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Primary human immunodeficiency virus infection: heightened awareness needed

初期人類免疫缺陷病毒感染：意識提升的需要

Primary human immunodeficiency virus infection is a distinct medical syndrome which is often not diagnosed. The importance of its early recognition lies in the potential for early therapeutic intervention for the individual, with consequent public health benefits for the community at large. Diagnosis requires a high index of suspicion in a person with a history of potential exposure. Early treatment with combination antiretroviral therapy should be considered once the diagnosis has been established. We report a local case of primary human immunodeficiency virus infection in a patient who presented initially with fever, lymphadenopathy, generalised skin rash, dry cough, splenomegaly, and aseptic meningitis.

初期人類免疫缺陷病毒感染是往往不能診斷的獨特醫學綜合病徵。其早期識別對於患者的盡早治療和對於社會的公共健康都極為重要。診斷中如發現病人的病歷紀錄顯示有潛在感染的機會，便須採取懷疑的態度。一旦診斷出病人受感染，就應考慮及早使用結合抗後濾過性毒菌的治療。我們報告了一個初期人類免疫缺陷病毒感染的病例，患者最初呈現發燒、淋巴結病、一般性皮疹、乾咳、脾脹大及無菌的腦膜炎。

Key words:
Acquired immunodeficiency syndrome/diagnosis;
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關鍵詞：
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Introduction

Primary human immunodeficiency virus (HIV) infection is a 'mononucleosis-like illness' occurring shortly after HIV infection (2 to 6 weeks).[1] Clinical features can be non-specific, and there is a spectrum of clinical severity on presentation. The condition is often self-limiting and hence often underdiagnosed. We report the case of a patient who presented to Princess Margaret Hospital with primary HIV infection, the first reported local case. Clinical features, differential diagnosis, diagnostic tests, and management of the patient's condition are discussed.

Case report

A 33-year-old, married, heterosexual, local Chinese man was admitted to the Infectious Disease Service at Princess Margaret Hospital in December 1996 with fever and skin rash. He reported a history of fever, malaise, and anorexia for 10 days, followed by the development of a generalised, non-pruritic skin rash, 4 days prior to admission. Further symptoms of headache, and dry cough, were reported shortly after admission. The patient had just returned from Japan after a 2-month holiday. He enjoyed good general health, with no past medical history of note, except for one episode of non-gonococcal urethritis, treated at the

Social Hygiene Clinic. The patient denied extramarital sexual activity, and his HIV status was unknown. On admission, the patient's body temperature was 38.5°C. He was found to have a generalised erythematous maculopapular rash over his trunk and limbs. There were no oral or genital lesions. Multiple, shotty lymph nodes, associated with mild tenderness, were felt in the neck, axilla, and groin. Meningism, in the form of neck rigidity and a positive Kernig's sign, was demonstrated. Fundi were normal. There were no focal neurological deficits. The cardiovascular and respiratory systems were normal. Splenomegaly (an increase of approximately two-finger breadths) was noted.

Initial investigations showed a haemoglobin level of 159 g/L (normal range, 140-180 g/L), and a white blood cell count (WBC) of 4.4 x 10^9 /L (normal range, 3.2-9.8 x 10^9 /L), with 66% neutrophils, 18% lymphocytes, 7% atypical lymphocytes, and 6% monocytes. Platelet count was 148 x 10^9 /L (normal range, 150-450 x 10^9 /L). The erythrocyte sedimentation rate was 25 mm/h (normal range, 0-20 mm/h). Liver function tests showed mild elevation of alanine aminotransferase (54 U/L [normal range, 0-35 U/L]). Renal function tests were normal. Blood, urine, stool, sputum and throat swab examinations for pathogens and parasites were negative. The Venereal Disease Research Laboratory test was non-reactive. A malarial parasite smear was negative. The monospot test, Widal's test, Weil-Felix test, as well as serological tests for Epstein-Barr virus, cytomegalovirus, and toxoplasma titres were negative. Chest X-ray and a plain computed tomography brain scan were normal.

Lumbar puncture showed an opening pressure of 18 cm H_2O. Cerebrospinal fluid examination showed lymphocytic pleocytosis, with a WBC count of 54 x 10^6 /L (normal range, 0-5 x 10^6 /L) of which 90% were lymphocytes. Red blood cell count was 2 x 10^6 /L, a normal glucose level and a raised protein level of 0.8 g/L (normal range, < 0.4 g/L) was noted. Cerebrospinal fluid tests for cryptococcus, bacterial antigens, and acid-fast bacillus smear were negative, and subsequent cultures and serological tests were also negative. The patient had a high oscillating fever for 2 weeks, after which his fever, rash and headache gradually subsided. He was given intravenous acyclovir for suspected meningoencephalitis in the first 3 days. The first HIV antibody test with enzyme-linked immunosorbent assay (ELISA) was positive for HIV type 1 (HIV-1), 5 days after admission. The concurrent Western blot test showed reactivity of two bands, whereas the second test 5 days later showed positivity of all bands. CD4 and CD8 counts were 438 and 1518 cells/μL respectively. The CD4/CD8 ratio was reversed (0.29). The patient commenced triple antiretroviral therapy (zidovudine, lamivudine, and indinavir) under the care of the Special Medical Service of Queen Elizabeth Hospital, but discontinued his treatment after 2 months. When the patient reattended the clinic 1 year later, his CD4 count was 505 cells/μL and the HIV RNA count was 4.3 x 10^3 copies/mL. No further antiretroviral therapy was offered, as the patient failed to attend subsequent follow-up.

Discussion

Primary HIV infection was first described in a nurse who sustained a needlestick injury in 1984. The clinical syndrome has since been well characterised.[1] Acute onset occurs 2 to 6 weeks after HIV infection, usually resolving after 1 to 2 weeks, though occasionally lasting longer.[1] Fifty percent to 80% of infected patients will undergo an acute seroconversion illness. The cumulative figure for HIV positive cases in Hong Kong was in excess of 1300 cases in Oct 1999,[2] although only a couple of cases of primary HIV infection have been recognised in a retrospective manner (personal communication, Dr Patrick Li). Most patients with symptomatic acute seroconversion probably either do not present to medical attention, or are not diagnosed when they do present. The phenomenon of underdiagnosis has been noted in developed countries,[3-5] and can happen even among doctors caring for people under close surveillance for HIV infection.[6]

The symptoms of primary HIV infection are listed in the Table. Not all patients develop all features, however. The Figure shows the approximate frequency of occurrence of various symptoms and findings associated with acute HIV infection as indicated by pooled data.[6] Differential diagnoses include influenza, rubella, syphilis, infectious mononucleosis, toxoplasmosis, cytomegalovirus infection, hepatitis, disseminated gonococcal infection, herpes simplex infection, typhus, and acute Crohn's disease. These alternative diagnoses can usually be excluded by careful examination of the patient and the use of appropriate laboratory tests. As symptoms of primary HIV infection are non-specific, efforts have been made to look for diagnostic clues. The presence of cutaneous, oral or genital mucosal signs, is useful in pinpointing the diagnosis.[7] Skin manifestations are usually in the form of a maculopapular rash or disseminated urticaria. The rash is more prominent centrally than peripherally, may involve the face, and the lesions are erythematous, non-pruritic, painless, and of approximately 5 to 10 mm in diameter. Oral mucosal lesions closely resemble

Table. Clinical features of primary human immunodeficiency virus infection

General	fever* pharyngitis* lymphadenopathy* arthralgia myalgia lethargy/malaise* anorexia/weight loss*
Dermatological	erythematous maculopapular rash* roseola-like rash diffuse urticaria mucocutaneous ulceration desquamation alopecia
Neurological	headache/retro-orbital pain meningoencephalitis* peripheral neuropathy radiculopathy brachial neuritis Guillian-Barré syndrome cognitive/affective impairment
Gastrointestinal	oral/oropharyngeal candidiasis nausea*/vomiting diarrhoea gastrointestinal bleeding hepatomegaly +/- splenomegaly* raised transaminase levels
Respiratory	cough* pneumonitis
Renal	rhabdomyolysis acute renal failure

* Clinical features noted in the case presented.

aphthous stomatitis and herpes simplex lesions, but have a wider distribution in HIV cases. Genital ulcers are seen in approximately one third of patients. About half of the patients with skin lesions also have oral, or genital ulceration, or both. This pattern of association between cutaneous and mucosal signs is uncommon in most of the differential diagnoses, and appears to be relatively specific for primary HIV infection.[7] Thus, it is important to examine these sites in a febrile patient presenting with rash. Syphilis can be readily differentiated by serology.

Enquiries regarding risk factors can also provide essential clues for the diagnosis of primary HIV infection. High-risk exposure in the preceding 2 to 4 weeks is distinguishing. Unless the doctor adopts a non-judgmental attitude, however, patients are unlikely to reveal details of any high-risk behaviour. Now that the spread of HIV infection has become predominant among the heterosexual population, the index of suspicion should be even higher in health care personnel. Our patient probably acquired his HIV infection during his trip to Japan, since the incubation period is compatible with his presentation. His wife was negative for HIV antibodies. The key diagnostic test for primary HIV infection is the HIV RNA assay. Human immunodeficiency virus RNA, usually at high levels of more than 50 000 copies/mL, can be detected

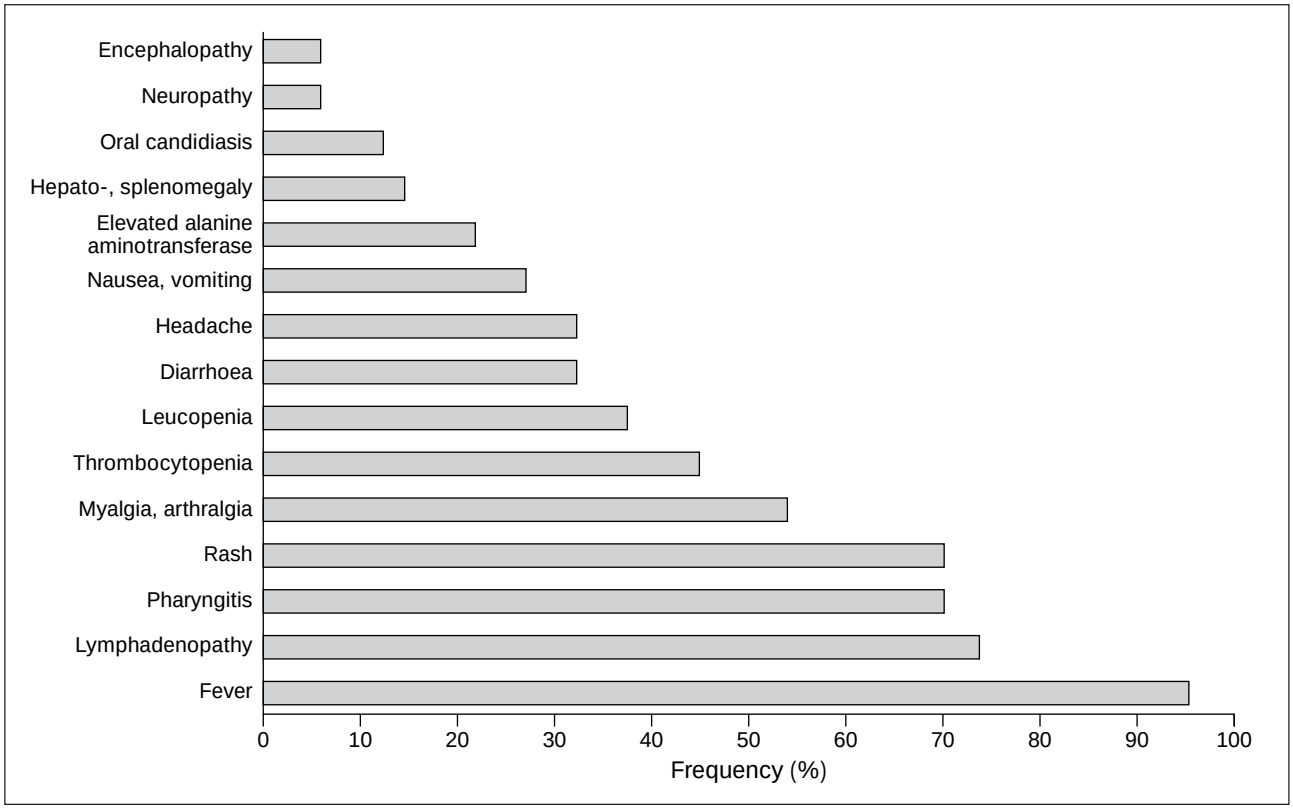

Fig. Common signs and symptoms associated with primary human immunodeficiency virus infection (based on 209 reported cases)[6]

in most cases in the first week following the onset of symptoms.[5,8] The HIV RNA assay has been available in Hong Kong since 1998. The diagnosis of acute HIV infection cannot be made with standard serological tests. The HIV antibody test (ELISA) detects only about 50% of patients in the early phase of primary HIV infection.[9] Serological tests first become positive approximately 22 to 27 days after acute infection. One or more bands on the Western Blot may become positive early, as in the present case. The p24 and gp160/120 antigens tend to be seen first, while reactivity to other viral proteins occurs over the ensuing weeks.[10] Hence, p24 antigen can be used alternatively if HIV RNA assay is not available. The detection of high-titre viral RNA or viral p24 antigen in a patient with a negative test for HIV antibodies, establishes the diagnosis of acute HIV infection. When clinical suspicion is high, both tests should be performed and repeated 2 to 4 weeks later. Other common anomalies are non-specific. These include thrombocytopenia, leucopenia, CD4+ lymphopenia, CD8+ lymphocytosis, and an inverted CD4:CD8 ratio.

Human immunodeficiency virus replicates rapidly with dissemination occurring early in the infection. There is a large viral burden in the early phase of infection, as documented by the use of the HIV RNA assay.[8] This is also the time when the virus is less variant in terms of the production of mutants. Recent studies have shown that the early introduction of highly aggressive antiretroviral therapy during acute HIV infection, greatly reduces plasma viraemia and restores the number of CD4 cells.[11] Intervention during primary HIV infection, when the viral burden 'set point' is achieved, may represent a special window of opportunity to effectively intervene in limiting viral replication. This may translate to a slower pace of CD4+ cell count decline and disease progression. A panel of experts has recommended that individuals identified during acute primary HIV infection should be treated with combination antiretroviral therapy to suppress virus replication to levels below the limit of detection of sensitive plasma HIV RNA assays.[12] Apart from antiretroviral therapy, the medical management of primary HIV infection is often symptomatic. Opportunistic infections such as *Pneumocystis carinii* pneumonia may occur during this phase of profound immunosuppression, and specific treatment will be required accordingly.[4] Co-infections, such as sexually transmitted diseases, should be considered.

The impact of the disease diagnosis on the patient and family members must be stressed, and proper counselling by trained personnel is mandatory. The diagnosis of primary HIV infection also has public health significance. As this is the period in which the patient is most infectious to others, proper counselling can decrease the chance of the infected patient transmitting the virus to sexual partners and others. Identification of the source of exposure for a given patient with primary HIV infection, may also reveal a network of further newly infected or highly infectious individuals requiring early intervention.

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