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Case Report

Pulmonary and intracranial miliary tuberculosis secondary to Behçet's anti-TNF alfa treatment[☆]

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ABSTRACT

Behçet disease is a rare vasculitis that affects vessels of different body parts, causing different kinds of manifestations. We report a case of a 47 years old woman who had a tumor necrosis factor alfa blocker prescription due to a Behçet's disease relapse. The patient then developed a cerebral and pulmonary tuberculous miliary due to immunodeficiency. The aim of this work is to show that tuberculosis infection is a common complication of the administration of tumor necrosis factor alfa blocker, and the importance to perform a tuberculosis screening before starting the treatment.

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Introduction

Behçet's disease, also known as Adamantiade–Behçet's syndrome, is a rare, systemic, and relapsing vasculitis that affects vessels (arteries and veins) of all sizes [1], with a venous tropism. The pathogenesis is poorly understood and still unknown [1], but many theories suspect an autoimmune mechanism, with an important inflammatory response to a possible bacterial or viral infection, in a genetically susceptible person.

It was first reported in 1924, by the Turkish dermatologist, Hulusi Behçet, who initially described it as a triad, with recur-

rent oral and genital aphthae, associated to hypopyon uveitis. However, as a multisystemic syndrome, it can also affect other body parts and have other manifestations, such as neurologic, pulmonary, cardiovascular, renal, and gastrointestinal affections.

The treatment of Behçet's disease depends on the clinical involvement and is classically based on corticosteroids and immunosuppressive drugs. Anti-tumor necrosis factor (TNF) alfa drugs are a good alternative for severe forms and are frequently used nowadays. It is a monoclonal antibody that binds with high affinity to the TNF alfa, causing a loss of bioactivity. However, their prescription increases the risk of infectious complications, especially severe tuberculosis, by the reactivation of a primary infection.

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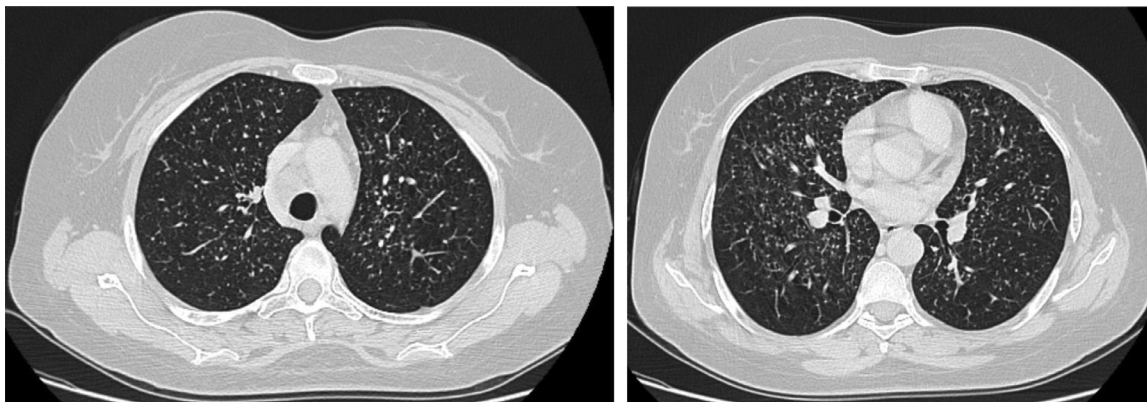


Fig. 1 – Axial unenhanced chest CT scan images showing several micronodules, uniformly distributed throughout the lung (hematogenous distribution), related to a tuberculous miliary.

Our case is about a patient, with cerebral and pulmonary tuberculous miliary, occurring during the treatment of a Behçet's disease by anti-TNF alfa.

We present this case to inform colleagues about the risk of tuberculosis reactivation in patients receiving immunosuppressive agents, and to clarify the management in case of its suspicion.

Case report

Forty-seven years old female patient, with a 4 years medical history of Behçet's disease, suffered from a bilateral recurrent uveitis, oral and genital aphthae, pseudofolliculitis, and a diffuse joint pain. She received corticosteroids and Azathioprine. The clinical evolution was marked by a relapse, which leads to the administration of anti-TNF alfa (Infliximab) in addition to corticosteroids.

The patient presented, few days after, a fever. Biological tests showed a lymphopenia. A thoracic radiography showed no particular abnormality, and a chest computed tomography (CT) scan was performed and showed micronodules uniformly distributed throughout the lung (hematogenous distribution), related to a tuberculous miliary (Fig. 1).

The patient received Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol association for 4 months, before being admitted in our structure. She had a cholestatic jaundice, with no other associated clinical sign. A hepatic cytolysis and cholestasis were found on her blood tests, and her prothrombin time was low (40%). Ultrasound was normal. Thus, the patient was hospitalized for the management of an anti-tuberculosis drug-induced hepatitis, and her treatment was stopped.

The clinical examination has shown a weakness of the 2 uppers limbs. Brain MRI showed multiple punctiform and nodular supra and infratentorial parenchymal lesions, predominant at the gray-white matter junction, unobservable in T1, with hyperintense signal on T2 and FLAIR weighted images, enhanced after contrast (Fig 2). A filling defect of the left transverse sinus, extended towards the sigmoid sinus and the

Table 1 – International criteria for Behçet's disease – point score system: scoring ≥ 4 indicates Behçet's diagnosis [10].

Sign/symptom	Points
Ocular lesions	2
Genital aphthosis	2
Oral aphthosis	2
Skin lesions	1
Neurological manifestations	1
Positive pathergy test*	1*

* Pathergy test is optional and the primary scoring system does not include pathergy testing. However, where pathergy testing is conducted one extra point may be assigned for a positive result.

homolateral jugular vein was also found, most likely due to his Behçet disease (Fig. 3).

The treatment decision was to continue anti tuberculosis regimen associated with anticoagulation therapy after normalization of PT, and corticosteroids. Anti-TNF alfa was stopped.

Discussion

Behçet's Disease is a vasculitis that affects vessels of all sizes and can affects every tissue and organ in the body. It affects young adults in their 20-30s, and men are more affected than women. Some authors describe a second peak in their 50-60s. Its prevalence is higher in Mediterranean, Middle Eastern, and Far Eastern countries, across the ancient silk trade route [1].

The diagnosis of this illness is based on clinical criteria (Table 1). No laboratory test is needed.

The neurological manifestations of the disease are frequent, severe, and found in almost 20 to 30% of cases. Sometimes, they can be inaugural, but in most cases, occur after 2 to 5 years after discovering the disease. Classically we distinguish 2 types of neurological impairment: parenchymal and non-parenchymal lesions [1,2].

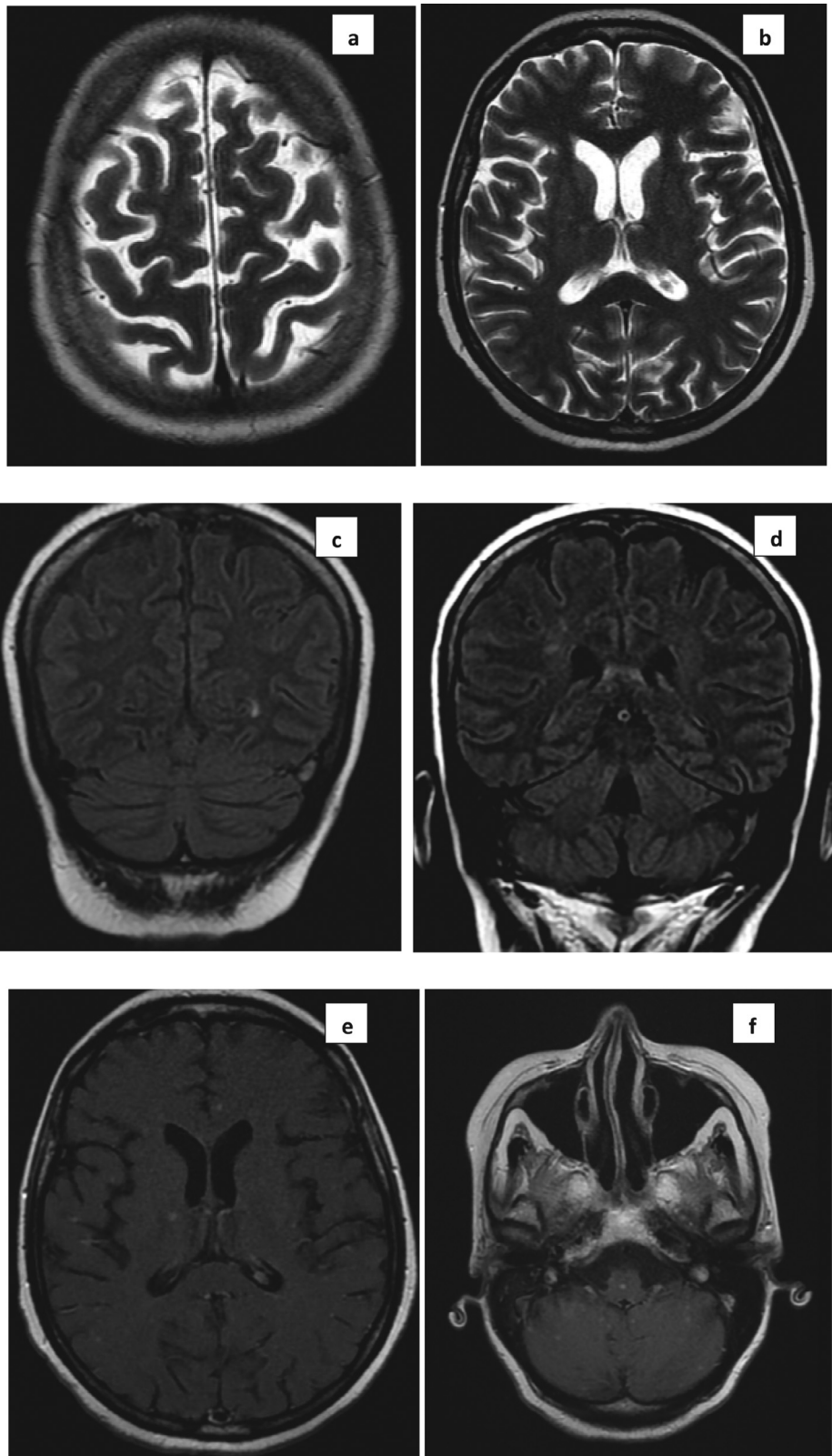


Fig. 2 - Multiple punctiform and nodular supra and infratentorial parenchymal lesions, predominant at the grey-white matter junction, with mild hypersignal on T2 WI (a, b) and FLAIR (c, d), enhanced after contrast (e, f).

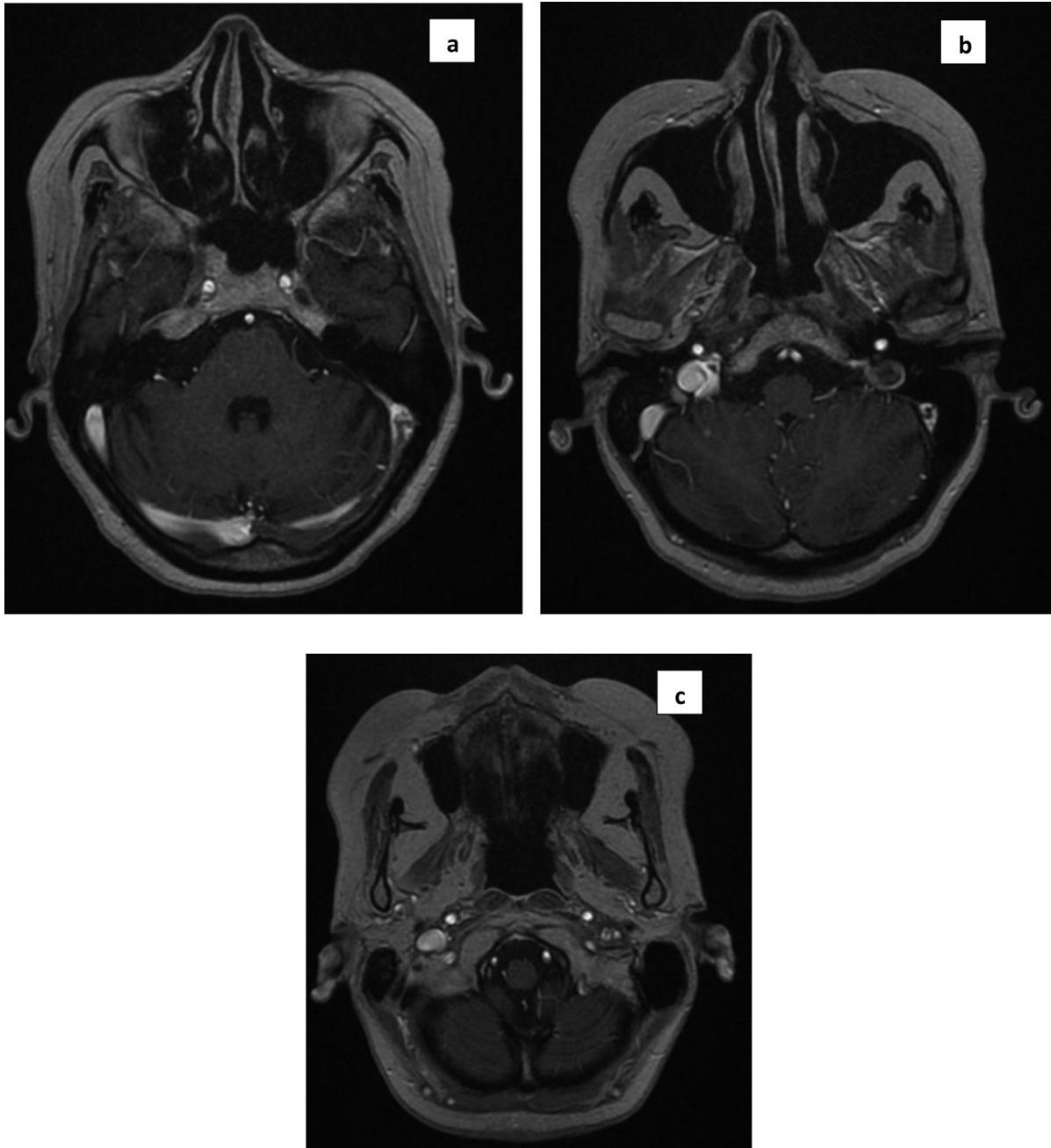


Fig. 3 – Filling defect of the left transverse sinus (a), extended towards the sigmoid sinus (b) and the homolateral jugular vein (c).

Parenchymal lesions (also called Neuro-Behçet) are more frequent and severe. It's dominated by a brainstem affection, especially midbrain and pons, followed by thalamic, basal ganglia, hemispheric and medullar lesions. The typical findings are small foci of hypersignal on T2, iso or hyposignal on T1. These lesions may be found in different shapes: circular, crescent-shaped, linear, or irregular [2,3].

Non-parenchymal lesions during BD manifestations are essentially:

- Vascular lesions (Angio-Behçet): with cerebral venous thrombosis, like in our case, and arterial vasculitis: stenosis, occlusions, dissections, and aneurysms.
- Aseptic meningitis [2].

Venous thrombosis is the most frequent non-parenchymal lesion found in BD. The most common filling defect sites are the superior longitudinal sinus, the transverse sinus, deep cerebral veins, and the cavernous sinuses [2,3].

The treatment and course are different between the 2 types. The prognosis is better in non-parenchymal involvement.

The management of this disease depends on many treatments, and has been improved by using TNF alfa inhibitors [4]. Despite their efficiency, there are some disadvantages regarding their safety.

The TNF seems to be one of the body's shields against tuberculosis [5]. It has a central role in the formation of granulomas, and its inhibition will cause the release of the tuberculosis bacillus and its dissemination. In fact, TNF alfa blockers are increasing the risk of tuberculosis reactivation [6]. Therefore, it is required to perform tuberculosis screenings before the prescription of TNF alfa blockers especially in endemic countries [5], and some authors insist on a systematical administration of isoniazid prophylaxis [5,6].

Tuberculosis miliary is a severe and rare form of tuberculosis. It is due to a hematogenous spread of the bacillus of Koch and it is accompanied by a hypercoagulability with high risk of thrombotic events [7] as in our case.

Central nervous system tuberculous involvement is the most severe form of the bacterial infection [8]. We can also divide the intracranial tuberculosis spectrum into 2 groups: meningeal and parenchymal tuberculosis. Meningeal tuberculosis can also be split into 2 forms: leptomeningitis (most common form of CNS tuberculosis, with leptomeningeal enhancement on post contrast T1 images) and pachymeningitis (focal or diffuse dural thickening).

On CT, intracranial tuberculous granulomas (or tuberculomas) appear as a round or lobulated lesion, with nodular or ring enhancement (target sign), associated to perilesional edema. This description is not specific to tuberculosis [8].

On MRI, in T1-weighted sequence MRI, the tuberculoma is iso-intense to hypo-intense compared to grey matter, with sometime a central region of hyperintensity representing caseation, and in T2-weighted sequence, it is iso-intense, or may sometimes have a central region of hypo intensity representing gliosis and abundant monocyte infiltration. Tuberculomas are surrounded by an area of hypersignal in T2, corresponding to perilesional edema. After gadolinium injection, an intense peripheral enhancement is observed. We generally notice a predominant localization at the grey-white matter junction [8,9]. Intracranial miliary tuberculomas involving the brain, cerebellum, brainstem, accompanied by tuberculous meningitis and miliary tuberculosis are very rare.

In this case, we have intracranial miliary tuberculomas in a patient with debilitated disease. The onset of the illness followed the treatment with Anti-TNF alfa. This association is not accidental; indeed, there is a large number of reports of tuberculosis in close association with the initiation of treatment with anti-TNF alfa.

Physicians should be aware of the increased risk of tuberculosis reactivation in patients receiving immunosuppressive agents. Before starting treatment with these agents, we should determine whether the patient has latent tuberculosis infection or not. On the other hand, if active tuberculosis is sus-

pected, treatment should be discontinued until the diagnosis is ruled out or the infection has been treated with antituberculosis agents.

Conclusion

TNF inhibition is considered a major advance in the treatment of Behçet. However, tuberculosis infection is a common and sometimes early complication of his administration. It can affect one or multiple organs. Thus, it is important to perform a tuberculosis screening before starting this treatment.

Patients treated with TNF alfa inhibitors should be warned of this risk and consult if signs suggesting tuberculosis (persistent cough, asthenia, weight loss, fever, and sweating) appear.

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