

PARADOXICAL ENLARGEMENT OF LYMPH NODES DURING THERAPY OF CENTRAL NERVOUS SYSTEM TUBERCULOSIS

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Paradoxical response (PR) to appropriate anti-TB therapy is encountered mainly in lymph nodes, brain and lungs.¹ It is well documented in lymph nodes, with some series quoting an incidence of 30%, whereas in the brain, PR incidence has been reported to occur at a lesser degree. In a recent publication of a small series of CNS tuberculoma, PR occurred in 16% of the patients.¹⁻⁴ In pulmonary TB, the paradoxical reaction is rarely observed, and it takes the form of respiratory distress syndrome.⁵ The prolonged fever occasionally seen in an otherwise satisfactory response to anti-TB may be another manifestation of PR.¹ Other tissues or organs in the human body may be affected by PR, but this has not yet been documented.¹ All the reactions described involve the initial site of the disease manifestation. We report a case of TB meningitis with cerebral and spinal tuberculomas, in which the PR affected the lymph nodes and not the CNS. Our purpose is to document this unique reaction and discuss its significance and possible mechanism.

Case Report

A 22-year-old Saudi male was admitted to a hospital in Makkah, Saudi Arabia, on July 1997, with 10 days' history of fever, headaches, photophobia and vomiting. He had a temperature of 38°C. He was drowsy and showed overt signs of meningeal irritation. Apart from a mild weakness of the lower limbs, the rest of his physical examination was normal. Investigations in the admitting hospital revealed white blood cell (WBC) count of $8.9 \times 10^9/L$ (20% lymphocytes, 80% polymorphs), Hb of 11.5 g/dL, and erythrocyte sedimentation rate (ESR) of 102 mm/hr. Chest x-ray was reported as normal. Contrast CT scan of the brain demonstrated a mild degree of hydrocephalus with significant dural enhancement. Cerebrospinal fluid (CSF) examination showed a turbid color with $400 \text{ WBC}/\text{mm}^3$ (95% lymphocytes, 5% polymorphs). The protein was 850

mg/dL and glucose was 2.4 mmol/L. No acid-fast bacilli (AFB) were seen, and both gram stain and India ink stain were negative. Latex agglutination test for *Escherichia coli*, *B Streptococcus*, *Pneumococcus*, and *Hemophilus influenzae* were negative. Because of the seriousness of the patient's condition, and in the presence of strongly positive purified protein derivative (PPD) of 15 mm and a strong suspicion of tuberculous meningitis, he was treated empirically with 600 mg rifampicin, 300 mg isoniazid, 1 g pyrazinamide, 900 mg ethambutol, dexamethazone of 5 mg i.v. 8 hourly, and pyridoxine of 40 mg orally daily. Despite 15 days of continuous medications, the patient's level of consciousness continued to deteriorate and he was, therefore, referred to King Khalid National Guard Hospital (KKNGH) for further management.

On assessment at KKNGH, the patient was found to have a temperature of 38.5°C and was semicomatose. He still had signs of meningeal irritation and had paraparesis of the lower limbs, with a power of grade III according to the MRC grading. Sensory level was difficult to judge and there was Babinski sign on the left side. There were no chest signs, lymphadenopathy, organomegaly or abdominal masses. MRI of the brain and spinal cord disclosed two small enhancing lesions in the left thalamus and the right basal ganglia regions. A small enhancing lesion in the thoracic spinal cord on T₂-weighted images was also found. The hydrocephalus seen in the previous brain CT scan became worse. Repeat chest x-ray showed a suspicious mild enlargement of the right paratracheal lymph nodes (Figure 1). CSF examination which was turbid showed a pressure of 300 mm H₂O. The WBC count was $85/\text{mm}^3$ (70% lymphocytes, 30% polymorphs). The protein was 1086 mg/dL and glucose was 4 mmol/L. No AFB were seen in the smear and were not grown from culture. Brucella titer was negative. ESR was 85 mm/hr. The blood chemistry was normal except for a high calcium of 3.2 mmol/L with normal phosphorus and normal parathyroid hormones. Angiotensin-converting enzyme was <10 mL (12-42 normal range). Rheumatoid factor, antinuclear factor, anti-DNA, and serology for syphilis and HIV were all negative.

With insertion of an external ventricular drain and correction of calcium, the patient's level of consciousness gradually improved. Because of the discomfort of the

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external shunt, the patient pulled it off 12 days after its insertion. Making use of the external CSF drainage, six large CSF specimens were sent for microscopy and culture on different occasions, but all were negative. Polymerase ligase chain reaction for mycobacterium DNA was positive in one of the CSF specimens. The pyrazinamide was increased to 2 g and ethambutol to 1.6 g, and dexamethasone was continued in a gradually tapering dose.

The patient remained afebrile and maintained consciousness until the 7th week after the institution of anti-TB therapy, when he started to have fever ranging between 37.8 to 38°C. Chest x-ray showed significant enlargement of the right paratracheal group of lymph nodes (Figure 2). Five days later, the right cervical, axillary and the left submandibular groups started to rapidly enlarge, and over two weeks they became superficial and filled up with pus. Multi-drug resistant mycobacteria, lymphoma and sarcoidosis were seriously considered. Dexamethasone, which was being given at 1.5 mg bid was discontinued, as diagnoses other than TB were considered. The investigations revealed Hb of 9.5 g/dL with megaloblastic picture, WBC of 10.8 mm^3 (with normal differential), and ESR of 120 mm/hr. The calcium level was 2.9 mmol/L and the rest of the biochemical tests were normal. Alpha-fetoprotein was also negative. Bone marrow biopsy revealed a hypercellular marrow with megaloblastic changes but no granuloma or malignant cells. Acid alcohol-fast bacilli were absent in the smear and also on culture. CT scan of the abdomen did not show organomegaly or lymph node enlargement. Repeat brain MRI did not show a significant change from the previous one, except for mild reduction in the degree of hydrocephalus. CSF examination showed 50 WBC/mm² (80% lymphocytes, 20% polymorphs), protein of 1180 mg/dL and glucose of 4.5 mmol/L. No AFB were seen in the smear nor grown from culture.

In consultation with infectious disease and pulmonary specialists, it was decided to add ciprofloxacin and clarithromycin to the patient's drug regimen, as multi-drug resistant mycobacteria was considered. It took one week to persuade the surgeons to aspirate the glands from the day they became significantly enlarged, as they feared seeding of resistant organism in neighboring tissues and the possibility of sinus formation.

Aspiration of the axillary group of lymphatic nodes yielded a purulent material. These were mainly dead AFB in the background of caseating granuloma containing giant cells, epithelioid histocytes, lymphocytes and necrotic tissue. The culture of the aspirate failed to grow tuberculous bacilli. The patient was continued on the standard anti-TB regimen, and ciprofloxacin and clarithromycin were discontinued. Within three weeks, the lymphatic nodes started to shrink and eventually disappeared six weeks later. This happened in the absence of steroid medication. The patient completed a 12-month

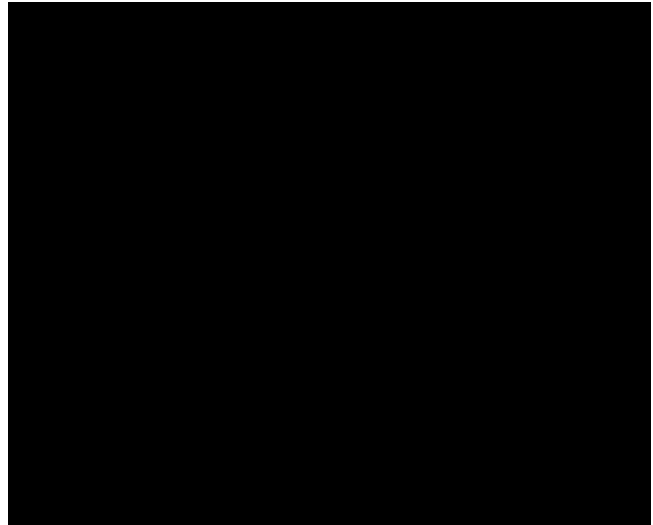


FIGURE 1. Repeat x-ray showed a suspicious mild enlargement of the right paratracheal lymph nodes.

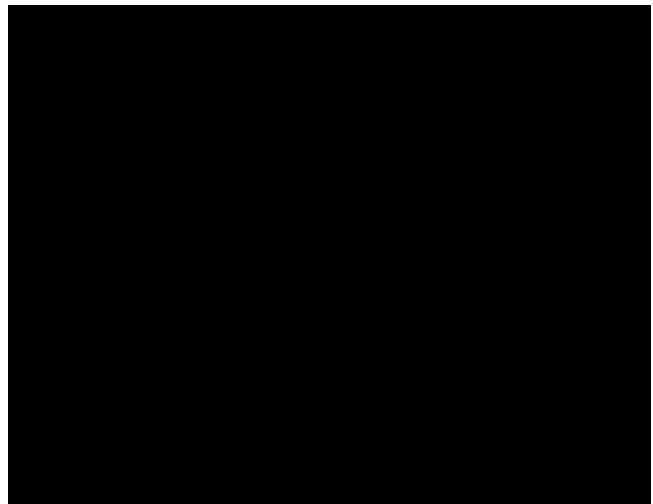


FIGURE 2. Chest x-ray showed significant enlargement of the right paratracheal group of lymph nodes.

course of anti-TB drugs, and when last seen in the clinic in September 1998, he was in perfect physical and mental health.

Discussion

The explanation of paradoxical response phenomena is still speculative. The proposed hypothesis suggests that there is interplay between the host's response and the direct effects of *Mycobacterium* compositions.³ The tubercle bacilli is structurally very complex, containing lipid, protein and polysaccharide, all of which are immunogenic.⁶ It is assumed that active TB can result in the depression of delayed type hypersensitivity (DTH) response (anergy). Once active TB is under control and the immuno-

suppression is resolved, enhanced DTH leads to activation and accumulation of lymphocytes at the site of bacillary deposition of toxins released by the dead bacilli.^{3,7-9} If the activation occurs at the site of microscopic foci, they become clinically significant, whereas macroscopic lesions show further enlargement.^{3,7-9}

DTH is considered to be responsible for many of the observed detrimental effects of TB, especially if the antigen is present in an excessive amount.¹⁰ The delay of PR in our patient and in previous reports supports this hypothesis.¹⁻³ However, in our patient, the strong reaction to the purified protein derivative skin test on presentation contradicts the "anergy" part of the suggested hypothesis, as this would indicate that the patient was not immunosuppressed on initial presentation.

The evolution of PR in the lymphatic nodes where large numbers of dead AFB were found in contrast to its absence in the CNS supports the notion that dead AFB or their products are important for the pathogenesis of PR.⁷⁻⁹ A review of the published literature shows the lymphatic nodes to be more prone to PR than other organs or tissues, probably by virtue of their function (as they are the most common site to be involved).¹⁻⁵ It is feasible to conclude that the antigenic load from the dead bacilli dictates the site of expression of PR.

In our patient, PR appeared while the patient was receiving steroids and resolved after their discontinuation. This observation casts doubt on the value of steroids in the prevention and treatment of PR, and adds to the present controversy on the role of steroids in PR.³ Some authors believe that timing, dose and duration of steroid therapy may all be of importance in the modulation of the inflammatory process, and hence they propose that tapering or discontinuation of steroids may be a risk factor for developing PR.³

It seems that a combination of host immunity, virulence of the bacilli, the site of the infection, the antigen load and the effect of chemotherapy may all play a role in the pathogenesis of PR.³

Our case report draws attention to the following points. First, PR can occur in sites remote from the initial manifestation of the disease, a factor which is important to recognize in order to avoid diagnostic confusion. Second, the role of steroids in PR is still controversial and will need well-designed controlled studies to reach a definite conclusion. Last, dead bacilli play a major role in the pathogenesis of PR and dictate the site to be involved, but future research is warranted to find the antigenic component which is responsible for the PR.

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