Unusual presentation of more common disease/injury

Paradoxical reaction to antitubercular therapy in miliary tuberculosis

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Summary

An 18-year-old boy presented with fever, weight loss and loss of appetite for 6 months duration. Investigation revealed raised erythrocyte sedimentation rate, negative sputum smear examination for acid-fast bacilli, x-ray and high-resolution CT chest showed bilateral, diffuse infiltration of lung parenchyma with miliary shadows. The patient was treated as a case of miliary tuberculosis with antitubercular therapy (ATT). On the 10th day of treatment the patient developed high-grade fever, cough and breathlessness. Chest x-ray showed an increased infiltration of lung parenchyma. The patient was diagnosed as a case of paradoxical reaction to ATT and was managed successfully with steroids.

BACKGROUND

Paradoxical reaction (PR) in tuberculosis (TB) is defined as transient worsening of symptoms and signs or the appearance of new lesions after beginning appropriate antitubercular therapy (ATT). This phenomenon has been recognised for many years.^{1 2} High index of suspicion is required for recognition of deterioration resulting from PR rather than from treatment failure, poor compliance, drug resistance or another infection. PR to ATT is usually self-limiting, respiratory failure and death have been described, mainly with miliary and pulmonary disease.³ In the last few years an increase in the frequency and severity of PR in association with HIV co-infection has been reported compared with both HIV-negative TB patients and co-infected patients before the introduction of antiretroviral drugs.⁴ We describe here a patient with miliary TB who developed PR to appropriate ATT.

CASE PRESENTATION

An 18-year-old boy presented with complaints of fever, weight loss and loss of appetite for 6-month duration. As per the patient, he was in an usual state of health 6 months ago when he started having fever which was of low grade, remittent and was associated with an evening rise in temperature. There was history of night sweats for the same duration. The patient also complained that he does not feel like eating anything and has lost around 11 kg in 6 months. There was no history of cough, expectoration of blood in sputum, pain in the abdomen, loose stool, burning during micturition, multiple joint pain, joint swelling or rashes over the body. There was no history suggestive of contact with a TB patient. For these complaints he had taken four courses of antibiotics but did not get relief. At presentation his pulse rate (PR)=102/min, blood pressure (BP)=116/70 mm Hg, relative ratio (RR)=18/min and temperature=100°F. On

general examination, the patient was thin built and had pallor. Abdominal examination revealed splenomegaly around three fingers below the left costal margin and rest of the systemic examination was normal.

INVESTIGATIONS

Investigations revealed haemoglobin (Hb) 9.0 g/dl, total leucocyte count (TLC) 6400/mm³, differential leucocyte count (DLC) P54 L42 E02 M02, urine analysis normal, erythrocyte sedimentation rate (ESR) 58 mm fall in the first hour, normal renal and liver function test, three early morning samples of sputum was negative for acid-fast bacilli (AFB) smear, tuberculin skin test was negative, chest x-ray showed diffuse, bilateral, discrete miliary shadows (figure 1). High-resolution CT (HRCT) of the chest showed bilateral diffuse infiltration of lung parenchyma with miliary nodules (figure 2). Ultrasonography of the abdomen revealed spleen size of 15 cm. Fundus examination revealed choroidal tubercles. Connective tissue disorder workup was negative. Test for HIV infection by ELISA was negative.

TREATMENT

On the basis of chronic history, anaemia, raised ESR, splenomegaly, miliary shadows on chest x-ray and HRCT chest and the presence of choroidal tubercles on fundus examination diagnosis of miliary TB was made and the patient was started on ATT, including isoniazid, rifampicin, pyrazinamide and ethambutol. At 10 days after starting ATT the patient presented to emergency department with complain of difficulty in breathing for 1 day duration. As per the patient, he was taking ATT regularly and was feeling better till 1 day prior when he started having dry cough and difficulty in breathing at rest. The patient also complained that he is running high-grade fever since 1 day. Compliance to ATT was confirmed from the

Figure 1 Chest x-ray showing diffuse infiltration of lung parenchyma with miliary shadows (more clear in magnified image).

patient's family members. At presentation PR=110/min, BP=110/68 mm Hg, RR=28/min, temperature=102°F and SpO₂ was 88%. Chest auscultation revealed diffuse bronchovesicular breath sounds all over the chest. Rest of the systemic examination was normal except for palpable spleen. Arterial blood gas showed hypoxaemia and respiratory alkalosis. Repeat investigations revealed Hb 8.6 g/dl, TLC 5800/mm³, DLC P60 L38 E01 M01, ESR had increased to 96 mm fall in the first hour, repeat chest x-ray (figure 3) showed increase in lung parenchymal infiltration as compared with initial x-ray, urine analysis—normal, renal function test—normal, liver function test—normal. Sputum Grams staining, sputum culture, blood culture was done to rule out any secondary bacterial infection causing this clinical worsening but all of them were negative. Repeat test for HIV infection by ELISA was negative. In view of the clinical and radiological worsening while on regular ATT, increase in ESR and absence of secondary infection, diagnosis of PR to ATT was made.

Figure 2 High-resolution CT chest showing bilateral, diffuse and discrete miliary nodules in lung parenchyma.

The patient was managed with oral prednisolone at a dose of 1 mg/kg, oxygen inhalation and continuation of ATT. The patient showed gradual recovery over a period of 10 days. He was discharged from the hospital on the 10th day and oral steroid was tapered over a period of 1 month.

OUTCOME AND FOLLOW-UP

The patient is under regular follow-up and has completed 4 months while on ATT. Currently the patient is

Figure 3 Chest x-ray showing increased infiltration of lung on tenth day of antitubercular therapy when patient presented with clinical deterioration.

asymptomatic, has gained 7 kg of weight. Repeat x-ray at the end of 2-month therapy is normal (figure 4).

DISCUSSION

Here, we have described a case of miliary TB in non-HIV-infected individual that developed PR to ATT. Diagnosis of miliary TB was made on the basis of clinical and radiological features, as sputum smear is reported to be positive in only one-third of the patients with miliary TB.⁵⁻⁷ Our patient developed worsening of clinical and radiological features on the 10th day of ATT. Compliance to ATT was confirmed from family members and tests were done to rule out secondary infection. PR to ATT is well known to occur in both HIV and non-HIV-infected individuals.⁸⁻⁹ Various manifestations of paradoxical reaction are described, such as worsening of fever, development of new or increase in the size of already existing lymph nodes and enlargement of cerebral tuberculomas, etc.¹⁰⁻¹² It is unpredictable in its timing (occurring anything from a few days to many months after the start of ATT) and in its duration and severity. Paradoxical worsening of pulmonary lesions, leading to respiratory failure, although rare, are more commonly noted in miliary TB than in non-miliary pulmonary TB among patients without HIV infection.¹³⁻¹⁵ They are associated with high fatality when it occurs in miliary TB.¹³ Ellis and Webb,¹⁶ noted unexplained sudden death in the early phase of treated pulmonary TB;¹⁷ in miliary TB, there are reports of the development of an adult respiratory distress syndrome;¹⁸⁻¹⁹ others have noted similar deterioration after starting ATT in patients with widespread pulmonary TB; deterioration in such patients is often accompanied by a sudden rise in ESR.²⁰ Respiratory failure in miliary TB is postulated to be secondary to extensive pulmonary

involvement and also due to a hypersensitivity reaction following initiation of bactericidal ATT. In turn, this leads to damage of the alveolar–capillary membrane leading to increased permeability resulting in respiratory failure.³ The development of subcutaneous tuberculous abscesses during the treatment of miliary TB has also been observed.²¹⁻²³ Campbell and Dyson,²⁴ reported node enlargement, appearance of nodes for the first time, in 30% of patients with lymph node TB during chemotherapy. Paradoxical node enlargement is encountered predominantly during the first weeks or months of chemotherapy, prompting clinicians to doubt their patient's compliance in taking their drugs or to suspect antibiotic-resistant bacilli. A similar paradoxical expansion of intracranial tuberculomas during ATT has been observed during the treatment of miliary TB or tubercular meningitis.²⁵ It has been postulated that the mechanism of PR in these cases of TB is rebound immunological response in the local tissue. The destruction of mycobacterium, and liberation of tubercular protein invokes an inflammatory response, a mixed-type 1 T helper cell (Th1) and type 2 T helper cell (Th2) response.²⁶ With this type of response the inflamed tissue becomes extremely sensitive to tumour necrosis factor α (TNF- α) and release of the cytokine causes necrosis, first involving the microvasculature and subsequently the whole tissue.²⁶ Corticosteroids, which are known to inhibit type 1 helper cell (Th1) activity and TNF- α production and stimulate Th2 cell activity, could contribute to regulation of the immune response in PR of TB.

Learning points

- Physicians should always think of paradoxical reaction (PR) to antitubercular therapy (ATT) when a miliary tuberculosis patient presents with clinical and radiological deterioration after starting ATT.
- PR to ATT is an inflammatory response; it does not necessarily indicate drug resistance, poor drug compliance or an inadequate response to therapy.
- ATT need not be altered or discontinued, although a short course of corticosteroids are useful in PR to ATT.

Competing interests None.

Patient consent Obtained.

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Figure 4 Normal Chest x-ray after 2 months of antitubercular therapy.

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