

Acquired C1 Inhibitor Deficiency



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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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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 colleagues²:

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).

3. The diagnosis of a coexisting lymphoproliferative malignancy can overshadow other medical issues, including recurrent angioedema, which may be attributed to a paraneoplastic phenomenon and not evaluated further.
4. Because the disorder begins later in life, many patients are taking multiple medications, and the episodes of angioedema are attributed to other causes such as drug reactions. Accordingly, patients may have multiple comorbidities, and the evaluation of angioedema may not take precedence until a severe attack occurs.
5. Complement abnormalities may fluctuate between normal and abnormal when the disorder first develops, becoming more consistently abnormal over the ensuing months. For this reason, mild abnormalities associated with a consistent clinical presentation should be followed over time.

RISK FACTORS

The most common causes of C1-INH-AAE are B-cell lymphoproliferative disorders and autoimmunity. The lymphoproliferative disorders range from monoclonal gammopathies of undetermined significance (MGUS) to B-cell malignancies. Approximately 35% of patients with C1-INH-AAE have MGUS. A recent review identified indolent lymphoma, especially splenic marginal zone lymphoma, and MGUS as the most common conditions associated with C1-INH-AAE.⁹ Other conditions associated with C1-INH-AAE include the human immunodeficiency virus, multiple myeloma, Waldenström macroglobulinemia, systemic lupus erythematosus, Churg-Strauss syndrome, xanthomatosis, and hepatitis B and other infections.

Overall, approximately 70% of patients with C1-INH-AAE are found to have an associated disorder.¹⁰ In half of these cases, the disorder is malignant (most often non-Hodgkin lymphomas [NHL]), and in the other half, the associated condition is benign (MGUS).²

CLINICAL FEATURES

The clinical presentation of C1-INH-AAE is difficult to distinguish clinically from HAE type 1 and 2 except that a family history is lacking and angioedema generally develops after the age of 40 years. Persons of any race or gender can be affected equally by C1-INH-AAE. Angioedema in C1-INH-AAE patients occurs in cutaneous and mucosal tissues and can involve any part of the body, but often presents as swelling of the face, lips, tongue, larynx, or extremities. Swelling episodes occur without urticaria and typically resolve within 2 to 5 days. Attacks are commonly triggered by stress, trauma, and viral infections, but often occur without an identifiable trigger.¹¹

Compared with urticarial swelling, the swelling of angioedema is deeper and longer lasting, is nonpruritic, and may be painful.¹² Angioedema may involve the gastrointestinal tract, leading to intestinal wall edema, which results in symptoms such as abdominal pain, nausea, vomiting, and diarrhea. Facial edema and abdominal pain were the most frequent symptoms reported in C1-INH-AAE patients.⁹ C1-INH-AAE can be life threatening, and acute laryngeal edema is the major cause of angioedema-related mortality. Around 50% of patients with C1-INH-AAE experience upper airway edema, and anoxic brain injury or death from upper airway obstruction can occur.^{13,14}

There are other more subtle differences between the clinical manifestations of the C1-INH-AAE and HAE described by Cicardi²:

1. Gastrointestinal attacks presenting as recurrent colicky abdominal pain, distention, vomiting, and/or diarrhea are less common in C1-INH-AAE compared with HAE. These types of attacks are reported by nearly 80% of patients with HAE type 1

and 2, whereas less than 50% of C1-INH-AAE reported gastrointestinal attacks.^{13,15}

2. In C1-INH-AAE, angioedema seems to affect the face more than the extremities, which is distinctly opposite from patients with HAE type 1 and 2, where swelling of the extremities is more typical.¹³ However, both disorders can cause swellings in the face and extremities.
3. Patients may describe a prodrome of erythema marginatum before cutaneous or gastrointestinal angioedema episodes, but it is extremely rare especially when compared with patients with HAE type 1 and 2.

C1-INH-AAE should be considered in a patient who presents with isolated angioedema (without urticaria) in the fourth decade of life or later without a family history of angioedema. All patients 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.

PATHOPHYSIOLOGY

C1-INH is a serine protease inhibitor that inhibits C1r and C1s in the classical complement system, production of FXIIa and kallikrein in the kallikrein-kinin system, and FXIa in the kallikrein-kinin and coagulation systems.^{16,17} C1-INH controls bradykinin generation via its inhibitory effects on FXIIa and kallikrein. Angioedema due to deficiency or dysfunction of C1-INH is mediated by the binding of bradykinin to bradykinin B2 receptors on endothelial cells.¹⁶

When there is a deficiency of the C1-INH protein, overactivation of the kallikrein-kinin system leads to bradykinin production. Inactive FXII and plasma prekallikrein are cleaved to their active forms FXIIa and kallikrein, respectively. Activated kallikrein cleaves high-molecular-weight kininogen to release bradykinin.^{16–18} Bradykinin binds to bradykinin B2 receptors on endothelial cells, leading to nitric oxide production, relaxation of the smooth muscle in the vessel wall, and increased vascular permeability.^{16,19} Vasodilation, increased vascular permeability, and localized fluid extravasation result in angioedema.^{16,20}

Acquired angioedema due to deficiency of C1-INH, or C1-INH-AAE, occurs when there are acquired (not inherited) deficiencies of C1-INH. Although the exact pathophysiology is unclear, evidence suggests that there are 2 major mechanisms that can cause a C1-INH-deficient state in C1-INH-AAE:

1. Overconsumption of C1-INH by neoplastic lymphatic tissue and
2. The production of anti-C1-INH autoantibodies.^{16,17,20,21}

As such, C1-INH-AAE has historically been classified into type I (absence of C1-INH autoantibodies) and type II (presence of C1-INH autoantibodies).²²

Initially, it was thought that malignant lymphoproliferation and autoimmunity were uniquely responsible for the 2 types of C1-INH-AAE: type I (paraneoplastic overconsumption of C1-INH) and type II (autoimmune production of anti-C1-INH autoantibodies).¹⁰ It was thought that lymphoproliferation and autoimmunity were uniquely responsible for Type I and Type II C1-INH-AAE because initial cases of C1-INH-AAE were reported in association with lymphoproliferative disease,^{23–28} and there was evidence that C1-INH reduction was due to consumption by lymphatic tissue. Hauptmann and colleagues²⁹ investigated the properties of splenic lymphosarcoma tissue resected from a patient with AAE and splenic lymphosarcoma and demonstrated that in vitro incubation of lymphosarcoma tissue with guinea pig serum led to complement depletion. Schreiber and colleagues²³ also investigated the properties of lymphoid tissue from a

patient with AAE and B-cell lymphoproliferative disorder with lymphoid cells infiltrating the pulmonary parenchyma and found that *in vitro* incubation of lung biopsy tissue with human serum led to complement depletion. Geha and colleagues³⁰ found evidence that the mechanism of C1-INH consumption in B-cell lymphoproliferative disorders was due to the formation of idiotype/anti-idiotype immune complexes. The discovery of an autoreactive immunoglobulin G against C1-INH by Jackson and colleagues³¹ provided evidence that some cases of C1-INH-AAE could have an autoimmune basis.

Taken together, these cases supported a hypothesis that in type I AAE, malignant lymphoproliferation led to C1-INH overconsumption, and that in type II AAE, autoimmune production of anti-C1-INH autoantibodies led to inadequate C1-INH function.

However, subsequent reports have shown that the pathophysiology is not so clear. B-cell lymphoproliferative disorders were found to be equally prevalent in both type I and type II AAE, and monoclonal paraproteinemia can account for anti-C1-INH autoantibody production. On the other hand, anti-C1-INH autoantibodies are present in AAE patients both with and without underlying B-cell lymphoproliferative disorders, indicating that monoclonal B-cell lymphoproliferation is not the sole mechanism for anti-C1-INH autoantibody production.^{10,32}

In a case series of 42 patients with AAE, 21 patients had B-cell lymphoproliferative disorders (LPD) and anti-C1-INH autoantibodies, 11 patients had anti-C1-INH autoantibodies with no evidence of B-cell LPD, and 10 patients had B-cell LPD without anti-C1-INH autoantibodies.¹⁰

In another case series of 13 patients with AAE, anti-C1-INH autoantibody was present in 12 of these 13 patients who did not have a diagnosis of B-cell LPD at time of AAE diagnosis. Seven of these patients were subsequently diagnosed with monoclonal paraproteinemia and 1 patient was subsequently diagnosed with CLL. Although 5 of the 7 patients with an M-component had paraproteins that bound C1-INH, indicating that the paraproteins were anti-C1-INH autoantibodies, 2 patients produced paraproteins that did not bind C1-INH.³²

These case series in conjunction with cases of patients with C1-INH-AAE and autoimmunity without evidence of anti-C1-INH autoantibodies suggest that the type I and type II classification may be misleading.^{10,32–37} This is discussed in more detail in later discussion under Current Controversies.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for a patient presenting with angioedema is broad. Most causes of angioedema fall into 1 of 2 categories: histamine-mediated or bradykinin-mediated angioedema.²¹ Histamine-mediated angioedema (food allergy, drug allergy, stinging insect allergy, chronic idiopathic urticaria and angioedema, mastocytosis, mast cell activation syndromes, idiopathic histaminergic anaphylaxis) is typically associated with urticaria and responds to antihistamines, glucocorticoids, and/or epinephrine.^{21,38–44} Suspicion for bradykinin-mediated angioedema is raised when angioedema has the clinical features described in the Clinical Features section above (ie, no pruritus, no hives, no response to antihistamines/epinephrine).^{20,21} Angioedema can also be a clinical feature of thyroid dysfunction, Melkersson-Rosenthal syndrome, episodic angioedema with eosinophilia, nonepisodic angioedema with eosinophilia, and disorders causing generalized edema (such as capillary leak syndrome, nephrotic syndrome, cirrhosis, and heart failure).^{45–53} Aspirin/nonsteroidal anti-inflammatory drug—induced angioedema due to presumed aberrations in arachidonic acid metabolism can also be seen.⁵⁴

Bradykinin-mediated causes of angioedema include ACEI-induced angioedema due to inadequate bradykinin degradation and hereditary and acquired C1-INH

deficiencies due to bradykinin overproduction.^{12,38,55} As ACEI-induced angioedema is a clinical diagnosis, a detailed history regarding ACEI use is necessary when evaluating a patient with suspected bradykinin-mediated angioedema. ACEI angioedema can occur over a year after ACEI therapy is initiated and can occur up to 2 months after ACEI therapy is discontinued.⁵⁶

Hereditary and acquired C1-INH deficiencies are associated with alterations in complement levels.⁵⁵ Measurements of C4, C1-INH concentration, C1-INH function, and C1q can differentiate between hereditary and acquired C1-INH deficiencies (Table 1). Hereditary and acquired angioedema have similar clinical characteristics. However, 90% of patients with HAE present during the first or second decade of life, and most patients with C1-INH-AAE present after the fourth decade of life.⁵⁷ Also, HAE with C1-INH deficiency and HAE type II with low C1-INH function are associated with a family inheritance patterns in most cases (~75%), whereas C1-INH-AAE is not.^{12,58}

A quantitative or functional C1-INH deficiency with negative family history and low C1q is diagnostic of C1-INH-AAE.⁵⁹ C1-INH-AAE is historically classified into type I and type II based on absence and presence of anti-C1-INH autoantibodies, respectively, although this classification system is debated.²² Only specialized laboratories are able to identify anti-C1-INH autoantibodies.²⁰

MANAGEMENT

Management of C1-INH-AAE is aimed at symptom control as well as identification and treatment of any underlying disease.^{16,17}

Symptom Control

C1-INH-AAE symptom management is based on existing knowledge regarding effective therapies for HAE. Symptomatic treatment is achieved by regulating bradykinin activity using therapies found to be effective in HAE.

At baseline, avoidance of triggers reported to exacerbate bradykinin-mediated angioedema is recommended (social stressors, trauma, exogenous estrogens, tamoxifen, ACEIs). As C1-INH-AAE can present with laryngeal edema,^{60–62} an emergency care plan should be in place, and a written treatment plan for emergency care should be provided.¹⁷ Patients should have appropriate access to kallikrein-bradykinin-targeted therapies as part of their acute treatment and prophylaxis plans.

Acute Treatment

Acute treatment aims to reduce the severity and duration of each acute attack.⁶³ It was noted at the 2014 bradykinin-mediated angioedema expert consensus meeting that C1-INH concentrate can be effective in treating acute attacks. However, acute treatment of C1-INH-AAE differs from HAE in that some cases of C1-INH-AAE may

Table 1 Complement level patterns for hereditary and acquired C1 esterase inhibitor deficiencies					
Diagnosis	C1-INH	C1-INH Function	C4	C1q	Anti-C1-INH
HAE with C1-INH deficiency	Low	Low	Low	Normal	Absent
HAE type II	Normal	Low	Low	Normal	Absent
AAE type I	Low	Low	Low	Low	Absent
AAE type II	Low/normal	Low	Low	Low	Present

be resistant to treatment with C1-INH concentrate. Higher doses of C1-INH concentrate are often required to achieve a therapeutic response, especially in patients with anti-C1-INH autoantibodies.²¹

Published literature has reported the successful use of icatibant, a bradykinin B2 receptor antagonist, and ecallantide, a kallikrein inhibitor, in treating acute AAE attacks.^{64,65} In an observational study, icatibant was effective at treating 47 of 48 attacks in 8 patients with AAE.⁶⁵ Icatibant was also able to effectively treat facial and laryngeal AAE attacks resistant to treatment with C1-INH concentrate.⁵⁷ Ecallantide was able to effectively treat facial attacks in patients who did not respond or only partially responded to C1-INH concentrate.^{57,64} The fact that a bradykinin B2 receptor antagonist is able to treat acute attacks resistant to C1-INH concentrate highlights the importance of bradykinin binding to the bradykinin B2 receptor as a key step in symptom development.

Prophylaxis

Prophylactic therapy aims to prevent or reduce the frequency and severity of acute attacks (long-term prophylaxis) or prevent attacks during planned exposure to known attack triggers such as surgical procedures (short-term prophylaxis).⁶³

Short-term Prophylaxis

C1-INH concentrate was recommended for short-term prophylaxis at the 2014 bradykinin-mediated angioedema expert consensus meeting based on unpublished cases discussed at this meeting.²¹ In a case series of 10 patients with C1-INH-AAE, 5 patients received androgen therapy, 1 patient received C1-INH replacement, and 4 patients received no prophylaxis preoperatively. Significant perioperative airway complications or angioedema episodes were not reported in these patients.⁶⁶

Long-term Prophylaxis

C1-INH concentrate can also be used for long-term prophylaxis. C1-INH concentrate must be dosed at a minimum of twice a week, and long-term prophylaxis with C1-INH concentrate is often considered only for select patients who have 2 or more severe attacks per week.⁵⁷ If long-term prophylaxis is necessary, self-intravenous administration is possible and can help improve patients' quality of life.⁵⁸

Tranexamic acid has been used successfully for prophylactic therapy.^{7,57,58,67–69} However, tranexamic acid has potential adverse effects, and the risk for thromboembolism is particularly concerning for AAE patients with underlying malignancies.¹⁷

Androgens are an effective treatment option for C1-INH-AAE.⁵⁸ Long-term use of androgens must be accompanied by routine monitoring of transaminases, lipids, blood pressure, weight, menstrual irregularities, and liver ultrasonography.⁵⁸ Given this adverse side-effect profile and comparative lack of efficacy in C1-INH-AAE, the other previously mentioned therapeutic options are generally preferred over androgens, but patient preference is strongly considered.

Fresh frozen plasma (FFP) has not been investigated for the treatment of C1-INH-AAE.²¹ In HAE, concerns have been raised regarding the potential for FFP to cause acute worsening of symptoms, although a subsequent publication of 23 case reports (combined original case series and literature review) did not identify any exacerbation of attacks with FFP.⁷⁰ For now, the authors recommend avoiding FFP for C1-INH-AAE patients until it has been investigated specifically in the C1-INH-AAE population.

Treatment of Acquired Angioedema due to C1-INH Deficiency and Underlying Systemic Conditions

Successful control of associated conditions can lead to partial or complete remission of symptoms and reversal of complement abnormalities.

Rituximab has been used successfully to treat C1-INH-AAE. In many cases, rituximab can induce long-lasting remission of angioedema with normalization of C1-INH. Rituximab can be effective in cases that were refractory to corticosteroid and/or cyclophosphamide therapies (**Table 2**). The presence or absence of lymphoproliferative disease, and the presence or absence of anti-C1-INH autoantibody, does not appear to be consistently associated with the degree of response to rituximab (see **Table 2**).

Chemotherapy regimens used to treat underlying malignant lymphoproliferative disease have been associated with C1-INH-AAE remission in 9 cases.^{76–81}

PROGNOSIS

Once a diagnosis of C1-INH-AAE has been made, subsequent evaluation for systemic underlying medical conditions, such as lymphoproliferative and/or autoimmune disorders, is warranted.³⁸ The prevalence of lymphoproliferative disease in C1-INH-AAE has been reported to be higher than 70%.¹⁰

Even if an initial evaluation does not reveal a clear diagnosis of underlying conditions, routine monitoring is warranted. Patients without lymphoproliferative disease at time of C1-INH-AAE diagnosis can subsequently develop lymphoproliferative disease.^{7,32,82} In addition, patients with C1-INH-AAE are at higher risk of developing NHL compared with the general population.^{67,80,81}

Resolution of C1-INH-AAE appears to be associated with successful treatment of underlying lymphoproliferative and/or autoimmune disease. Reported cases of C1-INH-AAE treated with rituximab or chemotherapy have largely resulted in complete, or at least partial, remission (see **Table 2**).

CURRENT CONTROVERSIES

Pathophysiology

As mentioned under the Pathophysiology section, C1-INH-AAE has historically been classified into type I (without anti-C1-INH autoantibody) and type II (with anti-C1-INH autoantibody). However, published reports show that although C1-INH-AAE can be a clinical manifestation of LPD and systemic autoimmunity,^{23–31} LPD can lead to both C1-INH-AAE with and without anti-C1-INH autoantibodies, and systemic autoimmunity can lead to C1-INH-AAE in the absence of anti-C1-INH autoantibodies.^{10,32–37} It remains to be determined whether C1-INH-AAE cases represent a clinical spectrum of one pathophysiologic process, or if these C1-INH-AAE cases represent distinct entities. To answer this question, detailed studies investigating the disease processes leading to C1-INH-AAE are needed.

C1 Esterase Inhibitor Replacement Therapy

C1-INH-AAE cases can be relatively resistant to C1-INH replacement (ie, higher doses of C1-INH replacement are often required to achieve a therapeutic response).²¹ It has been proposed that long-term prophylaxis may lead to C1-INH resistance.⁵⁷ The presence of anti-C1-INH autoantibodies tends to be associated with C1-INH resistance.²¹

It remains to be definitively determined if the use of C1-INH replacement for long-term prophylaxis does in fact lead to C1-INH resistance. This question is important

Table 2

Acquired angioedema due to C1-INH deficiency treated with rituximab: baseline characteristics of patients and response to therapy

Author	Age	G	Location	Anti-c1-INH	Underlying Condition	RTX	Symptom Remission	C4	C1-INH	C1-INHf	Anti-C1-INH	Other Immunosuppressive Therapy
Lam et al, ⁷¹ 2012	80	F	Abdomen	NR	Splenic marginal zone lymphoma	1	Complete	—	N	—	—	—
Ziakas et al, ⁷² 2004	67	M	Abdomen	Yes	Clonal B-cell 2% infiltration of bone marrow	1	Partial	—	—	—	—	1
Levi et al, ⁷³ 2006	45	F	NR	Yes (IgG)	None	1	Complete	N	N	—	—	2
Levi et al, ⁷³ 2006	70	F	NR	No	Stage IV indolent follicular B-cell lymphoma	1	Complete	I	I	—	—	—
Levi et al, ⁷³ 2006	68	M	NR	No	None	1	Complete	N	N	—	—	2
Hassan et al, ⁷⁴ 2011	84	F	Extremities face	Yes (IgM)	MGUS (IgM)	1	Partial	—	—	—	D	—
Branellec et al, ⁶⁰ 2012	54	F	Abdomen extremities genitalia	Yes (IgM)	None	2	Partial	—	N	I	D	3
Branellec et al, ⁶⁰ 2012	79	M	Extremities genitalia	Yes (Igm)	MZL	2	Complete	—	N	I	D	4
Branellec et al, ⁶⁰ 2012	61	M	Face	Yes (IgA)	MGUS (IgA)	1 ^a	Ineffective	—	U	—	—	3
Branellec et al, ⁶⁰ 2012	51	F	Abdomen	Yes (IgG)	MGUS (IgG)	1	Complete	—	U	U	I	3
Branellec et al, ⁶⁰ 2012	82	F	Larynx	Yes (IgM)	None	1	Partial	—	U	—	U	—

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Table 2
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Author	Age	G	Location	Anti-c1-INH	Underlying Condition	RTX	Symptom Remission	C4	C1-INH	C1-INHf	Anti-C1-INH	Other Immunosuppressive Therapy
Branellec et al, ⁶⁰ 2012	80	F	Face	Yes (IgM)	MGUS (IgG)	1 ^b	Partial	—	U	—	—	—
Branellec et al, ⁶⁰ 2012	75	F	Face	No	MZL	2	Partial	—	I	—	—	3
Bygum & Vestergaard, ⁷ 2013	46	M	NR	No	SLL	NR	Partial	—	—	—	—	—
Bygum & Vestergaard, ⁷ 2013	69	M	NR	Yes (IgM)	Monoclonal B-cell lymphocytosis	1	Deceased	—	—	—	—	—
Kaur et al, ⁶² 2014	51	M	Larynx	NR	Monoclonal B-cell lymphocytosis	1	Complete	—	—	—	—	—
Dreyfus et al, ⁶¹ 2014	41	F	Larynx abdomen	Yes (IgG)	Myasthenia gravis, antiphospholipid syndrome	1	Complete	—	—	—	N	—
Sanchez-Cano et al, ⁷⁵ 2008	66	F	NR	Yes (IgM)	Sjogren Syndrome	2	Complete	—	—	—	D	—

Abbreviations: 1, monthly cyclophosphamide lead to remission but was stopped due to pneumocystis jirovecii pneumonia; 2, prednisolone (50 mg/d) in combination with cyclophosphamide (150 mg/d) ineffective; 3, corticosteroids ineffective; 4, 6 cycles of cyclophosphamide starting with third dose of RTX; Age, age in years; C1-INHf, c1 inhibitor esterase function; D, decreased; G, gender; I, increased; N, normalization; NR, not reported; Partial, decrease in severity and/or frequency of angioedema attacks; R, number of rituximab cycles (1 cycle is 375 mg/m²/wk for 4 weeks); RTX, Rituximab; U, unchanged.

^a Followed by 1-g infusion 1 year later.

^b Followed by four 1-g infusions over the following 3 years.

because it affects the decision to place patients on long-term prophylaxis with C1-INH concentrate.

It also remains to be established whether the presence of anti-C1-INH autoantibodies do indeed predict C1-INH resistance. Recommended starting doses of C1-INH concentrate may need to be higher for C1-INH-AAE with anti-C1-INH autoantibodies.

Rituximab Therapy

A diagnosis of C1-INH-AAE can precede a diagnosis of lymphoproliferative disease^{7,32,82} and confers an increased risk for developing NHL.^{67,80,81} An isolated case suggests that rituximab therapy for C1-INH-AAE without any underlying conditions and without detectable anti-C1-INH autoantibody can be successful at achieving angioedema symptom remission.⁷³ Whether rituximab therapy for C1-INH-AAE without any known underlying conditions may help prevent future development of lymphoproliferative and autoimmune disease is unknown.

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