Available online at www.medicinescience.org

CASE REPORT

Medicine Science International Medical Journal

Medicine Science 2020;9(2):512-4

A patient with hereditary angioedema and systemic lupus erythematosus: Coincidence or coexistence?

Gokhan Aytekin, Fatih Colkesen, Eray Yildiz, Sevket Arslan

Necmettin Erbakan University, Meram School of Medicine, Department of Internal Medicine, Division of Clinical Immunology and Allergy, Konya, Turkey

Received 27 November 2019; Accepted 15 January 2020
Available online 20.04.2020 with doi: 10.5455/medscience.2019.08.9196

Abstract

Angioedema is classified into two major groups: mast cell-mediated (histaminergic) and bradykinin-mediated angioedema. Hereditary angioedema and acquired angioedema are well-defined groups of bradykinin-mediated angioedema. Both hereditary angioedema and acquired angioedema demonstrate a similar clinical presentation and can be challenging to differentiate. The prevalence of autoimmune diseases is higher in patients with HAE and lupus is an autoimmune disease associated with HAE. In this case, we aimed to present a male patient who was monitored with the diagnosis of HAE and developed systemic lupus erythematosus (SLE) in the follow-up and to discuss whether the patient had hereditary angioedema and concomitant lupus, or acquired angioedema secondary to SLE.

Keywords: Hereditary angioedema, lupus, hemolytic anemia, acquired angioedema

Introduction

Angioedema is self-limited, localized subcutaneous or submucosal swelling, which results from extravasation of fluid into interstitial tissues. Angioedema usually leads to non-pitting edema in areas with loose connective tissue, such as the face, lips, mouth, tongue, extremities, and genitalia. Although regarded as benign and self-limited, generalized angioedema of the larynx, upper airways and tongue may cause asphyxia.

Angioedema is classified into two major groups: mast cell-mediated (histaminergic) and bradykinin-mediated angioedema. Hereditary angioedema is a well-defined group of bradykinin-mediated angioedema. Hereditary angioedema (HAE) is an autosomal dominant disease due to a qualitative or quantitative deficiency in C1 inhibitor. Another rare clinical condition with C1 inhibitor deficiency is acquired angioedema secondary to lymphoproliferative, malignant or autoimmune conditions. Both hereditary angioedema and acquired angioedema demonstrate a similar clinical presentation and can be challenging to differentiate. The prevalence of autoimmune diseases is higher in patients with HAE [1-3]. Lupus is an autoimmune disease associated with HAE. [4,5]. However, autoimmune diseases such as lupus may also cause acquired angioedema with similar clinical manifestations.

In this case, we aimed to present a male patient who was monitored with the diagnosis of HAE and developed systemic lupus erythematosus (SLE) in the follow-up and to discuss whether the patient had hereditary angioedema and concomitant lupus, or acquired angioedema secondary to SLE.

Case Report

A 36-year-old male patient with multiple hereditary angioedema patients in his family was admitted to our clinic with recurrent attacks of angioedema in the upper extremities and neck area without any accompanying itching. The patient's history revealed that he had used enoxaparin for 6 months due to deep vein thrombosis a year ago, but he did not use any drugs that would cause angioedema. The patient reported that the angioedema attacks started 6 months ago and became more frequent in the past month. He stated that although he used the antihistamine and steroid treatments given at another center at the appropriate dose and time, he did not benefit. When he applied to our clinic, we realized that the the patient's angioedema was nonpruritic and C4: 0.0688 g/L [0.1-0.4], C1 esterase inhibitor level: 7.45 [18-40], C1 esterase inhibitor activity: 8% [70-130%]. As a result of the family

***Coresponding Author:** Gokhan Aytekin, Necmettin Erbakan University, Meram School of Medicine, Department of Internal Medicine, Division of Clinical Immunology and Allergy, Konya, Turkey,
E-mail: ayteking@gmail.com

history, clinical and laboratory findings, the patient was diagnosed with hereditary angioedema type 1. A patient who could not tolerate tranexamic acid treatment and did not want to use danazol was prescribed C1 esterase inhibitor and icatibant as on-demand therapy.

The patient presented to our clinic 3 months later with symptoms of fatigue, weakness, and yellowing of the skin and urine. The patient had no history of infection or drug use that would cause these symptoms. During the physical examination, the patient appeared pale and exhausted. The skin and sclera were icteric. Laboratory tests revealed hemoglobin: 4.4 g/L, platelet count: 119,000/mm³, lymphocyte count: 670 cells/mm³, lactate dehydrogenase (LDH): 787 U/L, total bilirubin/indirect bilirubin: 3.22 / 2.41 mg/dL, direct Coombs test (antibody and complement-mediated) and indirect Coombs test: 4 + and reticulocytosis. The patient was hospitalized with a preliminary diagnosis of autoimmune hemolytic anemia. Additional tests revealed ANA (anti-nuclear antibody) granular ++, anti-dsDNA: 1+, anti-cardiolipin immunoglobulin (Ig) G and IgM (+). No hematuria or proteinuria was detected. In the light of these findings, the patient was diagnosed with anti-phospholipid syndrome and systemic lupus erythematosus according to the Systemic Lupus International Collaborating Clinics (SLICC) criteria. An analysis of C1q to confirm whether the previously diagnosed HAE type 1 was secondary to current SLE was 26 mg/dL (12-26 mg/dL). The patient's angioedema was not considered to be associated with the current SLE.

After 3 days of pulse methylprednisolone therapy (1000 mg/day), oral prednisolone maintenance therapy 80 mg/day (1 mg/kg/day) was given. The patient is currently receiving treatment with prednisolone 4 mg/day, hydroxychloroquine 200 mg b.i.d., and azathioprine 100 mg q.d. In addition, administration of rituximab treatment is planned for 6 months.

Table 1. Laboratory results of the patient

	Reference values	12.11.2018 (when HAE was diagnosis)	05.07.2019
C4	0.1-0.4 g/l	0.0688	
C3	0.9-1.8	0.575	
C1 esterase inhibitor level	18-40	7.45	
C1 esterase inhibitory activity	%70-130	<8%	
C1q	12-26 mg/dL	26	
Hemoglobin (g/dl)	12.1-17.2	12.1	4.4
Neutrophils (/mm³)	1500-7.300	3900	6800
Lymphocytes (/mm³)	800-5500	800	670
Platelets (1000xcell/mm³)	150-400	150	119
Mean Corpuscular Volume (MCV)	80-100 fl	100	112
Lactate dehydrogenase (LDH)	135-225 U/L	300	787
Total bilirubin /	0.2-1.2 mg/dl		3.22 mg/dl
indirect bilirubin	0.1-0.7 mg/dl		2.41 mg/dl
0.1-0.7 mg/dl			+++
2.41 mg/dl			++++
Direct Coombs Test (IgG)			++
Direct Coombs Test (complement)	0.5-2.0		6.13
Indirekt Coombs Testi (antikor tarama)	0.3-2		<0.07
Reticulocytes %			Granulary (++) positive
Haptoglobin			+
ANA			negative
Anti ds DNA	0-20		54.3
Anti ENA profile			positive
RF			positive
Anti-Cardiolipin IgG			negative
Anti-Cardiolipin IgM			positive
Anti ENA profile			negative
RF	-20		54.3
Anti-Cardiolipin IgG			positive
Anti-Cardiolipin IgM			positive
Proteinuria			negative

C: complement, Ig: Immunoglobulin, ANA: antinuclear antibody, Anti ds DNA: anti-double stranded DNA, ENA: extracted nuclear antigens, RF: Rheumatoid factor,

Discussion

Hereditary angioedema (HAE) is a rare autosomal dominant disease due to a qualitative or quantitative deficiency in C1 inhibitor [6]. Angioedema is characterized by swelling of the subcutaneous and/or submucosal tissue in the form of attacks. It is also important that laryngeal attacks can cause asphyxia due to obstruction of the upper airways and that gastrointestinal attacks can mimic acute abdominal pain leading to unnecessary laparotomies.

In this case histamine-mediated angioedema was not considered because the patient had no complaints of pruritus, and angioedema was unresponsive to antihistamine and steroid treatment. Although the coexistence of HAE and lupus has been reported in the literature, the coexistence of HAE and SLE is very rare. The coexistence of hereditary angioedema and lupus was first reported in 1973 by Kohler et al [5]. With this rare coexistence, it is both important and challenging to determine whether the primary diagnosis is HAE accompanied by lupus or acquired C1 inhibitor deficiency secondary to lupus. The most significant clinical difference between the two conditions is the age of onset of the disease. Acquired angioedema typically occurs after the fourth decade of life [7]. Whereas, with HAE, the first attack occurs in childhood and adolescence in the majority of patients [8]. In addition, acquired angioedema patients often have an underlying lymphoproliferative, malignant or autoimmune disease. Unlike hereditary angioedema patients, acquired angioedema patients have less gastrointestinal involvement and laryngeal involvement is more common in these patients [9]. Unlike hereditary angioedema patients with a strong family history, family history is not expected in these patients. The most significant difference in terms of laboratory tests is the C1q level. While C1q levels are expected to be normal in hereditary angioedema patients, these levels are expected to be low due to increased catabolism of the C1q enzyme in acquired angioedema patients.

Donaldson et al. reported the prevalence of lupus in HAE patients as 2.2% [10]. Serezal et al. carried out a study with 6 patients (5 females and 1 male) diagnosed with both HAE and lupus at 7 centers in France between 1970-2013 [11]. In this study, the age at diagnosis of HAE was 17.5 years while the age at diagnosis of lupus was 20 years, and they were diagnosed much earlier for both diseases than our case. In a review of 13 patients with HAE and lupus, Massa et al. identified a history of HAE in 9 of the patients and accepted that the other cases of HAE developed due to a de novo mutation [12].

In various studies, the coexistence of HAE and SLE has been associated with deficiencies in the classical complement pathway [13]. SLE develops in about three-quarters of patients with congenital C4 deficiency [14]. Due to C4 deficiency, the inadequate clearance of immune complexes following infections may contribute to the development of lupus [15]. In HEA, C4 levels are also low due to increased catabolism and therefore, the risk of developing SLE may be increased [16].

Conclusion

In conclusion, the coexistence of HAE and SLE is rare, yet possible due to a joint disorder in the complement pathway. Clinicians who study this group of patients should also consider SLE as one of the possible causes in HAE cases with different clinical findings.

Competing interests
The authors declare that they have no competing interest.

Financial Disclosure
All authors declare no financial support.

Ethical approval
Ethics committee approval is not required in retrospective studies.

References

1. Lipsker D, Hauptmann G. Cutaneous manifestations of complement deficiencies. Lupus. 2010;19:1096-106.
2. Nzeako UC, Frigas E, Tremaine WJ. Hereditary angioedema: a broad review for clinicians. Arch Int Med. 2001;161:2417-29.
3. Brickman CM, Tsokos GC, Balow JE, et al. Immunoregulatory disorders associated with hereditary angioedema. I. Clinical manifestations of autoimmune disease. J Allergy Clin Immunol. 1986;77:749-57.
4. Khan S, Tarzi MD, Dore PC, et al. Secondary systemic lupus erythematosus: an analysis of 4 cases of uncontrolled hereditary angioedema. Clin immunology. 2007;123:14-7.
5. Kohler PF, Percy J, Campion WM, et al. Hereditary angioedema and "familial" lupus erythematosus in identical twin boys. Am J Med. 1974;56:406-11.
6. Cicardi M, Aberer W, Banerji A, et al. Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema Int Working Group. Allerg. 2014;69:602-16.
7. Fremeaux-Bacchi V, Guinnepain MT, Cacoub P, et al. Prevalence of monoclonal gammopathy in patients presenting with acquired angioedema type 2. Am J Med. 2002;113:194-9.
8. Bork K, Meng G, Staubach P, Hardt J. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. Am J Med. 2006;119:267-74.
9. Zanichelli A, Azin GM, Wu MA, Suffritti C, Maggioni L, Caccia S, et al. Diagnosis, Course, and Management of Angioedema in Patients With Acquired C1-Inhibitor Deficiency. J Allerg Clin Immunol Practice. 2017;5:1307-13.
10. Donaldson VH, Hess EV, McAdams AJ. Lupus-erythematosus-like disease in three unrelated women with hereditary angioneurotic edema. Ann Int Med. 1977;86:312-3.
11. Gallais Serezal I, Bouillet L, Dhote R, et al. Hereditary angioedema and lupus: A French retrospective study and literature review. Autoimmunity Reviews. 2015;14:564-8.
12. Massa MC, Connolly SM. An association between C1 esterase inhibitor deficiency and lupus erythematosus: report of two cases and review of the literature. J Am Academy Dermatol. 1982;7:255-64.
13. Pickering MC, Botto M, Taylor PR, etal. Systemic lupus erythematosus, complement deficiency, and apoptosis. Advances Immunol. 2000;76:227-324.
14. O'Neil KM. Complement deficiency. Clin Reviews Allerg & Immunol. 2000;19:83-108.
15. Suzuki Y, Nihei H, Mimura N, et al. A case of hereditary angioneurotic edema associated with systemic lupus erythematosus. Japanese J Med. 1986;25:281-7.
16. Carpenter CB, Ruddy S, Shehadeh IH, et al. Complement metabolism in man: hypercatabolism of the fourth (C4) and third (C3) components in patients with renal allograft rejection and hereditary, angioedema (HAE). J Clin Investigation. 1969;48:1495-505.