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Case Report

Meningoencephalitis tuberculosis as a paradoxical response to anti-tuberculous therapy in a child with pulmonary tuberculosis - a case report

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Paradoxical response is worsening of tuberculosis (TB) symptomatology and lesions during anti-tuberculosis therapy.[1-5] Patient with TB may develop new lesions or worsening of the disease due to several conditions, such as drug resistance, poor treatment compliance, non-tuberculosis disease, poor drug absorption, or paradoxical response to the therapy as well. Before concluding that the patient has paradoxical response, other conditions must be ruled out.[2,3]

Paradoxical response has been described in patients with cervical lymphadenopathy,[3] adult respiratory distress syndrome (ARDS),[4] intracranial tuberculomas,[5] and in HIV patients especially after having received antiretroviral therapy (ART).[6,7] Paradoxical response occurs in up to 25% of patients treated for TB and are more frequent in extra-pulmonary sites, particularly the central nervous system (CNS). It occurs due to penetration of isoniazid, pyrazinamide, and rifampicin into CNS. These drugs penetrate significantly into CNS; in fact, isoniazid and pyrazinamide are readily crossing into the CNS without meningeal inflammation. Cerebrospinal fluid (CSF) concentration of rifampicin is 10-20% of serum levels but increases in the presence of inflammed meninges.[5] The paradoxical lesion generally appears in the first 3 to 12 weeks after initiation of anti-tuberculous therapy, then without changing initial regimen (severe reactions can be treated with a short course of oral corticosteroids), the lesion will resolve spontaneously.[8]

This paper reports a case of meningoencephalitis tuberculosis as a paradoxical response to anti-tuberculous therapy in a child with pulmonary tuberculosis.

The case

A 7-year-old boy was admitted to the Emergency Departement (ED) with seizure. He had generalized tonic seizure for 15 minutes followed by decreased consciousness. Four hours before being brought to the hospital, he looked restless. He had been receiving anti-tuberculous therapy for two months regularly consisted of isoniazid, pyrazinamide, and rifampicin. He was brought regularly to the general practitioner every month and his body weight increased adequately.

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Physical examination revealed decreased consciousness, fever, neck stiffness, signs of upper motor neuron lesion with no cranial nerves paralysis. Laboratory examinations revealed hemoglobin 12.3 g/dl, WBC 8400/µl, blood glucose 68 mg/dl, sodium 126 mEq/l; other values were within normal limits. Analysis of CSF revealed the number of cells was 122/µl with mononuclear cells (80%), Nonne and Pandy reactions were negative, fluid glucose 40 mg/dl, protein 42 mg/dl, and there were no bacteria stained on Gram nor acid fast bacili found on smear. Culture of CSF for bacteria and *Mycobacterium tuberculosis* was negative. Examination using ^{99m}Technetium-Ethambutol with single photon emission tomography/computed tomography (SPET/CT) showed a response to ethambutol on the meningeal area meaning that there was TB infection in that site. We added streptomycin and oral corticosteroid to the regimen and increased the dose of isoniazid and rifampicin to maximal dose. After hospitalized for 12 days, his condition improved and he was discharged.

Discussion

Paradoxical response following anti-tuberculous therapy generally occurs within 1 to 3 months of initial treatment,[8] but there were also reports that it can develop between 3 weeks until 18 months after the initiation of the treatment.[2,7] Paradoxical response does not occur in every patient who have anti-tuberculous therapy; it depends on the host immune responses, tubercle bacilli virulence, the mycobacterial antigen load, the site of infection, and the effects of therapy.[2] Several mechanisms have been proposed for this response, yet precise mechanisms remain unclear. Most studies attributed to the development of a delayed type hypersensitivity reaction.[2,3,7] In active TB, the immune response is depressed, then when the anti-tuberculous therapy begins, the bacilli are killed and the immuno-suppression resolves. The dying mycobacteria become an antigen that attracts the lymphocytes and monocytes to the sites of TB lesions that may lead to enlargement of the foci; if it occurs at the sites of microscopic foci of TB, new lesions may appear.[2,7] On the other hand, the killed mycobacteria can release protein leading to hypersensitivity reaction.[2] Pulmonary TB infection related to more paradoxical response incidence than extrapulmonary TB. In person with depressed immune response like in HIV patients, deficiency of T-lymphocytes may lead to sequestration and compartmentalization of antigen-reactive lymphocytes within lymph nodes and body fluids. After initiation of ART, reduction of viral load and partial immune reconstitution allow an effective inflammatory response to previously unrecognized tubercle bacilli, and paradoxical response develops.[7]

Previously, our patient appeared well, but then he was ecperienced with seizure, decreased consciousness and signs of upper motor neuron lesion. He had been on anti-tuberculous therapy for two months with standard regimen. The parents gave him the drugs daily with good compliance, and made follow-up visits to the doctor regularly. Drugs resistance was unlikely since his parents as well as the doctors noticed that there was improvement in the patient's condition with increased body weight.

Paradoxical response in this patient mimics meningoencephalitis TB. Previous study revealed that paradoxical response mainly developed in CNS because isoniazid, rifampicin, and pyrazinamide significantly penetrated the CNS with or without inflamed meninges.[5] In order to prove that this patient had meningoencephalitis TB, we performed SPET/CT with ^{99m}Tc-Ethambutol as radiopharmaceutical, which showed an uptake of ethambutol on the meningeal area. SPET/CT imaging was performed by using a gamma camera to acquire multiple 2-D images, from multiple angles. A computer is then used to apply a tomographic reconstruction algorithm to the multiple projections, yielding a 3-D dataset. This data set may then be manipulated to show thin slices along any chosen axis of the body.

Ethambutol is a narrow spectrum antimicrobial, which is active against mycobacteria. It inhibits cell wall myolic acid synthesis and is used as a first line drug for the treatment of all kinds of tuberculosis. ^{99m}Tc-Ethambutol accumulates at the site of infection as early as two hours after injection, which then increases at four hours and persists until 24 hours.[10,11] This new method using ethambutol labeling has been proven in animal studies to support TB diagnosis due to limited yield of positive bacteriologic examination particularly in childhood.[10]

In case of paradoxical response, we do not need to discontinue or alter the regimen. Therapy should

be continued and in severe cases, oral corticosteroid can be administered. In this patient, because of the symptoms and signs of meningoencephalitis TB, we added streptomycin and oral corticosteroid to the regimen while continuing the previous drugs. Systemic corticosteroids in moderate doses for short duration are usually effective against paradoxical response as they reduce Th1 activity and enhance Th2 activity.[3] After 12 days of hospitalization, his condition improved and he could be discharged. On follow-up visits we noted that he showed further improvement without sequelae.

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