Clinical Note

Tuberculosis paradoxical reaction

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Tuberculosis is endemic in this part of the world. We frequently encounter patients with both pulmonary and extrapulmonary tuberculosis regardless of whether they are infected with human immunodeficiency virus (HIV) or not. It is not uncommon for physicians to see clinical or radiological, or both, worsening of the disease while their patient is on anti-tuberculous treatment, the so-called paradoxical reaction. We briefly describe an interesting case of paradoxical reaction and address how to approach such a clinical situation. An 18-year-old Saudi female presented to us with complaints of intermittent right flank swelling of one-month duration. The swelling progressively increased in size and would appear on standing and disappear on lying down. There was no associated abdominal pain or other gastrointestinal or urinary symptoms. The patient denied history of fever, weight loss, or backache. She was diagnosed to have multifocal skeletal tuberculosis involving the hyoid bone, right mastoid bone, right occipital bone, and first 2 cervical vertebrae 5 months before presentation. At that time, she presented to her local physician with fever, weight loss, hearing loss, and purulent discharge from the right ear, and swelling of the right side of the neck overlying the hyoid bone. A biopsy from the hyoid bone revealed caseating granulomas on histopathological examination. Smears for acid-fast bacilli, mycobacterial DNA probe and cultures of the biopsy tissue were not obtained at that time. Computed tomogram scan (CT scan) of the head and neck was performed then and revealed lytic lesions in the above mentioned bones. Since tuberculosis is endemic in the area, it was presumed that the patient has multifocal skeletal tuberculosis. The patient was treated with 2 months isoniazid, rifampin, ethambutol, and pyrazinamide, and was then continued on maintenance antituberculous therapy (isoniazid and rifampin). In the fourth month of treatment, the patient presented to us with the complaint of swelling in the right flank. The patient tolerated the medication well and was compliant with her treatment and follow up visits. Shortly after starting therapy, her fever, and ear discharge resolved and her weight and feeling of wellbeing improved significantly. On examination, the patient was afebrile and looked healthy. Abdominal examination revealed a nontender and soft fluctuant swelling in the right flank, which became prominent with the standing position. There were no overlying skin changes. Examination of the spine was normal. The rest of the physical examination was unremarkable. Her initial laboratory work up including blood counts, sedimentation rate, renal function, and liver function tests were within normal range of reference laboratory values. The x-ray of the chest was normal. Purified protein derivative (PPD) test was positive (>10 mm). Contrast CT scan of the abdomen revealed bilateral psoas abscesses (**Figure 1a & 1b**). The right one was bigger and extending down into the abdominal wall and pelvis. No previous images of the abdomen or dorsolumbar spine were available. The patient had no evidence of malabsorption and compliance to medication was assured. A CT guided aspiration of the right psoas abscess described on CT scan of the abdomen was performed for further evaluation. Gram staining of the aspirate was negative. Acid fast staining and mycobacterium tuberculosis DNA probe (MTB probe) were positive. We then added ethambutol, pyrazinamide, amikacin, and moxifloxacin to her current antituberculous regimen to cover for a possible

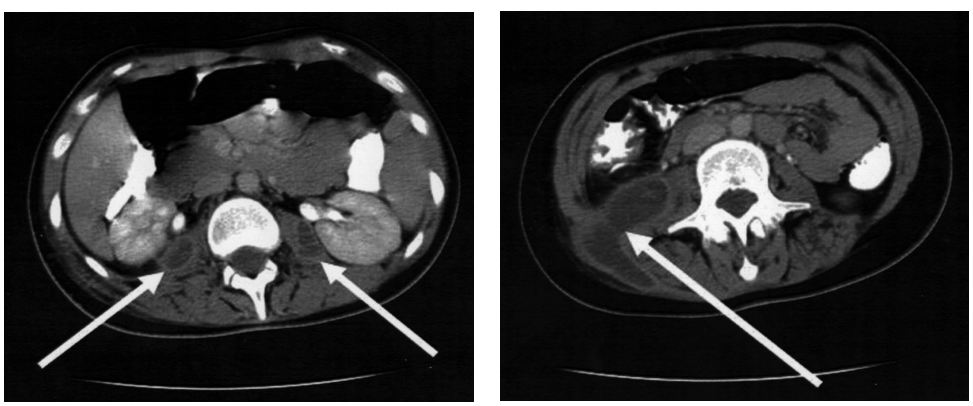

Figure 1 - Contrast computed tomogram scan of the abdomen showing **a)** bilateral psoas abscesses, **b)** the right one extending to the anterior abdominal wall.

drug resistant strain of mycobacterium tuberculosis. All bacterial, mycobacterial, and fungal cultures were negative at 8 weeks. Therefore, she was continued on isoniazid and rifampin with a diagnosis of psoas abscess related to a paradoxical reaction. A follow up contrast CT scan of the abdomen at 2 months revealed complete resolution of both psoas abscesses. At 6 months follow up, she was doing very well with no symptoms or signs of treatment failure.

Our patient had bilateral psoas abscesses in the setting of skeletal tuberculosis under treatment with initial improvement. Such lesions could represent new tuberculous psoas abscesses related to the development of de-novo drug resistance or nontuberculous infection. It could also represent progression of a preexisting and clinically silent tuberculous psoas abscesses due to drug resistance or non-compliance or malabsorption of anti-tuberculous drugs. A diagnosis of exclusion is then a paradoxical reaction. After ruling out noncompliance and malabsorption to drugs, the next crucial step in the management of this patient was to rule out a nontuberculous pathology and to differentiate between paradoxical reaction (defined as worsening of tuberculosis during appropriate antituberculous therapy) and treatment failure (defined as mycobacterial cultures positive after 3 months or acid fast smear positive after 5 months of appropriate treatment). Non-mycobacterial infection and drug-resistant tuberculosis were ruled out by appropriate cultures, and a paradoxical reaction was considered as the most likely explanation of the bilateral psoas abscesses. All the new antituberculous drugs added to patient's regimen were discontinued, and the patient was asked to continue isoniazid and rifampin for an additional 3 months to complete a total of 9 months treatment course. On follow up, she continues to do very well on the 2-drug maintenance therapy.

Paradoxical reaction (PR) or immune reconstitution inflammatory response is defined as clinical or radiological, or both, deterioration of preexisting tuberculous lesions, or the appearance of new lesions during the course of appropriate antituberculous therapy in a patient who initially improves.[1] This phenomenon has been reported to occur in 6-30% of patients receiving antituberculous therapy. Although previously believed to be more common in patients coinfected with human immunodeficiency virus (HIV), one small retrospective study indicates that this phenomenon is generally common in tuberculosis despite HIV status of the patients.[2] However, among HIV coinfected patients, PR is more common in those receiving highly active antiretroviral therapy (HAART). The PR is usually a mild, transient, and self limited phenomenon, however, it may deserve special attention in certain situations such as pulmonary miliary infiltrates causing respiratory failure, expansion of intracranial tuberculosis lesion causing raised intracranial pressure, enlargement of mediastinal lymph nodes causing mediastinal compression, severe sepsis and those with uncontrolled high grade fever. Enhanced inflammatory response as a result of increased mycobacterial antigen exposure from rapidly dying mycobacterium tuberculosis to sensitized lymphocytes following antituberculous therapy and immune reconstitution (especially in HIV coinfected patients receiving HAART therapy) are considered plausible explanations in the pathogenesis of PR.[3] There is no direct and reliable method to diagnose PR. It should be considered only after alternative diagnosis, poor drug compliance, malabsorption, and treatment failure (due to unrecognized drug resistance) have been excluded. Patients with mild to moderate PR are treated symptomatically, and those with severe life-threatening reactions should receive a short course of steroids to suppress the inflammation with close monitoring of the patient.[4] In certain conditions, surgical intervention may also be required to manage PR. Patient's antituberculous regimen should not be changed or discontinued. Under such circumstances, positive AFB smears and MTB probe should not be considered as evidence of active tuberculous infection as these could represent dead tuberculous bacilli. Similarly, positive PPD test and caseating granulomatous inflammation on the biopsy material of involved tissues represent enhanced inflammatory reaction to tubercular antigen derived from dying bacilli and not active infection. In summary, awareness of PR during tuberculosis treatment is very important since it is a diagnosis of exclusion and can pose a significant clinical challenge to the physicians.

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