CASE REPORT

Acquired Angioedema Associated With Hereditary Angioedema Due to C1 Inhibitor Deficiency

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Abstract

Angioedema caused by C1 inhibitor deficiency is a rare disorder that may be either hereditary or acquired, the latter being mainly associated with lymphoproliferative disorders. A 51-year-old woman who had suffered from episodes of acute peripheral edema since she was 12 was diagnosed with hereditary angioedema at the age of 40 and remained stable with stanozolol. Due to a worsening of her symptoms she was reassessed and low levels of C1q and an abnormal lymphocyte count were detected. Immunophenotyping of peripheral blood revealed 9% monoclonal lambda B cells with a follicular center phenotype. The histopathology was consistent with a grade II follicular lymphoma stage IV-A. With chemotherapy, the hematologic disease was controlled and C1q levels returned to normal values. This represents a rare case of a patient with hereditary angioedema who developed acquired angioedema due to a lymphoma that was associated with a reduction in the levels of C1q as her symptoms worsened.

Key words: Acquired angioedema. Hereditary angioedema. C1q. C1 inhibitor deficiency.

Resumen

El angioedema debido al déficit del inhibidor del C1 es una enfermedad rara y puede ser hereditario o adquirido. Este último se suele asociar a trastornos linfoproliferativos. Una mujer de 51 años de edad con episodios recurrentes de edemas de localización periférica desde los 12 años de edad fue diagnosticada de angioedema hereditario a los 40 años y se mantuvo estable con estanazolol. Coincidiendo con un aumento de la frecuencia de los síntomas se detectaron niveles bajos de C1q y linfocitosis. El inmunofenotipo de sangre periférica reveló un 9% de células B-lambda con fenotipo centrofolicular. La biopsia de un ganglio periférico mostró un linfoma folicular de grado II, estadio IV-A. La enfermedad hematológica se controló con quimioterapia. Los niveles de C1q volvieron a valores normales. Presentamos una paciente con angioedema hereditario que desarrolló un linfoma y en la que los niveles de C1q disminuyeron de forma simultanea al empeoramiento del angioedema.

Palabras clave: Angioedema adquirido. Angioedema hereditario. C1q. Déficit de C1INH.

Introduction

Angioedema due to C1 inhibitor (C1INH) deficiency can be either hereditary or acquired. Although its pathogenesis is not completely understood, an uncontrolled activation of the classical pathway of the human complement system is involved, leading to the generation of vasoactive peptides and extravasation of fluid caused by increased vasopermeability (reviewed in Agostoni et al [1]).

Hereditary angioedema (HAE) is a rare but life-threatening disease, with an estimated global prevalence of 2 to 10 cases per 100 000 inhabitants [1], and in Spain the prevalence is

at least 1.09 per 100 000 individuals [2]. It is inherited as an autosomal dominant trait through a mutation in the gene encoding C1INH, implying a deficiency in its synthesis (type I HAE) or an impairment of its function (type II HAE). In either case, it is associated with low functional activity of C1INH, low levels of C4, and, because C1 activation proceeds unabated, normal levels of C1q other than during angioedema attacks [1]. Clinically it is characterized by recurrent and self-limited episodes of subcutaneous and mucosal nonpruritic angioedema affecting the skin, gastrointestinal tract, and upper airways that subsides within 12 to 72 hours [1,3].

Acquired angioedema (AAE) is even more infrequent than HAE, with less than 100 cases reported in the literature [4]. It is characterized by an increase in the catabolism of C1INH and hyperactivation of the classical pathway of the human complement system by the production of immune complexes, such as the idiotype–anti-idiotype, or by the presence of anti-C1INH autoantibodies [4-6]. Classically it is classified as type I when related to B-lymphocyte proliferation, either true malignancies or monoclonal gammopathies of undetermined significance (MGUS), and type II when associated with autoimmune diseases and when autoantibodies against C1INH are produced [1,4,7,8]. Nevertheless, it has recently been described that in most patients with type I AAE, paraproteinemia or M component act as anti-C1INH autoantibodies [5,9]. In fact, half of the patients with AAE due to hematologic malignancies also have autoantibodies against C1INH, either at the time of onset of the angioedema or later in the course of the disease [4]. AAE has been also described in association with other disorders such as human immunodeficiency virus disease, multiple myeloma, gastric carcinoma, and myelofibrosis, among others [10].

HAE and AAE are clinically indistinguishable, only differing in terms of the lack of family history and a characteristic late onset in the acquired form, beginning in the fourth decade of life or later, whereas the inherited form is usually detected in the first or second decade. To confirm the diagnosis it is mandatory to study the complement levels in peripheral blood, including at least C4 levels (which are characteristically decreased), antigenic and functional C1INH, and C1q levels [11]. Typically, C1q levels, which are normal in HAE, are decreased in AAE due to the high consumption of C1INH and the elevated rate of catabolism of C1q. Thus, these 2 forms can be distinguished by the measurement of serum C1q [1,4,10]. Complement alterations typical of HAE and AAE are shown in Table 1.

Table 1. Complement Alterations in Angioedema Due to C1INH Deficiency[a]

	Antigenic C1INH	Functional C1INH	C4	C1q
HAE type I	↓	↓	↓	N
HAE type II	↑/N	↓	↓/N	N
AAE type I	↓	↓	↓	↓
AAE type II	↓/N[b]	↓	↓	↓

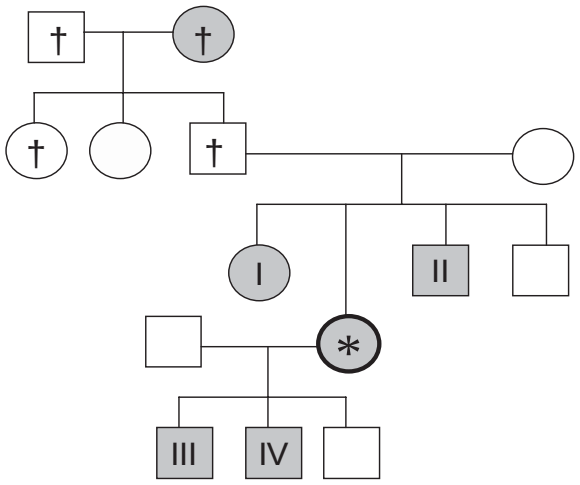
Abbreviations: AAE, acquired angioedema; C1INH, C1 inhibitor; HAE, Hereditary angioedema; N, normal.
[a] Adapted from Bowen et al [11]
[b] In AAE, normal values of antigenic C1INH are due to elevated levels of its cleaved form of 96 kDa.

Regarding the treatment, antifibrinolytics are more effective in AAE, whereas attenuated androgens are the treatment of choice in HAE [6,12]. Unlike in the hereditary form, only a partial response to C1INH plasma concentrate has been observed in AAE patients [4,13].

Case Description

A 51-year-old woman from Argentina had suffered from acute episodes of edema mainly localized in the extremities and elicited by compression since she was 12. At the age of 40 she presented an upper airway edema after dental treatment and was admitted to the Emergency Department of Hospital Vall d'Hebron in Barcelona, Spain, where she was initially treated with adrenaline and corticosteroids. Due to the lack of response to both drugs, she was treated empirically with 1000 units of C1 inhibitor plasma concentrate (Berinert). Laryngeal edema remitted progressively over the following 24 hours. She reported that her paternal grandmother suffered attacks of peripheral angioedema, her brother had experienced laryngeal edema, and her son also had recurrent episodes of edema affecting the upper extremities. Family pedigree and biochemical parameters of the affected relatives are shown in the figure. Routine blood tests performed a month after the laryngeal attack were normal and the complement study showed low C4 concentrations (8 mg/dL), diminished antigenic C1 INH (9 mg/dL), and normal levels of C1q (14 mg/dL). She was diagnosed with type I HAE. Treatment with stanozolol (2 mg daily) was started and the patient remained stable except for occasional mild abdominal pain. After 3 years in which she did not attend follow-up appointments, she presented with a 4 week history of recurrent and self-limited angioedema affecting the face and neck. Due to the worsening of her symptoms, blood tests were performed showing the following alterations: decreased C1q (6 mg/dL), low functional (45%) and antigenic levels (10 mg/dL) of C1INH, and an abnormal lymphocyte count (53% [3800 cells/L] peripheral lymphocytes, 10% cleaved). Based on suspicion of a lymphoproliferative syndrome, immunophenotyping of peripheral blood was performed and 9% monoclonal lambda B-cells with a follicular center phenotype were observed. On physical examination, enlarged peripheral lymph nodes were detected in 4 external lymph node chains (ranging from <0.5 to 2 cm). A computed tomography scan showed enlarged axillary, inguinal, and other lymph nodes adjacent to the left external lymph node chain. A lymph node biopsy was performed and the histopathology was consistent with a grade II (< 15% blast cells) nodular follicular lymphoma, stage IV-A. Tranexamic acid at doses of 500 mg every 8 hours was then started and stanozolol was increased to 2 mg every 12 hours in order to control the symptoms. Enzyme-linked immunosorbent assay did not reveal anti-C1 INH (immunoglobulin [Ig] G and IgM) or anti-C1q (IgG) antibodies. The patient required 4 courses of

A



B

	I	II	III	IV
C4, mg/dL	7	6	9	8
C1INH, mg/dL	12	10	13	9
fC1INH, %	42	45	48	33
C1q, mg/dL	18	17	14	20
Angioedema	no	yes	yes	no

Figure. Pedigree of the patient and biochemical measurements in the affected relatives. Five relatives of the patient had hereditary angioedema, although only 3 reported typical clinical symptoms of the disease. A, Pedigree of the patient's family, where the patient is indicated by an asterisk, dead relatives by a cross (precluding further analysis), and affected relatives are shown in gray. B, Analysis of complement concentrations in the affected relatives (I-IV). Normal values are as follows: C4, 12-52 mg/dL; C1INH, 15-35 mg/dL; fC1INH, >70 %; C1q, 2-22 mg/dL. C1INH indicates C1 inhibitor; fC1INH, functional C1INH.

chemotherapy with chlorambucil (0.2 mg/kg/d) and prednisone (1 mg/kg/d), each lasting 10 days and administered at monthly intervals. Regarding the clinical symptoms of angioedema, the patient remained stable after the remission of the lymphoma. Currently, she presents occasional (1-2 mild episodes per year) peripheral angioedema and her disease is controlled with tranexamic acid (500 mg/d). After 20 months, clinical remission of the hematologic disease was achieved and C1q levels were normalized (Table 2). As no autoantibodies to C1INH were observed, we consider that the patient developed type II AAE.

This represents a peculiar case of a patient with HAE due to C1INH deficiency who went on to show changes typical of AAE, leading to a diagnosis of lymphoproliferative disease prior to the appearance of clinical manifestations.

Table 2. Disease Course According to Biochemical Variables[a]

	1993 Diagnosis of HAE	1994	1996	1997	1999	2002 Lymphoma	2003	2004 Clinical Remission
C3, mg/dL	68 (85-170)	69 (85-170)	80 85-170)	81 (85-170)	72 (85-170)	93 (85-180)	91 (85-180)	85 (85-180)
C4, mg/dL	8 (9-40)	19 (9-40)	12 (12-52)	16 (12-52)	11 (12-52)	15 (10-40)	13 (10-40)	13 (10-40)
C1INH mg/dL	5 (15-35)	15 (15-35)	20 (15-35)	14 (15-35)	12 (15-35)	10 (15-35)	10 (15-35)	12 (15-35)
fC1INH, %	NA	NA	NA	55	45	45	42	55
C1q, mg/dL	14 (9-22)	11 (9-22)	12 (9-22)	12 (9-22)	11 (9-22)	6 (10-25)	9 (10-25)	12 (10-25)

Abbreviations: C1INH, C1 inhibitor; fC1INH, functional C1INH; HAE, hereditary angioedema; NA, not available.
[a] Normal ranges are indicated in parentheses.

Discussion

To our knowledge this is the first case of HAE associated with AAE during a malignant hematologic disease. We do not know if in the reported case the association of HAE and AAE is an epiphenomenon or if, as a result of an illness capable of inducing the consumption of C1INH and hyperactivation of the classical pathway of the human complement system, this reduction becomes symptomatic in a patient with low basal levels and dysfunction of this molecule.

Mature B-cell neoplasms or non-Hodgkin lymphoma, such as follicular lymphoma, represent 4% of all tumors [14]. The annual incidence of non-Hodgkin lymphoma ranges from 1.2 cases per 100 000 inhabitants in China to 15 per 100 000 in the United States of America [15]. HAE is even less frequent, affecting 1.09 individuals per 100 000 inhabitants in Spain [2]. Thus, the probability of both disorders occurring in the same patient is extremely low.

In fact, in the patient described, the clinical manifestations worsened while she was developing the follicular lymphoma, and the finding of low levels of C1q allowed an early diagnosis of her hematologic condition, as she did not have any other clinical manifestation of the hemopathy. Oddly, C1q levels returned to normal only when total remission of the hematologic disease was achieved, strengthening the hypothesis that when the consumption of the available C1q molecules and the hyperactivation of C1INH ceased, her complement levels returned to baseline and the symptoms stabilized.

Genetic studies to confirm the hereditary pattern of the angioedema (or to study the mutation in the C1INH gene) were not performed in the patient. However, the positive family history and the confirmation that 4 of them had low C1INH levels and activity strongly supported the diagnosis of HAE. Moreover, the early onset of clinical symptoms reinforced the diagnosis.

In AAE, the clinical presentation mostly involves peripheral angioedema of the head, neck, and extremities followed by abdominal pain [4,10]. The symptoms of AAE usually precede the underlying illness by between 0 and 7 years [10]. The average time to diagnosis of AAE from the onset of symptoms has been reported between 2.3 and 2.48 years [4,10]. In our patient both the diagnosis of the AAE and, consequently, the diagnosis of the lymphoma were reached earlier than previously reported. Because of the underlying presence of HAE, the sudden increase in symptoms prompted a reassessment of complement levels and low C1q was detected. This finding was crucial for the early diagnosis of the hematologic disease.

In conclusion, we present an unusual case involving the coexistence of HAE and AAE due to C1INH deficiency. This finding highlights the importance of careful follow-up in such patients.

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