CASE REPORT

Angioedema as the presenting feature of systemic lupus erythematosus

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SUMMARY

A young female in her early 20s presented with low-grade fever for 1 month, puffiness of face and abdominal distension for 15 days. Evaluation revealed pancytopenia with normocellular marrow, hypocomplementaemia and Coomb's positive haemolytic anaemia. She had angioedema with laryngospasm and worsening facial oedema which had dramatic response to steroids. Further workup lead to a diagnosis of systemic lupus erythematosus with neuropsychiatric involvement. Treatment with pulse steroids and cyclophosphamide resulted in dramatic improvement of her symptoms with no recurrence of angioedema during her follow-up visits.

BACKGROUND

Systemic lupus erythematosus can be misdiagnosed or missed if one is not aware of its varied presentations. Angioedema is one such rare presentation in which the possibility of lupus is easily overlooked. Associations of systemic lupus erythematosus and angioedema have been reported in the past but there are very few case reports where the presenting feature was angioedema.

CASE PRESENTATION

A 23-year-old married woman was symptomatic for 1 month with low-grade fever. During the last 15 days, she had noticed puffiness of face along with abdominal pain that aggravates especially with food intake. She had been having excessive menstrual bleeding for 10 days and new onset painful oral ulcers for a week. She sought medical attention at our hospital with new complaints of difficulty in swallowing and breathlessness at rest for 3 days. There was no history of any insect bite or recent drug intake that could have provoked her facial puffiness. She never had any pain or pruritus in her facial swelling. She had also noticed alopecia in the last 1 month, but there was no history of arthralgia, Raynaud's phenomenon or dryness of eyes and mouth. Her medical history was significant for two first trimester spontaneous abortions. There was no history of similar illness in family members.

On examination, she appeared pale, with facial puffiness more around her neck and jaw ([figure 1](#)). The swelling was non-tender. She had bilateral soft cervical lymphadenopathy in upper, mid and lower cervical regions that were non-tender, largest about 1 cm. She had an ulcer in her hard palate, cutaneous vasculitic lesions in the tufts of her toes and hepatomegaly. Fundus examination showed grade 2

hypertensive retinopathy. Her vitals were otherwise stable at admission.

INVESTIGATIONS

She had pancytopenia at admission. Haemoglobin was 69 g/L, total leucocyte count was 2.45×10^9 /L (neutrophils 51%, lymphocytes 46%), platelets were 140/L. Peripheral smear revealed no atypical cells. Her direct Coomb's test was 2+ (positive) and indirect Coomb's test 4+ (positive). She had only trace proteinuria, her renal and liver function tests were otherwise normal. Ultrasound of neck showed only cervical lymphadenopathy in levels 1b, 2, 3 and 4 with largest being about 1.5 cm. There was no evidence of parotitis or Vincent's angina. CT neck and thorax revealed a focal consolidation in left lower lobe apical segment.

In hospital she had worsening cytopenias. Bone marrow study done to rule out lymphoid neoplasm revealed a normal cellular marrow. Echocardiography of the heart showed a thin rim of pericardial effusion. As the suspicion for lupus was strong and considering her multisystem involvement, antinuclear antibody (ANA) test was done which was strongly positive (4+); homogenous pattern (by immunofluorescence) and extractable nuclear antigen profile showed antibodies to Sm (2+) and Sm/ribonucleoprotein (3+). In view of her history of recurrent abortions, associated antiphospholipid antibody syndrome was considered which was ruled out by negative tests for beta 2 glycoprotein antibodies and lupus anticoagulant. Contrast-enhanced CT of abdomen ruled out gastrointestinal vasculitis.

Patient developed swelling of lips and drop in oxygen saturation (84%), while breathing room air on day 7 of admission. Patient was treated with supplemental oxygen by mask and intravenous hydrocortisone 100 mg three times per day. Within next 24 hours, lip swelling reduced and oxygen saturation improved to 98% without supplemental oxygen. Her C3 levels were 0.175 g/L (normal 0.9–1.8 g/L); C4 levels were <0.0665 g/L (normal 0.1–0.4 g/L). C1 esterase inhibitor (C1-INH) levels were done to rule out hereditary angioedema; her values were 0.66 g/L (reference intervals 0.21–0.39 g/L). During subsequent week, she developed signs of altered mental status in the form of excessive crying, depressed mood, irrelevant talk and wandering behaviour. Cerebrospinal fluid analysis revealed 15 cells with lymphocytic predominance and normal protein and glucose. MRI brain was done considering the possibility of central nervous system (CNS) lupus and it was suggestive of vasculitis ([figure 2](#)).

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Figure 1 Facial puffiness and lip swelling at presentation and after treatment.

She satisfied the Systemic Lupus International Collaborating Clinics (SLICC) criteria for systemic lupus erythematosus¹ (anaemia, leucopenia, thrombocytopenia, serositis, alopecia and oral ulcers, psychosis, ANA and anti-Sm positivity, low complements).

DIFFERENTIAL DIAGNOSIS

1. Anaphylaxis.
2. Vincent's angina.
3. Glomerulonephritis.

TREATMENT

Piperacillin/tazobactam was given for 7 days for left lower lobe consolidation. Intravenous hydrocortisone was given for 5 days for angioedema causing desaturation. She did not require intubation and ventilation as her oxygen saturation and airway oedema improved with steroid therapy alone. She was later started on oral steroids (1 mg/kg prednisolone) for autoimmune haemolytic anaemia. She was given injection cyclophosphamide 750 mg/sqm for neuropsychiatric lupus. Hydroxychloroquine was given at a dose of 200 mg/day. Menorrhagia was treated with medroxyprogesterone acetate. She received septran prophylaxis, calcium and vitamin D supplementation and proton pump inhibitor also.

OUTCOME AND FOLLOW-UP

Her facial swelling subsided dramatically during stay in hospital. She was discharged with 1 mg/kg of prednisolone and has

followed up for four more visits for monthly cyclophosphamide pulses. There was no recurrence of angioedema and she felt subjectively better. Her complement profile was repeated and they were within normal limits. C3—0.93 g/L; C4—0.104 g/L; C1-INH—0.31 g/L.

DISCUSSION

Angioedema can be mast cell mediated (more common) or kinin mediated. Kinin-mediated angioedema is classified as hereditary or acquired. Hereditary angioedema (HAE) can be either type 1 or type 2 depending on whether the levels of C1-INH levels are intrinsically low or normal but functionally deficient.² A third type of HAE was proposed with normal levels of C1-INH occurring exclusively in women.³ Acquired angioedema (AAE) is less frequent in comparison with HAE. AAE is in turn classified as type 1 where excessive consumption of C1-INH occurs as in B cell lymphoproliferative neoplasm⁴ or as type 2 where autoantibodies to C1-INH are present.² Type 1 has decreased serum levels of functionally active C1-INH, whereas type 2 can have normal or elevated levels of functionally inactive C1-INH. A third type of AAE had been described in systemic lupus erythematosus with low levels of C1-INH and early products of complement cascade.⁵

Our patient had an AAE probably due to systemic lupus erythematosus. The absence of any prior history of similar symptoms or any history of angioedema in family members lead to a diagnosis of AAE. She had very low C3 and C4 levels reflecting complement consumption but an inappropriately elevated C1-INH which could be functionally inactive, fitting with AAE type 2. The recurrent attacks of abdominal pain, the sudden desaturation of the patient at room air probably due to laryngeal oedema, the swelling of lips and the dramatic response to steroids and immunosuppressive therapy later could all be well explained by angioedema. Investigation of angioedema further on C1q levels to differentiate from HAE⁶ and anti-C1-INH antibodies to distinguish the subtype of AAE were not done due to non-availability of these investigations in our institute.

It is of interest to note that in all the previously described case reports of angioedema associated with lupus, there was no disease activity during episodes of angioedema,^{3 7–10} whereas in our patient she had neuropsychiatric manifestations and MRI evidence of vasculitis. Another interesting observation is the age of presentation. In previous case reports, AAE has been described usually in the fourth decade, whereas our patient had symptoms in her early 20s.^{7 8 11–15} It has been postulated that the elevated kinin levels in AAE might confer an increased risk for CNS lupus by increasing vascular permeability and facilitating entry of antibodies, cytokines and chemokines in the cerebral circulation,^{16 17} although intrinsic antinervous tissue antibodies may also contribute. Our patient is under close follow-up receiving her monthly cyclophosphamide pulses. She feels subjectively better, and there has been no recurrence of angioedema in the subsequent 4 months. It remains to be seen whether it recurs later in life as recurrence is known.

Figure 2 MRI of brain showing swollen and hyperintense putamen and head of caudate nucleus bilaterally and focal hyperintensity of subcortical white matter of right middle frontal gyrus and posterior periventricular region.

Learning points

- Angioedema can be one of the presenting features of systemic lupus erythematosus.
- Acquired angioedema can be associated with central nervous system involvement in systemic lupus erythematosus patient.
- Steroids can be lifesaving in such conditions.

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REFERENCES

- Petri M, Orbai AM, Alarcón GS, *et al.* Derivation and validation of the systemic lupus international collaborating clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum* 2012;64:2677–86.
- Agostoni A, Aygören-Pürsün E, Binkley KE, *et al.* Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. *J Allergy Clin Immunol* 2004;114(3 Suppl):S51–131.
- Bork K, Barnstedt S-E, Koch P, *et al.* Hereditary angioedema with normal C1-inhibitor activity in women. *The Lancet* 2000;356:213–7.
- Cicardi M, Zingale LC, Pappalardo E, *et al.* Autoantibodies and lymphoproliferative diseases in acquired C1-inhibitor deficiencies. *Medicine* 2003;82:274–81.
- Cacoub P, Frémeaux-Bacchi V, De Lacroix I, *et al.* A new type of acquired C1 inhibitor deficiency associated with systemic lupus erythematosus. *Arthritis Rheum* 2001;44:1836–40.
- Bowen T, Cicardi M, Farkas H, *et al.* Canadian 2003 international consensus algorithm for the diagnosis, therapy, and management of hereditary angioedema. *J Allergy Clin Immunol* 2004;114:629–37.
- Habibagahi Z, Ruzbeh J, Yarmohammadi V, *et al.* Refractory angioedema in a patient with systemic lupus erythematosus. *Iran J Med Sci* 2015;40:372.
- Ali SI, Qayser Y, Roohi R. Subtle angioedema presented systemic lupus erythematosus: a case report. *Int J Case Rep Imag* 2013;4:631–4.
- Bienstock D, Mandel L. Facial angioedema and systemic lupus erythematosus: case report. *J Oral Maxillofac Surg* 2015;73:928–32.
- Lahiri M, Lim AY. Angioedema and systemic lupus erythematosus – a complementary association? *Ann Acad Med Singapore* 2007;36:142–5.
- DocSlide. A new type of acquired C1 inhibitor deficiency associated with systemic lupus erythematosus. <https://docslide.com.br/documents/a-new-type-of-acquired-c1-inhibitor-deficiency-associated-with-systemic-lupus.html> (cited 23 Dec 2017).
- Nettis E, Colanardi MC, Loria MP, *et al.* Acquired C1-inhibitor deficiency in a patient with systemic lupus erythematosus: a case report and review of the literature. *Eur J Clin Invest* 2005;35:781–4.
- Ochonisky S, Intrator L, Wechsler J, *et al.* Acquired C1 inhibitor deficiency revealing systemic lupus erythematosus. *Dermatology* 1993;186:261–3.
- Barilla-LaBarca ML, Giofrè D, Zanichelli A, *et al.* Acquired C1 esterase inhibitor deficiency in two patients presenting with a lupus-like syndrome and anticardiolipin antibodies. *Arthritis Rheum* 2002;47:223–6.
- Furlanetto V, Giassi KS, Neves FS, *et al.* Intractable acquired autoimmune angioedema in a patient with systemic lupus erythematosus. *Rev Bras Reumatol* 2010;50:102–6.
- Harbeck RJ, Hoffman AA, Hoffman SA, *et al.* Cerebrospinal fluid and the choroid plexus during acute immune complex disease. *Clin Immunol Immunopathol* 1979;13:413–25.
- Nakamura S, Yoshinari M, Saku Y, *et al.* Acquired C1 inhibitor deficiency associated with systemic lupus erythematosus affecting the central nervous system. *Ann Rheum Dis* 1991;50:713–6.

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