Case Report

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Fatal Recurrent Angioedema with Systemic Lupus Erythematosus in a Young Female: A Disturbing Decline

Internal Medicine Section

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ABSTRACT

Recurrent angioedema is a particularly puzzling problem for clinicians worldwide. The cause is often idiopathic with chronic angioedema recurring over weeks to months. Intake of certain drugs and contact with other offending agents can also induce chronic angioedema. In Systemic Lupus Erythematosus (SLE) patients, recurrent angioedema may be due to an acquired deficiency of C1 inhibitor (C1-INH) caused most probably due to formation of antibody against the C1-INH molecule. A 26-year-old female, who had SLE, presented to the Emergency Department with the chief complaint of puffiness of face, swelling of lips and bilateral lower limbs since one day, which occurred following application of aloe vera cream thrice within a duration of 24 hours. Upon investigations, absolute eosinophil count was raised while C4 and C1q levels were reduced. A diagnosis of acquired angioedema was made. The patient was managed with corticosteroids, cyclophosphamide, antibiotics, antihistamines, oxygen support and other supportive measures. However, the patient's condition declined further and she succumbed on day 5 of admission. Therefore, this report highlights the importance of chronic angioedema in a patient with SLE and the potential lethal outcome that it can result into.

Keywords: Allergic reaction, Autoimmune disease, Malar rash, Oedema

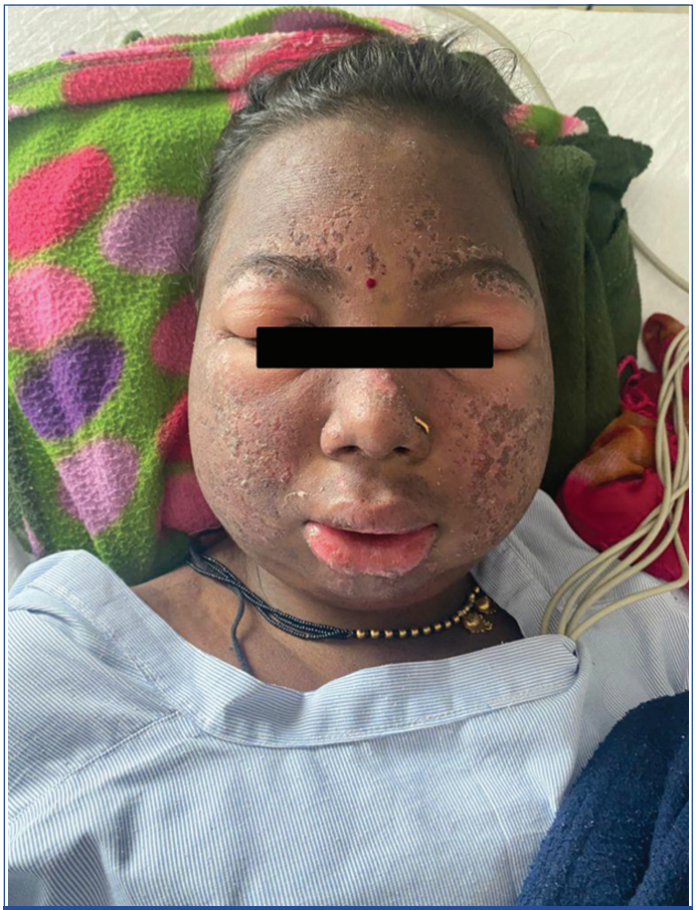
CASE REPORT

A 26-year-old female presented to the Emergency Department with the chief complaint of facial puffiness, swelling of lips and bilateral lower limbs since one day. She gave a history of applying aloe vera cream over her face three times, 24 hours prior to the appearance of facial puffiness. She had applied the gel for the erythematous raised rashes over her cheeks and nasal bridge without any formal prescription from a doctor [Table/Fig-1]. There was a similar episode of facial puffiness and swelling of lips and the tongue following aloe vera gel application one year ago for which she was admitted in Intensive Care Unit (ICU), and managed with injectable steroids and antihistamines (as per the hospital discharge documents). There was no history of fever, no history of frothy urine, oliguria or haematuria. She was a known case of Systemic Lupus Erythematosus (SLE) for four years and was on oral steroids (tablet prednisolone 40 mg once daily) and hydroxychloroquine 200 mg twice a day for the same. There was no history of thyroid disorder, hypertension, diabetes mellitus or any other co-morbidity. There was no family history of angioedema or SLE.

On general examination, pulse was 92 beats per minute and regular, blood pressure was 100/70 mmHg in right arm supine position. Facial puffiness was present along with swelling of lips, erythematous raised rash over her zygomatic area and nasal bridge was present along with pigmented lesions over bilateral zygomatic area and forehead. Bilateral non-pitting pedal oedema was present, and SpO_2 was 94 percent at room temperature.

On systemic examination, the chest was bilaterally clear, heart sounds were normal, abdomen was soft, non tender palpable spleen. The patient was conscious, and oriented with no neurodeficit. Provisional diagnosis was made as SLE with angioedema.

She was immediately admitted in the ICU, and was managed with injectable corticosteroids (injectable methylprednisolone 1 g i.v. OD), cyclophosphamide (500 mg i.v Stat), antibiotics (injectable meropenem 1 g i.v. BD, injectable, clindamycin 600 mg i.v. BD and injectable linezolid 600 mg i.v. BD), antihistamines (pheniramine maleate 2 cc i.v. six hourly), oxygen support and other supportive measures.



[Table/Fig-1]: Showing facial puffiness suggestive of angioedema.

Her laboratory investigations are mentioned in [Table/Fig-2]. The patient had reduced C4 levels (5 mg/dL) and C1q levels (<20 µg/mL). A final diagnosis of SLE with recurrent acquired angioedema was made. During the course of the hospital stay, her condition

deteriorated further. On the second day, the patient had continuous sinus tachycardia along with hypotension and on day three she was started on inotropic support for the same. However, she did not respond to the treatment and was intubated and taken on mechanical ventilator on day four of admission. She ultimately succumbed on day five of admission.

Laboratory parameters	Measured value
Haemoglobin	12.1 g/dL
Complete blood count	White Blood Cell (WBC) count-9800 cells/dL Platelet count-98000 cells/dL Absolute eosinophil count-650 cells/mcL
Renal function test	Creatinine-0.9 mg/dL Urea-17 mg/dL Sodium-135 mmol/L Potassium-4.5 mmol/L
Liver function test	Total protein-7.2 g/dL Albumin-3.6 g/dL Globulin-3.6 g/dL, Aspartate aminotransferase-21 units/L Alanine aminotransferase-29 units/L Alkaline phosphatase-103 IU/L Total bilirubin-1.3 mg/dL
C4	5 mg/dL
C1q	<20 µg/mL

[Table/Fig-2]: Showing laboratory parameters.

DISCUSSION

Angioedema refers to localised subcutaneous or submucosal swelling that arises as a result of extravasation of fluid in the interstitial tissues [1]. It usually affects areas with loose connective tissue. Recurrent angioedema continues to be a problematic disease for treating physicians due to the unclear pathophysiology and relapsing nature of the condition. Considerable information is available on recurrent angioedema, which deals with the probable triggers including food, medication, hereditary angioedema, and angioedema associated with underlying connective tissue disease [2]. Angioedema can be classified into two categories which are mast cell mediated and kinin mediated. Angioedma, mediated by mast cell, is frequently associated with urticaria, wheezing, and pruritus which occur following exposure to an indentifiable trigger. Kinin-mediated angioedema can occur in the absence of an identifiable trigger and in the absence of any clinical signs denoting degranulation of mast cells [3].

Usually, angioedema results in the formation of non-pitting oedema involving the face, lip, mouth, extremities, tongue, and genitals. In some extensive cases, it may involve the intestinal mucosa leading to intestinal stenosis and may also cause obstruction of the airway due to laryngeal oedema [3]. Angiodema, though mostly a benign and self-limiting condition, can also lead to life-threatening complications with mortality rate of 15-33% [4].

Angioedema can occur in patients who have reduced levels or abnormal function of regulatory complement protein, C1-INH [4]. Hereditary and acquired forms of C1-INH have been studied [4]. Suspicion of angioedema may arise in a patient presenting with typical clinical features and history of a new drug intake or patient having history of similar attacks in the past. Family history of such patients is of utmost importance to diagnose hereditary angioedema. Only few cases have been reported of acquired angioedema in patients with SLE and some of them had an unfavourable outcome when the patients had to be intubated and admitted in ICU due to obstruction of the airway. Kumar N et al., had reported a case of a young female who presented with angioedema with airway oedema with no known trigger. The airway oedema subsided with steroid therapy, and the patient was later diagnosed with SLE [1]. However, in the present case the patient was already known to have SLE with a known trigger in the form of aloe vera cream. Lahiri M and Lim AY, had reported a case of a 53-year-old female who had presented with angioedema and required tracheostomy as intubation was extremely difficult owing to the airway oedema [2]. The chest radiograph of this patient showed pneumonic infiltration along with evidence of lupus nephritis. She was suspected to have SLE with secondary antiphospholipid antibody syndrome or antiphospholipid syndrome (APS), which was confirmed based on positive anticardiolipin (aCL) and anti-β2-glycoprotein-1 (β2GP1) antibodies. However, aCL and β2GP1 antibodies were negative. Bienstock D and Mandel L, had reported a similar case of facial angioedema with SLE, which was a form of acquired angioedema [3]. Habibagahi Z et al., and Furlanetto V Jr. et al., had reported similar cases of refractory angioedema in a case of SLE such as described above [5,6].

Systemic lupus erythematosus is a multi-systemic autoimmune disease with unknown aetiology with varied clinical and laboratory findings and a wide variable course and prognosis [7,8]. It may present as a single episode or may show a relapsing and remitting course which may be associated or may be independent of lupus flares. Dhaou B et al., had reported a similar case report of recurrent relapses in a case of SLE over the course of four years [9]. Palagini L et al., had reported a rise in depression amongst patients of SLE due to it's relapsing and remitting nature affecting the quality of life [10].

In the case presented, angioedema occurred after local application of aloe vera cream which might be the trigger. She was given intravenous steroids and antihistamines in view of angioedema and intravenous antibiotics were also started to cover for any infection leading to flaring of SLE. As there was no urticaria, the mechanism of mast cell mediated angioedema is less likely, making kinin-mediated pathway the likely mechanism of action in this case. Absence of a family history makes hereditary angioedema less likely to be the causative factor. This led to suspicion of a rare disorder of C1 INH deficiency mediated recurrent angioedema in our patient. Although C1 INH couldn't be measured, the low levels of C4 and C1q at presentation made the diagnosis of acquired angioedema a likely possibility. In the absence of any lymphoproliferative disorder it was postulated that acquired angioedema was the most likely cause of recurrent angioedema in this case, which was associated with SLE and proved to be fatal. The patient had received intravenous steroids along with cyclophosphamide, thus covering for angioedema as well as lupus flare. However, even with all the efforts, she succumbed to severe angioedema, a rare complication associated with SLE. Even though numerous varied presentations of SLE have been reported [11], the disease still continues to puzzle clinicans throughout the globe.

CONCLUSION(S)

Although rare, recurrent angioedema can be a lethal complication associated with SLE even in the young population. Therefore, the treating clinicians should be well aware of this dangerous entity in order to prevent morbidity and mortality associated with SLE.

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