

# Idiopathic CD4+T-Lymphocytopenia - A Diagnostic Dilemma

Rohan Augustine\*, Mohammed Khalid\*, ZK Misri\*\*, Suresh Hegde\*\*

## Abstract

The devastating global impact of acquired immunodeficiency syndrome (AIDS) has greatly sensitized the public to the threat of new microbes that are capable of wrecking havoc on the world's population. The HIV virus infects and depletes CD4+ T lymphocytes. However cases have been described with profound CD4+T cell lymphocytopenia but without evidence of HIV infection, a condition now termed as "Idiopathic CD4+T-Lymphocytopenia". This unexpected revelation at the Ninth International AIDS Conference in Amsterdam was a cause of great public concern and extra ordinary media attention. Hence the Centre for Disease Control and Prevention in Atlanta (CDC) reviewed 23179 cases in the CDC AIDS reporting registry and performed interviews medical record reviews and laboratory analysis of blood specimens and finally identified 47 cases that met the CDC case definition of idiopathic CD4+ T cell lymphocytopenia (<300 CD4+Tcells /cumm or a CD4+cell count <20%of the total T cell on two occasions, no evidence of infection on HIV testing, absence of any defined immunodeficiency or therapy associated with depressed levels of CD4+ T cells).

We are hereby reporting one such case we encountered at our centre who presented with monoparesis and subsequently developed multiple cranial nerve palsy and deteriorating sensorium unresponsive to therapy which eventually turned out to be a case of "Idiopathic CD4+T-Lymphocytopenia" with cryptococcal meningitis

A 31years old lady from north Kerala presented with history of intermittent headache and fever for the past 3 weeks following which she developed acute onset of monoparesis of left upperlimb. For this she consulted a local physician in Kerala who advised a CT brain which showed a small infarct in the right posterior limb of internal capsule. She was then referred to our centre for further workup.

On presentation she complained of minimal weakness of left upper limb with persistent headache and behavioral changes. However she had no history suggestive of cranial nerve involvement, seizures, bladder and bowel disturbance or altered sensorium.

She had no history of tuberculosis, diabetes, hypertension, or any extramarital sexual exposure. Preliminary clinical examination was unremarkable. Investigations revealed Hb-10.2gm/dl, TC -7700cells/cumm, Platelets-276000, ESR-45mm/ hr. Peripheral smear, RFT and LFT were normal. Blood serology for VDRL, TPHA, HIV (Spot and ELISA) was negative. ANA and APLA were also negative. Her CSF analysis revealed protein 107 mg/dl, sugar 31mg/dl, cellcount-125cells with N-26, L -74. CSF PCR for TB and CSF VDRL were negative. CSF culture and India ink preparation were negative. X ray chest revealed a para hilar non-homogenous parenchymal infiltrate? Pulmonary tuberculosis. Sputum for AFB is negative. USG abdomen was normal.

A working diagnosis of chronic tubercular meningitis/ partially treated pyogenic meningitis was made and she was started on anti tubercular therapy and antibiotics. Patient did not respond to the above measures and by the end of second week showed signs of neurological deterioration in the form that she now developed bilateral papilloedema, and deteriorating sensorium. Anti edema measures were initiated and a repeat scan was done to rule out obstructive hydrocephalus which showed no fresh changes. Patient continued to deteriorate and developed right LMN facial palsy followed by left lateral

rectus palsy. In view of this deterioration a repeat CSF analysis was done. CSF showed a protein of 23mg/dl, sugar-5mg/dl, cellcount -5 cells, all lymphocytes. CSF India ink was positive for Cryptococcus and was further confirmed by culture. CSF polysaccharide antigen test for Cryptococcus was negative. HIV ELISA was repeated, but was found to be negative. In view of fungal meningitis being uncommon in an immuno competent host CD4 count was done which was 269cell/cumm. Further enquiry revealed a history of breeding pigeons at home. Patient was started on IV amphotericin in the recommended dosage. After 2 days patient worsened further and an MRI was done which showed superior saggital sinus thrombosis. Inj heparin was started but patient failed to respond and subsequently went into cardiac arrest secondary to brainstem dysfunction and transtentorial herniation.

## Discussion

The immunodeficiency syndrome of Idiopathic CD4+ T -lymphocytopenia was defined for Adults by the Centre for disease control and prevention (CDC) as

1. Depressed numbers of circulating CD4+T cell lymphocytes (<300cell/cumm or < 20% of total T cells) on more than one occasion.
2. No laboratory evidence of infection with Human Immunodeficiency virus Type I (HIV I) or Type II(HIV -2) .
3. Absence of any defined immunodeficiencies or therapy associated with depressed levels of CD4+T cells.

The CDC criteria for Children includes

1. CD4+T-cell count of <100cell/ cumm in children 0-23 months of age and of <300 cells/cumm in children 2-12 yrs of age or a CD4+T cell lymphocyte count <20% of total lymphocytes. On at least separate measurements
2. No serological evidence of infection on HIV testing (even if the Childs mother is HIV seropositive).
3. Absence of any defined immunodeficiency or therapy associated with T cell depletion.

The CDC reviewed 2,30,179 cases reported in the CDC AIDS

\*PG Internal Medicine; \*\*Consultant neurologist, KMC Mangalore  
Received: 03.03.2006; Accepted: 26.05.2009

Reporting System and finally found 47 cases that met all the criteria for Idiopathic CD 4+ T cell Lymphocytopenia Their study concluded the following differences of this condition from HIV associated CD 4+ T cell Lymphocytopenia.

- Although an unknown infectious agent of immunodeficiency cannot be ruled out definitively the epidemiological data did not suggest that the condition was caused by a transmissible agent as there was no case clustering, the limited number of sexual contacts, household contacts, and persons who donated blood to the affected patients were clinically well and had normal CD4 counts.
- All patients with Idiopathic CD4+ T-lymphocytopenia tested to date had serum immunoglobulin levels within or very near the normal range. These findings are in contrast to the elevated immunoglobulin levels in HIV infected patients and to the decreased levels typical of common variable immunodeficiency.
- The CDC did not observe a steady decline in CD4 cell count in contrast to advanced HIV infection, which is characterized by progressive depletion of CD4 count. Indeed several patients had a spontaneous reversal, partial or complete of lymphocytopenia which is highly unusual for HIV.
- As compared with HIV infected patients, the patients with Idiopathic CD4+ T-lymphocytopenia had lower percentages and counts of both CD8 cells and T (CD3+) cells raising the possibility of more generalized state of immunodeficiency. The ratios of CD4 to CD8 cells were uniformly less than one.79%of the cases studied had total lymphocyte count <1500 cells/cumm and 21% also had CD8+T cell lymphocytopenia.
- Opportunistic infections at or before the time of interview were the most common clinical illness. 40% of the patients had AIDS defining illnesses and 53% had other illnesses that were non AIDS defining and 6% were asymptomatic.

Our present case satisfied the case definition criteria of Idiopathic CD4+ T-lymphocytopenia by having no evidence of HIV infections on repeated testing (spot and ELISA) and having a CD4 count of 269cell/cumm. She neither had high-risk behavior or blood transfusions in the past hence reducing the possibility of HIV infection. She was also screened for other causes of immunosuppression like leukemia, diabetes, and immunosuppressive therapy. The possibility of common variable immunodeficiency seems unlikely as it is commonly characterized by recurrent sinopulmonary infections for several years, which was absent in our case. She had evidence of cryptococcal meningitis (CSF India ink and culture proven), an AIDS defining illness. Cryptococcal meningitis in HIV is generally encountered when the CD4 count is less than 100cells/cumm. Review of literature of the reported 47 cases of Idiopathic CD4+ T-lymphocytopenia revealed 4 cases of cryptococcal meningitis and one case each of pulmonary and extra pulmonary cryptococcosis. Five cases of cryptococcal meningitis in immunocompetent patients have been reported by P Sanchetee in JAPI, however estimation of CD4 count was not done as a part of their study. The possible source of cryptococcal infection in our patient could probably be traced to breeding of pigeons. The poor response to amphotericin could probably be attributed to low CD4 count.

In the present case estimation of serum immunoglobulin levels, serology for HTLV I and II could not be done due to cost constraints.

## Conclusion

At this point we can reasonably conclude that idiopathic CD 4 + T cell Lymphocytopenia is a rare syndrome, it is not new as cases have been reported as early as 1983, it is not caused by HIV I, HIV -2, HTLV 1, HTLV 2, is epidemiologically, clinically and immunologically different from HIV and does not appear to be caused by an infectious agent.

A high index of suspicion is to be maintained in their identification due to their poor response to therapeutic interventions.

It is a possible cause of opportunistic infections in the so-called immunocompetent host unless they are screened with CD4 Counts after an HIV negative report.

It is yet unclear whether in some patients idiopathic CD4+T cell lymphocytopenia develops as a consequence to an infection or the infection is the cause of low CD4 +T cell count.

Further studies of these cases could give us an insight into the complexities of the immune system and its role in host defense mechanisms.

## References

1. David D Ho, Yunzhen Cao, Tuofu Zhu, Charles Farthing et al: "Idiopathic CD4+T-Lymphocytopenia"-immunodeficiency without evidence of HIV infection NEJM 328:380-385.
2. Robert Duncan, C Fordham Von Reyn, George M Alliegro et al: "Idiopathic CD4+T-Lymphocytopenia"four patients with opportunistic infections and no evidence of HIV infection NEJM: 328:393-398
3. Thomas J Spira, Bonnie M Jones, Janet Nicholson, Renu B Lal et al: "Idiopathic CD4+T-Lymphocytopenia"an analysis of five patients with unexplained opportunistic infections NEJM: 328:386-392
4. Dawn K Smith, Joyce J Neal, Scott D Holmberg: unexplained opportunistic infections and "Idiopathic CD4+T-Lymphocytopenia" without HIV infection – an investigation of cases in United States. NEJM: 328:373-379.
5. Anthony S Fauci: CD4+T-Lymphocytopenia without HIV Infection – No lights, No camera, just facts NEJM: 328:429-431
6. Sanchetee P: " Cryptococcal meningitis in immunocompetent patients "JAPI. 1998; 46: 617-619.