

## **5: VL AND IMMUNOCOMPROMISED PATIENTS**

### 5.1 **What types of immunocompromised patients may be affected?**

Any condition reducing the cellular immune response will make VL more likely, more atypical and more resistant to treatment.

HIV infected patients are by far the most common group of immunocompromised patients that suffer VL co-infection, especially in Europe. European patients with HIV/VL co-infection have low CD4 (helper T lymphocytes) counts: 97 % of patients have CD4 cell counts of less than 500/ $\mu$ l and 80 % have CD4 counts of less than 200/ $\mu$ l.

Other immunocompromised patients that may be more susceptible to VL are those receiving corticosteroid and immunosuppressive therapy, patients with lymphoma, with leukaemia, with chronic hepatitis, renal transplant, sarcoidosis, Crohn's disease, systemic lupus erythematosus, thymectomised patients or those with ulcerative colitis.

In endemic areas for VL in Africa, South America and India severe malnutrition predisposes to VL and this may be a result of reduced ability to produce a cell mediated immune response.

### 5.2 **What atypical clinical presentations of VL might be seen in immunocompromised patients?**

The following table summarises clinical features of VL in 96 European patients with HIV co-infection:

Mean age (years)	29-33
Male	86%
Fever	88%
Hepatomegaly	79%
Splenomegaly	78%
Lymphadenopathy	50%

Bi- or pancytopenia	79%
Hypergammaglobulinaemia	72%
<i>Leishmania</i> serology positive	50%
CD4+ T cells/ $\mu$ l	
>500	3%
500-200	17%
<200	80%

Atypical clinical features are seen in some patients with HIV/VL co-infection.

The infection may be present in the skin with cutaneous, diffuse cutaneous or mucocutaneous leishmaniasis. The infection may be widely disseminated in the viscera and other organs may be involved. Diarrhoea, cough and difficulty in swallowing (dysphagia) may be common. Cryptosporidiosis (*Cryptosporidium* infection) may also cause diarrhoea in patients with HIV infection.

Patients with HIV/VL co-infection may have nodular or ulcerative lesions on the tongue (slide 36), oesophagus, stomach, rectum, larynx and in the lungs. Parasites may be seen in numerous sites with or without the presence of lesions.

*Leishmania* may be found in bone marrow aspirates and unexpectedly in skin biopsies (including biopsies of other lesions such as those of Kaposi's sarcoma) and in normal skin; duodenal biopsies; rectal biopsies; broncho-alveolar lavage; and in peripheral blood neutrophils.

In immunocompromised patients, VL may be rapidly progressive, resembling bacterial sepsis. Alternatively, VL may be unusually slowly progressive with a few, non-specific symptoms, and in some patients, VL may be entirely asymptomatic.

In HIV patients a clinical picture similar to that of VL may be caused by other opportunistic infections; disseminated mycobacterial infection; cytomegalovirus (CMV); salmonellosis and disseminated fungal infections (cryptococcosis). Lymphoma may also be suspected.

30 % of HIV/VL patients will die during treatment or within one month after treatment.

The mean survival with optimal treatment is only 12 months. Only 16 % will survive for more than 3 years. Death is seldom due to VL alone. A sterile cure cannot be achieved by any drug, and relapse is almost inevitable. The time to relapse is usually 3 - 6 months, with successive relapses becoming less typical and less acute, but occurring more frequently.

5.3 **What modifications are required to the methods of diagnosis for immunocompromised patients?**

In immunocompromised patients parasitological diagnosis has increased sensitivity. Microscopy of bone marrow aspirates is reported to be 94 % sensitive in immunocompromised patients and culture of bone marrow in an appropriate culture medium (Appendix 4) is reported to be 100 % sensitive. Sometimes it can be difficult and has to be repeated.

Immunocompromised patients may have circulating amastigotes in neutrophils in the peripheral blood (blood parasitemia). Microscopy of blood films may be useful and is said to be positive in 50 % of patients. Microscopy of buffy coat concentrated from blood by centrifugation (e.g. in an haemocrit centrifuge) increases sensitivity further and culture of buffy coat is said to be positive in 70 % of immunocompromised patients.

In contrast, because of the compromised immune response, serology has low sensitivity in immunocompromised patients.

20 - 40% of HIV/VL patients may be serologically negative and diagnosis must therefore rely on the parasitological detection of *Leishmania*.

5.4 **What modifications might be needed in treatment and supportive measures for immunocompromised patients?**

Patients with HIV/VL should be treated as outpatients wherever possible.

HIV/VL coinfection patients treated as outpatients, however, must be considered as highly infectious reservoirs in areas of active transmission because of the presence of amastigotes circulating in the blood.

Alternative treatments are as follows:

- (1) Pentavalent antimony at 20 mg/kg/day (without an upper limit on the dose) for 30 days (see section 4).

83% of the cases respond positively but 50% of them relapse from one to four

times between one month and 36 months after treatment. Toxicity of pentavalent antimony is greater in HIV patients and includes pancreatitis, blood abnormalities and drug allergies. Secondary effects often lead to interruption of the treatment.

- (2) Amphotericin B at 0.5 mg/kg by intravenous infusion daily or on alternate days until a total dose of 20 - 30 mg/kg has been given. Side effects of treatment by amphotericin B may be impairment of renal function, fever, chills, anaemia, low potassium levels in the blood (hypokalemia), or low magnesium in the blood (hypomagnesemia). These side effects may be minimised by pre-treatment with paracetamol or antihistamines and pre-hydration with oral fluids or intravenous saline.

After treatment, parasitology need only be repeated where there is no improvement in the clinical picture due to VL.

- (3) Maintenance treatment: the only treatment used to prevent relapse in HIV patients with VL (maintenance treatment) is at present pentamidine isethionate intravenously at 4 mg/kg once a month or 2 mg/kg every two weeks (this will also provide adequate prophylaxis against *Pneumocystis carinii*). The efficacy of this maintenance treatment has not yet been clearly established.

*In the current unsatisfactory chemotherapy situation, the most important objectives are to maintain a good quality of life for the patients, prevent relapses and avoid life-threatening infections.*

#### 5.5 **What minimal or special equipment and services are required for the management of VL in immunocompromised patients?**

The equipment and services are those described in sections 2, 3 and 4. In addition a reliable and rapid test for HIV infection must be available.

#### **Case histories of VL (immunocompromised)**

##### Case history - VL (immunocompromised) - 1

A 30 year old man addicted to heroin was admitted because of fever, cough and blood in the sputum (haemoptysis). He had a long history of chronic hepatitis, and AIDS had been diagnosed six months before, when cerebral toxoplasmosis occurred. He was disoriented and lethargic on admission. The skin was brown and dry, and there were a few petechiae on the lower limbs. He appeared to be severely malnourished, and his muscles were wasted. He had oral candidiasis and generalized lymphadenopathy. No visceral enlargement was felt.

He was pancytopenic, with a leukocyte count of  $0.9 \times 10^9/l$ , Hb of 7g/dl and platelet

count of  $11 \times 10^9/l$ . The aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT) and alkaline phosphatase (ALP) levels were slightly elevated. Laboratory tests also revealed the following values: serum protein, 55 g/l; CD4 lymphocytes,  $8/\mu l$ ; CD8 lymphocytes,  $295/\mu l$ ; and CD4/CD8 lymphocyte ratio, 0.03. An indirect immunofluorescence assay for antibodies to *Leishmania* was positive (titer, 1:80). A bone marrow aspirate contained many *Leishmania* amastigotes.

Treatment with meglumine antimoniate (20 mg/kg of pentavalent antimony) plus interferon gamma (four million units/day subcutaneously) was given over four weeks. After three days of therapy, he was afebrile and his general condition began to improve. At the end of therapy, pancytopenia had subsided, and a culture and smear of a newly obtained bone marrow aspirate were negative for *Leishmania* organisms. He died a few weeks later of cerebral lymphoma.