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Case report

Acquired Angioedema Due to C1 inhibitor Deficiency Caused by Non-Hodgkin Lymphoma in a Patient with Myasthenia Gravis

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Abstract

Acquired angioedema due to C1-inhibitor deficiency is a very rare disorder that usually appears in patients with lymphoproliferative and/or autoimmune diseases. This type of swelling is bradykinin mediated and does not respond to antihistamines, corticosteroids, or epinephrine. The symptoms usually appear in patients older than 40 years with recurrent episodes of angioedema without wheals. The family history is negative. The swelling could affect any tissue, but most frequently is located at the face, lips, tongue, larynx, or extremities. In the gastrointestinal tract, it causes pain, nausea, vomiting, and diarrhea. The upper respiratory airway oedema is a potentially life-threatening condition due to asphyxiation. The oedema attacks may precede the symptoms of the causative disease for months or years. In most cases, the treatment of the underlying disease resolves the angioedema episodes. Here we report a case of C1-INH-AAE caused by non-Hodgkin lymphoma in a patient diagnosed many years before with myasthenia gravis whose angioedema symptoms resolved after the specific treatment of lymphoma.

Keywords*: rare disease, bradykinin mediated angioedema, lymphoproliferative disease, autoimmune disease, angioedema attack*

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Introduction

Acquired angioedema (AAE) due to C1-inhibitor (C1-INH) deficiency (C1-INH-AAE) is a very rare disorder that usually appears in patients with lymphoproliferative and/or autoimmune diseases due to excessive activation of the classical complement pathway leading to depletion of C1-INH (1-3).

Clinically, C1-INH-AEE manifests with recurrent episodes of nonpruritic, nonpitting angioedema without urticaria which last two to four days and can involve any part of the body (4). As the symptoms of C1-INH-AAE can pre-

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cede a diagnosis of lymphoproliferative disease with months or years and confers an increased risk for developing non-Hodgkin lymphoma, the early diagnosis is very important (2).
We describe a case of C1-INH-AAE caused by non-Hodgkin lymphoma (NHL) in a patient diagnosed many years before with myasthenia gravis (MG).

Case presentation

The female patient was diagnosed with MG in 1990, at the age of 29, having very high levels of antibodies to acetylcholine receptors (264 nmol/l; normally < 0.25 nmol/l). Her symptoms started one year before with bilateral ptosis, diplopia, dysphagia, and fatigability. The patient underwent a thymectomy, but her symptoms did not resolve. The neostigmine test was positive. She received pyridostigmine a couple of months, even in high doses, with immunosuppressive therapy (Azathioprine), followed by a slight improvement of symptoms. Next, she underwent six sessions of plasmapheresis with good results for a period of about six months. When symptoms reappeared, she was prescribed systemic corticosteroids and pyridostigmine for a couple of years. Since 2000 the patient was no more willing to continue corticotherapy and since 2005 has reduced the dose of pyridostigmine. Between 2007 and 2020 the patient has been asymptomatic and without any treatment for MG.
In 2016, at the age of 51, the patient had an episode of angioedema without wheals with upper lip swelling which lasted 10 hours. After a couple of days, she had lower-lip oedema with a 12-hour duration. After 6 months she had oral mucosa swelling several times which lasted more than one day every time. The patient had twice massive tongue oedema, once associated with dyspnea and once with external neck oedema. During the next 4 months, the patient had some episodes of mild and moderate tongue swelling, colicky abdominal pain, and diarrhea. She had no family history of angioedema and denied having any food or drug allergy or taking angiotensin-converting enzyme inhibitors or other drugs. Laboratory tests for histaminergic angioedema were normal. Complement tests, performed in August 2018, showed low C4 (25 mg/l), low C1-INH antigenic (0.0319 g/l) and functional activity (8%), as well as low C1q level (46 mg/l). An increased titer of IgA antibody against C1-INH was measured and pancytopenia was observed.
Based on these results, the diagnosis of C1-INH-AAE was established. Because patients with this type of angioedema have an increased risk of lymphoproliferative diseases, especially non-Hodgkin lymphoma, further investigations were carried out. Abdominal ultrasound and CT evaluation showed splenomegaly (28/11/16.5 cm) with infiltrative appearance and some small subdiaphragmatic lymphadenopathy (15/8mm). Peripheral blood flow cytometry revealed an infiltration in approximately 13% of the mature B cells with CD19, CD45, CD20, CD79 positive phenotypes. Bone marrow biopsy confirmed the diagnosis of non-Hodgkin lymphoma with small B cells (probably from the marginal splenic area), positive for CD20 and negative for Cyclin D1. JAK 2 mutation was negative.
The patient was prescribed 6 doses of specific chemotherapy, with the regression of the lymphadenopathy and the splenomegaly. During the therapy period, the patient had two times mild oral mucosa swelling which resolved without any treatment.
At the six months post-treatment re-evaluation by CT, the lymphadenopathies disappeared, the dimension of the spleen was normal, and the patient reported no more angioedema symptoms. Complement parameters (C4, C1-INH -antigenic level and functional activity, C1q and antibodies - IgM, IgG, IgA against C1-INH) were within the reference range.

Discussion

C1-INH-AAE should be considered in patients older than 40 years who present with recurrent episodes of angioedema without wheals and negative family history for this condition (1-4). The swelling is most frequently located at the face, lips, tongue, larynx, or extremities (1). In the gastrointestinal tract, it causes pain, nausea, vomiting, and diarrhea. The upper-respiratory airway oedema is a potentially life-threatening condition due to asphyxiation.

In this type of angioedema, the swelling is bradykinin mediated and attributed to excessive consumption of the C1-INH or inhibition of C1-INH function by autoantibodies (2,4). In most cases, the excessive use of the C1-INH is caused by lymphoproliferative tissue (1-3), in the context of either malignant conditions, especially NHL (2,5), or benign ones, like monoclonal gammopathy of uncertain significance (2,6). The C1-INH neutralizing autoantibodies may be present at the same time with the lymphoproliferative disorder (LPD) or consecutively (1,3). Also, LPDs, especially B-cell types, have a higher incidence in patients with autoimmune diseases (3,7). Treating the underlying disease, will lead to the disappearance of the oedema episodes and to reverse the complement abnormalities in most cases (2,3).

MG in patients with LPDs were described. The conditions may appear at the same time, or many years one after the other (8,9). The association could be coincidental or resulting from common genetic or environmental risk factors (10). When they appear separately, the occurrence of LPDs may be the result of chronic MG (10).

Conclusions

This case emphasizes the importance of considering C1-INH-AAE in every patient over 40 years of age with recurrent episodes of swelling without wheals. A quantitative and functional C1-INH deficiency with negative family history for angioedema associated with low C1q level confirm the diagnosis of C1-NH-AAE. If C1q is normal, the presence of antiC1-INH- antibodies allow diagnosing this type of angioedema. The early diagnosis of this form of angioedema is essential considering that it responds only to drugs that regulate bradykinin activity and upper airway edema is a life-threatening condition. When C1-INH deficiency is proven, the patient should be investigated for prompt diagnosis of possible association with LPD and/or autoimmune diseases.

Abbreviations:

AAE: Acquired angioedema
C1-INH: C1-inhibitor
C1-INH-AAE: Acquired angioedema due to C1-inhibitor deficiency
LPD: Lymphoproliferative disorders
MG: myasthenia gravis
NHL: Non-Hodgkin lymphoma

Authors' contribution

NB and VN designed the study, collected and analyzed the data, wrote the original draft and approved the final paper.

LV and HF analysed the data, critically reviewed the paper and approved the final version of the paper.

Conflict of interest

None to declare.

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