CHAPTER 5

IMMUNOPATHOLOGY

Abstract

During the phase of acute infection, most patients manifest clinical symptoms of viral infection (called "seroconversion illness"). Many HIV-infected individuals remain asymptomatic in spite of continuing damage to their immune system. When the CD4 count falls markedly, AIDS-defining opportunistic infections usually appear. Patients with advanced HIV infection may develop neurological disorders and malignancies. Autoimmune antibodies may be produced against platelets, lymphocytes, neutrophils, and myelin. Antibody-mediated drug allergies are more frequent. Autoimmune disorders may occur in the early stages since the immune system is relatively effective. The origin of many autoimmune disorders is different, as compared to that of similar conditions in HIV-negative individuals.

5.1 – PRIMARY INFECTION

The gp 120 on the outermost envelope of HIV binds to cells bearing CD4 co-receptor (T-helper cells, monocytes, and macrophages). Soon after infection, HIV reaches the regional lymph nodes and stimulates both cellular and humoral immune responses. More and more cells bearing CD4 co-receptor get infected due to the flow of lymphocytes to the lymph nodes. Within a few days, there is leukopenia (decrease in white blood cell count) with an acute reduction in the level of circulating CD4 T-lymphocytes. The blood levels of virus and viral proteins are high (Levi, 1993). After 2–4 weeks, the immune responses to HIV results in a phenomenal increase in lymphocyte count mainly due to increase in CD8 T-cells (Cooper *et al*., 1988). The CD4 cell counts also reach pre-infection levels. Specific anti-HIV antibodies are present in the blood, about 2–3 weeks after infection, but this may be delayed in some patients. During the phase of acute infection, most patients manifest clinical symptoms of viral infection.

After the acute phase of primary infection, the levels of both intracellular and circulating HIV decline, probably due to specific lysis of HIV-infected cells by CD8 cytotoxic T-cells (Koup *et al.*, 1994). In vitro studies have shown that activated CD8 cells from HIV-infected patients produce soluble cytokines that inhibit viral replication in CD4 T-cells, without causing their lysis (Walker *et al.*, 1986). An increase in CD8 cell count is observed before seroconversion, in response to acute rise in HIV load and this probably plays a role in controlling virus production (Mackewicz *et al.*, 1994). Later the raised levels of CD8 cells decline but remain much higher than normal, throughout the course of the disease.

5.2 – ASYMPTOMATIC PHASE

After the acute phase resolves, many HIV-infected individuals remain asymptomatic even when the damage to their immune system continues. The damage involves the decline in *number* and *function* of CD4 T-cells. The *annual decline* in CD4 cell count averages 65 cells per µL. This works out to a *daily decline* of about 2×10^8 CD4 cells. This daily decline is compensated by the daily turnover of CD4 T-cells, which is about 2×10^9 in the asymptomatic phase and indicates considerable activity of both the virus and the immune system (Levi, 1993). There is a step-by-step *impairment of function* in CD4 cells. Initially, T-cells lose the ability to respond to recall the antigen, followed by loss of response to foreign cells and finally, loss of response to non-specific mitogens (Clerici *et al.*, 1989).

Mechanisms for Reduction in Existing Cells: Direct HIV-mediated cytopathic effects, such as rupture of T-cell membrane by replicating HIV, and cell fusion and syncytium formation; derangement of normal signalling mechanisms within T-cells leading to premature programmed cell death (called "apoptosis"); HIV-specific immune responses, such as cytotoxic CD8 T-cells, ADCC and NK cells; Binding of free gp 120 to the CD4 co-receptor of uninfected cells, making them the targets for attack by humoral and cellular immune mechanisms; and other mechanisms – autoimmune mechanisms, anergy, super antigens (super infecting organisms).

Mechanisms For Impaired Replacement: Infection of stem cells that produce precursors of T-cells; damage to thymic epithelial cells, which help maturation of T-cells; and prevention of T-cell proliferation in response to contact with many antigens by action of HIV proteins.

5.3 – ADVANCED HIV INFECTION AND AIDS

The decline in *number* and *function* of CD4 cells results in lowered production of cytokines like IL-2. This reduces the anti-HIV activity of CD8 cells. When the CD4 count falls below 200 cells per µL, monocytes, and dendritic cells (that bear the CD8 co-receptor) also get infected by HIV (Livingstone *et al.*, 1996). The HIV-infected CD8 cells contribute to the increase in viral load. The mechanism of

infection of monocytes and dendritic cells is not clear. They probably get infected in the thymus when they bear both CD4 and CD8 co-receptors on their surfaces. The disappearance of enlarged lymph nodes indicates poor prognosis. It implies that the immune system is losing the battle against HIV in the lymph nodes.

5.4 – OPPORTUNISTIC INFECTIONS

Though the cellular immunity is mainly affected, HIV destroys all aspects of the immune system. Organisms (that do not cause infection in immunocompetent individuals) cause disease by taking advantage of the lowered host immunity. The usual opportunistic pathogens are commensals (normal bacterial flora), environmental organisms (that do not affect immunocompetent individuals), and endogenous reactivation of dormant infection acquired at an earlier age. Other organisms that cause opportunistic infections include:

1. Bacteria: Mycobacterium tuberculosis, Mycobacterium avium complex, Salmonella
2. Viruses: Cytomegalovirus, Herpes simplex, Varicella-zoster, Epstein-Barr virus (EBV)
3. Fungi: Candida, Aspergillus, Histoplasma capsulatum, Coccidioides immitis, Cryptococcus neoformans, Pneumocystis
4. Protozoa: Leishmania, Toxoplasma gondii, Microsporidia, Cryptosporidia

AIDS-defining opportunistic infections usually appear when the CD4 cell count declines below 200 cells per µL. Since *Mycobacterium tuberculosis* is more virulent, reactivation of this disease can occur even with a relatively higher CD4 cell count (about 400 cells per µL).

Selection: Some of the opportunistic pathogens like *Listeria* and *Nocardia* that are commonly seen in other immune deficient patients, such as cancer patients on chemotherapy and recipients of transplants, are rare in HIV-infected individuals. Conversely, infections like disseminated candidiasis, commonly seen in cancer patients receiving chemotherapy, are rare in HIV-infected individuals. The mechanism for this type of selection is not known.

5.4.1 – Herpes zoster (Shingles)

Shingles is caused by Varicella-zoster virus, which has an infectious stage (chicken pox) and a dormant stage. The virus lives in the nerve tissue and may get reactivated when the immune system gets weakened, as in the elderly or in persons with HIV disease. About 20 per cent of persons who have had chicken pox may develop herpes zoster. The disease starts on one side of the body with pruritus, numbness, tingling, and severe pain in a belt-like pattern, along the dermatomes. Lesions are commonly seen on the trunk, but rarely, they may be present around the mouth, on the face, neck, scalp, in and around the ear, or at the tip of the nose. Few days later, a rash appears on the skin overlying the affected

nerve. A vesicular eruption follows. The fluid in the vesicles is highly infectious to others. The vesicles break open and form crusty scabs. Secondary infection of vesicles may require treatment with antibiotics. In most cases, the lesions disappear in a few weeks. In some cases, severe pain (called "post-herpetic neuralgia") can last for months or years. The antiviral drug acyclovir is given orally five times a day. The drug is given intravenously for severe cases. Newly approved drugs famciclovir and valacyclovir are given orally three times a day. Some of the drugs used to treat depression (nortriptyline) or epilepsy (pregabalin) are used to treat the severe pain of herpes zoster. Anaesthetics and/or steroids are being studied as nerve blockers. In 1999, the US Food and Drug Administration (FDA) approved the dermal patch form of lidocaine, an anaesthetic. Zostavax, a shingles vaccine developed by Merck, has been approved by the US FDA but this vaccine has not been studied in persons with immune deficiency, including HIV-infected persons (Fact Sheet 509, 2006).

5.4.2 – *Pneumocystis* pneumonia (PCP)

Pneumocystis is an opportunistic fungal pathogen that causes pneumonia (pneumocystosis) in the immunocompromised host. Organisms derived from humans and rats have been termed *Pneumocystis jiroveci* and *Pneumocystis carinii*, respectively. New nomenclature is still evolving. The taxonomical classification of *Pneumocystis* as a fungus is based on: (a) analysis of gene sequences for ribosomal RNA, mitochondrial proteins, and major enzymes, (b) presence of beta-1,3-glucan in the cell wall, and (c) efficacy of anti-fungal drugs that inhibit beta-glucan synthesis in animal models. In contrast to most fungi, *Pneumocystis* lacks ergosterol and is not susceptible to anti-fungal drugs that inhibit ergosterol synthesis (Walzer, 2005). PCP is among the common opportunistic infections in HIV-infected individuals with decreasing CD4 cell counts. The earliest manifestations of PCP are fever, dyspnoea, and dry cough. Cotrimoxazole is the drug of choice for preventing and treating *Pneumocystis* infection. Pentamidine is usually inhaled as an aerosol to prevent PCP, while it is used intravenously for treatment. Alternative drugs for treatment include atovaquone, clindamycin-primaquine combination, and trimetrexate-leucovorin combination (Walzer, 2005). In comparison with cotrimoxazole, dapsone seems almost equally effective as a therapeutic agent, while pentamidine aerosol is less effective as a prophylactic agent (Fact Sheet 515, 2006). Pentamidine aerosol may cause change in taste, nausea, vomiting, dyspnoea, dizziness, chest pain or tightness, cough, headache, or weakness. When given intravenously, the drug can cause serious adverse effects such as pancytopenia, hyper- or hypo-glycaemia, hyperkalaemia, cardiac arrhythmias, or damage to pancreas, liver, or kidneys (Fact Sheet 537, 2006). Atovaquone is indicated in patients with mild to moderate PCP, who cannot take cotrimoxazole or pentamidine. However, dapsone and cotrimoxazole belong to the sulpha group of drugs and may cause allergic skin rash, accompanied by fever. Allergic reactions can be overcome by

using a desensitising procedure: patients are initially started on very small doses of the drug and the dosage is progressively increased till they can tolerate the full dose (Fact Sheet 515, 2006).

5.4.3 – Candidiasis

Candidiasis is a common opportunistic infection in HIV-infected persons and commonly affects the mouth (called "thrush"), throat, or vagina. The fungus may spread deeper into the throat and cause oesophagitis or spread to heart, brain, joints, and eyes. Pharyngeal infection manifests as sore throat, with pain during swallowing, and loss of appetite. Vaginal infection causes pruritus, burning, and thick whitish discharge. Clinically, candidiasis appears as white patches (much like cottage cheese) or red spots. In healthy persons, the normal immune function and presence of commensal bacteria keep candida in check. Use of broad-spectrum antibiotics kill commensal bacteria and may trigger candidiasis. The first-line treatment comprises use of anti-fungal creams, lozenges (that dissolve in the mouth), and vaginal pessaries. Systemic anti-fungal agents such as amphotericin B (given orally or intravenously) are indicated if the infection has spread to the other parts of the body (Fact Sheet 501, 2006).

5.4.4 – Molluscum Contagiosum

Molluscum contagiosum is an opportunistic skin infection, caused by a virus. The lesions are painless, non-pruritic, and have a hard white core. Lesions are commonly found on the face or groin. Shaving with a razor blade can spread the infection. It can also be spread by fomites (non-living materials such as clothing) that come in contact with a lesion. Several methods are available for treating molluscum and recurrences of lesions may need re-treatment. Cryocautery with liquid nitrogen and electrocautery are the common methods used to burn the lesions. Chemicals such as trichloroacetic acid and podophyllin are effective but cannot be used on sensitive skin or near the eyes. Surgical removal of the lesions can be painful and may leave scars. Topical application of tretinoin or oral administration of isotretinoin (both acne drugs) reduces the oil in the skin and consequently, the upper layer of the skin peels off. Antiviral drugs such as cidofovir or imiquimod may be topically applied (Fact Sheet 513, 2006).

5.4.5 – Abnormalities in Cell-Mediated Immunity (CMI)

CMI is essential for defence against intracellular organisms, which are protected from antibody-mediated destruction. The intracellular organisms include all viruses, some bacteria (*Mycobacteria*, *Salmonella*), protozoa, and fungi. HIV affects all the following three mechanisms by which CMI functions.

Delayed-Type Hypersensitivity (DTH): The intracellular organisms are killed by macrophages, which have been activated by cytokines produced by activated CD4

T-cells. In the early stage of symptomatic HIV disease, loss of DTH is responsible for predominance of skin and mucosal infections. Candidiasis of skin and mucosa, primarily controlled by CMI, are common in HIV infection.

Cytotoxic T-Lymphocytes: On activation by cytokines produced by activated CD4 T-cells, they kill virus-infected cells and malignant cells. Loss of this ability in HIV infection leads to reactivation of viral infections and development of malignancies.

Natural Killer (NK) Cells: These specifically kill virus-infected or tumour cells. Defective activity of NK cells is commonly seen in advanced HIV disease.

5.4.6 – Abnormalities in Humoral Immunity

Antibodies enhance phagocytosis of microorganisms by neutrophils and macrophages by a process called "opsonisation". HIV causes a non-specific stimulation of B-cells leading to overproduction of Ig molecules, particularly IgA and IgG, resulting in hyper-gammaglobulinaemia. B-cells fail to respond though more Ig molecules are produced. In late stages of HIV disease, reactivation of infections, such as cytomegalovirus infection, does not produce IgM response. The IgA and IgG antibody responses may be poor, after vaccination. HIV adversely affects all the functions of macrophages viz. chemotaxis (migration to the site of infection), phagocytosis, intracellular killing, and presenting of antigens to T-cells. Impairment of function of neutrophils leads to increased vulnerability to *Staphylooccus aureus* infection of the skin and pneumonia. ARV drugs (zidovudine (ZDV), ganciclovir) and infection with *Mycobacterium avium* complex (MAC) can cause neutropenia. Autoimmune antibodies may be produced, against platelets, lymphocytes, neutrophils, and myelin. Antibody-mediated drug allergies are more frequent in HIV-infected individuals.

5.5 – HYPERSENSITIVITY REACTIONS

In spite of diminished immune response, HIV-infected individuals exhibit an increased frequency of hypersensitivity reactions, as compared to that in HIV-negative immunodeficient patients and immunocompetent individuals. These reactions may or may not be drug-related. Hypersensitivity reactions related to drug use are anaphylaxis and anaphylactoid reactions (rare), angioedema and urticaria, erythematous skin rash, hypersensitivity in viscera, maculopapular skin rash, and systemic illnesses. Hypersensitivity reactions are caused by numerous drugs such as atavaquone, carbamazepine, cephalosporins, clindamycin, cotrimoxazole, sulfadiazine, dapsone, delaviridine, fluconazole, isoniazid, rifampicin, thiacetazone, neviraprine, penicillins (including synthetic penicillins like amoxicillin), and phenytoin. Dermatitis, eosinophilic folliculitis, localised maculopapular skin rash, morbilliform maculopapular rash, pruritus, rhinitis and sinusitis, and severe local reaction to bites and stings are reactions that are not drug-related.

5.5.1 – Clinical Manifestations

The drug-related hypersensitivity reactions begin about 7–12 days after ingestion of the first dose and are characterized by fever followed by skin rashes. Patients with prior exposure may develop reactions within few hours of administration of the first dose. These reactions may also be delayed and may develop up to 2 weeks after the drug is withdrawn. The skin rash is usually pruritic, erythematous, maculopapular, and most prominent on the trunk and upper extremities. Patients who are on intermittent therapy such as twice-weekly prophylaxis for prevention of PCP may manifest symptoms that wax and wane with each dose. Drug-related hypersensitivity reactions are commonly caused by drugs containing *sulpha* group, such as cotrimoxazole, sulphonamides, and dapsone. Hypersensitivity to multiple drugs has been reported. Cotrimoxazole is known to exhibit cross-hypersensitivity with sulfadiazine, amoxycillin, and dapsone.

5.5.2 – Pathogenesis

The aetiology of hypersensitive reactions in HIV-infected persons is not clear, but it is believed to be immune-mediated. However, these reactions do *not* represent the four main types of immune-mediated hypersensitivity, as described by Gell and Coombs (Carr *et al*., 1991). The drug hypersensitivity reactions in HIV-infected individuals are *not* mediated by IgE because: (a) most of the IgE-mediated reactions occur within 1 hour of administration of the drug, while in HIV-infected persons, the onset of drug reaction is delayed, (b) other features of IgE-mediated reactions (angioedema, bronchospasm, hypotension) do not occur, and (c) fever, which is seen in drug hypersensitivity reactions in HIV-infected persons, is not a feature of IgE-mediated reactions.

5.5.3 – Mechanisms for Hypersensitivity Reactions

Immune Dysregulation: Irrespective of the causative drug, skin biopsies show epidermal and dermal infiltration by activated CD8 T-cells and macrophages. Cytokines (IL-6 and IL-1-beta) and tumour necrosis factor-alpha may have a role in pathogenesis. HIV infection enhances the sensitivity of CD8 T-cells to drugs, allowing hypersensitivity to develop.

Immune Activation by HIV: HIV-induced immune activation could be another cause.

Dose and Duration of Therapy: Treatment of PCP with high doses of cotrimoxazole is associated with high frequency of hypersensitivity reactions, as compared to the frequency seen with low doses of the same drug used in prophylaxis of PCP. Longer duration of treatment also increases the frequency of drug hypersensitivity reactions.

Structural Similarities of Drugs: Cotrimoxazole, sulphonamides and amoxycillin have a similar benzene-associated para-amino group. *Slow acetylators* (individuals

who slowly metabolise the drugs by acetylation) may be at a greater risk for developing hypersensitivity to sulphonamides.

5.6 – NEUROLOGICAL DISORDERS

HIV infection is frequently associated with disorders of the peripheral and central nervous systems, which may be caused by HIV itself, cellular interactions, and neurotoxins produced by HIV-infected macrophages. The degree of neurological deficit (which is due to HIV infection of microglial cells) correlates with the extent of immune dysregulation. HIV does not directly enter the brain in the early stages of the disease, but probably enters the CSF at the time of seroconversion. In late stages of the disease, HIV enters the brain by any of the following routes – chronic infection of the meninges, blood-borne infection via infected T-cells and mono-cytes (seems more likely), and infection by cell-free viruses, since the blood-brain barrier breaks down in many patients with AIDS (Petito & Cash, 1992).

Cytokines and Neurotoxins: Increasing impairment of the immune system activates compensatory mechanisms, which produce various cytokines (Wesselingh *et al.*, 1994) and toxins. Probably HIV initiates neurological damage, which is enhanced by toxins. These cytokines and toxins damage neural tissues that may be secondarily infected by HIV from circulating infected cells. This can happen only if the circulating cells have macrophage-tropic (or syncytium-inducing) subtype of HIV, since the microglial cells are of macrophage lineage. Neurotoxic components of HIV are probably gp120 and the regulatory genes *tat* and *nef*. Macrophage lineage cells facilitate damage of neurons and seem to release neural toxins that affect astrocytes and oligodendrocytes.

HIV-Related Neurological Disorders: Patients with advanced HIV infection may develop neurological disorder, such as AIDS dementia complex, vascular myelopathy, and peripheral neuropathy. Less common neurological complications such as seizures, transient neurological deficits, and aseptic meningitis occur when the CD4 count drops below 200 cells per μL. These complications may be associated with AIDS dementia complex.

5.7 – MALIGNANCIES

Malignancies are more frequent in immunodeficient disorders, including drug-induced immunodeficiency (Penn, 1990). The malignancies seen in HIV-infected patients are similar in cellular origin and clinical behaviour to those seen in other forms of immunodeficiency. Kaposi's sarcoma, non-Hodgkin's lym-phoma, and cervical carcinoma are currently recognised as "AIDS-defining malignancies". Though Hodgkin's disease and cancers of rectum and anus also have an increased incidence in HIV infection, they are currently not included in surveillance criteria for AIDS (Reynolds *et al.*, 1993). However in HIV-infected individuals, there is no increase in frequency of cancers of lung, colon, breast, and prostate, as compared to that in the general population.

Malignancies may occur in HIV-infected persons due to immunodeficiency, aberrant production of cytokines and activation of oncogenic viruses. The process of cell division and differentiation causes genetic aberrations. Many of the genetically altered cells die, but some may survive with the potential for further change, which may lead to the development of malignancies. In immune competent individuals, the immune system prevents malignancies by removing pre-malignant cells, particularly those induced by oncogenic viruses, and clearing foreign antigens that may chronically stimulate the immune system and promote excessive proliferation of cells.

In HIV-induced immunodeficiency, these immune mechanisms are impaired. Latent viruses such as EBV and human papilloma virus (HPV) may also be activated in the immunodeficient state and may contribute to neoplastic changes. EBV and HPV may be involved in the pathogenesis of non-Hodgkin's lymphoma and cervical cancer, respectively. Human herpes virus type 8 is probably linked to development of Kaposi's sarcoma (Chang *et al.*, 1994; Lennette *et al.*, 1996).

5.7.1 – Non-Hodgkin's lymphoma

Lymphoma is cancer of B-lymphocytes. Development of lymphomas is distinctive of HIV-infection. EBV is found in all lymphomas of central nervous system, Hodgkin's disease, and in a majority of non-Hodgkin's lymphomas. This suggests that EBV may be linked to the development of malignancies either directly, as oncogenes, or indirectly, by inducing the production of oncogenes within the host (Gregory *et al.*, 1991). *Cytokines* such as IL-5, IL-6, and IL-10 are detected in reactive lymph nodes of HIV-infected patients. The increased production of these cytokines probably contributes to cellular proliferation leading to malignancy. Lesions of non-Hodgkin's lymphoma may occur in the bone, abdomen, liver, brain, and in many other parts of the body. Lymphomas are treated by chemotherapy. In addition, radiotherapy may be used. Lymphomas of the central nervous system are difficult to treat. Genetically engineered monoclonal antibodies are being studied as possible treatment for non-Hodgkin's lymphoma (Fact Sheet 512, 2006).

5.7.2 – Kaposi's sarcoma

This AIDS-defining malignancy is the most frequent neoplasm in HIV infection but its incidence has dropped dramatically after introduction of ARV therapy. Men outnumber women by 8:1. Before the advent of the HIV epidemic, the disease affected elderly men of Eastern European or Mediterranean background. Kaposi's sarcoma usually affects the skin or mucous membranes of mouth, nose, or eye. It is one of the most visible signs of AIDS because the lesions (purple or red spots on white skin; bluish, brownish, or black spots on dark skin) appear frequently on the face, arms, and legs. It can spread to the liver, lungs, gastrointestinal tract, and lymph nodes (Fact Sheet 511, 2006).

The disease is characterised by development of tiny blood vessels (microangiogenesis). It is a unique malignancy that initially requires a growth factor, but

later probably produces its own growth factors to maintain its proliferative capacity. Human herpes virus type 8 has been found in Kaposi's sarcoma, which may or may not be associated with HIV infection. This type of herpes virus probably spreads both vertically and sexually and is present in up to 20 per cent of HIV-infected individuals (Chang *et al.*, 1994; Lennette *et al.*, 1996). *Tat*, the regulatory gene in HIV that accelerates viral replication, is probably responsible for tumour promotion (Ensoli *et al.*, 1994). Cytokines such as basic fibroblast growth factor, oncostatin M, tumour necrosis factor, IL-6, and IL-1-beta (produced by both Kaposi's sarcoma cells and activated endothelium) may stimulate migration, invasion, and proliferation of endothelial cells. This results in angio-proliferation seen in Kaposi's sarcoma (Ensoli *et al.*, 1994; Corbiel *et al.*, 1991; Miles *et al.*, 1992). Beta-human chorionic gonadotrophin, the pregnancy hormone, has an anti-tumour effect (Lunardi *et al.*, 1995). This hormone may confer protection against this disease in women and is probably the reason for predominance of Kaposi's sarcoma in men.

5.7.3 – Carcinoma of Uterine Cervix

Carcinoma of the uterine cervix and its precursor lesion (called "cervical intraepithelial neoplasia" that predisposes to invasive cancer) are found frequently in HIV-infected women. Squamous cell carcinoma of anus, which occurs in HIV-infected men, is probably caused by the same mechanisms as that for cervical carcinoma – infection with HPV and immune dysregulation.

HPV Infection: This stimulates proliferation of epithelial cells of cervix and anus and also promotes genetic instability (which leads to further genetic changes within these cells, resulting in malignancy). Specific oncogenic types of HPV (usually 16, 18, 31, 33, and 35) that are associated with neoplastic changes possess E6 and E7 genes. These genes interact with regulatory proteins. The tat protein of HIV can directly activate HPV.

Immune Dysregulation: In an immunocompetent individual, the CMI response to HPV infection is regulated by cytokines like tumour necrosis factor-alpha, interferon-gamma, and tissue growth factor-beta (Zur Hausen & de Villiers, 1994). But in HIV-related immunodeficiency, the cytokine pathways are disrupted and host defence mechanisms are impaired. In HIV-infected women, the increase in frequency and severity of cervical dysplasia and shedding of HPV is inversely related to decrease in the CD4 cell count (Petry *et al.*, 1994)

5.8 – AUTOIMMUNE DISORDERS

These may manifest clinically in the early stage of HIV disease since the immune system is relatively effective. The genesis of many of these disorders shows important differences, when compared with that of similar conditions in HIV-negative individuals. Autoimmune syndromes may be of the following types:

Antibody-Mediated Syndromes: These include production of auto-antibodies against platelets, red blood cells, cardiolipin, and parietal cells of gastric mucosa. The possible mechanisms for antibody-mediated syndromes are: (a) increased production of IL-1 and IL-6 by HIV-infected macrophages and monocytes, which cause non-specific stimulation of B-cells by bypassing their usual pathway for stimulation, (b) activation of cytomegalovirus or HIV by "anti-self" B-cells, (c) increased production of lymphotoxins and tumour necrosis factor by macrophages and monocytes that may destroy CD8 T-cells, thus reducing suppression of B-cell activity by CD8 cells, and (d) "molecular mimicry": production of cytotoxic anti-lymphocyte antibodies by dysregulated B-cells and when antibodies directed against HIV glycoprotein gp-41 react with MHC Class II molecules (Hoffmann *et al.*, 1991).

CD8 T-Cell Mediated Syndromes: These comprise conditions like polymyositis, lymphocytic interstitial pneumonitis, cardiac myositis, and chronic active hepatitis. Auto-reactive CD8 T-cells infiltrate the affected tissues or organs. In HIV-negative individuals with similar disorders, the CD4 T-cells infiltrate. There is a marked increase in CD8 lymphocytes in peripheral blood. Estimation of level of CD8 lymphocytosis may help in identifying individuals at high-risk of developing CD8 T-cell mediated autoimmune disorders.

Demyelinating Syndromes: Guillian-Barré syndrome, multiple sclerosis-like illness, and demyelinating polyneuropathy may occur early in HIV infection. Their pathogenesis is not well understood.

Immune-Complex Mediated Syndromes: Circulating immune complexes containing detectable HIV antigens are commonly found in HIV-infected persons. These immune complexes may be deposited on vessel walls at any stage of HIV infection and may cause an arteritis, which is similar to polyarteritis nodosa. Primary vasculitis is rare in HIV infection, and is usually secondary to drug reactions or opportunistic infections.

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