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AIDS with Disseminated Tuberculosis

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Summary:

Tuberculosis (TB) and Human Immunodeficiency Virus (HIV) have been closely linked since the emergence of the Acquired Immune Deficiency Syndrome(AIDS). Worldwide, TB is the most common opportunistic infection affecting HIV-seropositive individuals,and it remains the most common cause of death in patients with AIDS. By producing a progressive decline in cell-mediated immunity, HIV alters the pathogenesis of TB, greatly increasing the risk of disease from TB in HIV-coinfected individuals, and leading to more frequent extrapulmonary involvement, atypical radiographic manifestations, and paucibacillary disease, which can impede timely diagnosis. Although HIV-related TB is both treatable and preventable, incidence continues to climb in developing nations, wherein HIV infection and TB are endemic and resources are limited. We report the case of a 45 year old gentleman who presented with generalized lymphadenopathy, whose lymphnode biopsy was consistent with TB; however following poor response to anti-TB treatment, he was found to be serologically positive for HIV.

Key Words: Acquired Immune Deficiency Syndrome(AIDS), Human Immunodeficiency Virus(HIV), Lymphadenopathy, Tuberculosis(TB).

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Introduction:

HIV associated TB remains a major global public health challenge, with an estimated 1.4 million patients worldwide, particularly in Asia and Africa. Co-infection of TB with HIV leads to challenges in both the diagnosis and treatment of tuberculosis, especially given an increase in the rates of drug resistant tuberculosis, including multi-drug (MDR-TB) and extensively drug resistant TB (XDRTB).[1]AIDS, first recognized in 1981, is caused by the retrovirus HIV, which progressively decreases cellular immunity. The virus has two subtypes: HIV 1 and HIV 2. HIV 1 is the cause of the global pandemic, while HIV 2 causes a similar pattern of weakness as HIV 1 but progresses slowly and is less transmissible.[2]There are many opportunistic diseases in AIDS,varying according to the CD_4count. TB may occur at any stage of HIV disease and is frequently the first recognized presentation of underlying HIV infection.[3]In addition, most TB/HIV-coinfectedpatients have extrapulmonary or disseminated forms of TB.[4] With an estimate of 350,000 deaths per year, TB accounts for a quarter of all AIDS-related deaths, and is the most common cause of death for people living with HIV.[5]Apart from the diagnostic and therapeutic challenges among TB/HIV co-infected patients, there is also the especial difficulty in obtaining correct history, with most patients concealing the history of sexual exposure and drug addiction, important factors in the epidemiology of HIV.[4]Treatment of coinfection is challenging, however the principles of treatment of active TB in HIV-infected patients are the same as those for HIV-uninfected patients. All HIV-infected patients with diagnosed active TB should be started immediately on both anti- TB treatment as well as antiretroviral therapy.[6]Close collaboration between HIV and TB control programs among clinicians, health care institutions, and public health programs is necessary in order to integrate care and improve medication adherence and TB treatment completion rates, reduce drug toxicities, and maximize HIV outcomes.

Case presentation:

A45-year old normotensive newly diagnosed diabetic Bangladeshi gentleman presented to DMCH on 11.3.2014 with the complaints of fever for 9 months and multiple lumpy swellings in different parts of the body for 2 months. Thefever was low grade, continued, not associated with chills & rigors, with no evening rise and subsided on taking antipyretics.He also complained

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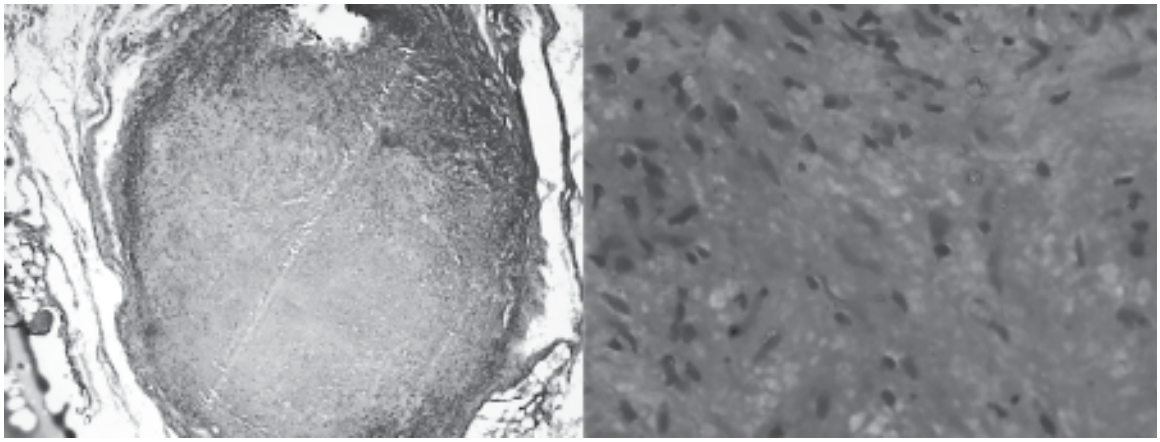

Fig.-1: *Histopathology of lymph node biopsy showing granulomatous inflammationincluding areas of caseation consistent with TB.*

of occasional cough with production of scanty sputum, whitish and non-foul-smelling. He had been initially diagnosed as a case of Pulmonary TB on the basis of blood tests, sputum and chest X-ray, and started on anti-TB therapy which he continued for two months.

With no improvement of his symptoms and gradual worsening of his general condition which included the onset of severe nausea and vomiting, he stopped taking his medications himself. However, there was no blood loss, un-consciousness, convulsion, blurring of vision, morning headache, focal deficit or bone pain. He denied any contact with TB patients, however was unsure of his BCG vaccination. He is non-smoker and non-alcoholic, with no history of blood transfusion or i/v drug abuse. He was in Dubai for 2 years and Malaysia for couple of months 10 years back. He was married, had two children, and denied any history of extramarital sexual exposure.

On examination, he was cachectic,dehydrated,severely anaemic and moderately icteric.His pulse was 94 beats/min, and blood pressure was 110/70mmHg. There weremultiple non-tender enlarged lymph nodes along both cervical chains and right inguinal region,which were discrete, variable in size(largest measuring 3x3cm),firm in consistency, not fixed with underlying structures or overlying skin, with no discharging sinus. There was a tender scar over right inguinal lymph node.Systemic examination revealed no abnormality. Funduscopy was normal.

Investigations showed Hb-7.7 mg/dl, WBC-3210 /cumm, platelets- 54000/cumm. MCV-74fl. Retuculocyte count 0.89%.Peripheral blood film showed microcytic hypochromia with target cell with thrombocytopenia. Initial Serum Na^+ was 121 mmol/l most likely due to vomiting and later corrected to 138mmol/l. Liver function test revealed elevated liver enzymes (ALT-173 U/L,AST-483 U/L) and raised serum bilirubin - 20.56mg/dl. The bilirubin levels declined to 46 ìmol/L after abandoning anti-TB treatment.

With lymphoma being one of the differential diagnoses, we also did serum LDH and Alkaline Phosphatase levels which were both raised at 729 U/L and 479 U/L respectively.GGT was elevated at 234 U/L. VDRL, Hb_SAg were negative. Lymph node biopsy revealed granulomatous inflammation consistent with TB with areas of caseation (Figure 1).However, on further probe into the reason for poor response to anti-TB treatment, we tested the patient for HIV. ELISA was positive for HIV1 and HIV2. With the confirmed diagnosis of disseminated TB with drug-induced hepatitis and HIV/AIDS, we proceeded to counsel his spouse and arranged for concomitant anti-retroviral as well as anti-TB treatment.

Discussion:

A cachectic patient presenting with generalized lymphadenopathy brings a variety of differential diagnoses to mind. Among them, especially in a country like Bangladesh, disseminated TB is the most plausible differential, and the commencement of anti TB chemotherapy is justified, especially given the caseating granulomatous lesion found on lymph node biopsy. The possibility of a different diagnosis, or co-infection with

HIV arose, in the context of our patient, mainly due to the poor response to anti TB treatment despite 2 months of uninterrupted therapy.

In addition, the patient had become icteric, and there was a persistent rise of liver enzymes, and the question of drug-induced hepatitis arose. The blood film showed pancytopenia with raised LDH. With an additional differential of granulomatous lesion in liver in mind, we did a GGT level too, which turned out to be elevated. Although this patient's liver enzymes reduced following discontinuation of anti-TB treatment, they failed to return to normal; this, along with a raised GGT level leads to the possibility of TB dissemination to the liver.

AIDS is a progressive deterioration of the immune status of the individual, characterized by the progressive depletion of the CD4 T lymphocyte population, which represents a major target of viral infection by the causative HIV.[7] The clinical consequences of HIV infection encompass a spectrum ranging from an acute syndrome associated with primary infection to prolonged asymptomatic state to advanced disease, classified by the CDC according to CD4 T lymphocyte count.[7]

The mechanisms of immunity against *M. tuberculosis* and control of *M. tuberculosis* infection depends on a T-cell immune response comprising CD4 and CD8 cells , as well as Th1 and Th2 cytokines, including IFN-ã, tumor necrosis factor (TNF)-á and IL-2. [8]

In immunocompetent persons with pulmonary TB, antigen-specific CD4 T cells accumulate in the lung.[9] Progressive loss of CD4 T cells and susceptibility to opportunistic infections like TB are hallmarks of HIV-1 infection. After HIV-1 seroconversion, the risk of active TB is greatly increased in persons who are latently infected with *M. tuberculosis.*[10] *In* contrast to the majority of other opportunistic infections, the risk of developing TB is substantially increased before CD4 T-cell loss is profound, with evidence of TB incidence doubling within the first year of HIV-1 infection.[3]

Systemic T-cell responses against *M. tuberculosis*, especially type 1 cytokines responses, are impaired in HIV-1–infected adults.[11]

T cells play an important role in maintaining the integrity of granuloma formation in the human lung.[12] Susceptibility to active TB in HIV-1–infected persons who are latently infected with *M. tuberculosis* is likely related to the inability of local immune mechanisms to control the *M. tuberculosis* infection. This includes dysregulation of the interaction between lymphocytes and alveolar macrophages. Also, studies show that in addition to a total CD4 T-cell deficit, the function of mycobacteria-specific CD4 T cells is significantly impaired in the lung of HIV-1–infected persons, which may account for the HIV-1–associated elevated risk for developing tuberculosis,[9] as with our patient.

Thus, when we found that our case was responding poorly to anti TB treatment, with high index of suspicion, we screened him for HIV, which turned out to be positive. Western Blot test and CD4 cell count has also been planned.

Given that our patient is a case of Category C according to CDC classification,[7] his management involves simultaneous treatment with anti-retroviral therapy(ART) as well as anti TB chemotherapy Category II. As the patient had drug induced jaundice, he was to be commenced on SHE therapy consisting of Streptomycin, INH and Ethambutol for 3 months, followed by only the latter two drugs for 6 months.

As for ART, the combination of two NRTI with one NNRTI is available and it is the first choice.[6]Researchers recommend that for patients with CD4 counts <50 cells/mm^3, ART should be initiated within 2 weeks of starting TB treatment.

In patients with CD4 counts e"50 cells/mm^3, who present with clinical disease of major severity as indicated by clinical evaluation, ART should be initiated within 2 to 4 weeks of starting TB treatment. In patients with CD4 counts e"50 cells/mm^3 who do not have severe clinical disease, ART can be delayed beyond 2 to 4 weeks of starting TB therapy but should be started within 8 to 12 weeks of TB therapy initiation. Rifabutin is the preferred rifamycin to use in HIV-infected patients with active TB disease on a protease inhibitor (PI)-based regimen, because the risk of substantial drug interactions with PIs is lower with rifabutin than with rifampin.[6]

Conclusion:

As the incidence of AIDS is increasing at an alarming rate in Bangladesh, a high index of suspicion needs to be employed in the diagnosis and further treatment of TB showing poor response to anti TB treatment, as

there is a considerable possibility of co-infection with AIDS and in such patients, screening of the patient for HIV is of paramount importance.

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