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Rare Case of Idiopathic CD4 Lymphocytopenia with Cryptococcal Meningitis

Authors
Deepak K J[1], Aravind G N[2]
[1]Post Graduate in Internal Medicine Bangalore Medical College and Research Institute Bangalore
[2]Associate Professor Department of Internal Medicine Bangalore Medical College and Research Institute, Bangalore, India

Abstract
Cryptococcus neoformans can infect not only HIV-positive patients and non-HIV-infected immunocompromised patients, but also apparently immunocompetent patients.[1-3] With a declining incidence of AIDS-related cryptococcosis in the HAART era, and increasing use of immunosuppressants worldwide, non-HIV infected individuals (with or without predisposing factors) may become the predominant infected group[1-4]. In contrast to immunocompromised patients, few reports have described the variety of C. neoformans, clinical presentation, cerebrospinal fluid (CSF) parameters and prognosis associated with cryptococcal infections among immunocompetent individuals. Such knowledge can assist in the clinical management of cryptococcosis.

Introduction

Idiopathic CD4 lymphocytopenia (ICL) is a syndrome first defined in 1992 by the Centers for Disease Control and Prevention (CDC) as "a documented absolute CD4 T lymphocyte count of less than 300 cells per cubic millimeter or of less than 20% of total T cells on more than one occasion, no evidence of infection on HIV testing, and the absence of any defined immunodeficiency or therapy associated with depressed levels of CD4 T cells"[5] Since then, it is widely accepted that ICL is a rare, heterogeneous syndrome not caused by HIV-1, HIV-2, HTLV-I, or HTLV-II and not appearing to be caused by any transmissible agent.ICL is usually detected after the occurrence of an opportunistic infection in a person without known immunodeficiency or immunosuppression. The clinical course, immunologic characteristics, CD4 T-cell kinetics, long-term outcome, and prognosis of this syndrome remain poorly defined**.**

Case Report

A 29 year old male patient presented to the medicine department casualty with the history of severe right sided hemicranial headache of 15 days duration and on and off altered sensorium since last two days. Patient was an alcoholic with last drink 3 days ago, smoker, and did not have any other co-morbidities like hypertension or diabetes. Patient did not have history of fever or vomiting. no h/o giddiness. no h/o seizures, loss of consciousness or head injury in the past. no history of chronic head ache in the past.

At presentation patient was afebrile, pulse was 86/m,blood pressure was 130/80mm of Hg.

patient was conscious ,oriented and didn't have altered sensorium at presentation. He had minimal neck stiffness but no other signs of meningeal irritation. Other examination of the central nervous system was normal and examination of other systems did not reveal any abnormality.

Patient was admitted with suspicion of cortical vein thrombosis/alcohol dependence syndrome and further investigations were carried out. His routine investigations were apparently normal. (Table 1) CT scan of brain with contrast was done in the outside hospital and was found to be normal. Hence MRI and MR venogram was planned. MRV and MRA were normal. Contrast enhanced MRI showed signs of meningitis (Fig.1). Patient was planned for lumbar puncture and CSF analysis which showed high CSF pressure, CSF protein of 187mg/dl, sugars of 17mg/dl and 90 cells which were 100% lymphocytes. ADA levels were normal. TBPCR of CSF was negative and india ink for cryptococcus was positive. cryptococcal antigen for C. Neoformans was also positive. Hence a diagnosis of cryptococcal meningitis was made and started on injection amphotericin B and tablet Flucanozole 400mg. Patient was tested for HIV 1 AND 2 on 2 ocassions (ELISA) and both the times was found negative. In view of the strong suspicion, western blot was done which was again negative.CD4 counts were done at the National Institute of Virology which was found to be 274 with 12% of total T cells in circulation.

We again went back to the history and enquired about recurrent infections in the past and hospital admissions for infections in the past, suspecting immunodeficiency syndromes but patient didn't have any such infections in the past. Agammaglobulinemia/hypogammaglobulinemia was suspected and Ig and IgM levels were tested and were found normal. Repeat CD4 Count was done and was found low. With the available reports and search of literature, a diagnosis of Idiopathic CD4 Lymphocytopenia was made.

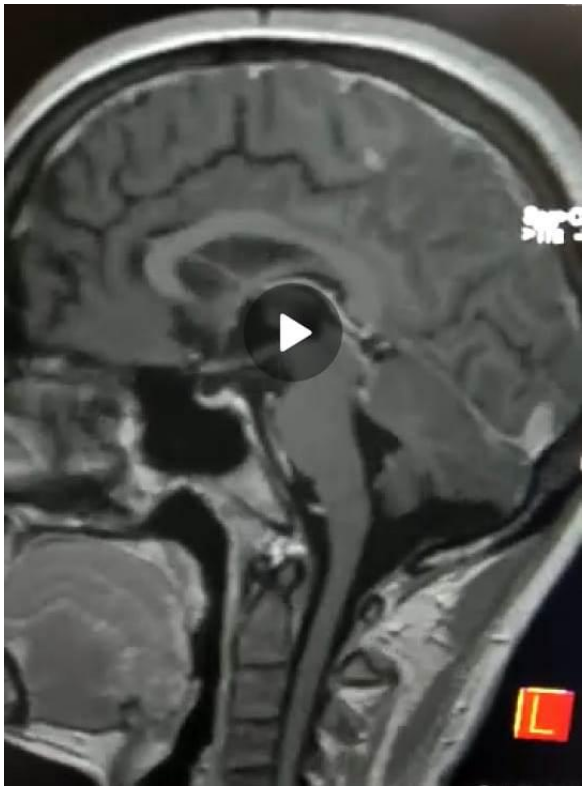

Figure 1 Meningeal Enhancement on MRI

TEST	VALUE
haemoglobin	18.0
Total count	11,100
Differential count	N78,L14,M6
HIV 1 2	negative
LFT	normal
RFT	normal
Serum electrolytes	normal
fundoscopy	normal
USG abdomen	normal
Routine urine	normal
RBS	116
Test name	results
Csf protein	187mg/dl
Csf sugar	27mg/dl
Csf cell count	90cells/100%lymphocytes
Csf ADA	03
Csf TB-PCR	negative
Csf india ink	positive
Csf bacterial culture	negative
Csf cryptococcal antigen	positive
Western blot	negative
P24	negative
IgG serum	12.9g/l
IgA serum	210mg/dl
IgM serum	210mg/dl

Discussion

Cryptococcus is a yeast like fungi. Until recently cryptococcal strains were separated into 2 species, cryptococcus neoformans and c. gatti both of

which can cause cryptococcosis in humans. the two varieties of c.neoformans-grubii and neoformans correlate with serotypes A and D respestively. c. gatti although not divided into varieties, also is antigenically diverse, encompassing serotypes B and C. most clinical laboratories do not routinely distinguish between c.neoformans and c. gatti or among varieties, but rather identify and report all isolates simply as c.neoformans.[5]

ICL is a heterogeneous condition diagnosed typically in middle age, usually after an opportunistic infection, although it can also be an incidental laboratory finding. In a few patients, lymphocytopenia in routine complete blood counts had been largely overlooked for several months or years before eventually ICL was diagnosed resulting from an opportunistic infection. This raises the possibility that CD4 T lymphocytopenia exists long before an opportunistic infection occurred in those patients. Data obtained from blood banks confirm the rare existence of a small population of otherwise healthy persons with low CD4 T-cell counts (0.25%-0.5% of blood donors), although it is not clear if this represented a transient or persistent low count. Cases were clearly identified as early as 1983 and were remarkably similar to the clinical features of ICL that had been identified decades earlier. although as a result of immune deficiency, certain patients with ICL develop some of the opportunistic infections particularly cryptococcosis, non tubercular mycobacterial infections seen in HIV infected patients, the syndrome is demographically, clinically and immunologically unlike HIV infection and AIDS. many patients with ICL remained clinically stable and their condition did not deteriorate progressively as is common with seriously immunodeficient HIV infected patients. approximately 15% of patients with ICL experience spontaneous reversal of CD4+lymphocytopenia. immunological abnormalities in ICL are somewhat different from those of HIV infection.ICL patients have increases in CD4+T cell activation with decrease in Cd8+ cells and B cells. furthermore, immunoglobulin levels are either normal or decreased in patients with ICL as compared to usual hypergammaglobulinemia of HIV infected individuals. there has been no epidemiologic evidence to suggest that a transmissible microbe was involved. The cases of ICL have been widely dispersed with no clustering. It is highly likely that there is no common cause however there may be common causes among subgroups of patients that are currently unrecognised.[5]

In 2006 G.LUI et al studied cases of cryptococcosis in immunocompetent patients and found that a substantial proportion of patients with cryptococcosis were apparently immunocompetent. They tend to present with indolent forms of meningitis with c. neoformans var. grubii and c.gatti being the most common causes of such disease. [6]

In 2009 Dimitrios I Zonios et al studied the spectrum of diseases in ICL and found that cryptococcosis and non tubercular mycobacterial infections were the commonest opportunistic infections in ICL. Certainly, appearance of these 2 infections in an HIV-negative patient should lead to an investigation for the possibility of ICL. Manifestations of HPV infection and of dermatomal zoster were common in previous studies, and the possibility of this diagnosis should be considered, especially in an HIV-negative patient with disseminated and recalcitrant condylomata acuminata and warts or multidermatotomal VZV infection. ICL patients are susceptible to PCP and several cases have been previously reported. Investigation toward alternative diagnoses at disease presentation should always include lymphoproliferative diseases or lymphomas and other forms of immunodeficiency, such as common variable immunodeficiency.[7]

In conclusion ICL is a heterogenous yet distinctive condition that is quite different clinically and immunologically from infection with HIV. Experimental cytokine therapies such

as IL7 and IL2 that could improve survival and CD4 expansions could be contemplated for further studies. Patients at risk for progression but without active opportunistic infections could be potential candidates for such experimental approaches.

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