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Case Report

Asthma Appeared under Adalimumab

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Abstract

Adalimumab is a human monoclonal antibody used against Anti-tumor necrosis factor (TNFα), commonly in chronic inflammatory bowel diseases. The general tolerance of anti-TNF α is good, but they can cause significant adverse effects, particularly tuberculosis. A pulmonary attack in these context is sometimes encountered, in connection with an extra-intestinal manifestation of the disease, or secondary to therapies used as anti-TNF α.

A 54-year-old patient with ileocecal-coecale Crohn's disease dependent on corticotherapy, presented dyspnea of progression, associated with a cough, after introduction of treatment with adalimumab. Thoracic imaging was in favor of an interstitial pathology, and functional analysis allowed a diagnosis of secondary asthma due to adalimumab. The symptoms disappeared a few months after the cessation of TNF-α, and after recourse to a corticotherapy.

This is to our knowledge the second clinical case of proven asthma, secondary to anti-TNF-α treatment by adalimumab, with regression of symptomatology at cessation of treatment, and after use of a corticotherapy. Clinicians using this treatment should be aware of this possible complication of this treatment.

Keywords: *Adalimumab; Crohn's Disease; Asthma; Corticotherapy*

Abbreviations

TNF: Anti-tumor Necrosis Factor; BK: Koch *Bacillus*; IDR: Intra Dermo Reaction

Introduction

Anti-tumor necrosis factor (TNF) are now widely used in many inflammatory pathologies (inflammatory rheumatism, Crohn's disease, psoriasis), TNF playing a major role in the inflammatory process. Nevertheless, these immunosuppressive therapies have a major infectious risk, particularly in the tuberculosis reactivations. However, a part from infectious complications, some cases of side effects common to all these "biological" treatments with type of angioedema, bronchospasm and the rare cases of asthma described during the administration of the drug.

Case Report

A 54-year-old male, a chronic smoker weaned 25 years ago, without a personal history of asthma; Follow-up since 2006 for ileocecal Crohn's disease, dependent on corticotherapy, non-primary responder to Infliximab, having benefited in 2016 from a resection ileocecal following a sub-occlusive Syndrome secondary to a Stenosis of 06cm DAI with two enteric-enteral fistula pathways, post-operative endoscopic control has objectively relapsed the disease at the Rutgeertz I3-graded anastomosis, requiring the patient to be placed under Adalimumab: 160mg to S0, 80mg to S2 and 40mg every two weeks.

The digestive response was quickly effective, however, after one month of treatment onset (3rd cure), she began to present a dry, straight cough associated with unusual dyspnea. These symptoms suggestive of bronchial hyper reactivity gradually aggravated, and the severity of the situation imposed a therapeutic window and the realization of a causal balance. The infectious balance (finding BK in sputum, IDR with Tuberculin) eliminated an infectious origin. The radiological screen (lung Rx and high-resolution thoracic CT) excluded a secondary parenchymatous injury to Crohn's disease. A plethysmography with a DLCO was supplemented to eliminate an alveolar

impairment that may be secondary either to Crohn's disease or to Humira. The patient was put under corticotherapy inhaled with very good clinical and functional evolution; And the diagnosis of secondary asthma at Adalimumab was retained and the patient was put under bronchodilators as well as an oral corticotherapy and spray with good clinical and radiological evolution.

For Crohn's disease, the patient was maintained by the Azathioprine at a dose of 2.5 mg/kg with good clinical and endoscopic evolution.

Discussion

The Tumor Necrosis Factor is a pro-inflammatory cytokine that plays a key role in the genesis of several pathologies. Anti-Tumor Necrosis Factor have thus constituted an advance in the treatment of several inflammatory diseases and in particular Crohn's disease. Among them are two monoclonal antibodies directed against the soluble and membrane TNF by attaching to the p55 and p75 receptors: Infliximab, partially murine, and Adalimumab, completely humanized. The main side effects of this new therapeutic class are mainly infectious, including a major risk of tuberculosis reactivation (relative risk varies according to the studies, overall from two to sixteen for Monoclonal antibodies). In addition, allergic reactions have been reported mainly with infliximab, and an increase in the risk of neoplastic or dysimmunitary disease is suspected (mainly lupus).

TNF plays a critical role in initiating and amplifying bronchial inflammation in asthma. It is produced by cells of innate immunity. It can also be produced by smooth muscle cells. It is stored in mast cells and quickly released during the IgE-dependent. Its reaction activates the adhesion molecules leading to the migration of eosinophils and neutrophils into the airways. It activates and epithelial cells which leads to the release of cytotoxic mediators, oxygen radicals with the consequence of chronic inflammation and remodeling. Regardless of these effects it also acts on bronchial hyper-responsiveness. Patients with refractory asthma have an up-regulation of the TNF axis [1,2].

Thus, logically, anti-TNF have been studied in the treatment of asthma but the tests of anti-TNF in asthma have not yielded satisfactory results.

Paradoxically, a single case of adalimumab-induced asthma is found in the literature. In a woman treated for PR [3,4]. The hypothesis of cytokine production by TH1 is explicated by decrease in the clinical expression of asthma (as the TH1 and TH2 mechanisms cancel). The introduction of anti TNF Results in the suppression of the TH1 response hence the abolition of the expression of the TH2 response leading to the expression of clinical signs of asthma.

In our presentation, the infectious hypothesis was ruled out, there was no argument for a neoplasia or auto immune pathology, no environmental exposure, no other drug introduced.

The Physiopathology of these cases of "asthma" appearing under anti-TNF is unclear. The anti-TNF would modify the Cytokine environment, with the promotion of the response TH 1, hence the abolition of the expression of the TH2 response leading to a bronchial hyperreactivity thus, the bronchi, inflamed, will secrete more mucus, which Also participates in the expression of clinical signs of asthma [5,6].

Conclusion

In conclusion, the onset of respiratory manifestations under anti-TNF treatment must, as a priority, seek an infection, including tuberculosis. However, asthma must be evoked in the face of signs of bronchial hyperreactivity. His knowledge is important because in some cases this pathology can be empowered to stop the anti-TNF and require the introduction of a corticotherapy. A simple clinical and paraclinical surveillance by chest X-ray is therefore necessary in subjects under TNF treatment. In the slight test doubt, it will be necessary to complete the explorations with a thoracic CT scan, functional respiratory tests.

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