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Angioedema and Waldenström macroglobulinemia

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KEYWORDS

Angioedema.
Waldenström's macroglobulinemia.
Lymphoproliferative diseases.

Abstract:

We describe a patient with angioedema diagnosed with Waldenström's macroglobulinemia in complete remission after adequate therapy. In this type of patients, lymphoproliferative diseases must be taken into account in the differential diagnosis of angioedema.

PALABRAS CLAVE

Angioedema.
macroglobulinemia de Waldenström.
Enfermedades linfoproliferativas.

Angioedema y macroglobulinemia de Waldenström

Resumen:

Describimos a un paciente con angioedema diagnosticado de macroglobulinemia de Waldenström en remisión completa después de una terapia adecuada. En este tipo de pacientes hay que tener en cuenta las enfermedades linfoproliferativas en el diagnóstico diferencial del angioedema.

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Introduction

Acquired angioedema is a disorder, characterized by recurrent attacks of non-itching, self-limiting subcutaneous edema (or angioedema) and can present with life-threatening airway obstruction or with abdominal symptoms that mimic an acute abdomen, as upper respiratory tract and gastrointestinal tract are sites that are most often affected. Deficiencies in the inhibitor of the first component of human complement (C1-Inh) leading to angioedema can be either acquired or hereditary[1].

In acquired angioedema the activity of C1-Inh is decreased and, subsequently, serum complement factors 4 (C4) is low. Due to decreased levels of C1-Inh there is a continuous autoactivation of C1 leading to unrestrained activation of the classical pathway of the complement system. C1-Inh also inhibits factor XIIa and kallikrein, proteases belonging to the contact pathway. Increased vascular permeability due to massive bradykinin release via the contact pathway is thought to be the primary cause of symptoms in acquired angioedema[2].

Mechanisms causing acquired C1-Inh deficiency have been broadly investigated. Historically, acquired angioedema was defined as a constellation of syndromes, due to the many associated conditions such as lymphoproliferative diseases, systemic lupus erythematosus, primary myelofibrosis, autoimmune haemolytic anaemia, cryoglobulinaemia and liver hydatidosis[3]. Angioedema usually arises in the setting of an uncontrolled clonal proliferation of B lymphocytes. However, the mechanism by which clonal B cell disorders lead to depletion of C1-Inh and angioedema remains incompletely understood.

In Figure 1, the skin manifestations of a patient with Waldenström disease.

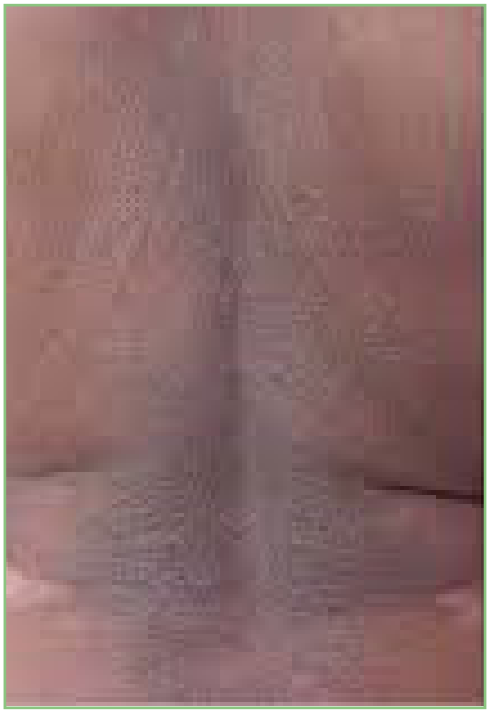

Figure 1. Cutaneous manifestations in the Waldenström disease.

Case report

A 69 year old male with a history of rheumatic heart disease and epilepsy presented to our hospital with 6 months history of recurrent swelling of the lips, without any associated urticaria. He had no evidenced triggers and his symptoms failed to respond to oral prednisone. He was taking acenocoumarol and bisoprolol since two years ago and lamotrigine since one month ago.

Physical examination was unremarkable with the exception of frequent angioedema. As part of the evaluation for her angioedema we performed a skin prick test with a series of common aeroallergens, foods (Bial Aristegui) and lamotrigine, with negative result. A complete blood count and biochemical examinations (glucose, urea, creatinine, uric acid, total proteins, AST, ALT, alkaline phosphatase, LDH, IgG, IgA and TSH) were normal. ANA, hydatid serology, HBs antigen, HBc antibody and HVC antibody were negative. Total IgE: 9.85 kU/L (normal range 0-100 kU/L). C3: 106 mg/dL (normal range 90-180 mg/dL), C4: 26.2 mg/dL (normal range 10-40 mg/dL), C1 inhibitor: 24.7 mg/dL (normal range 15-34 mg/dL), IgM: 1360 mg/ dL (normal range 40-230 mg/dL), Light Chains Kappa: 374 mg/dL (normal range 170-370 mg/dL), Light Chains Lambda: 178 mg/

dL (normal range 90-210 mg/dL), Kappa Lambda ratio: 2.101 (normal range 1.35-2.65). ESR: 35 mm (normal range 3-10 mm). Proteinogram showed a monoclonal aspect band in which a band characterized by IgM Kappa was detected. The patient was referred to Hematology Unit and he was diagnosed with Waldenström Macroglobulinemia. He was treated with rituximab, cyclophosphamide and dexamethasone, six cycles, with complete resolution of lips angioedema.

One year after completing the chemotherapy treatment, the patient remains asymptomatic, IgM: 198 mg /dL (normal range 40-230 mg/dL), with a proteinogram without appreciating monoclonal bands. However, the monoclonal IgM band reappeared one year and a half after completing the chemotherapy treatment, having remained stable and not symptomatic until now.

Figure 2 shows the monoclonal component contained in the proteinogram in urine

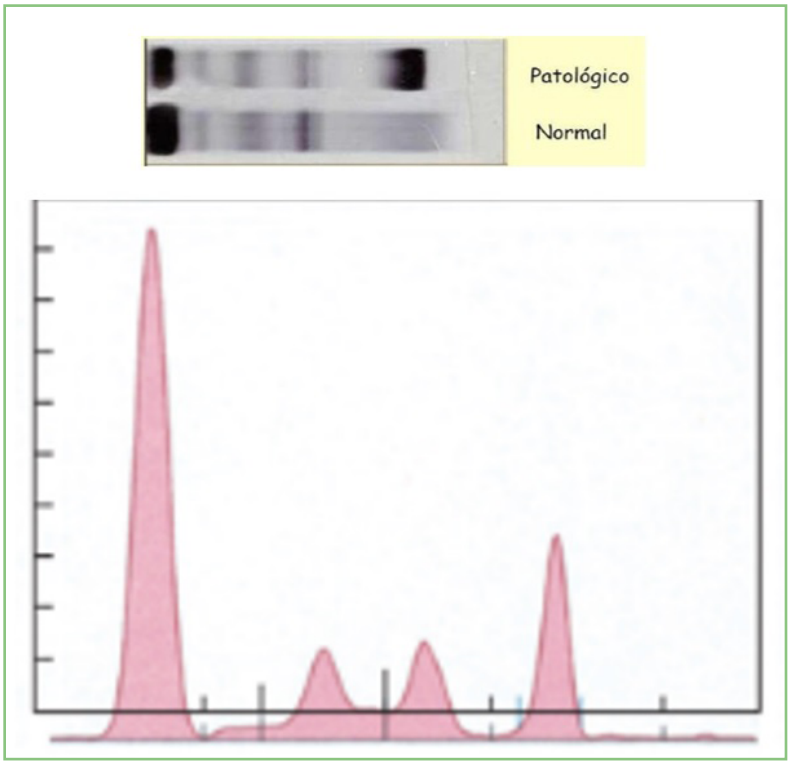

Figure 2. Laboratory diagnosis of a patient with Waldenström macroglobulinemia. Urine proteinogram.

Discussion

Angioedema without associated urticarial lesions suggests bradykinin-mediated pathophysiology and helps to narrow the differential regarding possible etiology. Angioedema is generally categorized into allergic, drug-induced, hereditary, acquired or idiopathic, based on etiology. Characteristic lab findings are associated with each category[4]. In contrast to hereditary angioedema, acquired angioedema is marked by the absence of a family history of angioedema and a later onset of symptoms, typically in the fourth decade of life or later[5].

The etiology of acquired C1-INH deficiency has been a matter of controversy. It was proposed that 2 separate forms of acquired C1-INH deficiency exist: type I, paraneoplastic, mainly associated with lymphoid malignancies; and type II, autoimmune, caused by autoantibodies to C1-INH. The most frequent lymphoproliferative diseases reported in association with acquired C1-INH deficiency are indolent lymphomas, and the most frequent histotypes are nodal and splenic marginal zone lymphomas and lymphoplasmacytic lymphomas/Waldenström disease, which suggests that the risk is confined to specific histotypes. The hypothesis that acquired C1-INH deficiency may depend on the proliferation of B cell clones recognizing C1-INH is supported by the fact that few case reports in the literature showed patients were cured of this condition by treatment with the anti CD20 monoclonal antibody rituximab[6].

Waldenström macroglobulinemia is a low-grade B cell lymphoproliferative disorder characterized by an IgM paraprotein. On extensive literature review, only few cases are reported of patients who presented with angioedema and were found to have Waldenström disease[7-12]. In most of these reports, levels of C4, C1q and C1 inhibitor are decreased. In our case levels of C4 and C1 inhibitor were normal. Khanfar A. et al. described a patient with normal determination of C4, C1q and C1 inhibitor that responded to treatment with the combination of bortezomib, rituximab and dexamethasone[11]. Zegers I.H. et al. described a patient with acquired angioedema that was successfully treated with a non-myeloablative allogenic stem cell transplantation to treat a

Waldenström disease because other known treatment options failed[12].

Conclusions

In conclusion we describe a patient with angioedema that was diagnosed of Waldenström macroglobulinemia in complete remission after appropiate therapy. We must take into account lymphoproliferative diseases in the differential diagnosis of angioedema.

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