Original Research Paper

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Varied Presentations of Paradoxical Upgrading Reactions in Pulmonary Tuberculosis

Medicine

KEYWORDS : paradoxical upgrading reaction, pulmonary tuberculosis, tubercular lymphadenopathy (LAP)

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ABSTRACT

Paradoxical Upgrading Reactions (PUR), usually observed in patients undergoing treatment for tuberculosis, is a phenomenon, characterized by transient worsening of both, the clinical symptoms and the lesions during appropriate anti-tubercular therapy. This reaction is mostly observed in cases of Tubercular lymphadenitis and less frequently in Pulmonary Tuberculosis. The reaction is related to hypersensitivity response to dying mycobacteria. These pose a challenge to the physicians to exclude all the causes/reasons (drug-resistant tuberculosis, non-compliance to the prescribed regimen or concomitant disorders unrelated to Tuberculosis) known to be responsible for worsening of the condition of the patient before classifying them as PUR.

We report four cases of tuberculosis (two cases of pulmonary tuberculosis, one case each of tubercular lymphadenitis and tubercular pleural effusion) who, during the course of treatment presented with varied symptoms and presence of new lesions. After detailed investigations, it was inferred that worsening of symptoms and appearance of new lesions during treatment, were due to Paradoxical upgrading reactions, a phenomenon observed in 20-30% patients of Tuberculosis.

This happening, is generally self- limiting and resolves without serious sequelae.

Introduction

Paradoxical Upgrading Reaction (PUR), commonly referred to as paradoxical reaction (PR) is defined as the worsening of pre-existing tuberculosis (TB) lesions on the basis of clinical or radiological findings or the development of new TB lesions in patients who were receiving appropriate anti-TB treatment and who were otherwise showing signs of improving.[1] Most of the reported cases have complicated the treatment of lymph-node or cerebral disease, with enlargement of nodes observed to be approximately 30% in one mega study. [2] This deterioration of TB may be evident in the form of development of tuberculoma, the expansion of lymph-nodes, the appearance of new lesions on chest radiography, and other varied presentations. [3,4] PUR is unpredictable in its timing, occurring within a few days to many months after the initiation of anti-tuberculosis chemotherapy and in its duration and severity.PUR is essentially being a diagnosis of exclusion, various factors such as poor compliance, drug resistance and secondary diagnosis, should be ruled out before labelling the case as PUR.

Case Report Series

Case 1:

A 14 year old female, known case of pulmonary tuberculosis (Figure 1), on ATT (Anti Tubercular Treatment) under DOTS (Directly Observed Treatment, Short course) Category 1 under RNTCP (Revised National Tuberculosis Control Program) presented after 67 days with an enlarged lymph-node in right supra clavicular region. There were no constitutional symptoms. Other than an enlarged lymph-node in the neck, the general physical examination was essentially normal. 2×3 cm in size, the lymph-node was inflamed and fluctuant (Figure 2). Aspiration of the lymph-node yielded pus. The aspirated pus was sent for cytology examination, gram staining, Ziehl Neelson (ZN) staining for acid fast bacilli (AFB) and culture for pyogenic organisms. Gram as well as ZN stain did not show any bacteria. Culture for pyogenic organisms yielded no growth after 48 hrs. After 10 days, the patient again presented with a swollen and painful lymph-node. Excision biopsy of the node was performed. The histo-pathological report revealed an acute on chronic inflammatory pathology (Figure 3), with no granulomas. Both Fungal and AFB stains and culture were nega-

tive. The patient was advised to continue ATT and steroids were added to the treatment. The wound healed and the patient improved without any further complication.

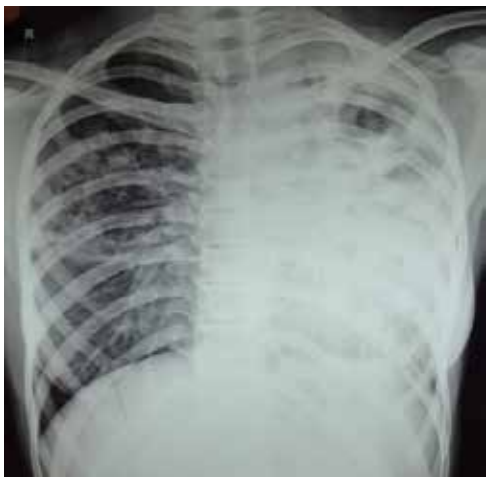

Figure 1 X-ray chest showing heterogeneous opacities in both the lungs

Figure 2 Picture showing the enlarged and inflamed lymph node

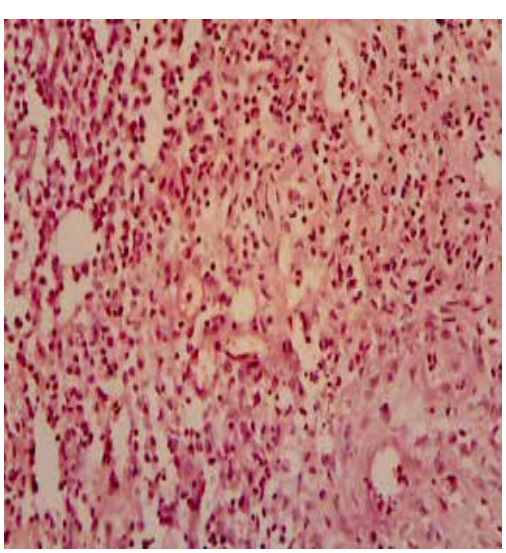

Figure 3 Histopathological picture of the biopsy of the lymph node

Case 2:

A 54 year old male presented to us with chief complaint of loss of weight. He had lost 13 kg in the past one month with no other complaint. On examination, he was well built and nourished and the general examination of all the systems was normal. His x-ray chest showed bilateral hilar lymphadenopathy. His haematological and biochemical tests were unrevealing. Serum ACE levels and 24 hour urinary calcium were also normal. His CECT chest showed enlarged, multiple hilar and mediastinal lymph-nodes (Figure 4). On bronchoscopy, biopsy of the enlarged lymph-nodes was obtained. The histopathological report was consistent with epthelioid cell granulomas showing central necrosis. The patient was diagnosed as a case of tubercular LAP and started with anti tubercular treatment. Patient showed response to treatment till 68 days, when he presented with complaints of breathlessness and pain on the right side of the chest. X-ray of the chest showed moderate pleural effusion on the right side (Figure 5). His CECT of the chest revealed bilateral pleural effusion (right more than the left) and ascites with abdominal lymphadenopathy (Figure 6A, 6B). Fluid from both, the pleural and abdominal cavity was aspirated and subjected to biochemical and cytological tests, fungal, gram and ZN stains and sent for culture for pyogenic and myco-bacteria. The reports suggested an exudative character of fluid from both sites. The stains for bacteria, fungi, and AFB were negative. With no growth, the culture reports were also inconclusive. After excluding all the causes it was summed up as PUR. Other than reassuring the patient, Steroids were added to the anti-tubercular treatment. The patient responded to the treatment and the steroids were tapered off in 4 weeks. X-ray of the chest, done after 1 month of this episode showed marked clearing of the effusion. The patient completed the treatment and CECT done at the end of treatment showed near normal lungs. (Figure 7)

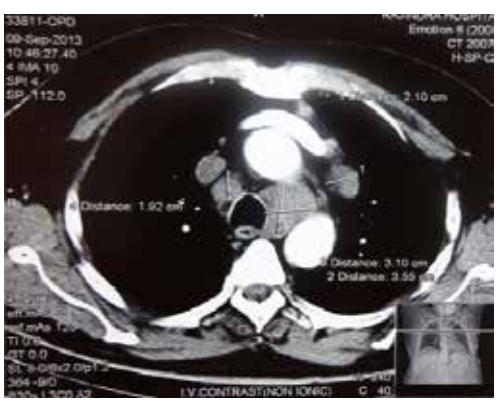

Figure 4 CECT of the chest showing enlarged mediastinal and hilar lymph node

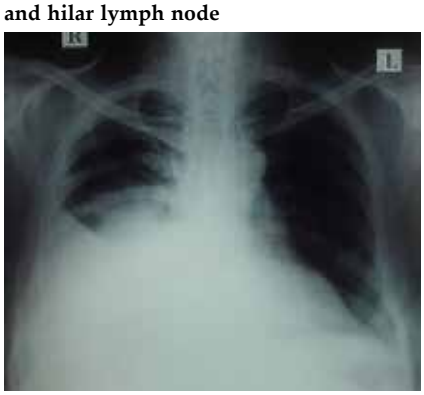

Figure 5 X-ray chest showing right sided pleural effusion

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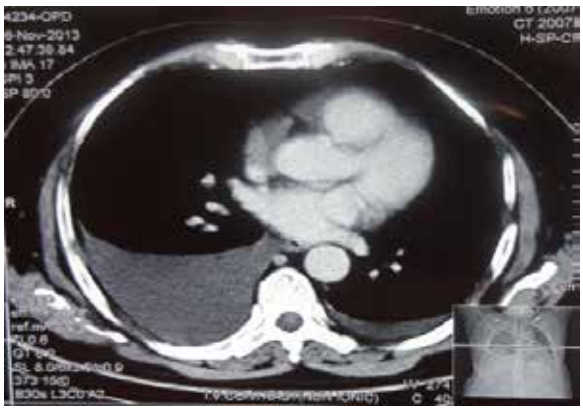

Figure 6a CECT chest with abdomen showing bilateral pleural effusion

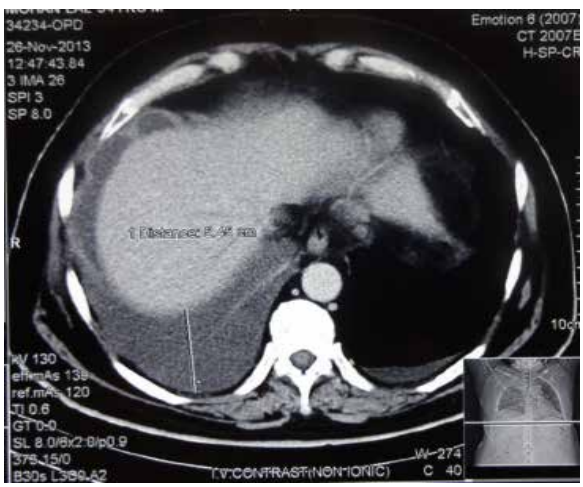

Figure 6b CECT showing ascites with abdominal Lymphadenopathy

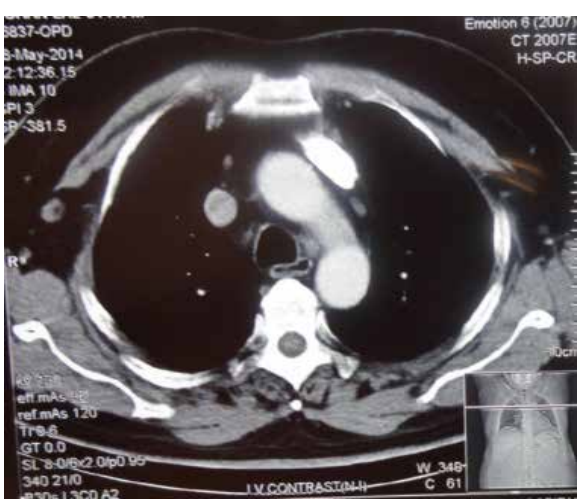

Figure 7 CECT of the chest showing normal lungs with no lymphadenopathy

Case 3:

A 65 years old male, known case of right sided tubercular pleural effusion (Figure 8), on ATT since 59 days, presented with chief complaints of pain in left side of the chest. The pain was dull and non-radiating in left infra-mammary and axillary region. There were no constitutional symptoms. Apart from normal general physical examination, the examination of the chest showed signs of pleural effusion on the left side, which were confirmed by the X-ray of the chest (Figure 9). About 1000 ml of straw coloured pleural fluid was aspirated and sent for investigations. The fluid was exudative in nature. No growth was seen on culture for AFB and pyogenic organisms. Patient was advised to continue ATT and methyl prednisolone 32 mg/day was added to the treatment. The steroids were gradually tapered off in a month. X-ray chest (Figure 10) done after one month of this episode show marked improvement. On excluding non-adherence and secondary diagnosis and on the basis of clinical presentation and investigations, this occurrence of pleural effusion on the contralateral side during the course of treatment was attributed to be a paradoxical upgrading reaction.

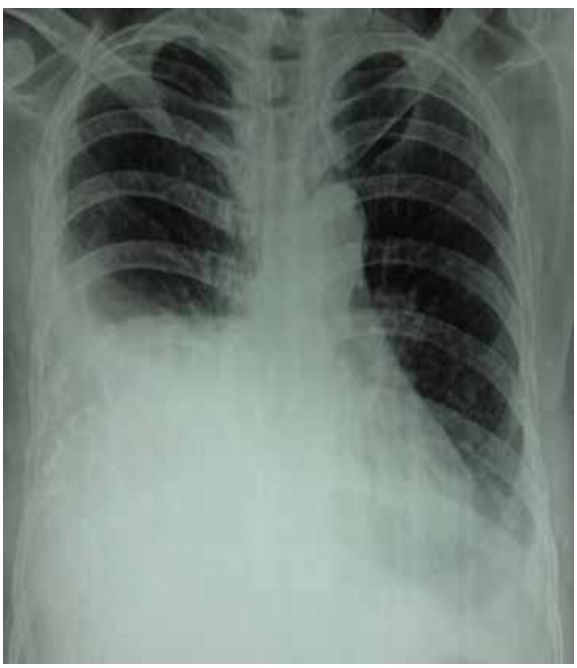

Figure 8 X-ray chest showing pleural effusion on the right side

Figure 9 X-ray chest showing a left sided pleural effusion.

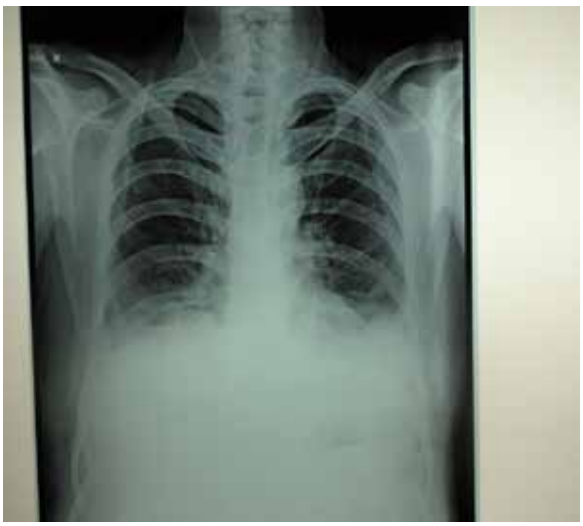

Figure 10 X-ray chest showing almost complete clearing of the effusion on both sides.

Case 4:

A 52 years old female patient known case of pulmonary tuberculosis (Figure 11) who was on treatment under RNTCP DOTS Category 1 and was responding to the treatment presented after 44 days with complaints of pain in the left side of chest in the mammary area along with increased cough with expectoration for past 5 days. The pain was non radiating and worsened during coughing. There was no history of fever, haemoptysis or breathlessness. General physical examination was essentially normal. Her haematological and biochemical tests were normal. Her chest x-ray (Figure 12) showed worsening of the lesions and a fluid level in on the left side in the middle zone. Patient's sputum was subjected to gram ZN and fungal stains. All the stains were negative. Sputum for culture for pyogenic organisms and fungi were negative. The sputum, sent for BACTEC culture for AFB was also unrevealing. Patient was advised to continue with ATT and methyl prednisolone 32mg/day was added to the treatment which was tapered off gradually. After one month of this presentation, along with the clinical improvement, her x-ray chest (Figure 13) showed marked improvement. Detailed history and all the tests pointed the worsening to be paradoxical reaction during course of treatment in pulmonary Tuberculosis.

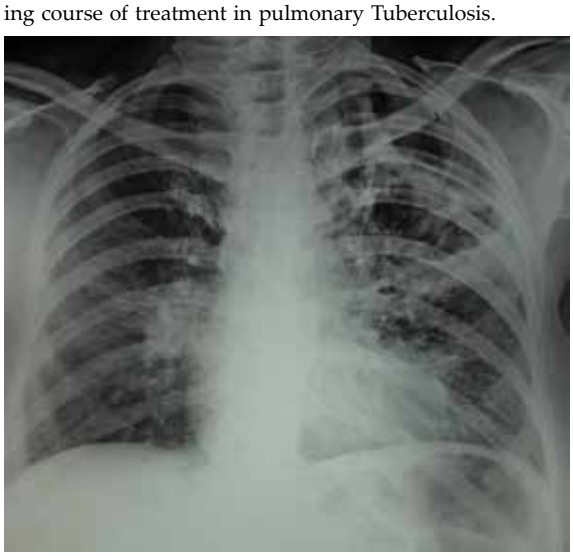

Figure 11 X-ray chest showing heterogeneous opacities in upper and middle zone of left lung.

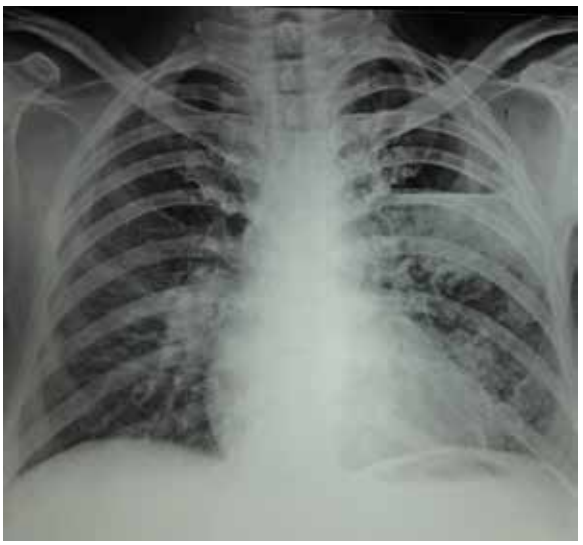

Figure 12 X-ray chest showing heterogeneous lesions in the upper and middle zone of the left lung with a fluid level.

Figure 13 X-ray chest after 1 month showing clearing of the lesions.

Discussion

A paradoxical upgrading reaction (PUR) is defined as the clinical or radiological worsening of pre-existing tubercular lesions or the development of new lesions in a patient of tuberculosis who initially shows a response to appropriate anti-tuberculosis therapy. [1] The exact mechanism of PUR is not well understood, but it has been attributed to host immunological reactions, with possible mechanisms including delayed hypersensitivity response, decrease in immune suppression and a reactive response towards mycobacterial antigens. [2] Later on when the mycobacterial load is significantly reduced after the initiation of anti-tuberculosis therapy, the inflammatory response as a result of reversal of cellular and cytokine patterns is thought to be responsible for this paradoxical phenomenon. [5] The clinical severity of paradoxical deterioration relies upon the exactness and appropriateness of immune recovery. An overwhelming immune-restitution may produce excessive immune-pathological damage at the tissue level. [6]

In both HIV-negative and HIV-positive patients, PUR often occurs in patients with disseminated and extra pulmonary tuberculosis, and is associated with a lower baseline

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counts of lymphocyte. [7,8,9] It is found to occur in 20–30% TB lymphadenitis patients. [10] PUR can occur anywhere from several days to many months after the start of ATT. Young age, male gender and local tenderness at the time of diagnosis are independently associated with PUR. In our present case series three patients were above 50 years and one patient was a child of 14 years of age.

In addition to constitutional symptoms such as fever and generalized weakness, the clinical symptoms and signs of paradoxical deterioration can manifest at the initial site of infection and or any other anatomical site. [10] The worsening or appearance of a pleural effusion, either in the ipsilateral or contralateral side is the most common presentation in the respiratory system, [11] on the other hand worsening of the pulmonary parenchymal infiltration is only seen occasionally. In our case series, 2 of the 4 patients presented with pleural effusion, one patient with worsening of the parenchymal lesions and solitary patient of pulmonary tuberculosis who presented with lymphadenopathy. All the patients initially showed a response to treatment before the demonstration of this phenomenon leading to worsening of the symptoms and appearance of an enlarged lymph node, bilateral pleural effusion, contralateral pleural effusion and worsening of the parenchymal lesions in the patients respectively. In all the patients despite detailed investigations, no cause for this worsening could be elaborated, thus labelling these happenings as PUR. Furthermore, all these patients continued with the same treatment along with the addition of steroids for short duration (28 days) and all the patients had a favourable response to the treatment, further validating that these transient episodes were Paradoxical worsening.

Such paradoxical worsening syndromes are a diagnostic challenge for the physicians for the reason that these clinical retrogressions may raise the suspicion of drug-resistant TB, non-compliance to the prescribed regimen or concomitant disorders unrelated to TB. [12] It is a challenge to exclude all the causes/reasons for worsening of the condition of the patient before classifying it as PUR.

The mainstay of PUR management is the continuation of anti-tubercular treatment without any modification of the drug regimen. Usually patients with enlarged lymph-nodes, pleural effusion or worsening of the parenchymal lesions as a presentation of PUR do not require any change in treatment, other than aspiration of the effusion, and occasionally excision of the lymph-nodes. Severe clinical deteriorations observed in patients with TB of the central nervous system and massive pleural effusion may require surgical interventions along with steroids. [13] Most patients recover uneventfully, only a few cases with central nervous system involvement may end up with residual neurological deficits.

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