Intractable acquired autoimmune angioedema in a patient with systemic lupus erythematosus

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ABSTRACT

Acquired angioedema is caused by different drugs and lymphoproliferative diseases, and rarely it has also been related to the presence of auto-immune disorders. We report the case of a 47 year old female with systemic lupus erythematosus (SLE) and severe cutaneous involvement who developed recurrent localized angioedema of the face, including lips and eye lids, upper limbs, and thorax, not associated with urticaria, and with reduced levels of C1 esterase inhibitor. Treatment with antimalarials, glucocorticoids, and pulse therapy with methylprednisolone associated with azathioprine did not improve her condition. The patient was also unsuccessfully treated with danazol, and she only showed clinical response after several sessions of plasmapheresis, including resolution of the extensive edema of the gastrointestinal tract.

Keywords: acquired angioedema, C1-INH inhibitor, systemic lupus erythematosus.

INTRODUCTION

Angioedema secondary to deficiency of C1 esterase inhibitor (C1-INH) can be hereditary [hereditary angioedema (HEA)], but it can also be acquired [acquired angioedema (AAE)]. Classically, angioedema is recurrent and it is not associated with urticaria, and it can involve the subcutaneous tissue, especially in the extremities, face, and trunk, and the mucosa of the respiratory and intestinal tracts, which can lead to laryngeal edema and acute obstructive abdomen, respectively.

Reports on acquired autoimmune angioedema secondary to systemic lupus erythematosus (SLE) have been rare, which motivated the current report.

CASE REPORT

This is a 47 year old female with a diagnosis of SLE (ACR criteria) for 5 years, with cutaneous rash (subacute cutaneous involvement), polyarthralgia, alopecia, malar rash, and photosensitivity. She had positive large speckled antinuclear antibody (ANA) 1/320, positive anti-Ro (SSA), and reduced levels of C3 and C4. The patient was taking prednisone, 10 mg once a day, and chloroquine, 250 mg once a day, and, two years ago, she developed localized angioedema, predominantly in the eye lids, lips, upper limbs, and trunk lasting 1 to 5 days. She showed poor response to anti-histaminic drugs and glucocorticoids (prednisone 60 mg/d), evolving with abdominal pain, diarrhea, and malabsorption, and endoscopy revealed angioedema of the mucous membranes. The levels of C1 esterase inhibitor (nephelometry) were low, 8 mg/dL (normal 15 to 34 mg/dL); the patient was treated with danazol, 200 mg twice a day, with discrete improvement. Azathioprine, 2 mg/kg/d, tranexamic acid, 1.5 gram/d, and pulse therapy with methylprednisolone, 1.0 gram for 3 days were also tried but without response. She underwent 10 sessions of plasmapheresis,

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which treated successfully the angioedema, including that of the gastrointestinal tract (GIT). Three to four months after the last episode of angioedema, which was under control, the patient was admitted once more with paraplegia over the last 24 hours and aspiration pneumonia secondary to disseminated adenocarcinoma of unknown origin with metastasis to the spinal cord and brain.

DISCUSSION

Type I AAE is secondary to increased catabolism of C1-INH and it is usually associated with lymphoproliferative diseases. Type II is secondary to the presence auto-antibodies against C1-INH, being characteristic of auto-immune disorders. Onset in adulthood and the lack of a family history differentiate AAE from hereditary types.[1-4] Even though it is a rare disorder, it has been reported in several different clinical situations: acquired immunodeficiency, multiple myeloma, Waldenström macroglobulinemia, gastric carcinoma, Sjögren's Syndrome, rectal adenocarcinoma, pulmonary carcinoma, SLE, chronic lymphocytic leukemia, Churg-Strauss vasculitis, and acute hepatitis B.[4] In the case reported here, the association between AAE and SLE was suggested by the long-standing history of angioedema along with clinical manifestations of SLE and absence of other etiologies. The recent development of a malignancy, three months after the last episode of angioedema, brought up an association with neoplasia not foreseen.

In the case of SLE that we reported, the history of recurring episodes of angioedema, abdominal pain, and localized non-pruriginous edema of the extremities suggested the diagnosis of angioedema secondary to deficiency of C1-INH. Angioedema can affect the airways, tongue, and larynx, which determine the severity of this disorder and a mortality rate of 15 to 33%.[5,6] Note that abdominal symptoms, like those referred by our patient, affect approximately 25% of the patients and they are secondary to edema of the intestinal mucosa and stenosis.[4]

As for laboratorial investigations, low levels of C4 and normal levels of C3 suggest the diagnosis of angioedema associated with deficiency of C1-INH. The levels of C1q will differentiate hereditary (normal levels of C1q) and acquired angioedema, which is associated with reduced levels of C1q, since it is consumed by circulating immune complexes.[7,8] The investigation of acquired angioedema is complemented by determining the presence of anti-C1-INH antibodies by enzyme-linked immunoassay (ELISA). This test was not done in our patient due to technical difficulties.

Regarding treatment, the use of purified concentrate of C1-INH has been well established.[5] High doses are necessary to treat acquired angioedema, approximately 12,000 U, which is much higher than the dose recommended for HAE (500-1,500 U), due to the exacerbated catabolism of C1-INH by auto-antibodies.[8,9] The administration of fresh frozen plasma is another alternative, but since it contains high levels of complement, it can exacerbate the previous symptomatology.[8,9]

Antifibrinolytics, such as tranexamic acid, should be used for long-term prophylaxis. The use of attenuated androgens, such as danazol and stanozolol, that stimulate the synthesis of C1-INH in the liver, is well-established in HAE; however, patients with the acquired form of the disease are resistant to this treatment, like the patient reported here. But Higa *et al*. reported a case of AAE in which the use of danazol led to remission.[10]

Recently, the use of rituximab (chimeric anti-CD20 antibody) in the treatment of AAE has shown to be effective in achieving remission of the episode of angioedema in non-responsive, difficult to control cases.[11-14]

The use of immunosuppressors (azathioprine, cyclosporin) associated or not with corticosteroids and plasmapheresis[15] can be effective,[9,15] which was the case of our patient.

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