Irish Medical Journal
Established 1867

Issue: Ir Med J; Vol 114; No. 9; P472

Acquired Angioedema in a Child with Systemic Lupus Erythematosus

A. Sokay[1], A. Byrne[2], OG. Killeen[3,5], D. Rea[4], TR. Leahy[1,6]

1. Departments of Paediatric Immunology, Children's Health Ireland at Crumlin, Dublin.
2. Departments of Paediatric Allergy, Children's Health Ireland at Crumlin, Dublin.
3. Departments of Paediatric Rheumatology, Children's Health Ireland at Crumlin, Dublin.
4. Departments of Paediatric Radiology, Children's Health Ireland at Crumlin, Dublin.
5. Department of Paediatrics, University College Dublin.
6. Department of Paediatrics, University of Dublin, Trinity College, Dublin.

Abstract

Presentation
A fifteen-year-old girl newly diagnosed with SLE presented acutely with facial swelling, dysphagia and dysphonia.

Diagnosis
Clinical and radiological features coupled with a low C1q level led to a diagnosis of acquired angioedema.

Treatment
The patient responded to treatment with C1-inhibitor concentrate.

Conclusion
Acquired angioedema can be a presenting feature or a complication of SLE.

Introduction

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease. It is caused by loss of self-antigen tolerance, leading to development of autoantibodies and immune complexes that can be deposited in tissues leading to organ damage. Angioedema (AE) is swelling of the submucosal and/or subcutaneous tissues by fluid extravasation into interstitial tissue.

It can be mast cell (allergic) or bradykinin-mediated. Bradykinin-mediated AE can be hereditary (HAE) due to mutations in the *SERPING1* gene, leading to reduction in C1-esterase inhibitor (C1-INH) enzyme levels or function, or acquired (AAE). We present a case of AAE in a paediatric patient newly diagnosed with SLE.

Case Report

Our patient (P1) presented with a history of gradual onset joint pain, headache, and fatigue. She had a malar rash, active synovitis, hypertension, haematuria and proteinuria. Results of other investigations are listed in Table 1. Juvenile SLE (JSLE) was suspected, and the patient commenced on a combination of oral prednisolone and hydroxychloroquine pending renal biopsy to ascertain renal involvement.

P1 subsequently developed acute, non-pruritic, non-pitting, painful swelling of the left side of her face associated with difficulty swallowing and speaking, and oral ulceration. She had no allergic history, no urticaria, and no known exposure to suspected allergens. A craniofacial MRI (Figure 1) demonstrated extensive angioedema in the cheek and neck region, a focal area of retropharyngeal oedema and supraglottic oedema in the region of the arytenoids. Laboratory investigations (Table 1) demonstrated elevated inflammatory markers, undetectable C1q levels, elevated anti-C1q antibodies, normal C1-INH antigen and function and no evidence of anti-C1-INH antibody levels.

Differentials considered at the time included Vincent's angina, allergic and idiopathic angioedema. However, the combination of clinical and laboratory features established the diagnosis of AAE[1]. P1 was treated acutely with C1 inhibitor concentrate (1,000 U) which resolved the swelling after three doses. P1 was prescribed and trained in self-administration of icatibant as emergency treatment for any subsequent episodes of AAE. A renal biopsy confirmed stage IV membrano-proliferative glomerulonephritis. Her JSLE is currently well controlled after addition of mycophenolate mofitil, and she has had no further episodes of AAE.

Figure 1: Axial T2 fat suppressed image demonstrating supraglottic oedema noted at the level of the arytenoid cartilages (Block white arrow). No oedema of the true vocal cords (not shown) was noted. There is oedema noted in the subcutaneous soft tissues below the mandible extending onto the anterior neck (thin white arrow).

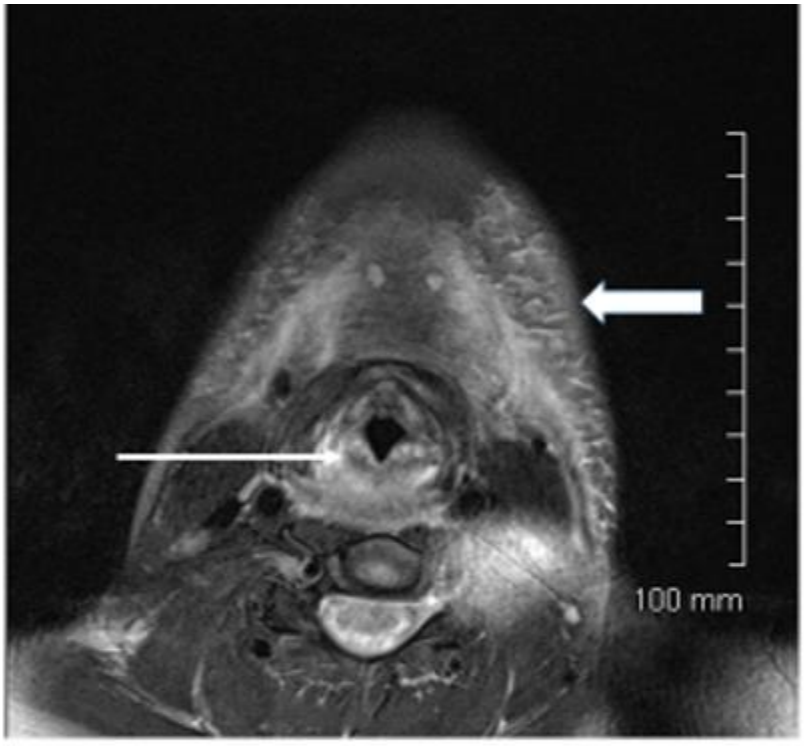

Table 1: Relevant Immunology laboratory results.

Parameter	**Value**	**Normal ranges**
White cell count (x 10^9/L)	11.39	(4.0-11.0)
Neutrophil count (x 10^9/L)	8.66	(1.8-8.0)
C-Reactive Protein (mg/L)	40	(< 10)
Erythrocyte Sedimentation rate (mm/Hr)	42	(1 - 9)
C3 protein (g/L)	0.56	(0.7-1.7)
C4 protein (g/L)	<0.08	(0.1-0.7)
C1q protein (mg/l)	<13	(50 – 250)
C1-INH antigen (g/L)	0.45	(0.15 - 0.43)
C1-INH function	normal	-
Anti-C1q antibodies	> 400	-
Anti-C1-INH antibodies	negative	-
Anti-nuclear antibody (ANA)	>1:160	-
Anti- DNA antibodies (Critidia)	1:160	-

Discussion

AAE was first described in 1972 in association with lymphosarcoma [2] and has subsequently been seen in association with other haematological malignancies [3; 4]. It can also be both a presenting feature and complication of SLE [5; 6]. SLE has been shown to represent an independent risk factor for hospitalization for angioedema [7]. The exact patho-physiology of AAE is unclear. It may be due to inactivation of C1-inhibitor by auto-antibodies or binding of C1-INH by anti-idiotype antibodies leading to formation of immune complexes that activate the C1 pathway, thereby consuming C1-INH.

The incidence of AAE is unknown, but in one centre was estimated to be approximately one tenth that of HAE[8]. AAE tends to occur in older females, particularly after the fourth decade[3; 4; 8], but rarely cases have been described in younger patients with JSLE similar to P1 [9]. Unlike HAE, there is a higher incidence of facial and laryngeal acute angioedema attacks [3; 4; 8]. Attacks can be life-threatening (due to airway obstruction from laryngeal oedema) and recalcitrant to standard treatment [3; 10]. Treatment of acute episodes includes C1-INH concentrate (given IV at a dose of 20mg/Kg) or icatibant, a selective competitive antagonist of the bradykinin type 2 receptor. Treatments used for long term prophylaxis include regular IV/subcut C1-INH concentrate, antifibrinolytic agents (e.g. tranexamic acid), attenuated androgens (e.g. danazol). More recently, lanadelumab, a monoclonal antibody to kallikrein that can be administered subcutaneously, has been used as long-term prophylaxis.

This case report highlights the need to consider both HAE and AAE in patients with SLE who present with acute angioedema, and the need to consider autoimmune conditions such as SLE and/or haematological malignancies in patients who present with bradykinin-mediated angioedema and no evidence of HAE.

Declaration of Conflicts of Interest:
None to declare.

Corresponding Author:
Dr Anitha Sokay
Immunology Department,
CHI Crumlin,
Dublin 12.
E-Mail: asokay.ire@gmail.com

References:

1. Bowen, T., Cicardi, M., Farkas H., Bork, K., Longhurst H.J., Zuraw B. et al. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. Allergy Asthma Clin Immunol 2010; 6:4
2. Caldwell J.R., Ruddy S., Schur P.H., Austen K.F. 1972 Acquired C1 inhibitor deficiency in lymphosarcoma. Clinical Immunology and Immunopathology Volume 1, Issue 1, October 1972, P 39-52
3. Cicardi M., Zingale L.C., Pappalardo E., Folcioni A., Agostoni A. Autoantibodies and lymphoproliferative diseases in acquired C1-inhibitor deficiencies. Medicine Baltimore 2003; 82:274-281
4. Gobert D., Paule R., Ponard D., Levy P., Frémeaux-Bacchi V., Bouillet L. et al. A nationwide study of acquired C1-inhibitor deficiency in France: Characteristics and treatment responses in 92 patients. Medicine Baltimore 2016 Aug 95,33 e4363.
5. Cacoub P., Frémeaux-Bacchi V., De Lacroix I., Guillien F., Kahn M.F., Kazatchkin M.D. et al. A new type of acquired C1 inhibitor deficiency associated with systemic lupus erythematosus. Arthritis Rheum 2001 Aug; 44, 8: 1836-1840.
6. Kumar N., Surendran D., and Bammigatti C. Angioedema as the presenting feature of systemic lupus erythematosus. BMJ Case Rep 2018.
7. Luo Y., Fan X., Jiang C., Ramos-Rodriguez A., Wen Y., Zhang J. at al. Systemic Lupus Erythematosus and Angioedema: A Cross-Sectional Study From the National Inpatient Sample. Arch Rheumatol 2019 Jan 28;34, 3:301-307
8. Zanichelli A., Azin G.M., Wu M.A., Suffritti C., Maggioni L., Caccia S. et al. Diagnosis, Course, and Management of Angioedema in Patients With Acquired C1-Inhibitor Deficiency. J Allergy Clin Immunol Pract 2017; 5:1307
9. Tekin Z.E., Yener G.O., Yüksel, S. Acquired angioedema in juvenile systemic lupus erythematosus: case-based review. Rheumatol International 2018 38: 1577-1584.
10. Thong B.Y., Thumboo J., Howe H.S., Feng, P.H.Life-threatening angioedema in systemic lupus erythematosus. Lupus 2001 10, 304-308.