

Case Report

Non-HIV AIDS presenting with adrenal histoplasmosis and pulmonary tuberculosis: a mesmerising case report and discussion

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ABSTRACT

Non-HIV AIDS or idiopathic CD4 lymphocytopenia (ICL) is an acquired immunodeficiency syndrome resulting in CD4 lymphopenia without any evidence of HIV infection or any other apparent cause of immunosuppression. A non-diabetic patient presented with adrenal histoplasmosis and UTI leading to adrenal failure. No immediate cause of immunosuppression was found, HIV, HTLV screening were negative. A CD4 count was done and the patient was found to be having non-HIV AIDS (idiopathic CD4 lymphocytopenia). He was treated and discharged. Few months later the patient presented again with adrenal failure & pulmonary tuberculosis. Adrenal FNAC showed persisting adrenal histoplasmosis. CD4 count found to be low again, but this time it was worse than the previous scenario.

Keywords: Non-HIV AIDS, Idiopathic CD4 lymphocytopenia, Adrenal histoplasmosis, Tuberculosis, Immunosuppression, Adrenal failure

INTRODUCTION

Non-HIV AIDS is a very rare disease entity characterised by opportunistic infections in the absence of HIV infection and other immunodeficiency states with a CD4 cell count of $<300/\text{mm}^3$ of blood or less than 20% of the total T-cell count on more than one occasions, usually 2-3 months apart. This condition was first described in 1992 in the US, and since then sporadic cases have been reported in various pockets of the world. The etiology of this disease is still unknown and till date there is no definite treatment of this condition except prophylactic & symptomatic treatment.

CASE REPORT

A 35 yr.old, non-diabetic, non-hypertensive male patient from Midnapore, West Bengal, India presented with complaints of generalised malaise, and low grade waxing and waning intermittent fever for the last 1 month. There

was also history of associated nausea & vomiting, pain abdomen and moderate weight loss for the same duration. All these symptoms were relieved temporarily by medications, only to relapse again. There wasn't any history of bloody vomiting, black stool or yellowish discoloration of the eyes and skin. The patient was a known smoker and alcoholic for many years. There was no history of similar illness in anyone in the family, no allergy history and no history of risky behaviour in terms of sexual habits.

General survey and systemic examination revealed presence of pallor, pulse rate-130 /min, BP-76/30 mm of Hg, hepatosplenomegaly along with generalised lymphadenopathy. Pigmentation in the tongue & skin was remarkably present directing our thoughts to a possible adrenal pathology. Other systems were within normal limits.

Investigations of this patient revealed the following results: Na-117 meq/L, K-5.2 meq/L, Urea-32 mg/dl,

creatinine-2.2 mg/dl, CBC, LFT & thyroid profile were normal. HbA1C -5.9%, HIV I/II, HBsAg, anti-HCV—all were negative twice. An 8:00 am morning serum cortisol was 5.61 nmol/L. Serum ACTH was 1250 pg. /ml. CT scan abdomen revealed bilateral adrenomegaly.

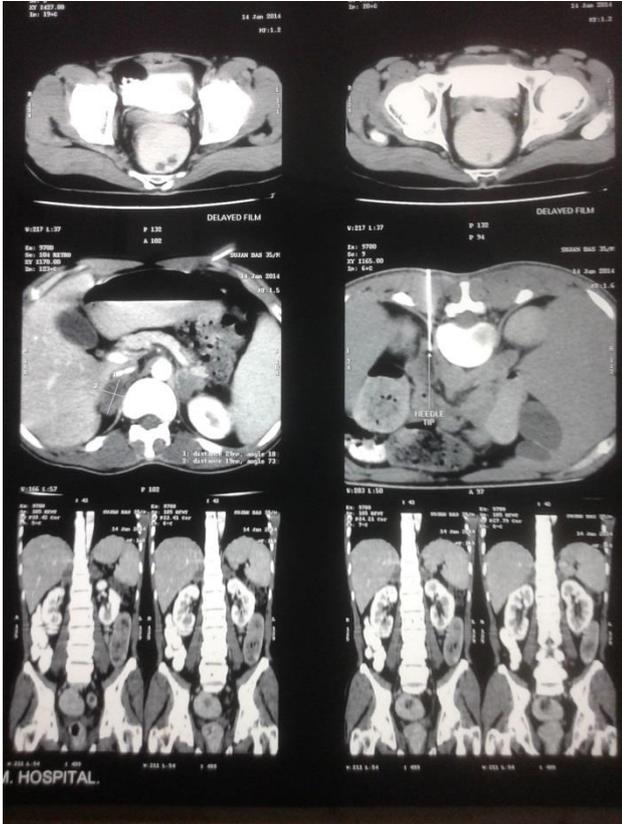


Figure 1: Bilateral adrenomegaly in the patient in CT scan abdomen.

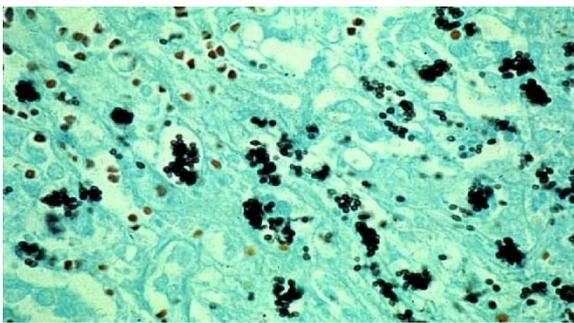


Figure 2: Adrenal gland FNAC specimen showing spores of *H. capsulatum* (Grocott's stain, *1000).

CT guided FNAC from the adrenal gland revealed necrotising inflammation consistent with histoplasma infection an axillary lymph node FNAC revealed lymphocytes with degenerated epithelioid cells and granuloma. Biopsy from the same gland showed extensive areas of necrosis with epithelioid granulomas, Langhans & foreign body type giant cells, fungal stain gave us small oval bodies morphologically resembling histoplasma capsulatum. Patient also had urosepsis along with acute renal failure (maintained CMD and normal

echo texture of both kidneys in a background of raised urea & creatinine), both of which were corrected subsequently with appropriate medications. Chest X-ray was normal, sputum for AFB, Montoux test—both were negative. Assays for HTLV-1 & 2 were also negative.

So, there was this patient, with adrenal failure due to disseminated histoplasmosis involving the adrenals, along with urosepsis, without any apparent cause of immunosuppression. On this background, a CD4 count was sent which eventually came out to be 240 cells/cu.mm. Absolute CD45 (lymphocyte gated) cell count was 751 cells/cu.mm. CD3 cell count and percentage was normal (80% of total, 627 cells/cu.mm). CD4 helper cell % was also normal—34.2% (technique: flow cytometry single platform technology).

A diagnosis of primary adrenal insufficiency due to adrenal histoplasmosis along with urosepsis resulting from non-HIV AIDS (ICL) was reached.



Figure 3: Bronchiectasis (Jan'14); HRCT.

The patient was treated with IV hydrocortisone along with adequate fluids, antibiotics & subsequently shifted to oral hydrocortisone and fludrocortisone after the patient was stabilised. For disseminated histoplasmosis, the patient was given liposomal amphotericin B for 10 days followed by oral itraconazole (200 mg bid). He was discharged at this stage after counselling for regular follow-up visits. During this time, his Urea/creatinine =

28/1.1 mg/dl, Na-135.7 meq/L, K-4.06 meq/L, counts were 6100 /cu.mm (N71L29).

After this, the patient didn't come for follow-up for several weeks. During this time, he went to some other doctors who had reduced his dosage of itraconazole. The patient presented again after one year with nausea, vomiting, dizziness and cough, followed by generalised weakness and malaise. On examination his BP was 80/52 mmHg, pulse rate-120/min, there were bronchial breath sounds in the left upper lobe of lung, along with mild crepitation. Serum sodium-122 meq/L, K+5.2 meq/L, urea-81 mg/dl, creatinine-2.2 mg/dl, LFT, haemoglobin-WNL, TC-18,800 cells/cu.mm. (N90L08E01M01), HbA1C-5.7%, HIV I/II –again non-reactive. Serum cortisol was found to be low with ACTH stimulation test (248.31 nmol/L after ACTH stimulation), T3, T4, TSH levels were also normal. Again a CT abdomen was done to see the status of the adrenal glands—it showed bilateral adrenomegaly and hepatomegaly (Figure 1: bilateral adrenomegaly in the patient in CT scan abdomen (Jan'14)).

CT guided FNAC from the adrenal glands this time revealed predominantly amorphous necrosis, degenerated cell debris & necrotic stroma along with many ghost like negative shadows of small, round to oval shaped spores—conforming to the morphology of *histoplasma capsulatum* (Figure 2: adrenal gland FNAC specimen

showing spores of *H. capsulatum* (Grocott's stain, *1000)).

AFB staining of the sample was also done to rule out adrenal tuberculosis; it was negative. There was an opacity in the left upper lobe of lung in skiagram—so a HRCT thorax was done which revealed fibrotic strands with bronchiectasis and infective changes in the left upper lobe of lung along with fibrotic strands also in the right upper lobe (Figure 3: bronchiectasis (Jan'14); HRCT)).

AFB staining of the sputum gave us sputum positive pulmonary tuberculosis. This time a CD4 & CD45 count was done again which have decreased further to 211 & 656 cells/cu.mm of blood respectively. The other fractions of CD3 & CD4% were normal (Table 1). This time he was again given supportive therapy in the form of fluids, IV hydrocortisone, antibiotics and other symptomatic management. Cat I ATD was also started along with full dose of itraconazole. Patient was stabilised, shifted to oral hydrocortisone and fludrocortisone and was discharged. During discharge his urea was 1.0 mg/dl, creatinine-25 mg/dl, sodium 130 meq/L, potassium- 4.3 meq/L and TC was 8400/cu.mm (N76L23M1). The patient was reviewed after 1 month; he was doing fine, taking all his medications properly and is on regular follow up.

Table 1: Fractions of CD45 & CD4.

Date	CD4 count Ref(448-1610/mm ³)	CD45 absolute count ref(1115-4000/mm ³)	HIV I/II	HbA _{1C}	Serum cortisol	MANIFESTATIONS
30/12/12	240	751	neg	5.9%	5.61 nmol/L	Adrenal histoplasmosis with adrenal failure with urosepsis
26/12/13	211	656	neg	5.7%	248.31 nmol/L (after ACTH stimulation)	Adrenal failure due to previous adrenal histoplasmosis with sputum positive PTB with bronchiectasis

DISSCUSION

There are two aspects of this case, the first one is that this patient presented with a spectrum of different diseases separated over time, the cause of which was eventually found out to be idiopathic T-cell lymphocytopenia, a disease which is not only rare but also very little understood. Secondly, this patient also showed signs of adrenal failure which is again quite uncommon in patients affected with histoplasmosis of the adrenal gland.

Idiopathic CD4 lymphocytopenia (ICL) was described in 1992 as an immunodeficiency syndrome characterized by

opportunistic infections and low CD4 T-cell counts in the absence of HIV infection. In spite of passage of almost two decades after the description of the disease, the clinical spectrum, etiopathogenesis and therapy of the disease remain obscure.

ICL is defined by a documented absolute CD4 T lymphocyte count of less than 300 cells per cubic millimetre or of less than 20% of total T cells on more than one occasion, usually 2 to 3 months apart, without evidence of HIV infection or any defined immunodeficiency or therapy associated with depressed levels of CD4 T cells.¹

ICL is said to be a heterogeneous disorder with a multitude of different conditions all of which share a common feature of reduced T-cells without any apparent cause of immunosuppression. The diagnosis of ICL is usually suspected when an opportunistic infection is identified in an apparently healthy individual. Most frequently reported infections are cryptococcal or mycobacterial disease (both tubercular & non-tubercular like *Mycobacterium avium* complex) and progressive multifocal leukoencephalopathy (PML) – that are usually seen in HIV-infected patients. Other infections like PCP (*Pneumocystis carinii* pneumonia), treatment resistant human papilloma virus (HPV) infection, Epstein-Barr virus (EBV) related lymphoproliferative disorders leading to B-cell lymphoma, varicella zoster virus (VZV) infection, histoplasmosis, Candidiasis, toxoplasmosis, aspergillosis, cytomegalovirus infection, and Leishmaniasis have also been reported. Autoimmune diseases (especially Sjogrens syndrome)² have been said to be associated with ICL, these patients are more prone to develop non-Hodgkin's lymphoma. Some of the patients have been found to be completely asymptomatic over a period of time in spite of low CD-4 counts, these subset of patients mostly have been found to possess low but stable CD-4 counts in sequential assays.

In a recent study, patients with ICL had impaired expression of CXCR4 almost exclusively in T cells, both naïve and memory subsets.³ In an immunodeficiency syndrome featuring warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM), mutations of the chemokine receptor CXCR4 leading to neutropenia and immunodeficiency were recognized.⁴ Other possible mechanisms proposed in the pathogenesis of ICL have been suggested to be in the Fas & Fas ligand,⁵ enhanced apoptotic deletion of T-cells,⁶ defective thymic maturation of T- cells,⁷ reduction in the p56 (Lck) kinase activity,⁸ reduced responsiveness of the circulating T-cells to IL-7 (may be due to IL-7 receptor defect),⁹ RAG1 & RAG2 gene mutations,¹⁰ a defect in the MAGT 1 (magnesium transporter gene),¹¹ defective production of TNF-alpha & IFN-gamma,¹² and a heterozygous dominant negative mis-sense mutation of the signalling adaptor protein Uncoordinated 119 (Unc119) that disrupts the association between Lck (lymphocyte specific kinase) and TCR (T-cell receptor).¹³

Currently there are no definite treatment options for this novel condition and treatment is generally aimed at preventing infections and malignancies by prophylactic antibiotics and medications as used in a case of HIV infected patient. Recently a trial of polyethylene glycol (PEG) conjugated recombinant-IL-2 subcutaneous injections in the dose of 250,000 U/m² weekly for a continuous period has shown promise. However further trials and results are needed for using this therapy on a regular basis. IFN- gamma was tried but without any result.¹³

The second aspect of this case was adrenal failure in a case of adrenal histoplasmosis. Adrenal histoplasmosis is one of the manifestations of extra pulmonary disseminated histoplasmosis caused by *histoplasma capsulatum*, a thermal dimorphic fungus. But though adrenal gland may be frequently involved in a case of disseminated histoplasmosis (approx. 80% Goodwin et al, 1980), the incidence of adrenal failure is quite a rarity in these subset of patients (Subramanian et al, 2005; Rajesh et al, 2010). In a study led by Kauffman in 2001, only 12 out of 58 patients with histoplasmosis had adrenal involvement & none of them had adrenal failure.

CONCLUSION

If a patient presents with diseases like concomitant histoplasmosis with or without tuberculosis & other infections, we must consider some cause of immunosuppression in that patient, the causes may be diabetes, HIV infection, or any other immunosuppressed conditions. In the absence of any apparent cause of immune suppression the possibility of idiopathic CD4 lymphocytopenia must be kept in mind, since this extremely rare condition is being diagnosed with increased frequency in various parts of the world. Also the possibility of development of adrenal failure in a case of adrenal histoplasmosis must be kept open and accordingly the patient must be followed up in subsequent visits.

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