

It Appears To Be AIDS, But Is It?

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The following is a case report of a patient being, presented in sections, and discussed by experts who have been invited to share their reasoning.

A 32-year-old male with a history of Type 2 diabetes and chronic liver disease secondary to hepatitis C virus, presented to an outside hospital with two weeks of fever and headache. He was diagnosed with “tuberculous meningitis” based on cerebrospinal fluid (CSF) chemistries and cell counts. He was started on standard first line anti-tuberculous therapy with oral steroids (prednisolone 30mg/day) and initially did well and was discharged. A week later he again developed headache, now with vomiting and generalized abdominal pain. He had lost an unspecified amount of weight and had fever and oral ulcers.

The patient was a farmer, belonged to Sind, and had never traveled out of the country. He gave a history of alcohol consumption almost daily for over 10 years and admitted to homo- and heterosexuality. He had no exposure to tuberculosis.

On examination, he was a thin, ill appearing man, awake, co-operative, mildly jaundiced and febrile. His oropharynx was erythematous and covered with white plaques of yeast. There was minimal ascites but no palpable organomegaly. His neck was supple and there were no neurological deficits. The rest of his examination was unremarkable.

Laboratory tests revealed a serum hemoglobin of 9 gm/dl, total leucocyte count (TLC) of 16,600/mm³, with 94 % polymorphonuclear leukocytes and 6% lymphocytes, and platelets of 51,000/mm³. Serum urea, creatinine and electrolytes were normal. Serum amino alanine transferase (ALT) was 97 IU (reference range 25-45), and alkaline phosphatase was 238 u/ml (reference range 67-114u/ml). Antibody to hepatitis C was reactive. Ultrasound of the abdomen showed minimal ascites, altered liver architecture suggestive of chronic liver disease and no organomegaly.

Because of the fever, headache and oropharyngeal candidiasis and a tenuous diagnosis of TB meningitis, lumbar puncture was repeated at this hospital. CSF chemistries showed glucose of 14 mg%, (concomitant blood sugar was 210 mg%), protein of 72 mg% (ref. range 25 – 45), red blood cells of 100 /mm³ and white blood cells 5/mm³. India ink stain showed

a profusion of encapsulated budding yeast and culture grew *Cryptococcus neoformans*. The Cryptococcal antigen was 1:8 in the CSF.

Antibodies to HIV I and II were negative by ELISA twice and by Western Blot. All three tests were done because of the strong clinical possibility of HIV/AIDS.

Dr. Sharaf Ali Shah: “This patient has a risk factor for HIV infection, i.e. hetero- and homosexual promiscuity. Moreover, wasting, oropharyngeal candidiasis and cryptococcal meningitis would seem to strongly resemble full blown AIDS. I will discuss the HIV tests in light of this case.

Several different types of serological tests are performed for the detection of anti-HIV antibodies; these include particle agglutination test, ELISA (Enzyme-linked immunosorbent assay) and Western Blot.¹ (Immuno fluorescence and radio immuno-precipitate tests are not available in Pakistan). These are very sensitive tests and false-negative results are uncommon.

Current ELISA format tests have almost 99% sensitivity and specificity for HIV. Positive predictive value is greater than 99% for strongly reactive samples.

PCR is a method of DNA or RNA amplification using whole blood or plasma to detect as few as one or several copies of viral RNA. This method is highly sensitive and useful for confirming HIV in indeterminate or antibody negative samples.

The usual cause of a false negative test is the ‘window period’; the time between acquisition of virus and seroconversion, a period that lasts up to 3 months and rarely exceeds 6 months.² In this particular patient the symptoms resembling AIDS suggests that he would have been serologically positive for several years, so the question of ‘window period’ does not arise.

An occasional cause of false negative result is related to the HIV subtype designated as ‘O’ on the basis of genetic variation.³ The routine serological tests readily detect subtypes ‘A – H’ but not subtype ‘O’. This subtype is prevalent primarily in Cameroon and other West African countries. Again, in this case there is no history of travel or exposure to individuals from endemic areas.

So in reference to this case I believe we are not dealing with an HIV/AIDS patient and one must look for causes of lymphopenia and opportunistic infections other than HIV/AIDS.”

In the second week of admission his TLC fell to 5,400/mm³. The calculated absolute lymphocyte counts (ALC) was 960/mm³ and 320/mm³ respectively (Normal 1,000-2000 mm³). Results of cytometry were: ALC: 670/mm³, absolute T lymphocytes: 494/mm³ (N 700-2000), absolute B lymphocytes: 176/mm³ (N 100-430), absolute CD4+: 400/mm³ (N 430-1000), CD4+:CD8+ ratio was normal.

Dr. Faisal Sultan: “We have a 32-year-old bisexual male with chronic liver disease secondary to hepatitis C, oral candidiasis and cryptococcal meningitis but with negative HIV serology (by two methods) and a negative Western Blot. He has T cell lymphopenia, thrombocytopenia and marked reduction in CD4+ cells. HTLV-I and II testing is not mentioned.

Assuming that the HIV ELISA has been repeated and is negative and HTLV-I and II are negative, this likely represents ‘idiopathic CD4+ T-lymphocytopenia’^{4,5,6,7,8}. This is a relatively rare entity that first took public stage at the Ninth International AIDS Conference in Amsterdam in July 1992. Epidemiologic heterogeneity and lack of a similar syndrome in sexual partners of those affected suggested a non-transmissible etiology. The relative preponderance of HIV risk factors in this group is likely explained by the fact that CD4+ testing is carried out much more often in this group; therefore there is a selection bias.⁹ Identification of cases with reduction in CD4+ goes back to the 1980s and coincides with the availability of CD4+ testing in the clinical setting. In addition, described cases of idiopathic immunodeficiency prior to the CD4+ era may be due to this entity. While inherent variability in ‘normal’ CD4+ was suggested as one cause for these depressed counts, the presence of clinical syndromes characteristic of immunosuppression would argue against these being normal¹⁰.

Typical clinical presentations have included wasting syndrome, cryptococcosis, mycobacterial infections, Pneumocystis carinii pneumonia, candidiasis, and Kaposi’s sarcoma. This patient has three of these conditions. The clinical course is typically non-progressive but CD4+ counts often remain depressed, though exceptions to this have been described.

Lymphocyte reduction may be seen due to a number of unrelated causes including chronic fungal infections, exposure to UV radiation, anti-lymphocyte antibodies and corticosteroid or cytotoxic agent use as well as being ‘idiopathic’. A case report in 1996 raised the possibility of exposure to HIV (without seroconversion) as a cause for reduction in CD4+ cells^{11,12}. No treatment recommendations exist other than conventional treatment for established infections that are recognized. For patients with persistently depressed CD4+ counts, secondary

prophylaxis makes intuitive sense”.

Dr. Naseem Salahuddin: “This patient was obviously immunocompromised and manifested two simultaneous fungal infections: candida in the oropharynx, which is seen not uncommonly in patients receiving steroids or prolonged antibiotics or both, and cryptococcal meningitis. Cryptococcosis, on the other hand is less common. This fungus is found worldwide in soil, decaying plant material and pigeon droppings. However a history of exposure or its absence to these elements is not relevant to diagnosis¹³. Transmission is by inhalation of basidiospores or unencapsulated forms leading to colonization of the airways. As in tuberculosis dissemination of the fungus may be either due to acute primary infection or reactivation of previously dormant disease. Large focal collections of organisms with some inflammatory response may occur in the brain but infections are usually diffuse. In severe infections the brain becomes swollen and soft.¹⁴

Manifestations of cryptococcosis may be acute or insidious¹⁵. This patient probably had a slow course with mild, non specific headache, fever and malaise. The CSF chemistries and cells were suggestive of chronic basilar meningitis which is why physicians elsewhere treated him as tuberculous meningitis. It was only when we looked for cryptococcus that we found it. During his hospital course he became progressively confused and obtunded. He probably had diffuse meningoencephalitis. His CSF did not improve despite optimum Amphotericin B.

A characteristic feature of cryptococcal meningitis is minimal or no nuchal rigidity. We have described 6 patients with cryptococcal meningitis among AIDS patients.¹⁶ The CSF in all cases was suggestive of chronic meningitis with lymphocytic pleocytosis, elevated protein and borderline to low glucose levels. India ink stain revealed encapsulated yeasts in all patients and CSF cryptococcal antigen was positive in three. Detection of latex agglutination cryptococcal capsular polysaccharide antigen in CSF is a very sensitive and specific indicator of CNS cryptococcosis.^{17,18} A serum titer of more than 1:8 is presumptive evidence of cryptococcal infection. AIDS patients with low CD4+ i.e. less than 100u/ml may also have pulmonary cryptococcosis.¹⁹ There was no evidence of disseminated or pulmonary cryptococcosis in the patient described.

Outcome of cryptococcal meningitis is generally not very good. Even with optimum treatment mortality is 25-30% and even after clinical cure, 20-25% relapse and 40% have residual neurological deficits.”²⁰

Hospital course: The patient was started on IV amphotericin B at 1mg/kg of body weight alone as Flucytosine is not available in Pakistan. Repeated CSF studies showed no

clinical or biochemical improvement in CSF parameters. Oral candidiasis did improve. Intravenous fluconazole was then added. The patient received a total of 1.2 gm of amphotericin B. He however, ultimately died with unresolving cryptococcal meningitis

Dr. Farheen Ali: “We have here an HIV-negative 32-year-old male, diagnosed with cryptococcal meningitis. His co-morbidities include chronic liver disease secondary to HCV and he has evidence of defective immune function with oral candidiasis and low CD4+ count. The history of corticosteroid therapy, given for a prior diagnosis of tuberculous meningitis, may have contributed to his depressed cellular immunity.

Although early studies of treatment of CNS cryptococcosis were done in HIV-negative patients, most of the recently published data have concerned therapy in HIV-infected individuals. Care must be taken to extrapolate these results. The principal antifungal agents for cryptococcal therapy remain amphotericin B, flucytosine and fluconazole, with the newer generation antifungals having either no activity against *C. neoformans* (echinocandins) or having data from only in vitro studies or animal models available (voriconazole).^{21,22} As the efficacy of current antifungal agents is sub-optimal, and concern for drug resistance is high, combination of agents, administered concomitantly or sequentially, are being increasingly recommended.^{21,23,24,25,26} A detailed review is beyond the scope of this article.

The National Institute of Allergy and Infectious Diseases (NIAID) Mycoses Study Group published practice guidelines for the treatment of cryptococcal disease, with the strength of each recommendation given based on available evidence.²⁵ For CNS disease in an HIV-negative patient, the preferred treatment option recommended consists of amphotericin B, 0.7–1 mg/kg/d, plus flucytosine, 100 mg/kg/d, for 6–10 weeks. The adverse effects of amphotericin B, especially renal dysfunction, along with the potential to increase drug levels and toxicity of flucytosine are the main drawbacks of this regimen. An alternative to this regimen is “induction” therapy with amphotericin B (0.7–1 mg/kg/d) plus 5-flucytosine (100 mg/kg/d) for 2 weeks, followed by “consolidation” with fluconazole (400 mg/day) for a minimum of 10 weeks. Fluconazole therapy may then be continued for as long as 6–12 months at a lower dose of 200 mg/d in immunocompromised patients. Some data does exist regarding combination therapy with amphotericin B and fluconazole but the evidence in patients with idiopathic CD4 lymphocytopenia is at best anecdotal.^{21,27}

The role of adjuvant immunotherapy, including pro-inflammatory cytokines like interferon (IFN)-gamma and tumor necrosis factor (TNF) and granulocyte transfusions, remains

inconclusive but has therapeutic potential.^{28,29} Aggressive measures to treat raised intracranial pressure is important to improve outcome. High volume, frequent lumbar punctures or shunting, if the former fails, may be done.³⁰ Acetazolamide has a limited role.³¹ Other prognostic indicators of cryptococcal meningitis include low CSF glucose, high CSF lactate, CSF cryptococcal antigen titre =1:1024, leucocyte count 20/mm³, age older than 60 years, altered level of consciousness, the presence of seizures, and central nervous system vasculitis.³²”

Discussion

One can learn several lessons out of this rather ponderous case. For at least several days we were convinced of his HIV-positive status, and had the tests repeated from three different laboratories before we accepted its true negativity. This, in spite of the fact that cryptococcal disease existed even in the pre-AIDS era.

Secondly, this patient was immunocompromised, i.e. had lymphopenia and moderate CD4penia, presumably secondary to use of steroids and diabetes. It may be argued whether only three weeks of steroid use and Type 2 diabetes which, we were told, was reasonably well controlled on oral hypoglycemic agents, could cause this severe degree of T cell lymphopenia. Could we therefore be dealing with a case of “Idiopathic CD4+ lymphopenia” and were steroids and diabetes simply “red herrings”? Nevertheless, fungal disease is seen not infrequently in patients with poorly controlled diabetes and/or on steroids. Hence, these two factors must be watched carefully as risk factors for fungal infections.

Finally, for clinicians in developing countries like ours, where TB is rampant, TB meningitis is diagnosed clinically with only supportive evidence of abnormal CSF chemistries and lymphocytic pleocytosis. Anti-tuberculous therapy and steroids are begun empirically, and the patient either gets better or does not. The lesson to be learnt here is to routinely look for other causes of basilar meningitis, and especially in cases where patients fail to improve or relapse soon after.

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