

Tuberculosis-immune reconstitution inflammatory syndrome

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ABSTRACT

The characteristic hallmark of immune reconstitution inflammatory syndromes (IRIS) is paradoxical worsening of an existing infection or disease process or appearance of a new infection/disease process soon after initiation of therapy. In view of the overlapping symptoms, its nonspecific nature and a challenging obscurity of diagnosis, a multidimensional diagnostic approach is suggested. We report a case of paradoxical tuberculosis IRIS hidden behind other nonopportunistic infections such as dengue, malaria, and urinary tract infection in a patient with acquired immunodeficiency syndrome.

Key words: Dengue-malaria co-infection, human immunodeficiency virus tuberculosis, immune reconstitution inflammatory syndromes, paradoxical, unmasking, urinary tract infection

INTRODUCTION

Treatment with highly active antiretroviral therapy (HAART) causes exuberant inflammatory responses to opportunistic pathogens that can lead to troublesome immune reconstitution inflammatory syndromes (IRIS). Suppression of human immunodeficiency virus (HIV) replication by HAART often restores protective pathogen-specific immune responses, but in some patients, the restored immune response is immunopathological and causes disease that is, IRIS. Infections by mycobacteria, cryptococci, herpes viruses, hepatitis B and C virus are the most common pathogens associated with infectious IRIS.^[1] Malignancy-IRIS and autoimmune IRIS occur less commonly. Infectious IRIS presenting during the first 3 months of therapy appears to reflect an immune response against an active (often quiescent) infection by opportunistic pathogens whereas late IRIS may result from an

immune response against the antigens of nonviable pathogens.^[1]

CASE REPORT

A 56-year-old man, chronic tobacco chewer, occasional alcoholic presented with complaints of easy fatigability, weight loss, mild dyspnea, low-grade fever since 10 days. On clinical examination, patient was febrile with body temperature of 38.3°C, pulse rate was 90/min, and blood pressure was 130/80 mmHg. He had mild pallor. Oral examination showed thrush on the tongue and soft palate. Palpation revealed multiple cervical, supra-clavicular, and axillary lymphadenopathy. Abdominal examination showed mild splenomegaly. The respiratory, cardiac, and neurological examination did not reveal any abnormality. Chest roentgenogram showed clear lung fields with mediastinal widening. On further investigations, he was found reactive to HIV-1 by ELISA, which was subsequently confirmed with Western Blot. His CD4 cell count was 41 (9%) and HIV viral load was 888,806 copies/ml. Hemoglobin was 8.5 g%; total leukocyte count (TLC) was 6700 cells/cumm with low platelet count of 75000/cumm. Serum bilirubin was 0.8 mg/dl, aspartate transaminase (AST) was 32 mg/dl, and Alanine Transaminase (ALT) was 38 mg/dl. Serum creatinine was 0.9 mg/dl, serum sodium was 135 meq/l, and potassium was 3.9 meq/l.

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Thyroid function test and cortisol levels were within normal range. Urine examination revealed 5–7 pus cells/high power field (hpf), culture showed no growth. BACTEC blood culture was performed in which no growth was detected after 48 h. Peripheral blood smear was negative for malarial parasite. Sputum testing was negative for TB by acid-fast staining and *Pneumocystis carinii* pneumonia (PCP) by Gomori silver methenamine stain. Ultrasound of the abdomen revealed a diffuse abdominal adenopathy around celiac axis, periportal, preaortic mesenteric and iliac nodes with normal liver, kidney, and mild splenomegaly. Meanwhile, biopsy of cervical lymph node confirmed necrotizing granulomas with positive staining for acid-fast bacilli suggestive of tuberculosis (TB). Culture of the lymph node sample was performed for *Mycobacterium tuberculosis* using BACTEC MGIT 960 system the results of which were positive after 3 weeks. Drug sensitivity was obtained by line probe assay the reports of which were obtained after 6 weeks indicating sensitivity to all first-line anti-TB drugs. Meanwhile, patient was diagnosed as a case of disseminated lymph node TB with HIV infection based on the AFB staining reports and was empirically started on four first-line antituberculous treatment (ATT) of rifampicin, pyrazinamide, ethambutol, and isoniazid along with cotrimoxazole as prophylaxis for PCP. Tablet fluconazole at 100 mg once daily was added for oral thrush. With treatment, patient became afebrile after 8 days. Fifteen days after starting ATT, the patient was started on HAART in a combination of emtricitabine, tenofovir, and efavirenz.

During the period of recovery in hospital 3 days after starting HAART, the patient again developed high-grade fever (39.8°C) and mild jaundice. Hemoglobin was 9.8 g%, TLC was 8800/cumm, platelets were 58,000/cumm. Peripheral blood smear detected schizonts, trophozoites, and ring forms of *Plasmodium falciparum* with blood films showing 2% parasitemia. Furthermore, the ELISA test for dengue IgM antibodies came strongly positive. Serum bilirubin was 2.2 mg/dl, AST was 102 mg/dl, and ALT was 98 mg/dl. After 3 days of treatment with artesunate and doxycycline, patient became afebrile, and the liver function tests got normalized.

However, 4 days later, patient again developed an episode of high-grade fever (40.2°C). Hemoglobin was 10 g%, TLC was 9000/cumm, platelets were 180,000/cumm., procalcitonin level was 25 ng/dl.

BACTEC blood cultures were negative, and peripheral blood smear was negative for malarial parasite. Urine microscopy showed 15–20 pus cells/hpf and urine culture revealed 10^5 colonies of *Pseudomonas aeruginosa*. Based on the sensitivity profile, patient was treated with imipenem and levofloxacin. Patient was afebrile after 4 days and repeat urine study was normal.

Despite being on above intravenous antibiotics for urinary infection, AKT and ART, the patient again developed high-grade fever (40°C) after 7 days. Patient had normal blood counts. BACTEC blood culture and urine culture for bacteria and fungi were negative. Peripheral blood smears for malarial parasite was negative. ELISA testing for Cytomegalovirus, Epstein-barr virus, Toxoplasma IgM were negative. Two-dimensional echo showed an adequate left ventricle and right ventricle functions; no regional wall motion abnormality was detected; left ventricular ejection fraction was 50%. There was no evidence of endocarditis on two-dimensional-echo or blood culture. Fibrinogen was 343 mg/dl, ferritin was 109 ng/ml, triglycerides were 242 mg/dl, Lactate Dehydrogenase was 380 IU/L. Empiric addition of antifungal caspofungin to the treatment armamentarium did not resolve the fever. Thyroid function tests were normal. ANA and antihistone antibodies were negative, and hence drug-induced lupus was ruled out. Magnetic resonance imaging scan of the brain showed a normal study. All drugs were stopped to look for the possibility of Drug fever, but the fever continued. A positron emission tomography-computerized tomography scan (PET-CT) was done which showed multiple enlarged, centrally necrotic bilateral supra and infra diaphragmatic lymphnodes with multiple hypoenhancing splenic lesions, and discrete tiny nodules in lungs suggestive of infective process like TB. With all work up being negative and a suspicion of IRIS, we repeated the CD4 counts after 1 month of starting ART. CD4 count had jumped to $0.306 \times 10^6/L$ (38%), and viral load was well suppressed with 801 copies/ml. A clinical diagnosis of TB-IRIS was made, and the patient was started on 1 mg/kg/day dose of prednisolone with which fever subsided in 48 h. Steroids were gradually tapered in the next 6 weeks and finally stopped and ATT as well as ART were continued. A final diagnosis of IRIS with paradoxical worsening of TB lymphadenitis on commencement of HAART was thus made.

DISCUSSION

Although IRIS is a well-established entity, uncertainty exists with regards to its true prevalence, pathogenesis and management, and research in the field is hampered by lack of a consistent definition of the syndrome. The western literature quotes the incidence of IRIS to be high at 20% or more in patients started on HAART. But the Indian studies find these figures to be around 4–7%.^[2-4]

Paradoxical IRIS is used to describe IRIS in patients who are already receiving treatment for an opportunistic disease, and in whom immune recovery after subsequent initiation of ART triggers the clinical deterioration of that disease during the initial months of treatment. In contrast, Unmasking IRIS denotes the clinical event in which opportunistic disease, which was quiescent at the time of ART initiation, becomes clinically manifest because of ART-induced immune recovery.^[5] The pathophysiology of the syndrome is believed to involve a combination of factors, including the reconstitution of immune cell numbers and function, redistribution of lymphocytes, defects in regulatory function, changes in T-helper cell profile, the underlying antigenic burden, and host genetic susceptibility.^[4,6]

In our case, initially, the diagnosis of IRIS was obscured by the occurrence of unusual co-infection of malaria and dengue. The positivity of dengue-IgM ELISA at the same time when *P. falciparum* was detected in the blood smear made us believe that it was probably a nosocomial new dengue-malaria co-infection. Reports of malaria and dengue co-infection are scarce. Since the first case reported in 2005, only few case reports and two descriptive studies have been published from India and Pakistan, Southeast Asia, French Guyana, and Brazil although these infections are hyperendemic in these areas.^[7,8] The treatment and prognosis of this dengue-malaria co-infection were not different in our HIV patient when compared to other cases in other immune-competent patients reported in the literature.^[8] The recurrence of fever after treatment of malaria-dengue co-infection was due to urinary tract infection (UTI) with *P. aeruginosa*. Whether this new infection was a separate nosocomial infection due to prolonged hospital stay or a part of unmasking of pseudomonas UTI as IRIS cannot be said. It responded to the sensitive drugs, and patient

was completely afebrile after 4 days of treatment initiation. The procalcitonin levels (a marker for infection) decreased from 25 ng/dl to 0.4 ng/dl. Patient remained afebrile for 3 days after which high-grade fever reappeared. This time a PET-CT scan was performed which showed an increase in sizes of abdominal lymph nodes and new granulomatous infiltrates in the spleen suggestive of TB. The findings of the PET-CT scan along with the concurrent jump in the CD4 count from 41 cells/mm³-301 cells/mm³ within 30 days of starting HAART supports the diagnosis of TB-IRIS. In our case, although care was taken to prevent the development of TB-IRIS by starting ART 2 weeks after starting ATT in view of low CD4 counts, this strategy could not prevent the development of paradoxical TB-IRIS.

Tuberculosis-IRIS is the most commonly occurring IRIS worldwide. Even though paradoxical reactions were known to occur during treatment of TB in the pre-HIV era, it is considerably more common in HIV-infected persons, especially those on HAART. The majority of the patients (70%) with TB-IRIS have extrapulmonary manifestations of TB-IRIS as was noted in a study^[9] and also in our case. Paradoxical enlargement of lymph nodes accompanied with fever is the most common manifestation. Other clinical findings may include worsening infiltrates or new pleural effusion on chest radiograph, mediastinal and/or peripheral, skin or visceral abscesses, arthritis, and osteomyelitis.^[2,3,6] Onset of features of TB-IRIS is usually within 3 months of ART initiation risk factors for TB-IRIS include the presence of extrapulmonary/ disseminated TB, lower pre-ART CD4 T-cell count, pre-ART plasma viral load >100,000 copies/mL, and earlier initiation of ART after starting ATT.^[10] All these risk factors were present in our case. Diagnosis is one of exclusion and requires a battery of different investigations to rule out other opportunistic infections which can occur at very low CD4 counts. The diagnosis may be delayed by existence of other nonopportunistic endemic infections or nosocomial infections in case of prolonged hospitalization as in our case. Treatment failure, other opportunistic infections, and drug reactions are the differential diagnosis and often need to be excluded.^[2] Most reported IRIS cases resolve within several weeks simply by treatment

of the opportunistic pathogen and continuing ART. Unless clinical presentation is life-threatening, there is no rationale for discontinuing ART. Occurrence of IRIS does not require changing existing maintenance therapy, for an infection in question. Invasive diagnostic procedures can be avoided if this condition is recognized. A brief course of systemic prednisolone (1 mg/kg/day for 1–2 weeks followed by a slow tapering) appeared to be beneficial, especially if symptoms are severe, as was seen in our case.^[11]

CONCLUSION

The differential diagnosis of pyrexia of unknown origin (PUO) in a patient of HIV started on HAART is many, often overlapping and require extensive evaluation. In *Mycobacterium*-TB infection in HIV, immune reconstitution should be considered in patients when there is emergence or worsening of the clinical/radiological manifestations of TB with or without positive acid-fast bacilli smear results obtained from the involved organs, exclusion of other potential causes of the symptoms and signs after an extensive diagnostic evaluation, particularly drug fever and other related infection. And exclusion of drug-resistant TB or other causes that could explain the persistence or relapse of TB.^[2] The development of nonopportunistic infections like malaria, dengue or UTIs in a patient started on HAART occurring as a part of unmasking IRIS needs further evaluation as such associations have not been previously reported. The role of PET-CT scan in the evaluation of PUO has been well-established.^[12] It can be used as a diagnostic aid in cases of strongly suspected immune reconstitution to demonstrate increase in size and number of lymph nodes and involvement of lymphatic organs like spleen as a marker of exuberant inflammatory reconstitution after starting HAART. The syndrome is often nonfatal and can be managed by anti-inflammatory and steroid therapy without stopping the HAART or ATT, provided a timely diagnosis is made.

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