

Case Report

HIV Negative CD4+ Lymphocytopenia with Tuberculosis in a Young Arab Patient

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INTRODUCTION

Severe acquired deficiency of helper-T cell in the absence of HIV infection is a rare disorder of multiple etiopathogenesis and heterogeneous clinical features. One such disorder, known as idiopathic CD4+ lymphocytopenia (ICL), remains clinically stable and, in contrast to HIV infection, does not usually deteriorate over time^[1,2]. The criteria for diagnosis of ICL includes a CD4+ T-lymphocyte count of $< 300/\text{mm}^3$ or $< 20\%$ of total lymphocytes on at least two successive occasions and without evidence of HIV infection or other known causes of immunodeficiency^[3]. Patients with ICL have been reported since 1989 from different populations and have led to a much publicized search for another immunosuppressive retrovirus^[2,4,5,6].

HIV infection is rare in Saudi Arabia. According to 1997 WHO report for the East Mediterranean Region^[7], only 334 cases of AIDS have been recorded so far in this country. Out of 725 consecutive patients investigated by us for cellular immunodeficiency over a period of 10 years (1988-1998), only 60 adults were found to have very low CD4 counts. All of them, except the patient being reported here, were HIV positive. In this report, we document the first likely case of ICL in an adult of Arab extraction, which meets the CDC criteria for this diagnosis. ICL is the diagnosis of exclusion requiring exhaustive serological and molecular tests to exclude even exotic infections, though, it is uncertain how this diagnosis can be established beyond reasonable doubt in the developing world with meager resources. The following case highlights this diagnostic dilemma.

CASE REPORT

A 39-year-old Saudi male presented with a history of fever, night sweat, dry cough and increasing dyspnea for the last few weeks as well as

a loss of appetite and weight over the last four months. There were no associated risk factors for HIV infection. Apart from a raised temperature (39°C), he had oral candidiasis, and a slightly enlarged liver. The ESR was raised (70 mm/hr), with lymphopenia ($\text{WBC } 4 \times 10^9/\text{mm}^3$, 13% of them were lymphocytes) and mild normocytic anemia (Hb 11.2g/dl). Routine biochemical tests were normal. A raised serum alkaline phosphatase (2965 IU/L) test for isoenzymes was not available, however other liver function tests were normal suggesting bone origin. An X-ray disclosed right-sided pleural effusion and a cavitating tuberculous lesion in the left upper lobe (Fig. 1). Mycobacterium tuberculosis was cultured from the pleural fluid. Tuberculin test using $10\text{ IU/PPD}/0.1\text{ml}$ was negative. The patient was put on a combination anti-tuberculosis regimen (INH 300 mg OD /Rifampicin 450 mg OD /Ethambutol 800 mg OD /Pyrazinamide 40 mg OD) which was compatible with the sensitivity profile. Three weeks later, the patient showed symptomatic improvement both clinically and radiologically (Fig. 2) although he continued to have intermittent high-grade temperature (40°C). A repeated routine blood culture, including culture for *Candida* remained negative. Apart from decreasing alkaline phosphatase to an almost normal level, repeated laboratory data (ESR, WBC count) remained unchanged. Arrangements for a bone scan could not be completed as the patient suddenly developed right-sided hemiplegia due to left intracerebral hemorrhage (Fig. 3). No other features on the CT scan could be identified. Cerebrospinal fluid analysis was normal apart from a slightly raised protein (66 mg , normal 45 mg/dl). No acid fast bacilli or other identifiable organism could be seen on a special stain and culture did not show any growth after one and six weeks incubation. Due to a falling hemoglobin and the presence of occult blood in the stool, an upper

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GIT endoscopy was carried out. It revealed severe candidal esophagitis (confirmed by culture), for which the patient received mycostatin 2 mg Q 6hr. A colonoscopy, which was done due to the occurrence of severe bleeding per rectum, showed multiple superficial ulcers reminiscent of CMV infection.

A light microscopy of punch biopsy was compatible with severe non-specific colitis. Immunohistology for CMV was not available. A coagulation study was completely normal at this stage. Due to continuing lymphopenia and the presence of esophageal candidiasis, the question of acquired immunodeficiency syndrome was raised. Flow cytometry (Becton & Dickonson) revealed severe CD4+ lymphopenia (CD3+ 280 μ L, CD4+ 130/ μ L, CD8+ 140/ μ L, CD19+ 10/ μ L, NK 300/ μ L and activated T-cell 11%). Serum immunoglobulins by radial immunodiffusion (RID) were within normal range, apart from a slightly elevated IgM (IgG 1661 mg/dl, IgA 69 mg/dl, IgM 385 mg/dl). An HIV antibody test using Abbott HIV-1/HIV-2 3rd generation plus ELISA kit which covers both M and O subtypes was negative on three occasions performed 2-3 weeks apart. Tests for HIV P24 or viral RNA were not available. Antibodies to HTLV-1 and HTLV2 were also negative.

Other available microbiological and serological work-ups were insignificant, apart from a detectable level of IgM anti-CMV, suggesting either recent infection or reactivation. CMV culture facilities were not available. Except for colitis, there was no ocular or other obvious clinical features suggestive of disseminated CMV infection. The patient was, however, put on gancyclovir for two weeks without obvious clinical improvement. Repeated lymphocyte subsets showed persistent CD4 lymphopenia. Bone marrow examination suggested infective hemophagocystic syndrome, however, no identifiable pathogen could be seen or grown on culture. The patient showed a downhill course and developed *staphylococcus epidermidis* septicemia and *Kelebsiella* could be cultured from the urine. Intravenous antibiotics were given according to the sensitivity profile but the patient deteriorated further and lost consciousness. At this stage, he was transferred to ICU and was prepared for CT and a possible lumbar puncture, but he showed profuse bleeding from mouth and nose and died in the next day.

Results of coagulation study at this stage confirmed the picture of DIC (PT 19.8 sec, control 11.5 sec; PTT 86.5 sec control 28 sec; International Normalized Ratio (INR) 2.7; FDP > 20mg/ml, normal < 5mg/ml; fibrinogen 1.2g/l, normal 2 - 4g/L).



Fig. 1: X-ray showing right-sided pleural effusion and a cavitating tuberculous lesion in the left upper lobe



Fig. 2: X-ray showing symptomatic improvement to the patient both clinical and radiological



Fig. 3: Ultrasound showing development of right-sided hemiplegia due to left intracerebral hemorrhage

DISCUSSION

This patient showed a laboratory profile compatible with HIV-negative severe acquired CD4 lymphocytopenia. He presented with pulmonary tuberculosis and opportunistic infections such as esophageal candidiasis, possible CMV colitis and cerebral vasculitis. We believe these were secondary to his immunodeficiency rather than the cause of his lymphopenia as cerebral hemorrhage and symptoms of colitis started one month after admission.

Cytomegalovirus infection is an important human pathogen in the immuno-compromised host. Infections in these patients may be due to reactivation of latent virus or infection with exogenous virus. Symptoms include fever, encephalitis and gastro-intestinal infections including ulcerative colitis^[8]. Because our patient was immunosuppressed, had intermittent fevers, was found to have active colitis and with the only identifiable serological marker of IgM antibodies against CMV virus, we considered a possible CMV infection or reactivation. Furthermore, as IgM response is transient, the presence of this antibody is used to indicate recent infection^[9] particularly in the absence of viral isolation methods.

Similarly tuberculosis may not be the sole cause of lymphopenia in this patient as lymphopenia is commonly associated with extensive infection^[10]. Furthermore, the persistence of CD4+ T-lymphocytopenia despite the apparent symptomatic improvement, is against the expected normalization of the count following treatment^[11]. Tuberculosis has been reported as a cause of CD4+ lymphopenia in some African countries^[12] but no such association has been reported in Arabs in spite of a common occurrence of pulmonary tuberculosis in this part of the world. In a separate investigation to examine the role of tuberculosis in acquired CD4 lymphocytopenia, we investigated 45 Arabs with pulmonary tuberculosis including 30 cases with advanced unilateral or bilateral disease; none of these had severe lymphopenia compatible with ICL definition.

Our patient is a young Arab with no risk factor for HIV infection. There was no obvious cause for secondary immunosuppression such as severe kidney or liver disease, disseminated bacterial, fungal or viral infection at least at the time of presentation. There was also no known exposure to immunosuppressive chemicals nor was there any evidence of autoimmune disease or malignancy, which could have suggested immunosuppression^[2,13,14,15,16]. This patient had general lymphopenia, which is considered to be a distinguishing finding from HIV-positive infection in which CD4+ T-lymphocytes remain selectively affected until the

disease is far advanced^[1]. In addition, this patient had normal serum immunoglobulins, which is in agreement with almost all reported cases of ICL^[2] in contrast to the almost universal hypergammaglobulinemia of HIV-infected persons^[1]. Similarly, low CD4 could be a feature of common variable immunodeficiency but it is associated with hypogammaglobulinemia. Although we could not extensively search for HIV using sensitive assay such as PCR-based molecular techniques, this infection is very unlikely in the absence of any risk factor, negative serology and normal family members and other house hold contacts. Furthermore, the short time over which our patient deteriorated would not allow such investigations to be feasible or to permit a repeat of the CD4 count after his infection was resolved. It is possible that this patient represents a rare form of late onset primary cellular immunodeficiency, which in some races (e.g. Arabs) may assume a violent course. HIV-negative CD4 lymphocytopenia, therefore, demands an aggressive approach to diagnosis and treatment. Unfortunately, this may not be available in most district hospitals in developing countries. As more sensitive tests become available for the diagnosis of viral and other emerging bacterial infections, ICL may become a shrinking entity. For the meantime, however, ICL remains an enigmatic and perhaps seductive diagnosis, at least in the developing world.

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