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Case Report

Paradoxical Reaction in an Immunocompetent Internal Medicine Resident Suffering from Tubercular Lymphadenitis

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ABSTRACT

A tuberculosis associated Paradoxical Reaction (PR), aka tuberculosis associated immune reconstitution inflammatory syndrome (TB-IRIS) is defined as the worsening of clinical or radiological findings, following the initiation of appropriate antitubercular treatment, in the absence of evidence of disease relapse or any another probable diagnosis. PR is not uncommon. It is reported in up to 35% of immunocompromised patients with HIV co-infection and in fewer than 5% of immunocompetent patients. We are presenting a case of PR in an immunocompetent host, who is an internal medicine resident, discussing the entity and also highlighting the occupational health hazards in health care workers (HCWs).

Key words: Paradoxical reactions (PR) in tuberculosis; PR in an immunocompetent host; TB-IRIS; Nosocomial TB in HCWs.

CASE PRESENTATION

A second year internal medicine resident at Govt. Medical College and Guru Nanak Dev Hospital, Amritsar developed high grade fever with chills and rigors alongside night sweats. The fever got relieved by antipyretics only to reappear again. There was no history of burning micturition, loss of weight or loss of appetite. The complete blood examination showed haemoglobin to be 10gram% with anemia of chronic disease in peripheral blood film, ESR 67 at the end of the first hour. Total leucocyte count was 6700 with neutrophils being 68% and lymphocytes as 30%. The typhi dot (IgM) was tested positive while antigen testing for malaria was tested negative. The blood and urine cultures were sterile. The chest x-ray was normal. The patient was put on intravenous ceftriaxone and tablet azithromycin for one week. The patient also took a full course of antimalarials by himself during this week. The fever and night sweats continued with appearance of dry cough as the newest symptom. Sputum for Acid fast bacilli examination and culture was requested. Mantoux test was also ordered. While the cultures came negative, the Mantoux at 17mm size was highly suggestive of tuberculosis. Meanwhile, the cough became severe. CECT of the chest was done and it showed enlargement of hilar lymph nodes with necrotic areas suggestive of

tuberculosis (picture 1). Serum anti nuclear antibody assay, serum calcium levels, serum angiotensin converting enzyme levels were requested to look for other possible causes of hilar lymphadenopathy. All were in the normal range. CECT and Mantoux based probable diagnosis of tubercular hilar lymphadenitis was made and the patient was started on antitubercular treatment (ATT). The symptoms started to improve. The fever subsided and the cough totally resolved. The patient remained thoroughly compliant. But after around 25-27 days of initiation of ATT, there was a rebound of symptomatology and in much severe form. The cough was wild and severe. The patient was unable to speak in even short sentences. The speech was markedly interrupted with bouts of violent cough. There was sudden onset of dyspnoea which became progressively severe every passing day. Keeping in mind the possibility of drug resistance, cartridge based nucleic acid amplification technique to test drug resistance (CB-NAAT-R) was requested. It turned out to be negative. Laboratory examination was again done to check for any superadded infection and it was non-significant. CECT was requested and it showed enlarged mediastinal lymphnodes, the size of whom had increased than the previous film. It also showed involvement of newer lymph nodes as well. There was accompanying collapse of the lower part of the right lung (picture 2). The chest X-ray also showed massive hilar lymphadenopathy which was not appreciable in previous X-ray (picture 3). Endoscopy based ultrasound guided transneedle aspiration (EBUS) of bronchial specimens was done. The polymerase chain reaction examination of the samples confirmed of mycobacterium. After excluding non compliance, drug resistance, drug reaction or superimposed secondary infections - the probable diagnosis of paradoxical reaction or TB-IRIS was made. The patient was started on short- tapering course of oral corticosteroids. ATT was continued as previously. The patient improved again. He has completed his full course of ATT, is CBNAAT negative and his CECT has showed resolution of lymphadenopathy and collapse. He is now hale and hearty.

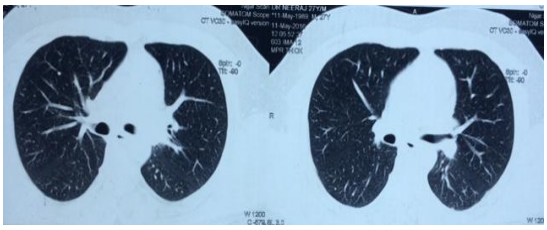

Fig1- showing enlarged hilar lymphadenopathy with necrotic areas

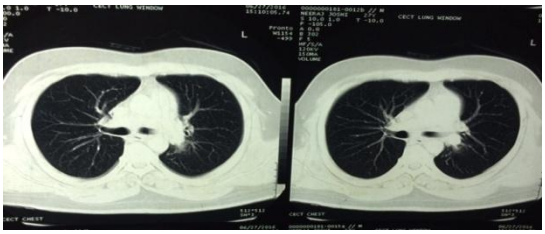

Fig 2 showing enlarged mediastinal lymph nodes and collapse of right lower lung

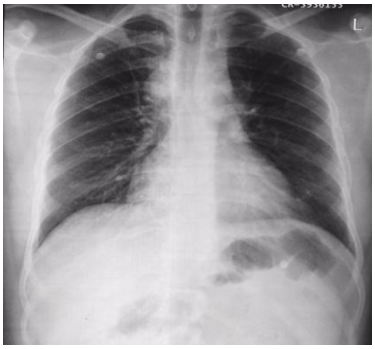

Fig 3 showing massive hilar lymphadenpathy.

DISCUSSION

Paradoxical reactions during ATT (new or recurrent TB symptoms or signs occurring after initial response to treatment) although more common in HIV-TB co infection after initiation of ART, may also occur in patients irrespective of HIV infection or ART. These paradoxical reactions are believed to reflect an immunologically mediated deterioration rather than ATT failure. IRIS is believed to result from disregulated recovering immune responses, leading to exaggerated inflammation directed at the opportunistic pathogens. IRIS may be associated with certain infectious (e.g. mycobacteria, varicella zoster and cytomegalovirus) or it can be of non-infectious etiology when

associated with autoimmune or neoplastic conditions. [1]

Enlargement of the existing nodes is the most common manifestation, seen in around 25% of the patients with tubercular lymphadenitis. PR may have central nervous system manifestations like development of tuberculous meningitis and new or enlarging tuberculomas. While pulmonary manifestations may include recurrent fevers, worsening pulmonary infiltrates and enlarging pleural effusions. [2]

Paradoxical TB-IRIS is a "diagnosis of exclusion". Its diagnosis is based on: [3]

1. Characteristic clinical presentation,
2. Temporal relationship to the initiation of ART and
3. Exclusion of alternative explanations for clinical deterioration.

Important differentials to the entity being- superimposed opportunistic infections, drug reaction, treatment failure (e.g. due to non compliance or drug resistance), and treatment relapse. These conditions must clearly be excluded to make the diagnosis of IRIS.

The most accepted theory behind pathogenesis of paradoxical response is the "immune restitution or reconstitution "theory which suggests the phenomenon to be the interplay between host's immune response and the direct effect of mycobacterial products. [4-6] Protein derivatives of mycobacteria in active tuberculosis lead to depression of delayed type of hypersensitivity response due to activation of monocytes. This results in increased interleukin levels that lead onto a state of immunosuppression. Also, specific antigens such as D-Arabino-D-galaction from tubercle bacilli lead to production of immunosuppressive concentration of prostaglandin-E2. When ATT is started, the mycobacterial load gets significantly reduced. This leads to "reversal" of the cellular and cytokine patterns – a phenomenon described as "immunological restitution or reconstitution." This restitution leads to inflammatory response resulting in a paradoxical phenomenon. An "overwhelming immunorestitution" may produce excessive immunopathological damage at the tissue level. The clinical severity of paradoxical deterioration is dependent on the exactness and appropriateness of immune recovery.

The treatment is largely symptomatic. Most of the times only re-assurances or simple pain killers are enough as large number of cases recover well without any complications. The complicated ones require use of immunomodulators such as steroids or infliximab [7] along with necessary and appropriate surgical interventions. A tapering- short course of steroids in the management of PR has widely been used with success.

Although not so uncommon, the case report on TB-PR or TB-IRIS hereby is discussed to increase the clinical acumen of the Indian physicians dealing with about one third of the total tuberculosis patients of the world. While on one hand, the common causes for recurrence or worsening of symptoms during treatment (failure, resistance, relapse) warrant stoppage of first line ATT; the ATT must be continued in cases of TB-PR. A profound knowledge of the condition along with good follow up is pivotal for good management of the cases.

Second and equally important part of the discussion is the risk of nosocomial TB amongst health care workers (HCWs). Owing to the simple logic that probability of nosocomial transmission of tuberculosis is higher than the transmission occurring in the general population, prevalence of tuberculosis in health care workers (HCWs) is considerably higher than that in the general population. There is plenty of data across, Africa, [8,10] India, [9] and Europe that substantiates this fact. The incidence being 11.2 cases/1000 - 17.3/1000. Physicians in training were found to have a high risk of developing active tuberculosis after nosocomial transmission. [9] That's approximately 1.5 to 3 times higher than in the general population. In a chest hospital in charge of regional tuberculosis care, the

incidence was 30 to 90 times higher, and was highest among physicians. Amongst these, drug resistance was detected in 23 (49%), 18 (38%) of whom had MDR tuberculosis. [10] Shockingly, In the Hamburg Fingerprint Study, 80 % of the TB cases in HCWs were caused by infections at the workplace. In a similar Dutch study 43 % of all cases were work-related. [11]

Extremely large load of 'open' cases, delays in their diagnosis and optimal treatment, inadequate infection control measures and deficiencies in knowledge and awareness are the important factors responsible for this nosocomial transmission. Facilities to isolate infectious patients admitted to hospitals are scarce. Overcrowded wards and inpatients coupled with their poor architecture that has poor provisions for adequate ventilation and sunlight, further compound the grim scenario. [9]

There is a dire need to protect HCWs from nosocomial hazards. Considerable attention is needed to improve infection control practices by HCWs. Pre-employment screening for active disease may not be enough to prevent the occurrence of these incidents. Detection of latent infection with interferon gamma release assays, the use of preventive treatment are things of future that can save the skin of HCWs and their role should be evaluated in Indian setup. The guidelines and legal frameworks are already there in books. Perhaps it's the "will" that is lacking, and that too at numerous levels. Keeping a high index of suspicion among our colleagues with TB symptoms and warranting prompt action to address the situation, might perhaps, be the first step in right direction.

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