

Relapsing Polychondritis Associated With a Lymphoplasmocytic Lymphoma and Eritema Nodosum

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Relapsing polychondritis is a disease of unknown etiology characterized by episodic inflammation of cartilaginous tissues. More rarely, it has been described as a paraneoplastic phenomenon mainly associated with myelodysplastic syndromes or other haematologic diseases. We present a case of relapsing polychondritis associated to low degree lymphoplasmocytic lymphoma whose picture was punctuated by cutaneous erythema nodosum and anterior uveitis. The clinical evolution was satisfactory with glucocorticoids and rituximab treatment.

Key words: Relapsing polychondritis. Paraneoplastic syndrome. Lymphoma. Erythema nodosum.

Policondritis recidivante asociada a linfoma linfoplasmocítico y eritema nodoso

La policondritis recidivante es una enfermedad de etiología desconocida que se caracteriza por episodios recurrentes de inflamación de los tejidos cartilagineos. En raras ocasiones se ha descrito como un cuadro paraneoplásico, principalmente asociado a síndrome mielodisplásico y a diferentes tipos de neoplasias hematológicas. Presentamos un caso de policondritis recidivante asociada a linfoma linfoplasmocítico de bajo grado que, en su evolución, presentó afección cutánea en forma de eritema nodoso y uveítis anterior. La evolución clínica posterior fue satisfactoria, con tratamiento inmunosupresor con glucocorticoides y rituximab.

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Manuscript received October 4, 2005; accepted for publication March 21, 2006.

Palabras clave: Policondritis recidivante. Síndrome paraneoplásico. Linfoma. Eritema nodoso.

Introduction

Relapsing polychondritis is an unfrequent multisystemic disease with an unknown etiology, characterized by the recurrent inflammation of cartilage tissues and that in the long term lead to their destruction. It basically affects the ears, the nose, peripheral joints and the tracheobronchial tree.^{1,2} The eye is also a target tissue, in the form of scleritis and uveitis.³ The skin manifestations of relapsing polychondritis are less frequent and erythema nodosum is one of the possible manifestations.⁴ In 30%-35% of the cases it is associated with other autoimmune or systemic diseases.^{1,2} As other rheumatic disease, relapsing polychondritis has also been described as a paraneoplastic syndrome, associated mainly to myelodysplastic syndrome, myelomas and lymphomas.⁵

We describe the case of a patient with the diagnosis of relapsing polychondritis and low grade lymphoplasmocytic lymphoma that, during its course, presented an episode of anterior uveitis and erythema nodosum.

Clinical Case

A 67 year old male was sent by his family physician for study after presenting a 4 month course of consistent, and self-limited episodes of monochondritis on both ears accompanied by intense fatigue and a 39°C fever. The patient had a history of smoking and had been diagnosed with emphysema. On examination, he presented left ear inflammation (Figure). Cardiac sounds were normal. On pulmonary examination rales could be heard in both lung bases. There were no cervical, axillary or groin lymphadenopathies. The rest of the general exploration, including skin and joints, was normal. When



Figure 1. Acute chondritis of the left ear.

laboratory testing was done there was macrocytic anemia (hemoglobin, 11.6 g/dL; mean cell volume [MCV], 107 μ L), with a normal white blood cell count and normal platelets. C reactive protein (CRP) was 5.6 mg/dL, and the erythrocytation rate was (ESR), 98 mm in the first hour. Tumor markers were negative and the thyroid hormones were normal. Antinuclear antibodies (ANA), anti-ENA, ANCA, and the rest of the humoral immunity tests were negative. Repeated cryoglobulin testing was negative. The chest x-ray showed a discreet diffuse interstitial infiltrate and a thoracoabdominopelvic tomography showed subcarinal calcified adenopathies as well as lymph nodes of a non significant, in a prevascular situation and in the superior mediastinum. Apart from this, very marked panacinar emphysema was noted, especially in both of the superior lung lobes. The peripheral blood smear evidenced 12% immature granulocytes protein electrophoresis showed a gamma monoclonal band. Immunoglobulin quantification evidenced an elevation of IgM (683 mg/dL), with normal IgG and IgA. Serum immunoelectrophoresis showed an IgM monoclonal kappa spike. A bone marrow aspirate was done and an increase in the lymphocyte count was found, mainly B lymphocytes CD19, with kappa clonality, with a brilliant CD20 phenotype, CD22⁺, CD24⁺, CD5⁺, CD23⁻, FMC7⁺, CD10⁻, CD38⁺, CD11c⁻, CD103⁻, correlating with IgM kappa low grade lymphoplasmocytic lymphoma. Hematopoiesis and the platelet series were normal.

Initially the patient was treated with prednisone 50 mg/day, with an important improvement of the symptoms and the analytical parameters. When we attempted to diminish the steroid dose the patient had a new onset of chondritis accompanied by 38.5°C fever, associated to unilateral anterior uveitis, confirmed by the ophthalmology department.

After the diagnosis of low grade lymphoplasmocytic lymphoma, treatment with prednisone at a dose of 1 mg/kg/day was instituted, as well as anti-CD20 monoclonal antibody therapy with rituximab (Mabthera®), associated with osteoporosis limiting measures based on calcium supplements and vitamin D at a physiologic dose, apart from risedronate. The clinical and laboratory evolution was satisfactory: IgM diminished to 309 mg/dL (paraprotein reduction >50%). Eight months after diagnosis, the patient presented nodular, hard and painful skin lesions in a pretibial distribution. A biopsy was done and a diagnosis septal panniculitis was done and was compatible with erythema nodosum. Further evolution has been satisfactory from the point of view of his primary illness but has presented, as complications, a moderate non-traumatic vertebral compression of D₁₂ and pneumonia due to *Pseudomonas aeruginosa* that had to be treated in the hospital and was successfully cured with standard treatment.

Discussion

Relapsing polychondritis is an infrequent illness characterized by inflammation and destruction of the cartilage. It affects men and women equally and is more prevalent in caucasians.^{1,2} It is manifested mainly in the fifth and sixth decades of life and, though its cause is unknown, certain genetic predisposition and an association to HLA-DR4 has been observed.⁶

The most frequent manifestations in relapsing polychondritis are constitutional symptoms such as fatigue, loss of appetite, weight loss and fever. Cartilage affection occurs in 85%-95% of cases depending on the series reviewed.^{7,8} Swollen tissues most frequently affected are the ears, the nasal septum, the larynx and the upper respiratory airway, the latter especially in women. Repeated episodes can lead to its destruction and in advanced fases can produce a marked deformity on the nose and the ears ("saddle" deformity on the nose and "cauliflower" ears). Respiratory complications are the first cause of mortality in this illness and oscillate between 10% and 50% of cases.^{2,7}

Joint manifestations occur in 50 to 80% of cases in the form of oligoarthritis and/or acute migrating polyarthritis, asymmetric and non erosive.^{7,8} Eye affection occurs in 18% to 22% of the patients. The most common manifestations are scleritis and episcleritis, as well as keratitis, uveitis, and iritis with a lesser frequency.³ In a review of the medical literature we have found a recently diagnosed patient with relapsing polychondritis and exophthalmos, in whom a later diagnosis of MALT type orbital lymphoma was done.⁹ In 36% of patients there can be skin lesions, generally non-specific and that

sometimes can simulate those seen in Behçet's disease. The histological examination of these lesions commonly yields vasculitis, skin vessel thrombosis, and septal panniculitis.⁴ There is no correlation between the skin affection and that of the cartilage. The appearance of skin lesions is significantly more frequent in those cases in which the relapsing polychondritis is associated to myelodysplastic syndromes.

Cardiovascular affection is not as infrequent (24%-52%) and represents the second cause of death. The most characteristic manifestations are aortic and mitral valve insufficiency, aneurisms and vasculitis of small to large caliber vessels in different organs (central and peripheral nervous system, renal and mesenteric arteries, among other localizations).

There are 6 criteria described by McAdam in 1976, used to make the diagnosis of relapsing polychondritis: bilateral ear chondritis, non erosive seronegative inflammatory polyarthritis, nasal chondritis, eye inflammation, respiratory tract chondritis, and audiovestibular affection. Three criteria are needed for diagnosis of the disease.⁹ Damiani and Levine¹⁰ have reviewed these criteria recently, including histologic confirmation and/or the response to immunosuppressive treatment, with at least one of the clinical criteria proposed by McAdam being enough, or chondritis in 2 or more anatomically separate regions. This notwithstanding, today the histological criteria is widely discussed for diagnosis, except in doubtful cases, because of the great risk for perichondral infection. Relapsing polychondritis is associated to other systemic or autoimmune diseases in 30%-35% of cases: membranoproliferative glomerulonephritis, mixed essential cryoglobulinemia, systemic vasculitis, systemic lupus erythematosus, rheumatoid arthritis, lung fibrosis, autoimmune thyroiditis, and/or Sjögren's syndrome.^{1,2} Less frequently it has been described as a paraneoplastic phenomenon, especially related to myelodysplastic syndromes, monoclonal gammopathies, and/or lymphomas.^{2,5,11-14} The association with myelodysplastic syndromes is more frequent in older age males and can be manifested with skin lesions as is the case with our patient.

Our patient started with the usual clinical symptoms and signs of polychondritis and responded to steroid treatment, fulfilling the criteria modified by Damiani and Levine. The diagnosis of low grade lymphoplasmocytic lymphoma with associated IgM kappa monoclonal gammopathy was reached afterward and was treated with an increase in the steroid dose. During his course of illness he developed eye and skin manifestations in the form of uveitis and erythema nodosum, which tend to be infrequent. Due to the persistence of the constitutional signs and symptoms and the lymphocyte phenotype we decided to associate monoclonal anti-CD20 antibodies to his treatment

(rituximab), at a usual dose for lymphoma, showing an objective therapeutic response and remission of the symptoms. This response is in agreement with the role that rituximab has in the treatment of lymphoplasmocytic lymphoma and Waldenström's macroglobulinemia, in which it constitutes the indicated therapy when cytopenia is present.¹⁵

Posterior evolution has been satisfactory though some complications, such as a spontaneous vertebral collapse of D₁₂, in spite of preventive treatment with calcium supplements and risedronate, as well as pneumonia due to *P aeruginosa*, possibly facilitated by the underlying neupathy and the immunosuppression caused by therapy with steroids and rituximab, have been seen.

In conclusion, when faced with a diagnosis of relapsing polychondritis with skin manifestations in an older patient and/or a poor response to initial steroid treatment, we believe that a possible association with myelodysplastic syndrome or other hematologic malignancies must be ruled out. In the case that a low grade lymphoma is the underlying cause, treatment with rituximab is a good therapeutic option.

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