*Case Report*

# *A Rare Presentation of Systemic Lupus Erythematosus as Angioedema in a Peripheral Hospital*

***Mia MR[1], Khan ANMN[2], Mustofa MG[3] and Tajkia T[4]***

1) **Dr. Mohammad Rajibe Mia, Associate Professor, Department of Endocrinology, President Abdul Hamid Medical College Hospital , Jafrabad , Karimganj , Kishoreganj*

2) *Professor (cc) Dr.A.N.M. Naushad Khan, Principal, Head of the Department of Anaesthesia, President Abdul Hamid Medical College Hospital , Jafrabad , Karimganj , Kishoreganj*

3) *Dr. Md. Golam Mustofa, Assiatant Professor, Department of Orthopedic, President Abdul Hamid Medical College Hospital , Jafrabad , Karimganj , Kishoreganj*

4) *Dr Tanzina Tajkia, Assistant Professor, Department of Physiology, President Abdul Hamid Medical College, Karimganj, Kishoregonj.*

**** Address of Correspondence***

## Abstract

*Angioedema is an immune-mediated tissue swelling that can be life-threatening if it compromises the airway. This makes prompt diagnosis and management of the condition excruciatingly important. It can be hereditary or associated with infections, malignancies, and autoimmune diseases. There have been reported cases in the literature where Systemic lupus erythematosus patients developed acquired angioedema raising suspicion of a possible association between the two conditions.*

*We describe a case of a patient with unknown medical issues, presenting with acute onset of her first episode of angioedema with airway irritation, periorbital swelling and lips swelling. Because of the rarity of awareness of the possible association of our conditions of interest, there was an inevitable delay in diagnosis and the patient was eventually diagnosed to have Systemic lupus erythematosus and associated acquired angioedema as its first presentation.*

*This case report highlights the importance of maintaining high suspicion for Systemic lupus erythematosus in patients with an isolated first episode of angioedema.*

***Keywords:*** *internal medicine and rheumatology, bradykinin mediated angioedema, lupus flare, angioedema, systemic lupus erythematosus.*

## Introduction

Systemic lupus erythematosus (SLE) is a systemic inflammatory condition with autoimmune pathophysiology, characteristic of autoantibodies causing end-organ damage[1]. The clinical presentation is widely variable including cardiovascular emergencies (pericarditis, cardiac tamponade, myocardial infarction, thrombosis), neurological (stroke), pulmonary (pulmonary hemorrhage/ edema), and even renal (lupus nephritis)[2]. Since mortality in SLE patients is approximately five times higher than in the general population, it is very important to timely recognize different presentations of lupus patients, and to initiate the appropriate treatment without delay.

Angioedema (AE) can be a life-threatening immune-mediated inflammation of skin/subcutaneous tissue risking airway compromise. Also known as angioneurotic edema, AE is associated with 15-33% of SLE patients[3]. However, it is important to establish it as the first clinical presentation of SLE for timely diagnosis. It is to emphasize a prompt systematic approach for management to reduce mortality and morbidity from angioedema in SLE patients.

We present a rare case of facial angioedema as the first presentation of SLE to a peripheral medical college hospital, discussing the barriers in diagnosis and delayed treatment due to the rarity of the presentation.

## Case report/ presentation

A 18 year- old girl with no significant past medical history presented to Otolaryngology (ENT) department with throat irritation with facial swelling. First consulting ENT specialist request for neuromedicine consultation and make differentials as drug reaction or angioedema. Treated with antihistamin and steroid and also antibiotics. However, her symptoms were not improving. This patient got admission in female medicine ward of President Abdul Hamid Medical College Hospital, Kishoregang, Bangladesh. On examination we found periorbital swelling, puffiness of face and oedematus swelling of both lips. But she denied having difficulty breathing. A review of systems were otherwise unremarkable. The patient's medications list was unremarkable for any triggering medications including angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs). On physical examination there was bilateral periorbital swelling, puffiness of face and oedematus swelling of both lips with pink-colored depigmented scaly plaques with hyper pigmented borders on the face. There was no signs of tongue swelling.

Initial laboratory findings revealed urine RME normal, borderline hemoglobin (10.1 g/dl), white blood cell (WBC) count (1500/cmm) and high erythrocyte sedimentation rate (ESR) (65 mm at 1st hour), platelet count 115000, peripheral blood film bicytopenia (low WBC, low platelet) serum creatinine 1.26 mg/dl, ultrasonography whole abdomen normal, CRP 2.15 mg L, ALT 107 U/L, S.creatinine 0.8 mg/dl, S.bilirubine 0.7 mg/dl, S.IgE 261.54 KIU/L (< 150 KIU/L). Subsequent laboratory report shows urine RME : plenty RBC, ANA:198.02 u/ml (strong positive : >60.00), anti-ds DNA 3.15 (positive: >1.11). Up to this patient was diagnosed as Systemic Lupus Erythematosus (SLE) with angioedema and referred to Bangabandhu Sheikh Mujib Medical University (BSMMU) for further evaluation.

**SLE Clinic of BSMMU:**

ANA : strongly positive; ani-ds DNA : 496.o u/ml (>75u/ml=positive); HBsAg, anti-HCV, anti-HBc(total), urine culture, TSH, FT4, S. electrolytes all were normal range. LDH : 314u/L(120-246u/L); urinary total protein(UTP)/24 hours = 0.31gm/day; 24 hours urinary volume = 1600 ml/day, urinary protein was "++".

From BSMMU treatment was given with hydroxichloroquin, prednisolone, indomethacin, calcium and PPI. With these evaluation and treatment her clinical conditions began to improve with the eventual resolution of angioedema.

In the setting of an improving disease course, the diagnosis of SLE with Angioedema become more definitive. On her subsequent OPD follow-up she was doing well and angioedema had not recurred.

## Discussion

Angioedema (AE), also known as angioneurotic edema, is the acute onset of immune-mediated skin tissue edema involving the subcutaneous layer mostly commonly in the periorbital region or lips[4]. It can be either hereditary (HAE) or acquired[5]. There are two common types of hereditary angioedema depending on C1-esterase inhibitor mutations affecting either secretion or functionality of the protein[6]. A third type is a familial form with normal C1 esterase inhibitor (C1-INH) titers and function[7].

Acquired angioedema (AAE) can be associated with lymphoproliferative diseases such as lymphoma, monoclonal gammopathy of uncertain significance, neoplasias, infections, and, more recently coming to light, systemic lupus erythematosus (SLE)[8].

Two main mechanisms are known for AAE. Type 1 involves accelerated catabolism of C1 esterase inhibitor and type 2 is characterized by the presence of an autoantibody against the enzyme[9].

The definitive pathophysiology of AAE in SLE is unclear at this time. Hereditary AE has been reported in SLE patients, but there is an increasing concern about AAE in SLE as well now. SLE patients have demonstrated a significantly high number of acetylated modifications of C1-inhibitor (C1-INH) and high autoantibody titers for C1-INH[10]. While another study suggests that C1-INH levels can be normal in SLE individuals, but significantly less reactive to C1s and C1r with no identified autoantibodies or mutations. This study on 8 patients raised the possibility of distinct pathophysiology for SLE AAE not previously known[11].

SLE and AAE patients may have other comorbid conditions but lymphoma should be ruled out in most high-risk individuals with AAE. Treatment and management are urgently indicated for airway protection and to avoid fatalities. Concomitant treatment of SLE with steroids, cyclophosphamide, hydroxychloroquine, etc in AAE-diagnosed patients has shown complete resolution of symptoms which emphasizes that the association is not likely by chance[12,13].

We present a case of angioedema as the first presentation of SLE, which was misdiagnosed as drug reaction. Due to low concern of AAE as a presentation of SLE, the patient was treated for multiple other etiologies before initiation of lupus treatment.

Hereditary may be seen in up to 2 % of SLE patients. On the other hand, acquired AE in lupus is rare and the prevalence of SLE in AE is expected to be less than 1%[14]. Therefore, for diagnostic purposes, there should be suspicion of non-allergic causes as well. C1-INH with complement levels can aid in diagnosis.

Immunosuppressive therapy results in the normalization of C3, C4, and C1-INH levels along with the resolution of angioedema[15]. Among AE-related comorbidities in patients with SLE, the atopic disorder, Leukocytoclastic vasculitis, infections, and eosinophilia are common.

There's a "third type" of C1-INH-AAE in clinically silent SLE patients with low C1-INH antigenic and functional levels along with hypocomplementemia, both of which normalized with a resolution of AE after immunosuppressive therapy. If there is C1-INH deficiency, C1q levels are found to be decreased in about 70% of patients with AAE, compared with HAE[16].

If the cause is determined to be C1-INH deficiency due to increased breakdown, both Danazol and Stanozolol (synthetic steroids) can be tried for treatment, although there have been reports of the paradoxical flare of lupus-like disease when both HAE, as well as non-C1 INH dependent angioedema, were treated with danazol. Rituximab has also demonstrated success in treatment-resistant acquired angioedema due to a deficiency of C1-INH inhibitor in a small pool of patients[17].

Most patients are treated with high-dose steroids - both for angioedema and active lupus, though lupus activity may be suppressed at the time of presentation with AAE. Steroids work to reduce angioedema swelling caused by non-histaminergic mechanisms, with minimal adverse effects[18]. In severe emergency cases, C1-INH can also be administered, as well as a fresh frozen plasma or solvent/detergent-treated plasma[19].

## Conclusions

Well-timed diagnosis and management of AE that is the first presentation of SLE can help reduce morbidity and mortality in our patients. It is important to realize the mechanism that is more commonly C1-INH dependent to be able to provide the most accurate treatment. High suspicion should be maintained for SLE among possible etiologies when patients present with isolated, first episode of AE. Treatment of SLE in AAE patients with high dose steroids, aids in therapy, as well as C1-INH concentrate, rituximab and fresh frozen plasma as part of general management of life-threatening AE.

## References


1. Systemic lupus erythematosus. Manson JJ, Rahman A. Orphanet J Rare Dis. 2006;1:6. [PMC free article] [PubMed] [Google Scholar]
2. The spectrum of clinical manifestations, outcome and treatment of pericardial tamponade in patients with systemic lupus erythematosus: a retrospective study and literature review. Rosenbaum E, Krebs E, Cohen M, Tiliakos A, Derk CT. Lupus. 2009;18:608–612. [PubMed] [Google Scholar]
3. Acquired angioedema in juvenile systemic lupus erythematosus: case-based review. Tekin ZE, Yener GO, Yüksel S. Rheumatol Int. 2018;38:1577–1584. [PubMed] [Google Scholar]
4. Masqurades of angioedema and urticaria. Van Dallen RG, Maddox DE, Dutta EJ. Ann Allergy Asthma Immunol. 2002;88:10–14. [PubMed] [Google Scholar]
5. Angioedema. LoVerde D, Files DC, Krishnaswamy G. Crit Care Med. 2017;45:725–735. [PubMed] [Google Scholar]
6. C1 inhibitor and hereditary angioneurotic edema. Davis AE 3rd. Annu Rev Immunol. 1988;6:595–628. [PubMed] [Google Scholar]
7. Clinical practice. Hereditary angioedema. Zuraw BL. N Engl J Med. 2008;359:1027–1036. [PubMed] [Google Scholar]
8. Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. Agostoni A, Aygören-Pürsün E, Binkley KE, et al. https://doi.org/10.1186/1710-1492-6-14 J Allergy Clin Immunol. 2004;114:0–131. [PMC free article] [PubMed] [Google Scholar]
9. Acquired C1-inhibitor deficiency in a patient with systemic lupus erythematosus: a case report and review of the literature. Nettis E, Colanardi MC, Loria MP, Vacca A. Eur J Clin Invest. 2005;35:781–784. [PubMed] [Google Scholar]
10. Low levels of IgM and IgA recognizing acetylated C1-inhibitor peptides are associated with systemic lupus erythematosus in Taiwanese women. Tsai KL, Liao CC, Chang YS, et al. Molecules. 2019;24 [PMC free article] [PubMed] [Google Scholar]
11. C1 inhibitor functional deficiency in systemic lupus erythematosus (SLE) Jazwinska EC, Gatenby PA, Dunckley H, Serjeantson SW. Clin Exp Immunol. 1993;92:268–273. [PMC free article] [PubMed] [Google Scholar]
12. Facial angioedema and systemic lupus erythematosus: case report. Bienstock D, Mandel L. J Oral Maxillofac Surg. 2015;73:928–932. [PubMed] [Google Scholar]
13. Acquired C1 inhibitor deficiency revealing systemic lupus erythematosus. Ochonisky S, Intrator L, Wechsler J, Revuz J, Bagot M. Dermatology. 1993;186:261–263. [PubMed] [Google Scholar]
14. Immunoregulatory disorders associated with hereditary angioedema. I. Clinical manifestations of autoimmune disease. Brickman CM, Tsokos GC, Balow JE, et al. J Allergy Clin Immunol. 1986;77:749–757. [PubMed] [Google Scholar]

15. Clinical similarities among bradykinin-mediated and mast cell-mediated subtypes of non-hereditary angioedema: a retrospective study. Schulkes KJ, Van den Elzen MT, Hack EC, Otten HG, Bruijnzeel-Koomen CA, Knulst AC. Clin Transl Allergy. 2015;5:5. [PMC free article] [PubMed] [Google Scholar]

16. Acquired angioedema. Cicardi M, Zanichelli A. Allergy Asthma Clin Immunol. 2010;6:14. [PMC free article] [PubMed] [Google Scholar]

17. Angioedema and systemic lupus erythematosus--a complementary association? Lahiri M, Lim AY. https://annals.edu.sg/pdf/36VolNo2Feb2007/V36N2p142.pdf. Ann Acad Med Singap. 2007;36:142–145. [PubMed] [Google Scholar]

18. Prophylactic therapy for hereditary angioedema. Longhurst H, Zinser E. Immunol Allergy Clin North Am. 2017;37:557–570. [PubMed] [Google Scholar]

19. Emergency treatment of acute attacks in hereditary angioedema due to C1 inhibitor deficiency: what is the evidence? Longhurst HJ. Int J Clin Pract. 2005;59:594–599. [PubMed] [Google Scholar]