

Multifocal Tuberculosis with Prolonged Paradoxical Reaction: A Case Report

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Abstract

This is a case report describing successful treatment of a challenging case of an 18-year old previously healthy high school male student with multifocal tuberculosis involving the spleen and mediastinal and abdominal lymph nodes confirmed by histopathology of splenectomy tissue. The patient initially responded well to anti-tuberculosis therapy with complete resolution of fever and improvement in his general health and weight. However, two months after initiation of anti-tuberculosis therapy, the patient developed paradoxical reaction manifest as recurrence of fever that persisted for five months and was associated with enlargement of lymph nodes. The fever failed to abate with continuation of the same anti-tuberculosis therapy. Despite reassurance that the fever was due to a prolonged paradoxical reaction, a decision was made by the family to seek advice in another hospital where lymphoma was excluded again by histopathological examination of an excisional lymph node biopsy that revealed caseating granulomatous lymphadenitis and negative tuberculosis stain, culture, and polymerase chain reaction. The patient was continued on anti-tuberculosis therapy and treated with corticosteroids that resulted in complete resolution of fever and subsequent full recovery from his tuberculosis.

Keywords

Tuberculosis; Paradoxical reactions; Anti-tuberculosis therapy

Introduction

Paradoxical tuberculous reactions are defined as worsening of pre-existing tuberculous lesions or the appearance of new tuberculous lesions in patients whose clinical symptoms initially improve with anti-tuberculosis (TB) treatment^[1]. Paradoxical reaction has been reported in 5–35% of patients receiving treatment for TB^[1-3]. Paradoxical reaction (PR) may cause significant morbidity and may sometimes be fatal^[3]. Its timing, severity and duration are unpredictable. It may occur anytime during treatment and sometimes even after completing the anti-tuberculosis therapy^[4-7].

Differentiation of PR from treatment failure, resistance, another infection or another diagnosis is important and often challenging and difficult to the unexperienced physicians.

Case Report

An 18-year old previously healthy high school male student presented to the infectious diseases outpatient department in February 2017 with lethargy and intermittent fever for 12 months. His fever was episodic, occurring once every 3 to 4 weeks and

lasting for 7 to 10 days. The temperature ranged from 38-39.5°C as measured by the patient at home. He denied night sweating, but he lost 4 kg of weight (55 to 51 kg). He denied eating raw cheese, drinking raw milk or visiting animal pens. No family history of TB or traveling to malaria endemic areas. On examination the patient was ill-looking and underweight (height 162 cm, weight was 51 kg, BMI was 19.4), with a pulse rate of 85 beats per minute, blood pressure of 110/70 mmHg, respiratory rate of 16 breaths per minute, and temperature of 37.8°C. He had small inguinal lymph nodes and splenomegaly about 3 cm below the costal margin. The rest of examination was normal. Computerized tomography scan showed generalized cervical, mediastinal and abdominal lymphadenopathy and splenomegaly. Tuberculosis skin (tuberculin) test showed no induration. Laboratory investigations revealed white blood cells $6.86 \times 10^3/\mu\text{L}$ (neutrophils $4.74 \times 10^3/\mu\text{L}$, lymphocytes $1.31 \times 10^3/\mu\text{L}$), hemoglobin 12.3 g/dL, platelets $425 \times 10^3/\mu\text{L}$, total protein 89 g/L, albumin 33 g/L, alkaline phosphatase 92 U/L, aspartate aminotransferase 34 U/L, alanine aminotransferase 32 U/L, gamma-glutamyl transferase 15 U/L, total bilirubin 4 $\mu\text{mol/L}$, Na 136 mmol/L, K 4.5 mmol/L, urea 2.9 mmol/L, creatinine 42 $\mu\text{mol/L}$, C-reactive protein 11.5 mg/L, ESR 5 seconds, antinuclear antibodies 1:160, rheumatoid factor was negative (11 IU/L), serology for HIV1,2 antibodies, hepatitis C virus +antibodies, hepatitis B virus surface antigen, and Brucella abortus and Brucella melitensis antibodies was negative, Epstein-Barr virus (EBV) and Cytomegalovirus (CMV) IgM antibodies were negative, EBV and CMV IgG antibodies were positive, and lactate dehydrogenase was mildly elevated (266 U/L; N: 1-240). Blood culture for Brucella was negative.

Chest roentgenogram showed mild central peribronchial wall thickening with unremarkable lungs parenchyma and no pleural effusion or pneumothorax. Computed tomography (CT) of the chest showed multiple small subcentimetric lymph nodes in both axillary, subpectoral groups, mediastinal, and epiphrenic lymph node groups with the largest measuring 9 mm in the aortopulmonary group. The lung parenchyma was normal with no masses, nodules or pleural effusions. Computed tomography abdominal scan showed mildly enlarged liver measuring about 19 cm on sagittal diameter with homogeneous CT density and no evidence of focal liver lesion or intrahepatic radicles dilatation. There was abnormal heterogeneous enhancement of the spleen with no focal lesion seen.

The jejunal loops showed diffuse nodular thickening of their mucosal folds. The rest of the ileal and large bowel loops were unremarkable. There was diffuse enlargement of the abdominal and pelvic lymph node groups, the largest lymph node was situated in the external iliac group measuring 14.3 mm. The rest of the abdominal structures, namely the gallbladder, pancreas, adrenal glands and both kidneys were unremarkable, and there was no evidence of free fluid.

Upper gastrointestinal endoscopy on 27 February 2017 was unremarkable using the pediatric colonoscope that was advanced up to mid-jejunum. Multiple random jejunal biopsies taken during the examination showed no pathological diagnosis.

He underwent splenectomy and excisional lymph nodes biopsy *via* laparotomy. Histopathology showed extensive caseating granulomatous inflammation of the spleen and atypical lymphocytic infiltration of the lymph nodes and no malignancy. Molecular studies excluded lymphoma. No tissue samples were submitted for TB stain, culture and sensitivity, or polymerase chain reaction.

A diagnosis of multifocal tuberculosis involving the spleen and mediastinal and abdominal lymph nodes was made. On 25 March 2017, the patient was started on anti-tuberculous therapy (body weight 48.5 kg) comprising isoniazid 300 mg po once daily for 18 months, rifampicin 600 mg po once daily for 18 months, pyridoxine 40 mg po once daily for 18 months, pyrazinamide 1250 mg po once daily for two months, and ethambutol 800 mg po once daily for two months. The patient tolerated and adhered to the treatment well. Fever resolved and the patient felt better during the initial phase of treatment, but his fever and lethargy recurred after completing the 2-month course of pyrazinamide and ethambutol. He could not continue studying in the university. On follow up, his inguinal and axillary lymph nodes had enlarged. Repeat computerized tomography also showed further enlargement of cervical, mediastinal and abdominal lymph nodes. On 19 October 2017, *i.e.*, seven months into therapy, the patient underwent excisional biopsy of one of the right axillary lymph nodes to rule out lymphoma or other missed pathology. Histopathology confirmed the presence of caseating granulomatous lymphadenitis compatible with TB. A diagnosis of resistant TB versus PR was

made. In addition to continuing isoniazid and rifampin, pyrazinamide, ethambutol and moxifloxacin 400 mg daily were added as a trial for one month, during which, he continued to have fever and lethargy indicating that resistant TB was unlikely. TB culture of the excised lymph node was subsequently proven to be negative, adding more evidence that resistant TB was unlikely, and that PR was most likely the cause of his persistent fever. Pyrazinamide, ethambutol and moxifloxacin were discontinued, and the patient was initiated on prednisone 40 mg daily for two weeks followed by tapering by 5 mg every week. Fever, abdominal pain, and lethargy subsided, and the patient felt markedly better. However, the fever recurred shortly after discontinuing steroids, so a second course of steroids was given. The patient's anti-tuberculous therapy was continued for a total of 18 months following which the patient had fully recovered, regained his normal weight (56 kg), and resumed his study at the university.

Discussion

Paradoxical TB reaction is defined as a clinical or radiological worsening of pre-existing TB lesions or the development of new lesions, in patients receiving anti-tuberculous medications who initially improve on treatment^[1,6]. The reaction occurs in up to 30% of patients^[3,6,7]. Yu *et al.*^[5] retrospectively reviewed the medical records of 467 non-HIV-infected patients with lymph node TB between 1997 and 2007, and prospectively enrolled patients with newly diagnosed lymph node TB between 2008 and 2013. Eighty-three (18%) patients had PRs. The median time of onset of the PRs was two months (interquartile range 1–4) after the initiation of anti-TB treatment; 57 (69%) PRs were early (occurring within four months) and 26 (31%) PRs were late (occurring more than 4 months).

Brown and colleagues reviewed records of 1817 patients treated for TB; 82 (4.5%; 95% CI 3.6–5.5) patients experienced PR, the site of which varied by ethnic group^[8]. Extra-pulmonary TB involving lymph node was found to be significantly more common among South Asians than Blacks adjusted for other ethnicities. Those of Black ethnicity conversely exhibited more pulmonary involvement than people of South Asian and White ethnicity. HIV was strongly associated with the development of PR^[8]. Table 1 shows a summary of previously published reports of PR.

Paradoxical reaction is a diagnosis of exclusion. Poor compliance, drug resistance, progression of

original disease and wrong or other concurrent diagnoses should be ruled out. The reaction is likely to be due to an abnormal immune-mediated response to mycobacterial antigens. Garcia Vidal and colleagues^[9] explained the occurrence of PR on two immunological hypotheses. The first theory is the reconstitutions of host response after the start of anti-tuberculosis chemotherapy and the second is hypersensitivity reactions to antigens released by dying tubercle bacilli^[9]. They suggested that a minimum of four weeks of initial improvement should elapse before the occurrence of PR. Hawkey and colleagues^[7] observed that increased production of cytokines as TNF- α and proinflammatory chemicals secreted by macrophages and monocytes play a central role in the development of PR.

As TB is endemic in Saudi Arabia, physicians commonly encounter the challenge of TB paradoxical reactions requiring revision of the diagnosis to exclude resistant tuberculosis, nonadherence to therapy, wrong diagnosis, or missing another concurrent diagnosis as possible alternative cause of this adverse reaction. Baseline microbiological and pathological investigations are important in the diagnosis of tuberculosis to exclude the possibility of wrong diagnosis should a PR occur in the future. In our case, the splenectomy tissue unfortunately was not submitted to the laboratory for TB stain, culture, or polymerase chain reaction, and the diagnosis was made solely on the bases of histopathological examination of the spleen. The occurrence of severe PR with relapse of fever, further enlargement of lymph nodes and continuing weight loss led to the revision of the diagnosis and taking another biopsy from another tissue, namely, an axillary lymph node that confirmed the presence of caseating granulomas. The possibility of lymphoma was always in mind as the response to anti-tuberculosis treatment was suboptimal. Immunohistochemistry examination of the splenic and lymph node tissues excluded lymphoma. TB culture and sensitivity and GeneXpert PCR testing of the lymph node biopsy ruled out resistant tuberculosis and was important to design an appropriate management plan. A one-month trial of anti-tuberculosis therapy for possibly resistant TB led to no improvement thus confirming that the constitutional symptoms were indeed due to PR. The lack of microbiological test in this case added to the challenges faced during the management. The two PRs experienced by our patient responded well to a short course of corticosteroids therapy.

Table 1. Summary of previously published papers reporting tuberculous paradoxical reactions

Reference	Site of Paradoxical Reaction	Conclusion and Manifestations
Celotti <i>et al.</i> , 2018 ^[10]	Brain	A patient diagnosed with tuberculous meningitis and started the anti-TB therapy and dexamethasone. On second attempt to taper steroid the patient had cognitive impairment with decreased level of consciousness.
Elzein <i>et al.</i> , 2019 ^[11]	Superficial femoral artery and inferior mesenteric artery	A patient diagnosed with bilateral mycotic tuberculous superficial femoral artery aneurysm (SFA) aneurysm and inferior mesenteric artery (IMA) pseudoaneurysm. Two weeks after starting anti-TB therapy the patient complained of pain and further increase in the size of SFA aneurysm with subsequent rupture of IMA pseudoaneurysm from which he succumbed to death.
Geerdes-Fenge <i>et al.</i> , 2018 ^[12]	Clavicular lymph nodes	Tuberculous hepatitis with generalized lymphadenopathy complicated by two episodes of PR in clavicular lymph nodes.
Kaplan <i>et al.</i> , 2018 ^[13]	Brain	Multidrug-resistant tuberculosis involving lung, supine and lymph nodes. At seven months into treatment with anti-TB therapy, MRI showed increase in the size of brain lesion with surrounding edema.
Kim <i>et al.</i> , 2018 ^[14]	Spinal cord	A renal transplant patient diagnosed with miliary TB based on bronchoalveolar culture and chest X-ray. Two weeks after initiation of anti-TB therapy, the patient experienced progressive paraparesis with sensory loss below the level of the 10 th thoracic vertebra (T10) diagnosed as PR and surgical resection of the spinal mass was performed.
Ko <i>et al.</i> , 2018 ^[15]	Brain	Miliary TB involving brain, lung and kidney. Firstly, the lesions were suspected of metastatic renal cell carcinoma and radiotherapy was started without improvement. Four weeks after anti-TB therapy the brain symptoms relapsed, and new brain lesions developed on MRI.
Machida <i>et al.</i> , 2018 ^[4]	Brain	Onset of PR 10 years after complete treatment of tuberculous meningitis with headache and worsening of pre-existing visual disturbance.
Machida <i>et al.</i> , 2018 ^[16]	Brain	A patient diagnosed with tuberculous meningitis and multiple periventricular tuberculomas. One month after initiation of anti-TB therapy, tuberculomas increased in number and size.
Oba <i>et al.</i> , 2017 ^[17]	Pericardium	A patient diagnosed with mediastinal tuberculous lymphadenitis, three months after anti-TB therapy were started, he presented with fever and dyspnea, CT showed worsening mediastinal lymphadenitis and newly developed pericardial effusion, the drainage was done, PCR and culture were negative. He was diagnosed with paradoxical TB pericarditis.
Okazaki <i>et al.</i> , 2016 ^[18]	Lung	Pulmonary TB with new PR lesions in the lung
Özer <i>et al.</i> , 2016 ^[19]	Brain	The patient diagnosed with tuberculous meningitis, 45 days into treatment with anti-TB therapy, he developed right central facial paralysis with left sided hemiparesis, MRI showed enlargement of the same lesion in the brain.
Takata <i>et al.</i> , 2019 ^[20]	Lung	A patient with small cell lung cancer, three days after completing a course of chemotherapy, he developed fever, cough with purulent sputum and diagnosed with pulmonary TB. Ten days after starting anti-TB therapy he developed fever, tachycardia and the size of the original opacities increased, and new lung opacities developed.
Wangai <i>et al.</i> , 2017 ^[21]	Lung and mediastinal lymph nodes	Tuberculous splenic granulomatous lesion complicated by PR causing plural effusion with mediastinal lymphadenopathy
Zheng and Shafi, 2018 ^[22]	Abdomen (Peritoneum)	PR during management of peritoneal TB causing perforated viscus and pneumoperitoneum

CT: Computerized tomography; MRI: Magnetic resonance imaging; PCR: Polymerase chain reaction; PR: Paradoxical reaction; TB: Tuberculosis

Another diagnostic challenge in our patient was the negativity of the TB skin test before and even after completion of therapy, which might have been caused by malnutrition. Physicians should rely on their clinical sense and the constellation of findings rather than any laboratory or individual TB diagnostic tests.

In summary, PR is not uncommon in the course of TB treatment in HIV-negative patients, but the outcome is excellent. Further studies and tests are needed to understand the pathophysiology of PR and to develop therapeutic and preventive strategies.

Conflicts of Interest

The authors declare no conflict of interest.

Disclosure

The authors did not receive any type of commercial support either in forms of compensation or financial for this study. The authors have no financial interest in any of the products or devices, or drugs mentioned in this article.

Ethical Approval

Obtained.

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مرض السل متعدد البؤر مع انتكاسات رجعية أثناء العلاج

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المستخلص. هذا التقرير يصف حالة علاج ناجحة لمريض بالدرن متعدد البؤر على الرغم من نوبتين من انتكاسات رجعية أثناء العلاج والتي تم السيطرة عليها باستخدام الكورتيكوستيرويد مع الاستمرار بالأدوية المضادة للدرن. الهدف هو تنبيه الأطباء حول هذه التفاعلات أثناء علاج المرض بمضادات الدرن.