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(CASE REPORT)

Paradoxical tuberculous reaction to anti-tnfα discontinuation: a complex case of miliary tuberculosis and macrophagic activation syndrome with hepatic manifestations

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Abstract

Tuberculosis reactivation during anti-TNF-alpha therapy paradoxically worsened following reconstitution of pathogen-specific immune responses after cessation of TNFα antagonist treatment and initiation of anti-bacillary therapy. We report the case of a 46-year-old woman who was prescribed a tumor necrosis factor blocker (anti-TNF) for a relapse of Behçet's disease. The patient developed pulmonary miliary tuberculosis following the reactivation of latent tuberculosis, despite a normal pre-therapeutic work-up. Discontinuation of anti-TNF and initiation of anti-bacillary drugs triggered a paradoxical tubercular reaction (PTR). The diagnosis of paradoxical reaction to anti-tuberculosis drugs was evoked by the clinical and biological deterioration and the appearance of miliary cerebral tuberculosis and cerebral venous thrombosis after a period of clinical improvement. Although this phenomenon has been documented, it represents a major challenge for clinicians. The peculiarity of this case lies in its association with a macrophagic activation syndrome (MAS) with hepatic involvement, retained on clinical-biological and histological criteria. The overlap between MAS and PTR makes it difficult to diagnose these two entities with certainty. The patient responded favorably to moderate-dose systemic corticosteroid therapy with progressive degression, and the reintroduction of anti-tuberculosis drugs.This work aims to highlight the importance of close monitoring of TB patients on anti-TNFα therapy for early diagnosis and management of complications to improve the prognosis of these complex patients.

Keywords: Macrophagic Activation Syndrome; Anti-Tnfα; The Paradoxical Tubercular Reaction; Behçet; Hepatic Manifestations; Miliary Tuberculosis

1. Introduction

Targeted biotherapy, including tumor necrosis inhibitor factor (TNF), is commonly used to control the activity of chronic inflammatory diseases [1]. Since TNF and other pro-inflammatory cytokines, as well as those secreted by Th1 lymphocytes, play an essential role in orchestrating inflammation and activation of the host's response to infection, these treatments are known to promote the development of serious infectious side effects such as tuberculosis reactivation [2]. Discontinuation of anti-TNFα therapy, as recommended on diagnosis of tuberculosis, may be accompanied by immune reconstitution, with recovery of anti-mycobacterial immune responses [3]. Although there are no consensual diagnostic criteria, paradoxical tuberculosis reaction (PTR) is one of the most common forms of immune reconstitution and is classically defined as the worsening of lesions present at diagnosis or the appearance of new lesions, after initiation of anti-tuberculosis treatment, in the absence of an alternative diagnosis or therapeutic failure[4]-[7] .Macrophagic activation syndrome (MAS) is a rare pathology with a severe prognosis, defined by

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inappropriate activation of macrophagic cells. It may be primary or secondary and complicates other conditions: neoplasia, infectious diseases such as tuberculosis, or autoimmune diseases [8]. We report here a case of paradoxical worsening of tuberculosis following discontinuation of anti-TNF complicated by MAS with hepatic manifestations, in a highly immunocompromised HIV-negative patient.

2. Case report

We report the case of Mrs. Z. B, aged 46, who has been treated for Behçet's disease since 2006, with the following symptoms: recurrent bilateral uveitis, recurrent bipolar aphthosis, pseudofolliculitis, and diffuse arthralgia of the joints. The patient benefited from bolus and oral corticosteroid therapy and also received long-term immunosuppressive treatment with azathioprine .The clinical course was marked by multiple recurrences, which led to the administration of a tumor necrosis factor (TNF-alpha) inhibitor; infliximab, after a normal pre-therapeutic workup (the last injection was received in January 2020). Two months later, the patient presented with prolonged fever, night sweats, and altered general condition. A chest CT scan revealed bilateral micronodules in the lung parenchyma (Figure 1). Acid-fast bacilli were observed in a sample of bronchoalveolar lavage fluid. Treatment with infliximab was discontinued, and antituberculosis treatment was initiated for pulmonary miliary tuberculosis, followed by a phase of clinical improvement. However, during the 5th week, the patient was hospitalized in the gastrology department for a recurrence of fever, cholestatic jaundice associated with vomiting, and an altered general condition. The patient also reported visual fog and headaches. Clinical examination confirmed weight loss of 07 kg in 2 months, with muscular weakness in the 02 lower limbs, and no hepatosplenomegaly.

The biological assessment showed: anemia 7g/dl (normochromic normocytic regenerative), white blood count was 6770/mm3 lymphopenia 600 /mm3, thrombocytopenia: 60 000/mm3, PT: 55%, cytolysis: ASAT: 8 times upper normal limit (ULN), ALAT: 4 *ULN. cholestasis: PAL: 2*ULN and GGT: 8 * ULN with total bilirubin at 82 with direct bilirubin at 62, hyponatremia at 121mEq/l, hypokalemia at 2.5 mEq/l an inflammatory syndrome with C-reactive protein: 60 mg/l, hyperferritinemia 2517 µg/l, hypertryglyceridemia: 2.96 g/l, fibrinogen was low1g/l, factor V:61% elevated LDH: 715 UI/l. In addition, an autoimmunity test and liver serology panel (A, B, C, E, HIV, EBV, and CMV) were negative. Abdominal ultrasound: steatotic liver, no dilation of intrahepatic bile ducts or main bile duct. A liver biopsy was performed as part of the etiological work-up, showing portal spaces enlarged by collagen fibrosis forming septa without regenerative nodules, hepatic trabeculae made up of balonized cells, and the site of inflammatory foci made up of lymphocytes and plasma cells, with the presence of macro vacuolar steatosis over 67%. The patient underwent a medullogram, which showed the presence of some haemophagocytosis images (Figure 2).

A cerebral CT scan was performed, given the weakness of the lower limbs and the headaches, and found to be normal. We decided to complete our investigation with a cerebral MRI, which showed cerebral tuberculosis miliaria and total cerebral venous thrombosis of the left transverse sinus extending to the sigmoid sinus and jugular vein. (Figure 3), (Figure 4).In light of the clinical-biological presentation, the diagnosis of paradoxical tuberculous reaction (PTR) triggered by the discontinuation of anti-TNF drugs, associated with MAS with hepatic manifestations, in this highly immunosuppressed HIV-negative patient was retained based on clinical, biological, and histological arguments. our multidisciplinary management (gastroenterologist - internist - pulmonologist and neurologist) consisted of continuing anti-bacillary drugs with a reintroduction regimen (ETHAMBUTOL 20 mg/kg /d OFLOXACINE 400 mg 2*/d, gradual introduction of ISONIAZIDE with a maximum dose of 200mg/d) over a period of 9 months, and early initiation of systemic corticosteroid therapy of 0.5 mg /kg /d and anticoagulant for cerebral venous thrombosis.The clinical and biological evolution was favorable, confirming our diagnosis, with clinical improvement after 3 weeks and a normalization of the liver tests after one month of treatment.

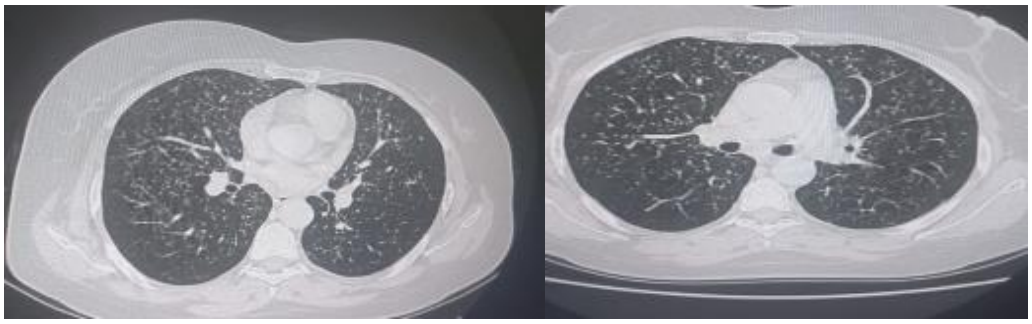


Figure 1 Axial unenhanced chest CT scan images showing several micronodules, uniformly distributed throughout the lung (hematogenous distribution), related to a tuberculous miliary

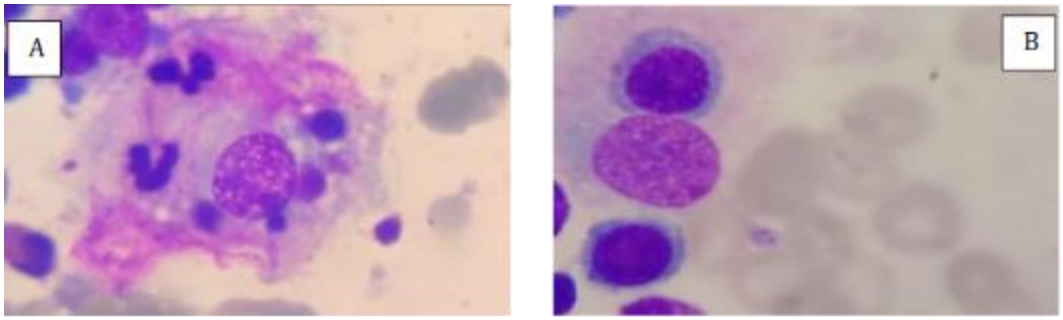


Figure 2 Images of hemophagocytosis (A, B) (myelogram using manual staining with MGG)

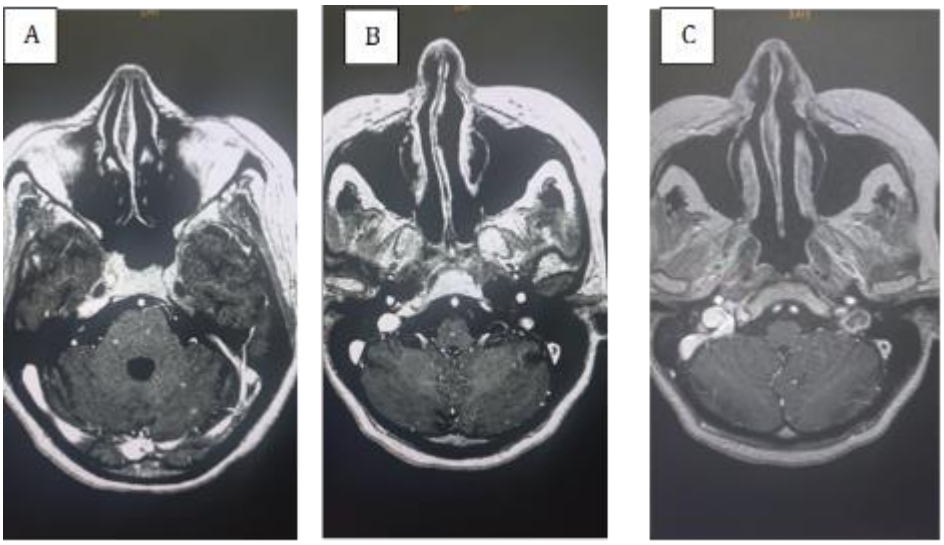
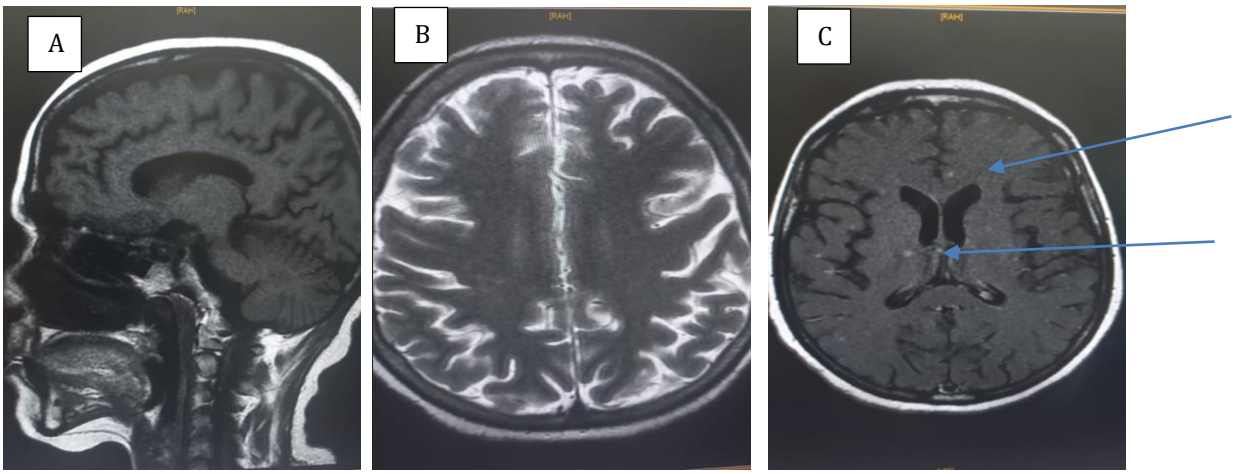


Figure 3 Filling defect of the left transverse sinus, extended towards the sigmoid sinus and the homolateral jugular vein (A, B, C: T1 axial injection)



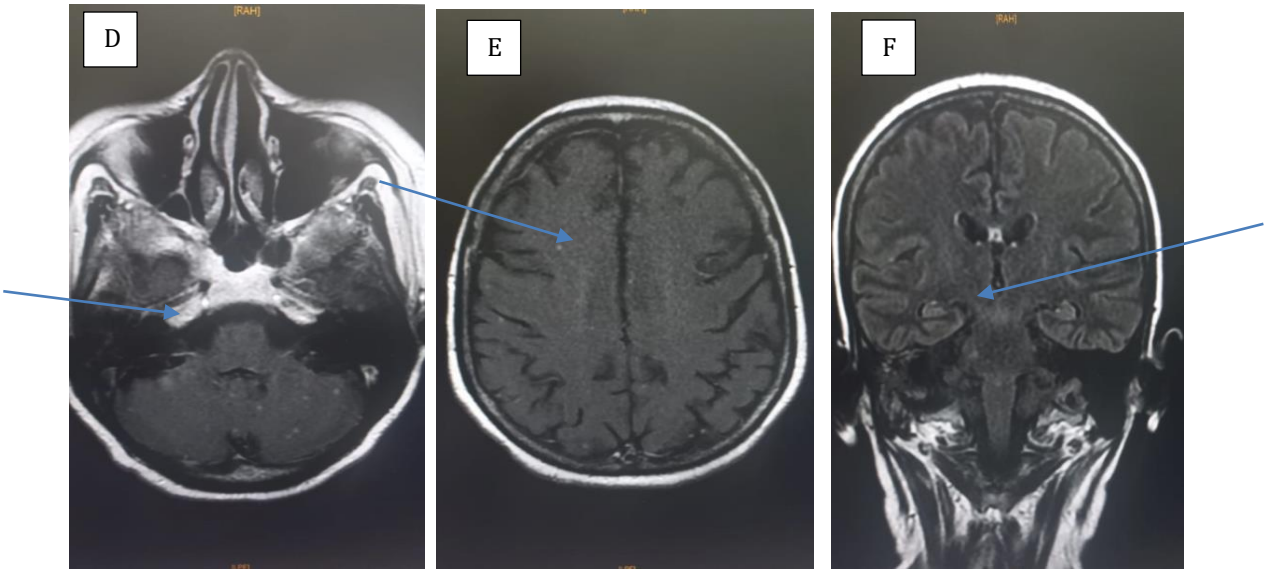


Figure 4 Punctiform and nodular supra- and infratentorial parenchymal lesions, predominant at the junction of the gray-white substance (A: sagittal T1, B: Axial T2, (C, D, E): axial T1 injected, F: coronal FLAIR

3. Discussion

We describe the case of our patient who presented with reactivation of tuberculosis during anti-TNFα therapy for her Behçet's disease followed by a paradoxical response to discontinuation of the TNFα antagonist complicated by macrophagic activation syndrome.

Reactivation of tuberculosis has been described following infliximab-induced immunosuppression[9]. In light of this observation, it would seem essential to perform systematic and repeated tests in the event of unexplained fever on anti-TNF therapy. Most cases of tuberculosis on anti-TNF therapy are reactivations of latent tuberculosis, which explains the short delay between the start of treatment and the onset of the disease [10], [11]. This mechanism is the most likely in this case, despite a normal pre-therapeutic workup.

In our case, good compliance with anti-tuberculosis treatment and discontinuation of infliximab improved our patient's clinical condition. However, after a period of 5 weeks, a clinical and biological decline was observed, with the appearance of a cerebral tubercular miliary. This clinical picture corresponds to a paradoxical reaction to anti-tuberculosis drugs, defined as the aggravation of pre-existing tuberculous lesions or the appearance of new tuberculous lesions in patients whose clinical symptoms had initially improved with anti-tuberculosis treatment [12]- [16].

Paradoxical tuberculosis reaction (PTR) with worsening tuberculosis is an elimination diagnosis that requires ruling out treatment failure due to poor compliance, antibiotic resistance, or drug interaction [17].

After stopping infliximab treatment, its effects persist for 3 to 4 weeks, depending on the dose [18]; this could explain the latency period between the start of treatment and the development of the paradoxical reaction described in our observation. There is no consensus on the exact time frame for confirming or refuting a diagnosis of PTR. However, published studies report that most cases occur between 14 and 160 days after the start of anti-tuberculosis treatment, with a median of 40 days [19]- [22]. Exceptional cases of later paradoxical reactions (up to 10 years) have been documented, but a delay of more than 6 months is atypical and should prompt reconsideration of the diagnosis [23], [24]. On the other hand, the presence of a free interval of at least two weeks (with initial clinical improvement followed by secondary worsening) is an important element in the diagnosis.

The prevalence of paradoxical tuberculosis reaction is estimated at between 5% and 30% of cases, depending on the site of infection and the patient's clinical background. [25]. In HIV-uninfected subjects, the presence of paradoxical disseminated tuberculosis and, in particular, neurological and/or lymph node involvement are risk factors for RPT. Other factors have been reported inconsistently in the literature (lymph node size, sweating, fever, anemia, hypoalbuminemia, lymphopenia). The role of gender as a potential risk factor has not been established [26].

No modification or interruption of anti-tuberculosis treatment is necessary in the event of a paradoxical reaction. Early recognition and treatment of this complication with systemic corticosteroids may result in a more favorable outcome [27]-[31]. However, some severe cases are refractory to corticosteroids, and symptoms of PTR persist and worsen. In such situations, alternative anti-inflammatory agents have been tried, and some case reports suggest the use of thalidomide [32], [33], tissue necrosis factor α antagonists [34], [35] and interferon-γ [36] for corticosteroid-resistant RPT. A pragmatic management algorithm synthesizing the available data and recommendations is proposed [37].

The originality of this observation lies in the exceptional nature of the "Infliximab- Tuberculosis paradoxical response-MAS" sequence. Macrophage activation syndrome (MAS) is an immune system dysfunction related to hyperactivation of medullary macrophages. The diagnostic criteria were recently redefined by a group of experts [38]. In our case, the diagnosis of MAS with hepatic involvement was retained on a set of clinical (fever), biological (pancytopenia, hyperferritinemia, hypertriglyceridemia, and hypo fibrinogenemia), and presence of hemophagocytosis in the bone marrow.

The link between infliximab treatment and MAS is paradoxical. On one hand, infliximab neutralizes TNF-alpha, a pro-inflammatory cytokine involved in MAS. On the other hand, MAS sometimes occurs after infliximab treatment. One possible hypothesis is that infliximab initially inhibits the macrophagic system, leading to compensatory phenomena. As the anti-TNF effect wears off, these compensatory phenomena may be exacerbated, leading to a "rebound effect" and the onset of MAS. The time to onset of MAS is 3 months after the last infliximab injection, which supports this hypothesis[39]. The association between MAS and tuberculosis is rare. Described since 1993, it occurs mainly in extrapulmonary forms of the disease, with frequent involvement of hematopoietic organs[40]-[42]. Several clinical observations have been reported, highlighting the rarity of this association and the difficulty of the diagnosis[43].

Hepatic manifestations of MAS (cytolysis, hepatocellular insufficiency, cholestasis) are found in 40-60% of cases [44]-[46]. In a retrospective study reporting 30 cases of MAS with hepatic involvement, hepatic manifestations were the reason for hospitalization in 19 of these patients [46]. The combination of fever, jaundice, hepatomegaly, or splenomegaly was present in 50% of patients. Elevated aminotransferases were a constant feature. Liver biopsy (LBP) is useful both for the histological diagnosis of MAS and for determining its etiology. The exact role of liver biopsy remains to be defined. It may be proposed as a first-line treatment for adult MAS in cases of rapidly progressive liver damage with no obvious diagnosis, or when coagulation abnormalities contraindicate bone marrow biopsy.The treatment of tuberculosis-associated macrophagic activation syndrome (MAS) is the subject of much debate. The use of corticosteroids or immunosuppressants is controversial due to the risk of worsening tuberculosis infection[47].

4. Conclusion

Initiation of anti-tuberculosis therapy in a setting of profound immunosuppression requires close monitoring. This monitoring aims to detect and manage potential complications, including anti-tuberculosis drug toxicity and paradoxical reactions to anti-tuberculosis drugs. The occurrence of macrophagic activation syndrome is a poor prognostic factor. The overlap between MAS and paradoxical reaction to anti-tuberculosis drugs makes it difficult to diagnose these two entities with certainty, but corticosteroid therapy is indicated in both cases. Our clinical presentation's goal is to alert clinicians that the management of a tuberculosis patient on Anti TNF is complex and requires multidisciplinary management, and close monitoring is essential to improve prognosis.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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