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Case Report

Acquired Angioedema Associated with Lymphoproliferative Disorders

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Keywords

B-lymphoproliferative disorder · Splenic marginal zone lymphoma · Complement · Diagnostic challenge

Abstract

Introduction: Acquired angioedema due to C1 esterase inhibitor deficiency (C1INH-AAE) is most associated with lymphoproliferative disorders (LPDs), particularly low-grade B-cell subtypes. The condition remains under-recognized with long diagnostic delays due to various challenges including a lack of awareness of the condition. ***Case Presentation:*** We discuss 4 cases of C1INH-AAE associated with low-grade B-cell LPDs, including various diagnostic and management challenges. As our cases illustrate, constitutional symptoms or overt manifestations of LPD at diagnosis are often absent. Hence, a comprehensive multimodal approach to screening for an underlying B-LPD is important when a diagnosis of acquired angioedema is made. Levels of complement C4, C1q, and C1INH are useful for diagnosing C1INH-AAE and for monitoring disease activity. Changes in these parameters may also indicate relapse of the underlying hematological malignancy. Treating the underlying disorder is important as this commonly leads to clinical improvement with decreased episodes of angioedema and normalization of complement studies. ***Conclusion:*** Awareness of C1INH-AAE can lead to an early diagnosis of hematological malignancies. The absence of

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constitutional symptoms emphasizes the need for a comprehensive multimodal approach to screening for LPD in C1INH-AAE. C4, C1INH level, and function are useful for monitoring disease activity.

Introduction

Acquired angioedema due to C1 esterase inhibitor deficiency (C1INH-AAE) is a rare disorder with an estimated prevalence of 1:600,000 [1]. It typically presents after the fourth decade of life without family history of angioedema [2]. Due to reduced C1INH function, there is activation of the contact system and accumulation of bradykinin, a vasodilator, resulting in angioedema without urticaria [3].

C1INH-AAE is most associated with lymphoproliferative disorders (LPDs), particularly low-grade B-cell subtypes (B-LPDs) [4]. However, patients do not commonly present with constitutional symptoms nor other overt symptoms associated with LPD, hence posing a diagnostic challenge.

Due to its rarity, the pathogenesis, diagnosis, and management of the condition remain incompletely understood. Laboratory diagnosis is characterized by decreased levels of C1INH protein and/or function (Table 1) and reduced levels of C4 and C1q. Additionally, although the presence of autoantibodies to C1INH in AAE has been known for a long time, there is no available assay in Australia to confirm these.

Treatment of the condition is based on small studies using treatments for hereditary angioedema (HAE), such as the bradykinin antagonist icatibant, used for emergency management of angioedema. However, these are not registered or approved for the treatment of C1INH-AAE. Treating the underlying B-LPD is important as this commonly leads to improvement or resolution of the angioedema in parallel with normalization of the complement studies [5].

Case Report

This was a single-center case series including 4 cases of C1INH-AAE associated with B-LPD including the diagnostic challenges and management. The objective of our report is to improve awareness of the condition in both the general medical and specialist population.

A 79-year-old man presented in 2009 with recurrent angioedema affecting the abdomen and lips without constitutional symptoms. C1INH-AAE was suspected due to results shown in Table 1 which were obtained at the time. Bone marrow examination (BME) showed three small nodular aggregates of small mature lymphocytes with dense chromatin and minimal cytoplasm (<5% of cellular content). Immunophenotyping reported a kappa light chain-restricted (dim) B-cell population (approximately 2.3% of total events) which expressed CD19, CD20, and CD5 with variable CD22 and CD200/5 expression. These cells were negative for CD10 and CD23, consistent with small lymphocytic lymphoma (SLL). There was no nodal disease on CT chest to pelvis. He was treated with monthly rituximab and cyclophosphamide for 12 months with good response. In 2018 and 2021, he re-developed symptomatic AAE that coincided with detection of a SLL clone. He received 6 cycles of monthly rituximab and cyclophosphamide in 2018 and 4 doses of weekly rituximab in 2021, leading to the resolution of angioedema.

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Table 1. Clinical and laboratory features of the patients pre- and post-lymphoma-directed therapy

Case	Tests	Pre-treatment	Post-treatment	Reference range
1	C4, g/L	<0.03	0.15	0.13–0.40
	C1q, mg/L	<35	NA	118–238
	C1INH level, mg/L	82	315	195–440
	C1INH function, mg/L	34	112	≥70%
	IgG, g/L	9.7		6.5–15.2
	IgA, g/L	1.03		0.76–3.89
	IgM, g/L	0.8		0.3–2.3
	SPEP, g/L	Normal		
2	C4, g/L	<0.03	0.23	0.13–0.40
	C1q, mg/L	NA	NA	118–238
	C1INH level, mg/L	27	370	195–440
	C1INH function, %	14	Normal	≥70%
	IgG, g/L	14.5		6.5–15.2
	IgA, g/L	2.71		0.76–3.89
	IgM, g/L	2.6		0.3–2.3
	SPEP, g/L	IgM kappa; this is barely visible and not able to be quantitated		
3	C4, g/L	<0.03	0.21	0.13–0.40
	C1q, mg/L	<35	NA	118–238
	C1INH level, mg/L	27	NA	195–440
	C1INH function, %	9	Normal	≥70%
	IgG, g/L	9.2		6.5–15.2
	IgA, g/L	0.7		0.76–3.89
	IgM, g/L	0.8		0.3–2.3
	SPEP, g/L	Normal		
4	C4, g/L	<0.03	<0.03	0.13–0.40
	C1q, mg/L	33	NA	118–238
	C1INH level, mg/L	82	140	195–440
	C1INH function, %	39	55	≥70%
	IgG, g/L	7.4		6.5–15.2
	IgA, g/L	0.73		0.76–3.89
	IgM, g/L	2.1		0.3–2.3
	SPEP, g/L	Normal		

*C1INH, C1 esterase inhibitor; Ig, immunoglobulin; NA, not available; SPEP, serum protein electrophoresis.

A 77-year-old man presented with 2 episodes of tongue angioedema, and at the time of his second presentation with angioedema, complement results were as shown in Table 1. A hematological malignancy was suspected as he recently suffered a splenic laceration after routine colonoscopy. C1INH-AAE was diagnosed, and monoclonal B cells were found on

peripheral blood immunophenotyping ordered at the time of his investigation for angioedema. He had splenomegaly (13 cm), and BME reported interstitial aggregates of small lymphocytes comprising CD20-positive B cells and CD3-positive T cells with normal cytology. Overall, the infiltrate occupied less than 5% of the cellular content. Immunophenotyping showed a kappa light chain-restricted (dim) B-cell population (approximately 9% of total events) expressing CD19, CD20, CD22, CD23, and weak CD25. There was no expression of CD5, CD10, CD11c, CD103, or CD123, consistent with splenic marginal zone lymphoma (SMZL). He was treated with 6 cycles of rituximab and bendamustine, with resolution of angioedema and resolution of complement assay abnormalities.

A 68-year-old man presented with abdominal pain in 2021 and was found to have splenomegaly (20 cm) and small bowel edema on abdominal CT. When this was further assessed by a hematologist, he described a 5-year history of recurrent angioedema affecting the abdomen, face, throat, and scrotum without constitutional symptoms. C1INH-AAE was diagnosed, and BME showed multiple lymphoid aggregates which are made up of mixture of T and B cells. There was no abnormal antigen expression by immunohistochemistry and in-situ hybridization to suggest clonality of the B cells. Immunophenotyping reported two distinct clonal B-cell populations, each approximately 2.4% of total events. The first population was kappa light chain-restricted (dim) expressing CD19, CD20, CD22, CD23, and CD25. It was negative for CD5, CD10, CD11c, CD103, and CD123. The second population was lambda light chain-restricted expressing CD19, CD20, and CD22. It was negative for CD5, CD10, CD11c, CD23, CD25, CD103, and CD123. A very small group of cells had higher lambda light chain expression; however, some also appeared to bind kappa light chains, likely representing non-specific binding. He was diagnosed with a low-grade B-LPD, most likely SMZL. He was treated with 4 doses of weekly rituximab and chlorambucil, with resolution of angioedema, improvement of the splenomegaly (16 cm), and resolution of the abnormalities on his complement assays.

A 53-year-old man presented with angioedema affecting the abdomen, oropharynx, face, and neck without constitutional symptoms. Complement C4, C1q, and C1INH levels and functions were all reduced, which in conjunction with late-onset symptoms raised the possibility of C1INH-AAE. BME showed mild diffuse increase in small mature lymphocytes with high nuclear-cytoplasmic ratio, mature chromatin, and minimal cytoplasm, in an interstitial distribution without nodular or paratrabecular aggregates. Immunophenotyping reported very small (approximately 2.5% of total events) kappa-predominant B cells expressing CD19 and CD20 without co-expression of CD5 or CD10. The angioedema episodes were relieved by icatibant initially, but subsequently, the condition became treatment-refractory. He underwent a diagnostic and therapeutic splenectomy. The spleen architecture was essentially normal, composed of red and white pulp in appropriate proportions. The lymphoid cells were small and mature in appearance, with a normal distribution of B and T cells. Immunophenotyping initially reported a mixed population of B cells with marginal kappa light chain predominance (approximately 3:1) but without a definitive marker of a malignant B-cell phenotype (approximately 11.5% of total events). A subset of CD21-negative mature B cells showed a more obvious kappa light chain predominance (approximately 7:1) without any other phenotypic evidence of malignancy. Subsequently, clonal expansion was detected by IgG gene rearrangement analysis of splenic B cells, consistent with B-LPD.

In view of the ongoing symptoms of angioedema post-splenectomy, he was treated with four doses of weekly rituximab with good clinical response. Subsequent episodes of angioedema have been less frequent and milder up to 2 years after his rituximab. Now (30 months after rituximab), he remains symptom-free for 6 months despite ongoing low C1INH levels and function.

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Discussion

C1INH-AAE is reportedly rare, with an estimated prevalence of 1:600,000; however, it is likely an under-recognized condition [1, 6]. It should be a differential diagnosis of isolated angioedema without urticaria, particularly in patients without angiotensin-converting enzyme inhibitor (ACE-I) exposure. Angioedema may affect the skin and upper airways; involvement of other anatomical sites, such as the gastrointestinal tract, sometimes provides another clue to the diagnosis. Consistent with the cases described here, C1INH-AAE usually presents after the age of 50 (the median age at diagnosis is 64 (56–70) years). It is also said to be more common in females, although this was not observed in our small series [4].

C1INH-AAE is most associated with LPD (62.8%), followed by monoclonal gammopathy of uncertain significance (MGUS) (27.7%), autoimmune disorders (10.6%), and solid organ tumors (5.3%) [4]. The prevalence was 10.7% in a retrospective study screening 131 patients with various LPDs for complement and C1INH levels [5]. Interestingly, only 2.3% of these patients experience significant angioedema. Among low-grade LPDs, subtypes most associated with C1INH-AAE are SMZL, followed by SLL (or chronic lymphocytic leukemia), lymphoplasmacytic lymphoma, and MALT lymphoma. Due to the association with MGUS, serum electrophoresis should always be carried out when a diagnosis of C1INH-AAE is made.

The pathogenesis of C1INH-AAE remains incompletely understood. One theory is clonal B-cell proliferation, leading to production of neutralizing antibodies against C1INH [7], resulting in C1INH dysfunction. This theory is supported by the occurrence of C1INH-AAE in association with autoimmune disease and MGUS. Another theory contends that overactivation of the classical complement pathway by neoplastic lymphoid tissue results in C1INH depletion. This was demonstrated in 5 patients with C1INH-AAE associated with various LPDs and multiple myeloma, showing increased catabolism of C1INH in vivo compared to healthy subjects [8]. C1INH regulates bradykinin by inhibiting the production of factor XIIa and kallikrein. Kallikrein cleaves high-molecular-weight kininogen to produce bradykinin which binds to endothelial receptors, causing vasodilation [9]. In C1INH-AAE, like in HAE, C1INH dysfunction results in bradykinin accumulation and resultant angioedema [10].

Diagnostic delay is common, with a recent retrospective cohort study of 50 patients from 4 European countries by Baeza et al. [6] in which they reported a median diagnostic delay of 1.1 (0.5–2.6) years from the onset of angioedema. Possible reasons are lack of awareness of the condition, misdiagnosis of the angioedema symptoms as part of the hematologic disorder as well as other diagnostic challenges discussed below [6].

Other potential obstacles to making the diagnosis also exist. First, it may be difficult to distinguish HAE from C1INH-AAE. Although C1INH-AAE typically occurs in the fourth decade of life or later, Baeza et al. reported that 8.7% of patients were diagnosed before the fourth decade of life [6]. Additionally, although a markedly reduced C1q level (<50% of normal) strongly suggests C1INH-AAE, this is not always present [11]. C1INH-AAE is suggested by the lack of family history of angioedema, and gastrointestinal tract involvement is less common [12]. If the diagnosis remains unclear, genotyping for *SERPING1* may be required, a heterozygous mutation only present in HAE conferring C1 esterase deficiency (85%) or dysfunction (15%).

Second, laboratory diagnosis of C1INH-AAE is suggested by reduced complement C4, C1q, C1INH levels and functions (usually <50%); however, these abnormalities may fluctuate during the clinical course [6]. Additionally, the presence of autoantibodies to C1INH in C1INH-AAE has been known since the 1980s [13], but their presence can only be inferred from results in routine diagnostic assays as no commercial autoantibody assays are available. Development of these assays has been hindered by disease rarity, technical challenging aspect

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of ELISA assay for C1INH autoantibodies (e.g., lack of positive control for ELISA, low titer of autoantibody, and autoantibody-C1INH immune complex formation hindering detection of autoantibody), and lack of funding for this laboratory test.

Thirdly, our cases illustrate that the underlying LPD can be subtle. None of the patients had constitutional symptoms, lymphocytosis, cytopenia, or significant lymphadenopathy. Recommended methods for screening an underlying LPD include physical exam, full blood count, lactate dehydrogenase, beta-2-microglobulin, plasma urea, creatinine, serum calcium, serum protein electrophoresis, immunophenotyping of circulating lymphocytes for a monoclonal population, and CT of the chest, abdomen, and pelvis [14, 15]. Our cases illustrate that awareness of C1INH-AAE can lead to an early diagnosis of hematological malignancies. The protean manifestations also emphasize the importance of a multimodal approach to screening for LPD in these patients. It is also important to note that LPD may be diagnosed at the onset of AAE or up to 7 years later; hence, patients may require repeat screening in the future if the initial evaluation fails to uncover an underlying LPD [7, 16].

The treatment goals for C1INH-AAE are treating acute angioedema attacks, preventing future angioedema episodes, and treating the underlying disorder. There are no treatments registered or approved for acute angioedema episodes in C1INH-AAE; however, treatments for HAE (e.g., C1INH concentrate, the bradykinin-receptor antagonist icatibant) have demonstrated efficacy. Like other causes of bradykinin-induced angioedema, the swelling in C1INH-AAE does not respond to glucocorticoids, antihistamines, or adrenaline [17]. Hence, patient education and the provision of an emergency action plan are extremely important as airway involvement can be life-threatening. Rituximab, an anti-CD20 monoclonal antibody, has also been shown to be effective in preventing angioedema recurrence in patients with or without underlying B-LPD [18]. Identifying the underlying cause of C1INH-AAE is very important. Consistent with previous studies, our case series show that treatment of the underlying hematological malignancy commonly leads to improvement or resolution of the AAE, both clinically and biochemically (Table 1) [5]. Hence, C4 and C1INH levels and functions are useful for monitoring the activity of C1INH-AAE [16]. Changes in these parameters or recurrence of angioedema may indicate the relapse of underlying hematological malignancy.

Our understanding of C1INH-AAE remains limited to small and retrospective studies due to its rarity. Future research may be able to elucidate its pathogenesis and improve the diagnosis and management, for example, the pathogenesis of LPD causing C1INH-AAE, contact-based C1INH functional assays, and methods to measure autoantibodies against C1INH [4]. We agree with Baeza et al. [6] that an international registry would enhance the knowledge and awareness of C1INH-AAE. This would also allow for the gathering of more data for further studies.

Conclusion

Our cases contribute to the growing literature on C1INH-AAE, a rare condition which remains incompletely understood and under-recognized. Various diagnostic challenges are discussed, including the absence of constitutional symptoms associated with LPD in our patients. This emphasizes the need for a comprehensive multimodal approach to the screening of LPD in C1INH-AAE. Consistent with previous studies, treatment of the underlying LPD commonly leads to improvement or resolution of the angioedema in parallel.

Statement of Ethics

Ethical approval is not required for case reports in accordance with local guidelines. Written informed consent was obtained from all patients for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

K.L.R. and N.K.P. conceived of the presented idea and revised it critically for important intellectual content. J.Y.N. drafted the work and revised it critically for important intellectual content. J.Y.N., M.O., S.K.B., K.R., P.C., W.-I.L., M.C.C., K.L.R., and N.K.P. reviewed and contributed to the final approval of the version to be published.

Data Availability Statement

All data analyzed during this study are included in this article. Inquiries about data access should be made to the corresponding author.

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