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Case Report Open Access

Acquired Angioedema Revealing a B cell Non Hodgkin Lymphoma in a Tunisian Man

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Abstract

Angioedema is a condition described as a transient, non-pruritic, non-pitting and self-limiting local swelling of cutaneous and mucosal tissues that completely resolve in 1 to 5 days. Acquired C1-inhibitor deficiency or acquired angioedema (AAE) may be associated with a lymph proliferative disease. We report the case of a 52 year-old man, without medical history, presented recurrent edema affecting the face and the tongue which regressed spontaneously within 8 to 10 days. Serum compliment levels were as follows; CH50: 15 UI/mL (32-58), C4=0.008 g/L (0.162- 0.503), C3: 0,846 g/L (0.743-1.62), C1q=84 mg/L (100-250).

C1 esterase inhibitor protein level was 190 mg/l (150-350) with a functional rate at 30% (70-130%). Blood count showed leucocytis with lymphocytic predominance. Bone marrow biopsy showed a CD20+B cell non hodgkin lymphoma. The diagnosis of (AAE) revealing a B cell non Hodgkin lymphoma was retained and the patient had been treated by chemotherapy with good clinical course.

Keywords: Angioedema; B cell non hodgkin lymphoma; C1 esterase inhibitor

Introduction

Angioedema is a condition described as a transient, non-pruritic, non-pitting and self-limiting local swelling of cutaneous and mucosal tissues that completely resolve in 1 to 5 days [1]. It often presents with facial, tongue, laryngeal or abdominal edema and may be life threatening [2]. Acquired C1-inhibitor deficiency or acquired angioedema (AAE) clinical characteristic are similar to those of hereditary C1-inhibitor deficiency known as hereditary angioedema (HAE), however family history is absent in the first case. AAE potential association with a lymphproliferative disease requires thorough investigation since treating it may result in the definitive cure of angioedema. In this report we describe a patient presenting AAE revealing a B-lineage lymph proliferative disorder.

Case Report:

A 52 year-old man, without medical history, presented recurrent edema affecting the face and the tongue. This condition regressed spontaneously within 8 to 10 days. He was not on any short or long term medication. He had experienced recurrent dyspnea and loss of weight over the past three months. He denied any history of atopy and allergy.

Physical examination revealed a swelling of the tongue and the lips (Figure 1). There was no peri-orbital swelling or peripheral edema. Abdominal examination showed no hepatho-splenomegaly or masses. There was no muscle pain, joint swelling or lymphadenopathy.

Respiratory and cardiovascular examinations were unremarkable. Blood count showed leucocytes with lymphocytic predominance: White cell count: 17100/mm^3 (neutrophils: 6900, lymphocytes: 9200, eosinophil's: 100 monocytes: 1000), hemoglobin: 12 g/dL and platelet count: 487 × 103/mm^3 . C-reactive protein, liver and renal profile was normal. Anti-nuclear antibody and anti-neutrophil cytoplasmatic antibodies were absent. Chest X-ray and cardiac ultrasound were normal.

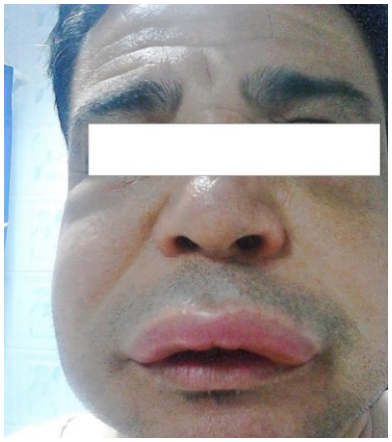

Figure 1: Tongue and lips swelling.

Immunophenotyping, done by flow cytometry, showed that 68% of lymphoid cells are of phenotype B CD 19+/CD5-, CD20+ and CD 22+. Mutates score was 1. This is in favor of a lymphoproliferative B syndrome. The bone marrow biopsy with immunohistochemistry was normal. Bradykinin-mediated angioedema was suspected. Serum compliment levels were as follows; CH50: 15 UI/mL (32-58), C4=0.008 g/L (0.162-0.503), C3: 0.846 g/L (0.743-1.62), C1q=84 mg/L (100-250).

C1 esterase inhibitor protein level was 190 mg/L (150-350) with a functional rate at 30% (70-130%). The patient had no family history of similar cases and the search for a C1 inhibitor deficiency was negative for his two children. Treatment was initiated with Danatrol® 600 mg/day.

A reduce in the duration of edema was noted however frequency did not change. After 3 months, a new bone marrow biopsy was done and showed a CD20+ B cell non hodgkin lymphoma. The patient had been treated by chemotherapy with good clinical course.

Discussion

Angioedema is a life threatening condition which often involves the subcutaneous tissue, the gastrointestinal mucosa, and the mucosa of upper respiratory tract. Urticaria is usually absent. Cutaneous angioedema cause deformities that can impair social life and impair the function of hand and feet [1]. Several subtypes have been described: Hereditary, acquired, allergen associated and idiopathic [3].

AAE differ from HAE by the absence of family history and the late onset of the disease typically within the fourth decade of life or after [4].

The typical biochemical picture of acquired C1-inhibitor deficiency is low plasma levels of C1-inhibitor function, C1-inhibitor antigen, C4 and C1q, with normal levels of C3 [5].

AAE can be classified as two types: Type 1 which can be observed in lymphoproliferative disease or para neoplastic syndrome and type 2 mostly seen in connective tissue disease [6]. AAE associated with lymphoproliferative disorder was first described in 1972 by Caldwell et al. [7]. These lymphoproliferative disorders range from monoclonal gammopathy of uncertain significance (MGUS) to non-hodgkin lymphoma.

Production of C1-inhibitor antibody without clinical or hematological evidence of lymphproliferative disorder can also be observed [8]. AAE associated with hematologic malignancy was found by Cicardi et al. in 35% of the patients presenting acquired angioedema while association with MGUS was found in 32% of the patients [9].

B-cell non-Hodgkin lymphoma (NHL) is the most frequent lymphoproliferative disorder responsible for recurrent angioedema. The most frequent histotypes are nodal and splenic marginal zone lymphomas. Angioedema can be the revealing symptom of NHL or it may follow the diagnosis [3].

Treatment of angioedema requires both prevention of recurrence and therapy for acute attacks. Prophylactic therapy includes education about avoidance of potential triggers factors, usage of anti-fibrinolytic agents, attenuated androgen, or plasma-derived C1-INH concentrate. Acute attacks are often managed with plasma-derived C1-inhibitor concentrate [5,8]. The bradykinin B2 receptor antagonisticatibant is a good alternative to plasma-derived C1-inhibitor for patients with acquired C1- inhibitor deficiencies which already proved its efficacy in HAE [10].

The second line in management of AAE consists in treatment of the underlying disease. This includes the use of chemotherapy and/or immunosuppressive agent. Proper control of the underlying disease may relieve the clinical symptoms of angioedema and variably reverse the biochemical abnormalities [5]. Rituximab as a treatment of B-cell lymphoma also proved effective in reducing attacks of angioedema [8].

In our patient, angioedema was the first symptom of NHL. He had low C4 and C1q levels consistent with an acquired angioedema. Aggressive investigation should be performed in such patients to uncover underlying lymphoproliferative disease.

Conclusion

Angioedema due to acquired deficiency of the C1-inhibitor is a bridging condition between autoimmunity and lymphoproliferation. Acquired angioedema may be secondary to an autoimmune disease or a lymphproliferative disorder as illustrated by the case of our patient. Symptomatic treatment is common to all forms of angioedema resting on anti-fibrinolytic agents, attenuated androgen, or plasma-derived C1-INH concentrate. Patients with AAE should be closely monitored because of its potential evolution into lymphoproliferative disease.

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