

Angioedema and Systemic Lupus Erythematosus – A Complementary Association?

Manjari Lahiri,¹MD, MRCP (UK), Anita YN Lim,²MRCP (UK), CCST (Rheumatology) UK RCP

Abstract

Introduction: We report angioedema as a rare presentation leading to a diagnosis of systemic lupus erythematosus (SLE). **Clinical Picture:** A diagnosis of angioedema was delayed in a patient presenting with limb and facial swelling until she developed acute upper airway compromise. After excluding allergic and hereditary angioedema, acquired angioedema (AAE) was suspected, possibly precipitated by respiratory tract infection. Associated clinical and laboratory features led to a diagnosis of SLE. **Treatment:** Management proved challenging and included high dose steroids and immunosuppressants. **Outcome:** The patient responded to treatment and remains in remission without recurrence of the angioedema. **Conclusion:** AAE occurs due to the acquired deficiency of inhibitor of C1 component of complement (C1 INH). Lymphoproliferative disorders and anti-C1 INH antibodies are well-described associations. However, one should also consider the possibility of SLE.

Ann Acad Med Singapore 2007;36:142-5

Key words: Complement C1 inactivator proteins, Angioneurotic oedema

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune multi-system disease of unknown aetiology with protean clinical and laboratory manifestations and a variable course and prognosis. We report angioedema as the initial presentation that led to a diagnosis of SLE in a middle-aged female.

Case Report

A 53-year-old Chinese female presented with swelling of the face, neck and left arm which was preceded by fever and coryzal symptoms. She had a previous history of psychiatric illness (schizophrenia with depressive features) following a stillbirth in 1993. However, in the absence of any further spontaneous fetal losses she was not suspected to have underlying connective tissue disease at that time. She reported allergy to penicillin and seafood (prawns) in the form of an urticarial rash several years before. However, she denied any recent exposures to drugs, food, insect venom stings and physical factors prior to the onset of facial and left arm swelling. She had no previous history of similar attacks, and no family history of angioedema. Her past medical history was otherwise unremarkable. She had defaulted follow-up with her psychiatrist, and had not been

on any regular medications. At the time of presentation, she appeared depressed, but had no overt psychotic symptoms.

On examination, she was frail and thin. She had erythematous swelling of her left arm without tenderness or induration, initially suggestive of cellulitis. This was associated with bilateral periorbital swelling and erythema, for which a differential diagnosis of angioedema or orbital cellulitis was entertained. There was no pedal or sacral oedema. She had livedo reticularis, but no urticaria. Fundoscopy revealed left central retinal vein occlusion (CRVO). Laboratory investigations showed pancytopenia, with a haemoglobin of 7.9 g/dL (normal range, 10.7 to 14.9), a white cell count of $3.69 \times 10^9/L$ (3.30×10^9 to 9.66×10^9), an absolute lymphocyte count of $0.9 \times 10^9/L$ (1.04×10^9 to 2.86×10^9) and a platelet count of $90 \times 10^9/L$ (162×10^9 to 427×10^9). Serum urea was 13.4 mmol/L (normal range, 2 to 6.5), creatinine 116 mmol/L (50 to 90), albumin 20 gm/L (38 to 48) and C-reactive protein 6 mg/L (0 to 10).

She was treated empirically with oral antibiotics ciprofloxacin and clindamycin in view of the history of penicillin allergy. On the second day of admission she developed acute respiratory distress with stridor, and uvular and epiglottic oedema necessitating intubation in the operating theatre with a view to tracheostomy the event of

¹ Department of Medicine, Division of General Medicine and Rheumatology, National University Hospital, Singapore

² Department of Medicine, Division of Rheumatology, National University Hospital, Singapore

Address for Correspondence: Dr Manjari Lahiri, Department of Medicine, Level 3, Main Building, National University Hospital, 5 Lower Kent Ridge Road, Singapore 119074.

Email: manjari_lahiri@nuh.com.sg

failed intubation. The otorhinolaryngologists diagnosed extensive angioedema. A chest X-ray at this point also showed bilateral interstitial shadows suggestive of pneumonia. The ophthalmologist was consulted to rule out the possibility of cavernous sinus thrombosis. Magnetic resonance imaging (MRI) of the orbits (Fig. 1.) confirmed angioedema only. She was transferred to intensive care, where she was treated with high dose dexamethasone. However, her antibiotics were continued (ciprofloxacin was changed to levofloxacin) in view of the pneumonia, though the “cellulitis” was now thought to have been part of the extensive angioedema process and not infective in origin.

In view of the long-standing neuropsychiatric history on treatment until up to 3 years ago, livedo reticularis, CRVO and pancytopenia, SLE with secondary antiphospholipid syndrome was suspected. This was confirmed when further investigations revealed positive antinuclear antibody (ANA) with titres of >1:640, antibodies to double stranded DNA (dsDNA) >250 IU (normal <25 IU), low C3 at 13 mg/dL (normal, 85 to 185) and C4 at 5 mg/dL (10 to 50), positive anti-Ro and anti-La antibodies, IgG and IgM anticardiolipin antibodies (ACLA) at 69.6 GPL units/mL and 13.9 MPL units/mL respectively (normal <13.9 and 11.3 units/mL respectively) and positive lupus anticoagulant (LAC). In addition, she had clinical evidence of active lupus nephritis (24-hour urine protein of 1.71 gm/day, creatinine clearance 33 mL/min and active urine sediment).

She required prolonged mechanical ventilation in the intensive care unit (ICU) because of refractory angioedema. She was treated with intravenous corticosteroids (dexamethasone was changed to intravenous hydrocortisone on day 2, followed by pulsed high-dose methylprednisolone on day 5). Intravenous cyclophosphamide was added later on day 7 after the pneumonia had settled with antibiotics. As she was expected to have a difficult airway in the event of failed extubation, the intensivists subjected her to a daily “leak test” in which they deflated the endotracheal-tube cuff and watched for air-leak around it. In the absence of air-leak, they presumed residual laryngo-tracheal oedema and kept her intubated and ventilated. She had a stormy ICU stay complicated by an episode of urosepsis and gastrointestinal bleeding. In all, she required 8 days of mechanical ventilation. After 8 days, her leak test was negative and she was finally successfully extubated after first testing with a tube exchanger in place. Anticoagulation was held off at that time in view of the ongoing gastrointestinal bleeding.

In the outpatient setting, she has since received high-dose oral corticosteroids and 4 monthly pulses of intravenous cyclophosphamide, which have been complicated by severe steroid-induced osteoporotic spinal fractures, several bouts

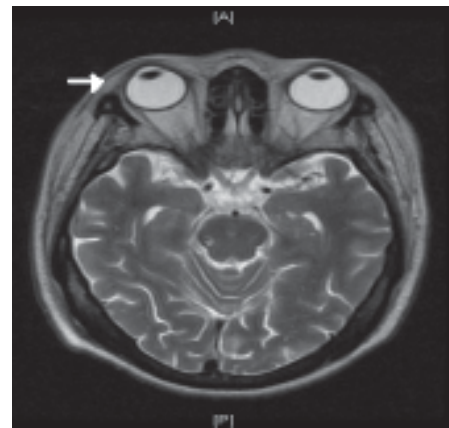


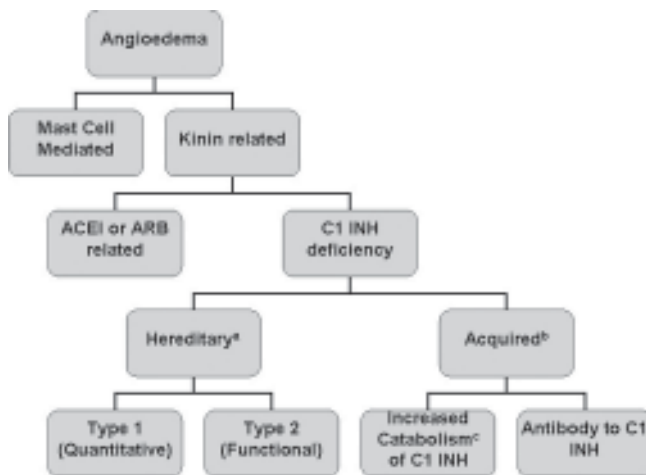
Fig. 1. MRI of the brain and orbits (T2 weighted image) showing angioedema and no evidence of cavernous sinus thrombosis. Arrow shows periorbital angioedema.

of sepsis and 2 episodes of herpes zoster. She was anticoagulated with warfarin later in the outpatient setting in view of her CRVO, pregnancy loss and positive antiphospholipid antibodies. Her maintenance treatment includes prednisolone 6 mg and azathioprine 75 mg daily. She is also on atypical antipsychotics prescribed by the psychiatrist. She is currently well; with proteinuria <1 g/day, creatinine clearance of 81 mL/min, normal full blood counts and improved mood. Her C4 complement had normalised on the first follow-up visit to 11 mg/dL (normal, 10 to 50), and further increased subsequently to 59 mg/dL at last follow-up, though C3 levels remain slightly low at 83 mg/dL (normal range, 85 to 185).

Discussion

Life-threatening angioedema requiring mechanical ventilation has been reported before in lupus patients.^{1,2} Though not common, it may present as a single episode or may remit and relapse in association with or independent of lupus flares.¹⁻³ Severe respiratory tract infection has been reported to be a precipitating factor.²

Angioedema can broadly be classified into 2 types (Fig. 2) – mast cell-mediated, which is by far the most common type seen in clinical practice, and kinin-mediated. The former may be associated with urticaria, wheezing and hypotension. A trigger can usually be identified, typically an allergen causing a type-1 hypersensitivity reaction, radiocontrast media causing direct mast-cell degranulation or a non-steroidal anti-inflammatory drug (NSAID) causing excessive leukotriene production through inhibition of cyclooxygenase (COX). Kinin-mediated angioedema, on the other hand, is characterised by angioedema in the absence of an identifiable trigger, and without urticaria or other features of mast cell degranulation as described above.



ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker; C1 INH: C1 inhibitor

^a A third type of hereditary angioedema has been reported.⁵

^b A third type of acquired angioedema has been postulated in lupus.³

^c Associated with a lymphoproliferative disorder.

Fig. 2. Approach to angioedema.

The most well described type of kinin-mediated angioedema is hereditary angioedema (HAE) due to deficiency of inhibitor of the C1 component of complement (C1 INH). This results in angioedema with a variable age of onset usually without an apparent trigger, although minor trauma, pregnancy and infections have often been described.⁴ There is usually a strong family history as HAE is an autosomal dominant condition. C1 INH deficiency leads to activation of complement and production of C2 fragment with vascular permeability-enhancing activity through the stimulation of the kallikrein – bradykinin pathway. Traditionally, 2 types of HAE have been described – deficiency of C1 INH antigen and a functional deficiency. However, a third hereditary form of angioedema has been reported in women, and appears to be unrelated to an abnormality in C1 INH.⁵

Angiotensin converting enzyme inhibitors (ACEIs) and to a lesser extent, angiotensin II receptor blockers (ARBs), have been associated with kinin-mediated angioedema due to inhibition of degradation of bradykinin.⁶ This mechanism is independent of C1 INH and is well reported.

Another type of kinin-mediated acquired angioedema (AAE) is also well described.⁷ This may be due to anti-C1 INH antibodies or enhanced catabolism of C1 INH in association with lymphoproliferative disorders. A later age of onset, absence of family history and low levels of C1q distinguish this from HAE. As opposed to HAE, which may be seen in up to 2% of lupus patients, AAE in lupus is rare. A third type of AAE in lupus has been postulated

associated with classical pathway mediated hypocomplementaemia (low C3 and C4), transient low C1-INH antigenic and functional levels, elevated IgG anti-CLR/C1q antibody, absence of anti-C1 INH autoantibodies and lymphoproliferative disease, and absence of clinical SLE activity during acute angioedema. Resolution of angioedema with immunosuppressive therapy was associated with normalisation of C3, C4 and C1-INH levels.³

Lupus patients with AAE may have an increased predilection for involvement of the central nervous system (CNS) due to the kinin-mediated increased vascular permeability in the CNS. Psychosis is usually a predominant feature.⁸

Danazol or stanozolol have been used for treatment, although paradoxically there are reports of a flare of lupus-like disease both when HAE as well as non-C1 INH-dependent angioedema were treated with danazol,^{9,10} C1 INH concentrate has been used in the research setting. Most patients receive high-dose steroids – both for the angioedema and active lupus, though lupus may be quiescent at the time of presentation with AAE. Recently, rituximab has been successfully used in 3 patients with AAE not associated with SLE, of whom 1 had anti-C1INH IgG, and another had indolent follicular B-cell lymphoma.¹¹

Our patient presented with angioedema and pneumonia. Careful history taking and physical examination revealed livedo reticularis and central retinal vein occlusion, which led to the suspicion and subsequently confirmation of the diagnosis of SLE. The distribution of angioedema was unusual, with extensive involvement of the left upper limb besides the head and neck, mimicking cellulitis. This led to a delay in the diagnosis until she developed acute upper airway compromise requiring endotracheal intubation and mechanical ventilation. We think antibiotics are unlikely to be the trigger as they were started in hospital after the onset of the angioedema and continued almost unchanged until after resolution of the episode. The absence of urticaria also made mast cell-mediated angioedema less likely. A more likely trigger could have been the respiratory infection which has been reported previously by Thong et al.² The delayed onset and the absence of a family history would be unusual for hereditary angioedema. This leads to the suspicion of the rarer acquired C1 INH deficiency-mediated angioedema. Though C1 INH and C1q levels were not measured at the time of presentation, the low levels of C4 which subsequently normalised with treatment are suggestive of possible AAE in our patient. As anti-C1 INH antibodies have never been described in SLE to date, and a search for a lymphoproliferative disorder proved unyielding, we speculate that our patient had the “new, third type of AAE”³ described above.

Our patient received intravenous steroids and

cyclophosphamide for both the lupus flare and angioedema. Danazol was withheld due to the conflicting evidence in the literature. She is under close follow-up, and has so far not had a relapse of the angioedema.

Conclusion

AAE is a rare kinin-mediated angioedema due to acquired deficiency of inhibitor of C1 component of complement. Management may be challenging. Apart from investigations to look for an underlying lymphoproliferative disorder, one should also consider and look for evidence of SLE.

REFERENCES

1. Ko CH, Ng J, Kumar S, Hurst M. Life-threatening angioedema in a patient with systemic lupus. *Clin Rheumatol* 2006;25:917-8.
2. Thong BY, Thumboo J, Howe HS, Feng PH. Life-threatening angioedema in systemic lupus erythematosus. *Lupus* 2001;10:304-8.
3. Cacoub P, Fremeaux-Bacchi V, de Lacroix I, Guillien F, Kahn MF, Kazatchkine MD, et al. A new type of acquired C1 inhibitor deficiency associated with systemic lupus erythematosus. *Arthritis Rheum* 2001;44:1836-40.
4. Bowen T, Cicardi M, Farkas H, Bork K, Kreuz W, Zingale L, et al. Canadian 2003 International Consensus Algorithm for the Diagnosis, Therapy, and Management of Hereditary Angioedema. *J Allergy Clin Immunol* 2004;114:629-37.
5. Bork K, Barnstedt SE, Koch P, Traupe H. Hereditary angioedema with normal C1-inhibitor activity in women. *Lancet* 2000;356:213.
6. Seidman MD, Lewandowski CA, Sarpa JR, Potesta E, Schweitzer VG. Angioedema related to angiotensin-converting enzyme inhibitors. *Otolaryngol Head Neck Surg* 1990;102:727-31.
7. Geha RS, Quinti I, Austen KF, Cicardi M, Sheffer A, Rosen FS. Acquired C1-inhibitor deficiency associated with antiidiotypic antibody to monoclonal immunoglobulins. *N Engl J Med* 1985;312:534-40.
8. Nakamura S, Yoshinari M, Saku Y, Hirakawa K, Miishima C, Murai K, et al. Acquired C1 inhibitor deficiency associated with systemic lupus erythematosus affecting the central nervous system. *Ann Rheum Dis* 1991;50:713-6.
9. Donaldson VH, Hess EV. Effect of danazol on lupus-erythematosus-like disease in hereditary angioneurotic oedema. *Lancet* 1980;2:1145.
10. Fretwell MD, Altman LC. Exacerbation of a lupus-erythematosus-like syndrome during treatment of non-C1-esterase-inhibitor-dependent angioedema with danazol. *J Allergy Clin Immunol* 1982;69:306-10.
11. Levi M, Hack CE, van Oers MH. Rituximab-induced elimination of acquired angioedema due to C1-inhibitor deficiency. *Am J Med* 2006;119:e3-5.