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*Case Report*

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# Paradoxical Reaction to Antituberculosis Complicating Bacilifere Pulmonary Tuberculosis

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**ABSTRACT**

Tuberculosis is still an endemic disease in many countries. Paradoxical reaction (PR) to antituberculosis drugs is a rare complication seen in patients on antituberculosis treatment. We report the case of a 58-year-old man who had been presenting for two months with a cough, signs of tuberculosis impregnation and uncalculated weight loss. Bacciloscopies were positive. We started the patient on antituberculosis treatment. One month later, the patient developed confusion and abdominal pain. The laboratory work-up and various radiological examinations (cerebral CT scan, cerebral MRI) revealed no abnormalities. Abdominal CT scan showed: a peritoneal effusion of low abundance with nodular infiltration of the fat of the great epiploon. After ruling out all other etiologies for the confusion, we retained the diagnosis of paradoxical reaction to anti-tuberculosis drugs. The patient received corticosteroid therapy with marked neurological improvement.

**Keywords:** Pulmonary Tuberculosis, Paradoxical Reaction, Corticoid

## Introduction

Pulmonary tuberculosis is a chronic, progressive mycobacterial infection. In 2020, around 9.9 million new cases of tuberculosis (127/100,000) were recorded worldwide [1]. Most new cases occurred in Southeast Asia (43%), Africa (25%) and the Western Pacific (18%) [2.3]. Several complications have been observed in the course of anti-tuberculosis treatment. These include the paradoxical reaction to tuberculosis. Paradoxical reaction refers to the increase in pre-existing lesions or the appearance of new tuberculosis lesions (clinical or radiological) following the introduction of an effective anti-tuberculosis treatment, with no evidence of poor compliance, malabsorption, drug interaction or resistance to treatment [4]. PR occurs in 6-30% of patients treated with anti-tuberculosis drugs, regardless of the type of tuberculosis [1]. Extrapulmonary tuberculosis accounts for around 80% of PR cases [5]. It is most often seen in cases of tuberculous meningitis or miliaria. Its severity and prognosis depend on the initial site of tuberculosis and the site of new lesions. We report a case of pulmonary tuberculosis that is unusual in its course, its association with abdominal tuberculosis and the occurrence of anti-tuberculosis PR.

## Case Presentation

A 58-year-old man from Bizerte had a history of thrombophlebitis of the right lower limb in 2017, compressive pericarditis complicated by heart failure following an antivitamin K overdose in 2017, and depression in 2011. In June 2023, he consulted our pulmonology department for a cough, weight loss, asthenia and anorexia that had been evolving for two months. Clinical examination was normal except for a body mass index of 17 kg/m$^2$. Chest X-ray showed a left apical infiltrate (figure 1). bacilloscopy was positive.

Biological tests revealed a hemoglobin level of 12 g/dl and a leukocyte count of $9.1\times10^9$ /l (neutrophils = 8.5 $\times10^9$ /l; lymphocytes = $0.7\times10^9$ /l). blood ionogram, liver and kidney function tests were normal. HIV serology was negative. The patient was started on a combination of rifampicin (RMP), pyrazinamide (PZA), ethambutol (EMB) and isoniazid (INH), with good compliance and tolerance.

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**Figure 1:** Xray showing Left apical excavated infiltrate

After four weeks of treatment, the patient presented with confusion and abdominal pain. Biological tests and various radiological examinations (cerebral CT scan, cerebral MRI) revealed no abnormalities. A chest X-ray showed a worsening of pre-existing lesions and the appearance of new ones (Figure 2). Bacilloscopies were positive after 1 month's treatment, and abdominal CT scans showed: a small peritoneal effusion with nodular infiltration of the fat of the greater omentum, and vesicular lithiasis (Figure 3). After eliminating all other etiologies of confusion, and in view of the appearance of new abdominal lesions, we retained the diagnosis of paradoxical reaction to anti-tuberculosis drugs. The patient was put on corticosteroids at a dose of 1 mg/kg with a good clinical evolution (disappearance of confusion and return of appetite), and the anti-tuberculosis treatment was continued.

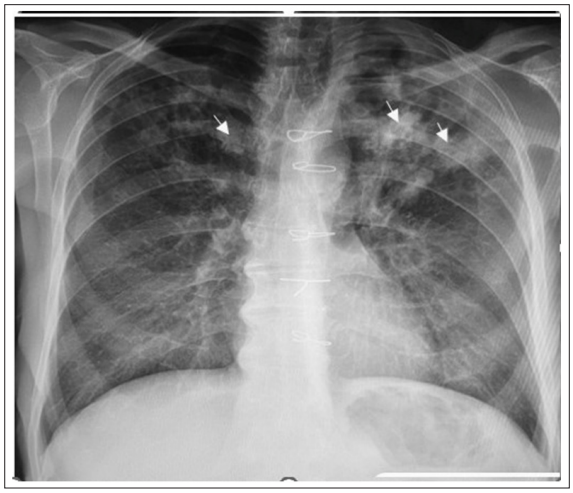

**Figure 2:** Xray: Left apical lesion increase and appearance of a new right apical infiltrate (wight arrows)

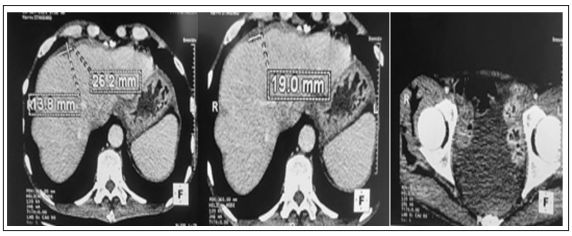


**Figure 3:** abdominal scan: peritoneal effusion of low abundance with nodular infiltration of the fat of the great epiploon, vesicular lithiasis

**Discussion**

In our patient, not immunocompromised (and not infected with HIV), we retain the diagnosis of bacilliferous pulmonary TB associated with abdominal tuberculosis. The appearance of confusion and worsening of imaging and the appearance of an abdominal localization of tuberculosis under well-conducted anti-tuberculosis treatment may enter into a paradoxical reaction to anti-tuberculosis treatments. RP is found in 6 to 30% of patients treated with antituberculosis for all forms of TB combined [1]. Extrapulmonary TB are responsible for about 80% of RP cases. They are dominated by meningitis and miliaria [5].

The paradoxical reaction corresponds to the increase of pre-existing lesions or the appearance of new tuberculosis lesions following the introduction of effective anti-tuberculosis treatment, without argument for poor compliance, malabsorption, drug interaction or resistance to treatment [6].

Paradoxical reaction under TB treatment is reported especially in people infected with HIV. Immune reconstitution syndrome (IRS) is classic in such patients. During this syndrome, infectious or autoimmune phenomena relapse or appear de novo after initiation of antiretrovirals. SRI-type TB outbreak often follows initiation of antiretroviral therapy in patients with TBVIH co-infection [7].

The delay of appearance of the paradoxical reaction in our patient is of the order of four weeks which agrees with the data of the literature. In fact, the literature reports this delay between 2 to 4 weeks [6,8].

The etiopathogenesis of the paradoxical reaction is attributed to the immune response due to treatment. Currently, the hypothesis of an exaggeration of the specific immune response against antigens associated with Mycobacterium tuberculosis is the most supported. Immunity is initially impaired by TB itself because of its immunosuppressive effect. In a second step, it is gradually corrected under antituberculosis treatment: pro-inflammatory effect released and exaggerated (increase pro-inflammatory cytokine synthesis IFNγ and TNFα) and anti-inflammatory effect deficient (decreased cytokine anti-inflammatory synthesis IL10) [9].

In the literature the treatment of the paradoxical reaction of antituberculosis is not well codified. Therapeutic management most often uses corticosteroids. The use of anti-TNFα in corticosteroid-resistant forms is promising [5,6,10]. We put our patient on corticosteroid with good evolution.

The prognosis is generally good, except in neurological forms where the risk of sequelae is significant.

**Conclusions**

RP under anti-tuberculosis treatment is more readily encountered during extrapulmonary TB. It is important to systematically search by imaging a cerebral or spinal location during miliaries or meningitis because it can be asymptomatic. The presence of a neurological localization of RP changes the duration of antituberculosis treatment. There is no consensus on the use of corticosteroid therapy.

**Contributors**

MS, CA and DS participated in the management of the patient. MS, MS, AC, MZ, CA and DS participated in design of the report, collection of the data and writing of the manuscript. All the authors have read and approved the final version of the manuscript.

**Competing interests:** None declared

**Patient consent**

A written and signed consent to publication was obtained.

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