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ADALIMUMAB INDUCING LUPUS: CASE REPORT

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INTRODUCTION

In recent years, the use of immunobiological therapy in the treatment of chronic immunologically mediated inflammatory diseases has increased exponentially.

One of the main reasons is its proven effectiveness in the clinical and laboratory control of these diseases, being considered in the literature an important therapeutic advance.

Immunobiologicals are drugs produced by living organisms in complex processes, using molecular biology techniques. In rheumatology, most of these drugs are monoclonal antibodies or fusion proteins directed against specific targets implicated in the pathogenesis of autoimmune diseases [(1).]

Among the various agents available in rheumatological practice, TNF-alpha inhibitors (infliximab, adalimumab, etarnecept, golimumab and certolizumab) are the most widely used due to the pioneering nature of the molecules and the experience gained by rheumatologists in their daily practice.

Patients using immunobiologicals have a higher risk of opportunistic or serious infections (in Brazil, particularly tuberculosis) compared to patients receiving conventional synthetic Disease Modifying Antibody Drugs (DMARDs).

Several other adverse effects are well described in the literature, including mild systemic symptoms, infusion, hematological, neurological reactions, immunogenicity, occurrence of solid neoplasms and other less frequent ones. More recently, the induction of autoimmune diseases has been published. [(2).]

This report concerns a patient with spondyloarthritis with a 40-year follow-up, accompanied by the first author, who developed lupus after 3 years of using adalimamab.

CASE REPORT

Patient JCD, male, 29 years old, was admitted to the hospital in 1984 with asymmetric polyarthritis of the lower limbs for about two months, developing an episode of oral aphthae, genital lesions and conjunctivitis. He reported the occurrence of anterior uveitis.

On physical examination, in addition to polyarthritis, without axial involvement, he presented painful aphthae in the oral mucosa, typical circinate balanitis and plantar lesions (blenorrhagic keratoderma).

The diagnostic hypothesis of complete Reiter's Syndrome (currently called spondyloarthritis – reactive arthritis) was made, and he was treated with low doses of corticosteroids, antibiotics and non-hormonal anti-inflammatory drugs (indomethacin).

The clinical and laboratory picture evolved with episodic joint crises, presenting initial and progressive symptoms of axial involvement, mainly cervical spine.

After four years of evolution, the disease showed significant activity, being treated with a pulse of methyl prednisone for three days and introduced oral sulfasalazine and methotrexate, in weekly doses, in addition to the maintenance of indomethacin, showing excellent evolution, with episodes of cervical pain and occasional arthralgias.

In 2017, he developed important clinical and laboratorial activity, with severe polyarthritis and cervicalgia, and therapy with subcutaneous adalimumab was introduced twice a month, with an excellent response for three years.

In 2020, he presented significant respiratory symptoms and was admitted to another service with suspected Covid-19 Syndrome, presenting significant lung involvement. The SARS-CoV-2 test was negative through RT-PCR.

We re-evaluated the patient and he presented a significant decline in general condition, polyarthritis of large and small joints, persistent fever, with significant pulmonary involvement.

In the laboratory investigation, he presented normochromic and normocytic anemia (Hb = 9.8 g/Dl, Hto = 32%), leukocytes - 5200 mm3, platelets 150000 mm^3, ESR - 125 mm, CRP - 58 mg, positive FAN 1/640 with homogeneous pattern, creatinine 0.8 mg/Dl, negative anti-DNA antibody, as well as other autoantibodies investigated and Type I urine without alterations.

Pulmonary computed tomography showed interstitial involvement with small bilateral pleural effusion, and the echocardiogram showed pericarditis, with discrete pericardial effusion.

Adalimumab was suspended and oral prednisolone was introduced, 1 mg/kg of weight/day, with rapid clinical and laboratory response.

The anti-histone antibody test was positive, confirming the diagnostic hypothesis of drug-induced Lupus-like.

Since the only immunobiological available is golimumab, also an anti-TNF-alpha inhibitor, in a shared decision, we decided to introduce it while maintaining oral methotrexate, weekly, which has shown excellent progress to date.

DISCUSSION

The first report of drug-induced lupus erythematosus was described by Hoffman in 1945, when a patient presented an uncharacteristic hypersensitivity reaction after treatment with sulfadiazine [3]. From this report onwards, publications multiplied, and today there is an extensive list of agents involved in this adverse effect, capable of inducing a clinical picture, also known as lupus-like.

The adverse effects of immunobiologicals can be classified as early or late. Opportunistic or serious infections are more frequent in the first year of treatment [1], while, for example, the development of solid tumors is later and described in long *follow-up* of patients.

Knowledge of the patient profile, careful risk/benefit assessment and effective use of Evidence-Based Medicine (EBM) concepts allow for rationalization of procedures that make immunobiological therapy increasingly safe and effective.

Key elements for this careful evaluation include age greater than 60 years, chronic obstructive pulmonary disease, chronic renal failure, use of glucocorticoids (prednisone equal to or greater than 7.5m) [1].

There is, however, a significant percentage of patients who do not respond to immunobiological treatment in clinical practice. In general, we can distinguish two types of treatment failure: primary, when there is no response to the therapy introduced, and secondary, when an adequate response initially occurs, but over time the disease becomes active again [4].

It is a known fact that every biological agent is potentially immunogenic. The production of anti-drug antibodies can neutralize or remove the circulating immunological agent that may reduce the effectiveness of the desired effect or induce adverse effects [4].

The immunogenicity of a therapeutic protein can have profound effects on the safety of the product. Loss of efficacy and changes in the safety profile are not necessarily correlated, requiring constant long-term epidemiological surveillance.

There is no known pathogenetic mechanism to explain the emergence of autoimmune diseases with the use of TNF antagonists. In recent studies, some proposals have been described to explain their pathophysiology. The main and most accepted one is that

these blockers act by inducing apoptosis in inflammatory cells. The consequent release of antigenic particles during this process can stimulate the development of autoantibodies in susceptible individuals. The justification for this proposal is the significant increase in nucleosomes after treatment with infliximab[5].

In the last decade, publications have demonstrated the real possibility of developing autoimmune diseases resulting from the use of immunobiologicals [6].

Recently, Jeries et al.[7] described a case of lupus with the presence of cutaneous vasculitis and mononeuritis multiplex in a patient with ankylosing spondylitis. The neurological manifestation occurred two weeks after the use of infliximab. The patient then presented with cutaneous vasculitis and positivity for antinuclear antibodies and positivity for anti-double-stranded DNA. Infliximab was discontinued and high doses of corticosteroids, hydroxychloroquine and mycophenolate mofetil were introduced, evolving with complete recovery from the drug-induced lupus condition.

Santos et al describe two cases of anti-TNF-induced lupus and review the literature [8].

Other publications describe other characteristics of the clinical pictures and agents, such as the article published by Shidahara et al., describing lupus induced by a biosimilar drug to infliximab with nephritis, lupus in children [10] , lupus in the treatment of psoriasis[11] and inflammatory bowel disease[12].

CONCLUSION

Drug-induced lupus is a condition that has been described for a long time, and the specialized literature points to several well-known drugs in this regard. It is well recognized that procainamide and hydralazine present a high risk of developing drug-induced lupus. The clinical characteristics are very similar to systemic lupus erythematosus, except for a more insidious presentation and complete resolution with drug withdrawal.

In the present case, the patient presented an important clinical picture, with severe systemic manifestations after three years of use of the anti-TNF alpha agent (adalimumab). The presence of anti-histone antibody, in our report, in addition to the full clinical recovery, reinforce the hypothesis of drug-induced lupus.

There are published studies with other immunobiological agents, however, research protocols and effective epidemiological surveillance are necessary since they have been increasingly used in immunologically mediated diseases.

We declare no conflict of interest

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