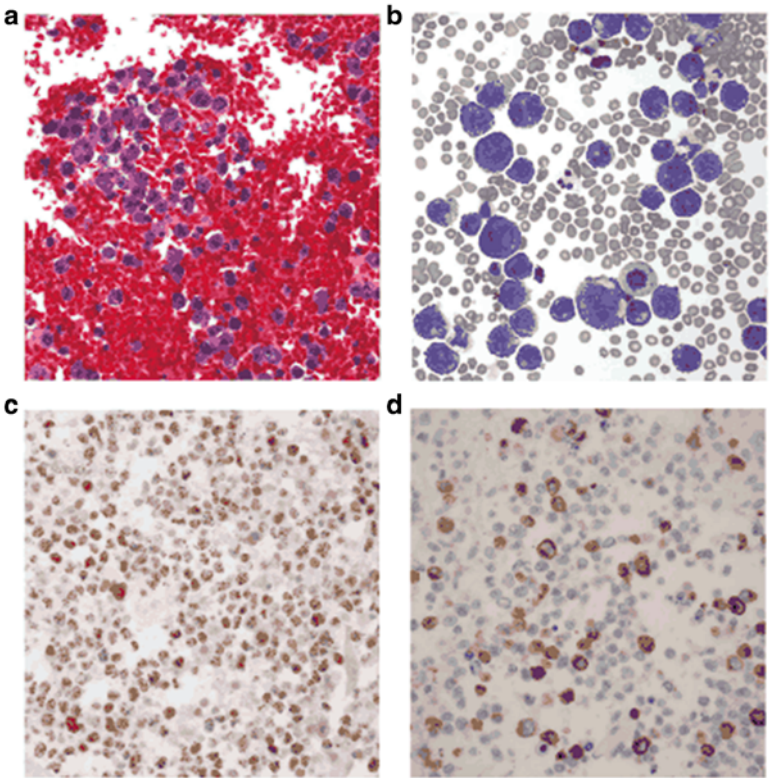

Fig. 14.1 Morphology, KSHV infection, and vIL-6 expression in PEL cells. Characteristic pleomorphic morphology of PEL cells from two AIDS-associated pleural effusions (**a**, **b**). KSHV-LANA (**c**) and vIL-6 (**d**) detection in PEL cells from a case of AIDS-associated extra-cavitary PEL (the images from the files of the laboratory of Pathology, CCR, NCI are a gift of Dr. S. Pittaluga)

morphology (Menon et al. 2012). Demonstration of KSHV infection is required for diagnosis of PEL, which is usually accomplished by immunohistochemical detection of KSHV-LANA (Dupin et al. 1999). Evidence of EBV infection is usually obtained by in situ hybridization of EBV-EBER (EBV-encoded RNAs) (Menon et al. 2012). The EBV latent membrane protein-1 (LMP1) is usually not detected in PEL. Immunophenotyping reveals the expression of CD138, CD45, and cytoplasmic CD3, in the absence of mature B-cell markers (Carbone et al. 1998; Gaidano et al. 1997). The differential diagnosis in cases of PEL includes other types of non-Hodgkin's lymphomas associated with lymphomatous effusions; many histologic subtypes of non-Hodgkin's lymphomas can present as a neoplastic effusion (Chan et al. 2003; Venizelos et al. 2005). Pyothorax-associated diffuse large-cell B-cell lymphoma is also considered in the differential diagnosis. This lymphoma develops in the pleural cavity in the setting of pyothorax in elderly HIV-negative patients is EBV-positive but KSHV-negative (Nakatsuka et al. 2002). The correct diagnosis of PEL requires integration of clinical presentation and correct interpretation of

histological, virological, and immunophenotypic characteristics of the tumor cells. The initial patient evaluation includes a complete blood count and comprehensive chemistry panel together with appropriate staging to estimate disease burden and provide a baseline to assess response to treatment.

First-line therapy of AIDS-associated PEL often consists of combination chemotherapy with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone)-like regimens, generally added to HAART antiviral treatment (link to chapter 27) (Boulanger et al. 2003; Valencia et al. 1999; Yarchoan et al. 2005). Complete remissions have been observed in a proportion of patients (43–57 % remissions). However, the 1-year overall survival rate is reported at 39.3 % and the mean survival of patients with PEL is less than 1 year, despite treatment (Boulanger et al. 2005; Simonelli et al. 2003). There is evidence that the anti-CD20 monoclonal antibody, rituximab, can have activity in PEL, even though PEL cells generally express no or very low levels of CD20 (Perez and Rudoy 2001; Siddiqi and Joyce 2008). The most frequent causes of death are PEL progression as a consequence of drug resistance, and complications related to HIV infection, including opportunistic infections.

Treatment of PEL arising after solid organ transplantation presents unique challenges: T-cell immunosuppression is required to prevent graft rejection but immunosuppression can be harmful to control KHSV infection. Thus far, 14 cases of post-transplant PEL have been reported; 7 post kidney, 3 post heart, and 2 post liver transplantation (Riva et al. 2012). It is important to note that at least in some of these cases the transplant recipients likely became infected with KSHV after transplantation, having acquired the virus from KSHV-infected cell the graft. In these cases, primary KSHV infection in severely immunosuppressed individuals may have played a critical role in PEL development. Treatment recommendations for post-transplant PEL include a combination of reduced immunosuppression, antiviral therapy, and CHOP chemotherapy (Riva et al. 2012). The mTOR inhibitor rapamycin, which is often used as immunosuppressant after transplantation, has shown some efficacy in the treatment of experimental PEL, probably attributable to inhibition of VEGF translation (Sin et al. 2007). However, two cases of post-transplant PEL have been reported in patients on rapamycin raising concerns (Boulanger et al. 2008).

Chemotherapy at either standard or high dose has rarely cured PEL and has generally not provided long-term survival. Thus, much effort is being placed on novel approaches based on improved molecular understanding of PEL. One of the difficulties lies in the ability to recruit sufficient numbers of PEL patients for enrollment into clinical trials, which are often necessary to appreciate therapeutic advances. However, novel approaches to PEL treatment have been tested in some patients, others have been suggested from preclinical studies and some are currently being tested or are planned. Antiviral therapy with intracavitary cidofovir was reported to prolong survival in four PEL patients (Luppi et al. 2005), suggesting that KSHV replication may contribute to PEL disease progression. Whether the drug targets the limited or periodic KSHV replication occurring in PEL cells or other KSHV-infected host cells is currently not clear. In part based on this experience with cidofovir, attempts have been made to purposely promote viral replication in PEL cells

and combine this approach with antiviral agents: the anti-seizure medication valproate, which promotes KSHV replication was combined with cidofovir or foscarnet, resulting in increased PEL cell death in vitro (De Clercq et al. 2001). However, induction of viral replication in PEL cells by use of phorbol esters compromised PEL apoptosis induced by the chemotherapeutic agents doxorubicin and etoposide (Sarek et al. 2013). A different approach was based on the observation that the KSHV latency gene vFLIP, a potent activator of the NFκB pathway is necessary for PEL survival and growth in vitro. The proteosomal inhibitor bortesomib, which inhibits NFκB signaling, promoted apoptosis of PEL cells in vitro (An et al. 2004). In addition, Nutlin-3, an activator of p53, induced massive cell death in PEL cells injected subcutaneously in mice (Sarek et al. 2007).

Another approach has been directed at modifying the PEL tumor microenvironment by targeting VEGF, which promotes vascular permeability and contributes to the accumulation of body cavity effusions that accompany a number of malignancies (Dvorak et al. 1991). PEL cells express VEGF at high levels, and VEGF is present at high concentrations in PEL effusions (Aoki and Tosato 1999). In a preclinical model of PEL growing in the mouse peritoneal cavity, antibody neutralization of VEGF delayed PEL progression (Aoki and Tosato 1999). In addition, the mTOR inhibitor rapamycin, which inhibits VEGF translation, was effective at reducing PEL growth in this preclinical mouse model (Sin et al. 2007). However, drug resistance developed rapidly, in part due to accelerated PEL secretion of the autocrine growth factor IL-10 (Gasperini and Tosato 2009). The combination of VEGF and IL-10 neutralization has been proposed but has yet to be tested. Besides IL-10, vIL-6 is an autocrine growth factor for PEL and an inducer of VEGF production, which is detected at high concentrations in PEL effusions (Aoki et al. 1999; Sakakibara and Tosato 2011). Unlike human IL-6, which activates the common signal transducer gp130 only after associating with the non-signaling IL-6 receptor chain, vIL-6 binds directly gp130 and activates its phosphorylation and downstream signaling (Aoki et al. 2001). Since gp130 is expressed in virtually all cells, whereas the IL-6 receptor has a more limited cell distribution, vIL-6 has the potential to activate all cells in the body, thus potentially contributing directly or indirectly to PEL cell growth. Neutralization of vIL-6 by either monoclonal antibodies or soluble gp130 has been proposed to reduce PEL progression, particularly in situations in which PEL is associated with KSHV-associated MCD or related MCD-like syndrome, where vIL-6 is believed to play an important pathogenetic role (Rose-John et al. 2007). Another experimental treatment approach to PEL has been based on the observation of the importance of the STAT3 signaling pathway, which is active in PEL cells at least in part due to PEL activation by the autocrine growth factors IL-10 and vIL-6 (Aoki et al. 2003). Expression of a dominant-negative form of STAT3, which serves as a competitive inhibitor of STAT3 binding to target DNA sequences, not only prevented STAT3 activity in PEL but also induced prominent apoptosis in vitro. Consistent with a role of active STAT3 in PEL survival, the JAK2 synthetic inhibitor tyrphostin AG490, which inhibits STAT3 phosphorylation, promoted PEL cell death in vitro (Aoki et al. 2003).

14.4 Conclusion

In summary, PEL is a rare malignancy usually occurring in patients with AIDS characterized by KSHV-infected large-cell lymphoma cells. Despite chemotherapy, the prognosis is poor. It is hoped that an improved understanding of the role of KSHV in PEL pathogenesis and the biochemical pathways sustaining PEL progression will identify new targets for treatment.

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Chapter 15
AIDS-Related Primary Central Nervous System Lymphoma

Jan Davidson-Moncada and Thomas S. Uldrick

Abstract Primary central nervous system lymphoma (PCNSL) is a rare extra-nodal B-cell non-Hodgkin lymphoma, which arises in the brain, spinal cord, meninges, or eyes. In individuals infected with HIV, PCNSL occurs with advanced immunosuppression and low CD4 T-cell count. It is considered an AIDS-defining malignancy. Unlike PCNSL in immune-competent hosts, AIDS-related PCNSL (AR-PCNSL) is almost exclusively caused by a cancer-causing herpesvirus, Epstein–Barr Virus (EBV, also known as human herpesvirus-4). While PCNSL in immune-competent patients and AR-PCNSL have pathologic and clinical overlap, AR-PCNSL is distinguished by its strong association with immunosuppression and viral etiology.

15.1 Introduction

Primary central nervous system lymphoma (PCNSL) is a rare extra-nodal non-Hodgkin lymphoma, which accounts for approximately 3–5 % of primary brain tumors. Prior to effective therapy for HIV, a large proportion of cases of PCNSL, especially in younger individuals, occurred in severely immune compromised patients with acquired immunodeficiency syndrome (AIDS) (Ziegler et al. 1984); therefore, PCNSL is considered an AIDS-defining malignancy (Raez et al. 1998). However, after the broad availability of highly activate antiretroviral therapy (HAART) in 1996 (Pipkin et al. 2011), the incidence of PCNSL in HIV-infected individuals has decreased by nearly 90 % (Wolf et al. 2005). Nonetheless, the

J. Davidson-Moncada
Medical Oncology Branch, Center for Cancer Research, NCI, Bethesda, MD, USA

T.S. Uldrick (✉)
HIV and AIDS Malignancy Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA
e-mail: uldrickts@mail.nih.gov

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incidence AIDS-related (AR)-PCNSL in the USA remains significantly elevated at an estimated 26 cases per 100,000 person-years among people with AIDS, and continues to affect mainly patients under the age of 50 (Shiels et al. 2011). In areas where HAART is available, most patients with AR-PCNSL are not taking HAART either because they are not aware they are HIV infected or because of poor adherence to HAART. At the same time that incidence of AR-PCNSL has decreased, there has been an increase in the incidence of PCNSL in immune-competent elderly patients, highlighting a changing epidemiology of PCNSL in the USA related to differences in the underlying pathogenic processes (Shiels et al. 2011).

15.2 Histopathology and Pathogenesis

PCNSL is a B-cell lymphoma with diffuse large cell morphology. The diagnosis should be distinguished from systemic lymphoma with CNS involvement, dural-based low-grade lymphomas, and other rare histologies presenting in the CNS (Rubenstein et al. 2008). PCNSL in HIV-infected and HIV-uninfected patients share some clinical and morphologic characteristics; however, pathogenesis differs in important ways.

Both AR-PCNSL and PCNSL in immune-competent hosts are multifocal angiocentric tumors that express pan-B-cell markers (CD20, CD19, CD22 and CD79a). These tumors are highly proliferative with high expression of Ki-67 (Braaten et al. 2003; Deckert et al. 2011; Lin et al. 2006). PCNSL generally has a post-germinal center phenotype. In immune-competent patients, immunohistochemistry suggests a majority of tumors have activated B-cell differentiation based on lack of CD10 and common expression of IRF4 (90 %), a transcription factor associated with lymphocyte activation. However the germinal center associated transcription factor BCL6 is also expressed in 60–80 % of cases (Larocca et al. 1998). In contrast, AR-PCNSL, the immunophenotype is generally BCL6 negative and IRF4 positive (Carbone et al. 1998a, b). This immunophenotype is also noted in post-transplant lymphoproliferative disorder (PTLD) (Abed et al. 2004). Additional characteristics of AR-PCNSL include expression of the plasma cell marker CD138, the activation marker CD30, and adhesion molecules CD11a and ICAM-1 (CD54) that may contribute to homing to cerebral blood vessels (Bashir et al. 1992).

There are several similarities between AR-PCNSL and PTLD. PTLD is a disorder of proliferating latently EBV-infected B-cells that may be clonal and sometimes presents with CNS-only manifestations. PTLD can occur either after solid organ (SOT) or hematopoietic stem cell transplants (HSCT) as a result of medical immunosuppression. In HSCT it usually occurs within 6 months post-transplant and the lymphoproliferation is of donor-cell origin prior to EBV-specific cytotoxic T-cell reconstitution, while in SOT >90 % is of recipient cell origin and may have a longer latency due to long-term T-cell suppression to prevent organ rejection (Heslop 2009). Both AR-PCNSL and PTLD often have immunoblastic features (Castellano-Sanchez et al. 2004). Like PTLD, AR-PCNSL tumor cells almost always have

evidence of EBV-infection, as noted by staining for EBV-encoded small RNA (EBER1) transcripts (MacMahon et al. 1991). AR-PCNSL is usually clonal based on polymerase chain reaction (PCR) evaluation of the immunoglobulin heavy chain gene (IgH) (Schmitt-Graff et al. 1995).

Acquired T-cell immunosuppression is a common risk factor for both AR-PCNSL and PTLD. In patients with HIV, the majority of cases of AR-PCNSL occur in severely immune compromised patients with AIDS, and CD4 counts <50 cells/μL. AR-PCNSL patients have been shown to lack EBV-specific CD4+ T-cells, irrespective of absolute CD4 counts, supporting lack of immune regulation of EBV-infected B-cells as a critical mechanism of EBV-driven oncogenesis (Gasser et al. 2007). This is in contrast to PCNSL in immune-competent patients, in which evidence of EBV infection of the tumor cells is rare (MacMahon et al. 1991). A range of EBV viral proteins are expressed in both AR-PCNSL and PTLD, including the EBV-associated nuclear antigens (EBNAs) 1, 2, 3A, 3B, and 3C; latent membrane proteins (LMP) 1 and 2; and leader protein (LP). This pattern of EBV protein expression is referred to latency III, and is remarkable among EBV-associated tumors for the broadest expression of viral proteins. EBV-encoded genes may play an important role in lymphomagenesis, and at the same time, EBV latency III lymphoproliferations are also the most immunogenic EBV-associated tumors and responsive to immune-based therapies.

At the molecular level, a high level of aberrant somatic hypermutations have been detected both in PCNSL in immune-competent patients and in AR-PCNSL (Table 15.1) (Gaidano et al. 2003; Travi et al. 2012; Wolf et al. 2005). In AR-PCNSL, recurrent mutations have been noted in 5' region non-coding region of *BCL6*, *c-MYC*, *and TTF* (Courts et al. 2008; Montesinos-Rongen et al. 2004). Additional insight into the molecular pathogenesis of PCNSL has mainly been evaluated in tumors from immune-competent subjects. In PCNSL not associated with AIDS, additional recurrent mutations have been identified (Table 15.1). Also, chromosomal abnormalities involving either *IgH* or *BCL6* breakpoints detectable by fluorescent in situ hybridization (FISH) (Montesinos-Rongen et al. 2002) or gains and losses of genetic materials detectable by comparative genomic hybridization (CGH) (Schwindt et al. 2009) have been noted in PCNSL not associated with AIDS. In one study conducted in HIV-uninfected patients comparing immune-privileged sites (IP-testis and CNS) to systemic DLBCL identified a loss in 6p21.32-p35.3 in IP-DLBCL (Booman et al. 2008). Analysis of candidate genes encoded in that region identified two separate clusters: one involved in apoptosis, and a second involved in the immune response, including regulation of HLA expression (Booman et al. 2008). More recently, L265P gain of function point mutation in *MYD88* (Montesinos-Rongen et al. 2011) has been noted to be a common recurrent mutation in PCNSL. This point mutation is also noted in a subset of activated B-cell diffuse large B-cell lymphomas (Ngo et al. 2011) and Waldenstrom's macroglobinemia (Treon et al. 2012). Point mutations in the coiled region of *CARD11* have also been noted. These later two genes are implicated in NFkB dysregulation in B-cell lymphomas.

Gene expression profiling in PCNSL has been limited due to relatively small sample sizes ($n<25$), and has been mainly performed on tumors from

Table 15.1 Molecular pathology of primary CNS lymphoma in immune-competent patients compared to AIDS-related primary CNS lymphoma and other EBV-associated lymphomas with a latency III viral protein expression pattern

	PCNSL in immune-competent patients	AR-PCNSL and other latency III EBV-associated lymphomas
Somatic gene mutations	*PIM1*, *c-MYC*, *TTF*, *PAX5*, *Fas* (*CD95*), *CARD 11*, *MYD-88*, *BLIMP1*, *TBL1XR1*	*BCL-6*, *c-MYC*, *TTF* (Gaidano et al. 2003)
Chromosomal abnormalities by FISH or CGH	*IgH and BCL6* breakpoints 6p21-32 deletions 12q gains	Unknown
Human gene expression studies	Compared to systemic DLBCL: high expression of *XBP1*, *c-MYC*, *PIM1*, IL-4 induced genes (Rubenstein et al. 2006); as well as extracellular matrix and adhesion-related genes: *osteopontin*, *CXCL13*, and *IL-8*	Unknown
Human microRNA (miR)	Compared to systemic DLBCL, further upregulation of miR associated with germinal center B-cell lymphomas (miR17-5p, miR-20a, miR-155), as well as those blocking B-cell differentiation (miR-9, miR-30b/c)	High miR155 expression (Wang et al. 2011)
EBV viral–human gene interactions	Not applicable	EBV-encoded LMP-1 interacts with cellular TRAFs, activating NFkB (Kung and Raab-Traub 2010) LMP-1 induces IRF4, these proteins are co-expressed in AR-PCNSL (Xu et al. 2008) LMP1 upregulates adhesion molecules LFA1 and ICAM, leading to tumor necrosis and vascular destruction as seen in AR-PCNSL (Cherney et al. 1998)
EBV encoded miR	Not applicable	EBV-encoded BHRF1 miR cluster enhances EBV's transforming potential

HIV-uninfected patients. Three published studies (Montesinos-Rongen et al. 2008; Rubenstein et al. 2006; Tun et al. 2008) demonstrated a transcriptional signature that somewhat resembles systemic DLBCL. However, several genes of interest have been identified as being significantly upregulated in PCNSL compared to systemic DLBCL, including genes encoding adhesion-related proteins (*CXCL13*), extracellular matrix genes (*SSP1*, *osteopontin*), (Tun et al. 2008), and the oncogenes *Pim-1*, *c-MYC*, and *Mina53*. Interestingly, increased expression of the transcription factors *XBP1* and *ATF6*, which are genes that regulate unfolded protein responses, was noted in one study. Transcriptional upregulation appears to be associated with by

paracrine interactions with CNS vasculature, which is in part driven by tumor and endothelial IL-4 expression (Rubenstein et al. 2006).

The role of microRNAs in normal lymphoid development as well as lymphomagenesis is an area of active research. miR-155, which plays an important role in germinal center biology and is associated with B-cell proliferation and lymphomagenesis (Davidson-Moncada et al. 2010), appears to be even more highly expressed in PCNSL than systemic DLBCL. Additional microRNAs that are upregulated compared to systemic DLBCL include miR-17-5p and miR-20a, which target *the c-MYC* pathway, as well as those blocking B-cell differentiation (miR-9, miR-30b/c), while several putative tumor-suppressor miRNAs (miR-199a, miR-214, miR-193b, miR-145) may be downregulated (Fischer et al. 2011).

Further research is required to evaluate molecular similarities and differences between AR-PCNSL and PCNSL in immune-competent hosts. It remains unknown which of the genetic abnormalities seen in PCNSL also exist in AR-PCNSL, but it is likely that some molecular abnormalities in AR-PCNSL are due to interactions between EBV-encoded genes, microRNAs and lymphomagenic human signaling pathways. For example, latency membrane protein-1 (*LMP1*) is a viral oncogene that encodes a homologue to CD40 that is constitutively activated. Interactions between the C-terminal activating regions of LMP1 and tumor necrosis factor receptor associated factors (TRAFs) can lead to upregulation of NFkB (Kung and Raab-Traub 2010). LMP1 also upregulates of IRF4 (Xu et al. 2008), a hallmark of AR-PCNSL, while downregulating the transcription factor BLIMP1, which is required for plasma cell differentiation (Vrzalikova et al. 2011). LMP1 itself is upregulated by IL-4 (Kis et al. 2011), and therefore IL-4-dependent signaling appears to be important in both types of PCNSL. Interestingly, mouse models of lymphomas expressing LMP1 are notable for a high degree of tumor necrosis and vascular destruction and in some cases tumor regression, mirroring what is noted in AR-PCSNL. These findings may be mediated by upregulation of adhesion molecules and induction of chemokine anti-tumor responses (Cherney et al. 1998). Furthermore, miR-155, which is transcriptionally targeted by IRF4, is highly expressed in the Latency III pattern of EBV-infected B-cells as well as PTLD and is associated with cellular proliferation (Wang et al. 2011). Additional epigenetic mechanisms of lymphomagenesis attributable to dysregulated expression of EBV-encoded proteins and microRNAs in B-cells, as well as abnormal innate and acquired immune responses in AIDS patients are also likely.

15.3 Clinical Presentation, Diagnosis, and Baseline Evaluation

Neurologic disorders are prevalent in AIDS patients, and may be due to HIV-associated pathology, opportunistic infections, neoplasms, drug effects, and cerebrovascular disease. AR-PCNSL most often presents with neurologic symptoms such as headaches, lethargy, confusion, visual complaints, seizures, or focal neurologic symptoms such as cranial nerve dysfunction or hemiparesis. It occurs most of

the time in patients with CD4 counts less than 50 cells/μL. CT-scans usually show ring-enhancing CNS mass lesions. The main differential diagnosis of such lesions in patients with AIDS includes toxoplasma encephalitis, the most common cause, followed by PCNSL. Other causes of mass lesions are cryptococcal mengioencephalitis and tuberculosis (Rosenblum et al. 1988). Before HAART, toxoplasmosis encephalitis occurred in 3–10 % of patients in the USA (Luft and Remington 1992). However, toxoplasmosis is much less frequent with HAART as well as medicines commonly used in patients with CD4 counts less than 200 to prevent *pneumocystis* pneumonia such as trimethoprim–sulfamethoxazole. In the HAART era, toxoplasmosis incidence is less than 1 %, but like AR-PCNSL, it is most commonly seen in medically underserved HIV-infected populations not on HAART.

AR-PCNSL occurs primarily in the brain parenchyma, and may disseminate to the leptomeninges. Spinal cord, ocular, and cranial nerve involvement is rare. Given advanced immunosuppression in this population, patients with AR-PCNSL are also at risk for concurrent opportunistic infections, including CNS infections such as toxoplasmosis, cryptococcus, or CMV (Bower et al. 2006). Preferred initial imaging in patients with HIV and neurologic symptoms include contrast-enhanced magnetic resonance imaging (MRI), although CT with contrast can be used if MRI is not available. In AR-PCNSL, these imaging studies can identify single or multiple CNS masses, which are generally ring-enhancing with central necrosis, but may also have diffuse or nodular enhancement (Fig. 15.1). Mass-associated edema is also common, and can be best noted on MRI fluid attenuated inversion recovery (FLAIR) sequence imaging. CT and MRI are useful in excluding significant mid-line shift that may make a lumbar puncture unsafe. Toxoplasmosis and AR-PCNSL have similar presentations and cannot be reliably distinguished based on imaging and clinical features.

Establishing a definitive diagnosis of cerebral mass lesions in patients with known or suspected HIV (Fig. 15.2) requires a medical history focusing on HIV and opportunistic infections, use of prophylactic antibiotics with anti-toxoplasmosis activity, and risks-factors for systemic malignancies, as well as physical exam including professional ophthalmology evaluation. Expedited evaluation should include the following studies: HIV ELISA and viral load, CD4 count, CNS and body imaging to evaluate for systemic infections or malignancies, toxoplasmosis serology, and lumbar puncture to evaluate cerebral spinal fluid (CSF) for leptomeningeal dissemination and/or CNS infection. In cases of suspected ocular involvement, vitrectomy is indicated (Abrey et al. 2005).

Lumbar puncture with CSF studies and nuclear imaging provide important diagnostic information to help differentiate between AR-PCNSL and CNS infection and identify concurrent pathologies. The discovery of an almost universal association of AR-PCNSL with EBV infection (Bashir et al. 1993; MacMahon et al. 1991) has led to use of PCR to detect EBV DNA in CSF in patients with suspected AR-PCNSL. Additional initial CSF studies to evaluate for leptomeningeal dissemination and/or infections include: opening pressure, cell count, protein, glucose, gram stain, cryptococcal Ag, cytopathology, flow cytometry and (PCR) evaluation for immunoglobulin heavy chain (IgH) clonal rearrangements, EBV (quantitative) viral load, JC virus, cytomegalovirus (CMV, also known as human herpesvirus-5),

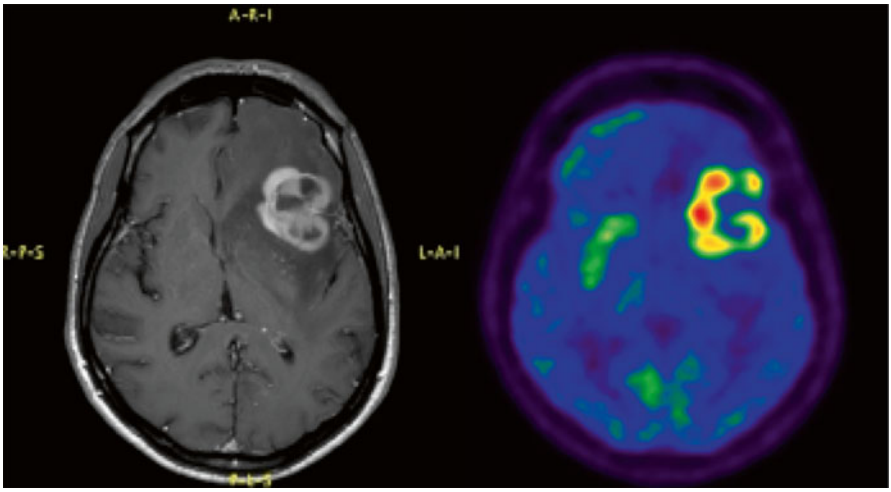

Fig. 15.1 *Left*: Gadolinium-enhanced T1 weighted magnetic resonance imaging in a patient with AIDS-related primary central nervous system lymphoma. *Right*: ^{18}F FDG-positron emission tomography in the same patient

and toxoplasmosis (Fig. 15.1). Other microbiology studies may be indicated in some cases based on MRI findings and patient history.

Two nuclear imaging modalities have been evaluated in patients with AR-PCNSL, thallium-201 (Tl-201) single-photon emission CT (SPECT) and 18(F) fluorodeoxyglucose positron emission tomography (FDG-PET). With either nuclear imaging modality, infections usually appear as hypometabolic lesions, whereas PCNSL or other tumors are hypermetabolic (Fig. 15.1). In patients with HIV/AIDS and low CD4 count (generally less than 100 cells/μL), sensitivity and specificity of nuclear imaging range between 80 and 100 % (Kasamon and Ambinder 2005). Combining imaging findings with data on toxoplasmosis serology (Skiest et al. 2000) and CSF EBV viral load can further increase diagnostic accuracy. The combination of Tl-201 SPECT with CSF-based testing increased the specificity and positive predictive value to nearly 100 % in one study (Antinori et al. 1999). However, it should be noted that EBV can be detected frequently in the CSF of patients with HIV/AIDS with systemic non-Hodgkin lymphoma or other diseases, and is not specific for AR-PCNSL (Corcoran et al. 2008). Furthermore, anti-toxoplasmosis titers can be elevated in patients with AR-PCNSL, and do not exclude concurrent pathology. For these reasons, despite technical advances in minimally invasive diagnostic tools for evaluation intracranial masses in AIDS patients, diagnosis of AR-PCNSL is done by pathological examination in nearly all cases.

CSF cytopathology as well as flow cytometry and IgH rearrangement studies may be useful in diagnosis of AR-PCNSL. The impetus for using CSF cytopathology as a diagnostic tool in PCNSL comes from studies utilizing this as adjunct in diagnosis of leptomeningeal involvement. CSF cytopathology can detect leptomeningeal spread in 15–40 % of untreated immune-competent PCNSL patients, and is

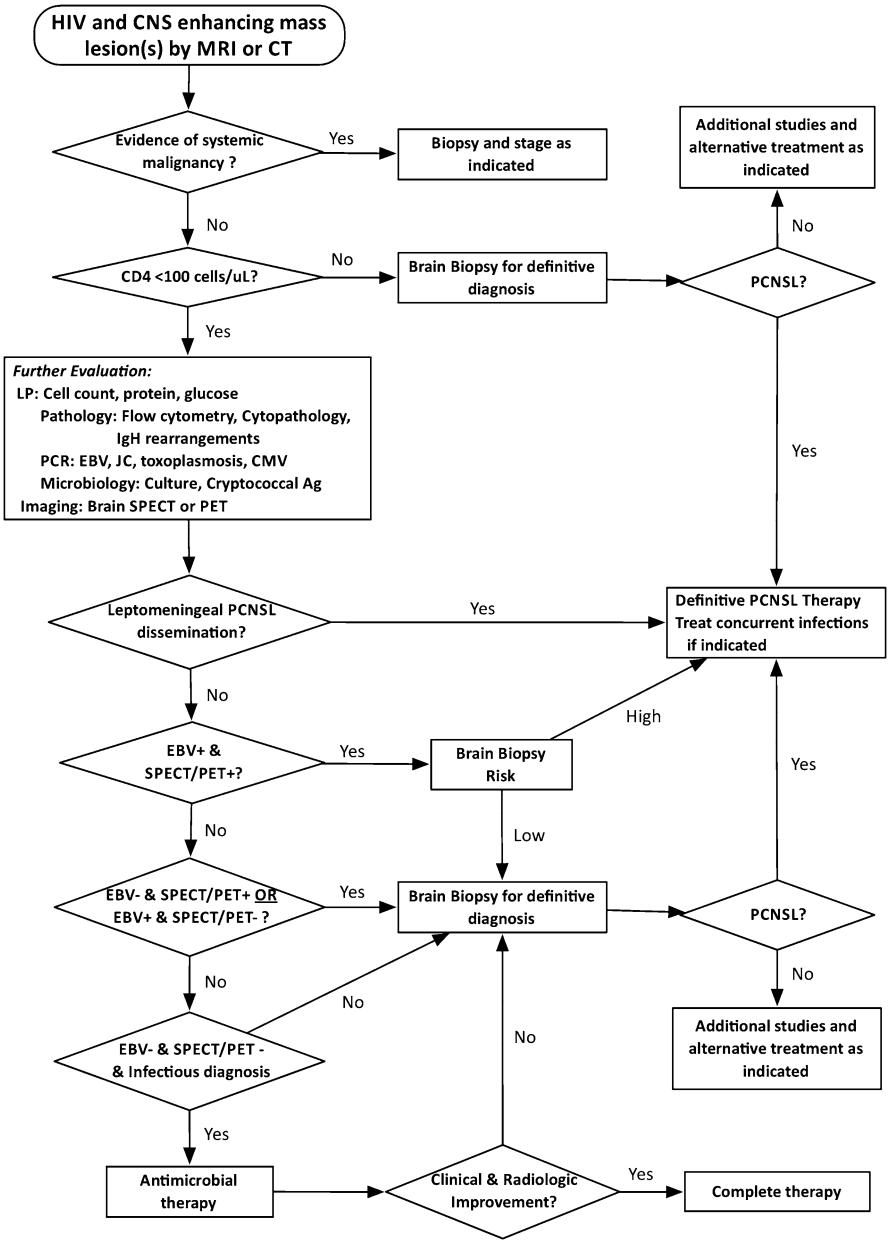

Fig. 15.2 An approach for evaluating of HIV-infected patients with central nervous system enhancing mass lesions

associated with higher tumor burden (Balmaceda et al. 1995; Ferreri et al. 2003; Fischer et al. 2008). Multi-parameter flow cytometry is also useful for detecting leptomeningeal involvement of both systemic diffuse large B-cell lymphoma and PCNSL,

and is more sensitive than cytopathology (Kraan et al. 2008; Schroers et al. 2010). IgH PCR studies of CSF can also detect clonal IgH rearrangements in patients with PCNSL, and provides important information that can be integrated with cytopathology and flow cytometric findings (Ekstein et al. 2006; Fischer et al. 2008). It should be noted that the utility of flow-cytometry and IgH PCR in AR-PCNSL remains to be fully defined, still it is reasonable to integrate these minimally invasive studies into the initial diagnostic evaluation of patients with AIDS and ring-enhancing CNS masses. In AIDS patients with ring-enhancing CNS masses, pathologic demonstration of leptomenigeal dissemination of lymphoma can establish a definitive diagnosis.

Despite these advances in minimally invasive diagnostic tools, histologic diagnosis remains the gold standard for diagnosis of AR-PCNSL, and biopsy is required in many cases for definitive diagnosis. As AR-PCNSL is a multifocal malignancy, craniotomy with resection of a lesion is generally not performed unless there is another indication such as decompression of mass effect or concern for an abscess. Stereotactic brain biopsy has a diagnostic yield of 85–90 % in evaluation of cerebral lesions in patients with AIDS, and is generally associated with low mortality, although the overall morbidity rate is approximately 8–10 % mainly due to intracranial bleeding (Davies et al. 1995; Iacoangeli et al. 1994; Luzzati et al. 1996; Skolasky et al. 1999). However, thalamic or basal ganglia lesions are associated with a significantly increased risk of morbidity, often from bleeding (McGirt et al. 2005). In AIDS patients with a CD4 count less than 100 cells/μL, positive EBV viral load in the CSF and lesions consistent with AR-PCNSL by nuclear imaging, biopsy of such high-risk lesions may be relatively contra-indicated. In such cases, diagnosis of AR-PCSNL can usually be established based on results of these established noninvasive studies (Fig. 15.2).

In 1998, the American Academy of Neurology issued recommendations to guide diagnostic evaluation of AIDS patients with ring-enhancing lesions (1998). However, this algorithm does not include more recent molecular diagnostics or flow cytometry, which are sensitive for detecting B-cell malignancies in the CSF (Kraan et al. 2008). Furthermore, this and other algorithms include a trial of empiric antibiotics for toxoplasmosis, which is no longer advisable given diagnostic advances and dramatically improved survival of patients with AIDS in the HAART era. An alternative algorithm for patients with AIDS and enhancing CNS masses that takes into account these new findings is proposed in Fig. 15.2. It should be noted that evaluation in some patients, for example those with inconclusive imaging and laboratory studies in which brain biopsy is felt to be dangerous can be challenging, and the best approach will require balancing various risks. Also, this algorithm should be considered a suggested guide, and readers should be alert for new developments or new official guidelines in this area.

AR-PCSNL and other CNS infections occurring in patients with AIDS can be associated with a rapid deterioration of functional and neurologic function. Patient performance status should be assessed using an Eastern Cooperative Oncology Group (ECOG) performance scale. Cognitive function should be monitored using serial scoring of Mini Mental Status Examination (MMSE). Given the rapid and sometimes irreversible decline in performance status in patients with untreated

AR-PCNSL or untreated CNS infections and improved long-term outcomes in AIDS patients treated with HAART, expedited evaluation is crucial. Long-term neurologic function, quality-of-life, and survival are likely affected by the course of action taken during the initial diagnostic evaluation (Abrey et al. 2005).

15.4 Treatment and Prognosis

The advent of effective combination antiretroviral therapy, also known as HAART heralded a new era for HIV-infected patients. Control of HIV-replication and associated immune reconstitution lead to a decrease in deaths from opportunistic infections and dramatically improved overall survival for many AIDS patients. Studies of outcomes for HIV-related diseases are usually divided between the pre-HAART era (before 1996) and the era when HAART became broadly available in the USA and Europe (after 1996) (Ricard et al. 2012). Among populations with access to HAART, one of the great advances has been the prevention of malignancies occurring in the setting of very low CD4 counts, such as AR-PCNSL. However, despite improvement in overall survival attributable to HAART (Bayraktar et al. 2011; Bower et al. 2006; Diamond et al. 2006; Hoffmann et al. 2001; Newell et al. 2004; Skiest and Crosby 2003), patients who do develop AR-PCNSL still have an overall mortality close to 90 % at 2 years (Achenbach et al. 2011; Norden et al. 2011).

HAART is a necessary part of treatment of AR-PCNSL, and immune reconstitution is considered the main driver of this effect. Control of HIV viremia allows for T-cell immune reconstitution, and improved immunosurveillance against this immunogenic, virally associated malignancy. In rare cases, HAART alone has even been associated with complete resolution of PCNSL, (Aboulafia and Puswella 2007), presumably due to improved T-cell function.

Pilot (Aboulafia et al. 2006; Jacomet et al. 1997) and retrospective studies (Hoffmann et al. 2001; Nagai et al. 2010; Newell et al. 2004; Pipkin et al. 2011) suggest further improvements in outcomes may be possible in this patient population with lymphoma directed therapeutics and appropriate supportive care that includes prophylaxis and treatment of opportunistic infections, and in some cases, short courses of steroids to manage neurologic symptoms. However, delayed diagnosis (Haldorsen et al. 2005), heterogeneous approaches to diagnosis (Cingolani et al. 1998; Davies et al. 1995; Kaufmann et al. 1996; Skiest et al. 2000; Skolasky et al. 1999), poor performance status (Raez et al. 1998), and infectious (Mahindra and Grossman 2003; Remick et al. 1990) or malignant (Ahsan and Neugut 1996) co-morbidities may be significant additional risk factors that effect overall survival. Unlike systemic non-Hodgkin lymphoma in patients with AIDS, for which dramatic improvements in overall survival have been achieved through prospective therapeutic studies, advances in AR-PCNSL has been limited by lack of prospective studies. As such, there is no consensus on how to treat AR-PCNSL.

The major definitive treatment modalities for PCNSL are whole brain radiation therapy (WBRT), chemotherapy, and the anti CD-20 monoclonal antibody, rituximab.

However, there are no completed prospective lymphoma directed studies that have been performed in patients with AR-PCNSL in the HAART era. With the exception of HAART, which is indicated based on evidence showing improved overall survival, therapeutic interventions for AR-PCNSL are based on case series and expert opinion, or extrapolation from studies performed in immune-competent patients with PCNSL.

In AR-PCNSL, radiotherapy has been the predominant treatment modality since the beginning of the AIDS epidemic. Radiation has good activity against PCNSL. However, focal radiotherapy is associated with high recurrence rates and hence WBRT is recommended. Even WBRT is unlikely to treat leptomeningeal disease outside the radiation field. In retrospective studies performed in the pre-HAART era, median overall survival with WBRT alone was less than 6 months; death was generally from either other complications of AIDS or from progressive PCNSL. A more recent study performed in the HAART era has demonstrated 3-year survival of 64 % in patients with pathologically confirmed AR-PCNSL treated with HAART and WBRT (>30 Gy). Doses of WBRT (~40 Gy), recommended for better and more durable disease control, however, are associated with debilitating and at times life-threatening neurotoxicity (Correa et al. 2004; Nagai et al. 2010; Skiest and Crosby 2003; Wolf et al. 2005). Therefore, radiation-sparing approaches to AR-PCNSL are highly desirable.

High-dose methotrexate, either alone or in combination regimens, is the best-studied radiation-sparing approach to PCNSL in patients without HIV. However, many regimens evaluated in PCNSL in immune-competent patients also contain high-dose cytarabine, which adds substantial toxicity and may not be appropriate for patients with AIDS. A pilot study of high-dose methotrexate 3 g/m^2 performed in ten patients with histologically confirmed AR-PCNSL in the pre-HAART era (Jacomet et al. 1997) demonstrated a complete response rate of 30 %; however, median overall survival was only 2 months. Further evaluation of radiation-sparing approaches is required in the HAART era.

Rituximab, a monoclonal antibody directed against CD20, is an important immunotherapy that has been evaluated in the treatment of PCNSL and PTLD, and is a rational agent in AR-PCNSL, in which 100 % of lymphoma cells express CD20. One challenge has been determining whether a therapeutic concentration rituximab can be obtained in the central nervous system. Pharmacokinetic studies have shown that CSF levels are approximately 0.1–1 % that of serum during peripheral administration (Larouche et al. 2011; Rubenstein et al. 2003). Though this may appear to be an insufficient concentration, it represents 1–10 times more than needed to saturate 80–95 % of CD20 positive cell surface (Chow et al. 2002). Furthermore, tumor-associated breakdown of the blood–brain barrier likely allows for increase accumulation at the site of the tumor. Indeed tumor accumulation of yttrium-90-labeled anti-CD20 antibodies can be demonstrated in a majority of patients with PCNSL (Maza et al. 2009).

Clinically, a retrospective study examined the addition of rituximab to high-dose methotrexate and ifosfamide on outcomes in newly diagnosed PCNSL in HIV-negative patients. The addition of rituximab increased the CR rate (100 vs. 68.4 %; $p=0.02$) and 6-month progression-free survival (94.1 vs. 63.2 %; $p=0.04$) (Birnbaum et al.

2012). A subsequent prospective multicenter study evaluating rituximab in combination with high-dose methotrexate and temozolomide had a 63 % complete response rate. Patients went on to receive consolidation therapy with high-dose cytarabine and etoposide, and mature results from this study are forthcoming.

Overall, the results of trials in HIV-uninfected patients with PCNSL suggest that radiation-sparing modalities can achieve good results. While patients with AR-PCNSL may be more susceptible to toxicities from such regimens because of their severe underlying acquired immunodeficiency, such approaches are appropriate to consider at the HAART era. However, there are no completed studies of radiation-sparing approaches with HAART in AR-PCNSL. Curative-intent, radiation-sparing treatment of AR-PCNSL is currently under investigation in a prospective study evaluating of rituximab, high-dose methotrexate, and HAAART in patients with AR-PCNSL (NCT00267865).

15.5 Conclusion

AR-PCNSL is a rare AIDS-defining malignancy with a high mortality. The advent of the widespread distribution of HAART has led to a substantial decline in incidence and a modest improvement in overall survival. For AIDS patients who develop AR-PCNSL, diagnostic as well as therapeutic challenges exist. A streamlined evaluation of CNS masses (Fig. 15.2) may lead to earlier diagnoses and treatments, and improved outcomes. All patients should be started on HAART, and given the lack of a standard therapy, should also receive curative intent lymphoma directed therapy, ideally within a clinical trial.

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Chapter 16
Plasmablastic Lymphoma

Huan-You Wang, Ida Wong-Sefidan, and Erin Reid

Abstract Plasmablastic lymphoma (PBL) is a rare, aggressive lymphoma that is mainly seen in the human immunodeficiency virus (HIV)-positive population. It is a mature large B-cell lymphoma exhibiting plasmablastic morphology and with terminal B-cell, namely plasma cell-like, differentiation. PBL has a tendency to occur in the oral cavity; however, extraoral involvement is not infrequently encountered. While PBL shares some overlapping morphologic and immunophenotypic features with other mature B-cell lymphomas, PBL is currently classified as a distinct entity in the 2008 World Health Organization (WHO) Classification Tumors of Haematopoietic and Lymphoid Tissues (Swerdlow et al., WHO classification of tumours of haematopoietic and lymphoid tissues; 2008).

16.1 Introduction

Plasmablastic lymphoma (PBL) is a rare B-cell lymphoma that predominately arises in patients with HIV infection. PBL was originally described by Delecluse et al. (1997). It was documented as a variant of diffuse large B-cell lymphoma (DLBCL) with distinctive immunohistological features consistent with plasmacellular differentiation; the initial cases describing PBL cells expressed VS38c, frequently stained positive for CD79a, and demonstrated monoclonal rearrangement

H.-Y. Wang, M.D., Ph.D.
Department of Pathology, University of California San Diego Moores Cancer Center, 3855 Health Sciences Drive, La Jolla, CA 92093, USA

I. Wong-Sefidan, M.D. • E. Reid, M.D. (✉)
Division of Hematology/Oncology, Department of Internal Medicine, University of California San Diego Moores Cancer Center, 3855 Health Sciences Drive, La Jolla, CA 92093, USA
e-mail: egreid@ucsd.edu

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of the immunoglobulin (*Ig*) heavy chain gene. In these first reported cases, all presented in the oral cavity, and a majority of patients were infected with HIV. Since the initial description of PBL, a number of case reports and series have been published further describing this unique lymphoproliferative disorder, which has now been documented to occur at many other sites other than the oral cavity. While PBL shares some overlapping morphologic and immunophenotypic features with other mature B-cell lymphomas, it is currently classified as a distinct entity in the 2008 World Health Organization (WHO) Classification Tumors of Haematopoietic and Lymphoid Tissues (Swerdlow et al. 2008).

PBL can be a diagnostic challenge given its atypical morphology and immunohistochemical profile similar to other lymphomas with plasmablastic differentiation such as primary effusion lymphoma (PEL) and plasmablastic plasma cell myeloma (PCM). The clinical outcome is typified by a highly aggressive course. At present, there are no established standard of care treatments for PBL in the era of highly active antiretroviral therapy (HAART). In addition to specific therapy for PBL, HAART appears to be an important component of management. With increased understanding of the pathophysiology of PBL, more targeted therapy and future treatment options may be available for this unique and aggressive B-cell lymphoproliferative disorder.

16.2 Epidemiology

The relationship between PBL and immunosuppression has been clearly established. PBL is most commonly diagnosed in the setting of HIV infection, and to date, a majority of patients with PBL have concurrent HIV (Delecluse et al. 1997; Castillo et al. 2010a). PBL can be seen in HIV-negative patients as well (Castillo et al. 2010a; Liu et al. 2011; Teruya-Feldstein et al. 2004). However, even in HIV-negative cases, immunosuppression often plays a large role in pathogenesis as a number of HIV-negative patients have immunosuppression from solid organ transplantation, steroid therapy, or concurrent malignancy (Castillo et al. 2010a; Teruya-Feldstein et al. 2004; Ustun et al. 2009). Other cases of PBL occur in setting of decreased immune surveillance, such as in advanced age (Colomo et al. 2004).

PBL accounts for 2.6 % of all HIV-associated non-Hodgkin lymphomas (NHLs) (Carbone et al. 1997). Given that the majority of patients with PBL have HIV, the disease in the USA occurs predominantly in males. The median age at diagnosis in the HIV population is 38 years (Castillo et al. 2008). Due to its rarity, it is not clear as to whether there are racial or ethnic predispositions. However, PBL has been reported in Europe, Asia, Africa, Australia, South America, and North America (Castillo et al. 2012; Castillo and Reagan 2011).

16.3 Pathogenesis

PBL is, in essence, an aggressive mature large B-cell lymphoma that exhibits plasmablastic morphology and terminal B-cell, namely plasma cell-like, differentiation. The postulated normal counterpart of PBL is the plasmablast (Stein et al. 2008). By analyzing mutations of *Ig* variably heavy chain (IgVH) for somatic hypermutation and BCL-6 genes, Gaidano et al. divided PBL of the oral cavity into at least two sub-groups: a subset that carries the molecular clues of germinal center (GC) transit (hypermutated IgVH with subset of which showing antigen stimulation) and thus conceivably originates from a B-cell subset corresponding to post-GC cells, and another subset that appears to originate from naïve B-cells (devoid of IgVH mutations) (Gaidano et al. 2002).

16.4 Clinical Presentation

Clinical presentation of PBL is varied. PBL can be the initial presentation of HIV infection (Castillo et al. 2008, 2012). PBL has a tendency to occur in the oral cavity; however, extraoral involvement is not infrequently encountered (Castillo et al. 2008). Since its initial report in the oral cavity in patients with HIV in 1997 (Swerdlow et al. 2008), PBL has been found to occur outside of the oral cavity in both HIV-infected and uninfected patients. It has been reported to arise in the retro-orbit (Liu et al. 2011), nasal cavity (Liu et al. 2011); jaw (Liu et al. 2011); parotid gland (Bishop and Westra 2010); larynx (Stephenson et al. 2013); bone marrow (Liu et al. 2011; Chuah et al. 2009); lung (Chuah et al. 2009); gastrointestinal tract including esophagus (Mani et al. 2008), stomach, small intestine (Cha et al. 2010; Wang et al. 2012), colon (Liu et al. 2011), and ano-rectal region (Brahmania et al. 2011); liver (Tani et al. 2013); retroperitoneum (Dholaria et al. 2012); testis (Sagues et al. 2012); penis (Sun et al. 2011); vulva (Chabay et al. 2009); skin (Tiong et al. 2013), and bone (Liu et al. 2011). Central nervous system (CNS) involvement including the orbit, leptomeninges, and parenchyma as well as peripheral nervous system involvement has been reported to occur with systemic disease at time of diagnosis, or at time of relapse (Ustun et al. 2009; Zhang et al. 2012; Gao et al. 2013).

A high percentage of cases of PBL present with masses in the oral cavity. Masses in the gingiva, hard palate, and alveolar mucosa are common. PBL also may arise from areas next to the oral cavity such as the mandible (Hansra et al. 2010; Tsachouridou et al. 2012). Patients typically present with symptoms localized to the disease site(s), though others may present with systemic symptoms such as fatigue, unexplained fevers, drenching night sweats, or weight loss (Castillo et al. 2010a). With CNS involvement, symptoms such as altered mental status, headaches, or blurry vision are common (Ustun et al. 2009).

HIV-positive cases usually present either as early stage IE (extranodal) disease or advanced stage IV disease (Teruya-Feldstein et al. 2004; Castillo et al. 2008, 2012).

There is a paucity of data documenting associated laboratory abnormalities at times of diagnosis; however, lactate dehydrogenase (LDH) was noted to be elevated in a majority of patients in one series (Castillo et al. 2012). The CD4+ count at diagnosis varies. In a study of 112 patients spanning from the early-HAART to present HAART era, the median CD4 count at diagnosis of PBL was at 178 cells/mm^3 (range, 10–498 cells/mm^3) (Castillo et al. 2008). The duration of HIV infection before diagnosis was 5 years (range, 0–20 years). In a smaller study of 53 patients in the HAART era, the median CD4+ count was 206 cells/mm^3 (range, 5–683 cells/mm^3), and the median viral load at presentation was 261,560 copies/mL (range, from undetectable to 4.7 million copies/mL) (Castillo et al. 2012). In this study, the duration between HIV infection and PBL diagnoses was 8.9 years.

16.5 Diagnosis and Evaluation

Clinical features are not adequate to distinguish PBL from other malignancies that arise in the oral cavity, such as carcinoma, melanoma, and other types of lymphomas. Given extraoral involvement can occur at many other sites, the differential diagnosis can range from carcinomas to other types of lymphoma or opportunistic infections. A biopsy of the mass lesion or enlarged lymph node is needed for diagnosis. Whenever possible, an excisional biopsy of suspected lesions is needed to further define the morphologic and immunophenotypic features of PBL, and distinguish it from other types of lymphomas and myeloma.

Full staging scans are indicated at the time of diagnosis. Given the rarity of the disease, the usefulness of PET scans for diagnosis and prognostication in PBL is not specifically established. There are only few case reports documenting FDG uptake in PBL of the oral cavity, and metastatic lesions of PBL affecting the skin, testis, and bone (Schichman et al. 2004; Hausermann et al. 2004; Makis et al. 2011). It must be noted that FDG uptake can occur in HIV-related adenopathy, and therefore false positivity with PET should be anticipated (Makis et al. 2011). Marrow involvement is not infrequent; bone marrow biopsies are recommended as for any aggressive lymphoma (Castillo et al. 2010a). Given its aggressive nature and reported cases of CNS involvement, a lumbar puncture to assess for CNS disease is appropriate as is CNS imaging in the setting of headaches or neurologic symptoms.

16.6 Pathologic Features

Morphology and Immunophenotype

The 2008 WHO classification of tumors of hematopoietic and lymphoid tissues (Delecluse et al. 1997) recognizes PBL as a distinct subtype of very aggressive mature large B-cell lymphoma (Swerdlow et al. 2008). While most of PBL occur de novo, secondary/transformed PBL from low-grade B-cell lymphoma including

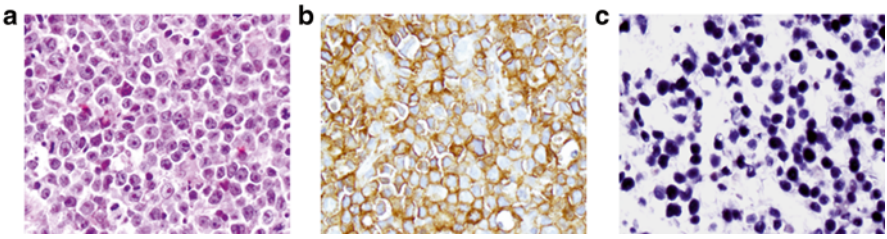

Fig. 16.1 (**a**, **b**) Representative microphotographs of a plasmablastic lymphoma (PBL) from an anal fistula in a 46-year-old male with HIV infection. H&E shows the atypical lymphoid cells which are large with oval nuclear contours, vesicular nuclear chromatin, conspicuous to prominent nucleoli and relative abundant cytoplasm (**a**). The lymphoma cells are positive for CD45 (**b**), as well as Oct2 and CD30 (not shown). These cells are negative for CD20, CD79a, and HHV-8/KSHV (not shown). (**c**) PBL cells from an oral cavity of a 32-year-old male are positive for EBV by in situ hybridization (EBER). All images original magnification 400×

follicular lymphoma and plasmacytoma have been described (Martinez et al. 2013; Ouansafi et al. 2010; Qing et al. 2011).

Histologically, PBL tends to show a diffuse and cohesive growth pattern (Delecluse et al. 1997). Cytologically, cells from PBL are medium-sized to large cells showing a spectrum of cytology ranging from pure immunoblastic morphology to immunoblasts or plasmablasts with more plasmacytic differentiation (Colomo et al. 2004; Stein et al. 2008). Typically, the lymphoma cells show centrally or slightly eccentrically located nuclei with round to oval nuclear contours, vesicular to condensed nuclear chromatin, one prominent centrally located nucleoli with or without recognizable perinuclear clearing mimicking perinuclear hof often seen in plasma cells (Fig. 16.1a). In addition, brisk mitoses and numerous apoptotic bodies are easily appreciated.

Immunohistochemically, the tumor cells from PBL are typically positive for plasma cell markers including CD138 and IRF4/MUM-1 and immunoglobulin light chain (kappa or lambda), activation markers such as CD30, and epithelial marker such as epithelial membrane antigen (EMA) and CD79a (Stein et al. 2008). However, they are negative or rarely positive for mature B-cell antigens including BCL-6, CD20, CD22, CD23, and PAX-5 (Colomo et al. 2004; Stein et al. 2008; Dong et al. 2005). CD45, commonly known as leukocyte common antigen (LCA) (Fig. 16.1b), shows unequivocal positivity in 71 % of the 14 PBL cases reported by Dong et al. (2005). The tumor cells are typically positive for Epstein Barr virus (EBV), not by immunohistochemistry (IHC) for latent membrane protein (LMP), but by in situ hybridization to assess the expression of EBV-encoded RNA (EBER) (Fig. 16.1c) (Dong et al. 2005).

Human herpes virus 8 (HHV-8), also known as Kaposi sarcoma herpesvirus (KSHV), is typically absent in PBL (Colomo et al. 2004; Stein et al. 2008), although occasional HHV-8/KSHV-positive PBL cases have been reported in the literature. For example, Dong HY et al. reported 60 % (6/10) HHV-8/KSHV positivity in the ten cases of PBL in which HHV-8/KSHV status was evaluated by polymerase chain reaction (PCR); however, only 10 % (1/10) showed HHV-8/KSHV positivity by

IHC (Dong et al. 2005). Goedhals et al. have also showed 12.5 % (1/8) HHV-8/KSHV positivity in the eight PBL cases analyzed by PCR, but none of them (0 %, 0/8) was positive for HHV-8/KSHS by IHC (Goedhals et al. 2008). Therefore, it is the view of the 2008 WHO classification of tumors of hematopoietic and lymphoid tissues that HHV-8/KSHV is absent in PBL (Stein et al. 2008). The current notion is that if a large B-cell lymphoma with plasmablastic morphology exhibits HHV-8/KSHV positivity especially by IHC, then it could represent one of the following three entities: extra-cavitary PEL (Carbone and Gloghini 2008), large B-cell lymphoma arising in HHV-8-associated multicentric Castleman disease (Isaacson et al. 2008), or an yet to be defined HHV-8/KSHV(+) large B-cell lymphoma recently proposed by one of the authors (Pan et al. 2012).

Differential Diagnosis

Some of the lymphomas that must be distinguished from PBL include the following:

(a) *Plasmablastic plasma cell myeloma*
PBL shares overlapping cytomorphologic and immunohistochemical features with those of plasmablastic PCM to the extent that Vega et al. claim these two entities have nearly identical immunophenotypic profiles except that EBV is absent in all seven cases of plasmablastic PCM but is present in all five cases of PBL they studied (Vega et al. 2005). While BCL-6, CD4, CD10, CD79a, and Pax-5 were detected more often in PBL than in plasmablastic PCM, no statistical significance between PBL and PCM was seen in any of the aforementioned markers. Thus separation of PBL from plasmablastic PCM has to be based on multiple parameters including, but not limited to, clinical history of PCM, presence or absence of paraprotein and the amount of paraprotein, lytic bone lesion, kidney function, morphology, immunophenotype, and genetics.

(b) *Extra-cavitary primary effusion lymphoma*
PBL can be confused with PEL, especially the extra-cavitary form, easily based on cytomorphologic features alone; therefore, the differential diagnosis between PBL and extra-cavitary PEL has to be based on other factors such as extensive immunophenotyping and presence or absence effusion in the body cavities. Generally speaking, the cells from PEL are larger and show more cytologic atypia (Fig. 16.2a). While PBL and extra-cavitary PEL share many overlapping immunohistochemical profiles, it is generally accepted that PBL is negative but extra-cavitary PEL is typically positive for HHV-8/KSHV (Fig. 16.2b) (Wang et al. 2010; Chadburn et al. 2004).

(c) *Large B-cell lymphoma arising in HHV-8-associated multicentric Castleman disease*
PBL should be differentiated from large B-cell lymphoma arising in HHV-8-associated multicentric Castleman disease (MCD), which occurs more often in HIV(+) patients with MCD (Isaacson et al. 2008; Oksenhendler et al. 2002). While both entities display plasmablastic cytomorphology, the neoplastic cells

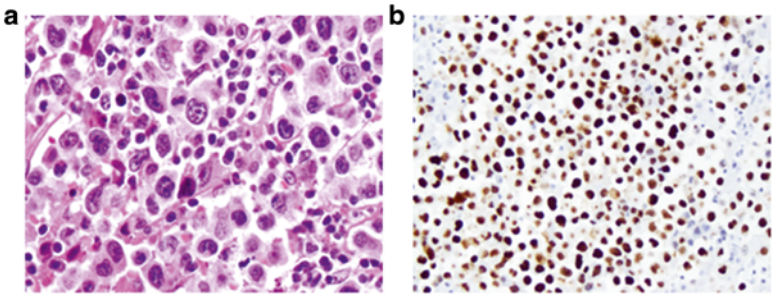

Fig. 16.2 Representative microphotographs of an extra-cavitary primary effusion lymphoma from an enlarged right inguinal lymph node from a 77-year old male with HIV and TB infection. The tumor cells are large with irregular to indented nuclear contours, relative abundant cytoplasm, and conspicuous nucleoli [(**a**) H&E, original magnification of 400×]. The lymphoma cells are strongly positive for HHV-8/KSHV [(**b**) original magnification of 200×]

from the large B-cell lymphoma arising in HHV-8-associated MCD generally express HHV-8/KSHV latency associated nuclear antigen (LANA), are typically positive for IgM and lambda-light chain restriction, and are negative for CD138 (Isaacson et al. 2008; Oksenhendler et al. 2002).

(d) *Other aggressive large B-cell lymphoma*
DLBCL, not otherwise specified (DLBCL, NOS) occurring in HIV(+) patients often exhibit plasmacytoid features (Gloghini et al. 2013). Despite cytomorphologic overlap between PBL and DLBCL, NOS in the setting of HIV infection, the latter can be easily distinguished by its expression of most of the B-lineage specific and associated antigens.

Genetic Aberrancies

C-MYC rearrangements have been reported to be the most commonly encountered cytogenetic abnormalities. For example, in a large study of oral PBLs, Boy et al. reported rearrangement of the *MYC* gene in 60 % of cases with the *IgH* locus as a partner gene in 51 % of cases (Boy et al. 2011). Similarly, Valera et al. reported *MYC* rearrangements in 49 % of 41 PBL cases they studied (Valera et al. 2010). By using fluorescence in situ hybridization, additional genetic abnormalities such as increased copy number of cyclin D1; gains of *MYC*, *BCL-2*, *BCL-6*, *MALT1*, and *PAX-5*; and aneuploidy for *BCL-6* were observed in 41, 20, 31, 41, 33, 32, and 28 % of cases, respectively (Boy et al. 2011; Valera et al. 2010). However, no rearrangements of *BCL-2*, *BCL-6*, *MALT1* (mucosa-associated lymphoid tissue 1), or *PAX-5* were detected in any PBL cases they examined (Valera et al. 2010).

By employing array-based comparative genomic hybridization (cCGH) technology, Chang et al. reported frequent segmental gains (>40 %) of 1p36.11–1p36.33,

1p34.1–1p36.13, 1q21.1–1q23.1, 7q11.2–7q11.23, 11q12–11q13.2, and 22q12.2–22q13.3, which correlated with segmental gains occurring in high frequency in DLBCL regardless of HIV status (Chang et al. 2009).

16.7 Treatment

A key aspect of the treatment of PBL is the use of combination cytotoxic chemotherapy, which has been shown to provide a significant increase in survival in HIV-positive patients with PBL (Castillo et al. 2010a). Patients treated with combination chemotherapy have an overall response rate (ORR) to chemotherapy of 77 %, with 46 % of patients achieving a complete response (CR) and 31 % a partial response (PR) (Castillo et al. 2010b).

HAART in addition to chemotherapy and/or radiotherapy can improve the prognosis of PBL (Antinori et al. 2001; Guan et al. 2010). Good responses with HAART alone have been reported, but such responses are not usually durable (Lester et al. 2004; Bibas et al. 2010). Correspondingly, relapsed PBL has been documented after cessation or interruption of HAART, and a subsequent drop in CD4 counts and rise in viral loads (Bibas et al. 2010; Francischini et al. 2010; Goto et al. 2011). These cases of recurrence after disruption of HAART substantiate findings that HAART is an important cornerstone in treatment of PBL.

Despite the wide use of combined chemotherapy, there is no standardized treatment for PBL. Many treatments have been employed including CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine), dose-adjusted EPOCH (etoposide, doxorubicin, vincristine, cyclophosphamide, prednisone), or CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, methotrexate, ifosfamide, etoposide, cytarabine) (Castillo and Reagan 2011). It is not currently known whether any particular treatment is more efficacious than others. A small study did not show any survival benefit comparing CHOP with more intense treatment, although the patients who received more intensive treatment may have had higher risk and more advanced disease, biasing the results (Castillo et al. 2010b). National Comprehensive Cancer network (NCCN) currently suggests more aggressive regimens such as dose-adjusted EPOCH, hyper-CVAD, and CODOX-M/IVAC (NCCN Guidelines 2013).

Newer drugs have been used in a few cases of PBL. Drugs used in multiple myeloma therapy, particularly the proteasome inhibitor, bortezomib, have been reported to be active in cases of PBL (Bibas et al. 2010). In a report of a case of newly diagnosed concurrent HIV and PBL, bortezomib was administered at a dose of 1.3 mg/m^2 intravenously on days 1, 4, 8, and 11. Bortezomib was administered because of the patient's poor hepatic, performance status, and inability to tolerate cytotoxic chemotherapy (Bose et al. 2009). The patient had a dramatic response by PET after two doses.

Radiation alone or in combination with combined chemotherapy has been utilized (Castillo et al. 2008, 2012). However, it is unknown whether radiation alone,

or combination radiation and chemotherapy is better than chemotherapy alone, particularly for stage I disease.

Due to the small number of patients with PBL, there is not a wealth of data regarding the utility of autologous stem cell transplants in PBL. A few case reports of autologous stem cell transplants in patients with HIV-positive PBL have found varying clinical outcomes (Castillo et al. 2012; Dawson et al. 2007). Given the few case reports of transplantation for PBL, few conclusions can be reached for this modality of treatment.

16.8 Prognosis

Prior to widespread HAART use, the prognosis of PBL was poor. HAART in addition to chemotherapy and/or radiotherapy appears to improve the prognosis of PBL (Antinori et al. 2001; Guan et al. 2010). In one retrospective study of HIV-positive patients from 2000 to 2010, median survival was 15 months (Castillo et al. 2008). However, longer survivals have been reported in the literature (Teruya-Feldstein et al. 2004; Lester et al. 2004; Noy et al. 2013; Panos et al. 2007). In a small retrospective study examining 19 patients with central pathology review confirmation of PBL, 1-year survival was 67 % for 12 newly diagnosed patients and two of six patients with relapsed refractory disease were alive 2 years post relapse (Noy et al. 2013). In another review of six HIV-positive patients with PBL, four out of six patients had a survival of 22 months or more. Interestingly, HIV-positive patients had a better overall survival (OS) than HIV-negative patients, possibly in part explained by immune reconstitution obtained with the addition of HAART (Castillo et al. 2010a).

In a study of 53 patients by Castillo et al., ECOG status ≥ 2, stage III–IV, age-adjusted IPI score, and MYC rearrangement were associated with a poorer OS on univariate analysis (Castillo et al. 2012). In another study of 157 patients, age ≥ 60, advanced stage, bone marrow involvement, lack of chemotherapy, HIV-negativity, and Ki-67 > 80 % were all prognostic factors in OS. The only independent factors in OS were advanced stage and lack of chemotherapy (Castillo et al. 2010a). Patients who are not treated with chemotherapy have a median survival of only 3 months (Castillo et al. 2010a). Oral versus extraoral involvement has not been shown to significantly alter OS (Castillo et al. 2010a). Due to the relatively few cases of PBL with CNS involvement, it is difficult to conclude whether or not CNS involvement portends a poorer survival; of the cases reported, median OS has ranged from months to a year or more (Dong et al. 2005; Panos et al. 2007; Rafaniello Raviele et al. 2009).

16.9 Conclusions and Further Considerations

PBL makes up an infrequent but distinct type of AIDS-related NHLs. Given its overlapping cytomorphologic and immunohistochemical features, it is important to distinguish PBL diagnosis from other mature aggressive large B-cell lymphomas.

More data and studies are needed to further clarify clinical prognosticators, and to determine the most effective treatments of PBL. Updated survival data in the age of newer and current therapy with HAART will be important to best describe PBL in the present era.

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Chapter 17
Hodgkin Lymphoma in Patients with HIV Infection

Michele Spina, Rosanna Ciancia, Accursio Augello, Massimiliano Berretta, and Umberto Tirelli

Abstract Hodgkin lymphoma (HL) is a type of lymphoma characterized by Reed-Sternberg cells and often associated with systemic symptoms. While not considered an AIDS-defining malignancy, it is one of the more common non-AIDS-defining cancers. Most cases of HIV-associated HD are associated with Epstein–Barr virus. HD in persons infected with HIV tends to involve relatively unfavorable subtypes (mixed cellularity and lymphocyte), to be relatively more aggressive, and to more frequently exhibit extranodal involvement. Many of the cases of HIV-associated HD occur in patients with only moderate immunosuppression. Also, unlike most AIDS-related non-Hodgkin lymphoma, the incidence of HIV-associated HD has not decreased with the widespread use of HAART. In the era of highly active antiretroviral therapy (HAART) the same regimens employed in HIV-negative patients with HL can be used in HIV setting with similar results.

17.1 Introduction

The availability of highly active antiretroviral therapy (HAART) has led to improvements in immune status among HIV-infected persons, reducing AIDS-related morbidity and prolonging survival. However, despite the impact of HAART on HIV-related mortality, malignancies remain an important cause of death (Bonnet et al. 2009). The use of HAART was also associated with reduced incidence of the two major AIDS-associated malignancies—Kaposi's sarcoma (KS) and high-grade non-Hodgkin lymphoma (NHL). However, among non-AIDS-defining cancers, an

M. Spina, M.D. (✉) • R. Ciancia • A. Augello • M. Berretta • U. Tirelli
Division of Medical Oncology A, National Cancer Institute,
via Franco Gallini 2, 33081 Aviano (PN), Italy
e-mail: mspina@cro.it

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increased risk of Hodgkin lymphoma (HL), anal cancer, lung cancer, and hepatocarcinoma has been observed since the widespread use of HAART (Biggar et al. 2006).

Although HL is included in the World Health Organization's categorisation of HIV-associated lymphomas, a number of questions remain regarding the relationship between HIV infection and HL. HIV-associated HL (HIV-HL) displays several peculiarities when compared with HL of the general population. First, HIV-HL exhibits an unusually aggressive clinical behavior, which mandates the use of specific therapeutic strategies and is associated with a poor prognosis. Second, the pathologic spectrum of HIV-HL differs markedly from that of HL in the general population (Tirelli et al. 1995). In particular, the aggressive histological subtypes of classic HL (cHL), namely mixed cellularity (MC) and lymphocyte depletion (LD), predominate among HIV-HL and pathologically, the tumor is characterized by an unusually large number of neoplastic cells, termed Reed-Sternberg (RS) cells. Finally, despite the great improvement in chemotherapy and supportive care, optimal staging and treatment is still a matter of controversy.

17.2 Epidemiology

In the HIV-negative population of western countries, HL is one of the commonest malignancies diagnosed in young adults, with six cases of HL observed per 100,000 inhabitants under 45 years of. The epidemiology of HL is characterized by a peculiar age distribution pattern—a bimodal incidence curve with a first peak around the age of 30 and the second peak around the age of 50 years—that has been taken as suggestive of an infectious etiology. In immunosuppressed patients, HL occurs more frequently than in the general population of the same age and gender. In part because of the relative high frequency of HL in the population groups at high risk for HIV infection, a marked change in risk of HL was not initially appreciated in HIV-infected individuals, and HL was not included in the spectrum of HIV-defining cancers. However, with the spread of the epidemic and longer survival of infected people, the impact of HL was better recognized. A number of studies (Biggar et al. 2006; Serraino et al. 1997; Dal Maso et al. 2003; Clifford et al. 2005) strongly support the evidence that HIV-infected persons have, overall, a tenfold higher risk of developing HL than HIV-negative persons. Such an excess risk is more pronounced in HIV-infected individuals with moderate immunosuppression; this is a different pattern than that observed for KS or certain other types of NHL such as primary central nervous system lymphoma (PCNSL) (Serraino et al. 1997). Thus, the epidemiological pattern of HL in HAART era substantially differs from those observed for KS or NHL—two neoplasms which drastically decreased after the introduction of HAART—and this pattern raises several new questions with regard to the relationship between degree of immunodeficiency, persistent viral infections, and cancer.

Of some interest is the recent observation of Powles et al. who have investigated the occurrence of cancers in a prospective cohort of 11,112 HIV-positive individuals, with 71,687 patient-years of follow-up (Powles et al. 2009). Standardized incidence ratios

(SIRs) were calculated using general population incidence data. The incidence of HL in the HIV cohort was higher than in the general population (SIR 13.85; 95 % CI, 9.64–19.26). There was a significant increase in the SIRs across the three study periods (1983–1995: 4.5; 1996–2001: 11.1 and 2002–2007: 32.4). Multivariate analysis demonstrated that HAART was associated with an increased risk of disease (SIR 2.67; 95 % CI, 1.19–6.02). Further multivariate modeling by class of antiretroviral agent showed that of the three classes of antiretroviral therapy, only the non-nucleoside reverse transcriptase inhibitors were associated with a significant increase in the incidence of HIV-HL (HR 2.20; 95 % CI, 1.03–4.69); the reason for this association is not understood. The increased risk of HL with HAART might be explained because the risk of HL peaks when CD4 counts range from 150 to 199 CD4 cells/μL (Serraino et al. 1997). As the overall effect of HAART is to increase the CD4 count level, it paradoxically may increase HL incidence, leading to speculate that, with severe immune suppression, the cellular background surrounding the RS cells may be altered. A potential mechanism emphasizes the role of the RS cells producing several growth factors that increased the influx of CD4 cell and inflammatory cells, which, in turn, provide proliferation signals for the RS neoplastic cells. One can imagine that in the case of severe immune suppression, there are insufficient CD4 cells to maintain this feedback loop and there is less growth of the RS neoplastic cells (Gloghini and Carbone 2007). In addition, HIV-HL is associated with Epstein–Barr virus (EBV) in almost all cases, in contrast to the general population, in which this association is only observed in 20–50 % according to histological type and age at diagnosis (Dolcetti et al. 2001). In summary, the use of HAART has improved the immunity of HIV-infected persons, diminishing the risks of developing other cancers or other opportunistic infections and paradoxically increasing the risk of HL.

17.3 Pathological Features

HIV-HL displays a number of different pathological features in comparison HL in HIV-negative patients. In fact, HIV-HL is characterized by the high incidence of unfavorable histological subtypes (i.e. MC and LD) (Tirelli et al. 1995). In the pre-HAART era, among HIV-infected persons, MC was the most frequent HL subtype and nodular sclerosis (NS) was less frequent than in HIV-uninfected persons. For each HL subtype, incidence decreased with declining CD4 counts, but NS subtype decreased more precipitously than MC subtype, thereby increasing the proportion of MC subtype of HL seen in persons with AIDS. Thus, the greater proportion of MC and LD subtypes appears specifically related to severe immunocompromise in AIDS. By contrast, in the HAART era, HIV-infected patients with modest immunocompromise are more at risk for the development of the NS subtype (Biggar et al. 2006).

HIV-HL exhibits special features related to the cellular background (presence of fibrohistiocytoid stromal cell proliferation) and the high number of neoplastic cells, and both these features may pose relevant difficulties in diagnosing and classifying the disease. This finding contrasts with the rather low population of neoplastic cells usually found in HIV-unrelated HL. Moreover, a high frequency of EBV association

has been shown in HL (80–100 %) tissues from HIV-HL (Carbone et al. 1999). The EBV genomes in such cases have been reported to be episomal and clonal, even when detected in multiple independent lesions. The elevated frequency of EBV association with HIV-HL indicates that EBV probably does represent a relevant factor involved in the pathogenesis of HIV-HL. An etiologic role of EBV in the pathogenesis of HIV-HL is further supported by data showing that LMP-1 is expressed in virtually all HIV-HL cases (Carbone et al. 1999). On this basis, HL in HIV-infected persons appears to be an EBV-related lymphoma expressing LMP1.

It should be noted that RS cells of classical HL in HIV-negative patients represent transformed B-cells that originate from pre-apoptotic germinal center (GC) B-cells (Klein and Dalla-Favera 2008). By contrast, most HIV-related HL cases express LMP1 and display the BCL6-/CD138+/MUM1 IRF4+ (for multiple myeloma-1 interferon regulatory factor-4), phenotype, thus reflecting post-GC B-cells (Carbone et al. 1999; Klein and Dalla-Favera 2008). The possible contribution of LMP1 to the loss of BCL6 expression seems plausible given that LMP1 can downregulate many B-cell specific genes. Loss of B-cell identity occurs during the normal differentiation of a GC B-cell into a plasma cell or memory B-cell.

17.4 Clinical Aspects and Treatment

As in HIV-NHL, one of the most characteristic features of HIV-HL is the widespread extent of the disease at presentation and the frequency of systemic "B" symptoms, including fever, night sweats, and/or weight loss >10 % of the normal body weight. At the time of diagnosis 70–96 % of the patients with HIV-HL have "B" symptoms and 74–92 % have advanced stages of disease with frequent involvement of extranodal sites, the most common being bone marrow (40–50 %), liver (15–40 %), and spleen (around 20 %) (Tirelli et al. 1995). HIV-HL tends to develop relatively early in the course of HIV infection with a median CD4+ cell count ranging from 275 to 306/μL (Tirelli et al. 1995). The widespread use of HAART has resulted in substantial improvement in the survival of patients with HIV infection and lymphomas, due to the reduction of the incidence of opportunistic infections, to the opportunity to allow more aggressive chemotherapy, and to the less aggressive presentation of lymphoma in patients in HAART in comparison with those lymphomas diagnosed in patients who never received HAART (Tirelli et al. 1995; Vaccher et al. 2003).

The Italian Cooperative Group on AIDS and Tumors (GICAT) has collected data on 290 patients with HIV-HL (Chimienti et al. 2008). Two hundred and eighty-one patients (87 %) were males and the median age was 34 years (range 19–72 years). Sixty-nine percent of patients were intravenous drug users. The median CD4 cell count was 240/μL (range 4–1,100/μL) and 57 % of patients had a detectable HIV viral load. MC was diagnosed in 53 % of cases, followed by NS in 24 % and LD in 14 %. Advanced stages of disease were observed in 79 % of patients and 76 % had B symptoms. The overall extranodal involvement was 59 % with bone marrow, spleen, and liver involved in 38, 30, and 17 %, respectively. The authors split the series into two subgroups: the first group was comprised of patients who received

HAART throughout the 6 months before the onset of HL (84 patients); the second group was comprised of those patients who never received HAART before the diagnosis of HL or for less than 6 months (206 patients). Briefly, in comparison with patients who never received HAART, patients who received HAART before the onset of HL were older, had less B symptoms, and had a higher leukocyte count, neutrophils count, and hemoglobin level. The following parameters were associated with a better overall survival (OS): MC subtype, the absence of extranodal involvement, the absence of B symptoms, and a prior use of HAART. Interestingly, three parameters were associated with a longer time to treatment failure: a normal value of alkaline phosphatase, a prior exposure to HAART and an international prognostic score less than 3 (Chimienti et al. 2008).

A similar study was carried out within the Spanish group GESIDA where the authors compared the clinical characteristics and outcome of 104 patients with HIV-HL, treated (83 patients) or not (21 patients) with HAART (Berenguer et al. 2008). No differences were found between the groups at baseline, but the complete remission (CR) rate was significantly higher in HAART group (91 vs 70 %, $p=0.023$). The median overall survival was not reached in HAART group and was 39 months in no-HAART group ($p=0.0089$); the median disease-free survival (DFS) was not reached in HAART group and was 85 months in no-HAART group ($p=0.129$). Factors independently associated with CR were a CD4 cell count >100 cells/μL and the use of HAART; CR was the only factor independently associated with OS (Berenguer et al. 2008).

The optimal therapy for HIV-HL has not yet been defined. Because most patients have advanced stages of disease, they have generally been treated with combination chemotherapy regimens. Even so, the CR rate remains lower than that attained in HL of the general population with the OS being approximately 1.5 years (Tirelli et al. 1995). Due to the low incidence of HIV-HD, no randomized controlled trials have been conducted. However, several phase II studies have evaluated the feasibility and activity of different regimens. In a prospective trial, conducted within the GICAT between March 1989 and March 1992, 17 previously untreated patients with HIV-HL were treated with epirubicin, vinblastine, and bleomycin (EVB). Overall, CR was achieved in 53 % of the group, lasting a median of 20 months. The median OS for the group as a whole was 11 months and the 2-year DFS was 55 % (Errante et al. 1994). In an attempt to improve upon these results, from 1993 to 1997, a second prospective trial consisting of full-dose EVB plus prednisone (EVBP) and concomitant antiretroviral therapy (zidovudine or didanosine) was conducted. The results of this trial in which 35 patients were enrolled showed a CR rate of 74 % and a 3-year OS and DFS of 32 and 53 %, respectively (Errante et al. 1999). The AIDS Clinical Trials Group (ACTG) reported the results of a phase II study in 21 patients treated with adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) for four to six cycles and primary use of G-CSF. Antiretroviral therapy was not used. The CR rate, on an intent-to-treat analysis, was 43 % with an overall objective response rate of 62 %. Median survival for all patients was 18 months (Levine et al. 2000). The widespread use of HAART allows the use of more aggressive chemotherapeutic regimens. Within the European Intergroup Study 59 consecutive HL-HIV patients were treated with Stanford V regimen, consisting of

Table 17.1 Results of prospective studies in HIV-HL

Regimen/reference	# of patients	Stage III–IV (%)	Response rate (%)	Complete remission rate (%)	Overall survival
EBV (Errante et al. 1994)	17	88	82	53	11 months
EBVP (Errante et al. 1999)	35	83	91	74	16 months
ABVD (Levine et al. 2000)	21	81	62	43	18 months
Stanford V (Spina et al. 2002)	59	71	89	81	59 % at 5 years
BEACOPP (Hartmann et al. 2003)	12	92	100	100	75 % at 3 years
ABVD (Xicoy et al. 2007)	62	100	87	87	76 % at 5 years
VEBEP (Spina et al. 2008)	71	70	78	67	69 % at 2 years

short-term chemotherapy (12 weeks) with adjuvant radiotherapy. This regimen was well tolerated and 69 % of the patients completed treatment with no dose reduction or delayed chemotherapy administration. The most important dose-limiting side effects were bone marrow toxicity and neurotoxicity. Eighty-one percent of the patients achieved CR, and after a median follow-up of 17 months 33/59 (56 %) patients are alive and disease-free. The estimated 5-year OS, DFS, and freedom from progression (FFP) were 59, 68, and 60 %, respectively. Probability of FFP was significantly higher ($p=0.002$) among patients with an international prognostic score (IPS) of <2 than in those with IPS >2, and the percentage of FFP at 2 years were 83 and 41 %, respectively. Similarly, probability of OS was significantly different ($p=0.0004$), and the percent survival at 3 years was 76 and 33 %, respectively, for IPS <2 and IPS >2 (Spina et al. 2002).

Within the German group, the very intensive bleomycin, etoposide, adriamycin, cyclophosphamide, oncovin, procarbazine, prednisone (BEACOPP) regimen has been tested in 12 untreated patients with a 100 % of CR rate but a high incidence of opportunistic infections (Hartmann et al. 2003). Recently, the results of a large prospective phase II study with ABVD have been published. Within a cooperative network in Spain, 62 patients with HIV-HL received the standard ABVD plus HAART. The scheduled six to eight ABVD cycles were completed in 82 % of cases. Six patients died during induction, 54 (87 %) achieved a CR, and two were resistant. The 5-year OS and event-free survival (EFS) probabilities were 76 and 71 %, respectively. The immunological response to HAART appeared to have a positive impact on OS ($p=0.002$) and EFS ($p=0.001$) (Xicoy et al. 2007). Finally, the GICAT has concluded the accrual of 71 patients in a prospective phase II study aiming to evaluate feasibility and activity of a novel regimen including epirubicin, bleomycin, vinorelbine, cyclophosphamide, and prednisone (VEBEP regimen). Seventy percent of patients had advanced stages of disease and 45 % had an IPS>2. The CR was 67 % and 2-year OS, DFS, TTF, and EFS were 69, 86, 59, and 52 %, respectively (Spina et al. 2008). The results of the largest prospective studies are shown in Table 17.1.

Recently, a stage-adapted approach has been reported on 112 patients with an excellent outcome similar to that of HIV-negative patients (Hentrich et al. 2012). Moreover, a comparison between patients with HIV-HL and patients with HL without HIV infection showed that HIV patients have more advanced stages of disease with more adverse prognostic factors; however, when these patients were treated with

ABVD, HIV infection does appear to not adversely affect OS or EFS (Montoto et al. 2012). Because a large proportion of patients with HIV-HL progress and relapse, the use of high-dose chemotherapy and autologous stem cell transplantation (ASCT), which is considered the gold standard for salvage therapy, has been tested in this setting. Several data from different groups, including the GICAT, have demonstrated the feasibility of this (Re et al. 2009). Different conditioning regimens, varying in their inclusion of total body irradiation, have been tested. Recently, the AIDS Malignancy Consortium demonstrated in a multiinstitutional trial that a regimen of a dose-reduced high-dose chemotherapy, including cyclophosphamide and busulfan and ASCT, is well tolerated and is associated with favorable DFS and OS probabilities for selected patients with HIV-associated NHL and HL.

17.5 PET Scanning

Positron emission tomography using [18F]-Fluoro-2-Deoxy-D-Glucose (FDG-PET) was first introduced in the management of lymphomas in the early 1990s. It is now recognized as an important tool for staging and treatment response assessment in HL and NHL. In HIV-negative patients, residual FDG PET avidity after two cycles of ABVD has been shown to predict poor prognosis and therefore has been proposed to guide future therapy (Gallamini et al. 2006). A negative PET scan after two cycles of ABVD predicted a 96 % 2-year progression-free survival (PFS). Nearly 80 % of the HL patients show a complete normalization of PET scan after two courses of ABVD. This phenomenon, called "metabolic CR," can be explained by the peculiar architecture and organization of the neoplastic tissue, where only few, scattered neoplastic cells (accounting for less than 1 % of the total cellular population) are surrounded by a population of non-neoplastic mononuclear bystander cells. The latter cells are probably responsible for the immortalization of RS cells in HD by stimulating cytokine production by other CD4+ lymphoid cells (paracrine loop) or by inducing cytokine production by the RS cells (autocrine loop). In cases presenting with bulky lesions at diagnosis, a negative early PET is often associated with a persisting bulky lesion of more or less unchanged size. The explanation might be that chemotherapy switches off the production of chemokines by the activated lymphoid cells, as described for TARC (thymus and activation-related chemokine). The latter can be measured in the serum of HL patients and its level is correlated with the quality of treatment response: for patients in CR TARC levels are much lower than in patients with stable or progressing disease.

PET scanning within the HIV framework can be problematic. Some preliminary reports suggested that FDG activity may correlate with detectable lymphoma. Although initial staging may not alter the treatment plan, it can provide additional information, assess areas of possible, and help foresee and possibly avoid further complications. However, PET scanning in the HIV-HL needs to be further studied. If PET is to be utilized, a baseline study is mandatory, since early PET interpretation is based on a site-to-site comparison of FDG uptake both before and after chemotherapy. Pitfalls are numerous in these patients in whom HIV-associated immunodeficiency

predisposes to infection, as does the use of aggressive immunosuppressive chemotherapy regimens. PET imaging requires cautious reading and pertinent clinical correlation to avoid misdiagnosing benign disease as malignant. This can pose a problem, for example, when hypermetabolic foci seen in the lung or esophagus, which are common sites of HIV- and/or chemotherapy-promoted infections. Nodal FDG uptake can be observed in lymphoma, various infections (e.g., Mycobacterium avium intracellular, Mycobacterium tuberculosis, Herpes simplex virus, among others) and other AIDS-related malignancies such as Kaposi sarcoma. In addition, stimulation of bone marrow following treatment with granulocyte colony stimulating factors induces a striking increase in FDG uptake in bone marrow. To take into account the possibility of minimal residual uptake, a semi-quantitative approach has recently been proposed for interim PET interpretation in the context of an international protocol for advanced-stage HL.

Finally, PET is useful for an accurate initial staging and it should be recommend to monitor treatment response. PET scans have prognostic value, and a negative scan is frequently associated with a favorable outcome. Significance of residual uptake at sites of disease needs further evaluation (e.g., biopsy). However, the use of FDG in the follow-up of HIV-HL patients who achieved CR cannot be routinely recommended and further studies are warranted to assess the possible value of such scans.

17.6 Conclusions

The outcome of patients with HIV-HL has improved in recent years with better combined antineoplastic and antiretroviral approaches. The main important challenges for the next years are: (a) to better understand the pathogenesis of HD and the ways that HIV interacts with this process; (b) assess in a randomized trial whether ABVD is the standard regimen in HIV setting; (c) to validate the role of PET scan both in the staging and in the evaluation of response; (d) to better understand the interactions between chemotherapy and antiretroviral therapy, in order to reduce the toxicity of both approaches; (e) to evaluate the use of new drugs (i.e., bortezomib) in this setting; (f) to evaluate the long-term toxicity of the treatment in cured patients.

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Chapter 18
Multicentric Castleman Disease

Mark N. Polizzotto, Thomas S. Uldrick, and Robert Yarchoan

Abstract Multicentric Castleman disease is a systemic disorder of lymph nodes characterized by inflammatory symptoms including fever, night sweats, cachexia, malaise, and lymphadenopathy together with laboratory abnormalities including anemia and hypoalbuminemia. These symptoms may be life-threatening. The diagnosis is based on specific pathological findings in affected lymph nodes. In individuals infected with HIV, multicentric Castleman disease is almost exclusively caused by infection with a cancer-causing herpesvirus, Kaposi sarcoma-associated herpesvirus (KSHV, also known as human herpesvirus 8). This may be considered a separate entity from the non-KSHV related or idiopathic form of multicentric Castleman disease and from unicentric forms of Castleman disease. While these disorders have pathological and clinical similarities, the KSHV-related form is distinguished by its pathological characteristics and unique viral etiology.

18.1 Introduction

One of the earliest signs of the AIDS epidemic in the early 1980s was the recognition of an increased occurrence of certain unusual tumors in the particular risk groups who also developed opportunistic infections. Tumors of lymphoid tissue were prominent among these, as was an unusual skin tumor called Kaposi sarcoma (KS) (MMWR 1981, 1982; Hymes et al. 1981; Ziegler et al. 1982). Along with several lymphomas, by the 1990s it was recognized that a hitherto uncommon

M.N. Polizzotto (✉) • T.S. Uldrick
HIV and AIDS Malignancy Branch, National Cancer Institute,
National Institutes of Health, Bethesda, MD, USA
e-mail: mark.polizzotto@nih.gov

R. Yarchoan
HIV and AIDS Malignancy Branch and office of HIV and AIDS Malignancy, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

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lymphoid tumor called multicentric Castleman disease (MCD) was occurring at increased rates in people with HIV/AIDS (Oksenhendler et al. 1996; Pluda et al. 1990). Following the discovery that a novel human herpesvirus, Kaposi sarcoma-associated herpesvirus (KSHV, also known as human herpesvirus 8) was the causative agent of KS (Chang et al. 1994), it was soon appreciated that both a rare lymphoma, primary effusion lymphoma (PEL), and almost all cases of MCD in people with HIV/AIDS were also caused by KSHV (Cesarman et al. 1995; Dupin et al. 2000; Nador et al. 1996; Soulier et al. 1995).

Rather than being a true clonal malignancy, or cancer, MCD is best considered a hyperproliferative state affecting mainly lymph nodes and spleen. Its clinical features are those of uncontrolled systemic inflammation and lymphoid proliferation, especially fever, night sweats, cachexia, malaise, and lymphadenopathy (Oksenhendler et al. 1996). These occur together with laboratory abnormalities including anemia and hypoalbuminemia that are themselves at least in part consequences of systemic inflammation (Oksenhendler et al. 2000; Polizzotto et al. 2013). In some cases, true clonal lymphomas may arise within lymph nodes affected by KSHV–MCD or in association with it (Dupin et al. 2000). Until recently, outcomes for patients affected by this disorder were dismal. The time to survival from diagnosis of KSHV–MCD was usually only one to two years, as patients succumbed to the severe inflammatory symptoms or to secondary lymphomas (Bower et al. 2011; Oksenhendler et al. 1996). However, with the transformation of care of the underlying HIV/AIDS and an appreciation of the viral etiology and pathogenic mechanisms of KSHV–MCD, new therapeutic modalities are being developed that appear to be both improving short-term outcomes (Bower et al. 2007; Gérard et al. 2007; Marcelin et al. 2003; Powles et al. 2007; Uldrick et al. 2011) and reducing the long-term sequelae of KSHV–MCD, including secondary lymphomas (Gérard et al. 2012; Hoffmann et al. 2011).

18.2 Clinical and Pathological Features of MCD and Related Diseases: Historical Perspective and Current Understanding

Benjamin Castleman's name has been applied to a group of related but distinct disorders since his seminal description in 1954 of what is now known as unicentric Castleman disease, hyaline vascular variant (Casper et al. 2004b; Castleman and Towne 1954; Waterston and Bower 2004). This initial description was of patients with a single (unicentric) slowly enlarging mass in the anterior chest (mediastinum), which on pathological examination demonstrated an unusual pattern of atrophy (technically involution) of the central portion of the lymph node follicles (Castleman et al. 1956). This portion, called the germinal center, was instead replaced by protein material ('hyalinized') and an increase in local blood vessels. The cause of this disorder was, and remains, unknown. Patients rarely had systemic symptoms, and responded to local approaches, specifically surgical resection or irradiation of the affected node.

Some years after this initial description, a group of patients with similar unicentric lymph node masses but distinct histopathological features was recognized. In these cases, the germinal center was less prominently abnormal. Rather, the affected nodes were characterized by sheets of mature lymphocytes (plasma cells) replacing the normal architecture of the node follicle and interfollicular spaces. Vascularity was again increased, and in some cases the germinal center was involuted or reduced in cell number. In some cases, these findings occurred in solitary sites away from the mediastinum. These patients were in most cases asymptomatic, but a proportion did exhibit systemic inflammatory symptoms (including fever, cachexia, sweats, and malaise) or hematologic cytopenias (anemia or thrombocytopenia). This disorder was named the plasma cell variant of Castleman disease.

It was further recognized that in a proportion of patients with Castleman disease—predominantly but not exclusively those with systemic inflammatory symptoms or cytopenias—more than one lymph node or group of nodes was affected by the same pathological process (Gaba et al. 1978; Keller et al. 1972; Menke et al. 1996). Most, but not all, multicentric cases had the histopathological features of the plasma cell variant. Thus the description of MCD introduced an essentially clinical distinction, the presence of unicentric versus multicentric disease, to what had formerly been a histopathological classification and in doing so combined the two different pathological types (hyaline and plasma cell) under this new umbrella.

The etiology of these intriguing disorders remained elusive. In some cases, the nodal changes appeared to be secondary to an additional pathological process (Menke et al. 1996). Commonly this included lymphomas or certain slow growing infections (including mycobacterial infection) occurring elsewhere, presumably giving rise to Castleman disease as a consequence of lymphoid growth factors being present in abnormal excess. In the 1970s and 1980s a group of small molecules, now called cytokines, were discovered and found to act on lymphocytes to modulate their growth and inflammatory responses. It soon became evident that one such cytokine, interleukin 6 (IL-6) was responsible for many of the pathological and clinical findings of MCD, as well as contributing to the clinical features of those with symptomatic unicentric disease (Yoshizaki et al. 1989). Notwithstanding the discovery of IL-6, the underlying cause of the IL-6 excess remains unexplained in most cases. Nonetheless, the development of inhibitors of IL-6 (antibodies to the molecule itself, or to prevent the molecule acting at its specific receptor) has led to the use of these agents as a therapeutic modality in patients with symptomatic idiopathic Castleman disease (Nishimoto et al. 2000, 2005).

A further critical step in unraveling the etiology of many cases of MCD came with the discovery of KSHV. Because of its unusual epidemiology, including its tendency to occur in only some of the behavioral risk groups affected by HIV/AIDS, KS had long been suspected to be caused by an infectious agent. However its identity remained a mystery until Chang and Moore identified novel herpes viral sequences in KS tissue (Chang et al. 1994). This virus was subsequently found in the affected lymph nodes in most cases of MCD in patients with HIV/AIDS, and also in a minority of cases of MCD occurring in persons without HIV (Dupin et al. 2000; Soulier et al. 1995; Teruya-Feldstein et al. 1998). Further evidence for the

role of KSHV in the etiology of these cases of MCD emerged with the recognition that symptomatic flares in these patients were associated with high levels of KSHV in the peripheral blood and pathological evidence of KSHV infection in the involved lymph nodes. Furthermore, these viral levels improved with treatment or disease remission (Oksenhendler et al. 2000; Polizzotto et al. 2013).

Clinically, these KSHV-associated cases of MCD resembled their non-KSHV associated counterpart. The disease course is characterized by intermittent flares of inflammatory symptoms as described above, together with widespread and often marked lymphadenopathy and prominent splenomegaly (Bower et al. 2011; Oksenhendler et al. 1996). Nonspecific gastrointestinal and respiratory symptoms are also common, as are neurological symptoms including cognitive dysfunction and personality changes (Polizzotto et al. 2013). Flares are often severe and can be fatal. Common laboratory abnormalities include anemia, thrombocytopenia, low serum albumin levels, low serum sodium, and elevated blood inflammatory markers such as C-reactive protein (CRP) (Oksenhendler et al. 2000; Polizzotto et al. 2013). The clinical course waxes and wanes, but until recently has generally been fatal within two years of diagnosis, with patients succumbing to the severe inflammatory syndrome, concurrent infections, or progressing to lymphoma. The differential diagnosis of fever and adenopathy in the HIV-infected individuals is broad. As a result, KSHV–MCD may be difficult to diagnose and is often missed. Clinicians should be alert to the possibility of KSHV–MCD in patients with unexplained inflammatory symptoms and laboratory abnormalities resembling those described, and consider biopsy with adequate material (a substantial core or ideally excision of an affected nodes) to establish the diagnosis.

The pathology of KSHV–MCD bears substantial resemblance to idiopathic MCD. In affected nodes, the mantle zone and interfollicular zone are largely replaced by a plasma cell infiltrate forming characteristic concentric sheets (so-called onion skinning, named for the resemblance to the layered skins of the onion). These are polyclonal, but are usually restricted in secreting the lambda light chain and immunoglobulin M (IgM) (Chadburn et al. 2008; Cronin and Warnke 2009; Jones et al. 1999; Staskus et al. 1999). There are also increased numbers of blood vessels between follicles. However, unlike idiopathic MCD, a minority of cells in the affected node can be shown to be infected by KSHV using immunohistochemical stains for viral proteins. These occur predominantly toward the periphery of the follicle (Fig. 18.1) (Chadburn et al. 2008; Du et al. 2001). Furthermore, a proportion of these KSHV-infected cells are seen to express certain KSHV lytic proteins, suggesting the virus in its lytic (replicative) phase (Du et al. 2001).

It can therefore be seen that the historical progression of the recognition of these disorders has led to the current nomenclature. This unfortunately commonly gives rise to confusion, combining as it does local and systemic diseases whose etiology, pathological and clinical characteristics, optimal therapy, and prognosis are each distinct. A summary of these different types is given in Table 18.1. It could be argued that with the recognition of KSHV as the cause of a distinct group of cases of MCD, KSHV-associated MCD is best considered a separate disorder from the idiopathic

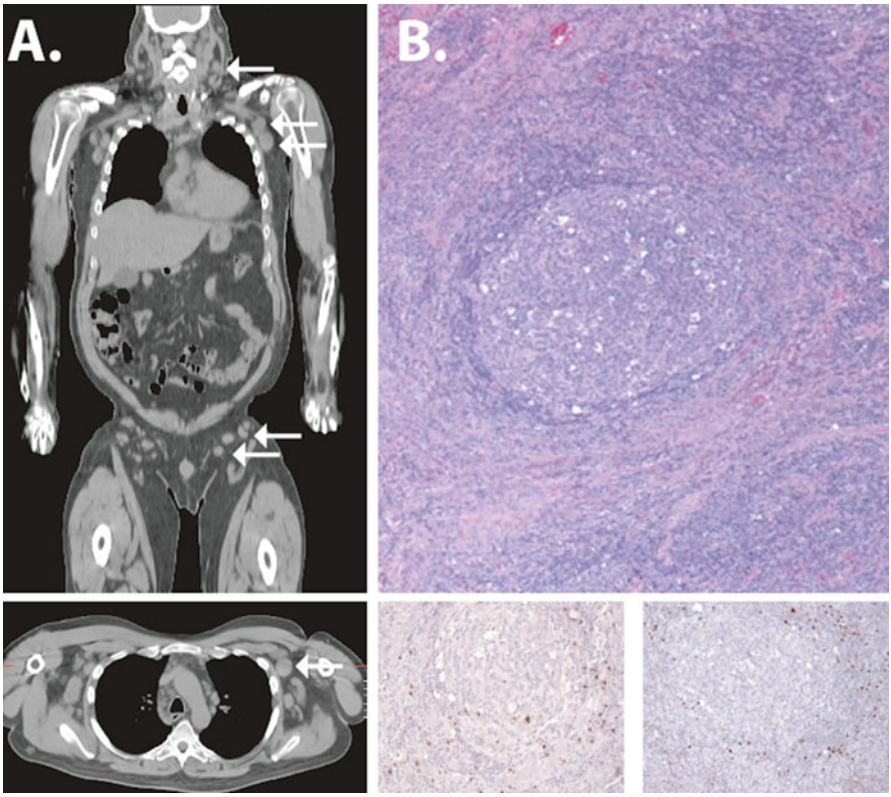

Fig. 18.1 Radiological and pathological findings in KSHV-associated MCD. Radiographic findings in a patient with KSHV-associated multicentric Castleman disease and HIV (*Panel A*, upper and lower rows) demonstrate key features of the disease through structural and functional imaging. In the *upper row*, whole torso coronal images obtained by computed tomography show widespread lymphadenopathy (*white arrows*) involving the cervical, axillary, and inguinal regions together with mild hepatomegaly. This patient was previously splenectomized so the spleen is not seen, but it is commonly markedly enlarged. In the *lower row*, sagittal images at the level of the axilla show the axillary nodal abnormalities in detail. Pathological sections (*Panel B*) stained with hematoxylin and eosin show characteristic changes including the plasma cell infiltrate in distinct sheets and an increase in vascularity. The *lower panels* show KSHV infected cells by immunohistochemistry: *lower left* demonstrates all KSHV infected cells (using an antibody to a viral latent protein, LANA) and *lower right* shows those KSHV infected cells in lytic phase and producing vIL-6 (using an antibody to vIL-6). Original magnification of all pathology sections was 20×. The authors gratefully acknowledge Dr Stefania Piitaluga, Laboratory of Pathology, National Cancer Institute for assistance with histopathological images; and Dr Corina Millo, Positron Emission Tomography Department, Clinical Center, National Institutes of Health for assistance with radiographic images

variants (be it unicentric or multicentric), albeit sharing certain histopathological features. As the overwhelming percentage of cases of MCD in patients with HIV/AIDS are KSHV-associated, the remainder of the chapter focuses on KSHV–MCD.

Table 18.1 Clinical and pathological characteristics of various forms of Castleman disease

	Unicentric		Multicentric	
	Hyaline vascular variant	Plasma cell variant[a]	Idiopathic	KSHV-associated
Pathological characteristics	Involved node shows germinal center involution: lymphocytes are depleted and replaced (hyalinized). Between follicles, fibrosis and increased blood vessels are seen. Plasma cells are not a feature	Germinal centers usually uninvolved or paucicellular, while the adjacent mantle zone is replaced by plasma cells infiltrate in concentric sheets. These extend between follicles with increased blood vessels	Affected nodes almost always resemble those of unicentric plasma cell variant, but are multiple. In rare cases multiple nodes showing hyaline vascular change are seen instead	Mantle zone and interfollicular zone replaced by plasma cell infiltrate in concentric sheets. Increased vessels between follicles. A minority of cells are KSHV-infected, some in 'lytic' phase
Location	Single lymph node or local chain, commonly mediastinal, may be very enlarged	Single lymph node or local chain, commonly abdominal	Multiple nodes throughout body. Spleen may be enlarged	Multiple nodes throughout body, particularly above diaphragm. Spleen commonly enlarged
Clinical setting	Highly variable in age presentation, but commonly early adulthood. Occurs in both genders	Highly variable in age presentation, but commonly in early adulthood. Occurs in both genders	Highly variable in age presentation. Occurs in both genders	Most common in HIV infection, including well-controlled disease
Etiology	Unknown, may be reactive	Unknown, may be reactive. A proportion of cases appear to be reactive to intercurrent lymphoma	Unknown, may be reactive. A proportion of cases appear to be reactive to intercurrent lymphoma. Most manifestations relate to increase in interleukin 6 levels	KSHV/HHV8 infection, usually in the setting of immune dysregulation (HIV infection) Manifestations relate to increase in viral and human interleukin 6 and other cytokines
Clinical symptoms	Symptoms uncommon	Fevers, cachexia, night sweats, malaise occur in some cases	Fevers, cachexia, night sweats, malaise occur in almost all cases	Fevers, cachexia, night sweats, malaise. Nonspecific respiratory and gastrointestinal symptoms may also be seen
Laboratory features	May not have any abnormalities	Hematologic cytopenias (most commonly anemia, thrombocytopenia) and low albumin levels in a minority of cases	Hematologic cytopenias (most commonly anemia, thrombocytopenia) and low albumin levels with elevated C-reactive protein	Hematologic cytopenias (most commonly anemia) and low albumin levels with elevated C-reactive protein
Treatment	Local therapy, most commonly surgical resection; radiation has been used in cases not amenable to surgery	Less well-defined than for hyaline vascular variant, but usually similar: Local therapy, most commonly surgical resection; radiation has been used in cases not amenable to surgery. Treatment of any precipitant	Systemic therapy, commonly directed at IL-6 inhibition. Chemotherapy may also be used Treatment of any precipitant	Systemic therapy, commonly directed at B-lymphocyte depletion by the monoclonal antibody, rituximab alone or in combination with chemotherapy KSHV virus directed therapies effective in some cases
Outcomes	Generally excellent	Generally excellent	Variable but improving with IL-6 directed therapies	Formerly very poor but improving with current regimens. May progress to large cell lymphoma

[a]Plasmacytic and plasmablastic variants are distinguished by some pathologists

18.3 Pathogenesis of MCD in HIV-Infected Patients: Role of Kaposi Sarcoma-Associated Herpesvirus and Immune Deficiency

The discovery of KSHV and its role as the cause of KS and MCD was pivotal in developing an understanding of these disorders, and of the crucial role that HIV infection plays in promoting the pathogenesis of KSHV–MCD. KSHV is a herpesvirus, most closely related to Epstein Barr virus (the cause of infectious mononucleosis) (Chang et al. 1994; Moore et al. 1996a, b). All herpesviruses including KSHV have in common a complex life cycle with two distinct phases (Jenner et al. 2001; Moore and Chang 1998; Paulose-Murphy et al. 2001; Staskus et al. 1999; Sun et al. 1999). The first of these phases is *latency*, in which a minimal set of viral genes is expressed, many of which are directed at the twin goals of promoting survival of the host cell (and so the virus itself) by modulating cellular survival pathways and of impeding the normal host immune response to the virally infected cell. The second, or *lytic*, phase is characterized by viral replication and expression of the full complement of proteins encoded by the virus's own genome. The host cell's machinery is commandeered in the service of viral replication, being turned over to produce progeny virus particles that in turn infect other cells or are transmitted to other hosts. Importantly, all current antiviral therapies affect only replicating virus. No strategy has been effective in disrupting latent herpesvirus infection, and infection once established is life-long.

Like other herpesviruses, KSHV modulates host pathways to facilitate its survival and replication. It does this in part by producing its own variations of certain critical host proteins, using genes acquired from the host by 'molecular piracy' during the course of the virus's evolution. Notable among these is a viral version (homolog) of the aforementioned human cytokine IL-6, called viral interleukin-6 (vIL-6) (Boshoff et al. 1997; Cesarman et al. 1996; Friborg et al. 1999; Moore et al. 1996b; Neipel et al. 1997; Sarid et al. 1998). In addition, KSHV directly affects the production of human IL-6 by several other mechanisms (Qin et al. 2009). The relationship of KSHV and its human host in normal circumstances is a delicate balance reflecting millennia of co-evolution. Prior to the HIV epidemic, most individuals infected with KSHV showed no clinical symptoms of infection and those that did occur (almost exclusively KS) were mainly in older individuals, presumably as a result of a diminution of the host immune response with advancing age (DiGiovanna and Safai 1981; Little and Yarchoan 2006). The introduction into the human species of HIV fundamentally disrupted this relationship, as HIV infects and destroys CD4+ T lymphocytes and so impairs the critical role of the host immune system in detecting and controlling KSHV infected cells and replication. Thus there is substantially less control of KSHV, leading to increased viral replication and the development of KSHV-associated tumors. Even when treated with antiretroviral therapies and achieving a normal CD4+ T cell count, HIV-infected patients continue to exhibit defects in their immune response that permit the development of KSHV-associated tumors, including KSHV–MCD (Bower et al. 2009; Powles et al. 2009; Shiels et al. 2010, 2011; Uldrick et al. 2010). Tumor development may be further enhanced by the presence of HIV-associated inflammation, and perhaps by direct interactions between HIV and KSHV at the cellular level (Aoki and Tosato 2007).

In KSHV–MCD, it appears that the crucial elements leading to the development of the tumor are dysregulation of viral replication and proliferation of KSHV-infected B-lymphocytes, with consequent marked elevations of human and viral cytokines. In particular, levels of both viral and human IL-6 are elevated during KSHV–MCD flares, as are KSHV viral loads (at least in part as a result of replication) and several other host cytokines including IL-10 (Aoki et al. 2001; Oksenhendler et al. 2000; Polizzotto et al. 2013). In addition, as noted above, affected lymph nodes show virus in its lytic (replicative) state in a substantial proportion of virally infected cells (Du et al. 2001). Notably, it has been shown that detectable KSHV replication in peripheral blood commonly precedes development of symptoms in patients later found to have KSHV–MCD (Stebbing et al. 2011).

Interestingly, KSHV–MCD develops most commonly in patients with relatively well-controlled HIV (CD4+ T lymphocyte count above 200 cells/mm^3) (Bower et al. 2011; Uldrick et al. 2011). There is also some evidence that its incidence has increased in recent years, following the widespread adoption in the developed world of highly active antiretroviral therapy for HIV (Powles et al. 2009). Taken together, these observations suggest that development of the full clinicopathological syndrome of KSHV–MCD may require a level of preservation of the host immune infrastructure and mechanisms that is absent in patients with the more profound immunodeficiency of uncontrolled AIDS. It is also possible that its development requires longer survival with HIV than was seen early in the epidemic.

It should also be noted that similar inflammatory symptoms to those seen in KSHV–MCD have recently been described in KSHV-infected patients without pathological evidence of KSHV–MCD (Uldrick et al. 2010). These patients presented with a constellation of fevers, cachexia and laboratory abnormalities including cytopenias, hypoalbuminemia, and elevated CRP. However, lymphadenopathy and splenomegaly were not prominent and the pathognomonic nodal changes of KSHV–MCD were not demonstrable, in some cases even with repeated lymph node biopsies. Patients showed evidence of KSHV replication and disturbances of human and viral IL-6 similar to those seen in KSHV–MCD flares. Many of these patients had other KSHV-associated diseases (KS or PEL), suggesting that these tumors might contribute to or be the major source of the inflammatory abnormalities. This putative syndrome has provisionally been named the KSHV inflammatory cytokine syndrome (KICS) and a working case definition has been proposed (Polizzotto et al. 2012). Its pathophysiology, clinical outcomes, and relationship to KSHV–MCD are now being defined prospectively (NCT01419561).

18.4 Treatment of KSHV-Associated MCD in HIV-Infected Patients

Partly as a result of its recent recognition as a disease entity, rarity, and the consequent difficult in establishing high quality clinical studies, there is no standard therapy for KSHV–MCD (Bower 2010). This difficulty is further compounded by the

complexity of clinical studies in patients who have both HIV and an associated tumor or malignancy, where both life-threatening diseases must be successfully managed (Persad et al. 2008). Therefore the majority of articles describing therapy of KSHV–MCD have consisted of either retrospective case reports or series, or small prospective studies without control arms. Nonetheless, the evolving understanding of the unique aspects of the viral etiology of KSHV–MCD have suggested several novel approaches to therapy, and there is now emerging evidence that these therapies are having a positive impact on patients with KSHV–MCD, improving their symptom control and, importantly, long-term survival when compared to historical controls (Bower et al. 2007; Gérard et al. 2007, 2012; Hoffmann et al. 2011; Marcelin et al. 2003; Powles et al. 2007; Uldrick et al. 2011).

Early treatment strategies for KSHV–MCD reflected its unusual position at the interface of infectious diseases and clonal lymphoid malignancies. The first therapies studied generally approached the disease from one of these perspectives. One approach adapted a commonly used antiviral agent with known activity against herpesviruses, ganciclovir (Casper et al. 2004a). As noted above, this agent is activated by phosphorylation by KSHV and then acts on the replicating virus, becoming incorporated by the viral DNA replication enzyme (DNA polymerase) into the DNA chain and arresting further replication by preventing the addition of additional nucleotides to the chain. It can thus reduce the cell-to-cell spread of KSHV. In parallel, other investigators used single chemotherapy agents or combination chemotherapy regimens adapted from successful lymphoma strategies, particularly CHOP (doxorubicin, vincristine, cyclophosphamide, and prednisolone) (Oksenhendler et al. 2000). In both approaches, patients were usually started on antiretroviral therapy to control the associated HIV infection. Each of these approaches showed modest activity in KSHV–MCD but overall outcomes remained suboptimal.

More recently, the development of a humanized monoclonal antibody directed at the CD20 antigen on B-lymphocytes has opened a new approach to KSHV–MCD therapy. As noted above, many of the cytokine-producing cells in lymph nodes affected by KSHV–MCD express CD20. CD20-positive lymphocytes are also a major reservoir of KSHV infection in the infected host, potentially providing an ongoing source of replicating virus to perpetuate the disease state (Pyakurel et al. 2004). Several groups have now reported good results with rituximab therapy of KSHV–MCD (alone or following chemotherapy) in patients with KSHV–MCD, including patients who had previously failed other approaches, as measured by resolution of symptoms, viral replication, and cytokine abnormalities (Bower et al. 2007; Gérard et al. 2007). On the basis of these initial results and more recently reported long-term outcomes, rituximab has become perhaps the most commonly used initial therapy for symptomatic KSHV–MCD. Rituximab therapy of KSHV–MCD is associated with the development or progression of KS in a substantial minority of cases, and some approaches therefore use it in combination with chemotherapy agents that have some activity against KS spindle cells, including the liposome encapsulated formulation of doxorubicin (Hengge et al. 1993; Presant et al. 1993). It may also be that some patients, perhaps those with the most KSHV–MCD, would benefit from a therapeutic approach that combines rituximab with cytotoxic

chemotherapy agents directed at B cells. The question of when, how, and for whom to add chemotherapy to a rituximab therapy 'backbone' will be a critical issue in KSHV–MCD investigation in the coming years (Bower 2010).

An additional novel approach is targeted at KSHV, exploiting the virus's own enzymatic machinery to deliver a toxin specifically to KSHV-infected cells in which lytic replication is occurring (as it is in KSHV-infected plasmablasts in nodes affected by KSHV–MCD). This approach, called 'virus activated cytotoxic therapy' uses the combination of two agents, high-dose zidovudine (or AZT) and valganciclovir. Each of these is commonly used as a conventional antiviral drug, acting as described above as a chain terminator (zidovudine in the HIV reverse transcriptase, and valganciclovir in the herpes DNA polymerase). However, in this approach they function differently. Rather than interrupting DNA replication, each is activated through phosphorylation by two KSHV-encoded enzymes to moieties that are toxic to the infected cells (Davis et al. 2007). These enzymes are expressed by KSHV only in its lytic phase, and therefore this approach provides a method to selectively target and kill only those cells which are central to the pathogenesis of KSHV–MCD. This approach has been shown to be moderately effective in patients with symptomatic KSHV–MCD, again as measured by resolution of symptoms, viral replication, and cytokine abnormalities (Uldrick et al. 2011). This combination may also have a role in combination with other approaches, or in 'maintenance' or 'consolidation' therapy for patients who have completed therapy with other agents (Uldrick et al. 2012).

Further targets for therapy of KSHV–MCD are suggested by the critical role of human and viral IL-6 in its pathogenesis and symptomatology. Inhibitors of human IL-6 may not affect KSHV vIL-6, which has little antigenic similarity with hIL-6 and may also signal differently (Boulanger et al. 2004; Heinrich et al. 1998; Hu and Nicholas 2006; Meads and Medveczky 2004). However, while there has been little economic incentive to develop inhibitors of vIL-6 specifically, as noted above two monoclonal antibodies inhibiting IL-6 activity have been developed (one directed at the molecule itself, the other at its receptor). One, tocilizumab, has been approved by the US Food and Drug Administration and is now in clinical use in several rheumatologic diseases while siltoximab is now RDA approved for idiopathic MCD. Alone or in combination with other drugs, these may in the future provide add to the armamentarium against KSHV–MCD.

18.5 Prevention of KSHV-Associated MCD and Related Lymphomas in HIV-Infected Patients

The role of the oncogenic virus KSHV in the pathogenesis of KSHV–MCD and other tumors raises the possibility that preventive strategies directed at the virus, over and above management of immune deficiency through control of the HIV infection, may be of benefit in preventing the development of these tumors. There are currently no vaccines against KSHV, and as our understanding of its transmission remains incomplete even behavioral risk modification strategies are limited.

However, there is at least proof in principle that KSHV-related disorders can be prevented with antiviral agents: ganciclovir, when used for cytomegalovirus retinitis, was incidentally found to reduce the risk of KS (Martin et al. 1999). This observation, together with the fact noted above that asymptomatic KSHV replication commonly precedes the onset of symptomatic KSHV–MCD and data showing that ganciclovir can be used as prophylaxis for KSHV replication, suggests that carefully targeted preventive antiviral strategies may be of use in the future (Casper et al. 2008). A better understanding of the precipitants of KSHV lytic replication is likely to be a crucial step in this direction.

On a related front, significant progress has been shown in preventing the most feared complication of KSHV–MCD through effective therapy. As noted above, as many as 20 % of patients with KSHV–MCD previously progressed to large cell lymphoma. In the majority of lymphomas arising in this setting, the malignant cells show evidence of KSHV infection with plasmacytic features and immunoglobulin expression that distinguish them the cells of PEL, the other lymphoma established to be caused by KSHV. Rarely, large cell lymphomas not associated with KSHV are also seen. The lymphomas in the setting of KSHV–MCD carried a poor prognosis and was one of the most common causes of death. Recent studies of patients treated with rituximab, with or without chemotherapy, have shown evidence of reductions in lymphoma incidence as well as good control of the symptoms of KSHV–MCD (Gérard et al. 2012; Hoffmann et al. 2011). It remains unclear if this is a specific outcome of CD20+ B-lymphocyte depletion by rituximab (since the most common lymphomas arising in KSHV–MCD are B-cell lymphomas) or a general consequence of reduction of the local and systemic inflammatory milieu with treatment. Further studies to extend this observation will be crucial.

18.6 KSHV-Associated MCD in Resource-Limited Countries

As has been discussed elsewhere, the co-occurrence particularly in parts of sub-Saharan Africa of high endemic rates of oncogenic virus infection (including KSHV) and an epidemic of HIV infection (until recently uncontrolled) has led to very high rates of virally associated malignancies (Mbulaiteye et al. 2006). For example, in sub-Saharan Africa KS is among the most common cancers. Intriguingly though, until recently cases of KSHV–MCD has only rarely been reported from this region (Beukes and Thiart 2012). This is particularly notable as KSHV–MCD is reported in immigrants from these regions in the USA and Europe (Uldrick et al. 2012).

There are a number of possible explanations for this apparent discrepancy. Until widespread rollout of antiretroviral therapy in Africa through the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the United States President's Emergency Plan for AIDS Relief (PEPFAR), most HIV in this region was untreated. It may therefore be that many patients succumbed to other sequelae of profound immunodeficiency before the development of KSHV–MCD. Furthermore, as noted above

KSHV–MCD commonly occurs in patients with at least relatively well-controlled HIV, and it may be that at least some level of immune competence is required for the full clinicopathological syndrome to manifest. Perhaps the most important contribution to the paucity of reported KSHV–MCD in this region that the relatively undeveloped and under-resourced state of clinical and pathological services in this region has hampered recognition of this complex diagnosis. KSHV–MCD clinically may be mistaken for uncontrolled mycobacterial infection, lymphoma, or other chronic infective and inflammatory processes. Given the magnitude of the burden of tuberculosis in Africa, empiric anti-mycobacterial therapy of suspected lymphadenopathic tuberculosis is relatively common throughout this region. Even in cases where lymph node sampling is performed, limited tissue sampling, and in some instances inadequate resources to complete a comprehensive pathological assessment likely contribute to missed diagnoses. The very high untreated mortality of KSHV–MCD and the emergence of relatively low cost therapies that are potentially deliverable in resource-limited settings (such as ganciclovir with or without high dose zidovudine) suggest that improved surveillance for and recognition of KSHV–MCD has the potential to deliver important health benefits for people with HIV/AIDS in resource-limited settings (Casper et al. 2004a; Gopal et al. 2012; Uldrick et al. 2011).

18.7 Conclusion

The advent of the AIDS epidemic has brought new prominence to this hitherto uncommon lymphoproliferative disorder, and further led indirectly to the discovery of a new oncogenic virus, KSHV, and the recognition that MCD caused by KSHV is a distinct entity with unique pathophysiology and therefore additional specific therapeutic targets. Building on this knowledge, new therapies have greatly improved outcomes for patients with HIV and KSHV–MCD, including important improvements in long-term survival and reduction in the risk of lymphomas. There is the prospect of continued improvements as new agents become available. The challenges of preventing this disease in those most susceptible, and of bringing these improvements in outcomes to the resource-limited settings most affected by HIV/AIDS, continue to occupy researchers and clinicians.

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Part V
Human Papillomavirus-Associated Cancers

Chapter 19
Cervical Cancer and HIV

Elizabeth A. Stier

Abstract Cervical cancer or cancer of the cervix uteri is an abnormal growth of squamous or glandular epithelial cells caused by persistent infection with the oncogenic or high-risk types of the human papillomavirus (HPV). While most HPV infections of the cervix are transient, persistent HPV infections of the cervix may cause cervical intraepithelial neoplasia (CIN) and subsequently develop into invasive cervical cancer (ICC). HIV-infected women are more likely to have persistent HPV infections, and are also more likely to develop CIN and ICC compared with women without HIV. Cervical cancer in the HIV-infected woman is considered an AIDS-defining illness. The successful introduction of cervical cancer screening programs with cervical cytology, otherwise known as the Papanicolau (Pap) test (which may detect treatable premalignant CIN lesions) has been associated with a 70 % decline in cervical cancer incidence and mortality. Cervical cancer screening recommendations may now include HPV testing and are constantly evolving for HIV-infected and non-infected women. Primary prevention with prophylactic HPV vaccines should prevent cervical cancer in the future; trials assessing immunogenicity and efficacy in HIV-infected women are ongoing. Early stage ICC is treated surgically whereas advanced ICC is managed with chemoradiation.

19.1 Introduction

Cervical cancer is the second most common cancer among women worldwide, however, about 86 % of the cases occur in low resource countries. In countries where cervical cancer screening with cervical cytology is routinely performed, the incidence and mortality of cervical cancer has decreased to one-third of pre-cervical cytology screening levels.

E.A. Stier, M.D. (✉)
Boston University Medical Center, Boston, MA 02118, USA
e-mail: elstier@bmc.org

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Cervical cancer was designated an AIDS-defining illness in 1993 (see Chapter 2). The widespread use of antiretroviral therapy (ART) has been associated with a substantial decrease in the other AIDS-defining malignancies—Kaposi's sarcoma and lymphoma; however, the incidence of cervical cancer has increased such that cervical cancer remains a significant cause of morbidity for HIV-positive women (Shiels et al. 2011).

HPV is the causative agent for cervical cancer. Persistence of cervical infection with HPV is necessary but not sufficient for the development of cervical cancer. HPV prevention with prophylactic vaccination is likely to have a significant role in decreasing the future incidence of this and other HPV-associated malignancies.

19.2 Epidemiology

While in developed countries cervical cancer is the tenth most common type of cancer in women (9.0 per 100,000 women), in developing countries it is second only to breast cancer as the most common type of cancer (17.8 per 100,000) and cause of cancer deaths (9.8 per 100,000) among women. In Africa, Central America, and Southern Asia, cervical cancer is the primary cause of cancer-related mortality among women (WHO/ICO Information Centre on HPV and Cervical Cancer 2010). In Eastern and Western Africa, incidence and mortality rates of invasive cervical cancer (ICC) have been estimated at 35 and 25 per 100,000 women, respectively (Forman et al. 2012) (see Chapter 4).

The relative incidence of cervical cancer in HIV+ compared with HIV-women is unclear—studies have estimated these rates at 1.5–8 times that of the general population (Einstein and Phaëton 2010). Unfortunately, cancer registries have not been established in lower income countries; however, it has been estimated that in Uganda and South Africa the relative risk of cervical cancer in HIV+ women is about twice that of the general population (Mbulaiteye et al. 2011). In Tanzania, 30 % of women diagnosed with cervical cancer were HIV-positive, and these women were significantly more likely to present with cervical cancer at a younger age and more advanced stage compared with women who were HIV-negative (Matavelo et al. 2012).

19.3 Etiology

In the 1990s, HPV was identified as the causative agent of cervical cancer. HPVs are a large family of small double-stranded DNA viruses that infect squamous epithelia. The 30–40 HPV genotypes affecting the genitalia vary in their oncogenic potential; HPV types 16 and 18, accounting for approximately 65–70 % of cervical cancers worldwide, are 2 of approximately 15 HPV types identified as oncogenic or high-risk (HR). Certain low-risk HPV types, including types 6 and 11 are largely responsible for genital warts or condyloma (see Chapter 7).

Genital HPV infections are the most common sexually transmitted infections in women, and have a peak prevalence between ages 18 and 25. Most of these HPV infections clear spontaneously (or at least become clinically undetectable), but in 10 % of immuno-competent women, these infections persist (i.e., they are detected for greater than 1 year). It is the persistent HR HPV infections that may cause changes in the cervical epithelium leading to the development of cervical cancer precursors—high-grade squamous intraepithelial lesions (HSIL) also known as cervical intraepithelial neoplasia (CIN) 2 or 3—and possible progression to ICC.

It is now understood that infection with HPV requires a micro-abrasion in the genital epithelium to the level of the basement membrane. In the cervix, the infection site is typically a group of cells in the transformation zone, where the squamous epithelium of the ectocervix transitions to the glandular epithelium of the endocervix. HPV is then able to infect a small group of basal keratinocytes. If the host immune system does not clear the infection, then the HPV infection persists, and may lead to cellular changes in the epithelium that are associated with the histologic findings consistent with an active HPV infection (koilocytosis, low-grade SIL and HSIL).

The timeline for these transformative changes in the cervix is best illustrated by the ages associated with peak prevalence: HPV infection is most commonly detected in women at ages 15–25, HSIL in women 25–35, and ICC in women over age 45. Thus, as a conservative estimate, HPV infection typically persists for at least 10–20 years before transformation to cervical cancer occurs.

HPV prevalence in women with normal cytology varies significantly with age and geographic location—in North America HR HPV prevalence in women under age 25 is 20+ % whereas the prevalence in women 35+ is under 10 %. There does, however, seem to be significant regional variation—in the Caribbean and Eastern Africa, the regionally adjusted HPV prevalence is 35 % (compared with 9 % in Western Europe and 5 % in North America) (Forman et al. 2012).

HIV-positive women have a far higher prevalence of HPV infections, a greater likelihood of persistent infection and are more likely to be infected with multiple HPV types compared with HIV-negative women. Some studies have found that HPV prevalence and persistence is higher in women with lower CD4 counts; however, results have not been consistent. In addition, the likelihood of prevalent HPV infections in HIV-positive women with normal cytology does not vary with age. Studies of HIV+ women since the widespread availability of HAART do not consistently show lower HPV infection rates compared with studies from the pre-HAART era.

Studies in South Africa and Kenya of HIV+ women with normal cervical pathology have revealed that HPV is detectable in 44–55 % and that HPV 16 is detectable in 3–7 % of subjects. Age has not been predictive of HPV infection. The relationship of low CD4 counts to HPV prevalence, incidence and clearance have been inconsistent across studies. However, independent of CD4 count, HPV was more likely to persist in HIV-infected patients, with a South African study finding that only 6 % of women with HR HPV cleared the infection over the following 18 months (Denny et al. 2008; De Vuyst et al. 2012).

Approximately 70 % of ICCs worldwide are associated with HPV 16 and/or 18. Although there is sparse data to date, multiple studies in Africa (including Kenya,

South Africa, Mozambique, and Zambia) identifying HPV genotypes in ICC in HIV-positive women have found the combined prevalence of HPV16 and/or 18 to be 54–86 % (Denny et al. 2012; Naucler 2011; De Vuyst et al. 2011).

19.4 Screening and Early Detection

In countries where cervical cancer screening with Papanicolau (Pap) testing (cytology) is routinely performed, the incidence and mortality of ICC has decreased to one-third of pre-Pap screening levels. The standard of care based on cervical cytology screening is as follows: an abnormal cervical cytology will trigger a referral for colposcopic evaluation of the cervix with directed biopsy for histology. Colposcopy is evaluation of the cervix after application of acetic acid 5 % (and sometimes Lugol's solution, a strong iodine stain) under magnification. Any abnormal areas are biopsied and then clinical follow-up is determined by the histologic findings. Untreated CIN3 has a 30 % chance of progressing to invasive malignancy whereas women who have undergone treatment for CIN3 are very unlikely to subsequently be diagnosed with ICC. Therefore biopsies showing HSIL or CIN2-3 are considered premalignant conditions. Treatment of HSIL involves ablation (e.g., cryotherapy or laser) or excision by cervical conization (loop electrical excisional procedure—LEEP or "cold knife") of the entire cervical transformation zone. In HIV-negative women, recurrence rate of HSIL following treatment by ablation or excision of the transformation zone is under 10 %. In addition, colposcopic directed biopsy or cervical conization may identify early, asymptomatic ICCs which can be treated by conization or simple hysterectomy. It is the treatment of premalignant lesions and diagnosis of earlier stage cervical cancers that has contributed to the decrease in incidence and mortality of ICC.

Despite the apparent success of the Pap test, cases of cervical cancers still occur in countries where routine cervical screening is performed. This is likely due to missed Pap tests, inadequate follow-up or inaccurate cytology results. While cervical cytology has been very effective in eradicating squamous cervical cancer, it has had minimal effect on lowering rates of glandular cervical cancers (which comprise 10–25 % of cervical ICCs).

HIV-positive women are more likely to have abnormal cervical cytology, with prevalent rates of 25 % and cumulative risk of abnormal cytology of 77 % over 10 years (Massad 2008). Under current guidelines, a woman with an abnormal cytology would be referred for colposcopic evaluation of the cervix with directed biopsy. Similar to HIV-negative women, an HSIL cervical biopsy is an indication for treatment. However, the recurrence rate of HSIL in the HIV-positive patient is over 50 % (Reimers et al. 2010) which is significantly higher than in HIV-negative women. Thus, in HIV-positive women, follow-up after treatment is critical and the goal of treatment is cancer prevention, not HPV eradication.

As an abnormal cervical cytology may indicate abnormalities elsewhere in the lower genital tract—it is important to closely evaluate the vagina, vulvar and peri-anus

at the time of colposcopy, especially if the source of abnormal cells is not found in the cervix. In addition, CIN, especially in HIV-positive women, is strongly associated with intraepithelial lesions of the vagina, vulvar, peri-anus, and anus.

Commercial testing for HR-HPV DNA (first commercially available in the 1990s) has been shown consistently to be superior to cytology in terms of its sensitivity and negative predictive value and is becoming a major tool in cervical cancer screening of women age 30 and older, at least in some developed countries. A single negative cervical HPV test with a normal cervical cytology in such women is associated with an exceedingly low rate of cervical cancer in the next 5 years, allowing screening intervals to be considerably lengthened.

Current recommendations for screening of HIV-infected women include more frequent surveillance and careful follow-up; this likely accounts for the minimal increase in cervical cancer incidence despite the higher burden of premalignant disease. The role of HPV testing for cervical cancer screening in HIV+ women remains unclear as prevalence rates for oncogenic HPV are much higher in HIV-infected women 30 and over compared to the general population.

HPV testing has not been adopted as a standard cervical cancer screening strategy in HIV-positive women age 30 and older. However, there may be a role for this strategy in (at least) some populations of HIV-positive women. In a cohort of 420 HIV-infected and 279 HIV-uninfected women from the Women's Interagency HIV Study (WIHS) enrolled in 2001–2002, the 5-year risks of CIN2+ in women with baseline normal cervical Pap test and negative HR-HPV testing were comparable to the risks in HIV-negative patients at 0.3–0.4 %. Notably, within this WIHS cohort HPV prevalence was low; only 12 % of the HIV-positive and 9 % of the HPV-negative women had HR-HPV detected at baseline with normal cervical cytology for these women, the 5-year risks of CIN2+ were 5 % regardless of HIV status. The risks of CIN2+ for HIV-infected women did not differ by baseline CD4 counts. No women in this cohort were diagnosed with cervical cancer at up to 9 years of follow-up (Keller et al. 2012). Thus, utilizing HPV testing as a component of cervical cancer screening strategies may be cost effective, at least in populations of HIV-positive women with a low prevalence of HR HPV.

19.5 Cervical Cancer Screening in Developing Countries

Cervical cancer screening programs are being slowly introduced to sub-Saharan Africa where screening rates range from 2 to 20 % in urban areas and 0.4 to 14 % in rural areas. Cytology specimens have to be transported to a central laboratory, processed, read and then the results need to be communicated to the patient; if abnormal, follow-up evaluations then need to be conducted. Due to difficulty in accessing patients, especially in rural locations, inadequate transportation systems in which specimens may be lost, broken or significantly delayed, central laboratories with slow processing, and poor communication systems, cervical cancer screening with cytology has proved especially difficult to successfully implement in low resource settings.

Therefore, in low resource settings, the emphasis has been on developing inexpensive techniques that can be implemented in a single visit by trained nurse providers ("see and treat"). Visual inspection with acetic acid (VIA) or visual inspection with Lugol's iodine (VILI) followed by treatment of abnormal findings with cryotherapy has been the most widely promoted, although with variable success (Brower 2011).

A study of over 1,000 HIV+ women from India with no prior history of cervical cancer screening compared VIA, VILI, HPV testing (HC2) and cytology, to assess the test characteristics of the different screening options in a resource limited setting. All women underwent colposcopy with directed biopsy regardless of findings from screening; 55 (5 %) of the women were diagnosed with CIN2,3 and five with ICC. HPV testing detected all cases of CIN3+, and had 95 % sensitivity for the detection of CIN2+ (95 %), however as 26 % of the women tested positive for HPV, the specificity was only 77 %. The likelihood of a positive test with VIA, VILI, and cytology (ASCUS+) was 15, 15, and 8 %, respectively, whereas the sensitivity for CIN2+ was 84, 89, and 63 %, respectively. Thus, in this setting, cytology was outperformed by all other modalities and it was suggested that if HPV testing became affordable, then HPV testing followed by VIA would be most effective means of screening for CIN2+ of the cervix (Joshi et al. 2012).

19.6 Prevention with Vaccination

Prophylactic HPV L1 virus-like particle vaccines are highly efficacious in preventing CIN2/3 lesions caused by HPV 16/18 for women without HPV 16 and/or 18 at the time of vaccination. Data from clinical trials of these vaccines, together with post-vaccine surveillance, indicate that they have a good safety profile. As the current HPV vaccines provide protection against only two of the 15 oncogenic HPVs, they will not eliminate cervical cancer or other HPV-associated ano-genital diseases, but could reduce the incidence of cervix cancer by up to 65–70 % if effectively delivered to adolescent females prior to the onset of sexual activity (Stanley 2012). Newer vaccines with activity against a wider range of HPV types are now under development.

Trials of HPV vaccination in HIV+ women and men have shown that there is appropriate immunogenicity in this patient population (Kojic 2014; Wilkin et al. 2010). A trial comparing the immunogenicity of the bivalent compared with the quadrivalent HPV vaccine found that both were immunogenic although the bivalent vaccine was associated with higher anti-HPV-18 antibody titers (Toft et al. 2014). The efficacy of HPV vaccination in HIV-positive women and men has not yet been demonstrated and is being evaluated in ongoing studies. HPV vaccination is recommended in HIV-positive women (and men) through age 26 and has an excellent safety profile.

Prophylactic HPV vaccination has not been shown to be effective in preventing persistent HPV infection and associated neoplasia in women with evidence of prior HPV infection of the genotypes within the vaccine. However, a randomized study of the prophylactic HPV vaccine for HIV-negative women with CIN2/3 treated with LEEP found that patients who received HPV vaccination had a decreased risk for recurrent CIN2/3 (Kang et al. 2013).

As the prevalence of antibodies to type 16 HPV and/or 18 is very high (40 %) in HIV-positive women from South Africa, Botswana, and Brazil, it is very important that vaccination occur prior to the onset of sexual activity to have maximal benefit (Firnhaber et al. 2011).

19.7 Invasive Cervical Cancer

In the general population, the majority (69 %) of cervical cancers are squamous carcinomas (associated with HPV 16 [59 %] and HPV 18 [13 %]) and 25 % are adenocarcinoma (HPV 16 [36 %]; 18 [37 %]). Data is limited on the histologic distribution of cervical cancers in HIV-positive populations. A retrospective analysis in South Africa found that squamous carcinomas represented more than 90 % of invasive cancers detected among both HIV+ and HIV-women (Simonds et al. 2012).

Early cervical cancer (stage IA–IB2) is typically asymptomatic and has an excellent prognosis. Cervical cancer can spread by direct extension (to the uterine corpus, vagina, parametria, bladder, or rectum) or by lymphatic or hematogenous dissemination. Advanced cervical cancer (stage 2+) may present with vaginal bleeding, pelvic or lower back pain, hematuria or other bladder or bowel complaints.

The diagnosis of ICC is made by histologic examination of tissue. Early stage cervical cancers may be detected during the workup for abnormal results of cervical cancer screening. Abnormal cervical cytology or positive HPV testing is followed by colposcopic evaluation with directed biopsy. If a cervical cancer precursor (HSIL) is found on biopsy, removal of the transformation zone by conization may allow for the detection of an occult cancer. Women with clinical evidence of invasive cancer such as a gross lesion require a pelvic exam and biopsy for histologic verification.

A retrospective review of 4,300 Kenyan HIV-infected women screened for cervical cancer with VIA, followed by colposcopy and LEEP found that 58 (1.3 %) were diagnosed with ICC. The mean age at diagnosis was 34 years (range 22–50 years) and 93 % had microscopic disease (stage IA1) (Mungo et al. 2013). Another retrospective study from South Africa found that HIV-positive women were diagnosed with ICC at a younger age and more advanced stage than HIV-negative women. However, treatment outcomes were comparable when controlling for stage and completion of radiation therapy (Simonds et al. 2012).

Recommended treatment options are based on cancer stage regardless of HIV status. Selected women with microscopic disease (stage IA1) may be treated with

cone biopsy or simple hysterectomy (removal of the cervix and uterus). Women with a nonbulky (≤4 cm) tumor confined to the cervix, uterus, upper third of the vagina (stage IA2, IB1, IIA1) without lymph node metastases are candidates for radical hysterectomy (removal of the uterus, cervix, and surrounding tissue including significant dissection around the ureters). However, chemoradiation is also a viable option for stage 1B and IIA disease.

The standard of care for the treatment of locally advanced cervical cancer (LACC) is concurrent chemoradiotherapy using cisplatin as the chemotherapeutic radiosensitizing agent. The use of this regimen as standard of care is based on multiple randomized, controlled trials (RCTs) that showed improved efficacy when cisplatin was added to radiation therapy, even in high-risk patients who had histologic evidence of metastatic disease in pelvic and/or para-aortic lymph nodes. There is little data available on the efficacy of standard chemoradiotherapy for treatment of LACC in the HIV+ women.

19.8 Conclusion

Although cervical cancer treatments have been improving in recent years, there is no question the largest opportunity to decrease the burden of HIV-associated cervical cancer is in prevention. Prophylactic vaccination against HPV will likely have substantial clinical benefits in HIV-infected women, especially if the vaccine is administered prior to sexual debut. However, the clinical trials of vaccination in HIV are ongoing, the efficacy and duration of immunity is unknown and likely only cancers attributed to HPV types 16 and 18 will be prevented with the current licensed vaccines.

Algorithms for screening in HIV-uninfected women might not apply to HIV as the course of disease from persistence to cancer appears to be different in the setting of HIV, particularly in those with a poor immune status. Also, treatments for cervical precancerous lesions in HIV should focus on cancer control rather than cure, as clearance of HPV in the setting of HIV is unlikely.

Because most cervical cancer trials are conducted in developed countries and have typically excluded the enrollment of HIV-positive women, there is minimal data particular to cervical cancer treatment in the setting of HIV. The burden of disease of HIV-associated cervical cancer in developing and middle-income countries is large, but only estimated at present. There is a pressing need to directly address potential drug–drug interactions of ART on standard and targeted cervical cancer treatments through pharmacokinetic trials, as well as finding ways to minimize dose delays and modifications due to marrow toxicities of both chemotherapy and pelvic radiation in the setting of HIV. Lastly, as locally advanced cervical cancer is more common among HIV+ women, better tolerated and improved treatments need to be evaluated (Einstein and Phaëton 2010).

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Chapter 20
Anal Cancer

Joel M. Palefsky

Abstract Anal cancer is a squamous cell cancer of the anal canal and perianal region that is very similar biologically to cervical cancer in terms of its association with oncogenic human papillomavirus (HPV), particularly HPV 16. Like cervical cancer, anal cancer occurs most often in a squamo-columnar transformation zone, and is preceded by squamous intraepithelial lesions. The incidence of anal cancer is considerably higher in HIV-infected men and women than in the general population and has increased since the introduction of highly active antiretroviral therapy. Anal cancer is now the fourth most common cancer among HIV-positive individuals. Unlike most other cancers occurring in the HIV-positive population, anal cancer is also potentially preventable through primary prevention (vaccination against HPV). Screening for and removal of high-grade anal squamous intraepithelial lesions may also be useful for secondary prevention of anal cancer among those who have already developed ASIL, similar to the successful model used to prevent cervical cancer. Studies are planned to determine if secondary prevention is effective in prevention of anal cancer.

20.1 Introduction

Recently, malignancies have become one of the most common causes of mortality in HIV-infected men and women. Unlike the most common HIV-associated malignancies, Kaposi's sarcoma and nonHodgkins lymphoma, the incidence of anal cancer has continued to increase among HIV-infected individuals well after the introduction of highly active antiretroviral therapy (HAART) (Fig. 20.1).

J.M. Palefsky, M.D. (✉)
University of California, 513 Parnassus Ave,
Box 0654, San Francisco, CA 94143, USA
e-mail: joel.palefsky@ucsf.edu

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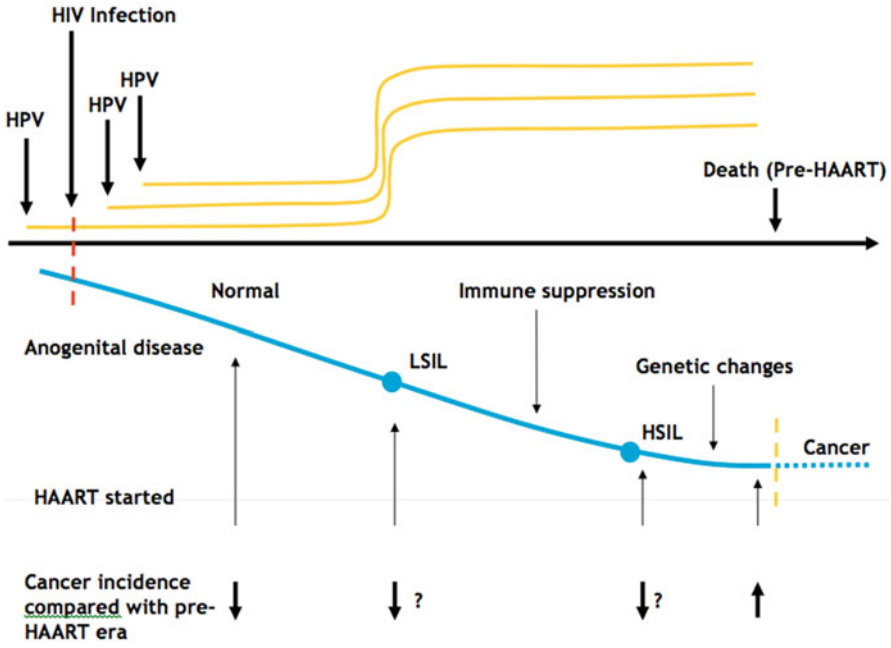

Fig. 20.1 Relationship between highly active antiretroviral therapy (HAART) initiation, anal squamous intraepithelial lesions, and incidence of anal cancer. Data suggest that immune response plays an important role in preventing development of low-grade anal squamous intraepithelial lesions (LSIL) and high-grade squamous intraepithelial lesions (HSIL). HSIL that persists accumulates genetic changes over time that are not reversible by antiretroviral therapy-induced immune reconstitution. With sufficient time and accumulation of cancer-inducing genetic changes, these lesions may progress to cancer. In the pre-HAART era, the incidence of anal cancer among HIV-infected MSM was modestly higher than among HIV-uninfected MSM. In the pre-HAART era, MSM may have died of competing causes before they had sufficient time to progress from HSIL to cancer and this may have limited the number of cases of cancer that developed. Since the introduction of HAART the incidence of anal cancer has increased among HIV-infected MSM. Initiation of HAART if the patient has no disease or LSIL at either a low or high CD4 level may prevent progression to HSIL, and may lead to reduced incidence of anal cancer compared to those who initiate HAART after having HSIL for a long period of time. The incidence of anal cancer may or may not be higher in this group compared with the pre-HAART era. Initiation of ART if the patient has early HSIL at either a low or high CD4 level may induce regression of HSIL, and may or may not lead to reduced incidence of anal cancer compared to those who initiate ART after having HSIL for a long period of time. The incidence of anal cancer may or may not be higher in this group compared with the pre-HAART era. Initiation of ART after HSIL has persisted for several years may not induce lesion regression whether the CD4 level is high or low, and the longer survival time in the absence of ASIL screening will allow the incidence of anal cancer to increase compared with the pre-HAART era

HIV infection may also accelerate the natural history of anal cancer, for which the mean age of diagnosis among HIV-infected individuals is lower than among HIV-uninfected individuals (Shiels et al. 2010). Among the more common malignancies occurring in HIV-infected individuals, anal cancer has one additional distinguishing feature—it is likely to be preventable.

Given the biological similarity between cervical and anal cancer, and the well-established success of cervical cancer prevention programs, it is possible that anal cancer may similarly be preventable. Like cervical cancer programs, anal cancer prevention programs may take the form of primary prevention or secondary prevention. Primary prevention consists of prevention of infection with the underlying etiologic agent, human papillomavirus (HPV), through prophylactic vaccination. Secondary prevention efforts are focused on those who have already been exposed to HPV and who have developed anal high-grade squamous intraepithelial lesions (HSIL), also called high-grade anal intraepithelial neoplasia (HGAIN). Identification of anal HSIL and removal of that lesion through a variety of methods is performed in an effort to reduce the risk of progression of that lesion to cancer. Secondary prevention has been shown to work very well to prevent cervical cancer, and is the basis of cervical cytology screening programs, with colposcopy and biopsy to diagnose cervical HSIL, and ablate it to reduce the risk of progression to cervical cancer. A similar approach to prevention of anal cancer has been advocated by several experts in the field (Palefsky 2009). Although it seems probable that adaptation of cervical techniques to the anal canal would be successful to reduce the risk of anal cancer, there are several challenges, particularly in HIV-infected individuals. These include large lesions, multifocal lesions, high incidence of new lesions and high recurrence rate after treatment. Well-designed clinical trials to demonstrate the efficacy of this approach have not yet been done and are urgently needed. A trial funded by the National Cancer Institute for this purpose, known as the Anal Cancer/HSIL Outcomes Research (ANCHOR) study will be initiated in the near future.

20.2 Incidence of Anal Cancer in HIV-Positive Men and Women

Anal cancer is biologically similar to cervical cancer in several ways. Like cervical cancer, anal cancer is associated with HPV infection, primarily HPV 16. The anal canal has a transformation zone at the anorectal junction that is similar to the main target of HPV infection in the cervix, the cervical transformation zone. At both of these anatomic sites, HPV infection leads to a series of epithelial changes that reflect various stages of HPV infection and HPV-associated transformation. HSIL includes loss of epithelial differentiation and abnormal mitotic activity, and is considered to be the precursor lesion to both cervical and anal cancer (Berry et al. 2014). Natural history studies show that the time from HPV infection to development of HSIL is relatively short, and usually occurs within just a few years. It would therefore appear that the long latency period to development of anal cancer primarily reflects the long period of time required for HSIL to progress to cancer (Pinto and Crum 2000).

Several studies have shown that anal HPV infection in women is as common or more common than cervical HPV infection (Kojic et al 2011; Machalek et al. 2012; Hessol et al 2013). Given the ease in which women acquire anal HPV infection, it is not surprising that in the general population anal cancer occurs more commonly among women than men. The incidence of anal cancer in the general population has

been rising by about 2 % among both men and women (Nelson et al 2013), with an inflection point in 1996, when the annual percentage increased even further. With a nearly 60 % rate of anal HPV infection among HIV-uninfected men who have sex with men (MSM), it is also unsurprising that the incidence of anal cancer in this group of men is much higher than men with no history of receptive anal intercourse (Chin-Hong et al. 2004; Nyitray 2012). The rate of anal HPV infection is even higher among HIV-infected MSM, and this group has the highest incidence of anal cancer of all (Machalek et al. 2012).

Given the many competing causes of mortality prior to the advent of HAART, and the long latency period typically required for HSIL to progression to anal cancer, the incidence of anal cancer was only modestly increased among HIV-infected MSM compared with HIV-uninfected MSM. When HAART was introduced, it was hoped that it would have the same beneficial effect on anal cancer incidence as on KS and NHL, reflecting immune reconstitution and improved immune response to the etiologic agents. However, it quickly became clear that individuals with prevalent HSIL were not undergoing regression to normal after initiating effective HAART (Palefsky et al. 2001; Palefsky et al. 2005), HPV infection was not being cleared and the incidence of HSIL was continuing unabated. Combined with the increasing survival due to fewer competing causes of mortality, and absence of organized screening or prevention programs for anal cancer, the incidence of anal cancer has increased, not decreased, in the HAART era (Shiels et al. 2012). Anal cancer is now the fourth most common cancer among HIV-positive individuals (Shiels et al. 2012). Several HIV-anal cancer database matches showed an incidence of anal cancer of 70/100,000 or more. More recent data from the NA-ACCORD study show an incidence of 131/100,000 HIV-infected MSM (Silverberg et al. 2002) rendering the incidence of anal cancer well above the highest incidences of cervical cancer anywhere in the world. Data from the Swiss Cohort study suggest that the increase may be leveling off (Franceschi et al. 2010).

It is not clear whether the incidence of anal cancer will continue to increase at the same rate in the future, or whether it may level off or even decrease. There are several competing factors that will ultimately determine the incidence of anal cancer in HIV-infected men and women. A factor that may reduce the incidence of anal cancer in the future is vaccination to prevent anal HPV infection with HPV 16 and HPV 18. However, it will be several decades before any reduction in the incidence of anal cancer due to vaccination is seen. Current uptake of the vaccine among males is low (Schmidt et al. 2013), and the full benefit of the vaccine may take even longer to realize unless vaccination uptake is improved. Another factor that may lead to a lower incidence of anal cancer in the future compared with current rates is changes in practice regarding higher threshold CD4 levels for initiation of HAART. It is hypothesized that immune response may be useful to control HPV replication and progression from HPV infection to HSIL. Those whose immune systems are less damaged by HIV might have a lower incidence of HSIL, and ultimately a lower incidence of anal cancer (Bertisch et al. 2013). Although not consistent from study to study, some have shown that men and women started on HAART have more

clearance of existing HPV infection and lower incident HSIL (Chiao et al. 2013). With the current clinical standard of practice moving increasingly toward initiating HAART earlier in the course of HIV infection and at higher CD4 levels, it is possible that this will have a long-term beneficial effect in reducing incident HSIL and cancer. Unfortunately most HIV-infected individuals were initiated on HAART at CD4 levels well below current guidelines, and they may not benefit from the earlier initiation of HAART described above. As described previously, aging of the HIV-infected population may also contribute to an increase in the burden of anal cancer in the future.

20.3 Pathogenesis of Anal Cancer

Consistent with their shared etiologic association with HPV, anal cancer and cervical cancer are both preceded a series of intraepithelial changes ranging from low-grade to high-grade. Low-grade changes are associated with few signs of cell transformation but instead primarily reflect cytopathic changes due to high levels of HPV replication. These changes are not believed to be precancerous. Anal low-grade anal squamous intraepithelial lesions (LSIL) is the most common form of ASIL and is associated with a wide variety of HPV types, both oncogenic and non-oncogenic (Hoots et al. 2009). Condyloma acuminatum is most often associated with HPV 6 or 11, but in HIV-infected individuals, a high proportion may be co-infected with HPV 16 or 18. Rather than reflect co-infection of individual cells with more than one HPV type (Richel et al. 2014), these probably reflect separate foci of clinically subtle HSIL, with HPV 6 or 11 causing the condyloma and HPV 16 causing the HSIL. HSIL is believed to be the true cancer precursor of anal cancer, similar to the role of cervical HSIL as the precursor to cervical cancer (Berry et al. 2014). Unlike anal LSIL, a high proportion of anal HSIL contain oncogenic HPV types (Hoots et al. 2009). Infection with multiple HPV types is particularly common in HIV-infected individuals but it is relatively uncommon to detect only non-oncogenic HPV types in these lesions. The rate at which these lesions progress to cancer is unknown and likely varies highly from person to person. Since the mean age at which HIV-infected individuals develop anal cancer is lower than the general population (Shiels et al. 2010), it is likely that the time of progression from anal HSIL to invasive cancer is shorter in this group.

The mechanisms that trigger invasion of the underlying basement membrane are not known. Ongoing HIV oncogenic protein expression, particularly E6 and E7 is necessary for maintenance of the transformed phenotype (Doorbar et al. 2012). The role of HIV in development of HIV-associated neoplasia is not fully understood. Attenuated immune response may lead to increased viral gene expression (Maglennon et al. 2014). HIV may also play a more direct role, with HIV proteins may be present in the epithelial microenvironment of HIV-infected individuals, even if they have well-controlled HIV viral loads on HAART (Tugizov et al. 2013).

20.4 Primary Prevention of Anal Cancer Through HPV Vaccination

The quadrivalent (qHPV) and bivalent HPV vaccines have both been shown to be highly effective at preventing persistent cervical HPV infection and high-grade cervical squamous intraepithelial lesions (CSIL) due to the types of HPV in the vaccines (Garland et al. 2007; Lehtinen et al. 2012). The quadrivalent vaccine is also effective at preventing genital warts in women due to HPV 6 or 11 (Dillner et al. 2010). Based on these and other data the quadrivalent and bivalent HPV vaccines were approved for routine use in females aged 9–26 years.

Recent studies have shown early evidence of effectiveness at the population level. Australian sexually transmitted infection clinics have reported a reduction in the proportion of women presenting with genital warts (Read et al. 2011; Ali et al. 2013), and in the USA, the proportion of women with high-grade CSIL that contain HPV 16 or 18 has declined (Powell et al. 2012) as has the prevalence of vaccine HPV types (Markowitz et al. 2013).

Recently the qHPV vaccine was shown to be effective at reducing the incidence of external genital warts in HIV-uninfected heterosexual men and MSM (Giuliano et al. 2011). In a substudy of anal canal HPV infection and anal canal anal squamous intraepithelial lesions (ASIL), the qHPV vaccine was also effective at reducing intra-anal persistent infection with vaccine HPV types and anal HSIL due to vaccine types (Palefsky et al. 2011). Based on these and other data, qHPV was approved for routine use in males aged 11–21 years. Vaccination is also approved for routine use in MSM and immunosuppressed males aged 22–26 years, and is approved, but not for routine use, in non-immunosuppressed males aged 22–26 years.

Although studies of HPV vaccination to prevent anal HPV infection, ASIL and anal cancer have not been done in women, the qHPV vaccine was approved for this indication in women based on similarity of anal cancer between men and women and the data from the Merck 020 protocol in men. The bivalent vaccine has not been studied for prevention of anal cancer, and the qHPV vaccine is the only vaccine approved for prevention of anal cancer in men or women. However in a post-hoc analysis of Costa Rican women vaccinated with the bivalent vaccine to prevent cervical HPV infection, CSIL and cervical cancer, there was a reduction in infection with HPV 16 and 18 in the anal canal of vaccinated women (Kreimer et al. 2011). These data provide encouragement that the bivalent vaccine may reduce the risk of ASIL and cancer in addition to CSIL and cervical cancer but studies are needed to demonstrate this.

HIV infection is not a contraindication to HPV vaccination and given their high risk of anal HPV infection and ASIL, HIV-infected men and women of vaccine-eligible age should be vaccinated. Several studies have shown that vaccination in HIV-infected men and women is safe (Wilkin et al. 2010). Nearly all HIV-infected individuals seroconvert in response to vaccination regardless of CD4 level. Titers may be lower in HIV-infected people and similarly aged HIV-negative individuals, but nearly all have titers well above those seen after natural HPV infection. Studies

of the efficacy of HPV vaccination to prevent anogenital disease in HIV-infected individuals have not yet been reported, and the duration of protection is unknown.

The qHPV and bivalent vaccines are preventive vaccines and work to prevent initial HPV infection. Consequently HPV vaccination is most effective among those who have not been exposed to vaccine types previously, i.e., are naïve to a given HPV type, as defined by being DNA-negative and sero-negative to that type. Studies have shown that despite a large number previous sexual partners, a high proportion of HIV-infected MSM over the age of 26 years are HPV DNA-negative and sero-negative to vaccine HPV types and would be considered "naïve" to these types (Wilkin et al. 2010; Sharma et al. 2013). However, it is possible that many men who would currently be classified as "naïve" to HPV-16 or HPV-18 were previously seropositive to these types, and sero-reverted to negative, a process that has been demonstrated to occur over time in healthy women (Sharma et al. 2013).

Despite the high rate of "naivete" to vaccine types and incidence of HPV infection in HIV-positive MSM over the age of 26 years, vaccination of HIV-infected individuals over the age of 26 years is controversial. If these men were previously seropositive, the value of vaccination is not clear and studies are needed to determine if vaccination affords these men the same protection that they would have received if they were truly naïve.

20.5 Secondary Prevention of Anal Cancer

In cervical cancer secondary prevention programs, cervical cytology, and to an increasing extent, adjunctive tests such as HPV DNA or RNA are used to identify women at risk of high-grade CSIL. The next step in the evaluation of these women is to visualize the cervix and vulvovaginal epithelium to localize the source of abnormal cells on cytology or positive HPV test, using a technique known as colposcopy. With the aid of the magnification provided by the colposcope and topically applied solutions such as 5 % acetic acid or iodine-based Lugol's solution, areas likely to be lesional are targeted for biopsy. Histologically confirmed high-grade CSIL is then removed using techniques such as loop electroexcision procedure or cryotherapy, depending on the setting. There is good evidence that high-grade ASIL is the precursor to anal cancer (Berry et al. 2014), and it is likely, although unproven, that removal of anal HSIL will reduce the incidence of anal cancer. Given the similarity between ASIL and CSIL, methods to identify those with anal HSIL are largely based on those used for cervical screening (Palefsky 2012). To identify anal HSIL, a technique known as high resolution anoscopy (HRA) can be performed, in which patients are examined under magnification with a colposcope, and with topical solutions such as 5 % acetic acid or Lugol's iodine to identify areas of ASIL visually. A biopsy of visible lesions is then performed for histologic confirmation.

Individuals a high risk of anal cancer can be considered for testing to identify anal HSIL (Palefsky 2009). These include HIV-infected men and women, regardless of mode of HIV acquisition, HIV-uninfected MSM, those with perianal HPV-related

lesions, women with a history of high-grade vulvar squamous intraepithelial lesions, vulvar and cervical cancer, and those who are immunosuppressed due to causes other than HIV. In the interest of minimizing morbidity, consideration should be given to screening only after the age of 30 years given the low incidence of anal cancer among those younger than 30 years of age.

Similar to cervical screening, there remains room for improvement in screening for anal HSIL. The most direct screening method is to perform HRA. However, HRA requires extensive training and experience and for optimal results an interdisciplinary team is needed that includes an anoscopist, pathologist, surgeon, and counselor/educator. Currently the number of clinicians performing HRA is limited given the extensive infrastructure and training required, and there are too few well-trained clinicians performing this technique to allow it be used as a true screening tool.

One of the more easily performed screening tools that may identify individuals who would benefit from HRA is anal cytology. Anal cytology is performed in a manner similar to cervical cytology but unlike cervical cytology, it may also be performed by patients themselves. Those with abnormal cytology are then referred for HRA. Like cervical cytology, the sensitivity of anal cytology is limited, and it tends to under-call the grade of lesion shown on HRA-guided biopsy (Palefsky et al. 1997; Roberts and Thurloe 2012). Given the high proportion of HIV-infected individuals expected to have abnormal anal cytology, the grade of cytology may also be used to triage patients. Ultimately all patients with any abnormality, including atypical squamous cells of undetermined significance (ASC-US) should be considered for HRA (Palefsky 2012). However, the positive predictive value for anal HSIL on biopsy is highest for those with anal HSIL on cytology, followed by those with atypical squamous cells-cannot rule out high-grade lesion (ASC-H) and low-grade squamous intraepithelial lesions (LSIL). Cost-effectiveness studies have shown that HIV-infected MSM should be screened annually with anal cytology if their cytology is normal, and that HIV-uninfected MSM should be screened every 2–3 years (Goldie et al. 1999). Although there are fewer data for the other at-risk groups, the anal cancer group at the University of California San Francisco recommends similar screening intervals for these groups according to their HIV status.

HPV testing is being used in the cervix as an adjunct to cervical cytology, or as a primary screening test to identify women who should have cervical colposcopy. Given the limitations of anal cytology, some have advocated anal HPV testing to identify those who should have HRA (Goldstone et al. 2012; Castle et al. 2013). HPV testing may be most useful when restricted to the HPV types most strongly associated with anal cancer such as HPV 16 or 18, and given the high prevalence of oncogenic HPV in HIV-infected patients, HPV testing may also be useful for its negative predictive value. Further studies are needed to define the best use of HPV-based tests.

Once identified on biopsy, every effort should be made to ablate or remove the lesion with the primary goal of reducing the risk of progression to cancer. However, to date no clinical trials have been performed that define the efficacy of anal HSIL treatment to reduce the incidence of anal cancer. Currently all clinicians who choose to screen for and treat anal HSIL are doing so based on the similarity between anal cancer and cervical cancer and the proven efficacy of treatment of cervical HSIL to prevent cervical cancer. Studies to determine if this approach is effective are urgently needed.

Another goal of anal HSIL treatment is relief of symptoms. In the perianal region, anal HSIL may cause bleeding, burning or itching, and patients may experience psychological distress due to its cosmetic appearance. Anal LSIL including condyloma acuminatum may also cause these symptoms. Unlike HSIL, LSIL is not believed to be precancerous. While treatment of LSIL will not likely reduce cancer risk, it is reasonable to treat it for symptom relief.

20.6 Diagnosis of Anal Cancer

Anal cytology and HRA-guided biopsy are primarily aimed at identifying anal HSIL, these should therefore be considered to be methods of anal "pre-cancer" screening. In contrast, digital anorectal exams (DARE) with palpation for intra-anal and perianal masses is a key element of anal cancer screening (Berry et al. 2014). Some anal cancers may also be detected at HRA (Fig. 20.2). Like cervical cancer, survival after treatment of anal cancer correlates inversely with the stage of diagnosis. Five-year survival after treatment of Stage 1 disease is as high as 70 %, and declines to about 20 % after diagnosis of stage IV disease (http://www.cancer.org/cancer/analcancer/overviewguide/anal-cancer-overview-survival-rates, accessed February 2, 2014) . In the absence of any organized anal cancer or HSIL screening program, diagnosis of anal cancer is often made when the patient presents with new anal pain that is not explained by any other obvious source of pain such as hemorrhoids, fissures, or infections. Lesions such as HSIL are usually painless and when patients develop pain, it may be sign of progression to cancer that is involving pain nerve fibers. Patients may also present with new patterns of bleeding, discomfort upon defecation or anal intercourse, or rapid growth of a mass. In those areas where active screening of HSIL is in place, a new category of anal cancer is being diagnosed, i.e., very early cancers that are too small to be palpable on DARE and

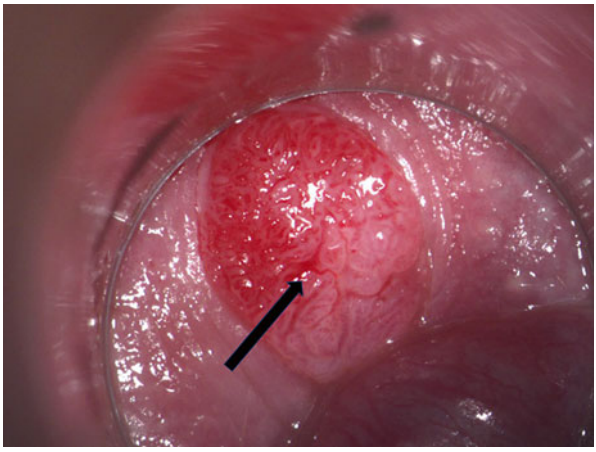

Fig. 20.2 Large area of anal cancer, as seen after application of 5 % acetic acid at high resolution anoscopy, indicated by *black arrow*. Cancerous lesion is raised, has clear borders, erythema, and atypical vessels

which are asymptomatic. These cancers are detected only on biopsy at HRA and are suspected when ulcers or highly atypical blood vessels are noted. Occasionally these may be unsuspected, with the appearance of otherwise unremarkable HSIL. This new category of anal cancer was adopted as part of the Lower Anogenital Squamous Terminology Project of the College of American Pathologists and American Society of Colposcopy and Cervical Pathology, called "Superficially Invasive Squamous Cell Carcinoma of the Anus" (SISCCA). SISCCA is defined as a lesion with less than 3 mm in depth and 7 mm in width (Darragh et al. 2012).

20.7 Treatment of Anal HSIL

Treatment for anal HSIL generally falls into 2 categories: (1) Local treatment with clinician- or patient-applied creams or liquids; (2) Clinician-applied ablative techniques such as electrocautery, laser or infra-red coagulation (IRC), and surgery. The choice of treatments will vary with the preference of the clinician, the clinical setting, the size and number of lesions, and the location of the lesions.

Treatment of Perianal HSIL

For smaller lesions (less than 1 cm in diameter) that are also limited in number (less than 3), 85 % trichloroacetic acid (TCA) or liquid nitrogen, or a combination of the two may be used (Singh et al. 2009). These modalities may be re-applied up to four times at 2–3 week intervals, and if not successful, a different modality should be tried. Some clinicians would use hyfercation in the office or infra-red coagulation (Fox 2012; Palefsky 2013). Studies in Europe have shown modest success with imiquimod for treatment of anal HSIL (Fox 2012), but HIV-positive patients may not respond as well to imiquimod as HIV-negative patients since the mechanism of action is immune-mediated through toll-like receptors. Like other topical treatments, imiquimod has not been approved by the US Food and Drug Administration for treatment of ASIL. Recently an AIDS Malignancy Consortium Phase I study showed that topical cidofovir is safe for treatment of perianal HSIL and showed signs of modest efficacy that should be confirmed in Phase II/Phase III studies (Stier et al. 2013). An additional option for extensive perianal disease is application of 5-fluorouracil (5-FU) cream. This drug has been used topically for many years to treat vulvar and vaginal SIL. It may be used to reduce the size lesions to permit treatment of remaining lesional areas with more targeted therapies such as IRC or electrocautery. Its toxicities include local pain, inflammation, and ulceration, which can range from mild to severe.

In general, surgery is reserved for treating those with the most extensive disease, those who require an examination under anesthesia to permit biopsies large enough to definitely exclude invasive cancer, or rarely, treatment of complications of office-based

procedures such as bleeding or infection. Larger perianal HSIL often requires more aggressive approaches in the setting of the operating room, such as IRC, electrocautery, laser and surgical excision with skin flaps (Pineda et al. 2007).

Treatment of Intra-Anal HSIL

Treatment approaches for intra-anal HSIL are similar to those described for perianal HSIL but there are fewer options (Palefsky 2013). Smaller lesions may be treated with 85 % TCA, but most require IRC, electrocautery or laser surgery. A high proportion of larger lesions may be treated with IRC, although the recurrence rate is high, as is the development of new lesions in areas that were not treated. A multicenter AIDS Malignancy Consortium Phase I safety study indicated that the efficacy of IRC to treat individual HSIL was about 65 % within a year, with up to three treatments, similar to results of previously published retrospective chart reviews (Stier et al. 2008). Electrocautery appears to have similar safety and efficacy to IRC (Marks and Goldstone 2012). Recently a randomized controlled trial of 156 patients with ASIL comparing imiquimod, topical 5-fluorouracil and electrocautery showed that of the three modalities, electrocautery was the most effective for intra-anal lesions. However, each modality was associated with a high risk of lesion recurrence (Richel et al. 2013). There was little difference between the modalities for treatment of perianal ASIL. As with perianal HSIL, the most extensive disease may require surgical excision and/or fulguration in an operating theater. When performed in conjunction with HRA, surgery was effective to treat extensive anal HSIL in a retrospective chart review, particularly when combined with post-surgery IRC to treat remaining lesions or early recurrences.

20.8 Treatment of Anal Cancer

Treatment of anal cancer is based on the stage of the disease. Stages 1–3 are typically treated with combined modality therapy (CMT) consisting of 5-fluorouracil and mitomycin, with radiation therapy. The National Comprehensive Cancer Network (NCCN) recommends 5-FU IV on days 1–4 and 29–32 with mitomycin IV on days 1–29 (National Cancer Comprehensive Network Clinical Practice Guidelines in Oncology, Anal Carcinoma, Version 2, 2014, NCCN.org, accessed February 2, 2014). A minimum of 45 Gy radiation therapy is given over 5 weeks with an additional 9–14 Gy considered for patients with T3, T4 or node-positive disease, or for those with residual disease after the initial 45 Gy. At some centers, intensity modulated radiation therapy is used instead of 3-D conformal radiation in an effort to reduce radiation-associated toxicity. Cisplatin has been assessed in place of mitomycin, but clinical trials have shown insufficient benefit to recommend that it replace mitomycin as the first-line chemotherapeutic agent in combination with 5-FU (Gunderson et al. 2012).

However, cisplatin may be useful as first-line therapy with 5-FU for patients who are expected to be intolerant of the hematologic toxicity associated with mitomycin-based regimen.

Prior to the advent of HAART, HIV-infected patients had poor survival rates for anal cancer with many unable to tolerate a full regimen of CMT. In recent years, however, HIV-infected patients with good HIV control on HAART and high CD4 levels have been shown to tolerate full-dose therapy and have similar survival rates to HIV-negative individuals (Deeken et al. 2012). The current recommendation is to treat HIV-infected patients with the standard regimen, although careful monitoring for toxicity is required and treatment breaks may be needed.

The primary role for surgery in the treatment of anal cancer is abdominoperineal resection for patients who fail CMT. In addition, local excision may be used to treat anal margin/perianal cancer provided that the surgery does not compromise anal sphincter function. With the recent recognition of SISCCA as a very early stage of invasive cancer that may develop in the perianal region or anal canal, there is substantial interest in determining whether SISCCA can be safely treated with wide local excision regardless of where in the anus it is diagnosed. Clinical trials will be needed to determine if this can become standard of care and an AIDS Malignancy Consortium trial to address this question will be initiated in the near future. If it does, then efforts to identify anal cancer at this very early stage will be important to effect a cure while minimizing the risk of toxicity associated with CMT.

20.9 Conclusion

Anal cancer is a problem of growing importance among HIV-infected men and women, and its incidence may continue to rise as an increasing number of HIV-infected men and women reach advanced age. Efforts need to be made to diagnose anal cancers as early as possible given the improved morbidity and mortality outcomes associated with earlier diagnosis. It is possible that routine performance of simple techniques such as DARE will lead to earlier anal cancer diagnosis, as will performance of HRA in some at-risk individuals. Despite the high likelihood of surviving anal cancer when detected early, prevention is highly desirable given the high rates of morbidity associated with successful treatment of anal cancer.

Fortunately, unlike many other cancers that occur in HIV-infected men and women, many cases of anal cancer are potentially preventable through primary prevention in the form of vaccination against HPV 16 and 18. However the impact of vaccination on anal cancer incidence will not be seen for several decades given the time required for those of vaccination age to reach the age at which anal cancer is typically diagnosed, and the high proportion of at-risk individuals who were exposed to HPV before vaccination became available. Further, the potential for vaccination to reduce anal cancer incidence is somewhat mitigated by relatively low vaccine uptake in the targeted age groups, especially in boys.

For those who have already been exposed to HPV, secondary prevention in the form of anal cytology screening and treatment of anal HSIL diagnosed on HRA-guided biopsy may be the best approach to reducing their risk of anal cancer. However, randomized, controlled trials of HSIL treatment to reduce the incidence of anal cancer are needed to assess the risk-benefit ratio of this approach before screening in at-risk populations will become standard of care. In the long-term, reduction of the incidence of anal cancer will likely be achieved through all three approaches—DARE, anal screening for, and treatment of anal HSIL, and HPV vaccination.

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Chapter 21
Other HPV-Associated Cancers (Oropharyngeal and Penile)

Kristina R. Dahlstrom and Erich M. Sturgis

Abstract Human papillomavirus (HPV) has been recognized as an etiologic agent in malignancies at several anatomic sites, including the oropharynx and the penis. The overwhelming majority of oropharyngeal and penile cancers are squamous cell carcinomas. It is estimated that approximately two-thirds of oropharyngeal cancers and half of penile cancers can be attributed to HPV infection. The incidence of HPV-associated oropharyngeal cancers is rapidly increasing in developed countries. Penile cancer remains rare in developed countries but constitutes a major cancer burden among men in developing countries. Compared with the general population, patients with HIV/AIDS are at increased risk for HPV-associated cancers, including oropharyngeal and penile cancers.

21.1 Introduction

Human papillomavirus (HPV) is the cause of 5.2 % of cancers worldwide and has been identified as an important etiologic agent by the International Agency for Research on Cancer (Chaturvedi 2010; Gillison 2008). Virtually all cervical cancers are attributable to HPV infection, as are 90–93 % of anal cancers, 12–63 % of oropharyngeal cancers, 36–40 % of penile cancers, 40–64 % of vaginal cancers, and 40–51 % of vulvar cancers; HPV16 is the main viral type involved in carcinogenesis

K.R. Dahlstrom, Ph.D.
Department of Head and Neck Surgery, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1445, Houston, TX 77030, USA
e-mail: kdahlstrom@mdanderson.org

E.M. Sturgis, M.D., M.P.H. (✉)
Department of Head and Neck Surgery, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1445, Houston, TX 77030, USA

Department of Epidemiology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1445, Houston, TX 77030, USA
e-mail: esturgis@mdanderson.org

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(Chaturvedi 2010; Parkin and Bray 2006; Walboomers et al. 1999). The main risk factors for HPV-positive compared with HPV-negative non-cervical cancers are high-risk sexual behaviors, immunosuppression (including immunosuppression due to HIV and immunosuppressive drugs required after organ transplant), and a prior HPV-associated cancer (Chaturvedi 2010). HPV-positive non-cervical cancers tend to be diagnosed at earlier ages than HPV-negative non-cervical cancers (Chaturvedi 2010). The ratio of non-cervical to cervical HPV-associated cancers differs by geographical region. Developed countries with established cervical cancer screening programs in place have higher proportions of non-cervical than cervical HPV-associated cancers, while developing nations without such programs have a high burden of cervical cancer that far outweighs the burden of other HPV-associated cancers (Chaturvedi 2010).

21.2 Oropharyngeal Cancer

The oropharynx contains the tonsils and base of tongue (lingual tonsil) and refers to the midportion of the pharynx immediately behind the oral cavity and above the larynx. Along with smoking and alcohol use, HPV is a major etiologic agent of oropharyngeal cancer, and oropharyngeal cancers may arise from either of two distinct etiologic pathways, one associated with HPV and one associated with tobacco exposure (Gillison 2009; Sturgis and Ang 2011). The incidence of oropharyngeal cancer is increasing in the United States (US) despite a decrease in smoking prevalence (Chaturvedi et al. 2011; Sturgis and Ang 2011). The prevalence of HPV in oropharyngeal cancer has increased significantly over time to the current prevalence of 70–80 % (Sturgis and Ang 2011). HPV16 is the chief type of HPV associated with oropharyngeal cancer, and more than 90 % of HPV-positive oropharyngeal cancers are positive for HPV16 (Kreimer et al. 2005; Sturgis and Ang 2011).

Approximately 60–80 % of HIV-positive individuals smoke, compared with fewer than 20 % of individuals in the general population. Between 25 and 40 % of HIV-positive individuals have a prevalent oral HPV infection, compared with only 5–10 % of individuals in the general population (Gillison 2009; Gillison et al. 2012). However, it remains unclear what proportion of oropharyngeal cancers among HIV-positive individuals should be attributed to HPV and what proportion should be attributed to smoking and alcohol use.

HPV-positive oropharyngeal cancer is often of nonkeratinizing histology (basaloid, lymphoepithelial, or poorly differentiated carcinoma), and patients typically present with late-stage disease characterized by small primary tumors and advanced nodal metastases (Gillison 2009; Sturgis and Ang 2011). These patients also have distinct demographic characteristics: compared with patients with HPV-negative oropharyngeal cancer, patients with HPV-positive oropharyngeal cancer typically present at younger ages and are more likely to be white men of high socioeconomic status (Gillison 2009; Sturgis and Ang 2011). Sexual behaviors, including younger age at first sexual intercourse, a history of sexually transmitted diseases, and high number

of sex partners, have all been associated with increased risk of HPV-associated oropharyngeal cancer. High number of oral sex partners is particularly strongly associated with HPV-positive cancers (D'Souza et al. 2007; Gillison et al. 2008; Gillison 2009).

The increasing incidence of oropharyngeal cancer in the USA is limited to the tonsils and base of tongue, oropharyngeal sites typically associated with HPV (Sturgis and Ang 2011). From 1973 through 2004, the age-adjusted incidence of oropharyngeal cancer at HPV-associated sites (base of tongue/lingual tonsil and tonsils) increased significantly, and this increase was especially pronounced from 2000 through 2004, when the annual percent change was 5.22 % ($p=0.016$) (Chaturvedi et al. 2008). Conversely, the incidence of cancers at sites not associated with HPV (oral cavity) remained stable through 1982 (annual percent change, 0.82 %; $p=0.186$) and decreased from 1983 through 2004 (annual percent change, −1.6 %; $p<0.001$) (Chaturvedi et al. 2008).

That the increase at sites associated with HPV is in fact due to an increase in the prevalence of HPV infection has recently been confirmed using oropharyngeal cancer tumor tissue from participants in the Surveillance, Epidemiology, and End Results Residual Tissue Repositories Program (Chaturvedi et al. 2011). In this study, the prevalence of HPV in oropharyngeal tumors increased from 16.3 % in the 1980s to 72.7 % in the 2000s, and between 1988 and 2004 there was a 225 % increase in the incidence of HPV-positive oropharyngeal cancer (from 0.8 cases per 100,000 individuals to 2.6 per 100,000), accompanied by a 50 % decrease in the incidence of HPV-negative oropharyngeal cancer (from 2.0 cases per 100,000 individuals to 1.0 per 100,000) (Chaturvedi et al. 2011). If these trends continue, it is expected that HPV-positive oropharyngeal cancer cases will constitute the majority of head and neck cancers in the next few decades and that the number of HPV-positive oropharyngeal cancer cases will surpass the number of cervical cancer cases by 2020 (Chaturvedi et al. 2011).

It is estimated that the odds ratio (OR) for HPV-positive oropharyngeal cancer among individuals with a prevalent oral HPV infection ranges from 3.6 to 230. Studies measuring evidence of a previous HPV infection as indicated by HPV seropositivity have reported odds ratios (ORs) in the range of 2.3–182 for HPV16 L1 antibodies and ORs in the range of 9.2–231 for HPV16 E6/E7 antibodies (Chaturvedi 2012). In contrast to the understanding of cervical HPV infections, large prospective studies confirming these risk estimates for oropharyngeal cancer are lacking, as is documentation of the natural history of oral HPV infections with data on clearance, re-infection, and malignant conversion. Additionally, identification is still awaited of a precursor HPV-positive oropharyngeal lesion analogous to cervical or anal intraepithelial neoplasia, which would allow for screening for oropharyngeal cancer as well as early diagnosis and treatment.

In addition to distinct demographic, behavioral, and clinical characteristics, patients with HPV-positive oropharyngeal cancer have outcomes not typical of those in patients with HPV-negative oropharyngeal or other head and neck cancers. In particular, patients with HPV-positive oropharyngeal cancer have much better overall, disease-specific, recurrence-free, and second primary tumor-free survival

rates than those with HPV-negative cancer (Ang et al. 2010; Fakhry et al. 2008; Peck et al. 2012; Sturgis and Ang 2011). HPV tumor status is now considered an important independent prognostic indicator. In a prospective phase II clinical trial that included patients with oropharyngeal and laryngeal SCC patients with HPV-positive patients responded better to induction chemotherapy and chemoradiation resulting in a 63 % lower risk of death and a 73 % lower risk of progression compared with HPV-negative patients (HR, 0.36; 95 % CI, 0.15–0.85 and HR, 0.27; 95 % CI, 0.10–0.75, respectively) (Fakhry et al. 2008). A retrospective review of a large phase III trial confirmed these results, with HPV-positive oropharyngeal patients having a 58 % lower risk of death and a 51 % lower risk of progression than HPV-negative oropharyngeal cancer patients (HR, 0.42; 95 % CI, 0.27–0.66 and HR, 0.49; 95 % CI, 0.33–0.74, respectively) (Ang et al. 2010). When recurrences do occur in patients with HPV-positive oropharyngeal cancer, these recurrences are more commonly at distant sites rather than local-regional recurrences, which are more typical head and neck cancer patients.

21.3 Penile Cancer

Penile cancer is relatively rare in developed countries, where incidence rates range up to 1.5 cases per 100,000 men pear year, but is much more common in developing countries, where incidence rates reach 4.4 cases per 100,000 men per year in Uganda and as high as 6.8 cases per 100,000 men per year in Brazil (Anic and Giuliano 2011; Backes et al. 2009; Bleeker et al. 2009). Penile cancer accounts for less than 1 % of cancers in adult men in Europe and North America and up to 10 % of cancers in adult men in less developed regions (Anic and Giuliano 2011; Bleeker et al. 2009; Miralles-Guri et al. 2009). Penile cancer is usually diagnosed among older men; the mean age at diagnosis is 60 years, and incidence is highest at 70 years (Bleeker et al. 2009). It is estimated that about 40 % of penile cancers can be attributed to HPV, and HPV16 accounts for 63 % of HPV-positive cases (Backes et al. 2009; Miralles-Guri et al. 2009; Parkin and Bray 2006).

As with oropharyngeal cancer, penile cancer is thought to arise from either of two distinct etiologic pathways, one related to HPV and one related to other factors. Risk factors for penile cancer include higher number of sex partners and a history of sexually transmitted diseases, factors that are also associated with HPV infection (Bleeker et al. 2009). Other risk factors for penile cancer include smoking, lack of circumcision, poor penile hygiene, phimosis, and inflammation (Backes et al. 2009; Bleeker et al. 2009; Castellsague et al. 2002; Dillner et al. 2000). HPV-associated penile cancer is thought to follow the same carcinogenic pathway as cervical cancer, including a persistent infection with high-risk HPV and genetic alterations necessary for malignancy to develop in an HPV-infected cell (Bleeker et al. 2009). However, the lower incidence rates and later age at onset of penile cancer compared with cervical cancer suggest that tissue- and hormone-specific differences may exist between cancers at the two sites (Bleeker et al. 2009).

Virtually all (95 %) penile cancers are squamous cell carcinomas, which can be further classified into at least four histological subtypes, keratinizing, basaloid, warty, and verrucous, with the keratinizing type being the most common (50–60 %) (Backes et al. 2009; Miralles-Guri et al. 2009). Several retrospective reviews have estimated the prevalence of HPV and the distribution of HPV types in invasive penile cancer (Backes et al. 2009; Bleeker et al. 2009; Miralles-Guri et al. 2009). These studies found that almost half of invasive penile cancer cases were associated with HPV and that the prevalence of HPV infection differed by histologic subtype (Backes et al. 2009; Miralles-Guri et al. 2009). The highest HPV prevalence was found among basaloid and warty types and the lowest prevalence among verrucous types. Miralles-Guri et al. estimated that 76 % of basaloid, 59 % of warty, 44 % of keratinizing, and 25 % of verrucous types were HPV positive (Miralles-Guri et al. 2009). In addition, HPV prevalence differs by geographical region, with the highest prevalence in Asia (59 %) and the lowest in South America (40 %) (Backes et al. 2009; Miralles-Guri et al. 2009). The most common HPV types found in penile cancer were HPV16 (75 %), HPV18 (12 %), and HPV6/11 (5 %) (Backes et al. 2009; Miralles-Guri et al. 2009).

Genital HPV infection in men is common: prevalence estimates range from 1.3 to 72.9 % (most >20 %), with the most common types detected being HPV6 and HPV16 (Anic and Giuliano 2011; Franceschi et al. 2002). Higher prevalence rates are reported in studies using more sensitive sampling techniques (i.e., a prewetted Dacron swab) and when multiple anatomic sites are sampled (Anic and Giuliano 2011). A US study reported higher prevalence rates in samples taken from the shaft (50 %), glans (36 %), and scrotum (34 %) than in samples taken from the perianal area (20 %), anal canal (18 %), urethra (10 %), and semen (5 %) (Anic and Giuliano 2011).

Penile intraepithelial neoplasia (PIN) is heterogeneous, and without histological confirmation, benign conditions are often misclassified as PIN (Anic and Giuliano 2011). It is estimated that 60–100 % of PIN lesions are HPV-positive, and one large case series reported prevalence rates of 41 % for HPV16, 22 % for HPV6, 15 % for HPV52, and 4 % for HPV11 (Anic and Giuliano 2011). High-grade PIN is considered penile carcinoma in situ, and development to this stage of PIN is rare; however, whereas the risk of progression to invasive disease in patients with cervical and anal intraepithelial neoplasia is known, the risk of progression to invasive penile cancer once high-grade PIN occurs is still unknown (Anic and Giuliano 2011).

Survival of patients with penile carcinoma has been evaluated using data from European and US cancer registries (Verhoeven et al. 2013). Data from the US SEER registry has shown that 5-year survival decreased from 72 % in 1990–1995 to 63 % in 2002–2007 while it increased nonsignificantly in Europe from 65 to 70 % during the same time period; however, these results should be interpreted with caution due to the limited number of cases (Verhoeven et al. 2013). Prognostic factors in penile carcinoma are primary tumor stage and extent of nodal involvement (Mosconi et al. 2005). Although few studies have investigated whether HPV is associated with prognosis, a small study of 82 penile carcinoma patients did not find a difference in 10-year survival between HPV-positive and -negative patients ($p = 0.830$) (Bezerra et al. 2001).

21.4 Increased Risk of HPV-Associated Cancers Among Patients with HIV/AIDS

HIV-positive patients have an increased risk of HPV-associated cancers, including oropharyngeal and penile cancers, compared with the general population. Moreover, the risk of these cancers appears to increase with time since AIDS onset. The increased risk is consistent with the increased incidence, prevalence, and persistence of HPV infections and increased smoking prevalence among HIV-infected individuals.

Analysis of more than 300,000 patients with HIV/AIDS from the AIDS-Cancer Match Registry documented that these individuals have an increased risk of HPV-associated cancers (Frisch et al. 2000). Patients with HIV/AIDS were seven times as likely as those in the general population to have HPV-associated cancers, and this risk increased significantly with time since AIDS onset. For invasive cancers, the risk of tonsillar cancer among men with HIV/AIDS was 2.6 times higher than among men in the general population, while no cases occurred among women with HIV/AIDS. The risk of penile cancer was almost four times as high among men with HIV/AIDS as among men in the general population, and the risk was especially elevated among men younger than 30 years (in situ penile cancer: relative risk [RR], 16.1; 95 % CI, 4.4–41.2 and invasive penile cancer: RR, 37.2; 95 % CI, 7.7–108.6) (Frisch et al. 2000). Furthermore, the risk of both in situ and invasive penile cancer was higher among blacks and Hispanics with HIV/AIDS while the risk was not statistically elevated among whites. When individuals were stratified by HIV-exposure category, the risk of invasive penile cancer was highest among intravenous drug users (RR, 7.1; 95 % CI, 2.8–14.6) and only slightly elevated among homosexual men (RR, 2.8; 95 % CI, 1.0–6.1) (Frisch et al. 2000).

Engels et al. found that among HIV-positive individuals, the overall standardized incidence ratio (SIR) for oral cavity/pharynx cancer was 1.7 (95 % CI, 1.1–2.5) and for penile cancer was 5.4 (95 % CI, 1.1–16) (Engels et al. 2008). Furthermore, the risk for oral cavity/pharynx cancer increased after diagnosis with AIDS (RR, 3.6; 95 % CI, 1.6–8.2). There were too few cases to evaluate incidence trends for penile cancer (Engels et al. 2008). These results were confirmed in a study by Chaturvedi et al. that included almost 500,000 individuals diagnosed with AIDS during 1980–2004 (Chaturvedi et al. 2009). The SIR for invasive oropharyngeal cancer was 1.6 (95 % CI, 1.2–2.1), but no significant increase in SIR was found with time since AIDS diagnosis. The SIRs for both in situ and invasive penile cancers were elevated (SIR, 19.7; 95 % CI, 13.2–28.3 and SIR, 5.3, 95 % SIR, 3.2–8.2, respectively), and there was a significant increase in in situ cancers (but not for invasive cancers) since time of AIDS diagnosis ($p < 0.001$) (Chaturvedi et al. 2009). When patients were stratified by HIV-exposure category, the risk of invasive oropharyngeal cancer was highest among heterosexual men (RR, 3.2; 95 % CI, 1.6–5.7), followed by intravenous drug users (RR, 2.1; 95 % CI, 1.3–3.2). For penile cancer, the risk of in situ cancer was elevated among men who had sex with men, intravenous drug users, and heterosexual men (RR > 20 for all subgroups), and the risk of invasive

cancer was elevated among men who had sex with men (RR, 4.4; 95 % CI 1.9–8.7) and heterosexual men (RR, 14.7; 95 % CI, 4.8–34.5) (Chaturvedi et al. 2009).

It is unclear to what extent immunosuppression plays a role in progression of HPV-associated cancers in patients with HIV/AIDS (Chaturvedi et al. 2009; Frisch et al. 2000). While the risk of in situ cancers appears to increase with time since AIDS diagnosis, such an increase was generally not seen for invasive cancers. This may signify that immune suppression facilitates the progression of premalignancies but is not relevant in later progression to invasive cancer (Chaturvedi et al. 2009; Frisch et al. 2000). Progression of disease may be due to other factors among individuals with HIV/AIDS that are as yet unknown (Frisch et al. 2000).

The incidence of HPV-associated cancer among people with HIV/AIDS remains high even after the use of highly active antiretroviral therapy (HAART). One possible explanation may be that HAART may not influence immunity to HPV or that immunologic control of HPV-related tumors is exerted only at early stages of tumor development (Chaturvedi et al. 2009). At the same time, the longer life expectancy of individuals in the HAART era may also lead to an increased risk of HPV-associated cancer because individuals with HIV/AIDS now live long enough to develop these cancers (Chaturvedi et al 2009; Gillison 2009).

21.5 Opportunities for Prevention

HPV16 and HPV18 are responsible for 70 % of cervical cancers and 90 % of non-cervical cancers. There are currently two HPV vaccines approved by the US Food and Drug Administration to protect against these types. Cervarix (GlaxoSmithKline) is a bivalent vaccine that protects against HPV16 and HPV18, while Gardasil (Merck) is a quadrivalent vaccine that protects against these and two additional viral types, HPV6 and HPV11. Because of the high global burden of HPV-positive cervical lesions and cervical cancer, initial clinical trials were limited to women; however, the vaccines have more recently been shown to be highly efficacious in preventing anogenital warts in males and anal precancer in men and women, and the vaccines are expected to prevent HPV-positive oropharyngeal cancer as well.

Initial results from population-based studies are encouraging. Significant reductions in the incidence of genital warts have been observed in Australia, where 65 % of eligible girls have been vaccinated. Among women aged 12–26 years, there was a 59 % reduction in the incidence of genital warts between 2004 and 2009. Concomitantly, there was a significant 39 % reduction in the incidence of genital warts among men aged 12–26 (Donovan et al. 2011). Herd immunity confers protection to heterosexual boys in areas where vaccine coverage is high (e.g., Australia); however, this is not observed when vaccination rates are low and may not extend to homosexual men, unless a substantial percentage of men are vaccinated (Brisson et al. 2011).

The US Food and Drug Administration approved Gardasil for routine use in girls and young women aged 9–26 years in 2006 and for use in boys in 2011. Unfortunately, the US Centers for Disease Control and Prevention estimates that in 2011, only

about half of girls in the USA of the targeted age range had received at least one dose, and only 35 % had received all three doses of the vaccine. Among boys in the USA, 8 % had received at least one dose, while only 1 % had received all three doses (CDC 2011). It is imperative that both boys and girls be vaccinated since HPV-associated disease occurs among both men and women, and in this decade HPV-positive oropharyngeal cancer is expected to surpass cervical cancer as the most common HPV-related cancer in the USA. In addition, vaccination programs ignoring boys will leave some men outside the proposed protective effect of herd immunity and at risk for oropharyngeal, penile, and anal cancers.

21.6 Conclusion

HPV is the cause of approximately two-thirds of oropharyngeal cancers and half of penile cancers. The incidence of HPV-associated oropharyngeal cancer is increasing, especially among middle-aged white men, and is expected to surpass the incidence of cervical cancer in this decade. The incidence of penile cancer is rare in developed countries but is high in areas where the burden of cervical cancer is high. Patients with HIV/AIDS are at increased risk for HPV-associated cancers compared with the general population. The HPV vaccine offers an opportunity for prevention of HPV-associated disease, including oropharyngeal and penile cancer; however, it is imperative that both boys and girls be vaccinated to protect all persons at risk.

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Part VI
Other HIV-Associated Cancers

Chapter 22
Lung Cancer in HIV Infection

Deepthi Mani and David M. Aboulafia

Abstract The term lung cancer is usually used to describe any of several types of primary tumors arising in the lung; common histological types include adenocarcinoma, squamous cell carcinoma, large cell carcinoma, bronchoalveolar cancer, and small cell lung cancer. Taken together, lung cancer is the most common non-AIDS-defining malignancy in HIV-infected individuals. Lung cancer risk appears to be two to five times greater in the HIV-infected persons compared to the general population, and most epidemiological studies find that the risk remains high even after adjusting for other factors like smoking intensity and duration. Often these patients present with advanced disease at a younger age but may have comparable survival compared with similarly matched lung cancer patients without HIV infection. Smoking cessation is the most effective preventive strategy.

22.1 Introduction

The advent of highly active antiretroviral therapy (HAART), consisting of multiclass antiretroviral drug regimens, has dramatically decreased HIV-associated morbidity and mortality in the economically developed world (Palella et al. 1998). As HIV infection has transformed from a fatal disease to a chronic condition, there has been renewed public and clinical interest in long-term morbidities, including

D. Mani
Division of Internal Medicine, Multicare Good Samaritan Hospital, Puyallup, WA USA

D.M. Aboulafia, M.D. (✉)
Division of Hematology and Oncology, Virginia Mason Medical Center,
1100 Ninth Avenue, PO Box 900 (C2-HEM), Seattle, WA 98111, USA

Division of Hematology, University of Washington, Seattle, WA USA
e-mail: David.Aboulafia@vmmc.org

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malignancies that occur disproportionately within this population. HIV-infected individuals have an increased propensity to develop both AIDS-defining malignancies (ADM), such as Kaposi's sarcoma (KS), non-Hodgkin lymphoma (NHL), and cervical cancer, as well as a number of non-AIDS-defining malignancies (NADM), including lung cancer, anal cancer, liver cancer, and Hodgkin's lymphoma (Deeken et al. 2012). Lung cancer is the most common NADM and the leading source of NADM mortality among HIV-infected individuals (Shiels et al. 2011). Lung cancer risk appears to be two to five times greater in the HIV-infected persons compared to the general population, and most studies show that the risk remains high even after adjusting for other factors, such as smoking intensity and duration (Kirk and Merlo 2011). Often these patients present with advanced disease at a younger age and yet may have a comparable survival compared with stage- and histology-matched lung cancer patients without HIV infection. This chapter briefly describes the epidemiology, risk factors, clinical characteristics, treatment, and outcome of HIV-associated lung cancer, as well as potential approaches to decrease the burden of lung cancer through smoking cessation initiatives.

22.2 Epidemiology

Epidemiologic studies of lung cancer among the HIV population commonly involve linkage of HIV/AIDS registries, observational databases, or clinical HIV cohorts to cancer registries. The risk of lung cancer is estimated by calculating the standardized incidence ratio (SIR), resulting in comparisons of observed cases occurring among an HIV-infected study population to the expected number of estimated cases from general population rates. These analyses have primarily been conducted in the USA and Europe. In the majority of the registry studies, SIRs are in the range of a two- to five-fold increase in lung cancer associated with HIV infection (Kirk and Merlo 2011). Two meta-analytic studies estimated the increased risk for lung cancer with HIV infection to be 2.6-fold (Grulich et al. 2007; Shiels et al. 2009). The risk of lung cancer in the setting of HIV infection appears to have remained relatively stable in the pre-HAART and HAART era (Engels et al. 2006; Patel et al. 2008).

22.3 Risk Factors

Smoking

Although there is a clear and consistent demonstration of elevated lung cancer risk among HIV-infected individuals compared with the general population, it is difficult to determine whether this elevated risk is due solely to the increased incidence of cigarette smoking in the HIV-infected population. Among HIV-infected individuals living in the USA, prevalence estimates of smoking range from 35 to 70 % compared

to approximately 20 % in the general population (Kirk and Merlo 2011; Rahmanian et al. 2011). Tobacco use may be even more common among HIV-seropositive intravenous drug users. Five studies directly accounted for individual smoking exposure among HIV-infected persons, and the risk for lung cancer associated with HIV infection was 1.2–3.6-fold higher compared to epidemiologically valid comparison populations who were not infected with HIV (Kirk and Merlo 2011). In four of the studies, the smoking-adjusted increase attributable to HIV infection was statistically significant, although in one it was not (Silverberg et al. 2011). In the largest cohort study in the HAART era, with individual level smoking data involving greater than 110,000 United States military veterans, the incident rate of lung cancer was 1.7 times higher in the HIV-infected veterans compared to uninfected veterans and remained significant after multivariable adjustment (Sigel et al. 2012). The true test of an independent effect of HIV infection on lung cancer risk would be to observe the effects of HIV among nonsmokers. Such an analysis may not be feasible due to the very low incidence of lung cancer among nonsmokers and the high prevalence of smoking among HIV-infected persons (Kirk and Merlo 2011).

HIV-Related Factors

Unlike the prototypical ADMs, KS and NHL, where the risk increases as immunosuppression becomes more pronounced, lung cancer may occur at any point in the course of HIV infection. The risk of HIV-associated lung cancer generally is not closely linked to a low CD4+ cell count or to an elevated HIV viral load, although there is evidence that prolonged moderate immunosuppression as seen in the HAART era may contribute to the risk. Organ transplant recipients on immunosuppressive agents have a lung cancer incidence rate comparable to HIV-infected patients (Grulich, et al. 2007).

HIV itself might have a direct oncogenic role. Though limited experimental data suggest that HIV *tat* (Trans-Activator of Transcription) gene product may modulate the expression of proto-oncogenes and tumor suppressor genes, amplification of HIV sequences in lung carcinoma has not been demonstrated (el-Solh et al. 1997; Wistuba et al. 1998). Other potential mechanisms for the role of HIV in the pathogenesis of lung cancer include accelerated lung damage through recurrent pulmonary infections and increased susceptibility to tobacco carcinogens through genomic instability (Kirk and Merlo 2011; Mani et al. 2012).

22.4 Clinical Characteristics

Lung cancer typically is diagnosed a decade or more earlier among HIV-infected persons compared to those without HIV infection (Mani et al. 2012). However, after adjustment for difference in the age compositions of populations at risk, the difference in the age at diagnosis of lung cancer (50 vs. 54 years) is relatively modest

between persons with AIDS and the general population (Shiels et al. 2010). The majority of patients with HIV-associated lung cancer are symptomatic at diagnosis (Mani et al. 2012). This is often due to the advanced stage of disease by the time lung cancer is diagnosed. Respiratory complaints are particularly frequent and most notably include cough (40–86 %), chest pain (25–75 %), and dyspnea (10–57 %). Fatigue is ubiquitous, and as many as 10–30 % of patients also will have hemoptysis. The signs and symptoms of lung cancer among HIV-infected persons mirror those of stage -matched lung cancer controls.

Non-small cell lung cancer (NSCLC) represents 67–86 % of primary lung cancers in patients with HIV; small cell lung cancer comprises another 6–14 % with unidentified subtypes accounting for the remaining percentage. Of the NSCLC, the most common histologic diagnosis is adenocarcinoma (30–67 %) followed by squamous cell (17–39 %), large cell (3–16 %), and bronchoalveolar (2–3 %) cancer in HIV-positive patients. The majority of patients present with either advanced stage III or IV disease. Recent HAART-era case series and cohort studies with morphology and stage data have described similar distributions of morphologic type and stage at presentation in HIV-infected lung cancer patients compared with HIV indeterminate or uninfected patients (D'jaen et al. 2010; Sigel et al. 2012).

Radiological features of lung cancer in HIV-infected patients appear to be similar to those in HIV-negative patients and include a parenchymal mass, more often peripheral rather than central, mediastinal lymphadenopathy and pleural effusions. A low clinical suspicion for malignancy, particularly in younger patients, and over reliance on non-diagnostic chest radiographs may result in delayed diagnosis of lung cancer in HIV-positive individuals (Brock et al. 2006).

22.5 Treatment and Outcome

Recommendations for the management of HIV-associated lung cancer are evolving. Historically, individuals with HIV-associated lung cancer have been excluded from participating in clinical trials (Persad et al. 2008). Surgery with curative intent remains the treatment of choice for localized disease, and there is increasing experience in using of radiation therapy and systemic chemotherapy for patients who do not have surgical options.

Data on the management of HIV-associated lung cancer are principally derived from uncontrolled retrospective analyses rather than prospective clinical trials. In a recent study, HIV-infected NSCLC patients who underwent surgery with curative intent were more likely to have pulmonary and extra-pulmonary post-operative complications, more rapid progression to disease recurrence, and poorer post-operative survival when compared to HIV-indeterminate patients (Hooker et al. 2012). HIV-infected lung cancer patients with CD4+counts less than 200 cells/mm^3 had shortened median survival compared with patients with higher counts. This finding runs contrary to prior studies that advocated surgery for HIV-infected patients regardless of immune status (Cadranel et al. 2006). However, the

lack of precision inherent in a small sample size precludes drawing any strong recommendations from these studies.

In the general population, patients with advanced NSCLC usually are treated with a combination of a platinum drug (cisplatin or carboplatin) and a third-generation, non-platinum drug (docetaxel, gemcitabine, irinotecan, paclitaxel, pemetrexed, or vinorelbine), resulting in a slight increase in survival and relief of cancer-related symptoms. Strategies to further improve survival of patients include the addition of targeted drugs to cytotoxic chemotherapy, such as epidermal growth factor receptor or anti-vascular endothelial growth factor monoclonal antibodies, receptor protein kinase inhibitors, and pursuing maintenance therapy with premetrexed after first-line chemotherapy (Makinson et al. 2011). There are potential drug–drug interactions and cumulative toxicity when HAART is combined with systemic chemotherapy (Rudek et al. 2011). Etoposide, taxanes, vinca alkaloids, and the anilinoquinazolines erlotinib and gefitinib are metabolized by cytochrome P450 (Harris et al. 1994; Li et al. 2007). All protease inhibitors inhibit CYP4503A4, but ritonavir, even in low doses, is the most potent inhibitor in the class (Shulman et al. 2002). Also, ritonavir inhibits the P-glycoprotein efflux pump protein, driving chemotherapeutic agents like vinca alkaloids and taxanes outside the tumor cells (Drewe et al. 1999). Protease inhibitors may be associated with a greater incidence of grade 4 hematological toxicity when used in conjunction with the aforementioned chemotherapy regimens and, in the case of nelfinavir and lopinavir, a heightened risk of diarrhea (Moyle et al. 2004; Makinson et al. 2011). The nucleoside analog zidovudine can exacerbate myelosuppression while other drugs in this class (stavudine, zalcitabine and didanosine) may aggravate peripheral neuropathy associated with cisplatin and taxane derivatives (Rudek et al. 2011).

In the HIV-infected population with NSCLC, the factors associated with increased survival include Eastern Cooperative Oncology Group Performance less than 2, HAART during chemotherapy, and a CD4+ count >200 cells/μl at NSCLC diagnosis (Makinson et al. 2011). Initial studies of patients with HIV and lung cancer implied that they may have a shortened survival compared to HIV-negative lung cancer controls. During 1996–2000, 24-month survival with lung cancer was only 10 % among people with AIDS, compared to 31 % in the general population in New York (Biggar et al. 2005). In Italy during 1999–2006, the risk of death among patients with lung cancer and AIDS was six-fold higher when compared to the general population (Zucchetto et al. 2010). Recent studies in the HAART era have yielded variable results. In a retrospective study of HIV-infected lung cancer patients collected from several clinics with experience in taking care of this population the median survival for those with advanced cancer was 9 months and was comparable to the median survival of Surveillance, Epidemiology and End Results (SEER) lung cancer participants (D'jaen et al. 2010). A recent analysis of HIV-infected and HIV-negative lung cancer patients collected from a SEER database between the years 2000 and 2005 showed no significant difference in clinical outcomes (Rengan et al. 2012). In addition, survival after curative resection in early-stage patients was similar in HIV-infected individuals and uninfected controls. These data suggest that HIV status should not be the most important determinant in therapeutic decision making in NSCLC.

22.6 Prevention

Smoking Cessation

As there are no unique clinical practice guidelines to implement smoking cessation efforts among HIV-positive persons, evidence-based treatments with demonstrated efficacy in the general population must be incorporated into the care of HIV-positive smokers.

There are a number of barriers and complicating factors that compromise the success of smoking cessation in the HIV-infected individuals. Smokers are more likely to be abusers of alcohol and illicit drugs, and tobacco use may increase when persons are under the influence of these substances; substance abuse also can be a risk factor for smoking cessation failure. HIV-infected individuals may have a number of psychological stresses and mental health challenges that contribute to smoking and make cessation more difficult. Some HIV-infected individuals may use tobacco to manage HIV-related symptoms and pain and perceive smoking as one way to cope with the stress of living with a difficult illness (Rahmanian et al. 2011; Lifson and Lando 2012). In addition, HIV-infected individuals may feel that they will ultimately die from AIDS, making smoking cessation less of a priority.

US Public Health Service guidelines recommend brief individual smoking cessation counseling with five components (known as the "5 A's") at each clinical encounter. Providers are advised to systematically *ask* about tobacco use, *advise* smokers to quit, *assess* willingness to quit, *assist* with quitting, and *arrange* follow-up. Smokers' telephone quit lines are cost-effective interventions with broad reach and demonstrated efficacy for long-term smoking cessation. Motivational interviewing is effective in increasing quit attempts. Cognitive behavioral interventions are additional strategies to help smokers quit or reduce cigarette smoking. These interventions are designed to modify critical cognitions and actions that maintain behaviors such as smoking by promoting the thoughts and skills necessary to create behavioral change. Given the widespread availability of cell phones throughout the world, delivery of interventions through cell phones may be feasible even in many resource-limited settings. The use of a proactive cell phone-based intervention that combines supportive counseling, motivational intervention, and materials/topics targeted to HIV-infected individuals in addition to usual care which includes physician advice to quit and access to nicotine replacement therapy is more likely to result in abstinence when compared to usual care alone (Gritz et al. 2013; Lifson and Lando 2012).

Medications approved by the US Food and Drug Administration (FDA) for smoking cessation include nicotine replacement therapy (patch, lozenges, inhalers, gum and nasal spray), bupropion, and varenicline. There are no known interactions between nicotine replacement therapy and HAART. Bupropion is metabolized by the hepatic cytochrome P450 CYP2B6 system, and its metabolism has been shown to be inhibited by protease inhibitors (nelfinavir, ritonavir), and a non-nucleoside reverse transcriptase inhibitor (efavirenz) in vitro (Hesse et al. 2001). Short-term ritonavir

administration does not significantly alter bupropion pharmacokinetics in healthy volunteers and no medication-associated adverse events were observed in a case series of 10 HIV-positive persons using either ritonavir, nelfinavir, or efaverinz with bupropion (Nahvi and Cooperman 2009). The results and tolerance recorded for varenicline in HIV-positive individuals are similar to those published in relation to seronegative patients and no drug interactions have been described to date with HAART and varenicline (Cui et al. 2012; Ferketich et al. 2013). Both bupropion and varenicline are associated with significant neuro-psychiatric symptoms, including behavioral changes, hostility, agitation, depressed mood, suicidal ideation, and attempted suicide. These symptoms have occurred in patients without preexisting psychiatric illness. Electronic cigarettes, also known as e-cigarettes are a diverse range of battery operated devices designed to imitate regular cigarettes and deliver nicotine via inhalation without combusting tobacco. E-cigarettes seem to have the potential to assist smokers to quit or reduce smoking by attenuating tobacco withdrawal (Bullen et al. 2013). E-cigarettes also have the potential to harm; researchers have detected toxins in e-cigarette fluid and vapor, but at much the same concentrations as with nicotine replacement therapy and lower than in cigarette smoke (Goniewicz et al. 2013). The FDA will need to make a number of regulatory decisions about product safety in the near future that could have significant implications in public health and possibly in HIV-infected individuals (Benowitz and Goniewicz 2013).

Despite the high prevalence of smoking and significant barriers to quitting among those with HIV, 30–60 % of HIV-positive smokers are contemplating quitting or preparing to quit smoking. In settings where HIV care is well organized and antiretroviral therapy is free of charge, HIV-infected smokers lose more life-years (12.3 vs. 5.1 years) to smoking than to HIV (Helleberg et al. 2013). Hence the importance of stopping smoking needs to be an ever present message during our clinical encounters (Rahmanian et al. 2011; Lifson and Lando 2012).

22.7 Screening

Lung cancer screening is a rapidly evolving field that has the potential to significantly reduce the burden of lung cancer. Early randomized control trials in lung cancer screening evaluated chest radiography with or without sputum cytology, and showed no reduction in lung cancer mortality.

The lack of a clear result from chest X-ray screening and the refinement of computerized tomographic (CT) scanning techniques led to the evaluation of CT scanning for lung cancer screening. The National Lung Screening Trial (NLST) compared the effects of low-dose helical CT and standard chest X-ray on lung cancer mortality. The, randomized national trial involved more than 53,000 current and former United States smokers between the ages of 55–74 years old who had at least a 30-pack per year smoking history. Among trial participants screened with low-dose helical CT there were 20 % fewer lung cancer deaths (National Lung Screening Trial Research Team 2011). The possible disadvantages of helical CT include the

cumulative effects of radiation from multiple CT scans; surgical and medical complications in patients who prove not to have lung cancer but who need additional testing to make that determination; and over diagnosis from the detection of cancers that never would have become symptomatic (Bach et al. 2012).

At the time of this writing (September, 2013), the American College of Chest Physicians, the American Society of Clinical Oncology, and the American Thoracic Society recommends screening for lung cancer using LDCT based primarily on results from NLST, with eligibility criteria that models closely on NLST (current or former smokers ages 55–74 years with a ≥30 pack-year history of cigarette smoking and ≤15 years since quitting). The recommendations also stipulate that screening should be offered only in clinical settings similar to those in the trial. The US Preventive Services Task Force final recommendations are pending, and its draft recommendation supports annual screening for lung cancer with LDCT in persons at high risk based on age and cumulative tobacco smoke exposure (US Preventive Services Task Force 2013).

The high prevalence of infectious and inflammatory conditions in HIV-infected patients can generate suspicious findings and increase the false-positive rate, resulting in significant anxiety and expense. The NLST study population, while ethnically representative of the high-risk US population of smokers, was a highly motivated and primarily urban group that was screened at major medical centers. In part for these reasons, the results may not accurately predict the effects of recommending low-dose helical CT scanning for other populations, including HIV-infected individuals. Also, other lung pathologies are more common in HIV-infected individuals, and these may yield more false-positive scans and make it particularly hard to apply the results of the NLST population to HIV-infected patients. Additional studies are needed to address this issue, perhaps by modeling the findings using studies of helical CT scans in a HIV-infected population.

22.8 Conclusion

Lung cancer risk is about two to five times greater in HIV-infected persons than in the general population, even after adjusting for smoking intensity and duration. HIV-associated lung cancer typically is diagnosed a decade or more earlier among HIV-infected persons. Adenocarcinoma is the most common histological type and the majority of patients are diagnosed with locally advanced or metastatic disease (stage IIIB or IV). As pulmonary infections are common among HIV-infected individuals, clinicians may not suspect lung cancer in this patient population, and this may lead to a delay in the cancer diagnosis. Surgery with curative intent remains the treatment of choice for localized disease, and there is increasing experience in using radiation therapy and systemic chemotherapy for patients who do not have surgical options. Though retrospective studies conducted during the pre- and early-HAART era reported shorter survival times among HIV-lung cancer patients than HIV-indeterminate or negative lung cancer patients, in the most recent of studies

performed in the HAART era, these two groups appear to have comparable survival times. Screening with low-dose CT scans is not yet routine in this high-risk population. As smoking plays a significant role in the development of HIV-associated lung cancer, people with HIV should be reminded of the hazards of smoking and encouraged to stop. Smoking cessation strategies with demonstrated efficacy in the general population should when possible be routinely incorporated into the care of HIV-positive smokers.

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Chapter 23
Hepatocellular Carcinoma in HIV-Positive Patients

Massimiliano Berretta, Paolo De Paoli, Umberto Tirelli, and Bruno Cacopardo

Abstract Hepatocellular carcinoma (HCC) is a primary tumor of the liver that arises from hepatocytes. The principal factors that increase the risk of HCC include infection with hepatitis B virus (HBV), infection with hepatitis C virus (HCV), alcoholism, and aflatoxin. Patients with HIV infection also have an increased risk of HCC, but the role of HIV and immunosuppression is unclear, and much of this risk appears to be because of co-infection with HBV and/or HCV. Whether HIV plays a direct role in HCC pathogenesis remains to be established, but it can increase the risk of HCC in individuals co-infected with HBV and/or HCV. The clinical course of HCC depends on stage of cancer disease, performance status, and comorbidities. Therapeutic options include liver transplantation, local antiblastic chemotherapy, and biological agents. In the HIV setting few data are available about treatment options. The increased longevity of patients with HIV appears to be contributing to an increased incidence of HCC in this population and imposes new strategies for prevention and therapeutic management of patients.

M. Berretta, M.D. (✉) • U. Tirelli
Department of Medical Oncology A, National Cancer Institute,
Via Franco Gallini 2, 33081 Aviano (PN), Italy
e-mail: mberretta@cro.it

P. De Paoli
Scientific Directorate, National Cancer Institute, Aviano, Italy

B. Cacopardo
Division of Infectious Diseases, Department of Clinical and Molecular Biomedicine,
University of Catania, Catania, Italy

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23.1 Introduction

HIV has been linked to malignancies since the beginning of the AIDS epidemic in 1981, when Kaposi's sarcoma was reported for the first in young never-married men. Soon thereafter, aggressive non-Hodgkin's lymphoma (NHL) was found to be linked to HIV and these two tumors were considered AIDS-defining when they occurred in an HIV-infected patient. Subsequently, invasive cervical cancer was also noted to be more common in HIV-infected patients and became the third AIDS-defining tumor. Since that time, numerous studies have shown that HIV infection raises the risk of a number of other tumors that do not confer a diagnosis of AIDS; these are called non-AIDS-defining cancers (NADCs). NADC cancers include carcinoma of the anus, testis, lung, skin (basal cell skin carcinoma and melanoma), Hodgkin disease, and hepatocellular carcinoma (HCC) (Dal Maso et al. 2009; Polesel et al. 2010; Pantanowitz et al. 2006).

The advent of highly active antiretroviral therapy (HAART) has dramatically extended the survival rates of patients with human immunodeficiency virus (HIV), leading to effective suppression of HIV and prolongation of life (Nunnari et al. 2005; Polesel et al. 2010). Most patients receiving HAART have an increase in their CD4 counts and a decrease in risk of AIDS-defining tumors associated with severe immunosuppression, such as Kaposi sarcoma or central nervous system lymphoma. However, as these patients live longer, we are seeing a rise in a wide range of other cancers, and cancer is an increasing cause of morbidity and mortality in HIV patients; in fact, in some recent studies, cancer is the most common cause of death in HIV-infected individuals (Bonnet et al. 2004; Simard et al. 2010, 2011; Meijide et al. 2013; Centers for Disease Control and Prevention 1993).

Zucchetto et al. evaluated the mortality for NADCs among 10.392 Italian patients with AIDS, who were diagnosed between 1999 and 2006, compared with the general population of the same age and sex. NADCs were the underlying cause of death for 7.4 % of HIV-infected patients. The authors found a 6.6-fold elevated risk of death for NADCs among persons with AIDS. Most of these cancers with significantly elevated standardized mortality rates (SMRs) have a viral etiology, including anal cancer, which is associated with a human papilloma virus (SMR 270), Hodgkin lymphoma, which is associated with Epstein Barr virus (SMR 174), and HCC, which is associated with chronic hepatitis B and C virus infections (SMR 11.1). In absolute terms, the most common cause of death for NADCs was lung cancer (24.6 %), followed by liver cancer and Hodgkin lymphoma (both with 11.9).

The particularly enhanced risk for infection-related cancers could be explained by the fact that the altered immune system in HIV-infected persons may reduce its ability to control and suppress the oncogenic viral process or tumors expressing foreign antigens (Dubrow et al. 2012). This mechanism is supported by Grulich et al. who compared, in a meta-analysis, the cancer risk for HIV-positive patients and organ transplant recipients. These populations had a common risk factor for cancer: immunosuppression. Indeed, most of the cancers seen with a higher frequency in both populations had a known infectious cause. The exact role of HIV-induced immunosuppression in the pathogenesis of NADCs remains controversial and may vary from tumor to tumor: certain tumors appear to be associated with low CD4

counts, while in other tumors this relationship is less clear or non-existent. Silverberg et al. analyzed a cohort of 19,280 HIV patients, followed from 1996 to 2007 and matched for age and sex with 202,303 HIV-negative persons. The authors found that the risk of mouth-throat cancer, anal cancer, colorectal cancer, lung cancer, and Hodgkin lymphoma rose as recent CD4+ cell count fell; even after adjusting for other cancer risk factors such as age, smoking status, substance use, and viral hepatitis. Longer duration of HIV infection and a history of repeated opportunistic or other infections are also considered as relevant risk factors for development of various NADCs. It has been suggested based on animal studies that some anti-HIV drugs may contribute to one or more NADC, but this has not been shown in humans.

Focusing on HCC, it is known that the major risk factor for HCC is liver cirrhosis, and in many countries, the most common cause of cirrhosis is infection with hepatitis C virus (HCV) or hepatitis B virus (HBV). Other causes of cirrhosis and HCC include alcoholism and, especially in part of Asia, aflatoxin exposure. HCC usually develops only after several decades of HCC or HBV infection. The role of HIV in the development of HCC is not clear; most HIV-infected patients who develop HCC re co-infected with HBV and/or HCV, and these are the major risk factors for the development of HCC. Evidence seems to suggest that HIV by itself is not a risk factor for HCC. It is not known whether HIV infection alone is a risk factor for HCC, and indeed, evidence from several large retrospective studies suggests it is not. There is some, although conflicting, evidence that among patients co-infected with HIV and either HBV or HCV, HCC is more common in patients with low CD4 counts, suggesting that HIV or HIV-induced immunosuppression may be a contributory factor in the development of HCC. HIV co-infection also seems to accelerate disease progression of HCC. The ability of HAART to reduce HIV-associated immunosuppression may thus be beneficial in reducing the risk of HCC. At the same time, patients receiving HAART have a prolonged survival, and in countries where HAART is widely used, the HIV-infected population is increasing in number and becoming more aged. These latter trends are contributing to a substantially increased overall burden of HCC in HIV-infected or AIDS patients. In addition to potential indirect effects on HCC risk through improvements in immune reconstitution and survival, HAART is known to have some direct hepatotoxic effects, which might be amplified among HIV-positive patients chronically infected with HBV or HCV. Whatever the contributory causes of the increased number of cases of HCC in the HIV-infected population, this is an increasingly important problem and there is an urgent need for more effective preventive, diagnostic, and therapeutic approaches.

23.2 HCC: A Rising Problem Among Patients with HIV

Epidemiology and Risk Factors

HCC is the commonest primary cancer of the liver and, according to the WHO report, the fourth commonest cause of cancer-related death. The estimated incidence of new cases worldwide is about 500,000–1,000,000 per year, causing

600,000 deaths globally per year. Although there are large areas of the world where the incidence of HCC is still unknown, several regions including parts of East Asia and sub-Saharan Africa are affected by a very high incidence of HCC (over 20 cases/100,000 population). Areas with moderately high risk (11–20 cases/100,000 population) include Italy, Spain, and Latin America; France, Germany, and the United Kingdom have instead an intermediate risk (5–10 cases/100,000 population). A relatively low incidence (less than five cases/100,000 population) is found in USA, Canada, and Scandinavia. The incidence of HCC has been rising in developed Western countries in the last two decades, driven in part by the increased prevalence of HCV infection and the rise of immigration rates from HBV-endemic countries. In addition, even though the incidence of HCC reaches its highest peak among persons over 65 years, an increased incidence among younger individuals has been noted in the last two decades both in the USA and Europe.

In HIV-positive patients, then incidence of HCC is substantially higher (82/10,000 according to the Data Collection on Adverse Events of Anti HIV Drugs) than in the general population. Overall, HCV infection is the strongest predictor for liver-related death, followed by HBV; many studies have confirmed this datum. The role of HIV is less clear. A large retrospective cohort study on US veterans demonstrated that HIV-positive persons had a higher risk to develop HCC than HIV-negative persons but, after adjusting for HCV and alcohol abuse, HIV status was not independently associated with cancer. The 2001 French Mortavic study (Rosenthal et al. 2003), a prospective 1-year cohort study involving 25,178 HIV-positive patients, showed a significant increase in death from end-stage liver disease (ESLD) and HCC, as compared to similar cohorts in 1995 and 1997; death due to ESLD rose from 1.5 to 14.3 % of all deaths, whereas deaths due to HCC rose fivefold, from 4.7 to 25 % of all deaths; interestingly, essentially all deaths from HCC were in patients with HCV co-infection. Throughout the same period, deaths directly due to AIDS fell from 91.6 % of all deaths (in 1995) to 48.7 %, suggesting that the increased longevity in the HAART era could be a reason for the increased HCC rate in the 2001 cohort. In a prospectively followed cohort of HIV-infected individuals in France, HCC deaths related to HCV infection also increased during the period from 2000 to 2005 (Bonnet et al. 2004). By contrast, the incidence of HCC development and related deaths among HIV–HBV co-infected individuals seemed to be relatively stable (Bonnet et al. 2004). A retrospective study conducted on a cohort of US veterans with hepatitis C between 1991 and 2000 showed that the incidence of HCC did not differ between HIV/HCV co-infected and HCV mono-infected patients in the HAART era, whereas it was significantly lower among HIV/HCV co-infected individuals previously to HAART introduction. This datum supports the premise that, in the pre-HAART-era, HIV patients did not survive enough to develop HCC. Other retrospective studies examining cohorts from countries where HAART is largely unavailable found the incidence of HCC to be lower or equal to average population rates, also supporting this conclusion.

In 2004, the Italian Cooperative Group on AIDS and Tumors (GICAT), while collecting data on malignancies occurring in HIV patients since 1986, identified a total of 41 consecutive patients with HCC (from a joint Italian and Spanish database) and retrospectively investigated the main epidemiological characteristics of

these patients as compared to a control group comprised of 384 HIV-negative patients diagnosed over the same period. The GICAT study emphasized the younger age of HIV-positive patients at the diagnosis of HCC (age 40–46 vs. 60–70 in HIV negatives). HCV infection was the main risk factor for HCC development in both HIV-positive and HIV-negative subjects. The median time to develop HCC after HCV infection was found to be around 22 years in HIV-positive patients: 10 years shorter than that reported among HIV-negative patients who acquired HCV infection with transfusion. Alcohol abuse (which is often associated with HIV risk behaviors) and insulin resistance (which causes nonalcoholic fatty liver disease and frequently occurs in HIV-infected individuals in part from certain antiretroviral drugs) are other potential risk factors for the earlier development of HCC among HIV-positive patients.

HIV–HBV and HIV–HCV Co-Infection: Prevalence and Significance of a Complex Interaction

Co-infection with HCV and/or HBV is common among HIV-infected persons, because of shared routes of transmission, although the prevalence of co-infection varies markedly according to the geographic origin and demographic characteristics of infected patients. Approximately 25 % of HIV-positive persons in the Western world have HCV co-infection. In a study of 3,048 patients in the European SIDA cohort, the prevalence of HIV/HCV co-infection was 33 % overall but 75 % in injection drug users (IVDUs). In the USA, the highest rates of HIV/HCV co-infection were also seen among IVDUs. In regard to HBV, up to 9 % of HIV-positive patients in Europe are co-infected with HBsAg (Konopnicki et al. 2005). In Italy, between 3 % and 4 % of HIV-infected individuals are chronic carriers of HBsAg. The recorded prevalence is likely to be inaccurate, however, because of the large number of patients with occult HBV infection, associated with detectable HBV DNA on quantitative PCR.

HCV usually leads to the development of HCC through the stage of cirrhosis, which can take 28–30 years to occur. Cirrhosis is almost a pre-requisite for the development of HCV-related HCC: HCV is not able to integrate into the host genome and the major hypothesis to explain hepatocarcinogenesis in patients with HCV is related to immune-mediated inflammation and hepatocellular injury. HBV chronic infection is another major cause of HCC but, differently from HCV, HCC may occur in HBsAg carriers without cirrhosis, because of the direct involvement of a number of viral-related factors (viral proteins, BCP mutation in the viral genome, pre-S deletion mutants). Furthermore, HBV has a retroviral intermediate stage in its replication, and can integrate its DNA into the host genome. This can lead to a variety of mutagenic consequences, including large inverted duplications, deletions, amplifications, and translocations, resulting in chromosomal instability. As expected, patients with HCV–HBV co-infection have yet a higher risk of developing HCC than those infected with just one or the other, and vaccination against HBV should be proposed to all patients with chronic hepatitis C who are not infected with HBV.

A number of studies have examined the role of HIV in the pathogenesis of HCC. In vivo studies in murine models have shown a potential role of the HIV *Tat* gene in liver tumorigenesis. In transgenic mice expressing this gene, a greater incidence of HCC as well as extrahepatic malignancies has been found, suggesting that the potential oncogenic effect of *Tat* gene is not liver-specific. There is suggestive evidence that *Tat* may have oncogenic activity because of its anti-apoptotic activity, pro-angiogenic activity, and ability to induce expression of growth factors, cytokines, and transcription factors. Although murine experiments suggested a direct role of *Tat* in HCC, a number of epidemiological studies have not shown a clear role of HIV itself on HCC development; in a large retrospective study by Giordano et al., for instance, the rate of HCC was not higher in HIV mono-infected patients without HCV or HBV infection than in general population. At the same time, however, there is a clear evidence that HIV can accelerate the progression of HCV- and HBV-liver disease to cirrhosis and HCC. In this regard, the presence of HIV alters the natural history of HCV infection, increasing the likelihood of chronicity (over 90 %) due to the lack of cCD4+ T-cell responses against HCV. Moreover, once chronic HCV infection is established, liver disease progression is much faster in HIV-infected patients, resulting in a higher frequency of cirrhosis and its complications compared to HCV mono-infected patients.

The molecular mechanisms of accelerated fibrosis in co-infected patients are not fully understood. The studies of Galastri et al. suggest that HIV gp120 may play a role by exerting multiple effects on human hepatic stellate cells (HSCs), modulating their phenotype in a profibrogenic way. Incubation of HSCs with gp120 significantly increased the migration of HSCs and their expression of proinflammatory cytokines, including monocyte chemoattractant protein-1 (MCP-1) and type 1 procollagen. Recent data suggest that the binding of HIV gp-120 to the CXCR4 coreceptor, which is expressed on the surface of hepatocytes and HSCs, is able to upregulate tumor necrosis factor (TNF)-related apoptosis, inducing ligand (TRAIL) R2 expression. By this mechanism, HIV infection may make hepatocytes more susceptible to liver injury. During HIV co-infection, increased liver damage may also be mediated by the effects of antiretroviral drugs and indirectly by immune reconstitution syndrome (Bonnet et al. 2004; Puoti et al. 2012).

Further prospective studies are needed to better evaluate the role of HIV role in subjects co-infected with HCC. It will be important to control for potential confounding factors in epidemiologic studies. In some studies, for example, not all HCV–HBV patients had been tested for HIV, thus implying the possibility to underestimate the prevalence of co-infected persons. Also, since time of infection with HBV or HCV is often missing, it is hard to calculate the effect of HIV-co-infection on the development of HCC. For example, if patients with isolated HCV or HBV acquired this infection earlier than HIV co-infected patients in a study, this variation in the duration of infection could contribute to an apparent effect of HIV infection. Given these considerations, key points of an ideal prospective study should include cross-testing for co-infections before individual allocation to groups, standardized screening for HCC and regular evaluation of HIV viral load in the co-infected cohort, in order to evaluate the potential effect of HAART-induced viral suppression on HCC pathogenesis.

Clinical Characteristics

During its initial stages, HCC is generally asymptomatic. In more advanced phases, hepatomegaly, jaundice, and abdominal pain may appear. Overall, the clinical presentation and prognosis considerably vary according to the number and size of tumor lesions. Liver cancer may appear either as a single nodular or infiltrating lesion with an eccentric growth or as a multinodular widespread tumor ab initio. In some patients HCC lesions have a slow growth rate, with a twofold increase in 20 months, while in others it can double in less than 1 month. Multinodular HCC is more often found in patients with more than one risk factor and needs to be classified as primitive multicentric HCC or metastatic cancer from a primitive HCC. This distinction has important clinical implications because primitive multicentric HCC are less aggressive and recur less frequently after ablation than metastatic cancers from a primitive HCC.

Amongst HIV-infected patients, cumulative clinical data suggests a more aggressive course of HCC. Patients with HIV from the HIV–HCC Italo-Spanish Group showed a more advanced and infiltrating HCC (also with extranodal metastases), a more advanced stage of cirrhosis at presentation and a reduced survival rate in comparison with HIV-negative patients. A 2007 US-Canadian multicenter retrospective study identified 63 HIV-infected patients with HCC from 1992 to 2005 and compared them to 226 HIV-negative HCC patients. Patients with HIV not only were younger and more frequently symptomatic than HIV-negative patients but also showed higher median α-fetoprotein levels. By contrast with other studies, tumor staging and survival were similar between cases and controls in this study. In untreated HCC cases, the presence of undetectable HIV-RNA was an independent predictor of a better survival. In a recent, large, multicenter, observational study, Berretta et al. (Berretta et al. 2011) confirmed that HIV-positive HCC subjects tend to be younger and to have a shorter survival time after treatment than HIV-negative patients.

HCC: Treatment Options

HCC treatment is usually classified as curative or palliative. The curative treatments are surgical resection, orthotopic liver transplantation (OLT), and local ablative therapies, including percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA). Surgical resection is the treatment of choice in solitary tumors less than 5 cm in diameter that are without vascular invasion or extrahepatic spread, developing in patients with preserved hepatic function who do not have portal hypertension; in this setting, the 5-year survival rate is about 50 %. OLT is the best option for cirrhotic patients with a solitary lesion less than 5 cm in diameter that is not a candidate for resection or with up to 3 lesions smaller than 3 cm, and where there is no vascular invasion or metastasis according to the Milan criteria. In these cases the 5-year survival rate can be as high as 70 %. In patients who are not eligible for resection or transplantation, owing to comorbidities, liver dysfunction or limited surgical

resources, PEI and RFA are a potential treatment for small tumors, usually less than 3 cm in size. For early-stage HCC, RFA has been reported to induce a complete response in about 80 % of patients, with a 5-year survival of 50 % and recurrence rates comparable to surgical resection.

Unfortunately, however, most patients with HCC have advanced disease at diagnosis. They are candidates for palliative treatments that include transarterial chemoembolization (TACE), chemotherapy, hormonal compounds, and immunotherapy. TACE has been shown to improve survival when applied to carefully selected patients. It is indicated for unresectable multinodular HCC, without vascular invasion or extrahepatic spread. To date, durable remission has rarely been reported with chemotherapy and no significant survival benefits have been conclusively demonstrated with this approach, probably because of the chemoresistance of HCC cells. More recently sorafenib (an oral multikinase inhibitor of the vascular endothelial growth factor receptor) prolonged median survival time as compared to placebo as well as time to radiologic progression in patients with advanced HCC, and it has been approved for advanced disease.

Other anti-angiogenic therapies that may have some utility in HCC are sutinib and the combination of bevacizumab and erlotinib; unfortunately, no data are available concerning their use in HCC patients infected with HIV. Also, mammalian target of rapamycin (mTOR) inhibitors have shown a certain rate of efficacy in small cohorts of patients with HCC, but these data need to be validated in wider clinical settings. The presence of sexual hormone receptors on HCC cells raised the possibility of using antiestrogens like tamoxifen against those HCC cases not amenable to resection: unfortunately, several trials failed to demonstrate any benefit either in terms of response or in terms of overall survival in patients with advanced HCC treated with tamoxifen.

HCC in patients with HIV is often advanced at presentation, not allowing curative therapeutic strategies. Until a few years ago, HIV infection was an exclusion criteria for liver resection or transplantation. An important concern was the risk of HIV progression after OLT, a poor post-transplantation prognosis, and eventually the waste of graft (Di Benedetto et al. 2008a, b; Terrault et al. 2012). Ettorre et al. (2003) showed that almost half of HIV-positive patients affected with end-stage liver disease were not suitable for surgical treatment and comprehensively only 28 % of them had the opportunity to receive a successful surgical treatment. An analysis of the GICAT cohort showed that in a series of 41 HIV-positive patients affected by HCC, 15 (35 %) of them fulfilled the Milan criteria and could potentially have been treated with OLT as a curative intent. However, none of them underwent liver transplantation; only two underwent surgical resection with a 2-year survival of 41 % in treated patients and 0 % in untreated cases.

Since the introduction of HAART, the outcome of HIV infection has dramatically changed. Patients with HIV have a substantially better long-term survival and as a consequence, liver transplantation needs to be considered to treat HCC. Several studies found that most HIV-positive patients who undergo a liver transplant have a good long-term survival (Di Benedetto et al. 2008a, b). Di Benedetto et al. (2008a, b) reported on a series of 7 HIV-positive patients with HCC that, by fulfilling the Milan

criteria, underwent OLT. After a mean follow-up of 232 days, the overall survival rate was 85.7 % and only one patient died; this individual had a functioning graft and no HCC recurrence, and died of a myocardial infarction. Radecke et al. reported that out of five cases of OLT in HIV-infected cirrhotic subjects, two had stable liver function and non-progressive HIV infection under HAART, 61 and 23 months after OLT, respectively; unfortunately, in this report, three out of five patients died due to graft failure. Clinical post-transplant management of OLT in HIV-positive patients is doubtless more complex than in the HIV-negative counterpart. The main reported problem in these patients has been an earlier and more aggressive HCV recurrence (experienced in about 33 % of patients), faster occurrence of hepatic fibrosis, a greater rate of rejection (from 33 to 38 %) (Di Benedetto et al. 2012) and a higher incidence of tacrolimus toxicity.

The outcome of HIV-positive liver recipients depends in part on the immunological status of the patient at the time of OLT. There is a considerable agreement about the necessity of a full virological control of the underlying HIV infection before OLT: in fact, transplanted patients with higher CD4+ cell counts and undetectable HIV viral load display clinical courses similar to HIV-negative recipients. Di Benedetto et al. proposed some criteria to select HIV-positive patients with HCC for OLT: firstly, patients must completely fulfill the Milan criteria. They should also have an undetectable HIV viral load (<50 copies/mL) and a CD4+ cell count more than 200/mL. After OLT, HAART needs to be reinstituted as soon as clinically possible, with the input a multidisciplinary transplant team (surgeons, infective disease specialists, and oncologists) with great experience in the management of pharmacologic interactions between HAART and immunosuppressive agents (see Table 23.1). In conclusion, the latest evidence suggests that OLT should be considered as a possible therapy for patients with HIV and HCC. Accurate selection protocols for this approach that take into account HIV status, HCC stage, and other factors are essential (Wood, 2012). At the present time, the key question is not *if*, but *who* should be referred to liver transplantation.

In the palliative setting, recent data on the use of sorafenib in unresectable HCC/HIV-positive patients showed that this treatment along with concomitant HAART is safe and feasible and that the response rates are similar to general population (Berretta et al. 2013). Unfortunately the number of HCC/HIV-positive patients analyzed is small and prospective and randomized trials are necessary to draw further conclusions.

HCC: Primary, Secondary and Tertiary Prevention

Prevention and early diagnosis are key points to the management of HCC, but, at present, there are no universal guidelines, especially when it occurs in HIV-positive patients (see also Table 23.2). Primary prevention in subjects with HIV should entail efforts to promote alcohol avoidance and when appropriate include strongly HBV. In fact, HCC was the first human cancer that was shown to be amenable to prevention using mass vaccination.

Table 23.1 Criteria for considering liver transplantation in HIV-infected patients (according to Di Benedetto 2008a, b)

Liver disease criteria
• Child-Turcotte-Pugh score ≥ B7; MELD score ≥14
Milan criteria:[a]
• No more than three tumor nodules
• No nodule greater than 5 cm in diameter
• Absence of macroscopic portal vein invasion
• Absence of recognizable extrahepatic disease
HIV infection criteria
Immunological criteria
• None of AIDS-defining opportunistic infections in the previous year
• CD4 cell count >200 cells/μL or >100/μL in case of therapy intolerance
Virological criteria
• Undetectable HIV viral load (<50 copies/mL) in the last 12 months or effective therapeutic options for HIV infection during the post-transplant period
General criteria
• Favorable psychiatric evaluation
• Social stability
• No alcohol abuse for at least 6 months
• No drug consumption for at least 2 years (patients who are on stable methadone maintenance programmes can be included and can continue on the maintenance programme after the procedure)
• No extrahepatic malignancy
• No pregnancy

[a]Patients with HCC who are being considered for liver transplantation should not have a needle biopsy due to the significant rate of needle-track seeding leading to recurrence post-transplant

Table 23.2 HCC prevention

Primary prevention
• Alcohol avoidance
• Avoidance of injection drugs
• Vaccination against hepatitis B
Secondary prevention
• Six-monthly ultrasonography + AFP
• Treatment of HCV and/or HBV co-infection
Tertiary prevention
• No significant options

Secondary prevention should include regular exams aimed at early detection of HCC. The European Association for the Study of the Liver (EASL) has proposed guidelines describing patient selection and surveillance intervals for HCC screening in HIV–HCV and HIV–HBV co-infected individuals. Six-monthly ultrasonography and alpha-fetoprotein (AFP) levels measurement are the two methods most commonly used to screen cirrhotic patients for HCC. The use of AFP alone for early diagnosis of HCC in HIV co-infected patients is not recommended and may be suggested only where and if ultrasonography is unavailable. In fact, even

though AFP values higher than 400 ng/ml are usually considered as diagnostic of HCC, false-positive AFP results can occur in HIV-infected patients as a result of HAART inducing substantial increases of AFP levels. The GICAT group, observed a more advanced HCC at diagnosis in HIV-positive patients, apparently unrelated to a true delay in diagnosis, and suggested shortening the interval for HCC screening in this patient population hepatocarcinogenesis can be a more rapid process in HIV-positive cirrhotic subjects.

Another point to consider in patients co-infected with HIV is the treatment of HCV and/or HBV. Treatment with IFN and ribavirin may induce a persistent clearing of HCV viremia in 27–40 % of HIV–HCV co-infected individuals and seems to reduce the risk of HCC in these cases. Moreover, HCV eradication in HIV co-infected patients results in a definitive improvement of liver function and it seems to improve tolerance to antiretroviral agents. In particular, therapy with pegylated-IFN alpha plus ribavirin appears able to slow down the rate of liver disease progression, although the likelihood of achieving a sustained virological response (SVR) is lower in co-infected persons than in those with HCV mono-infection. Based on available clinical results, 48 weeks of ribavirin and pegylated-IFN therapy at doses used for HCV mono-infected patients seems to be advisable. Unfortunately HCV therapy in HIV patients is not as well tolerated as in other patients; side effects include relatively more severe and frequent myelosuppression, more frequent anemia (especially in patients taking zidovudine), an increased risk of lactic acidosis, and a poorer response in patients with low CD4+ cell counts. HBV treatment also appears to substantially reduce HCC incidence in patients with severe cirrhosis and there are reasons to suspect the same effect in HIV co-infected patients. Patients in whom treatment for both HBV and HIV is planned should receive therapies that are effective against both viruses, and regimens such as lamivudine plus tenofovir or emtricitabine plus tenofovir are preferred. As far as we know, no relevant data on tertiary prevention (which aims to reduce HCC recurrence after resection) are available in HIV-positive individuals.

23.3 Conclusion

Currently, in areas where HAART is available, a rapid increase of HCC incidence is occurring among HIV-positive individuals. It is reasonable to hypothesize that in a few years, the burden of HCC in HIV-infected patients will increase developing countries as well. Considering the more aggressive clinical behavior and progression of HCC in co-infected patients, there is an urgent need for effective prevention programs, screening techniques, and specific management guidelines. Large, multicenter, randomized clinical trials are needed, in order to better define the criteria for surveillance and the effect of early diagnosis on outcome. In addition, important needs for future research include a further evaluation of the feasibility of liver transplantation and efficacy of new therapeutic agents.

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Chapter 24
Merkel Cell Carcinoma and Other HIV-Associated Skin Cancers

Nathalie C. Zeitouni and Bethany Lema

Abstract Cutaneous neoplasms are cancers that originate from the skin and are the most common malignancies in the USA. Patients with HIV and other immunocompromised diseases have not only a greater risk of developing common skin cancers such as basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma but also more unusual cutaneous tumors such as Merkel cell carcinoma (MCC), Kaposi's sarcoma (KS), and certain lymphomas.

MCC is a rare and aggressive cutaneous neoplasm of neuroendocrine origin, most commonly associated with increased ultraviolet radiation. A recently described polyomavirus (MCPyV) has been found present in the majority of MCC suggesting an oncogenic viral role in tumorgenesis. Immunosuppression may also contribute to MCC development given the tumor's increased incidence in patients with HIV, hematologic malignancies and in those who have undergone solid organ transplantation.

24.1 Merkel Cell Carcinoma

Introduction

Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine cutaneous tumor. MCC was first described in 1972 by Toker as "trabecular carcinoma" due to its histologic lattice-like structure (Izikson and Zeitouni 2011). With the discovery of the tumor's neuroendocrine origin, it was renamed MCC. Merkel cells are the

N.C. Zeitouni, M.D.C.M., F.R.C.P.C. (✉)
University of Arizona Cancer Center,
3838 N Campbell Avenue, Tucson, AZ 85719
e-mail: nathaliezeitouni@email.arizona.edu

B. Lema, M.D.
Department of Dermatology, Roswell Park Cancer Institute,
Elm & Carlton Streets, Buffalo, NY 14263, USA

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only skin cells with neuroendocrine function and are specialized touch receptors found in the basal layer of the epidermis. However, despite similarities in name, morphology, and ultra structural appearance between Merkel cells and MCC, there is lack of evidence to support a direct relationship between Merkel cells and the development of MCC. In fact, recent evidence suggests that MCC may instead arise from less differentiated stem cells in the skin (Izikson and Zeitouni 2011).

Given its aggressive nature, the timely diagnosis of MCC is necessary, and management is often approached in a multidisciplinary fashion (Izikson and Zeitouni 2011).

Epidemiology

Parallel to other rare cutaneous malignancies, the incidence of MCC is low but is rapidly increasing. Currently, there are approximately 1,500 newly diagnosed cases each year in the USA. The incidence has tripled from 0.15 cases per 100,000 in 1986 to 0.44 cases per 100,000 in 2001 and is now estimated at 0.50/100,000 (Heath et al. 2008; Wieland et al. 2011; Fields et al. 2011a). Interestingly, the incidence of MCC now exceeds that of cutaneous T-cell lymphoma but is still 100 times as rare as melanoma.

The risk of development of MCC in patients with HIV is about 13 times that of the normal population (Heath et al. 2008). In one study there was an increased risk of MCC in HIV patients (OR 2.65), and a substantial risk in AIDS patients (SIR 11) was also documented (Lanoy et al. 2010). In the HIV population, there is an earlier age of disease onset compared to immunocompetent persons (Izikson et al. 2011). The risk of MCC is also increased in other immunosuppressed populations and, for reasons that are not yet clear, appears to be particularly increased in patients with chronic lymphocytic leukemia (Heath et al. 2008; Paulson et al. 2013). Currently, there is no documented correlation between the CD4 count and the onset of MCC (Izikson et al. 2011). MCC may occur before or after a diagnosis of AIDS. There is a slight male predominance seen in both the general population and those with HIV. In immunocompetent patients, MCC occurs more commonly in fair-skinned Caucasian individuals. MCC, however, can arise in sun-protected non-head and neck areas in HIV patients, suggesting that ultraviolet radiation may play less of a role in this population. The median age of onset in immunocompetent patients is 69 years old while in the HIV population it was found to be 49 years old (Izikson et al. 2011). Time to diagnosis from HIV to MCC was 9.5 years in one study, which is longer than reported for other non-AIDS-defining malignancies (Izikson et al. 2011).

Pathogenesis

The exact etiology of MCC is unknown and is most likely multifactorial. The immune system clearly plays a role as demonstrated by the increased risk of development of MCC in patients with HIV or other immunodeficient conditions. In one study of 195

cases of MCC, 7.8 % had some form of immunosuppression, including bone marrow transplantation, HIV, organ transplantation, or leukemia/lymphoma (Heath et al. 2008). Furthermore, it was reported that 14.5 % of 1,024 persons with MCC were receiving or had received an immunosuppressant agent (Qian Zhan et al. 2009).

Chronic ultraviolet radiation contributes to the etiology as demonstrated by the high incidence of development of MCC on the head/neck and sun-exposed areas. Reportedly, there is a 100-fold increase in occurrence of MCC in patients who received UVA for psoriasis (Izikson and Zeitouni 2011). Concurrences of MCC with SCC and BCCs have also been reported (Izikson and Zeitouni 2011).

In 2008, Feng and colleagues from the University of Pittsburgh discovered a novel polyomavirus, which they called Merkel cell polyomavirus (MCPyV). Of 437 MCC tumors, 72 % demonstrated positivity for MCPyV and in some reports ~80 % of tumors were positive (Izikson and Zeitouni 2011). In a recent study, using monoclonal antibody to large T antigen, MCPyV was found in 97 % of MCC (Rodig et al. 2012). The MCPyV harbors a genomic mutation that allows it to integrate in infected cells; this occurs prior to the clonal expansion of MCC. MCPyV expresses both large and small T antigen as well as viral structural proteins in cells. In over 2,000 tissue samples of other malignant and premalignant tissue analyzed for the MCPyV, only a subset of small cell lung carcinoma samples showed abundant positivity. This finding suggests that at least one other neuroendocrine tumor besides MCC is associated with this virus (Fukumoto et al. 2013). MCPyV genomes have frequently been found in normal skin and other body sites and fluids, such as tonsillar tissue, respiratory secretions. In MCCs, however, the levels of MCPyV are over 60 times higher than the highest values of other tissues (Koljonen 2010).

In HIV-positive men, there is an increased prevalence of cutaneous MCPyV. Also, the MCPyV viral DNA load is significantly higher in patients with poorly controlled HIV infection (Wieland et al. 2011). In a recent study, MCPyV DNA was detected more frequently in the sera of HIV patients than in the sera of non-HIV patients (Fukumoto et al. 2013), suggesting that viremia is associated with host immunity.

The exact role of MCPyV in the pathogenesis of MCC is actively being researched.

Clinical Presentation

MCC typically presents as a solitary, rapidly growing, non-tender erythematous/pink nodule located frequently on the head and neck region (20 % periorbital), followed by the trunk and extremities. Ulceration may be present. Most tumors show rapid growth within the first 3 months, which is the average time from initial presentation to diagnosis. At time of consultation, the size of the primary tumor is usually less than 1 cm in ~20 %, between 1 and 2 cm in 40 %, and greater than 2 cm in 35 % (Qian Zhan et al. 2009). The median size is between 1.8 and 2.1 cm at the time of diagnosis (Koljonen 2010).

Given the nonspecific nature of MCCs, it can often be confused with benign conditions, such as cysts, lipomas, dermatofibromas, or vascular lesions. It may also be confused with other malignant tumors, such as non-melanoma skin cancer, lymphoma, or sarcoma. The acronym, AEIOU, was developed to aid in the clinical diagnosis of MCC: and stands for *A*symptomatic/lack of tenderness; *E*xpanding rapidly, *I*mmune suppression, *O*lder than 50 years old, and *U*ltraviolet-exposed site on person with fair skin. Heath et al. found that 89 % of 195 cases demonstrated three or more of these features (Heath et al. 2008). MCCs can frequently be associated with other types of cutaneous carcinomas on actinically damaged skin (Izikson and Zeitouni 2011; Qian Zhan et al. 2009). Metastatic MCC may present cutaneously as a 1–3 cm skin-colored or red nodules or indurated subcutaneous tumor that grow rapidly over 2–4 weeks (Izikson and Zeitouni 2011; Zeitouni et al. 2000). If metastases occur, the most common sites are skin, lymph nodes, liver, lung, and bone.

Histopathology

Histology and immunohistochemistry help to confirm the clinical diagnosis. Pathologically, the tumor consists of sheets of dermal small round blue cells with scant cytoplasm and medium-sized nuclei. Mitoses are abundant and chromatin is typically in a salt and pepper pattern. It is an ill-defined tumor which frequently extends into subcutaneous fat and/or muscle. Necrosis, vascular invasion, and perineural invasion are common features. Most MCC stain positive with cytokeratin 20 (CK 20), neuro-specific enolase, epithelial membrane antigen neurofilaments, CAM 5.2 and synaptophysin. CK 20 stains in a characteristic paranuclear dot pattern which is virtually pathognomonic for MCC (Izikson and Zeitouni 2011). MCC also stains positive for MCV large T antigen.

There are three main histologic types: intermediate (80 %), trabecular (10 %), and small cell type (10 %). The small cell pattern is difficult to distinguish from other blue cell carcinomas, particularly small cell lung cancer. Differentiation may be made based on thyroid-transcription factor-1 and CK7 positivity in small cell lung carcinoma compared to negative staining for MCC (Merkel cell carcinoma 2010). Furthermore, it is not uncommon to diagnose a collision tumor histologically, consisting of a BCC or SCC in combination with an MCC (Izikson and Zeitouni 2011; Qian Zhan et al. 2009).

Staging

In 2010, the American Joint Committee on Cancer (AJCC) published the new MCC consensus staging system (Table 24.1) that replaced several previous systems (Merkel cell carcinoma 2010). The current system, which incorporates an assessment of

Table 24.1 TNM criteria and stage groupings of the new AJCC staging system for Merkel cell carcinoma

T	N	M	Survival
Tx, Primary tumor cannot be assessed	*Nx*, Regional nodes cannot be assessed	*Mx*, Distant metastasis cannot be assessed	
T0, No primary tumor	*N0*, No regional node metastasis[a]	*M0*, No distant metastasis	
Tis, In situ primary tumor	*cN0*, Nodes not clinically detectable[a]	*M1*, Distant metastasis[e]	
T1, Primary tumor ≤2 cm	*cN1*, Nodes clinically detectable[a]	– *M1a*, distant skin, distant subcutaneous tissues, or distant lymph nodes	
T2, Primary tumor >2 but ≤5 cm	*pN0*, Nodes negative by pathologic exam	– *M1b*, lung	
T3, Primary tumor >5 cm	*pNx*, Nodes not examined pathologically; *N1a*, Micrometastasis[b]	– *M1c*, all other visceral sites	
T4, Primary tumor invades bone, muscle, fascia, or cartilage	*N1b*, Macrometastasis[c]		
	N2, In-transit metastasis[d]		

Stage		Stage grouping	
0	Tis	N0	M0
IA	T1	pN0	M0
IB	T1	cN0	M0
IIA	T2/T3	pN0	M0
IIB	T2/T3	cN0	M0
IIC	T4	N0	M0
IIIA	Any T	N1a	M0
IIIB	Any T	N1b/N2	M0
IV	Any T	Any N	M1

[a]"N0" denotes negative nodes by clinical, pathologic, or both types of exam. Clinical detection of nodal disease may be via inspection, palpation, and/or imaging; cN0 is used only for patients who did not undergo pathologic node staging

[b]Micrometastases are diagnosed after sentinel or elective lymphadenectomy

[c]Macrometastases are defined as clinically detectable nodal metastases confirmed pathologically by biopsy or therapeutic lymphadenectomy

[d]In-transit metastasis is a tumor distinct from the primary lesion and located either (1) between the primary lesion and the draining regional lymph nodes or (2) distal to the primary lesion

[e]Because there are no data to suggest a significant effect of M categories on survival in MCC, M1a-c are included in the same stage grouping

tumor (T), lymph nodes (N), and metastases (M), is based on prognostic analysis of 5,823 MCC cases from the National Cancer Data Base (Lemos et al. 2010). Both primary tumor site and pathological nodal status are now incorporated in staging and prognosis of MCC patients (Lemos et al. 2010).

Management

A multidisciplinary approach is often necessary for the treatment of MCC and may include radiological imaging, surgery, radiation therapy, and chemotherapy. The use of radiographic imaging such as magnetic resonance imaging (MRI), CT scan, and PET scan may be indicated for staging patients. PET scan has been shown to be more sensitive and as specific as CT scan for nodal evaluation. In a retrospective study PET/CT resulted in an increase in stage in 16 % of cases at baseline and identified metastatic disease (bone–bone marrow) better than CT at follow-up (Hawryluk et al. 2012).

Treatment of the primary tumor is surgical, with either wide local excision or Mohs micrographic surgery (MMS). Wide local excision with 1–2 cm margins to investing fascia of muscle or pericranium is generally needed. MMS has been shown to be effective in achieving tumor-free margin control and may be especially useful where tissue sparing is critical (Izikson and Zeitouni 2011).

At presentation, 27–30 % of patients will have clinical positive nodal disease (Lemos et al. 2010). Management of regional disease includes lymph node dissection, and/or radiation therapy and possible chemotherapy. Patients with clinically negative nodes can be offered sentinel lymph node biopsy (SLNB), elective lymph node dissection, radiotherapy, or observation. The rate of positive SLNB is between 19 and 38 % (Fields et al. 2011a) and is recommended for most Stage I patients. Routine use of immunohistochemistry on SLN is highly suggested in order to more accurately identify micrometastases. SLNB has been shown important for staging, prognosis and for determining therapy; however, its impact on recurrence or survival remains unknown.

MCC is a radiosensitive tumor with both adjuvant or definite radiation therapy (RT) playing a role in its management. Numerous studies, mostly retrospective, have investigated the use of adjuvant radiation therapy and have found that it may improve locoregional disease (Rush et al. 2011). It has an unclear effect on distant recurrences or disease-specific survival. There are few studies assessing the use of RT alone for microscopic disease found on SLNB, but it appears that RT may offer similar local control as compared to complete lymph dissection (Fields et al. 2011a). Definitive radiation therapy has been shown to achieve good in-field control rates and can be offered to patients with inoperable disease or used in selected cases of residual disease post-surgery (Rush et al. 2011).

Systemic chemotherapy is recommended for patients with distant metastatic disease either at presentation (7 %) or at relapse time following therapy. No standard chemotherapy regimen has been established for treating metastatic MCC but generally platinum-based combination therapy or etoposide has been used. Chemotherapy may carry substantial toxicity risk. Overall, two-thirds of patients may respond to chemotherapy, but response rates are short and recurrences are quite frequent. Chemotherapy has not been shown to increase survival (Izikson and Zeitouni 2011; Qian Zhan et al. 2009). Due to its similarities to small cell lung carcinoma, the same chemotherapy regimens are used for MCC, including antimetabolites, bleomycin, cyclophosphamide, anthracyclines, and platinum derivatives (Izikson and Zeitouni 2011; Qian Zhan et al. 2009).

Chemotherapy can be used for locally advanced disease and recurrence, as well as for therapy of *in-transit* metastases with isolated limb perfusion or limb infusion methods (Zeitouni et al. 2011). *In-transit* metastases refer to metastases located in subcutaneous or intradermal tissue and deep lymphatics, manifesting as multiple subcutaneous nodules. *In-transit* metastases usually occur after surgical resection of the primary tumor. Isolated limb perfusion or infusion allows for high dose chemotherapy, such as melphalan, to be administered to an extremity while reducing systemic toxicities (Zeitouni et al. 2011). By isolating the extremity, the dosage of chemotherapy may be increased leading to more effective tumor targeting, and may prevent amputation (Zeitouni et al. 2011).

In HIV patients, studies on the effect of antiretroviral therapy on MCC progression are lacking. Because of the association of MCC with immunosuppression, it is possible that initiation or adjustment of antiviral therapy could be beneficial in selected patients, although it is not clear that it would be effective once the tumor has developed (Wieland et al. 2011). Reducing iatrogenic immunosuppression should be attempted when clinically feasible.

In summary, the recommended treatment of MCC:

- Surgical resection with either wide local excision with 1–2 cm margins or MMS of the primary tumor.
- Consideration of sentinel lymph node biopsy for patients with clinically negative nodal disease. Regional lymph node dissection and/or radiation therapy for those with positive nodal disease.
- Adjuvant radiation therapy for local or regional control in lymph node-positive cases, locally advanced disease, or local recurrence following surgery.
- Definitive radiation therapy for inoperable cases.
- Consideration of systemic chemotherapy for selected locally advanced disease, recurrence, and distant metastases.
- Consideration of antiretroviral therapy in HIV patients.
- Consideration of decreasing iatrogenic immunosuppression.

Prognosis

MCC is associated with both a high morbidity and mortality rate. Following initial therapy, patients may develop local recurrence (25–30 %), regional disease (52–59 %), or distant metastatic disease (30–36 %). The median time to recurrence is about 8 months, with 90 % of recurrences developing within 2–3 years of diagnosis. Lemos et al. found a 5-year overall survival of 40 % and relative survival of 54 % (Lemos et al. 2010). According to the new staging system, primary tumor size ($\leq$ 2, >2 cm) and pathological nodal status both affect prognosis (Lemos et al. 2010). Estimation of 5-year survival varies from 18 to 64 % depending on stage of disease. Immunosuppressed patients have a poorer MCC specific survival (Paulson et al. 2013).

In a recent study, microscopic nodal status was not associated with recurrence or survival; rather clinically positive nodes increased the risk of death, and lymphovascular

invasion was strongly associated with disease-specific mortality (Fields et al. 2011b). Patients with occult primary tumor (Stage IIIB) appear to have a more favorable outcome than patients with known primary of similar stage (Lemos et al. 2010). In one study, there was no correlation between Breslow thickness of the primary biopsied MCC and clinical stage of disease or survival (Izikson et al. 2012), while another study found that increasing tumor thickness was associated with poor disease survival (Lim et al. 2012).

Tumors on the lip carry a worse prognosis, and location may be an independent prognostic factor in head and neck MCC. In regard to HIV patients with MCC, the average survival after MCC diagnosis in a recent study was 18 months (Izikson et al. 2011).

Follow-Up

Patients should be monitored closely with full skin exams and lymph node evaluation every 1–3 months for the first year, then every 3–6 months for the second year, then followed on a yearly basis. Patients should also be encouraged to perform monthly complete skin exams. Imaging with PET/CT may be valuable as a restaging tool.

Key Points for persons MCC and HIV

- MCC is more commonly seen on non-sun-exposed areas compared to immunocompetent patients.
- Increased risk of development of MCC in HIV patients when compared to immunocompetent population
- Age of diagnosis approximately 20 years earlier; average age of 49 years compared to 69 years for immunocompetent
- Average length of time between diagnosis of HIV and development of MCC: 9.5 years
- No clear relationship between CD4 count and MCC development and/or survival rates established.
- Need for aggressive management, possible antiretroviral therapy.
- Survival rates decreased when compared to immunocompetent patients.

24.2 Kaposi Sarcoma (KS) (See Separate Section on Kaposi Sarcoma)

Kaposi sarcoma was the most common skin cancer seen in HIV-infected patients during the first years of the AIDS epidemic. With the introduction of HAART, the incidence of KS has greatly decreased but there is still a substantially increased risk (OR 21.58) (Lanoy et al. 2009). In the USA, it is still the second most common tumor in HIV-infected patients after lymphoma. Its incidence varies considerably in

different regions, and in some countries in Africa, it is the most common tumor overall. Please see the sections on Kaposi sarcoma and Kaposi sarcoma-associated herpes virus (KSHV) for more information about this tumor (Crum-Cianflone et al. 2009; Jessop 2006).

24.3 Squamous and Basal Cell Carcinomas

Squamous cell carcinoma (SCC) is a type of skin cancer derived from the squamous epithelial cell of the epidermis, whereas basal cell carcinoma (BCC) is derived from the basal cell layer of the epidermis. They are the most common types of skin cancer; with approximately three million cases of BCC and 700,000 cases of SCC diagnosed yearly (Skin Cancer Foundation 2012). While they are both associated with chronic actinic damage, SCC also can be associated with the human papilloma virus (see HPV). The rate of development of non-melanoma skin cancers in the HIV population is about 3–5 times that of the general population (Rieger et al. 2008). Further, they tend to develop at a younger age in the HIV population and are less frequently located on sun protective areas when compared to the general population. In the HIV population, SCCs tend to be more aggressive in terms of recurrence and risk of metastases whereas BCCs have not been shown to behave differently when compared to the general population (Rieger et al. 2008). Lastly, due to the increased incidence of high-risk HPV in the HIV population, SCCs in the anogenital, mucosal, digital areas are more prevalent.

Clinically, SCC appears as erythematous keratotic papules or plaques which may be eroded. They are most commonly seen on the sun-exposed areas including head, neck, dorsal arms, and upper chest in the immunocompetent population. They are associated with chronic daily sun exposure. BCCs are described as pearly papules or nodules with telangiectasias on sun-exposed areas. They are associated with intermittent sunburns and sun exposure. Histopathology can confirm the suspected clinical diagnosis of BCC/SCC. Treatment approaches for these carcinomas include surgical excision, MMS, topical immunomodulators, cryotherapy, electrical dissection and curettage, photodynamic therapy, chemotherapy, and radiation therapy.

24.4 Lymphomas (See Other Sections on Lymphomas)

Non-Hodgkin B-cell lymphoma (NHL) is more prevalent in the HIV population (OR 2.41), particularly in patients with <200 CD4 cells/mm^3 (Fields et al. 2011b; Rieger et al. 2008) and is considered an AIDS-defining illness (Silverberg et al. 2011). Cutaneous T-cell lymphoma (CTCL) and Sezary syndrome may also be increased in the HIV population. Various forms of B-cell NHL may involve the skin. Clinically, cutaneous NHL often presents as erythematous, indurated nodules that may ulcerate. A high percentage of cases of B-cell NHL are associated with an Epstein–Barr virus, especially in HIV individuals; the percentage involvement varies among different forms of lymphoma (Rieger et al. 2008). CTCL presents as

erythematous scaly plaques in sun-protected areas. However, in HIV, these plaques may be seen in atypical locations and present at an earlier age of onset compared to the general population (Rieger et al. 2008). The incidence of B-cell NHL has decreased in HIV patients since the advent of HAART therapy.

24.5 Melanoma

Melanoma is an aggressive malignant tumor of melanocytes. There are approximately 120,000–150,000 new cases diagnosed worldwide annually (Skin Cancer Foundation 2012). Clinically, melanoma presents as an irregular dark brown to black macule, papule, plaque, or nodule. However, melanoma may also present as a red or skin colored tumor. It most commonly appears on the back of men and the lower extremities of women, but may present anywhere where there are melanocytes including mucosal surfaces and nail beds. When diagnosed early, melanoma is curable. Invasive disease may require surgery, sentinel lymph node biopsy, lymph node dissection, radiation, or chemotherapy. Some epidemiologic studies have found an increased incidence of melanoma in HIV-infected patients, while other studies have not found an increase (Lanoy et al. 2009). However, melanoma has found to be more aggressive in this population, presumably due to the immunosuppression. The disease-free and overall survival rate of HIV persons with melanoma is decreased (Silverberg et al. 2011; Rodrigues et al. 2002).

24.6 Conclusion

Patients with HIV are at a high risk for developing a number of cutaneous carcinomas such as MCC, Kaposi's sarcoma, lymphoma, BCC, and SCC; melanoma is elevated in some but not other studies. All these tumors may also be more aggressive in HIV-infected patients necessitating timely diagnosis. HIV patients should have regular full body skin exams in order to assess, promptly diagnosis, and treat any skin cancers.

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Chapter 25
Conjunctival Carcinoma

Kenneth O. Simbiri and Erle S. Robertson

Abstract Conjunctival carcinoma encompasses several eye neoplasms that include squamous cell carcinoma (SCC) and malignant melanoma. In both cases the patients tend to be older males, often with a significant history of chronic sun exposure. Ocular surface squamous neoplasia (OSSN) is a term used to describe conjunctival or corneal neoplastic growth; it encompasses a range of conditions from simple dysplasia to conjunctival intraepithelial neoplasia (CIN) and invasive SCC. There is evidence that conjunctival squamous cell carcinoma (CSCC) is becoming more common, more aggressive, and affecting more young people, especially women. Immunocompromised patients, including those infected with HIV, are predisposed to developing these neoplasms. There is mounting evidence that one or more infectious agents, especially types of human papillomavirus, may be involved in the pathogenesis of CSCC, but there is still some uncertainty about the etiologic role of these agents and additional research is needed.

25.1 Introduction

Squamous cell carcinoma (SCC) is among the most common neoplasm of the conjunctiva (Kestelyn et al. 1990). The etiology of cancer of the conjunctiva appears to be multifactorial. Several risk factors have been identified or suggested, such as smoke, human immunodeficiency virus (HIV) infection, ultraviolet (UV) light, history of pterygium, and human papillomavirus infection (HPV) (Newton et al. 1996). It is most often seen in sub-Saharan Africa and other regions with a high prevalence of HIV and intense sunlight. HPV has been proposed as an etiologic agent, but its role remains uncertain.

K.O. Simbiri • E.S. Robertson (✉)
Department of Microbiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA
e-mail: simbirik@upstate.edu; erle@mail.med.upenn.edu

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While there has been considerable interest in HPV as a cause of conjunctival squamous cell carcinoma (CSCC), the heterogeneous prevalence of high-risk HPV types in different studies suggest that only a subset of cases of CSCC can be attributed to these viruses (McDonnell et al. 1986). Differences in detection methods, populations, or geographic distribution could contribute to the variation in HPV infection rates in CSCC (McDonnell et al. 1986). HPV is considered the main etiologic agent in proliferative ocular surface, lachrymal sac lesions, and pterygium worldwide, and it has been suggested that HPV types 16 and 18 may play a critical role in the oncogenesis of conjunctival cancers (Hirst et al. 2009; Palazzi et al. 2000). HPV are a group of host-specific DNA viruses with oncogenic subtypes that have also been shown to act as carcinogenic agents in the development of cervical cancer, anal carcinoma, penile carcinoma, and oropharyngeal carcinoma (Hirst et al. 2009; Simbiri et al. 2010). The E6 oncoprotein, encoded by HPV16 or HPV18, is known to interact with the well-known tumor suppressor p53 to promote its degradation, while the E7 oncoprotein interacts with the retinoblastoma protein (pRB) and results in E7-induced pRB inactivation. The E5 virus protein cooperates with E7 to transform cells and enhances the ability of E7 to induce proliferation, and with E6, to immortalize cells (Helt and Galloway 2003; Scott et al. 2002; Song et al. 1998; Peralta-Zaragoza et al. 2006).

25.2 Clinical Presentation of CSCC and Related Conditions

Ocular surface squamous neoplasia (OSSN) is term used to describe a conjunctival or corneal neoplastic growth; this term encompasses a spectrum of conditions, ranging from simple dysplasia to conjunctival intraepithelial neoplasia (CIN), to invasive CSCC (Simbiri et al. 2010). CSCC is typically a "low-grade" malignancy with relatively little potential for invasion and metastasis (Chisi et al. 2006). Given its location on the eye, it can cause substantial morbidity, patient distress, and disability even when small. Also, similar to cancer of the uterine cervix, CSSC has a high rate of recurrence after treatment and may in some cases metastasize. Moreover, CSCC often shows rapid onset and progression, and in the early stages, a mild dysplasia, often resembling a pinguecula, pterygium or even a phlyctenule, may occur. Progressive growth of the lesion results in an elevated, fleshy mass of pink tissue that develops in the interpalpebral space. These irregularly shaped neoplasms develop a rich intrinsic blood supply from the surrounding conjunctiva and episclera, with large-diameter "feeder vessels" emanating from the mass. Thus conjunctival neoplasms may initially pose cosmetic concern for patients on routine ocular examination. Larger lesions may interfere with lid function, causing dry eye complaints and possibly dellen formation on the adjacent cornea. Advanced, invasive lesions may compromise the episclera, sclera, cornea, or angle structures. Pain may be a significant factor in later stages due to associated keratitis, uveitis, or rise in intraocular pressure. A representative HIV-1-infected OSSN patient from Botswana with OSSN is shown in Fig. 25.1.

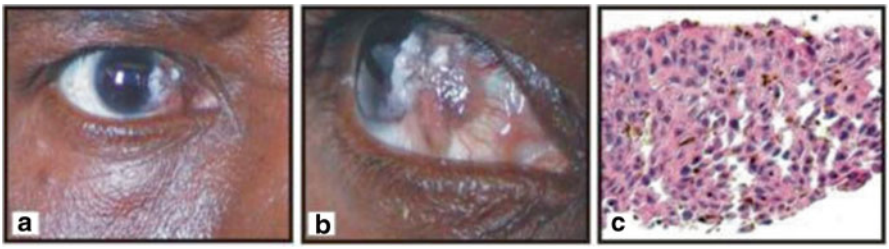

Fig. 25.1 Representative patient with OSSN (**a**) and a closer lateral view (**b**). (**c**) H&E staining showing features of in situ carcinoma characterized by full thickness changes in nuclear: cytoplasm ratio, nuclear pleomorphism, dyskeratotic cells, and presence of koilocytes Simbiri et al. (2010)

25.3 Other Conjunctival Tumors

Melanomas can develop in the conjunctivae, although these tumors are relatively rare. The lesions may present as flat or nodular pigmented area, although amelanotic conjunctival melanomas have been documented. Like SCC, they typically develop at the limbal margin. As with the carcinomas, vascularization takes place, with numerous feeder vessels supplying the lesion. Unlike carcinomas, however, conjunctival melanomas tend to become multicentric if not promptly diagnosed and managed. Melanomas tend to progress more rapidly, and are more invasive into underlying ocular tissues. Hence it is not uncommon to see associated uveitis or secondary glaucoma if the lesion invades the anterior chamber.

Prior to the AIDS epidemic, ocular involvement of Kaposi sarcoma (KS) was an extremely rare phenomenon, with fewer than 30 cases reported before 1982. However, KS is one of the most common AIDS-related tumors, and up to one in five patients with AIDS-related KS may have some form of ocular involvement (conjunctiva, eye lids, or orbit) (Grulich et al. 2001; Mikropoulos et al. 2011). Conjunctival Kaposi sarcoma has been reported as the initial sole manifestation of HIV infection in a number of reports.

Lymphoma can also involve the conjunctivae. In particular, mucosal-associated lymphoid tumor (MALT) can arise in the conjunctivae, appearing as a salmon-colored patch. This tumor is relatively benign and, like gastric MALT, has been hypothesized to be related to local infection with *Helicobacter pylori* (*H. pylori*).

25.4 Epidemiology of CSSC and Association with HIV Infection

The incidence of CSCC varies geographically (declining with greater distances from the equator), with Uganda having 1.2 cases per 100,000 persons per year, compared to the UK with fewer than 0.02 cases per 100,000 per year (Ateenyi-Agaba

1995). In the USA, it is a rare disorder, with an incidence of 0.03 per 100,000 persons per year. It has been noted that the relatively high incidence in Kampala, Uganda, is in part due to the high prevalence of HIV infection. Multiple case series have shown a higher prevalence in male patients and the elderly, with the most frequently reported location being the limbus (Ateenyi-Agaba 1995).

CSSC has for some time been suspected as having an infectious origin. One reason for this is the sharp increase in the incidence of CSCC among patients infected with HIV (Restelli et al. 2005; Chisi et al. 2006), as well as in patients with other forms of immunodeficiency, such as transplant recipients (Macarez et al. 1999; Shelil et al. 2003). CSCC has emerged as an HIV-associated cancer that is increasing in incidence in Uganda and other sub-Saharan African countries over the past two decades, and this increase has been particularly striking in the young and in women (Chisi et al. 2006; Porges and Groisman 2003). The striking association of CSCC with HIV infection and its geographic localization in certain regions of Africa, where there is a high prevalence of several oncogenic viruses, are consistent with, although not proof of, an infectious etiology.

Prior to the HIV pandemic, OSSN was noted to occur predominantly in the elderly, for whom it is the third most common oculo-orbital neoplastic condition after melanoma and lymphoma. In addition to advanced age and male sex preponderance, other risk factors linked to its pathogenesis have included ultraviolet light B, immunosuppression in organ transplant recipients, cigarette smoking, and in some settings HPV (Simbiri et al. 2010). In Africa it is becoming more common, more aggressive, and more likely to affect young people, especially females. Africa also has a high prevalence of HPV infection with prevalence of about 25 % in women of age 15–74 years. OSSN is currently the most common ocular neoplastic condition overall among adults in Africa. Findings demonstrated a strong association between OSSN and HIV-1 infection applying to all tumor stages. In a study in Uganda, HIV-positive participants were often markedly immunosuppressed at the time of diagnosis and their early mortality was high. Almost all of the tumors were in the interpalpebral area of the conjunctiva, which supports the concept of UV radiation as a co-factor in the etiology of OSSN (Simbiri et al. 2010). In a high percentage of HIV-infected patients presenting with OSSN, the conjunctival tumor was the first sign of HIV and, in the majority of cases, OSSN was also the only detectable manifestation of HIV (Spitzer et al. 2008).

The increasing incidence and prevalence of OSSN and its association with the HIV pandemic has been described in many sub-Saharan African countries. The role of HIV pathogenesis in CSCC is hypothesized to be through immunosuppression, which then permits activation of oncogenic viruses such as HPV and other herpesviruses, as well as the growth of other infectious pathogens in the conjunctiva (Simbiri and Robertson 2012). Moore and colleagues using a digital transcriptome subtraction (DTS) method did not detect viral sequences from three conjunctival carcinoma tissues from Uganda (Feng et al. 2007). As noted, CSCC is also on the rise in developing nations, particularly in sub-Saharan Africa. The increased use of highly active antiretroviral therapy (HAART) in some of the sub-Saharan countries is beginning to show some impact on the risk of HIV-associated tumors, as has been seen in developed countries, although data are scanty at this time. It is hoped that

these HIV therapies will also lower the rates of conjunctival cancers, although it is also possible that rates will increase as patients live longer with HIV infection (Spitzer et al. 2008).

25.5 Pathogenesis and Possible Role of Infectious Agents

It has been established that infectious agents play an important role in the etiology of certain human malignancies, and are thought to be responsible for around 18 % of the worldwide cancer burden (less than 10 % in developed nations and up to 27 % in developing nations). Much of the burden of cancer incidence, morbidity, and mortality occurs in the developing world, with infectious agents attributing to most malignancies of the cervix and vulva (HPV), stomach (*H. pylori*) (Fox et al. 2000; Ferreri et al. 2006a), and liver (hepatitis B and C viruses) (Ferreri et al. 2006c). Other important tumors caused by infectious agents include Kaposi sarcoma (Kaposi-sarcoma-associated herpesvirus, also called human herpesvirus-8 [KSHV/HHV-8]), and most types of non-Hodgkin lymphoma (Epstein Barr virus and for certain types also KSHV/HHV-8).

Infectious agents display diverse geographic variation in their prevalence and patterns of disease, including oncogenesis. There is evidence that several microorganisms may play a role in different conjunctival malignancies, including HPV in conjunctival papilloma and CSCC; HIV in CSCC and Kaposi sarcoma; KSHV/HHV-8 in conjunctival Kaposi sarcoma; and *H. pylori*, *Chlamydia*, and hepatitis C virus (HCV) in ocular adnexal mucosa-associated lymphoid tissue (MALT) lymphomas. Unlike cervical cancer, where a predominantly single infectious agent, HPV was found in greater than 99 % of lesions, multiple organisms may play a role in the etiology of certain ocular neoplasms by acting through various mechanisms of oncogenesis, including chronic antigenic stimulation and the expression of oncoproteins by the infectious agents. Similar to a number of other human malignancies, the role of infectious agents in conjunctival carcinomas is most likely a co-factor to genetic and environmental risk factors (Mikropoulos et al. 2011).

Oncogenes are genes that have the potential to cause cancer through mechanisms including disruption of cell cycle mechanisms or interference with apoptosis. They can either develop from a mutated or dysregulated cellular gene, called a proto-oncogene, or can be encoded by infectious agents. High-risk variants HPV 16 and HPV 18 may drive carcinogenesis by inactivating tumor suppressor gene products p53 and pRb. HPV-E6 and the E7 oncoproteins also increase transforming growth factor beta (TGF-β) promoter activity (Peralta-Zaragoza et al. 2006). Notably, TGF-β controls proliferation, differentiation, and other functions in most cell types. Compared to the high-risk HPV type 16 and type 18, the E6 and E7 oncoproteins of HPV type 6 are seemingly less effective at transforming epithelial cells in vitro (Halbert et al. 1992). This finding correlates with the fact that HPV types 6 and 11 are most frequently associated with the benign conjunctival papilloma, whereas the high-risk HPV types 16 and 18 are most frequently associated with CIN and CSCC (Song et al. 1998).

An additional mechanism whereby infectious agents may be involved in the etiology of conjunctival or other systemic neoplasms is by inducing a state of chronic antigenic stimulation. A systemic example is illustrated by the linkage between infection with *H. pylori* and chronic atrophic gastritis, an inflammatory precursor of gastric adenocarcinoma (Mikropoulos et al. 2011). Also, regression of gastric MALT after eradication of *H. pylori* infection with antibiotics is consistent with this hypothesis (Mikropoulos et al. 2011). Similar regression of disease has been reported in ocular adnexal MALT lymphoma after treatment with antibiotics against *Chlamydophila psittaci* (Ferreri et al. 2004).

H. pylori is a spiral-shaped Gram-negative bacteria that infects a large proportion of the population worldwide (Mikropoulos et al. 2011). In developing countries up to 70–90 % of the population is infected (primarily during childhood), whereas in developed countries the prevalence of infection is lower, at 25–50 % (Mikropoulos et al. 2011). In most cases the organism causes no symptoms in the host, yet it has been recognized as the cause of duodenal ulcers and gastric adenocarcinoma, and can be found in greater than 90 % of gastric mucosa-associated lymphoid tissue (MALT) lymphomas. *H. pylori* has also been identified in conjunctival carcinoma tissues (Ferreri et al. 2004). *H. pylori* evades host adaptive and innate responses by frequent antigenic variation, and host antigen mimicry. Even so, the host immune and inflammatory responses to *H. pylori* can increase cellular damage and turnover, thereby promoting carcinogenesis. Whereas eradication of *H. pylori* leads to regression of early gastric MALT lymphoma in up to 80 % of cases, its eradication has not been reported to have a similar effect on conjunctival MALT lymphoma lesions. The only study assessing treatment against this organism on ocular lesions was conducted by Ferreri et al. in Italy to assess rates of *H. pylori* gastric infection in patients with ocular adnexal lymphoma (Ferreri et al. 2006b). Of note, the study did not in fact examine *H. pylori* or its DNA in conjunctival MALT lymphoma lesions. Out of the 31 patients with ocular adnexal MALT lymphoma, 10 (32 %) had gastric H. pylori, and 4 were treated solely with *H. pylori* eradicating antibiotics (erythromycin 500 mg twice a day, omeprazole 20 mg twice a day, and tinidazole 500 mg twice a day, for 7 days) (Ferreri et al. 2006b). The ocular adnexal MALT lymphoma in these patients showed no response. Six additional patients received *H. pylori* eradicating antibiotics concurrently with other therapies (doxycycline, rituximab, or orbit irradiation) achieving lymphoma regression in all cases. Interestingly, three of the patients who were positive for gastric *H. pylori* infection had *C. psittaci*-positive conjunctival MALT lymphomas. Treatment with *H. pylori* eradicating antibiotics led to no measurable conjunctival lymphoma regression in these three patients (Ferreri et al. 2006b). Although this may raise doubts about the putative role of *H. pylori* in sustaining the growth of this MALT lymphoma, it may also simply highlight the sensitivity of organisms to the specific antibiotics used. Furthermore, clearance of gastric *H. pylori* may not amount to clearance of conjunctival *H. pylori*, and it is also that previous infection with *H. pylori* may have lingering effects promoting MALT lymphoma of the conjunctiva. Other pathogens that may contribute to various conjunctival tumors include Chlamydia and HCV. HCV is a major etiologic agent of hepatocellular carcinoma, but has also been linked to B cell lymphomas.

It is possible that different infectious agents in different geographical locations contribute to oncogenesis, with host genetic make-up also playing a role.

Of interest, an increase in OSSN has been observed in the genetic disease Xeroderma pigmentosum (XP). OSSN occurs predominantly in the elderly, but in patients of XP, as in patients with HIV infection, it tends to occur at a younger age (6–22 years) (Gupta et al. 2011). OSSN appears to be more aggressive than usual in patients with XP (recurrence rate 64.3 %). Patients with XP are unable to repair the DNA that is damaged by ultraviolet rays. This can lead to somatic mutations and the resulting development of oncogenic cells and cancer. This inherent defect accounts for the increased susceptibility to OSSN and the younger age at presentation (Gupta et al. 2011). Some reports have noted a younger age in intraepithelial cases compared with invasive SCC (Palazzi et al. 2000). Bilateral involvement is encountered very frequently in patients of XP (Gupta et al. 2011).

In patients with XP, simple excision of conjunctival intraepithelial or invasive neoplasia was reported to be associated with a 24–50 % recurrence rate (Gupta et al. 2011). Excision with intraoperative control of the surgical margins and adjunctive cryotherapy has been reported to reduce recurrence rates to 12 % (Song et al. 1998; Peralta-Zaragoza et al. 2006). A high overall recurrence rate of 64.3 % has been observed; the rate of new or recurrent tumors was 25 % for intraepithelial squamous carcinoma and 83 % for invasive SCC. Up to four recurrences were noted in a single patient. There is increased tendency of XP patients with OSSN to develop fresh or recurrent lesions. A majority of these patients develop recurrence of the tumor despite a meticulous tumor excision and adjunctive cryotherapy (Gupta et al. 2011).

25.6 Prevention and Treatment

While there is evidence that infectious agents may play a role in CSCC, the use of anti-infectious approaches to prevent or treat this condition has not been extensively studied. An effective vaccine for HPV has now been approved, and it will be interesting to see if the use of this vaccine is associated with a decrease in CSCC; if so, this would support an important role for HPV (Spitzer et al. 2008).

Immunomodulatory agents such as topical interferon alpha and the gastric-acid inhibitor oral cimetidine have led to conjunctival papilloma regression. In addition to its apoptotic effect on tumor cells, interferon alpha exerts its antiviral action by preventing the replication of latent virus in the tissues. While there is evidence that HPV plays some role in a subset of conjunctival papillomas, host immune status likely plays a role in pathogenesis and will likely affect the response to treatment (Manns et al. 2001; Midena et al. 2000; Morgenstern et al. 2003).

Even though conjunctival papilloma may persist for extended periods of time, with reported recurrence rates of 6–27 %, spontaneous regression can be seen. Also, cure is possible with current therapies. In cases where large lesions cause symptoms or cosmetic defects, and periodic observation would be futile, surgery remains the treatment of choice with double freeze-thaw cryotherapy to the remaining conjunctiva to

prevent tumor recurrence. Additionally, topical interferon alpha-2b and mitomycin C have been employed in the treatment of recurrent conjunctival papillomas (Manns et al. 2001; Morgenstern et al. 2003).

A high recurrence rate of CSCC has been seen even after cryotherapy, radiation, and chemotherapeutics. Several treatments have been utilized in an attempt to reduce recurrence rates, including topical mitomycin C, 5-fluorouracil, and interferon alpha (Manns et al. 2001; Morgenstern et al. 2003). There is a need for improved therapies, especially those that can be utilized in resource-limited regions.

25.7 Conclusions

CSCC and its precursor lesions are most commonly seen in regions with high sunlight exposure, and their increased incidence with HIV infection suggests an infectious etiology. It is relatively uncommon in the USA and Europe, and substantially more common in sub-Saharan Africa, especially in regions near the Equator. There is some evidence that certain types of HPV may be involved in the pathogenesis of these tumors, but the evidence is not as robust as for other infection-associated tumors, and more research is needed.

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Chapter 26
Malignancies in Children with HIV Infection

D. Cristina Stefan

Abstract About 2 % of children with HIV will develop a cancer as their AIDS-defining disease; this rate is enormous when compared with the incidence of malignant disease in the general pediatric population of around 0.013 %. In the United States and Europe, non-Hodgkin lymphoma (NHL) is the most frequently encountered cancer in children with AIDS. In Sub-Saharan Africa, however, the most frequently encountered malignancy in children with HIV is Kaposi sarcoma (KS). Both NHL and KS are the result of viral infections, with human herpes virus 8 (HHV-8) and Epstein–Barr virus (EBV) respectively. HIV amplifies the oncogenetic effect of these viruses in a number of ways. This results not only in an increase in incidence of the respective cancers, but also in a more rapid progression. HIV-induced immunodeficiency predisposes children to developing progressive neutropenia during chemotherapy; antiretroviral medication can reduce this effect but raises difficulties associated with complex drug interactions. Tuberculosis and malnutrition, which are frequently encountered in the low-income countries where most of the children with HIV live, add further challenges to the management of cancer.

26.1 Changes in the Incidence of Childhood Cancers Associated with the HIV Epidemic

In the adult population subgroup infected with HIV, the lifetime incidence of cancer has been found to be as high as 40 % (Flint et al. 2009). Certain tumors, such as Kaposi sarcoma (KS), or non-Hodgkin lymphomas (NHLs) are much more frequently encountered in the adult HIV-positive population subgroup, and for this

D.C. Stefan, M.D., Ph.D. (✉)
Department of Paediatrics and Child Health, Tygerberg Hospital, Stellenbosch University, Cape Town 7550, South Africa
e-mail: cs@sun.ac.za

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reason have been identified as AIDS-defining cancers. Invasive cervical cancer is also an AIDS-defining tumor. However, besides these three, numerous other non-AIDS defining malignancies are found more frequently in HIV-infected adults: the list includes Hodgkin lymphoma, anal cancer, lung cancer, liver cancer, non-melanocytic skin cancer, myeloma, leukemia and conjunctival tumors (Engels et al. 2008).

Similarly, the HIV epidemic in children (0–14 years) was associated with an increase in the incidence of certain cancers, especially NHL, soft tissue tumors, cancer of the uterine cervix in adolescent girls, as well as thyroid and pulmonary neoplasms. It is estimated that about 2 % of children with HIV will develop a cancer as their AIDS-defining disease, as compared to an incidence of malignant disease in the general pediatric population of around 0.013 % (Mueller 1999). The highest incidence increase with AIDS in the United States and Europe was observed for NHL, followed by leiomyomas and leiomyosarcomas, associated with Epstein–Barr virus (EBV) infection. The incidence increase of KS in children was modest, in these regions, by comparison with its increase in adults living with HIV. In Sub-Saharan Africa, however, the most frequently encountered malignancy in children with HIV is KS, as will be shown below.

With the development of tests to screen blood products for HIV and the use of antiviral drugs to prevent materno-fetal transmission during birth, the incidence of HIV infection in children has fallen dramatically in the United States and Europe, and it is now very unusual to see HIV-associated tumors in children. By contrast, the prevalence of HIV infection remains high in Africa and other resource-limited regions, and HIV-associated malignancies are an important clinical problem. In African children, the incidence of Kaposi sarcoma and, to a lesser extent, that of Burkitt lymphoma (BL), soared in children, after the onset of the AIDS epidemic (Ziegler and Katongole-Mbidde 1996; Newton et al. 2001). This has been attributed to the fact that in Central Africa, as far as Cameroun in the west and Malawi in the south, KS was already endemic, with incidence rates greater than 6/1,000, before the advent of AIDS. At the same time, high rates of BL of 4–5/1,000 existed in parts of Uganda and Tanzania before the AIDS epidemic; in other parts of Central Africa the rates were lower: 0.2/1,000 in males and 0.04/1,000 in females (Cook-Mozaffari et al. 1998). Even the smaller rates of BL appear huge when compared with European standardized incidence rates, which, during the AIDS epidemic, did not rise over 3.94/million (Marcos-Gragera et al. 2010). The way in which the AIDS epidemic exacerbated the endemic rates of these cancers will be discussed in the next section.

There are no epidemiologic data on HIV-associated tumors for the whole African continent and in fact, collecting more complete and accurate epidemiologic data would help substantially by informing further research which could lead to clinical advances in this area. This said, statistics that are available from various countries exemplify the changes in the incidence of cancers in HIV-positive children. In Uganda it was found that the probability of acquiring KS was 95 times higher in children with HIV while the probability of developing BL was 7.5 times higher, but no increase in risk was seen for other cancers (Newton et al. 2001). In Zambia,

beside the clear increase in the incidence of KS, several other cancers were noted more frequently after the onset of the AIDS epidemic: NHL, nasopharyngeal carcinoma, rhabdomyosarcoma and retinoblastoma (Chintu et al. 1995). In South Africa the probability of developing BL was found to be over 46 times higher in children living with HIV than in the general pediatric population (Stefan et al. 2011).

26.2 Oncogenesis in HIV Infection

The list of malignancies that appear more frequently in people infected with HIV is extensive. However, only a few cancers are highly prevalent in this population group: KS, NHL and invasive cancer of the uterine cervix. They are considered to be AIDS-defining conditions, together with infections like tuberculosis, candidiasis, *Pneumocystis jiroveci* pneumonia and others. It is significant that with the exception of a large subset of NHL, the above cancers are also, almost always, caused by infections. KS is the result of infection with human herpesvirus 8 (HHV-8) also known as KS herpes virus (KSHV). Burkitt's lymphoma and other AIDS-associated lymphomas (primary central nervous system lymphomas, diffuse large cell lymphomas, Hodgkin lymphoma, primary effusion lymphomas) as well as leiomyomas and leiomyosarcomas are caused mainly by EBV. Cancer of the uterine cervix is caused by high-risk strains of human papilloma virus (HPV) (Flint et al. 2009).

Smooth muscle tumors—leiomyoma and leiomyosarcoma—are also encountered in children with HIV; in one study in the United States, they represented the second most common tumor (Mueller 1999). The presence of EBV, in latent form, in these tumors was signaled initially by McClain et al. (1995). Jenson et al. (1997) have observed a high presence of the virus in these neoplasms, averaging 4.5 viral genomes per cell. Additionally, the monoclonality of EBV within a given tumor is interpreted as evidence of the viral involvement in the oncogenetic process. It remains, however, unclear how the abnormal cell division is induced by EBV. It was suggested that certain viral proteins, which continue to be produced by the virus in its latent state, may interfere with the mTOR system, which regulates cell division (Purgina et al. 2011).

It is generally accepted that HIV does not have any intrinsic oncogenic activity, but instead promotes the oncogenesis induced by the viruses mentioned above. This effect is caused, on the one hand, by an inefficient immune surveillance against both oncogenic viral agents and the tumor cells they may produce. On the other hand, the HIV-associated chronic hyperactivity of the immune system mediated by cytokines, stimulates the immune cells' proliferation, which in turn enhances the replication of oncogenic viruses within those cells. Secondarily, the cytokines promote the growth of blood vessels in the tumor tissue. The inefficient immune surveillance may also explain why other cancers, not known to be associated with infectious agents, appear slightly more frequently in HIV-infected children (Flint et al. 2009).

26.3 The Influence of the HIV Infection on the Clinical Presentation of Malignancies in Children

The immunodeficiency in AIDS might result, in theory, in faster progression of the malignant disease. This could be expressed by more advanced or widespread cancers at the first presentation, a poorer response to treatment and a reduced survival rate. It is also possible that the symptoms and signs of the cancer would be altered by the immune suppression, as the immune response is often contributing to generating the signs and symptoms of a disease. There is a dearth of information in the literature on these aspects, due to the relative rarity of cancer in children coupled with a relative rarity of HIV in this age group in resource-rich regions, with the resulting difficulty of finding enough cases to comply with the power requirements of the studies. Africa offers a unique opportunity of comparing the clinical presentation of KS and BL, which remain endemic in HIV-negative children, alongside to the epidemic form, which is associated with AIDS.

With regard to KS, there is evidence pointing to a more disseminated disease at presentation in HIV-infected versus non-infected children, including more frequent visceral involvement. There is more frequent lymph node involvement than skin involvement by KS in children with HIV (Gantt et al. 2010). The epidemic has been associated with an increase of the incidence of KS in females, who are also comparatively more often infected with HIV at birth than males are.

In BL, the most frequent localization of the tumor is facial, irrespective of the HIV status (71.4 % in HIV-positive, 76.6 % in HIV-negative); however, children with retroviral infection have significantly more frequent liver and thoracic involvement, as well as lymphadenopathy. As a consequence, there are significantly more children presenting in advanced stage (stage D) in the HIV-positive subgroup compared with the HIV-negative (37.15 versus 20.3 %, respectively), with the corresponding effect on the survival rates (Orem et al. 2009).

In conclusion, KS and BL, whose endemic variants coexist, in Africa, with their epidemic variants associated with AIDS, offer an opportunity to assess the effect of HIV infection on the clinical manifestations and course of cancers. Retrospective studies of these two diseases, in children with and without HIV, point to a faster progression of the malignancies in the presence of immune deficiency, with more disseminated forms involving more often thoracic or abdominal organs. The consequence of this negative influence is a poorer prognosis.

The literature on smooth muscle tumors and HIV was reviewed by Purgina et al. (2011). Out of the 64 cases published worldwide, only 19 were under 10 years of age and a further 3 were aged between 10 and 20 years. They found that the most frequent localization (but without a breakdown on age groups) was the central nervous system, followed by the lung and gastrointestinal tract. Other sites involved were bones, serosa and genito-urinary tract. In one-third of cases the tumors were either multiple or recurrent. The clinical progression appeared to be slow, with most of the deaths reported being due to other causes than tumor growth or dissemination.

26.4 Particularities of the Management of Malignant Disease in Children with HIV and Cancer

While studies conducted in NHL before the development of the highly active antiretroviral therapy (HAART) suggested that AIDS-associated NHL was best treated with low-dose chemotherapy regimens (Kaplan et al. 1997), increasing evidence indicates that standard cytostatic or radiotherapy protocols should be preferred instead of low-dose protocols (Spina et al. 2011; Re et al. 2009; Galicier et al. 2007). Cancer chemotherapy is associated with a severe immune response depression due to myelotoxicity. In children with a healthy immune system, the leucopaenia induced by cytostatics is transient and will redress itself during the intervals between therapeutic doses. They are, however, susceptible to severe infections during the neutropenic spells. In contrast, prior to the development of HAART, children whose immunity was compromised by HIV would often not recover but would develop a progressive neutropaenia during the course of their treatment (Chanock and Pizzo 1995). They were thus even more prone to developing infection during cancer chemotherapy. The answer to this complication, however, does not consist in using a low-dose cytostatic protocol but rather in efficient infection prevention by controlling the child's environment, by applying strict hygiene measures and using well-planned prophylactic antibiotherapy, guided by the oncology unit's cumulative antibiogram and by the knowledge of the infectious agents that are usually being encountered in AIDS (Chanock and Pizzo 1995). Excessive neutropenia is presently less of a problem in patients who are receiving HAART, but can still pose difficulties in patients who have very low nadir CD4 counts.

There is evidence that peripheral stem cell transplantation, which assists with the reconstitution of the immune system, can be of use in the treatment of children with HIV-associated malignancies. Should a bone marrow transplant be indicated, the child may possibly benefit from receiving HIV-resistant (naturally resistant or genetically modified) bone marrow cells, in an attempt to cure the retroviral infection (Krishnan and Forman 2010). This is an area of ongoing research.

Most specialists with experience in the field now feel that radiotherapy should be given in standard doses (and not in reduced doses) irrespective of the HIV status of the patient. There is evidence that in HIV-positive children the toxicity of irradiation is higher, mainly for the mucosa of the digestive tract. Furthermore, radiotherapy was clearly shown to reduce the $CD4^+$ cell counts, both in HIV-negative and positive patients. This reduction is persistent over several years. There are no published data yet to document the extent of the potential increase in risk for opportunistic infections in HIV positive patients who receive irradiation. While there is no evidence to support the initiation of HAART at the onset of radiotherapy or before it in such cases, the use of prophylactic antibiotics is common (Housri et al. 2010).

Leiomyomas and leiomyosarcomas are most often treated by surgical resection. They are not sensitive to chemotherapy, but radiotherapy has been used in conjunction with surgery (Purgina et al. 2011).

There is convincing evidence that HAART has a beneficial role in the management of AIDS malignancies. Antiretroviral therapy reduces the HIV viral load and allows for restoration of the depleted $CD4^+$ lymphocytes and, consequently, the immunity of the patient improves. Kaposi sarcoma can undergo complete or partial remission after initiation of HAART even without other specific therapy. This has been best studied in adults but can also occur in children (Niehues et al. 1999), to the extent where it appears logical to consider HAART as a first line of treatment in childhood KS, while cytotoxic drugs constitute the second line or agents to be used in patients with extensive disease (Mosam et al. 2012; La Ferla et al. 2013). Caution should be used, however, in conducting antiretroviral therapy on patients with KS, as a substantial increase in the volume of the lesions may occur after a few weeks or months of treatment, due to the immune reconstitution inflammatory syndrome (IRIS). In this condition, the reconstitution of the $CD4^+$ cell number stimulates the immune system and leads to additional inflammatory reaction around the cancerous lesions. Depending on the localization of these lesions (for instance close to the airways), IRIS may be fatal; the addition of chemotherapy may control the process (Letang et al. 2013).

The effect of antiretroviral treatment in NHL, including BL, is not as well defined, but it is thought to be beneficial: HAART can potentially make patients better tolerate standard-dose chemotherapy and thus improve considerably the prognosis of the patients. An analysis of 87 patients treated for NHL in the same institution found that only 14.3 % of the subjects not receiving HAART achieved complete response to chemotherapy, compared with 57.6 % of those taking antiretrovirals ($p \leq 0.0001$). The mean survival time was similarly extended from 4.8 to 14 months respectively ($p = 0.01$) (Cornejo-Juárez et al. 2008). This was not, however, a randomized trial and it is possible that HAART administered prior to treatment also affected the type and extent of lymphoma over and above any effect seen during treatment.

While there is an increase of cervical intraepithelial lesions incidence in people infected with HIV, and while cervical cancer is an AIDS-defining disease, the evidence accumulated so far does not find a clear effect of HAART on the incidence of cervical pre-cancerous lesions or on the course of the cervical cancer once it develops, with or without treatment (Adler 2010). Also, HAART is not, by itself, effective treatment for non-AIDS-defining cancers. These appear in individuals who are infected with HIV but are not necessarily immunocompromised and may not have an indication for HAART. These cancers remain relatively rare in children, although their incidence increased slightly.

There are too few cases of use of HAART in smooth muscle tumors, but the data accumulated so far point to a stabilizing effect on the course of the malignancy (Purgina et al. 2011).

Finally, the use of HAART in conjunction with cancer chemotherapy calls for careful planning and close monitoring, due to possible drug interactions, as both cytotoxic agents and antivirals may be metabolized by the same hepatic enzymes (cytochrome P450 group), with consequent increase or decrease in the actions of some of the agents involved (Mounier et al. 2009). More research is needed to define such interactions.

Tuberculosis, malaria and malnutrition are frequently seen in children with malignancies and AIDS, especially in low-income countries. Irrespective of the potential influence of the HIV epidemic, studies have reported a high incidence of tuberculosis in children with cancer (Stefan et al. 2008). The association of tuberculosis, HIV and malignant tumors in children creates difficulties in diagnosis and impacts on the survival rate.

There is substantial evidence that the co-operation of malaria and EBV is important in the pathogenesis of BL; however, the mechanisms involved are still unclear. For instance, it has been shown that during malarial infection the replication of EBV is enhanced, and the treatment of malaria is significantly reducing the EBV viral load (Donati et al. 2006). It is hypothesized that HIV contributes to the pathogenesis by inducing immunodeficiency, but these interactions are incompletely understood at this time.

Malnutrition in children with cancer is frequently seen and not necessarily related to AIDS. During cytotoxic therapy, malnourished children have a higher rate of profound neutropaenia, resulting in a higher risk of severe infections and death (Israëls et al. 2009). A thorough evaluation of the nutritional status of children with cancer on admission—even more so if they are infected with HIV—and a nutrition plan established by a dietician with experience in cancer management would be very useful in these cases.

26.5 Conclusion

In conclusion, although HIV does not cause cancer by itself, it strongly facilitates the oncogenetic action of other viruses: HHV-8, EBV and HPV. This explains the significant increase of the incidence of malignancies known to be induced by the above agents. Other cancers were also observed more frequently in children with HIV, probably due to inefficient immune surveillance against malignant cells. The infection with HIV worsens the prognosis of cancers. A contributor to this is the relatively more severe and prolonged neutropenia during the treatment with cytotoxic drugs, which opens the gate to potentially lethal infections. There is evidence that HAART aids in the recovery from neutropenia, thus facilitating the administration of standard chemotherapy protocols. Coexistent tuberculosis, malaria and malnutrition, much more prevalent in low-income countries, add to the complexity of cancer management in children with HIV.

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Part VII
Supportive and Therapeutic Strategies

Chapter 27
cART and Supportive Care for HIV-Associated Malignancies

Ronald T. Mitsuyasu

Abstract cART is an abbreviation for combined antiretroviral therapy and generally refers to a three- or four-drug combination regimen of antiretroviral medications, which is considered standard treatment for human immunodeficiency virus-1 (HIV-1) infection. Another name for cART is highly active antiretroviral therapy (HAART). This treatment is important for suppressing HIV-1 replication and has greatly increased the longevity of individuals with this infection. As part of the treatment of malignancies in HIV-infected patients, cART and other supportive measures such as antiemetics, hematopoietic growth factors, blood transfusions, prophylactic and therapeutic antibiotics, anti-diarrheal medications, and psycho-social support for each individual undergoing the stressful therapy for these often life-threatening cancers have greatly enhanced both the efficacy and tolerability of these treatments and allowed patients to achieve remissions and/or cure of their cancers.

27.1 Combined Antiretroviral Therapy as Treatment for HIV and Cancer

Cancers have been a recognized part of the Acquired Immune Deficiency Syndrome (AIDS) since the initial recognition of this disease in 1981 (Hymes et al. 1981; Ziegler et al. 1982, 1984a, b). Initial reported mortality from Kaposi's sarcoma (KS) and non-Hodgkin's lymphoma (NHL), the two most common of these AIDS-associated

R.T. Mitsuyasu, M.D. (✉)
UCLA Center for Clinical AIDS Research and Education (CARE Center),
University of California, Los Angeles, CA, USA
e-mail: rmitsuya@mednet.ucla.edu

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malignancies, was extremely high, in the range of 40 % at 2-years for KS and 80 % at 1-year for NHL with what then was considered standard chemotherapy (Longo et al. 1984; Moss et al. 1984; Ziegler et al. 1984a, b). With the advent of combination antiretroviral therapy (cART), not only have HIV treatment outcomes improved, but the ability to dose intensify cancer treatment regimens has increased, allowing better control of cancer, fewer treatment-related serious adverse effects and complications, higher remission rates, more durable remissions, and longer survival. It has been reported that HIV-associated diffuse large B cell lymphoma can be successfully treated with a regimen that involves highly active antiretroviral therapy (HAART) being temporarily stopped during therapy. However, there is a general consensus among most clinicians with expertise in this area that when possible, HIV should be controlled with HAART if possible during the treatment of HIV-related malignancies and other diagnosed cancers in patients with HIV/AIDS (Lim et al. 2005; Thiessard et al. 2000; Little et al. 2000). Single and multi-institutional studies have shown that HAART can be administered along with anticancer therapy as long as attention is paid to pharmacokinetic interactions and overlapping toxicities. The increasing occurrence of cancer as a major part of the HIV/AIDS epidemic and the recognition of cancer as a leading cause of death in HIV have led to a greater emphasis on initiating treatment with cART earlier and to continue its use when possible during management of patients who develop cancers during the course of their disease.

27.2 Drug Interactions Between cART and Chemotherapy

Of concern has been the potential for significant drug interactions between some of the currently used antiretroviral drugs (ARVs) and some chemotherapeutic and other treatments for malignancies. Given the relatively small number of these patients and the need to get life-saving ARVs out to the HIV-effected community as quickly as possible, with a few exceptions, little attention was focused on the interactions of cancer therapies with ARV, and few pharmacokinetics studies were undertaken early on in the AIDS epidemic to assess the degree and influence of these drug interactions on the outcome of patients with AIDS and cancers (Ratner et al. 2001). Some of these adverse drug interactions have been found empirically in the course of treating HIV-infected individuals with specific malignancies, such as the well-known enhanced myelosuppressive effects of many cytotoxic chemotherapy drugs with zidovudine and the serious increase in irinotecan gastrointestinal toxicities with certain protease inhibitors for HIV (Kaplan et al. 1997; Corona et al. 2005; Makinson et al. 2001). With the growing realization that cancer is now a growing problem in HIV, especially as the population of HIV-infected individuals ages and because of increased longevity in the setting of continued immunodeficiency, and with the ever growing list of available new cancer treatment agents, it has become increasingly important that HIV-treating physicians and oncologists know and be able to make appropriate dosage adjustments for possible cancer therapy–ARV interactions and to avoid certain combinations of drugs which may lead to severely

enhanced toxicities. Most clinical trials protocols for treatment with cytotoxic chemotherapies now require that patients not receive zidovudine when receiving myelosuppressive chemotherapy or will restrict the use of dideoxynucleosides or other drugs that may significantly induce peripheral neuropathy (PN) when using cancer therapies with high potential for PN. More recently the National Cancer Institute's (NCI) Clinical Therapy Evaluation Program (CTEP) has embarked on formally assessing the pharmacokinetic/pharmacodynamic (PK/PD) interactions of antiretroviral drugs with new investigational cancer agents in conjunction with the NCI-supported AIDS Malignancy Consortium (AMC). These phase I PK/PD studies will hopefully enable greater participation of HIV-infected patients with cancers in general oncology clinical trials for various cancers, thus making the results of these phase II and III trials more widely applicable and avoiding the previous situation where HIV patients would be excluded from studies of new investigational cancer drugs, because of concerns about unknown and potentially harmful drug interactions with antiretroviral treatments.

27.3 Supportive Care for HIV Patients Receiving Cancer Treatments

Another important principle in the management of individuals with cancer and HIV is the need to provide adequate medical and logistical support for patients needing to receive therapy for their cancers. It is well known that patients with HIV, especially those with advanced HIV disease, e.g. those with lower CD4 counts or a history of prior opportunistic or other infectious diseases, generally have poorer marrow tolerance to the myelosuppressive effects of chemotherapy and, in some cases, radiotherapy as well. High rates of infections have been reported in trials of chemotherapy for HIV-associated lymphoma with regimens such as R-CHOP and R-EPOCH (Kaplan et al. 1997, 2005), which may be avoided to a large degree with the use of hematopoietic growth factors, such as granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF), blood transfusions and the use of prophylactic antibiotics (Kaplan et al. 1994; Scadden et al. 1991; Barta et al. 2012; Sparano et al. 2010). In a lymphoma trial conducted by the AMC, the routine use of prophylactic antibiotics dramatically reduced the incidence of severe infections in patient receiving intensive chemotherapy (Sparano et al. 2010).

Neurologic complications of HIV also may confound the management of patients with HIV and cancers, as peripheral neuropathy is a common complication of HIV and a not infrequent side effect of some ARVs and several anticancer drugs (e.g. vinca alkaloids, cis-platinum, oxaliplatin, bortezomib, etc.). In addition, progressive cognitive impairment due to progressive and long-term effects of HIV or to central nervous system (CNS) involvement with malignancy may impact the patient's ability to adhere to HIV, cancer treatments, and associated therapies for complications or side effects of these treatments.

Management of nausea, vomiting, pain, diarrhea, rashes, headaches, and other side effects of cancer and HIV therapies is critical and can be very effectively controlled with prophylactic treatments or mitigated post-hoc with standard antiemetics, anti-diarrheals, analgesics, etc. to allow patients to better tolerate and continue to receive important drug treatments.

As with anyone diagnosed with a life-threatening disease such as cancer, psychological support and the ability to listen to the patient's and their caregiver's concern are critical for the successful outcome of treatment. With the added burden of having HIV and the many financial, social, and logistical issues for providing the care that this engenders, it is particularly important to assure that a working support system is in place to assist the patient in maneuvering the health care system and getting the help they need to receive optimal care. In this regard, the concept of Patient Navigators (PNs) has received considerable attention as a means of facilitating patient access and their ability to navigate the complex medical and social-financial situation caused by diseases such as cancer and HIV. With the assistance of the Center to Reduce Cancer Health Disparities (CRCHD) within the NCI, the AMC has piloted and is investigating the usefulness of PNs as a means of improving access of HIV cancer patients to AMC clinical trials and for increasing the ability of individuals from racial/ethnic minorities and other underrepresented groups (such as women) to take part in these clinical trials and to maneuver the complexities of obtaining required diagnostic and therapeutic procedures and services for their malignancies. Understanding the special burdens faced by cancer patients with HIV, especially as it relates to obtaining needed social and psychiatric services to help deal with social ostracism and isolation, lack of transportation, loss of insurance, unemployment, poverty, homelessness, drug use, under- or poor-nutritional state and multiple co-morbid diseases is critical in allowing patients to fully benefit from the many recent advances in cancer diagnostics and therapy which have occurred in the past few decades. Unfortunately, faced with severe budget deficits, many state- and locally-funded organizations and programs set up to provide social services, case managements, and other support services have had their funding dramatically reduced, making it more difficult for individuals to adhere to the strict treatment schedules required for some of the more complicated treatment regimens.

27.4 Cancer Screening in HIV

Early diagnosis and established prevention strategies for many cancers should also be considered in the routine management and follow-up of the HIV-infected individual. Age-appropriate American Cancer Society (ACS), NCI and United States Prevention Services Task Force (USPSTF) cancer screening guidelines should, as a minimum, be followed for screening HIV-infected individuals for cancer and/or precancerous lesions, as they would be for non-HIV-infected adults. In addition, routine monitoring for cervical and anal dysplasia and intervention for high-grade squamous intraepithelial lesions (SIL) have been recommended or are under

evaluation to determine the best frequency for monitoring in HIV-infected patients, where the relative risk of cervical and/or invasive anal cancer is higher than in the general population. Whether HIV patients would benefit or should be checked and monitored more closely or more frequently for certain AIDS-related cancers (ADC) or non-AIDS-related cancer (NADC) because of their higher risk of developing these malignancies remain to be determined. Future prospective studies will be needed to assess the efficacy and cost effectiveness of some of these routine screening procedure in HIV.

27.5 Conclusion

Significant advances in understanding and treating cancers have occurred in the past several years. Similarly, the ability to treat HIV and to provide a normal life expectancy to individuals with HIV infection has improved dramatically. Subsequently, malignancies in HIV is now emerging as a growing problem and will require greater vigilance on the part of primary care providers to identify these cancers and a heightened awareness on the part of HIV physicians and oncologists about the many complications and special needs of individuals who have these diseases concurrently.

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Chapter 28
Stem Cell Transplantation

Christine Durand and Richard Ambinder

Abstract Stem cell transplantation (SCT), also referred to as bone marrow transplantation or hematopoietic SCT, is a treatment in which hematopoietic stem cells are administered to a patient, usually as treatment for hematologic cancer or bone marrow failure. Prior to infusion of stem cells, patients receive fully myeloablative or reduced-intensity chemotherapy both to reduce tumor burden and to allow engraftment of the stem cells. There are several potential sources of the hematopoietic stem cells in clinical use. In autologous SCT, hematopoietic stem cells are collected from the patient prior to chemotherapy and infused after treatment to rescue the hematopoietic system. In allogeneic SCT, hematopoietic stem cells are donated by a close relative or genetically matched unrelated individual and infused after conditioning chemotherapy. Availability of suitably matched donors remains a major limitation to SCT and new advances now allow for more flexibility in matching human leukocyte antigens (HLA) between donors and recipients. Alternative stem cell sources include the use of partially matched relatives, partially matched unrelated donors, and umbilical cord fetal blood.

C. Durand
Division of Infectious Diseases, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA
e-mail: cdurand2@jhmi.edu

R. Ambinder (✉)
Division of Hematologic Malignancies, Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
e-mail: rambind1@jhmi.edu

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28.1 Introduction

Stem cell transplantation (SCT) is the standard treatment for a variety of hematologic malignancies for which human immunodeficiency virus (HIV)-infected patients are at increased risk, including primary-refractory lymphoma, relapsed lymphoma, and aggressive leukemia. Early in the epidemic, HIV infection was considered a contraindication to high-dose chemotherapy and SCT. With effective antiretroviral therapy (ART) the morbidity and mortality of HIV infection have been dramatically reduced. In addition, substantial improvements in SCT have occurred, such as prophylaxis against opportunistic infections and the use of leukocyte growth factors. With these advances, HIV-infected individuals are now being offered curative SCT therapy for treatment of hematologic malignancy. Outcomes of autologous SCT in HIV-infected individuals are now considered similar to the general population. In allogeneic SCT, there are a growing number of successful case reports and series. Close attention to interactions between antiretroviral medications to treat HIV, conditioning chemotherapy administered pre-transplant, and immunosuppressants administered post-transplant is required. Of note, there has been a long-standing interest in the possibility that SCT could lead to the cure of HIV infection.

28.2 Hematologic Malignancies Associated with HIV Infection

Many types of hematologic malignancy are associated with HIV infection and acquired immunodeficiency syndrome (AIDS). Aggressive B cell lymphoma was among the "AIDS-defining" conditions that could lead to a clinical diagnosis of AIDS early in the epidemic, even before the virus had been identified. With the widespread institution of ART, the epidemiology of cancer in the HIV/AIDS population has changed, but hematologic malignancies remain a major cause of morbidity and mortality (Shiels et al. 2011). In the USA, hematologic cancers still account for more than one third of all cancers diagnosed in individuals with HIV/AIDS (Shiels et al. 2011). In the era of ART, the absolute numbers of AIDS-related malignancies such as non-Hodgkin lymphoma (NHL) have decreased but NHL represents a greater proportion of deaths in individuals with AIDS, as a result of substantial success in reducing infection-related mortality (Shiels et al. 2011).

NHL is the most common hematologic cancer in individuals with AIDS (Shiels et al. 2011). Whereas some types of NHL have almost disappeared with ART, such as primary central nervous system lymphoma, and others have substantially decreased, such as diffuse large B cell lymphoma, Burkitt lymphoma seems unaffected. Similarly Hodgkin lymphoma (HL) has not decreased and may be on the rise (Shiels et al. 2011). Finally, rates of myeloma and certain types of leukemia, such as acute myelogenous leukemia (AML), are also increased in this population.

28.3 Role of AutoSCT in the Treatment of Malignancy in HIV-Infected Individuals

In the early years, aggressive chemotherapy in HIV-infected individuals with lymphoma resulted in an unacceptably high risk of treatment-related death with no clear survival benefit (Gates and Kaplan 2002). These early studies made reduced-dose treatment regimens the standard of care and SCT was not considered in this patient population. After implementation of effective ART in 1997, several studies showed that HIV-infected patients could tolerate standard dose regimens (Gates and Kaplan 2002). These improvements were attributed to ART as well as to the institution of routine prophylaxis against pneumocystis pneumonia and herpes virus reactivation. These successes opened the door to explore high-dose therapy with stem cell rescue in the form of autologous SCT, which was the standard treatment for relapsed or primary-refractory lymphoma in the general population.

Autologous SCT to treat lymphoma in HIV-infected individuals has been instituted at several centers. It has also been studied in small cooperative group trials (Ambinder 2009). In these cohorts, the rate of infectious deaths has not been significantly increased and mortality has primarily been attributed to cancer progression or treatment-related organ toxicities such as veno-occlusive disease (Ambinder 2009). The current consensus is that outcomes of autologous SCT in HIV-infected individuals with relatively well-controlled HIV disease are essentially equivalent to outcomes in the general population. There has also been no clear deleterious impact of autologous SCT on the long-term management of HIV infection in these patients. Amounts of HIV virus in the plasma are not significantly increased and immunologic recovery after autologous SCT also appears to be comparable to the general population (Ambinder 2009).

28.4 Role of AlloSCT in the Treatment of Malignancy in HIV-Infected Individuals

The favorable outcomes of autologous SCT in HIV-infected individuals have encouraged consideration of allogeneic SCT in HIV-infected individuals with aggressive hematologic malignancies such as leukemia, and in those who require salvage therapy for unresponsive lymphoma. As in autologous SCT, the use of ART to control HIV disease is critical to outcomes in allogeneic SCT. Early in the AIDS epidemic, survival in HIV-infected patients receiving allogeneic SCT was less than 15 % (Gupta et al. 2009 and Hütter and Zaia 2011). With effective ART and other advances, survival with allogeneic SCT is now greater than 50 % (Gupta et al. 2009 and Hütter and Zaia 2011).

In addition to concerns regarding increased mortality, there has been speculation that HIV-infected individuals might be at risk for SCT complications such as graft failure and/or graft-versus-host-disease (GVHD). This potential risk is hypothesized

to be a result of underlying immunologic dysfunction caused by HIV, which is thought to persist even with effective ART. For example, in the solid organ transplant setting, although overall survival and organ/graft survival rates are generally comparable between the HIV-infected and uninfected transplant recipients, higher than expected episodes of organ rejection are observed (Stock et al. 2010). Based on the small studies to date in HIV-infected individuals receiving allogeneic SCT, disproportionate rates of graft failure and/or GVHD have not been observed (Gupta et al. 2009; Hütter and Zaia 2011).

28.5 ART During SCT in HIV-Infected Individuals

The extraordinary success of ART in controlling and reversing clinical disease due to HIV infection has allowed for curative SCT therapies to be extended to HIV-infected individuals. At the same time, the complexity of ART combinations necessitates focused approaches related to drug interactions, drug toxicities, and drug interruptions. There are more than 20 approved antiretroviral medications. The major classes of drugs include nucleoside or nucleotide analogue reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase inhibitors, a fusion inhibitor, and a CCR5 chemokine receptor antagonist. Unique challenges associated with specific drugs or drug classes exist as well as more general challenges to maintenance of any antiretroviral regimen during SCT.

Overlapping organ toxicities can occur with antiretrovirals and chemotherapeutic agents (Rudek et al. 2011). Zidovudine or AZT is an NRTI and was the first approved antiretroviral drug. Prior to the development of combination drug regimens, AZT monotherapy was used in HIV-infected individuals during SCT (Hütter and Zaia 2011. With the development of less toxic alternatives, AZT is now contraindicated during SCT as it can cause myelosuppression (Rudek et al. 2011). Other overlapping organ toxicities for which monitoring is required during SCT and concurrent ART include kidney toxicity, which can occur with the NRTI tenofovir, and peripheral nerve toxicity which occurs with older NRTIs such as stavudine (d4T) and didanosine (ddI) (Rudek et al. 2011).

Drug interactions between ART, antineoplastic agents, and immunosuppressants used to prevent GVHD are another management challenge in SCT for HIV-infected individuals (Rudek et al. 2011). Interactions due to antiretrovirals in the PI class are the most common. In most cases, two PIs are used in combination; one PI is used at a dose designed to inhibit HIV replication and a second PI, ritonavir, is used at a lower dose designed to inhibit the cytochrome P450 enzyme system in order to increase the concentration and therapeutic efficacy of the first PI. This approach is known as “ritonavir-boosting” and is critical to the efficacy of this drug class. Other drugs are now being developed to effect PI boosting in place of ritonavir. The strategy has been extremely effective and ritonavir-boosted PIs are components in

certain recommended first-line ART regimens. Many drugs, including chemotherapeutic agents and immunosuppressants are also metabolized by the cytochrome P450 system and in the presence of PIs, serious interactions can occur (Rudek et al. 2011). In some cases, these interactions can be managed with close monitoring of drug levels though concerns remain that the levels of critical cancer drugs or immunosuppressants may be compromised. In other instances—for example, with myeloablative conditioning regimens and/or the use of high-dose cyclophosphamide, interruption of PI-containing regimens is standard practice for at least a few days (Rudek et al. 2011). Another antiretroviral drug implicated in drug interactions during SCT is the NNRTI efavirenz. Efavirenz is an alternative to the use of PIs in the first-line ART regimens but induces, rather than inhibits, the cytochrome P450 enzyme system. During SCT, efavirenz use also requires close monitoring of levels of several critical medications (Rudek et al. 2011).

Mucositis, nausea, and vomiting are common side effects of cancer chemotherapy and may prevent patients from taking any medications by mouth for extended periods of time. Unfortunately, non-oral formulations of ART have not been widely developed (Swindells et al. 2011). The only non-oral formulations of antiretrovirals that are currently available include intravenous AZT and the fusion inhibitor enfuvirtide (T20) which is administered as a subcutaneous injection (Swindells et al. 2011). AZT is contraindicated during SCT due to bone marrow suppression. T20 is rarely used except as salvage therapy for HIV-infected patients with multidrug resistant virus and can cause painful injection site reactions (Swindells et al. 2011).

With interruption of ART, detectable levels of HIV in the blood typically return within a few weeks. Although rebound viremia can be managed without adverse clinical outcomes in most cases, there have been cases during SCT in which ART interruption and rebound of virus resulted in a febrile syndrome similar to the acute retroviral syndrome described in primary HIV infection (Hütter and Zaia 2011). Interruption can also increase the risk of developing antiretroviral drug resistance particularly when components of the ART regimen have different half-lives. Efavirenz has a half-life of 36–100 h and remains detectable long after levels of other antiretrovirals in a standard regimen have disappeared (Rudek et al. 2011). This discrepancy in rates of drug elimination will result in a period of functional efavirenz monotherapy and a significant risk of developing HIV drug resistance which will compromise the efficacy of future ART. In addition to these clinical implications, avoiding any interruptions in ART may also be important to emerging strategies that propose to use SCT in the pursuit of an HIV cure.

28.6 Donor Sources in SCT in HIV-Infected Individuals

Many patients who need allogeneic SCT are unable to find an human leukocyte antigens (HLA)-matched donor. Approximately 70 % of patients do not have an HLA-matched sibling and only half of those patients will find a matched unrelated

donor in the national registry. The proportion of individuals who cannot identify a donor is even higher among racial and ethnic minorities, which are also disproportionate affect by HIV infection. Alternative donor sources have been developed and studied in the general population but have not been investigated in HIV-infected individuals. These newer strategies include the use of partially matched or haploidentical relatives or cord blood stem cells (Brunstein et al. 2011). In the past, haploidentical SCT was associated with increased mortality due to high rates of GVHD but this has been reduced with the use of high-dose, post-transplantation cyclophosphamide as GVHD prophylaxis (Brunstein et al. 2011). Concerns remain with regard to cord blood transplant as higher rates of non-relapse mortality have been reported in a recent cooperative group study (Brunstein et al. 2011); however, cord blood SCT may also offer unique benefits related to the role of SCT in HIV cure (Petz et al. 2012).

28.7 Persistence of HIV in Hematopoietic Cells

HIV preferentially infects activated $CD4^+$ T cells, and as part of the retroviral lifecycle, the virus stably integrates into the host cell genome. Activated $CD4^+$ T cells only have a lifespan of 1–2 days but a subset of activated $CD4^+$ T cells will become resting memory $CD4^+$ T cells. Memory $CD4^+$ T cells are long-lived cells that are designed to survive for the life of the individual in order to maintain immunologic memory. As a consequence of this process, if an HIV-infected activated $CD4^+$ T becomes a resting memory $CD4^+$ T cell, HIV will survive indefinitely within that cell (Eisele and Siliciano 2012). Resting memory $CD4^+$ T cells are quiescent and do not actively produce virus, but if these cells are reactivated, they can produce HIV and reestablish active infection (Eisele and Siliciano 2012). In all HIV-infected individuals, resting memory $CD4^+$ harboring latent HIV can be detected and the frequency of these cells is stable over time despite treatment with ART (Eisele and Siliciano 2012). This reservoir of latently infected resting memory $CD4^+$ T cells is the major impediment to viral eradication.

There has been interest in whether hematopoietic progenitor stem cells are directly infected by HIV and whether these cells are an additional barrier to cure. The majority of studies on this subject in the pre-ART era reported extremely rare detection of HIV in the hematopoietic progenitor/stem cell compartment (McNamara and Collins 2011). The prevailing consensus was that viral detection was due to the presence of $CD4^+$ T cells which traffic between the blood and the bone marrow. In the ART era, debate has continued. One study reported evidence of HIV infection in $CD34^+$ hematopoietic progenitor cells in patients on ART (McNamara and Collins 2011), but follow-up studies in which $CD4^+$ T cells were carefully excluded from samples have not confirmed HIV infection of $CD34^+$ cells (Durand et al. 2012a). Thus, consensus remains that latently infected resting memory $CD4^+$ T cells represent the primary obstacle to cure (Eisele and Siliciano 2012).

28.8 Role of SCT in HIV Cure

The concept that HIV infection is limited to hematopoietic cells led to efforts in the 1980s to cure AIDS with SCT by replacement of the hematopoietic compartment (Hütter and Zaia 2011). These studies, which occurred prior to the use of effective ART, did not demonstrate success. Decades later, interest in allogeneic SCT as a means to eradicate HIV has been revived. This came to attention with a remarkable report of HIV cure in an HIV-infected patient who was treated for AML with myeloablative chemotherapy and allogeneic SCT (Hütter et al. 2009). The patient was originally known as the Berlin patient, because he received his cancer treatment from a German oncologist, Dr. Gerard Hütter, in Berlin. The patient is now known to the public as Timothy Ray Brown and is a community activist and strong advocate for research efforts focused on an HIV cure.

For treatment of his AML, Brown received myeloablative chemotherapy, total body irradiation, and allogeneic SCT from an "HIV-resistant" donor (Hütter et al. 2009). This unique donor was homozygous for a naturally occurring genetic mutation in one of the cell surface receptors, CCR5. The mutation, known as CCR5Δ32, is a 32-base pair deletion that results in a complete lack of expression of CCR5 on the cell surface. The majority of HIV variants require binding to the CCR5 receptor to infect cells. These viruses are known as R5-tropic variants. Other strains of HIV use the cell surface receptor, CXCR4 to enter cells, but these X4-tropic variants are rarely transmitted, and typically evolve in late-stage AIDS. Between 5 and 15 % of Caucasians of Northern European-descent are CCR5Δ32 heterozygotes and carry one copy of the mutation which does not confer HIV-resistance. Less than 1 % of Caucasian individuals homozygotes, and, carrying two copies of the allele, are resistant to HIV-acquisition [Petz *et* Homozygosity for the mutation is even rarer in racial and ethnic minority populations (Petz et al. 2012)].

Due to the rarity of this genetic polymorphism, it has been relatively difficult to identify other matched CCR5Δ32 homozygous donors to test this approach. Several strategies have been developed to overcome this challenge (Durand et al. 2012b). First, there are now technologies capable of genetically engineering patient $CD4^+$ T cells and/or $CD34^+$ hematopoietic progenitor cells to lack CCR5 and CXCR4 (Durand et al. 2012b). This approach has been tested in early phase clinical studies and appears to be safe and well tolerated. A significant impact of this approach on clinical outcomes in patients has not yet been demonstrated (Durand et al. 2012b). Current challenges of the strategy include optimizing the levels of engraftment and the survival of the genetically modified cells (Durand et al. 2012b). One application of this method that is in preclinical development is a combination of gene therapy tools to mutate CCR5 or CXCR4 in hematopoietic progenitor stem cells from HIV-infected individuals with hematologic malignancies who require autologous SCT (Durand et al. 2012b).

Cord blood SCT may provide another way to overcome the lack of CCR5Δ32 homozygous donors. A program to genetically screen cord blood units for the CCR5Δ32 mutation has been implemented (Petz et al. 2012). This initiative has

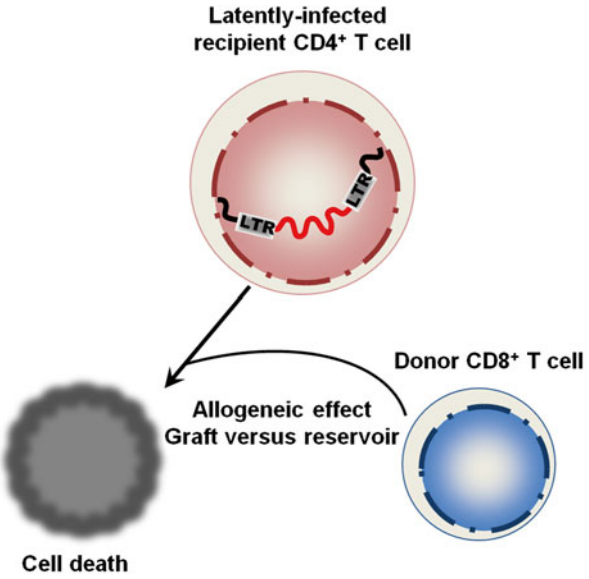

Fig. 28.1 Impact of the allogeneic effect on HIV latently infected cells. The allogeneic effect occurs as a result of donor $CD8^+$ lymphocytes which are present within the stem cell transplant product. These donor lymphocytes eliminate host hematopoietic cells. This effect is nonspecific and results in favorable graft-versus-tumor-effects as well as unfavorable graft-versus-host-disease. This allogeneic effect should also eliminate latent HIV infection by killing latently infected host $CD4^+$ T lymphocytes and causing a "graft-versus-viral-reservoir" effect

identified more than 100 CCR5Δ32 homozygous units, with an ultimate goal of identifying 300 units. Due to less stringent requirements for HLA matching with cord blood SCT, it is predicted that this inventory would translate into a 27 % chance of identifying a matched CCR5Δ32 homozygous unit for an HIV-infected Caucasian adult who requires SCT (Petz et al. 2012).

The possibility that allogeneic SCT could eradicate HIV infection even without CCR5Δ32 donors is also being considered. In the process of allogeneic SCT, donor $CD8^+$ T cells in the stem cell product eliminate recipient hematopoietic cells, due to alloreactivity (Fig. 28.1). This process, known as the allogeneic effect, is responsible for the graft-versus-tumor-effect as well as GVHD. The transition from a recipient hematopoietic system to a donor hematopoietic system occurs over weeks to months. Once all hematopoietic cells detected in the peripheral blood are donor in origin, the SCT recipient is said to have achieved full donor chimerism. Since all identified HIV reservoirs are in hematopoietic or hematopoietic-derived cells (Eisele and Siliciano 2012), the HIV reservoir in the recipient should disappear once full donor chimerism is complete. The donor cells must be also protected from acquiring HIV during this process for cure to be achieved. In the case of Timothy Ray Brown, the donor cells were protected by the CCR5Δ32 mutation (Fig. 28.2). With allogeneic SCT using standard donors, ART may provide the same protection (Fig. 28.3). This latter protective effect might be considered analogous to the ability of ART to prevent HIV acquisition in utero, or after a high-risk needle-stick exposure.

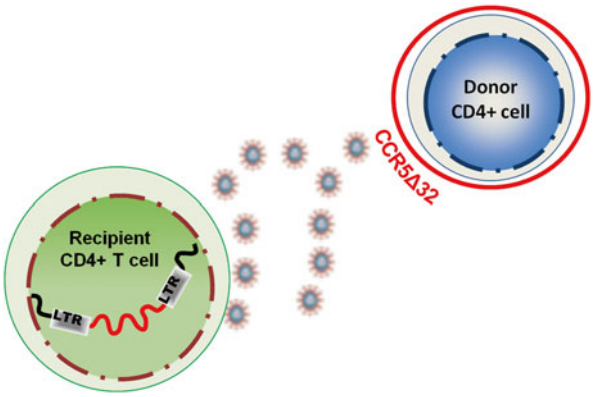

Fig. 28.2 HIV-resistant donor cells. The Berlin patient received an SCT from a donor who was homozygous for a naturally occurring 32-base pair deletion in the cell surface receptor CCR5. Homozygosity for this deletion, CCR5Δ32, results in a lack of expression of the CCR5, which in addition to CD4 is the co-receptor used by HIV to infect cells. Thus, the transplanted donor hematopoietic system could not be infected by HIV from the recipient

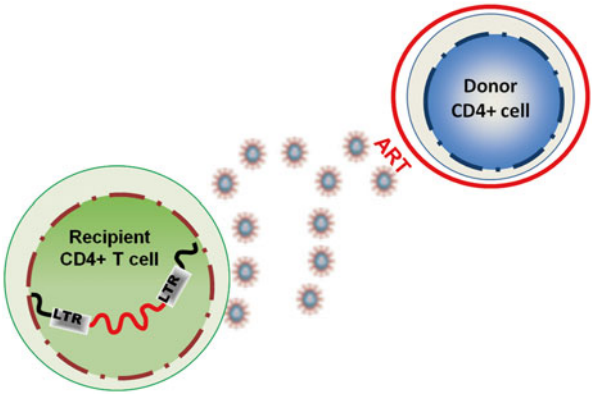

Fig. 28.3 Antiretroviral therapy to prevent donor cell infection. During the process of SCT and the transition from a recipient to donor hematopoietic system, continuous ART may prevent infection of the transplanted cells. If in concert, all host cellular reservoirs of HIV are eliminated by a combination of chemotherapy and the allogeneic effect, this could lead to HIV cure

28.9 Conclusions

SCT is the treatment of choice for several hematologic malignancies which are increased in the HIV-infected population. With continued improvements in HIV therapies and SCT strategies, evidence suggests that SCT can and should be offered to persons living with HIV/AIDS for treatment of cancer. There are special risks to

consider in this population related to underlying immunodeficiency as well as the challenges of administering ART, chemotherapy, and immunosuppressants in combination. Prospective trials of autologous SCT have not demonstrated increased mortality or treatment-related complications. Further data is emerging related to the use of allogeneic SCT in this population but there are encouraging reports in the literature. Further investigation in outcomes of SCT using alternative donor sources is needed. Beyond curing malignancy, the prospect of achieving HIV cure with SCT remains an exciting opportunity that promises to bring new insights into the fields of SCT and HIV/AIDS.

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