Chapter 7
Systemic Diseases with an Increased Risk of Oral Squamous Cell Carcinoma

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Introduction

There is a growing awareness of the important relationships between systemic inflammatory diseases, infections, genetic disorders, medical therapies and cancer risk. A number of systemic disorders have been associated with an increased risk of head and neck squamous cell carcinoma. These include autoimmune conditions, genetic syndromes, infections, iatrogenic causes such as haematopoietic stem cell transplantation and graft-versus-host disease and rare associations including novel drugs. This chapter will discuss conditions which confer an increased risk of head and neck squamous cell carcinoma, as well as review the evidence for diseases which have been historically associated with oral cancer.

Autoimmune Polyendocrinopathies

Introduction

The autoimmune polyendocrinopathy syndromes are a heterogeneous group of disorders, characterised by the development of multiple autoimmune phenomena. This group consists of autoimmune polyendocrine syndrome type 1 (APS-1) and type 2 (APS-2) and x-linked polyendocrinopathy, immune dysfunction and diarrhoea

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Peter A. Brennan et al. (eds.), *Premalignant Conditions of the Oral Cavity*, Head and Neck Cancer Clinics, https://doi.org/10.1007/978-981-13-2931-9_7

(XPID) syndrome [1]. APS-1 is also known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) and has a known association with oral squamous cell carcinoma.

APS-1 (OMIM 240300) is a rare autosomal recessive syndrome caused by mutations in an autoimmune suppressor gene known as *AIRE*. This gene encodes a transcription factor and is involved in the generation of self-tolerance [1]. The classic triad of conditions present in this disorder includes mucocutaneous candidiasis, hypoparathyroidism and adrenocortical insufficiency, and the presence of two of these conditions is required for diagnosis [2].

Epidemiology

APS-1 is a rare syndrome and is most prevalent in the Finnish, Iranian, Jewish and Sardinian populations [3]. The majority of presentations occur under the age of 18 years, with mucocutaneous candidiasis the initial presenting feature in 60% of cases, followed by the development of hypoparathyroidism and adrenocortical insufficiency [2]. Italian and Finnish case series have reported the median age for initial diagnosis of mucocutaneous candidiasis as 6.5 years and 5.4 years, respectively [2, 4]. However, a large Finnish series reported that some patients did not develop the diagnostic dyad until adulthood [2].

Pathophysiology

The syndrome is caused by mutations in the *AIRE* gene, which is involved in the generation of self-tolerance. However the clinical presentation is diverse, so it is considered likely that the pathophysiology is more complex than abnormalities in this one gene [5]. *AIRE* has an important role in the elimination of autoreactive thymocytes during the development of the immune system [5]. If this process fails, then autoreactive T-lymphocytes will be released into the circulation, potentially causing end-organ damage and accompanying autoimmune disease.

Chronic mucocutaneous candidiasis (CMC) is the most commonly observed feature of APS-1, and it is suggested that a T-cell defect with a resultant poorly developed response to *C. albicans* may be the cause of this opportunistic infection [6]. APS-1 patients mount a satisfactory humoral immune response to *Candida* species and thus are not at risk of systemic candidiasis [5]. Further research into the mechanisms of this specific immunodeficiency have shown the presence of autoantibodies to IL-17F, IL-17A and IL-22 in APS-1 patients [7, 8]. These are key cytokines involved in defence against mucocutaneous candidal infection. Thus it appears that the increased susceptibility to mucocutaneous candidal infection in these patients is also a manifestation of autoimmunity.

Clinical Features

In addition to the classic triad of chronic mucocutaneous candidiasis (CMC), hypoparathyroidism and adrenocortical insufficiency, the clinical presentation can include a variety of less common conditions, including insulin-dependent diabetes mellitus, hypothyroidism, hypogonadism, pernicious anaemia, hepatitis, diarrhoea, keratitis, alopecia, vitiligo and enamel hypoplasia [9]. The most common initial manifestation of the condition is CMC, which may present in infancy and early childhood. Candidiasis may affect the skin, nails, oesophagus and oral and vaginal mucosa [4]. Oral candidiasis persisting beyond the newborn period and in association with any form of endocrinopathy or the rarer components of the syndrome (e.g. keratoconjunctivitis or vitiligo) should alert the clinician to the possibility of APS-1 [2, 3].

Oral and oesophageal candidiasis in APS-1 patients may present as mild intermittent angular cheilitis but may also cause significant disease. Clinical manifestations include erosive, hyperplastic and atrophic forms of candidiasis, leukoplakia-like areas of the oral mucosa and oesophageal webbing and strictures [9]. CMC is also the most common manifestation of APS-1 and is present in all adult patients with the syndrome [2]. The majority of APS-1 patients are colonised by *C. albicans* [6].

Symptoms related to the endocrine components of the syndrome may be subtle initially, and a high index of clinical suspicion is required. Symptoms of hypocalcaemia may be non-specific, such as muscle cramping during infections and mild paraesthesia or clumsiness [3]. Adrenal insufficiency presents with extreme fatigue, pigmentation, weight loss and hypotension. These conditions are potentially life-threatening, so identification of patients with unusual or chronic oral mucosal candidal infection could be the key to prompt investigation and recognition of potentially serious endocrinopathies.

Oral Cancer Risk

The largest case series of APS-1 published to date, involving 92 Finnish patients, has demonstrated that the prevalence of oral and oesophageal squamous cell carcinoma (SCC) in this patient group is up to 10% in patients over the age of 25 years [6]. The patients diagnosed with oral or oesophageal SCC in this series were aged between 29 and 44 years. In the general population, the mean age at diagnosis for oral and oesophageal SCC is greater than 60 years, and it is considered an uncommon disease in younger people. The literature contains several case reports regarding young patients developing multiple oral SCCs in the context of APS-1 [10, 11].

The role of chronic candidal infection in the aetiology of oral and oesophageal SCC has been a topic of considerable debate. Historical animal studies have demonstrated the generation of carcinogenic chemicals such as nitrobenzylmethylamine by *C. albicans*, with an associated increase in the incidence of oral SCC [12]. A study conducted in Finland utilising *C. albicans* species isolated from APS-1 patients found that these organisms could synthesise potentially carcinogenic levels

of acetaldehyde from glucose and alcohol [13]. Experts in the field consider that given the long duration of candidal infection in APS-1 patients and the tendency for oral and oesophageal SCCs to develop in sites of chronic candidal infection, this infection is an important factor in the development of the malignancy. However the extent of this role is as yet unknown. Given that the syndrome features a number of phenomena related to abnormal T-cell function and that these cells have a key role in antitumour effects, it is likely that the relationship to the development of malignancy is more complex than simply chronic candidal infection.

Given the high rate of oral and oesophageal SCC in young people with APS-1 and the potential contribution of chronic mucosal candidal infection to carcinogenesis, it is important that appropriate management and screening are undertaken in this population. APS-1 patients should have regular reviews by a multidisciplinary team comprising oral medicine specialists, otolaryngology/head and neck surgery and endocrinology specialists. Careful attention to screening of the oral and oesophageal mucosa should be maintained, and any suspicious lesions should be biopsied. It is recommended that treatment of oral and oesophageal candidiasis should be aggressive [2–4, 6]. This may be best achieved with a combination of topical and systemic therapy, and careful attention should be paid to monitoring for resistant strains of *C. albicans*, as this is a concern with the potential long-term use of azole antifungals in this patient cohort [14]. It is recommended that the use of azole antifungals is limited to two to three courses per year in order to reduce the risk of generation of resistance [3]. It is essential that patients with APS-1 are educated regarding the risk of oral and oesophageal cancer and that they clearly understand the index symptoms and self-monitoring procedures and know when to alert a clinician. They should also be counselled regarding avoidance of other known risk factors for oral and oesophageal SCC such as smoking, alcohol and betel quid use.

Lupus Erythematosus

Introduction

Lupus erythematosus (LE) is a group of diverse persistent autoimmune inflammatory diseases which frequently affect the skin and oral mucosa. Discoid lupus erythematosus (DLE) is the most common chronic form of cutaneous lupus. It is characterised by persistent scaly, disc-like plaques on the scalp, face and ears and may cause pigmentary changes, scarring and hair loss. The oral mucosa may be involved.

Epidemiology

The prevalence of DLE has been reported to be less than five in 10,000 individuals [15]. The most common age of onset of DLE is between 20 and 40 years [16]. It affects both females and males, with a slight female predominance. The female-to-male ratio

has been reported between 3:2 and 2:1 compared with 12:1 in systemic lupus erythematosus (SLE) [17]. Unlike SLE, there does not seem to be any racial predisposition to DLE. However, reports in the United States suggest that DLE may be slightly more common in Black Americans than in White Americans [18]. Smoking has been linked to both the development and severity of DLE [19].

Clinical Presentation

The typical cutaneous manifestations of DLE are white keratinised plaques with elevated borders, central atrophy, radiating white striae and telangiectasia. It has a prolonged clinical course and can persist for many years despite various treatments. Oral manifestations are present in up to 25% of patients and are located most commonly on the buccal mucosa, followed by the gingivae, labial mucosa and vermillion of the lip [20]. Oral mucosal lesions have an irregular white border with telangiectasia, surrounding a central atrophic area in which there may be small white papules. It may also present as irregular erythematous areas without a keratotic component. Oral manifestations may be present without cutaneous lesions. DLE is more likely to affect the palatal mucosa than lichen planus, and the typical appearance of an erythematous area with radiating white striae can sometimes differentiate the lesion clinically from lichen planus and lichenoid reactions to metal restorations (typically amalgam) or medications [21]. DLE lesions frequently appear on the lower lip, due to the photosensitive nature of this condition.

Pathophysiology

DLE is an autoimmune disease; however the precise pathophysiology of the disorder is unclear. It is suggested that UV light-induced epidermal inflammation, autoantigen localisation and basal keratinocyte apoptosis contribute to the process. However, it is likely that multiple components of the innate and adaptive immune system are involved in the pathogenesis of this condition [22].

Management

If symptomatic, the oral manifestations of DLE are managed in a similar manner to other oral mucosal inflammatory conditions. This is primarily with topical corticosteroids and immunomodulators, although on occasion, systemic immunosuppression may be required, particularly for refractory lower lip lesions.

Oral lesions in DLE need close clinical monitoring, given the possibility of developing dysplasia or malignancy in these sites. In order to rule out the presence of dysplastic change, incisional biopsy may be required, in some cases serially as

part of active clinical monitoring. UV-B light exposure can precipitate DLE lesions and increase the risk of sun-related malignancy; therefore it is important to examine the lips carefully and give sun protection advice.

Oral Cancer Risk

The evidence regarding oral carcinoma development in sites affected by oral DLE lesions is limited to a number of case reports. The risk of developing malignant change in oral mucosal DLE is uncertain [21]. DLE-related malignant transformation affecting the lip has been reported, particularly in males. However this is confounded by the fact that this is a sun-exposed site and the excess risk may be due to ultraviolet radiation rather than the underlying inflammatory disorder [23].

Fanconi Anaemia

Introduction

Fanconi anaemia (FA) is a rare disorder with a heterogeneous clinical picture. It is primarily an autosomal recessive inherited condition [24]. The condition is caused by mutations in one of at least 21 genes known to be involved in the pathogenesis of the condition [25]. These genes are involved in DNA repair, and cardinal features of FA are genomic instability and extreme sensitivity to DNA cross-linking agents. Clinically the condition is characterised by variably expressed congenital abnormalities, early bone marrow failure, and an increased risk of cancer, particularly acute myeloid leukaemia and squamous cell carcinomas of the head and neck and anogenital regions [26].

Epidemiology

FA is found in all races and ethnic groups and has a worldwide prevalence of one to five per million. It is slightly more common in males. Average life expectancy is 20 years [26]. Given the heterogeneity of clinical presentations, the age of diagnosis can be extremely variable. The majority of patients will develop haematological abnormalities, and the median age of onset of these is 7 years [27]. Patients with a more severe phenotype tend to develop bone marrow failure and haematological malignancy at an earlier age. However a cohort of patients with mild manifestations of FA have survived into early adulthood, and the development of solid tumours such as head and neck SCC at a young age has been the first indication of the presence of the condition [28]. In addition, the use of haematopoietic stem cell

transplantation has enabled the survival of patients with more severe manifestations of FA, and the development of solid tumours in these longer-term survivors with FA has become a significant issue [27].

Researchers comment that it is possible that the condition is more common than previously thought, due to under-recognition of the variety of clinical manifestations which are possible in the disorder [29].

Pathophysiology

The majority of cases of FA are autosomal recessive, with the exception of FANCB which is x-linked [30]. The disorder results from biallelic inactivation of one of at least 21 genes which have been identified as related to the condition [25]. The proteins encoded by genes involved in FA are essential for the repair of DNA interstrand cross-links.

Due to its critical role in DNA repair, FA is considered a "caretaker gene disease" and is grouped with other similar conditions including ataxia telangiectasia, Bloom syndrome, hereditary non-polyposis colorectal cancer and hereditary breast/ovarian cancer syndromes [26].

Research into the molecular genetics of FA has established significant interactions between the FA and BRCA pathways, which are associated with hereditary forms of breast and ovarian cancer. It has been confirmed that two of the FA genes are BRCA1 and BRCA2 [25]. The DNA repair pathway mediated by these genes and their protein products is now known as the FA-BRCA pathway, and further research is ongoing into the mechanisms of increased cancer risk related to these genetic abnormalities.

The mechanisms by which the genetic abnormalities cause disease manifestations in FA are gradually being elucidated. It is suggested that the genomic instability resulting from ineffective repair of DNA damage results in increased cancer development [31]. The mechanisms by which other disease manifestations occur are less clear; however it is thought likely that the FA proteins participate in other ways to preserve genomic integrity and that deficiencies in these processes lead to susceptibility to other diseases and abnormalities [27, 32].

Clinical Features

Clinical manifestations of FA range from very severe congenital abnormalities to mild clinical features. The major features of the condition are congenital malformations (short stature, radial-ray anomalies, café au lait spots, cardiac and renal anomalies), early bone marrow failure, hypersensitivity to DNA cross-linking agents and an increased risk of haematological and solid malignancy. Multiple other congenital anomalies have been reported in association with FA; however up to 40% of patients

have no major physical malformations [30]. Comprehensive reviews exist on the anomalies associated with this disorder [33]. Given the wide phenotypic variation, it is important that FA is considered in any child or young adult diagnosed with aplastic anaemia, myelodysplastic syndrome, acute myeloid leukaemia or squamous cell carcinoma of the head and neck region [30, 34]. FA should also be considered in a young person who has an abnormally severe adverse response to chemotherapy or radiotherapy [29]. A family history of multiple cancers and/or excessive toxicity from radiotherapy or chemotherapy should trigger the clinician to consider FA [25].

Diagnosis of FA is based on a combination of observed clinical features and laboratory testing, which consists of demonstrating hypersensitivity to DNA cross-linking agents by exposing cells from the peripheral blood, bone marrow or skin to diepoxybutane or mitomycin C [33]. Cells from patients with FA will exhibit increased rates of chromosomal breakage when exposed to such agents. Additional genetic testing is performed to identify the specific mutation present and assign the patient to a complementation group [30]. Some correlation between genotype and phenotype has been established, with a more severe phenotype associated with complementation groups FANCD1 and FANCN. However there are few other strict associations between specific complementation groups and their clinical manifestations [30].

Oral Cancer Risk

One of the most significant features of FA is the dramatically increased risk of SCC of the head and neck region (HNSCC). Studies based on case series and large FA registries have estimated the risk as 500–700 times higher than the general population [31, 35].

Previously, the survival rate for patients with FA was poor due to early-onset bone marrow failure and haematological malignancy. However with the improvements in therapy for this condition, particularly the use of haematopoietic stem cell transplantation (HSCT), patients are surviving longer, and the high incidence of solid tumours in this population is becoming evident. Life expectancy with FA is still relatively short (median 20 years), and it is possible that studies still underestimate the risk of solid tumour development due to competing causes of mortality [27, 36]. Patients with a milder disease phenotype may survive to young adulthood without the development of haematological abnormalities, and unusually early presentation with a solid tumour such as HNSCC may be the first manifestation of FA in these patients [28, 37].

HNSCCs are the second most common cancer in FA patients, and the cumulative incidence of developing HNSCC is 14% by 40 years of age [35]. FA patients develop HNSCC at a very young age compared to the general population, with a mean age of 32 years at development of first HNSCC [28]. Case reports of the development of HNSCC in FA patients as young as 13 years exist [38].

The role of traditional risk factors for HNSCC in FA patients is not as significant as in the general population, with only a quarter of patients in a large cohort study having been exposed to alcohol or tobacco prior to the development of HNSCC [28]. This is in contrast to the general population, where at least 75–85% of HNSCC may be attributable to a history of tobacco and alcohol exposure [39].

In the same cohort study, which represents the largest case series of HNSCC in FA patients ($n = 35$), the most common site of HNSCC in FA patients was the oral cavity, particularly the tongue, in concordance with previous studies [28]. In this series two patients developed a second HNSCC, and half of the patients developed a second tumour (anal, cervical, vulvar or cutaneous SCC). Half of the patients experienced recurrence of their tumour [28].

Survival rates for FA patients with HNSCC are significantly poorer than the general population. In one cohort study, 64% of the patients died as a result of HNSCC. Five-year cause-specific survival rates were only 47% in this group [28]. In contrast, survival rates in other studies for patients under 35 years of age and treated for HNSCC are >55% [40, 41]. It has been suggested that the genomic instability in FA leads to the development of more aggressive tumour types and early recurrence [28].

Due to FA-mediated sensitivity to radiation and chemotherapy, the mainstay of treatment of HNSCC in this population is surgery. Studies have shown that FA patients can tolerate standard surgical procedures for HNSCC, including free flap reconstruction [28]. If haematological abnormalities are present, then these may present difficulties perioperatively and require the involvement of a haematologist [28]. Radiation-induced pancytopenia is a rare complication in the general population but has been observed significantly more frequently in FA patients, and complications such as severe mucositis are more common [28]. Radiotherapy can be used for management of HNSCC in FA patients; however close monitoring is required to detect toxicity, and dosage reductions may be required [42]. FA patients are extremely sensitive to toxicity from chemotherapeutic agents commonly used as adjunct treatment modalities for HNSCC, particularly cisplatin-based chemotherapy regimens, as these drugs are cross-linking agents. These factors mandate modifications of adjunct chemotherapy and radiotherapy regimens in this patient population [28, 32, 43]. Ideally, management of HNSCC in FA patients should be surgical, necessitating good screening programmes in order to detect tumours early, when they are amenable to primary surgical resection [34, 43].

Recommendations on screening for FA patients advise that examination of the oral cavity and oropharynx should begin at 10–12 years of age, particularly if the patient has undergone HSCT or has any oral mucosal manifestations of GVHD or leukoplakia. Patients with abnormal oral mucosa will require six to eight weekly examinations, and those with normal mucosal appearance should be examined at least three monthly [28, 34, 35, 44]. A low threshold for biopsy of oral mucosal abnormalities should be maintained, as the aim of screening is to detect HNSCC when the tumours are small and amenable to primary resection.

An additional consideration for clinicians involved in the diagnosis and management of HNSCC is that in up to 20% of patients with FA described in the literature,

the development of HNSCC at a young age is the first presenting feature of undiagnosed FA [37]. These patients had only mild physical manifestations of FA and few or no haematological abnormalities. It is important to maintain a high index of suspicion and refer appropriately for screening for FA in young patients with HNSCC. It is particularly important that these patients are identified prior to commencement of therapy, given the high level of toxicity which will be experienced by FA patients treated with standard HNSCC treatment protocols including radiotherapy and chemotherapy with cross-linking agents [37].

Two major areas of controversy in the literature are regarding the nature of the relationship between HNSCC risk in FA patients and their exposure to human papilloma virus (HPV) and HSCT and/or graft-versus-host disease (GVHD).

High-risk HPV-related SCC of the oropharynx is increasing in incidence in the general population and more particularly in young people diagnosed with HNSCC [45]. When considering the high risk of HNSCC in patients with FA, researchers have suggested that the immunodeficiency state associated with FA leads to increased mucosal susceptibility to infection with viruses such as HPV and also increased sensitivity to known carcinogens such as alcohol and tobacco smoking [35]. The basis of the theory regarding HPV as a significant factor in the aetiology of HNSCC in FA patients is that the HPV16 E7 oncoprotein has been demonstrated to interact with the FA pathway and that genes involved in the FA pathway are critical for the repair of DNA damage induced by E7 [46, 47]. Additionally, case series from North America have demonstrated a high rate of high-risk HPV DNA in HNSCCs from FA patients [48]. In stark contrast, however, examination of HNSCC cases from FA patients in Europe failed to demonstrate this link, and in fact the majority of tumours were negative for HPV DNA [49]. In view of this conflict within the literature, it is difficult to establish the true nature of the relationship between high-risk HPV and HNSCC in FA patients. However many centres recommend HPV vaccination for all FA patients in the hope that it may assist in preventing some of these malignancies [28, 31, 32, 34, 46].

The use of haematopoietic stem cell transplantation (HSCT) has led to significantly improved survival for patients with FA. The increased longevity conferred by HSCT has allowed other features of the cancer susceptibility of FA to emerge, leading to the observation of a dramatically increased risk of HNSCC and other epithelial cancers in patients with FA [34]. In FA patients, the extreme sensitivity to chemotherapy and radiotherapy has led to alterations in HSCT protocols to reduce transplant-related mortality [30]. A cohort study comparing the risk of SCC and SCC-related mortality between two groups of FA patients showed that the rate of SCC development in transplanted patients was 4.4 times higher than those who did not receive transplants [31]. This relative risk is of similar order to non-FA patients receiving HSCT; however the increased risk on top of the already high baseline FA risk of HNSCC leads to a very significant overall increased risk of HNSCC in these patients [50]. Transplanted patients also developed HNSCC at an earlier age than non-transplanted patients (median 18 years vs. 33 years). This study also demonstrated that acute and chronic GVHD were significant risk factors for development of HNSCC in this population [31]. The study found that survival and outcomes fol-

lowing diagnosis of HNSCC were poor in both cohorts, with a median survival of 13 months [31]. A study of 13 FA patients with HNSCC following HSCT showed a median survival time of 6 months [44].

In summary, FA is a genetic disorder with a greatly increased risk of malignancy, particularly HNSCC. Clinicians should maintain a high index of suspicion for this condition in young people diagnosed with HNSCC. Treatment regimens require alteration in this patient population due to increased toxicity in response to chemotherapy and radiotherapy. Very intensive clinical monitoring and surveillance regimes are essential for all FA patients, in order to detect HNSCC whilst still amenable to primary surgical resection.

Dyskeratosis Congenita

Introduction

Dyskeratosis congenita (DC), an inherited disorder of telomere function, is characterised by a classic clinical triad of dysplastic nails, lacy reticular pigmentation of the upper chest and/or neck and oral leukoplakia. Individuals with this disorder have an increased risk of bone marrow failure, pulmonary fibrosis and other cancers. The condition may be x-linked, autosomal dominant or autosomal recessive [51].

Epidemiology

The prevalence of DC in the general population is not known, and it is believed to be rare. As of 2015, one reviewer was aware of at least 400 families in the world [52].

Pathophysiology

The mode of inheritance of DC varies by the affected genes:

- X-linked: *DKC1*
- Autosomal dominant: *TERC* and *TINF2*
- Autosomal dominant or autosomal recessive: *ACD*, *RTEL1* and *TERT*
- Autosomal recessive: *CTC1*, *NHP2*, *NOP10*, *PARN* and *WRAP53*

The link between DC and cancer is ascribed to the finding that patients with DC have defects in telomere maintenance. Telomeres are complex DNA-protein structures that protect chromosomal ends from degradation and inappropriate recombination [53].

Patients with DC have very short telomeres, and mutations have been identified in telomere biology genes, thus predisposing these patients to carcinogenesis. To date there has been no comprehensive quantitative analysis of cancer risk in DC [54].

Clinical Presentation

Dyskeratosis congenita is characterised by a classic clinical triad of dystrophy of the nails, lacy reticular cutaneous pigmentation and oral leukoplakia. Mucosal leukoplakias are seen in approximately 80% of patients and are most frequently present on the oral mucosa. Areas of leukoplakia typically involve the lingual mucosa, buccal mucosa, palate and most commonly tongue. The leukoplakia may become verrucous, and ulceration may occur. Patients also may have an increased prevalence and severity of periodontal disease, dental caries, hypoplastic enamel and hypodontia [55].

Patients with DC are at increased risk for progressive bone marrow failure (BMF), myelodysplastic syndrome (MDS) or acute myelogenous leukaemia (AML), solid tumours (usually squamous cell carcinoma of the head/neck or anogenital cancer) and pulmonary fibrosis. Other findings can include abnormal pigmentation changes not restricted to the upper chest and neck, eye abnormalities (epiphora, blepharitis, sparse eyelashes, ectropion, entropion, trichiasis) and dental abnormalities (caries, periodontal disease, taurodontism). Although most patients with DC have normal psychomotor development and normal neurologic function, significant developmental delay is present in the two variants which include cerebellar hypoplasia (Hoyeraal-Hreidarsson syndrome) and bilateral exudative retinopathy and intracranial calcifications (Revesz syndrome). The onset and progression of manifestations of DC vary—at the mild end of the spectrum are those who have only minimal clinical signs with normal bone marrow function and at the severe end are those who have the complete diagnostic triad and early-onset bone marrow failure [52].

Cancer in patients with DC usually occurs in the third decade with head and neck cancer and MDS being the most common malignancies. In older patients MDS/AML is more prevalent. Patients with moderate or mild forms of DC or those who have received haematopoietic stem cell transplant for bone marrow failure related to DC are more likely to develop solid tumours, whereas patients with severe forms of DC usually die from the disease before the development of malignancy.

Management

Treatment is tailored to the individual. Haematopoietic cell transplantation (see previous section) is the only curative treatment for bone marrow failure and leukaemia but historically has had poor long-term efficacy. If a suitable donor is not available, androgen therapy may be considered for bone marrow failure. Treatment of other cancers is tailored to the type of cancer. Cancer therapy may pose an increased risk

for prolonged cytopenias as well as pulmonary and hepatic toxicity, due to the underlying manifestations of DC. Treatment of pulmonary fibrosis is primarily supportive, although lung transplantation may be considered [51, 54, 56].

Genetic counselling regarding the risk to family members depends on accurate diagnosis, determination of the mode of inheritance in each family and results of molecular genetic testing. Once the DC-related pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at an increased risk for DC is possible [52].

Oral Cancer Risk

Data from the United Kingdom Dyskeratosis Registry indicated that the crude rate of malignancy amongst approximately 300 patients was 10% [56].

The quantitative risk of developing any cancer in DC is approximately 50-fold that of the general population, and the risks of specific malignancies are very high, in the thousands-fold for squamous cell carcinomas. The most frequent solid tumour in DC is head and neck squamous cell carcinoma, comprising 40% of all cancers found in these patients [54]. Head and neck cancer risks and outcomes in this population are similar to those encountered in Fanconi anaemia, as discussed above.

Palmoplantar hyperkeratosis

Introduction

Palmoplantar hyperkeratosis is a group of hereditary disorders of keratinisation involving hyperkeratosis of the palms and soles.

Epidemiology

The prevalence of the disorder in the general population is unknown but is likely to be less than 1 in 1,000,000. It usually manifests clinically at a very young age [57].

Pathophysiology

Two different forms of palmoplantar hyperkeratosis have been mapped to the type 1 and type 2 keratin gene cluster on chromosome 17, although palmoplantar hyperkeratosis has been shown to be heterogeneous clinically and genetically. The disorder may be caused by mutations in keratins as well as nonkeratins [58].

Clinical Presentation

Clinically and histopathologically different forms of palmoplantar hyperkeratosis exist. These may be distinguished by the pattern of the palmar and plantar keratoses, the age of onset of the disease and the occurrence of any associated features. The combination of palmoplantar keratosis with oral hyperkeratosis was first described by Fred et al. in 1964, and subsequent case reports of hyperkeratosis affecting the palms, soles and oral mucosa exist [59]. Oral manifestations have been described as presenting on the labial attached gingivae and areas of the oral mucosa affected by friction and irritation. The oral hyperkeratosis often has a symmetrical distribution and appears in early childhood or puberty, and the lesions increase in severity with age. Subungual and circumungual hyperkeratosis maybe an associated feature [60]. There is a strong association with oesophageal carcinoma in these patients [61].

Management

Management is focused on surveillance for early detection and treatment of oesophageal dysplasia. Surveillance includes annual gastroscopy with biopsy of any suspicious lesion together with screening biopsies from the upper, middle and lower oesophagus. This is coupled with dietary and lifestyle modification advice and symptom education. Genetic counselling can be offered to patients and family members once a family history has been established [62].

Oral Cancer Risk

There are significant associations between palmoplantar hyperkeratosis and oesophageal cancer [58, 62]. Although the oral lesions are generally considered benign, case reports of oral cancer in patients with palmoplantar hyperkeratosis, which is likely to have occurred in areas of oral leukoplakia related to the condition, exist [63].

Xeroderma Pigmentosum

Introduction

Xeroderma pigmentosum (XP, OMIM 278700) is an autosomal recessive genetic disorder characterised by an inability to repair DNA damage caused by ultraviolet light exposure. Individuals with this disorder have an increased risk of developing

skin cancer, and about 50% of children with XP will develop a cutaneous malignancy by the age of 10 years. Most patients with XP develop multiple skin cancers (basal cell carcinoma, squamous cell carcinoma, melanoma) in sun-exposed areas such as the face, lips, eyes, eyelids and scalp [64, 65]. Review of the literature has revealed a number of case reports of oral cavity neoplasms in individuals with XP, particularly squamous cell carcinoma of the tip of the tongue, a presumed sun-exposed location [66]. An increased risk of other forms of cancer exists in this syndrome, and gliomas of the brain and spinal cord; tumours of the lung, uterus, breast, pancreas, stomach, kidney and testicles; and leukaemia have been reported in individuals with XP [67]. Neurological symptoms are also a feature of the syndrome.

Epidemiology

XP has variable prevalence, affecting one per million in the United States, 2.3 per million in Western Europe and 45 per million in Japan [68]. Affected populations have also been described in North Africa and the Middle East, with less clearly understood frequency.

Pathophysiology

The genes affected in XP are involved in the repair of DNA damage secondary to ultraviolet light exposure. The processes affected include the nucleotide excision repair and post-replication repair pathways. The result is an accumulation of damaged DNA, which can result in increased malignant potential and neurological problems. Direct damage to the DNA of neural cells can also occur, but the precise mechanisms of this are still unclear [68].

Clinical Presentation

XP predominantly affects the eyes and sun-exposed skin and usually presents in infancy or early childhood. Affected children can develop sunburn after spending just a few minutes in the sun, and the redness and blistering can last for weeks. The skin is dry and scaly with irregular pigmentation. Extreme ocular sensitivity to UV light is a characteristic feature, with resultant abnormalities of the conjunctiva, cornea, eyelashes and eyelids. Photophobia, keratitis and eyelid thinning are common features. Benign conjunctival growths are also a feature of the condition. Approximately one third of individuals with XP may develop neurological abnormalities including hearing loss, gait abnormalities, dysphagia, dysphonia and seizures [68].

Management

The mainstay of management involves avoiding exposure to sunlight. Regular periodic skin screening examinations and local management of skin cancers are required. Skin cancers may be managed surgically or medically with topical chemotherapeutic agents such as fluorouracil. Oral isotretinoin or acitretin may be used as a means of preventing the development of skin cancers but is teratogenic and has a number of other serious side effects. Regular ophthalmological screening is also required for the management of ocular complications [68].

Oral Cancer Risk

There is no published evidence quantifying the risk of oral cancer in patients with XP. A number of case reports have been published regarding oral squamous cell carcinomas in patients with XP, and the majority of these were on the tongue tip, which is arguably also a sun-exposed area [66].

Haematopoietic Stem Cell Transplantation and Graft-Versus-Host Disease

Introduction

Haematopoietic stem cell transplantation (HSCT) and bone marrow transplantation (BMT) have become the mainstay of treatment for a variety of diseases, including acute and chronic leukaemias, inherited immunodeficiencies and assorted haematological disorders. Successful transplantation can result in cure of many of these conditions. Improvements in transplant protocols and techniques have led to reductions in peri-transplant morbidity and mortality and prolonged survival following transplant, and the impact of transplant-related late effects has now become more evident. The prevention and management of transplant complications such as graft-versus-host disease (GVHD) and late second malignancies has become a significant focus of research. Studies on the development of solid tumours following HSCT have identified that there is a significantly increased risk of head and neck squamous cell carcinoma (HNSCC) in this patient group and that this is largely related to graft-versus-host disease. Graft-versus-host disease involves an immunological attack on the host by the transplanted immune cells from the donor. This section will consider the relationship between graft-versus-host disease and the risk of HNSCC.

Epidemiology

Acute graft-versus-host disease occurs in up to 80% of HSCT recipients [69, 70]. Risk factors for the development of acute GVHD include a HLA-mismatched donor, older donor age and the use of a female donor for a male recipient [70].

Chronic graft-versus-host disease (cGVHD) occurs in up to 80% of adult long-term survivors of HSCT [71]. Chronic GVHD is less common in children, occurring in up to 25% of children receiving HSCT [72]. The most significant risk factor for the development of chronic GVHD is a history of acute GVHD. Other risk factors for chronic GVHD include HLA-mismatched donors, older patient and donor ages, female donor to male recipient and the use of mobilised peripheral stem cells rather than bone marrow as the transplant source [70].

Early reports of solid tumour risk related to HSCT were confounded by the widespread use of total body irradiation (TBI) as part of the conditioning regime, leading to an increased risk of second malignancy. Over recent years, techniques of conditioning for HSCT have changed significantly, and it is likely that this will influence future outcomes regarding solid tumour risk. Increased understanding of the role of acute and chronic GVHD in the aetiology of second malignancies, particularly HNSCC, has led to changes in transplant techniques and GVHD prevention strategies.

Males appear to have a higher risk of post-HSCT solid tumour development, particularly squamous cell carcinoma (SCC) of the skin and oral cavity.

The risk of solid tumour development increases with time after transplant, with long-term survivors (>10 years) having a 25× increased risk of oropharyngeal cancer [73].

Studies have demonstrated that TBI used as part of transplant conditioning at a young age (younger than 10 years) leads to a greatly increased risk of development of a solid malignancy. However, this effect was limited to non-SCC solid tumours, and radiation-based conditioning did not lead to an increased risk of oropharyngeal SCC. Age at transplantation did not significantly affect the risk of GVHD-related oropharyngeal SCC [73].

Pathophysiology

Acute graft-versus-host disease develops in three distinct phases. Initially, tissue damage caused by conditioning regimens involving chemotherapy and radiotherapy leads to host tissue damage and the release of inflammatory cytokines. This results in increased expression of major histocompatibility complex (MHC) antigens on host antigen-presenting cells, allowing increased reactivity of donor cells against the host. Activated donor T-cells undergo clonal expansion and release

IL-2 and interferon gamma, leading to recruitment of cytotoxic T-cells and macrophages. A significant inflammatory response develops, which is further stimulated by molecules such as lipopolysaccharides which have been released from the damaged gut mucosa. The ongoing inflammation leads to further tissue damage and cytokine release, with amplification of the inflammatory response [74].

Chronic graft-versus-host disease is a "multisystem alloimmune and autoimmune-like disorder characterised by immune dysregulation, immune deficiency, impaired end-organ function and decreased survival" [75].

The fundamental pathophysiology of cGVHD relates to a situation of dysregulated and disordered immune reactivity against self and donor antigens [74]. The precise mechanisms of cGVHD are complex and likely to involve multiple elements of the donor and host immune systems. Pro-inflammatory T-cells play a major role; however regulatory T-cells and B-cells are also involved in the pathogenesis. Clinically and histologically cGVHD resembles a number of autoimmune diseases, including scleroderma, systemic lupus erythematosus, primary biliary cirrhosis, Sjogren syndrome and lichen planus [75].

Reduced intensity and non-myeloablative conditioning regimens were introduced with the aim of extending the availability of HSCT to patients who were deemed at high risk of complications related to traditional myeloablative pre-transplant conditioning [76]. Additionally, it was recognised that the "graft-versus-tumour" effect played a significant role in prevention of relapse. This refers to the ability of the donor T-cells to target and destroy any residual malignant cells in the host, such as may be the case after a non-myeloablative conditioning regime. The graft-versus-tumour effect has also been utilised in the development of protocols using donor lymphocyte infusions (DLI), in which a post-transplant patient is given infusions of immunocompetent lymphocytes from their original donor, to elicit a graft-versus-tumour effect with the aim of inducing remission [76]. However a significant graft-versus-tumour effect is often accompanied by active and sometimes severe graft-versus-host disease. Management of GVHD is a balance between high levels of immunosuppression to prevent it from occurring, which will lead to a reduction in the graft-versus-tumour effect and a higher risk of disease relapse, and the potential morbidity caused by severe GVHD.

Mechanisms of solid tumour development in post-HSCT patients or who have suffered from cGVHD are incompletely understood. Theories which have recently been suggested for the increased incidence of oral SCC in this patient cohort include the development of genomic instability in the mucosa following prolonged periods of inflammation and immunological "injury" by T-cells; long-term upregulation of cytokines which are known to be active in SCC, such as type 1 interferon; and possibly even a direct role of donor-derived cells in carcinogenesis [77–79].

Clinical Features

The classical clinical triad of acute GVHD is the involvement of the skin, gastrointestinal tract and liver. Skin manifestations include a maculopapular rash primarily affecting the palms and soles but which may affect any part of the body.

Gastrointestinal involvement is characterised by secretory diarrhoea which can be severe. Liver involvement manifests as jaundice and a cholestatic liver picture [69]. Oral mucosal involvement with acute GVHD is characterised by mucositis of varying severity [75].

Chronic GVHD has a variety of different features and organ involvement. The most commonly affected sites are the skin and oral mucosa. Oral mucosal manifestations of cGVHD include reticular white striae (or "lichen planus-like changes"), erythema, erosion and ulceration and hyperkeratotic plaques [80, 81]. Sclerotic cGVHD can lead to contraction of the skin around the mouth, causing microstomia, as well as fibrosis of the oral mucosa leading to trismus and limited flexibility of the oral mucosa. The major and minor salivary glands may also be affected by cGVHD, and this can lead to symptomatic xerostomia. Recurrent superficial mucoceles are also a feature [75].

Traditionally cGVHD was defined as occurring greater than 100 days post-transplant. However with the advent of reduced-intensity and non-myeloablative conditioning regimens, changes have been observed in the natural history of cGVHD. Some patients who have undergone reduced-intensity transplants will develop cGVHD very much later and may also develop signs of both acute and chronic GVHD following donor lymphocyte infusion (DLI) [82]. Hence the distinction between acute and chronic GVHD is now made based on clinical features rather than on time after transplantation. Various other presentations are also now recognised, such as "overlap" and "late acute" GVHD [80]. In an overlap presentation, features of acute and chronic GVHD are present simultaneously.

Diagnosis of cGVHD is made by recognising the presence of the "diagnostic" manifestations, as listed in the NIH criteria. The presence of a "diagnostic" sign or symptom establishes the presence of cGVHD without the need to perform further testing. The NIH criteria also list "distinctive" signs or symptoms, which are not sufficient to establish a diagnosis of cGVHD in isolation—further testing is required, such as histological diagnosis. A diagnosis of cGVHD is made if at least one diagnostic manifestation is present or at least one distinctive manifestation plus a positive diagnostic test, such as histopathological confirmation [80].

The only "diagnostic" manifestation of oral mucosal cGVHD is lichen planus-like changes. If this feature is present, then cGVHD may be diagnosed, without the requirement for a biopsy or further investigations. "Distinctive" manifestations include xerostomia, mucoceles, mucosal atrophy, ulcers and pseudomembranes [80]. Previous iterations of the diagnostic criteria included hyperkeratotic plaques without lichen planus-like features (leukoplakia) as a diagnostic criterion; however this has now been removed due to concerns that it represents a separate entity, with an associated risk of malignant transformation [80].

The major differential diagnoses for oral mucosal manifestations of cGVHD are inflammatory conditions such as oral lichen planus, from which it is clinically indistinguishable and infective processes such as oral candidiasis. If there is any doubt about the diagnosis, then consideration of the wider clinical picture is important, as is appropriate investigation of the oral mucosa to rule out infective or neoplastic processes.

Clinical manifestations which are considered "common" to both acute and chronic GVHD include pain, erythema, mucositis and gingivitis. The presence of these features is considered either diagnostic or distinctive for either type of GVHD [80].

Chronic GVHD can affect the skin, nails, genital mucosa, fascia, eyes, lungs and the gastrointestinal tract [83].

A variety of strategies have been employed in order to prevent the development of GVHD. The majority of these are directed at reducing the incidence of severe acute GVHD, as this is the strongest risk factor for the development of chronic GVHD, which has a significant impact on non-relapse mortality [84, 85].

The most commonly used agents to prevent GVHD are the calcineurin inhibitors cyclosporin and tacrolimus. These drugs are prescribed during the first 3 months following HCST and gradually tapered if there are no further signs of acute or chronic GVHD.

Newer strategies for prevention of GVHD have focused on T-cells, as these are necessary to cause the disease [84]. Depletion of T-cells in the donor graft can lead to significantly lower rates of GVHD but has risks of delayed immune reconstitution in the recipient and associated infective complications [86]. Techniques used for T-cell depletion include anti-thymocyte globulin and alemtuzumab (monoclonal antibody to CD52 receptor) [84].

Treatment of active acute GVHD relies primarily on corticosteroids and calcineurin inhibitors, although a wide range of other treatment options are available and are used as second-line treatment in steroid-refractory cases [69].

First-line treatment for chronic GVHD is with systemic corticosteroids and calcineurin inhibitors. Depending on the site of disease activity, a variety of topical and local therapies are also used. Comprehensive reviews exist on this subject [71, 87].

Management of active oral cGVHD is based on symptom control. It is not usually possible to produce a “normal” mucosal appearance therapeutically, and reticular, plaque-like and sclerotic lesions may be present even when the disease is dormant. Systemic corticosteroids and immunosuppressants are required if the oral mucosa is severely ulcerated, limiting oral intake and quality of life. Systemic treatment will usually be prescribed if another organ is also severely affected, particularly the lungs or liver. Otherwise, options for management of oral mucosal cGVHD include topical corticosteroids, topical immunomodulators such as tacrolimus ointment, topical anaesthetics for symptom control and agents used for the management of dry mouth symptoms. Severe, steroid-dependent or steroid-refractory oral cGVHD may also be treated with extracorporeal photophoresis [88]. Consensus documents have recommended that patients with severe oral cGVHD should be referred to an oral medicine team for specialist management [87].

Oral Cancer Risk

Recipients of HSCT are at a significantly elevated risk of oral SCC. In a large cohort study of HSCT recipients, the observed-to-expected ratio for oral SCC was 7.01 [73].

Further analysis has revealed that the strongest predictor of oropharyngeal SCC risk in HSCT recipients is chronic GVHD. Chronic GVHD has been identified to

lead to a three- to fivefold increased risk of SCC [73, 89]. This risk is present in the first 4 years post transplant and is also maintained greater than 5 years post transplant [73].

Immunosuppression is routinely used to prevent severe GVHD following HSCT. Studies have established that the duration of immunosuppression and exposure to certain immunosuppressive agents, particularly azathioprine, are related to the excess risk of oropharyngeal SCC following HSCT [50, 89–91]. Patients with severe chronic GVHD are usually exposed to a greater duration of immunosuppression than those with a milder course. An important case-control study showed that the risk of oral SCC was increased by eight times after greater than 24 months of immunosuppressive therapy for cGVHD [89].

Although beyond the scope of this chapter, effective management of oral cGVHD would appear to be an important factor in reducing the risk of late second malignancies in the oral cavity. Given the significant contribution that the duration of systemic immunosuppression has to the excess risk, it is desirable that optimal topical treatment is provided for oral cGVHD, in order to reduce the need to systemically immunosuppress these patients. Oral medicine and oral surgery specialists have an important role to play in the correct diagnosis of oral symptoms as being related to cGVHD, provision of optimal topical management of symptoms in order to reduce the need for systemic immunosuppression and screening for malignancy.

In view of the significantly elevated risk of SCC, including oral mucosal SCC, in the post-HSCT patient population, it is essential that effective screening measures are in place. The median time to development of oral SCC following HSCT is 6 years, so long-term screening is essential in order to detect malignancies early when they are more amenable to treatment [89]. Patient education plays an important role—patients should be counselled to seek dental or medical attention if they develop new changes or abnormalities in the oral mucosa. Recommendations from international consensus statements on the management of chronic GVHD have recommended that these patients should be referred to an oral medicine service for ongoing oral mucosal surveillance. Six monthly or more frequent oral mucosal examinations are recommended for patients at high risk of developing SCCs, such as those with severe cGVHD or Fanconi anaemia [81, 87, 92].

HIV

Introduction

Human immunodeficiency virus (HIV) infection is a known risk factor for a number of cancers. Kaposi sarcoma, non-Hodgkin lymphoma and cervical cancer are referred to as “AIDS-defining” cancers, signifying a progression to the acquired immunodeficiency syndrome (AIDS) state. However it has been increasingly recognised that HIV-positive individuals are at increased risk of a number of other

cancers, including anal carcinoma, lung cancer, hepatocellular carcinoma and Hodgkin lymphoma [93]. A number of case reports and case series have also reported an increased risk and demographically different behaviour of oral squamous cell carcinoma in HIV-positive individuals [94–97].

Research into the increased risk of malignancy in HIV has focused on the nature of HIV as an immunodeficiency state, comparable to iatrogenic immunosuppression; on the role of infective agents in the aetiology of malignancy in HIV-positive individuals; and on the contribution of highly active antiretroviral therapy (HAART) to malignancy risk.

Epidemiology

HIV infection is a major worldwide health issue but is particularly problematic in the developing world, where rates of infection continue to rise. UNAIDS data from 2015 estimate that 36.7 million people worldwide were living with HIV, 2.1 million people were newly infected with HIV in 2015, and 1.1 million people died from AIDS in the same year. The highest prevalence of HIV was in Africa [98].

In the United Kingdom in 2015, over 88,000 people were living with HIV and accessing care. There were 6095 new diagnoses of HIV during 2015. The age distribution of people seeking care for HIV is changing, with one in three people accessing care aged 50 years or over, compared to one in seven in 2005 [99].

Pathophysiology

HIV is a retrovirus, from the lentivirus group of this family. Two types have been identified—HIV-1 is the most common, and HIV-2 infection is confined to some areas of Europe and Western Africa. The virus consists of a lipid coat with glycoprotein gp120 expressed on the surface, mediating attachment to host CD4 cells. The virus contains single-stranded RNA, a core protein known as p24, a protease and a reverse transcriptase polymerase. Reverse transcriptase converts viral RNA into DNA, enabling it to be added to the host cell genome.

Following entry of the virus to the host, the gp120 glycoprotein binds to host CD4 T-cells and enters the host cell. Viral reverse transcriptase transforms the viral RNA into double-stranded DNA, which is integrated into the host cell genome. During subsequent transcription, the host cell machinery will produce viral mRNA, which then undergoes translation into the viral structural proteins gp160, p24 and p17. The enzymes protease and reverse transcriptase, along with the structural proteins and the viral RNA, are assembled into the viral capsid which is then budded from the host cell, forming a virion capable of further infection (Ref Kumar and Clark).

During this process, CD4 T-cells are destroyed by direct viral effects, as well as by CD8 cells and NK cells as part of the host immune response. This leads to a gradual depletion of host CD4 T-cells and a resultant immunodeficiency state. Immune activation also occurs which leads to increased numbers of CD4 cells becoming infected and destroyed and an increased susceptibility to inflammation and infection due to damaged mucosal surfaces.

As the disease progresses, the CD4 T-cell count will progressively drop. As this occurs, the prevalence of opportunistic infections increases. At a CD4 T-cell count of less than 200 cells/mm^3, the patient is at a high risk of AIDS-defining illnesses. These are primarily severe and/or unusual opportunistic infections; however the malignancies Kaposi sarcoma and some forms of lymphoma are considered AIDS-defining conditions.

Clinical Features

Primary HIV infection refers to the period between initial infection and the development of antibodies against the virus. During this period, the individual may develop symptoms of HIV seroconversion illness, which includes fever, lymphadenopathy, a maculopapular skin rash and myalgia. This is typically a self-limiting illness and has a wide range of differential diagnoses [100].

Following primary infection many individuals will remain asymptomatic for a period of time. As the viral load rises and the CD4 count decreases, more symptoms and signs will become evident, mainly related to opportunistic infections. If untreated, the median time to development of AIDS is 10 years. Persistent generalised lymphadenopathy may occur during this time.

Prior to the development of AIDS, the infection may become symptomatic. Symptomatic HIV-related conditions include systemic symptoms of fever, fatigue, diarrhoea and weight loss; infections including oropharyngeal candidiasis, herpes zoster and pelvic inflammatory disease; hairy leukoplakia; cervical dysplasia; peripheral neuropathy; and idiopathic thrombocytopenic purpura [100].

The development of AIDS is characterised by a significant decrease in the number of CD4 T-cells and a dysregulation of other elements of the immune system. Clinical manifestations of AIDS are listed in Box 7.1—these conditions are referred to as AIDS-defining conditions, and the presence of these diagnoses in conjunction with the CD4 T-cell count is used to define the progression to AIDS.

The development of highly active antiretroviral therapy (HAART) has changed the outcome of HIV infection dramatically. The condition is no longer considered universally fatal and the progression to AIDS inevitable; rather it is viewed as a chronic disease, which can be effectively managed with medications. Many of the symptomatic features of HIV infection as listed above will reverse with effective HAART. Successful treatment results in a low or undetectable viral load, rising CD4 T-cell count and improvement in symptomatic HIV disease manifestations.

Box 7.1 Centers for Disease Control and Prevention (CDC) AIDS-Defining Conditions [101]

- Bacterial infections, multiple or recurrent (in children aged <6 years)
- Candidiasis of the bronchi, trachea or lungs
- Candidiasis of the oesophagus
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month's duration)
- Cytomegalovirus disease (other than the liver, spleen or nodes), onset at age >1 month
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy attributed to HIV
- Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis or oesophagitis (onset at age >1 month)
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month's duration)
- Kaposi sarcoma
- Lymphoma, Burkitt (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of the brain
- *Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated or extrapulmonary
- *Mycobacterium tuberculosis* of any site, pulmonary, disseminated or extrapulmonary
- *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis jirovecii* pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- *Salmonella* septicaemia, recurrent
- Toxoplasmosis of the brain, onset at age >1 month
- Wasting syndrome attributed to HIV

HAART consists of a combination of medications which target different aspects of the viral lifecycle. The four major classes of drugs, their mechanisms of action, and some examples are listed in Table 7.1. HAART typically comprises at least two different reverse transcriptase inhibitors and at least one drug from another class. Combination therapy is required in order to avoid the generation of resistant strains of the HIV. HIV lacks error-correcting mechanisms for the process of reverse transcription, and this as well as its rapid replication rate leads to a high rate of

Table 7.1 Antiretroviral drugs [100]

Drug class	Mechanism of action	Examples
Entry inhibitors	Inhibit the entry of HIV to CD4 T-cell by preventing fusion and blocking chemokines involved in binding	Enfuvirtide Maraviroc
Nucleoside/nucleotide reverse transcriptase inhibitors	Inhibit transcription of viral RNA into DNA	Zidovudine Lamivudine Abacavir Tenofovir Emtricitabine
Non-nucleoside reverse transcriptase inhibitors	Inhibit transcription of viral RNA into DNA	Efavirenz Etravirine
Integrase inhibitors	Inhibit integration of viral DNA into host cell genome	Raltegravir
Protease inhibitors	Inhibit virion assembly prior to release from the host cell	Atazanavir Darunavir Ritonavir

mutation. This can lead to the generation of resistance very quickly. As such, compliance with HAART is particularly important, and resistance patterns are carefully monitored by HIV specialists.

Oral Cancer Risk

Data regarding the risk of head and neck squamous cell carcinoma in HIV-positive individuals has come mainly from small case series and analysis of registry data in epidemiological studies.

Epidemiological studies based on analysis of registry data have suggested a 2–4× increased risk of oropharyngeal cancer in HIV-positive individuals. These studies have also been unable to demonstrate a significant change in the incidence of oropharyngeal cancer in this patient population following the introduction of HAART [102–105].

Case series have reported that HNSCC tends to occur at a younger age (median 45 years in one study) and at a more advanced stage in HIV-positive individuals [94–96, 106, 107].

The contribution of known HNSCC risk factors such as smoking and alcohol to the development of cancer in HIV-positive individuals has been debated in the literature. Historically, studies have shown an increased rate of tobacco smoking in the HIV-positive cohort; however a meta-analysis failed to demonstrate a difference in the risk of smoking-related cancers between an HIV-positive population and an immunosuppressed population with a lower exposure to tobacco smoking [93]. Studies investigating the increased incidence of lung cancer in the HIV-positive population have established that the excess risk is not entirely attributable to smoking exposure [108].

The introduction of HAART has significantly changed the outlook following HIV diagnosis. HIV-positive individuals on HAART have an increased life expectancy and a lower rate of development of AIDS. This has led to a change in the range of clinical presentations, particularly related to cancer, in people living with HIV [109].

Theories regarding the aetiopathogenesis of HNSCC in HIV-positive individuals have focused on the roles played by immunosuppression, infection and exposure to risk factors.

A large study comparing rates of cancer in an HIV-positive population and an immunosuppressed population (transplant recipients) found a consistent pattern of increased risk of cancer of a variety of sites in both populations [93]. There were very few differences between the two groups in the prevalence of cancer types, apart from Kaposi sarcoma, liver and anal cancers, which were more prevalent in the HIV group. The authors comment that there was a clear increase in the risk of cancers which are definitely or theoretically linked to infection, such as Kaposi sarcoma (human herpes virus 8), lymphoma (Epstein-Barr virus) and cancer of the cervix and anus (human papilloma virus). This increase occurred to a similar extent in both the HIV-positive and post-transplant groups. However there were also increased incidences of cancers not linked to a known infective agent. The authors note that the exposure to risk factors for HNSCC such as smoking was very different in the two study groups, with transplant recipients having a smoking rate similar to the general population but the HIV-positive group having doubled the population smoking rate. Despite this, there was not a significant difference in rates of smoking-related cancers in between the groups. This study concluded that immunosuppression and its effects on immunity to oncogenic viruses play a very significant role in the risk of cancer in HIV-positive individuals.

Another study considering cancer incidence in HIV-positive individuals demonstrated an increased risk of HNSCC associated with increasing severity of immunosuppression and progression to AIDS [103].

Many studies have commented on the possible role played by human papilloma virus in the aetiology of HNSCC in HIV-positive individuals. Given the increased prevalence of other HPV-related carcinomas in this patient population, particularly cervical and anal carcinomas, it has been suggested that the increased risk of HNSCC may also be due to this infection [110]. Studies have shown that HPV infection prevalence is significantly higher in HIV-positive individuals, including high-risk strains such as HPV16 [111].

In the general population, an increasing prevalence of HPV-positive HNSCC has been observed, particularly oropharyngeal squamous cell carcinomas. High-risk viral strains such as HPV16 have been detected in these carcinomas. However the same trend has not been observed in oral cavity carcinomas, which have a lower prevalence of HPV positivity [112].

Despite a higher prevalence of HPV positivity and a modestly increased rate of HNSCC in the HIV-positive population, studies have not been able to demonstrate a definite relationship between HPV positivity and the increased risk of HNSCC in this cohort [110, 113].

A small case series in Japan reported that HIV-positive individuals had an increased risk of developing oral mucosal changes which were considered prema-

lignant and that this risk was the same as that conferred by smoking in their control population [114].

Overall, there is a paucity of information regarding the aetiopathogenesis of HNSCC in HIV-positive individuals. This malignancy is still relatively rare in this patient population, and very large prospective studies are required in order to establish clearer information regarding the condition. In addition, the majority of published data to date is from HIV registries in the developed world. It is not clear whether similar rates of HNSCC occur in the countries with the highest HIV prevalence.

Syphilis

Introduction

Syphilis is a sexually transmitted infection caused by the spirochaetal bacterium *Treponema pallidum*. Acquired infection is transmitted through direct person-to-person sexual contact. Vertical transmission from the mother to the baby causes a congenital infection. Most sexual transmission of syphilis occurs from the genital and mucous membrane lesions of primary and secondary syphilis. Syphilis has often been described as the great imitator because many of the symptoms and signs are difficult to distinguish from other diseases [115].

Epidemiology

Syphilis is a common, worldwide sexually transmitted disease, with approximately 10.6 million new cases reported in 2005 and 2008, according to the World Health Organization. Rates of syphilis infection have been rising over recent years, commonly as a co-infection with other sexually transmitted infections. In the United Kingdom over the period 2003–2012, the number of new diagnoses of syphilis in men rose by 61% and decreased in women by 16%. A recent report regarding the rate of syphilis infections in London in 2015 stated that from 2010 to 2015, the rate of syphilis infection in the city has risen by 163%. The majority of these cases are in men who have sex with men [116].

Pathophysiology and Clinical Features

The first stage of infection with *T. pallidum* is known as primary syphilis and represents local infection at the site of inoculation of the organism. The average incubation time is 2–3 weeks after which a painless papule appears at the site of inoculation.

The primary chancre will heal within 3–6 weeks. Systemic dissemination of *T. pallidum* occurs during the primary stage of infection.

Secondary syphilis develops within 4–6 weeks after the primary infection. This features a variety of systemic signs and symptoms and general malaise.

The third stage of untreated syphilis is termed latent syphilis. This is the period during which patients are asymptomatic but serologically positive.

The fourth stage is referred to as tertiary syphilis. Tertiary syphilis can arise as early as 1 year after initial infection or up to 30 years later. It may involve the central nervous system, cardiovascular system, skin or mucous membranes.

Syphilis is accompanied by additional sexually transmitted diseases in approximately 10% of cases, and syphilis-associated genital ulceration increases the risk of HIV transmission [117].

Clinical Features

Oral syphilitic chancres and mucous patches are usually painless unless they become secondarily infected. The chancre begins as a papule that erodes into a painless ulcer with a smooth, grey surface. A key feature is unilateral lymphadenopathy. Intraoral lesions may present as slightly raised asymptomatic papules with an ulcerated surface and may occur on the lips, tongue and buccal or labial mucosa. Both the chancre and mucous patches resolve spontaneously without treatment; however antibiotic therapy is required to eradicate the systemic infection.

Symptoms of secondary syphilis include generalised rash, fever, lymphadenopathy, malaise, alopecia, aseptic meningitis and uveitis. Maculopapular lesions on the palms and soles occur in 60–80% of patients with secondary syphilis. Up to 58% of patients will have mucocutaneous or mucosal lesions, mucous patches or condylomata lata (broad-based verrucal plaques) in the oral or genital regions [117]. Many other types of oral lesions associated with secondary syphilis have been reported, and they can resemble hairy leukoplakia, erythema multiforme, lichen planus and pemphigus vulgaris (Mignogna et al. 2009).

The classical lesion of tertiary syphilis is the gumma, a rubbery, ulcerated nodule. It is non-infectious and may involve the skin, mucous membranes, skeletal system and viscera. The gumma is a painless lesion that may become secondarily infected. These lesions may occur on the hard palate and can destroy this structure. Atrophic glossitis, the result of contracture of the tongue musculature after healing of a gumma, is viewed as a premalignant lesion [117].

The diagnosis of syphilis is made based on clinical presentation, examination of biopsy tissue using dark-field microscopy or polymerase chain reaction (PCR) and serological tests. Serological testing for syphilis is complex, and the reader is directed to recent guidance documents regarding the most appropriate mode of testing in particular patient groups [118].

Syphilis may be cured with appropriate antibiotic therapy, and these patients should be managed in specialist infectious disease clinics. Prompt diagnosis and antibiotic therapy are important due to the risk of further transmission of the disease and also to prevent long-term complications such as neurosyphilis and involvement of the cardiovascular system [118]. Intramuscular benzathine penicillin G is the first-line drug treatment for all stages of syphilis. The form of penicillin, dose and duration of treatment are determined by the stage and clinical manifestations of the disease. Oral doxycycline may be used in patients with a penicillin allergy.

Treatment may follow positive diagnostic test results or may be empirical. Empirical therapy should be considered in those with suspected early infection (a rash or ulceration) before serology results are available. Sexual contacts of patients with confirmed syphilis should be screened and offered presumptive treatment if follow-up may be problematic. The benefits of empirical therapy (prompt therapy) and risks (potentially unnecessary treatment) should be discussed with the patient.

Oral Cancer Risk

Tertiary syphilis may cause leukoplakic lesions, particularly of the tongue, and this lesion may undergo malignant transformation. This risk appears to persist even when adjusted for alcohol and tobacco exposure [119, 120]. Case series have reported a fourfold increase in SCC related to these lesions. However, these case reports are relatively old, and the risk may be attributable to the agents formerly used to treat the disorder, such as arsenic and heavy metals [117].

In one study of 63 patients with tongue neoplasia, 8% displayed serological positivity, leading the authors to suggest that syphilis serology screening should be routinely performed in patients diagnosed with oral cancer [121]. However it should be noted that in current practice, seropositivity for syphilis is uncommon amongst patients with oral malignancy [122].

Sideropenic Dysphagia (Plummer-Vinson or Patterson-Kelly Syndrome)

Introduction

Sideropenic dysphagia, also known as Plummer-Vinson or Patterson-Brown-Kelly syndrome is characterised by a triad of dysphagia, upper oesophageal web formation and iron deficiency anaemia. It is considered to be a premalignant condition and is associated with cancers of the upper digestive tract.

Epidemiology

This condition most commonly affects females in the fourth to sixth decade of life, although the syndrome has also been described in adolescents and children. Exact epidemiological data is not available; however the syndrome appears to be extremely rare [123].

Pathophysiology

The aetiopathogenesis of Plummer-Vinson syndrome is unknown, but it appears that the most important aetiological factor is iron deficiency. Other possible factors include malnutrition, genetic predisposition or autoimmune processes. Myasthenic changes occur in the muscles involved in swallowing due to the depletion of iron-dependent oxidative enzymes [123]. Atrophy of the oesophageal mucosa and formation of oesophageal webs are common mucosal manifestations.

An autoimmune mechanism has also been proposed, as the syndrome is frequently observed in association with rheumatoid arthritis, thyroiditis, coeliac disease and pernicious anaemia. Other factors such as nutritional deficiency and genetic predisposition are thought to play roles in the causation of the disorder [123].

Clinical Presentation

The dysphagia usually presents intermittently or progressively over years and is painless. Epithelial changes include koilonychia, atrophic glossitis, xerostomia and atrophic changes in the conjunctiva as well as the formation of post-cricoid oesophageal webs. Oral manifestations include stomatitis, angular cheilitis, glossitis and differential atrophy of the fungiform and filiform papilla, recurrent aphthous stomatitis, oral candidosis, erythematous mucositis and a burning mouth. Filiform papillae are the most susceptible to nutritional deficiency and disappear first, followed by the fungiform papillae. Regeneration of the papillae occurs in reverse order, but the vallate and foliate papillae on the posterior third are spared [123].

Diagnosis of iron deficiency anaemia relies on history, clinical examination and appropriate investigations. Radiographic and endoscopic examination of the pharynx may reveal the presence of oesophageal webs.

Iron deficiency anaemia causes epithelial atrophy, changes in epithelial cell kinetics and decreases the repair capacity of the mucosa. This allows carcinogenic and cocarcinogenic agents to act aggressively, predisposing the entire oral mucosa and oesophageal region to malignancy [124].

Management

Correction of the iron deficiency anaemia is the mainstay of treatment. Iron supplementation may be given orally or parenterally if required. Iron supplementation alone can resolve the dysphagia in many patients. Mechanical dilation of webs or strictures by endoscopy may be required. Regular clinical monitoring of the oral mucosa and endoscopic monitoring of the pharyngeal and oesophageal mucosa are necessary in order to identify potentially malignant lesions [123].

Oral Cancer Risk

Sideropenic dysphagia is a major risk factor for the development of squamous cell carcinoma of the upper gastrointestinal tract, with 3–15% of patients with sideropenic dysphagia developing oesophageal or pharyngeal cancer [125].

There are a few case reports of oral cancers in patients with sideropenic dysphagia; however the aetiopathogenesis of this is likely to be multifactorial [123, 126].

New Medications

Emerging risk factors for the development of HNSCC are drugs developed for treatment of advanced melanoma. The BRAF inhibitors vemurafenib and dabrafenib target mutated BRAF protein in melanoma cells and slow the growth of these tumours. They are licenced for the management of advanced or metastatic melanoma.

Immune checkpoint inhibitors such as PD-1 inhibitors pembrolizumab and nivolumab are monoclonal antibodies against cell-surface proteins involved in cancer cell evasion of antitumour T-cell activity. These drugs are used in the management of advanced or metastatic melanoma and metastatic non-small cell lung carcinoma.

Early studies of the BRAF inhibitors demonstrated an increased risk of cutaneous squamous cell carcinoma [127, 128]. However, since the drugs have been more widely used, a number of case reports of oral mucosal changes which have been linked to these drugs, including hyperkeratotic lesions, extensive inflammatory gingival changes and oral squamous cell carcinoma, have emerged [128–131].

Initially it was thought that these drugs would prolong life expectancy by a relatively short period; however a cohort of patients has emerged in whom the drugs have been successful in suppressing tumour activity, and they have survived for several years on therapy [127]. It is likely that more drug-related epithelial effects may become apparent as this cohort of patients grows, and it is important that a comprehensive oral mucosal screening examination forms part of ongoing therapeutic monitoring for these patients.

Rare Associations

A number of rare genetic disorders have been associated with a possibly increased risk of HNSCC. In many of these, the putative link is based on a small number of case reports. It is difficult to comment definitively on the risk of HNSCC in these situations given the rareness of the genetic disorders and the infrequency of reporting of head and neck malignancies.

HNSCC has been reported in association with Bloom syndrome; keratitis-ichthyosis-deafness syndrome; warts, hypogammaglobulinemia, infections and myelokathexis (WHIM) syndrome [132]; familial atypical multiple mole melanoma (FAMMM) syndrome/FAMMM-pancreatic cancer (FAMMM-PC) syndrome [133] and Gorlin-Goltz syndrome. Some authors suggest an increased frequency of HNSCC in ataxia telangiectasia and Li-Fraumeni syndromes; however there is little evidence in the literature to support this.

Basal cell naevus syndrome (OMIM 109400), also known as Gorlin-Goltz syndrome, is an autosomal dominant disorder caused by mutations in the PTCH1, PTCH2 and SUFU genes, which encode proteins involved in tumour suppression. The syndrome is characterised by multiple basal cell carcinomas, odontogenic keratocysts of the jaws, palmoplantar hyperkeratosis, skeletal and facial abnormalities and ectopic intracerebral calcification [134]. Three case reports of squamous cell carcinoma in patients with this disorder exist in the literature [135–137]. Some debate exists as to whether these lesions arise within odontogenic keratocysts, one of the primary manifestations of this syndrome, or form a separate part of the disorder.

Keratitis-ichthyosis-deafness syndrome (OMIM 148210) is due to sporadic or autosomal dominant or recessive inheritance of a mutation in the GJB2 gene, which encodes for a gap junction protein known as connexin 26. Clinically it is characterised by a variety of cutaneous abnormalities, sensorineural deafness, ocular abnormalities, immunodeficiency and mucocutaneous candidiasis and malignancy (squamous cell carcinoma and trichilemmal tumours) [138]. The literature contains four case reports of oral squamous cell carcinoma in patients with this syndrome [139–142]. Cutaneous squamous cell carcinoma is significantly more common [138].

Bloom syndrome (OMIM 210900) is an autosomal recessive inherited disorder with clinical features of short stature, cutaneous abnormalities including photosensitivity and telangiectasia, chromosomal instability, immunodeficiency and cancer predisposition. Due to the chromosomal instability, patients are at risk of accumulating somatic mutations which leads to the increased cancer risk [143]. A number of case reports of HNSCC in this cohort exist [144–146].

Epidermolysis bullosa (EB) is the title given to a heterogeneous group of inherited disorders, generally characterised by skin blistering and erosion. Simplex, junctional and dystrophic forms are recognised, with the dystrophic forms tending towards a more severe phenotype. Dystrophic EB is characterised by severe, widespread blistering of the skin, oesophagus, oral mucosa and conjunctiva, with associated scarring and loss of function. A significant clinical manifestation of EB is the

high rate of cutaneous squamous cell carcinoma, and the prevalence is up to 90% in the severe forms of dystrophic EB [128, 147, 148].

EB is widely reported as being a condition which predisposes to oral squamous cell carcinoma; however it is difficult to support this from the literature, with only a small number of cases reported [128–131, 147, 149, 150].

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