The early stages of HIV infection: clinical features and management

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The natural history of HIV infection is that of slowly progressive immunosuppression. It is essential to form an accurate idea of the stage of a patient's disease in order to provide appropriate counselling, plan follow-up, and to decide when to intervene with primary prophylaxis against major opportunistic infections or specific anti-retroviral therapy. This can be achieved by recognizing the prognostic importance of symptoms or signs in conjunction with laboratory tests.

Definition

Early HIV infection is defined as the period from seroconversion to the development of AIDS. The revised definition of AIDS includes a CD4+ lymphocyte (the T-helper cell) count of < 200 cells/ul. The median duration of this period of the disease is 10 years.

Seroconversion illness

The majority of patients do not recall this phase of the disease. However, when cohorts of HIV negative homosexual men were prospectively followed with 6 monthly HIV tests, just over half of the patients reported an infectious mononucleosis type illness coinciding with seroconversion. Acute HIV infection should thus be considered in the differential diagnosis of glandular fever when tests for Epstein-Barr virus are negative. It is important to recognize that serological tests for HIV are frequently negative during this phase of the illness.

The incubation period varies from 1-6 weeks. Typical clinical findings are non-exudative pharyngitis, lymphadenopathy, a maculopapular rash (which may involve the palms and soles), oral aphthous ulcers and meningo-encephalitis. Symptomatic therapy is all that's required. Other neurological manifestations of seroconversion include Bell's palsy and the Guillain-Barré syndrome (which differs from the classical syndrome only in that CSF pleocytosis is common). Haematological abnormalities during seroconversion include thrombocytopenia and neutropenia. The mean duration of seroconversion illness is 3 weeks.

Persistent generalized lymphadenopathy

Following seroconversion most patients have symmetrical generalized lymphadenopathy which persists for longer than 3 months. The nodes are typically < 2 cm in diameter and are not tender. Provided these features are present, biopsy is not indicated. Disappearance of lymphadenopathy is a sign of advancing immunosuppression.

Minor mucocutaneous manifestations

Mucocutaneous disorders occur in most patients sometime during the course of HIV infection and several are important prognostically.

As one would expect, dermatological infections are common. Shingles is particularly common in African patients. It is generally seen with mild immunosuppression. In HIV infected patients shingles is usually more severe and persists for longer. However, dissemination seldom occurs and the incidence of post-herpetic neuralgia is low. Acyclovir, 800 mg five times daily orally for 7 days, shortens the course of shingles. Intravenous acyclovir should be given for disseminated disease.

Fungal infections of the nails and skin are common and respond to topical therapy, but relapses are common. Staphylococcal folliculitis is also common and should be treated with topical antibiotics (eg, 2% erythromycin). Vulvovaginal candidiasis which is recurrent or refractory is a sign of severe immunosuppression in HIV infected women. Ketoconazole, itraconazole or fluconazole should be used if topical therapy fail.

Inflammatory dermatological diseases are very common and generally occur with moderate immunosuppression. The commonest is seborrhoeic dermatitis. Lesions are found in the usual facial sites (eyebrows, hairline, nasolabial folds and facial hair), but may also occur elsewhere on the body. Topical steroids are effective, although many prefer to use them combined with antifungals. Eczema and psoriasis occur more commonly in HIV infected patients and respond to conventional therapy. Prurigo and eosinophilic folliculitis cause disabling pruritus and dermatological consultation is advised for diagnosis and management.

Oral lesions should be routinely sought as they convey important prognostic information. Aphthous ulcers may recur or persist after seroconversion. Oropharyngeal candidiasis is very common and signifies severe immunosuppression. Angular stomatitis is generally due to candida and may occur in the absence of oral candidiasis. Topical treatment is generally effective but recurrences are invariable. Oral hairy leukoplakia is virtually pathognomonic of HIV infection and also occurs with severe immunosuppression. The lesions are best seen on the sides of the tongue. They are usually asymptomatic and are not pre-malignant. Topical podophyllin should be applied only if symptoms are present.

Neurological manifestations

Neurological disease due to HIV itself may occur in early disease. Meningo-encephalitis may recur after seroconversion. The Guillain-Barré syndrome, as well as its chronic variant, chronic idiopathic inflammatory neuropathy, may occur during seroconversion or later in the course of early disease. A sensorimotor peripheral neuropathy may occur in early or late HIV disease. It is usually painful in the initial stages. Amitriptyline 75-150 mg *nocte* generally affords relief.

Non-opportunistic infections

Severe bacterial infections due to non-opportunistic pathogens are particularly common in sub-Saharan Africa. Bacterial pneumonia, usually due to *Streptococcus pneumoniae* or *Haemophilus influenzae,* is common and frequently bacteraemic. Pneumococcal vaccine should be given as soon as the diagnosis of HIV is confirmed as pneumococcal infections typically occur with mild immunosuppression. An antibody response is generated provided the CD4+ lymphocyte count is > 200. Staphylococcal pyomyositis and non-typhoid salmonella bacteraemia occur frequently in Africa. These infections should be treated aggressively with prolonged courses (about 14 days) of antibiotics.

Pulmonary tuberculosis occurs very frequently and at an earlier stage of HIV infection in sub-Saharan Africa. Non-cavitary disease, principally involving the lower lobes, is characteristic in patients with advanced immunosuppression. Conventional anti-tuberculous chemotherapy is effective, but relapses occur slightly more often than in HIV negative patients.

Prophylactic INH for 6 or 12 months has been shown to reduce the incidence of tuberculosis in HIV infected patients. It should only be given if compliance can be assured, otherwise resistance may develop.

Constitutional disease

Symptoms of malaise and fatigue are commonly experienced with advancing immunosuppression. More ominous are mass loss, fever, and chronic diarrhoea. Although HIV infection *per se* can cause prolonged fever, opportunistic infections are found in most cases and these need to be excluded. The HIV wasting syndrome, an AIDS defining illness, is defined as the occurrence of significant mass loss together with either chronic fever or diarrhoea (see later).

Other manifestations

Haematological abnormalities occurring after seroconversion occur frequently. Thrombocytopenia is the commonest abnormality. It is usually mild, but severe thrombocytopenia may occur. The features are those of immune thrombocytopenic purpura. It responds to corticosteroids (but prolonged courses should be avoided) or splenectomy. Anti-retroviral therapy is also generally effective, and is preferred by many. A mild anaemia and neutropenia are also commonly seen.

Rheumatological symptoms of arthralgia (typically involving the large joints) or myalgia are common. Reiter's disease occurs with increased frequency in HIV infection. Non-steroidal anti-inflammatory drugs are generally effective.

Laboratory markers of disease progression

Not all patients with HIV infection develop the symptoms or signs discussed above. Asymptomatic patients may have advanced immunosuppression and would benefit from anti-retroviral therapy or primary prophylaxis directed against some of the major opportunistic infections. Laboratory markers of declining immunity are thus of great value in the management of HIV infection.

The most accurate predictor of disease progression is the CD4+ lymphocyte count. However, it is an expensive test and only available in major centres. Intercurrent infections, particularly viral and tuberculous, can transiently lower the count. Minor fluctuations are common. Simultaneous CD8+ lymphocyte count is generally done and the CD4+/CD8+ ratio (normally >1) also has prognostic value. Where available, the CD4+ count should be performed 6 monthly. After seroconversion, which transiently suppresses the count, a plateau phase occurs lasting for years in which the count slowly declines. Shortly before the onset of AIDS a more precipitous decline is usually seen.

The total lymphocyte count can be used if CD4+ lymphocyte counts are unavailable. Lymphopenia < 1.000/ul generally corresponds with a CD4+ count of < 200/ul. Other useful serological markers of disease progression are neopterin, beta-2 microglobulin and the re-appearance of HIV antigenaemia (the P 24 antigen is generally measured).

Anti-retroviral therapy in early disease

The use of specific anti-retroviral therapy (usually zidovudine) in early disease is controversial. A randomized trial showed that the annual rate of progression to AIDS is halved if zidovudine is given to asymptomatic patients with CD4+ lymphocyte counts between 200 and 500 cells/ul. However, later randomized studies showed that survival was the same if zidovudine was started early or delayed until the onset of AIDS (or a CD4+ lymphocyte count < 200) in patients with or without symptoms. The reason for this lack of long-term benefit is almost certainly due to the development of viral resistance, which is in most patients by 2 years.

Those who advocate early therapy argue that AIDS-free survival provides better quality of life. Against this must be weighed the cost and side effects of zidovudine. Another argument in favour of early therapy is that prolonged survival may be achieved by a later switch to other anti-retroviral therapy or by the use of combination therapy. Trials are currently in progress to address these issues.

The decision to commence early therapy should thus be individualized with the patient's active involvement. Unfortunately anti-retroviral therapy is currently considered too expensive for use in the public sector. Therapeutics in HIV changes rapidly and advice should be sought from experts in the field.