Acquired C1 Inhibitor Deficiency

Iris M. Otani, MD[a,*], Aleena Banerji, MD[b]

KEYWORDS

• Acquired angioedema • C1 esterase inhibitor deficiency • Rituximab
• Lymphoproliferative disorders • Anti-C1 esterase inhibitor autoantibody

KEY POINTS

- Acquired angioedema with C1-INH deficiency (C1-INH-AAE) should be considered when patients present with isolated angioedema without urticaria in the fourth decade of life or later without a family history of angioedema.
- A quantitative or functional C1-INH deficiency with negative family history and low C1q is diagnostic of C1-INH-AAE.
- All patients diagnosed with C1-INH-AAE should be evaluated for an underlying B-cell lymphoproliferative disorder at the time of diagnosis. If no disorder is found, repeat evaluation annually is recommended. A diagnosis of C1-INH-AAE can precede a diagnosis of lymphoproliferative disease and confers an increased risk for developing non-Hodgkin lymphoma.
- Treatment focuses on symptom control with therapies that regulate bradykinin activity (C1-INH concentrate, icatibant, ecallantide, tranexamic acid, androgens) and treatment of any underlying conditions.
- Rituximab has been used successfully to treat C1-INH-AAE.

INTRODUCTION

Angioedema is defined as transient localized swelling of the subcutaneous and/or mucosal tissues that can occur anywhere in the body and last for several days. The underlying cause of angioedema is not easily recognizable on clinical presentation. As angioedema can potentially be fatal, timely identification of the underlying cause is a critical step in ensuring effective treatments are administered for subsequent angioedema attacks.

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[a] Department of Medicine, Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine, UCSF Medical Center, 400 Parnassus Avenue, Box 0359, San Francisco, CA 94143, USA; [b] Department of Medicine, Division of Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Cox 201 Allergy Associates, Boston, MA 02114, USA
* Corresponding author.
E-mail address: iris.otani@ucsf.edu

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When angioedema without urticaria does not either respond to high-dose antihistamines or recur reproducibly after exposure to a specific drug or food, bradykinin-mediated causes should be considered. Angioedema that presents as nonpruritic, nonpitting swelling without urticaria lasting for 2 to 5 days is often considered to be mediated by bradykinin or the release of a vasoactive substance from mast cells and/or basophils.

Angioedema due to C1 esterase inhibitor (C1-INH) deficiency is one of the main causes of bradykinin-mediated angioedema. Testing for C1-INH deficiency is performed by measuring C1-INH antigen level, C1-INH function, and C4 levels in plasma. C1-INH deficiency can be due to a genetic defect (hereditary angioedema, HAE) or an acquired defect (acquired angioedema).

Acquired angioedema was first described by Caldwell and colleagues in 1972.[1] They described a 49-year-old patient with recurrent episodes of angioedema in the setting of lymphosarcoma and C1 inhibitor deficiency. The clinical presentation in this case was indistinguishable from HAE. Further review and evaluation defined the syndrome of acquired angioedema with 3 key elements:

1. Acquired deficiency of C1-INH,
2. Hyperactivation of the classic pathway of human complement, and
3. Recurrent angioedema symptoms.[1]

This condition is now referred to as acquired angioedema due to C1-INH deficiency (C1-INH-AAE). C1-INH-AAE is considered a subset of acquired angioedema, which more broadly includes other conditions such as angiotensin-converting-enzyme inhibitor (ACEI)–associated angioedema.

Although angioedema can be caused by many factors, bradykinin-mediated forms of angioedema are potentially life-threatening conditions, and therefore, appropriate diagnosis and management are critical. In this article, the authors specifically review the literature regarding C1-INH-AAE. This article reviews the epidemiology, risk factors, and clinical presentation of C1-INH-AAE and discusses the approaches to its diagnosis and treatment.

EPIDEMIOLOGY

C1-INH-AAE is a very rare disorder, and only several hundred cases have been reported in the literature to date. Experts in the field estimate that its prevalence may be between 1:100,000 and 1:500,000, based on their experience of identifying one C1-INH-AAE patient for every 10 HAE patients.[2,3] In the group of patients referred to a specialty center in Milan for angioedema due to C1 inhibitor deficiency since 1976, 77 had acquired and 675 had hereditary forms of the disease with a ratio of 1:8.8.[3,4] A 2010 literature review identified 168 probable cases.[5] Two national series in the United Kingdom and Denmark found that between 6% and 10% of angioedema cases were attributable to C1-INH-AAE.[6,7] Because the condition is so often overlooked, the actual prevalence is thought to likely be much higher.[8] In addition, recent data suggest an average lag of 5 years from initial symptoms to diagnosis of C1-INH-AAE.[6]

There are several factors that may contribute to this, as previously described by Cicardi and colleagues[2]:

1. Awareness of C1-INH-AAE is not widespread, and uncertainties regarding the pathogenesis and laboratory features of the disorder further complicate diagnosis.
2. There is no family history of swelling in C1-INH-AAE, so cases are often not detected through family screenings (distinct from HAE).