Paradoxical Response to Antituberculous Therapy

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Abstract

The term "paradoxical response" refers to the development of previously nonexistent tuberculosis lesions or worsening of pre-existing lesions during antituberculosis treatment. The etiology is still not clear but delayed type hypersensibility hypothesis is the most commonly accepted one. The paradoxical response can occur as an intracranial tuberculoma, pleurisy, pericarditis, contralateral new parenchymal lesions, progression of the pre-existing lesions or lymphadenopathy. We report a 35 year-old male patient with tuberculouos pleurisy which developed as a paradoxical response to antituberculous therapy.

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Key words: *tracheal wedge resection, lung cancer, technique*

Introduction

The term "paradoxical response to antituberculosis therapy" refers to the development of previously nonexistent tuberculosis lesions or worsening of preexisting lesions during antituberculosis treatment (1,2). Paradoxical responses have been described in patients with tuberculosis localized to the lymph nodes and in those with intracranial tuberculomas, adult respiratory syndrome or worsening lung lesions. Previously nonexistent pleurisy, pericarditis can also be seen. In some patients with tuberculosis and human immunodeficiency virus (HIV) induced immunosuppression a similar phenomenon of paradoxical exacerbation of the tuberculosis lesions can be observed. Orlovic et al. reported two such cases, one with a paradoxical tuberculous breast abcess (3). In many of these patients reported to have developed exacerbations, the paradoxical response is associated with the initiation of potent combination antiretroviral therapy (HAART). Narita et al. reported that a paradoxical exacerbation of tuberculous signs and symptoms may occur not only after tuberculosis therapy, but even more commonly, soon after the initiation of potent combination antiretroviral therapy in HIV infected tuberculosis patients (4).

Poor compliance with therapy, drug resistance, drug fever or another underlying condition must be ruled out before concluding that the treatment is the cause of the exacerbation.

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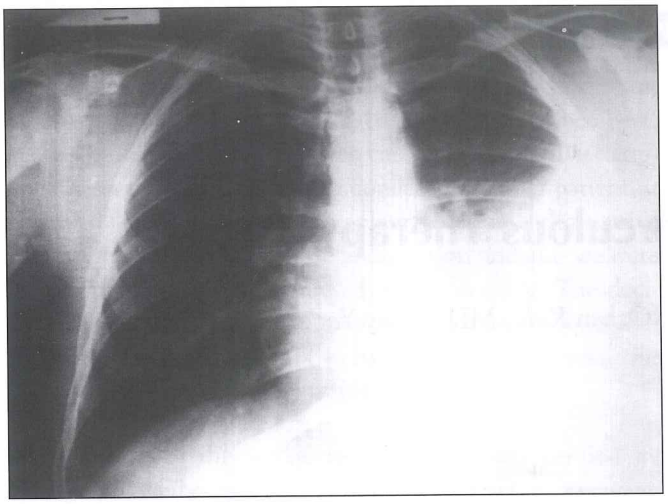

Figure 1. *Appearance of the lungs at the beginning of therapy.*

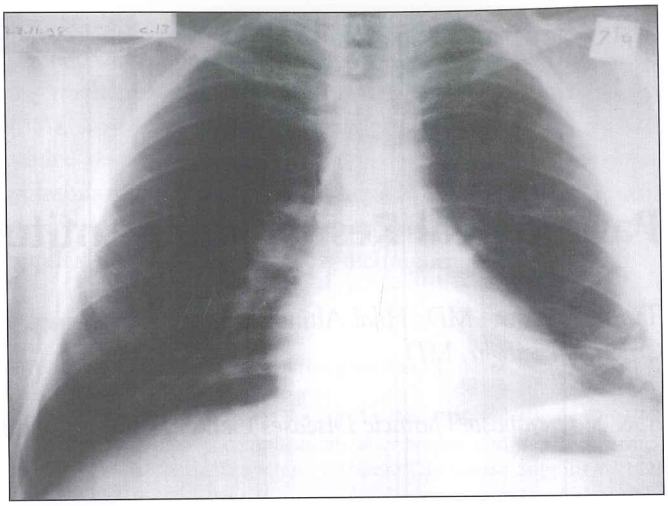

Figure 2. *Appearance after 4 months of treatment.*

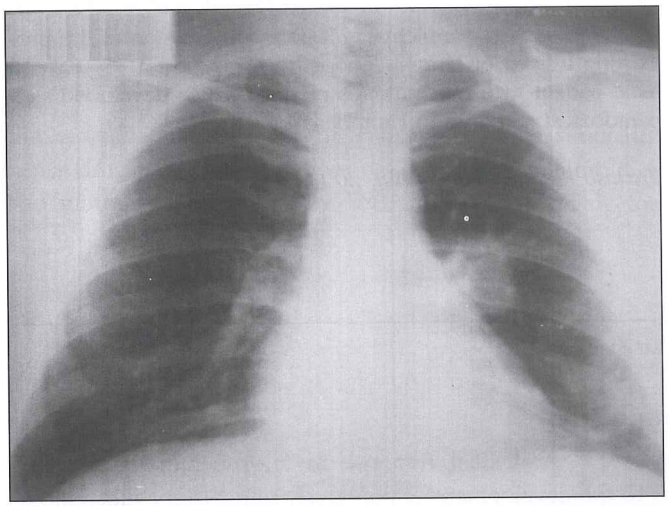

Figure 3. *Appearance after 6 months of treatment.*

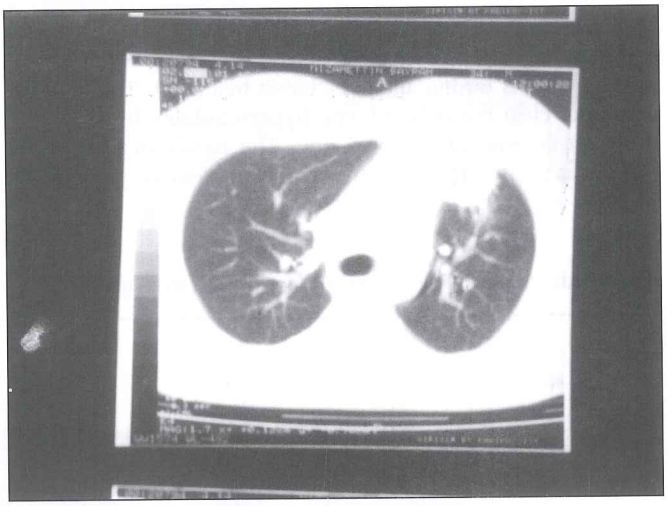

Figure 4. *Appearance after 6 months of treatment.*

The paradoxical response develops between 4 weeks and 18 months after the initiation of antituberculosis therapy (5). Development or worsening of an existing lymphadenopathy was the most commonly reported type of exacerbation following antituberculosis therapy (4). This paradoxical effect of treatment has been reported to develop in 25% of tuberculosis lymphadenitis cases and although no case controlled studies exist outside of patients with lymph node tuberculosis, exacerbation in the form of pleuresy is reported to occur in 16% of pulmonary tuberculosis cases (6,7).

The etiology of this response is not yet clear, but it is mostly attributed to the development of a delayed type hypersensitivity reaction. In active tuberculosis the immune system is depressed so that the organism cannot react. As the antituberculosis therapy begins, the bacilli are killed and the immunosuppression resolves. The mycobacterial antigens attract the lymphocytes to the media and a tuberculosis focus is generated. The TNF-α, secreted from the macrophages, causes tissue damage. This is a delayed type hypersensibility reaction (4,8).

In the new foci, pathology generally shows granulomatous inflammation with necrosis, but Koch bacilli cannot be demonstrated.

Clinically, the patients are generally well. Hydrocephaly can complicate the clinical picture in patients who develop intracranial granulomas.

Differences in the relationships between the chemotherapy effect, the mycobacterial antigen load, the location of the infection, the virulance of the bacilli and the immune response explain why this paradoxical response does not happen in every patient.

If a paradoxical lesion develops in the course of an optimal antituberculous therapeutical regimen, the therapy plan

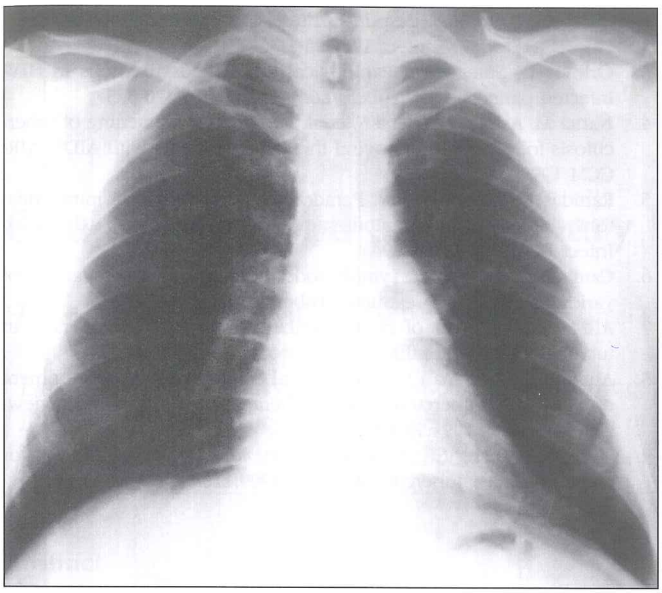

Figure 5. *Appearance 3 months after cessation of therapy.*

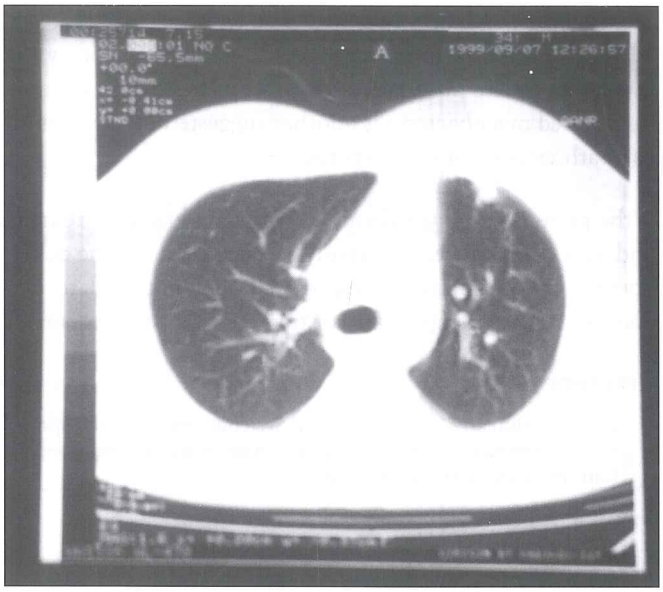

Figure 6. *Appearance 8 months after cessation of therapy.*

must not be changed and no other drug must be added. Only steroid therapy may occasionally be added to heal the intracranial pressure caused by the expansion of intracranial tuberculomas. The paradoxical lesions generally resolve spontaneously.

Case Report

A 35-year-old male, living in Istanbul, presented with pain on the left side and a cough. The patient had no other known diseases and his complaints had started only in the past 2 months. He was not on any medication. Two months ago, his wife was started on antituberculous therapy. The patient was a smoker and smoked 20 package/year cigarettes. He did not drink alcoholic beverages.

In physical examination, vital signs were normal. Breath sounds were diminished in the left lung and a dullness was noted by percussion. A meniscus shaped opacity was seen in the chest X ray (Figure 1). A PPD test led to a 15 mm induration. Pathological examination of the specimens obtained by thoracentesis and closed pleural punch biopsy revealed granulomatous lesions with necrosis and therapy with isoniazide, rifampicin, ethambutol and pirazinamide was started. At the end of two months, the effusion decreased and by the 4th month of therapy, the costophrenic sinus was almost normal in appearance in the posteroanterior X-ray (Figure 2). By the end of the therapy (6th month) the effusion had regressed but a smooth sided, homogenuous mass approximately 3 cm in diameter was seen (Figures 3). The patient was readmitted to the hospital for the investigation of this new lesion. There was no abnormality in the hemogram or other routine laboratory results. A thoracic computerized tomography revealed the presence of a paramediastinal lesion on the left upper lobe anterior segment level (Figure. 4). Transthoracal needle biopsy, guided by computerized tomography, was performed. Histology of the specimen revealed necrotizing granulomatous inflammation. The patient was followed for 2 months without any medication, since the antituberculosis therapy course had been completed. A progression in the diameter of the mass was noted and it extended towards the periphery. To be able to eliminate any other underlying condition, a fiberoptic bronchoscopy was done under local anesthesia which showed only edema on the mucosa of the left upper lobe and of the lingula. A chest X-ray taken after a period of 3 months showed that the lesion was getting smaller and one taken nearly eight months after the therapy had ended, showed that the lesion had disappeared completely (Figures 5 and 6).

Discussion

While receiving appropriate treatment, patients with tuberculosis occasionally have unusual paradoxical reactions with transient worsening of the lesions or the development of new lesions. This phenomenon has been described in patients with intracranial tuberculomas and and in those with tuberculous lymphadenitis. As presented in our patient, development of effusion or mass lesions can also be seen. The paradoxical reaction generally occurs 3 to 12 weeks after the initiaton of the antituberculosis therapy, but this period can be as long as 18 months in some cases (5,9). In our patient the paradoxical response developed 5 months after the start of therapy.

The mechanism of the paradoxical response is unclear. One hypothesis is that active tuberculosis can lead to immunosuppression and as this suppression is diminished as a result of the antituberculous therapy, enhanced focal immune responses can occur. Lymphocytes and macrophages are

recruited to the lesion sites and new necrotic foci occur by TNF-α secreted from macrophages. Development of hypersensitivity to the proteins of the tuberculosis bacilli released from killed mycobacteria is another suggested mechanism in the pathogenesis of this response.

If the presence of any other underlying condition is excluded and poor compliance, drug resistance are ruled out, the development of a paradoxical response should not lead to any changes in the therapy plan nor to any invasive procedures.

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