Case report

Response to rituximab in a patient with Wegener's granulomatosis refractory to conventional therapies

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INTRODUCTION

Wegener's Granulomatosis (WG) is a systemic granulomatous vasculitis that mainly affects the upper and lower respiratory tracts as well as the kidneys. It has two main clinical forms of presentation: generalized and localized. The use of cyclophosphamide has revolutionized the treatment of WG and is considered the drug of choice for control of this disease, however its toxicity limits its use for prolonged periods of time. The appearance of new drugs, including biologic therapy, has become a hope for patients who do not respond to conventional therapy or who have developed treatment-related complications.

Case report

We present the case of a 35 year old male patient with a personal history of intolerance to cotrimoxazole, systemic arterial hypertension in treatment with enalapril; chronic sinus disease and naso-sinus polyps that had undergone surgery on several occasions; bronchial hyperreactivity and WG diagnosed in 1999 on the basis of a nasal mucosa biopsy which was compatible with granulomatous necrotizing vasculitis; he also presented hemolytic anemia, mononeuritis multiplex, proptosis of the right eye, left orbital pseudotumor and positive anti-neutrophil cytoplasm antibodies (c-ANCA) with a titer of 1/640 with the presence of anti-proteinase 3 antibodies (72 U/ml). He received treatment with oral cyclophosphamide (2 mg/kg/day; approximately 36 g of accumulated dose) and oral steroids (1 mg/kg/day, in a descending pattern until reaching an approximate calculated dose of 8.5 g) for one year, achieving complete remission of the initial
manifestations. In 2001 he suffered a relapse of the nasal and sinus symptoms as well as left orbital pseudotumor, with a Birmingham Vasculitis Activity Score of 28 out of 63, and was treated with oral steroids at a dose of 1 mg/kg/day in a descending pattern (reaching an accumulated dose of 5 g of prednisone) and intramuscular methotrexate at a dose of 20 mg a week. We opted not to use cyclophosphamide in this occasion to avoid complications due to treatment. Methotrexate had to be suspended after a year due to elevated liver enzymes and, in order to maintain remission, he was started on azathioprine (150 mg/day), maintained for 18 months. In January 2008, while the patient was receiving no steroids or immunosuppressants and after not having visited his physician for at least 2 years due to work-related problems and having moved to another city, the patient was seen again with nasal and sinus symptoms that had lasted for at least 6 months. A computerized tomography (CT) scan of the nasal sinuses and facial bones was performed, finding occupation of practically all of the etmoidal cells, the sphenoid sinus as well as the frontal and maxillary sinuses and the nasal cavity, with lack of visualization of the median concha and destruction of the totality of the nasal septum and the median walls of the maxillary sinus and the bony trabecula of the etmoidal cells.

Discussion

WG is a necrotizing vasculitis that affects the upper and lower respiratory tract and, in most cases, the kidneys. Nasal disease is seen in up to 80% of cases and includes inflammation of the mucosa with nasal obstruction, ulcers and perforations of the septum, nasal bleeding and "saddle nose" deformity. Treatment is based on high dose steroids and associated immunosuppressants. The use of cyclophosphamide has revolutionized the treatment of WG type vasculitis and is considered the drug of choice for the control of the disease; however, its use is limited in the long term. The appearance of other drugs (such as mycophenolate mofetil, methotrexate, azathioprine, cyclosporine or immunoglobulins), local radiotherapy and biological treatments have become a beacon of hope for patients who do not respond to conventional therapy or who have developed treatment derived complications. B cell eradication with rituximab (4 weekly doses of 375 mg/m² or, occasionally, 2 doses of 1 g every 2 weeks) has induced complete but temporal remission in patients with ANCA associated vasculitis that have been proven resistant to conventional treatment in small studies improving disease in patients with subglottic stenosis, retrobulbar granulomas and sinus affection unresponsive to conventional therapy. However, cases in which granulomatous manifestations predominate do not seem to respond to rituximab. It repeated administration has been suggested and proven to be effective, although complications and adverse events might arise, making more studies on the subject necessary. Current trials are dealing with determining the effects and new indications for rituximab.

References