Paradoxical Response during Anti-tuberculosis Therapy

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Introduction

A paradoxical response in a patient infected with tuberculosis is generally defined as the clinical or radiological worsening of pre-existing tuberculous lesions or the development of new lesions in a patient who initially improves with anti-tuberculosis therapy. It occurs in about 10-15% of patients with a clinical diagnosis of *Mycobacterium tuberculosis* infection. Since a rapid and accurate diagnostic test is lacking, the diagnosis of this paradoxical phenomenon can only be ascertained when other differential diagnoses such as secondary infections, inadequate anti-tuberculosis therapy as a result of drug resistance, poor compliance, and adverse reactions due to therapy are excluded.

Clinical presentations

Paradoxical deterioration mostly occurs in patients with extrapulmonary and disseminated tuberculosis, like miliary tuberculosis and tuberculous meningitis. The median time to development of a paradoxical response is 60 days, ranging from 14 to 270 days in HIV-negative patients[1]. In addition to systemic reactions such as fever, the clinical symptoms and signs of paradoxical deterioration can be manifested in the initial site of infection as well as in an anatomical site other than that of the initial presentation. The central nervous system and the respiratory system remain the most common sites of involvement during paradoxical deterioration reported in literature[1]. For the central nervous system manifestations, patients may have headache, mental confusion, focal seizures, cranial nerve palsies, and cortical signs such as hemiparesis, paraparesis, and hemianaesthesia as a result of the enlargement or development of intracranial tuberculomas and hydrocephalus. The most common presentation in the respiratory system includes the worsening or appearance of a pleural effusion, either in the ipsilateral or contralateral side, whereas an increase in pulmonary parenchymal infiltration is only seen occasionally. Paradoxical responses can also occur in lymph nodes, skin and soft tissue, bone and tendon, and inside the abdomen.

Pathogenesis

The exact mechanism of this paradoxical response remains uncertain. Immunorestitution phenomenon has been suggested as a possible explanation. In patients with active *Mycobacterium tuberculosis* infections, there is a biased T-helper2 immune response as evident by an increase in the percentage of interleukin-4 and interleukin-10 positive lymphocytes together with a low percentage of interleukin-12 positive lymphocytes in the peripheral blood, especially in those patients with tuberculin anergy[2]. Furthermore, purified protein derivative-stimulated production of interferon-gamma by peripheral blood mononuclear cells was depressed, whereas levels of transforming growth factor-beta and interleukin-10 were increased[3]. However, when the mycobacterial load was significantly reduced after the initiation of anti-tuberculosis therapy, the cellular and cytokine patterns reverse which may result in an inflammatory response leading to a paradoxical phenomenon. The clinical severity of paradoxical deterioration is dependent on the exactness and appropriateness of immune recovery. An overwhelming immunorestitution may produce excessive immunopathological damage at the tissue level[4]. In HIV-positive patients, a paradoxical response may occur during reversal of the immunosuppressive state when highly active antiretroviral therapy (HAART) is co-administrated within 2 months of anti-tuberculosis treatment. This phenomenon appears more frequently in those patients with a significant reduction in HIV viral load and an increase in CD4-lymphocyte count after HAART[5].

Risk factors

In both HIV-negative and HIV-positive patients, paradoxical deterioration more frequently occurs in patients with extrapulmonary involvement and is associated with a lower lymphocyte counts at the baseline[6,7]. There is no difference in age, sex, and underlying co-morbidity in patients with or without a paradoxical response. At the time of paradoxical deterioration, a concomitant increase in the lymphocyte count and conversion of the tuberculin skin test is observed in a minority of patients[1,8]. However, whether interval lymphocyte counts and tuberculin skin tests can be used to predict the development of a paradoxical response requires further investigation.

Diagnosis

The diagnosis of paradoxical phenomenon is made by exclusion. Investigations should be performed to rule out other causes of clinical deterioration during anti-tuberculosis therapy such as secondary infections,

inadequate anti-tuberculosis therapy as a result of drug resistance, poor compliance, and adverse reactions due to therapy. In Hong Kong, patients received first-line anti-tuberculosis agents including isoniazid, rifampicin, pyrazinamide, and ethambutol as initial therapy. The overall prevalence of multi-drug resistant tuberculosis in Hong Kong remains less than 1% since year 2001[9]. Therefore, the diagnosis of a paradoxical response may not be difficult when the clinical deterioration occurs before the results of drug susceptibility are available.

Management

Patients with non-severe forms of paradoxical phenomenon such as recurrence of fever, enlargement of superficial lymph nodes, and increased pulmonary infiltrates or pleural effusion do not require specific treatment. Patients should be reassured and the anti-tuberculosis treatment should be continued. However, severe clinical deterioration may occasionally occur in patients with enlargement of intracranial tuberculomas with obstructive hydrocephalus, massive pleural effusions compromising respiratory function, and the development of deep seated abscesses leading to a pressure effect especially inside the abdomen or spine[1]. The uses of immunomodulators such as steroids along with surgical interventions such as insertion of a ventriculo-peritoneal shunt, thoracocentesis, and drainage of abscesses should be considered. A short-course and tailing dose of steroids in the management of paradoxical deterioration appears to be safe[1]. Most patients will recover uneventfully with either conservative treatment or a combination of medical and surgical management. Only a few cases with central nervous system involvement result in residual neurological deficits.

Conclusion

Paradoxical response during anti-tuberculosis therapy is not an uncommon phenomenon. A better understanding of the clinical presentation and pathogenesis can facilitate a diagnosis so that appropriate management can be made accordingly.

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