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Asthma Development Under Adalimumab Therapy: A Clinical Case Analysis

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Abstract **Case Report**

Adalimumab is a human monoclonal antibody against TNFa, frequently used in chronic inflammatory diseases such as inflammatory bowel disease. Anti-TNFa drugs are generally well tolerated, but in recent years their use has revealed significant adverse effects, in particular tuberculosis. Pulmonary involvement in these contexts is sometimes encountered, in association with an extra-intestinal manifestation of the disease, or secondary to therapeutics usedq such as anti TNFa. A 46-year-old female patient with cortico-dependent ulcerative colitis presented with progressive dyspnea and cough after initiation of Adalimumab therapy. Chest imaging was consistent with interstitial pathology, and functional analysis led to a diagnosis of asthma secondary to Humira. Symptoms improved a few months after discontinuation of anti-TNFa, and functional abnormalities subsequently disappeared almost completely after corticosteroid therapy. To our knowledge, this is the third clinical case of proven asthma secondary to anti-TNF therapy, with regression of symptoms on discontinuation of treatment, and after use of corticosteroid therapy. Clinicians using this treatment should be aware of this possible complication.

Keywords: Adalimumab, Asthma, Anti-TNF therapy, Corticosteroids, Ulcerative colitis.

INTRODUCTION

Anti-tumor necrosis factor (TNF) drugs are now widely used in many inflammatory diseases (inflammatory rheumatism, Crohn's disease, psoriasis), as TNF plays a major role in the inflammatory process. Nevertheless, these immunosuppressive therapies carry a major infectious risk, with numerous cases of tuberculosis reactivation in the lungs. However, alongside infectious complications, a few cases of side effects common to all these biological treatments, such as angioedema, bronchospasm and rare cases of asthma, have been described during drug administration.

OBSERVATION

This is a 46-year-old woman with a history of anxiety-depressive syndrome on treatment, with no personal history of asthma; followed up since 2014 for pancolitic hemorrhagic rectocolitis, cortico-dependent, resistant to 5ASA and intolerant of immunosuppressants (Azathioprine), requiring the patient to be put on Adalimumab (Humira40mg): 160mg at SO, 80mg at S2 then 40mg every two weeks. The digestive response was rapidly effective, but after a month from the start of treatment (3rd course), she began to present with a dry, hacking cough associated with unusual dyspnoea.

These symptoms, suggestive of bronchial hyperreactivity, progressively worsened, and the severity of the situation necessitated a therapeutic window and an etiological work-up. An infectious workup (sputum for BK, tuberculin TST) ruled out an infectious origin. Radiological workup (lung x-ray and high-resolution thoracic CT) ruled out parenchymal involvement secondary to the disease. Plethysmography and DLCO were performed to rule out alveolar involvement. The patient was put on inhaled corticosteroids with very good clinical and functional evolution; and the diagnosis of Asthma secondary to Humira was retained and the patient was put on bronchodilators as well as oral and spray corticosteroids with good clinical and radiological evolution.

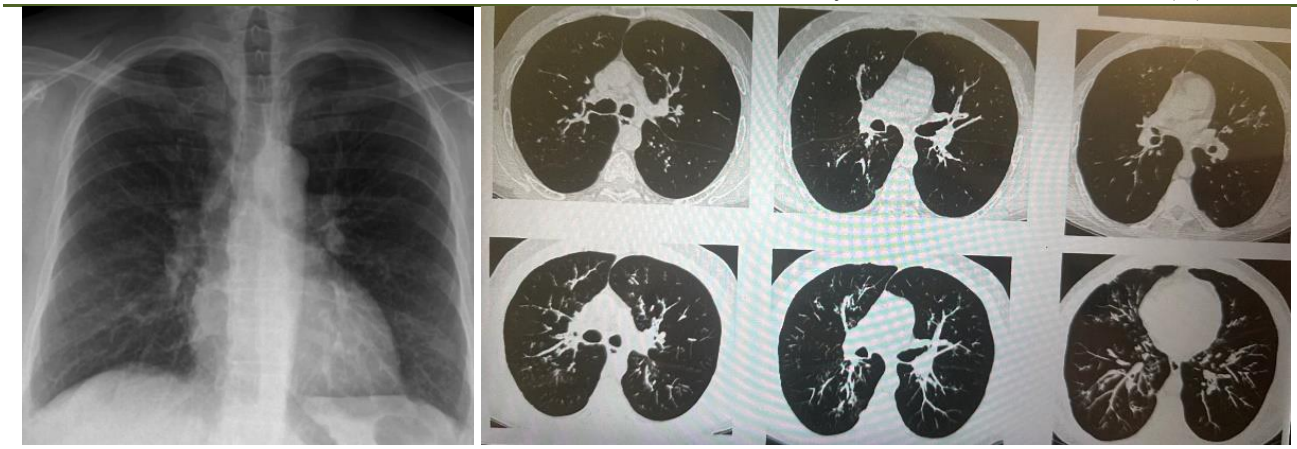

Figure 1 and 2: Chest X-ray and axial section of thoracic CT scan

DISCUSSION

Tumor Necrosis Factor is a pro-inflammatory cytokine which plays a role in the genesis of several pathologies. Anti-Tumor Necrosis Factor agents have therefore represented a breakthrough in the treatment of several inflammatory diseases. Among them are two monoclonal antibodies directed against soluble and membrane TNFa by binding to the p55 and p75 receptors: the partially murine infliximab, and the fully humanized adalimumab [1].

The main side-effects of this new therapeutic class are essentially infectious, with a major risk of tuberculosis reactivation (relative risk varies from study to study, but ranges from two to 16 for monoclonal antibodies) [2]. In addition, allergic reactions have been reported, especially with infliximab, and an increased risk of neoplastic or dysimmune disease is suspected (mainly lupus).

TNF plays a critical role in the amplification of bronchial inflammation in asthma. It is produced by innate immune cells. It can also be produced by smooth muscle cells. It is stored in mast cells and rapidly released during the IgE-dependent reaction. It activates adhesion molecules leading to the migration of eosinophils and neutrophils into the airways. It activates these cells and epithelial cells, leading to the release of cytotoxic mediators and oxygen radicals, resulting in chronic inflammation and remodeling. Independently of these effects, it also acts on bronchial hyper-reactivity.

Patients with refractory asthma have up-regulation of the TNF axis [3, 4].

Anti-TNF drugs have been investigated for asthma therapy; nevertheless, clinical studies have shown unsatisfactory outcomes.

Interestingly, there has been just a single documented instance of asthma produced by adalimumab, occurring in a lady undergoing treatment for rheumatoid arthritis [5, 6]. The authors propose that the production of Th1 cytokines results in a diminished clinical manifestation of asthma, since Th1 and Th2 processes counteract one another. The administration of anti-TNFa medications inhibits the Th1 response, eliminates the Th2 response, and results in the manifestation of clinical asthma symptoms.

In our case, the infectious hypothesis was ruled out, as there was no evidence of neoplasia or autoimmune pathology, no environmental exposure and no other drugs introduced. The clinical-radiological and functional picture was consistent with asthma, and clinical signs improved after Adalimumab was stopped and corticosteroid therapy initiated. The pathophysiology of these cases of anti-TNFa-induced asthma is unclear. Anti-TNFa drugs are thought to modify the cytokine environment, promoting the TH 1 response and, consequently, abolishing the expression of the response, leading to bronchial hyperreativitis. Inflamed bronchial tubes secrete more mucus, which also contributes to the expression of clinical signs of asthma [7, 8].

CONCLUSION

In conclusion, the appearance of respiratory manifestations under anti-TNFa treatment should, as a matter of priority, prompt a search for infection, particularly tuberculosis. However, signs of bronchial hyperreactivity should also raise the possibility of asthma. Knowledge of this condition is important, as in some cases it may become autonomous when anti-TNFa treatment is stopped, necessitating the introduction of corticosteroid therapy. Simple clinical and paraclinical monitoring using chest X-rays is therefore essential in patients on anti-TNFa therapy. If there is any doubt, additional investigations should be carried out, such as thoracic computed tomography and pulmonary function tests.

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