

Utility of Plasma Exchange in a Patient with Waldenström Macroglobulinemia and Recurrent Angioedema Secondary to C1 Esterase Inhibitor

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INTRODUCTION

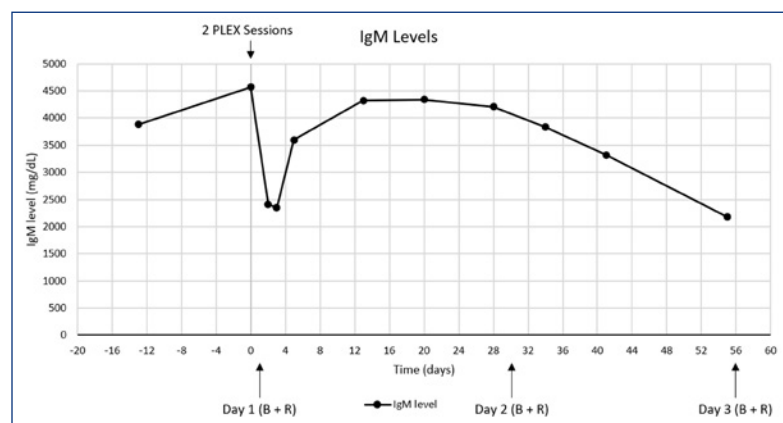
Acquired angioedema (AAE) is caused by either consumption or inactivation of C1 esterase inhibitor (C1-INH)¹ and is a rare, potentially life-threatening serious condition characterized by recurrent episodes of non-pitting edema of the skin or mucosa without urticaria.^{2,3} Unlike the more prevalent hereditary angioedema (HAE), which typically presents in adolescence and has a positive family history, AAE usually occurs in older adults and is often a paraneoplastic phenomenon.² In AAE, a previously normal individual develops acquired C1-INH dysfunction leading to uncontrolled activation of the classic complement pathway and bradykinin-mediated angioedema.^{2,4} This syndrome was first recognized in a patient with lymphoma and is most frequently associated with B-cell lymphoproliferative disorders or monoclonal gammopathies.² Indeed, up to 90% of AAE cases have an underlying clonal B-cell process such as non-Hodgkin lymphoma (e.g., marginal zone or lymphoplasmacytic lymphoma), Waldenström macroglobulinemia (WM), or monoclonal gammopathy of undetermined significance.^{5,6}

Waldenström macroglobulinemia is an indolent lymphoplasmacytic lymphoma defined by bone marrow infiltration with clonal lymphoplasmacytoid cells and a circulating monoclonal IgM paraprotein.⁷ Common manifestations of WM include anemia, lymphadenopathy, hepatosplenomegaly, and hyperviscosity from high IgM levels, while immunologic phenomena such as autoimmune neuropathy or cryoglobulinemia are also recognized.⁸ Although exceedingly rare, WM may present initially with angioedema.⁹ We report a case of a 67-year-old man who presented with isolated recurrent angioedema as the first manifestation of WM, caused by acquired C1-INH deficiency. This case highlights the importance of recognizing AAE in older patients with unexplained angioedema and illustrates the link between AAE and underlying lymphoproliferative disease, as well as unique management considerations such as plasma exchange before initiation of Rituximab therapy due to the possibility of a subsequent IgM flare.^{10,11}

CASE REPORT

A 67-year-old man presented to the emergency department (ED) with acute angioedema involving the tongue and difficulty speaking. The episode was unresponsive to epinephrine, dexamethasone, and diphenhydramine, necessitating nasotracheal intubation. Additional treatment included tranexamic acid (TXA) and fresh frozen plasma (FFP) with temporary improvement. He had experienced a similar episode of tongue swelling a few months earlier. Both episodes were isolated angioedema without associated rash or other systemic symptoms. His family history was notable for a father who had been diagnosed with WM and died five years after the diagnosis; however, there was no family history of angioedema. He reported not taking angiotensin-converting enzyme inhibitors. Physical examination revealed small left supraclavicular and right axillary lymphadenopathy. His complete blood count showed mild to moderate normocytic anemia, with hemoglobin levels ranging from 8.2 to 11.4 g/dL. Aspartate aminotransferase and alanine aminotransferase levels were elevated at 79 and 128 U/L, respectively. Complement levels were reduced, with C3 at 77 mg/dL, C4 at <8 mg/dL, and C1-INH at <8 mg/dL prior to FFP transfusion. C1q was measured at 4.4 mg/dL. Ultrasound showed hepatomegaly with multiple well-circumscribed echogenic masses, prompting magnetic resonance imaging (MRI). The MRI revealed two hyperintense liver lesions measuring 1.3 cm and 1.1 cm of unclear etiology, as well as splenomegaly (18 cm spleen). Bone marrow biopsy confirmed a diagnosis of lymphoplasmacytic lymphoma consistent with WM and AAE due to C1-INH deficiency. Further laboratory work-up showed an IgM level of 3883 mg/dL. Serum protein electrophoresis with immunofixation performed revealed an M-spike of 1.9 g/dL. IgA and IgG levels were within normal limits at 88 mg/dL and 834 mg/dL, respectively. Given his elevated IgM level of 4572 mg/dL, he underwent two consecutive prophylactic plasma exchange (PLEX) sessions with FFP as replacement fluid (to also replenish C1-INH) with good response. PLEX was performed using Spectra Optia Apheresis System (Software Version 3.7, TerumoBCT, Lakewood, CO) using peripheral veins. Patient's IgM level decreased from 4572 mg/dL to 2413 mg/dL. Both procedures were performed with acid citrate dextrose solution A (ACD-A) for anticoagulation and 1 gram Calcium Chloride

Figure 1. IgM levels through the course of treatment. Day 1 indicates the first day of chemotherapy. B + R: Bendamustine + Rituximab; PLEX: plasma exchange.



in 50 mL of Normal Saline via the return line throughout the procedure, titrated based upon citrate-related adverse events. The patient later was started on Bendamustine and Rituximab chemotherapy, after which IgM level rose to 4338 mg/dL but subsequently declined with ongoing therapy [Figure 1]. Although the serum viscosity during the initial presentation was not measured, it was within normal limits at 1.8 cP the day before the second cycle of chemotherapy.

DISCUSSION

WM-associated AAE is an illustrative example of how treating the underlying malignancy can resolve the paraneoplastic symptoms. In our case, bone marrow biopsy confirmed lymphoplasmacytic lymphoma with an IgM monoclonal protein, establishing WM as the cause of the patient's acquired angioedema. Similar cases have been described in the literature, though they are rare. Willows et al¹² reported a 73-year-old man with acquired C1-INH deficiency who had both angioedema and nephrotic syndrome from IgM deposition due to an underlying lymphoplasmacytic lymphoma; notably, both the angioedema and the renal pathology resolved after treating the lymphoma with Bendamustine-Rituximab. Our patient's course was comparable. Before the hematologic diagnosis was made, he suffered multiple life-threatening episodes of facial and oropharyngeal swelling unresponsive to medical treatment ultimately requiring intubation. Once WM diagnosis was established and definitive therapy was initiated, angioedema attacks ceased. This aligns with reports that cytoreductive treatment of the B-cell clone can significantly ameliorate or cure AAE.² In the French cohort, for instance, Rituximab-based therapy (alone or with chemotherapy) prevented further angioedema in about 79% of treated patients,⁶ underscoring that eradication or control of the B-cell disorder is essential for long-term remission of AAE.

From a pathophysiologic standpoint, it is worth noting that our patient's angioedema was the initial manifestation

of WM, with no other typical WM features such as hyperviscosity or constitutional symptoms at presentation except from mild anemia. AAE can precede the diagnosis of an overt lymphoma by months or even years.^{5,13} During this interval, patients may be misdiagnosed with idiopathic angioedema or allergies. In any patient over 40 with unexplained, recurrent angioedema and normal allergy testing, acquired C1-INH deficiency should be considered and complement studies (C4, C1q, C1-INH levels/function) obtained.^{5,14} Our case reinforces this point. Early recognition of AAE led us to perform appropriate evaluations (including immunofixation and ultimately bone marrow biopsy), resulting in the diagnosis of WM at an asymptomatic stage. This has important implications, as timely treatment of the lymphoma not only addresses the angioedema but also may prevent progression of the hematologic disease.

The management of acquired angioedema has two major components: acute treatment of swelling attacks and long-term prophylaxis or curative therapy targeting the underlying cause.² During acute angioedema episodes, especially if they involve the airway or cause significant discomfort, therapies that restore or bypass the deficient C1-INH are indicated. First-line treatments for acute attacks include plasma-derived C1-INH concentrate (if available) and bradykinin-pathway-targeted therapies such as Icatibant (a bradykinin B2 receptor antagonist) or Ecallantide (a kallikrein inhibitor), which have been well established in HAE and reported to be effective in AAE as well.^{6,15} In a cohort of AAE patients, Icatibant consistently relieved symptoms, and C1-INH concentrate was effective in >90% of treated attacks.⁶ If these specific agents are not available, guidelines note that fresh frozen plasma (FFP) can be used to supply functional C1-INH and terminate an attack. Our patient, for example, received FFP during the episode of tongue swelling prior to the definitive diagnosis (providing temporary improvement). Caution is warranted with FFP as it contains complement components that in theory could fuel further bradykinin generation, but in practice FFP has been life-saving when C1-INH concentrate is inaccessible. Supportive care, including securing the airway in laryngeal attacks, is critical, keeping in mind that standard allergy medications (epinephrine, antihistamines, corticosteroids) are typically ineffective in bradykinin-mediated angioedema.

Long-term prophylaxis in AAE aims to reduce the frequency and severity of attacks while the underlying disease is being evaluated or treated. Attenuated androgens such as danazol can raise hepatic production of C1-INH and have been used in both hereditary and acquired angioedema to diminish attack frequency.^{6,16} Antifibrinolytic agents like TXA are another option; TXA is thought to attenuate bradykinin formation (by inhibiting plasmin activation) and

has a modest prophylactic benefit in some patients.^{6,17} In the French study, 76% of patients on long-term TXA had a reduction in attacks, though about 13% developed thromboses as side effects.⁶ Our patient was initially started on tranexamic acid prophylaxis while diagnostic work-up was underway, which appeared to lessen the severity of his swellings. Various reports have shown that treating the associated lymphoproliferative disorder can lead to remission of AAE in the majority of cases.^{2,6} In our case, we proceeded with combination chemoimmunotherapy for WM.

The patient's lymphoma was treated with Bendamustine plus Rituximab, a standard first-line regimen for WM. We paid special attention to the initiation of Rituximab due to the risk of a transient IgM flare that occurs in approximately 30–50% of patients with WM following the initiation of Rituximab therapy, potentially worsening hyperviscosity symptoms.^{10,11} Although our patient had no initial hyperviscosity syndrome, his IgM level was significantly elevated, raising concern that a flare could trigger new symptoms or even paradoxically exacerbate the angioedema. To mitigate this risk, after multi-disciplinary discussions which included hematologist, immunologist, and apheresis practitioner, we implemented prophylactic PLEX before the first Rituximab dose. PLEX rapidly lowered his IgM burden and had the added benefit of removing any circulating anti-C1-INH autoantibodies or immune complexes, which likely provided temporary relief of his angioedema as well. In WM, it is generally recommended to consider PLEX for patients with very high IgM (for example, >4 g/dL) or evidence of hyperviscosity prior to starting Rituximab.^{7,18} Consistent with published guidance, our patient underwent two sessions of PLEX with one plasma volume, after which Rituximab was started without incident. Even though an IgM flare occurred after the initiation of Rituximab, its level did not exceed pre-Rituximab PLEX levels. Notably, his subsequent IgM levels continued to decline with therapy. This approach – using pre-Rituximab PLEX – has been reported to prevent Rituximab-related flares and was successfully employed in the case reported by Fornero et al as well.¹⁹

Beyond preventing IgM flare, PLEX can serve as an interim therapeutic measure in severe AAE. By removing pathogenic IgM and immune complexes, PLEX can transiently raise C1-INH functional levels, providing temporary relief until longer-term therapies take full effect. However, PLEX is a procedure that requires specialized nurses and physicians and is not available in all centers. It is typically reserved for special situations such as ours (imminent Rituximab use or refractory, life-threatening angioedema).

In summary, the cornerstone of AAE management in the context of WM is treating the lymphoma. To this date, our patient received three cycles of Bendamustine-Rituximab, and he responded to treatment marked by a >50% reduction in IgM level and complete resolution of his angioedema episodes. This outcome mirrors prior reports where successful

treatment of the B-cell malignancy led to disappearance of acquired angioedema symptoms.¹² It underscores that in secondary causes of angioedema, vigilance for an underlying disorder and its prompt therapy is key to curing the angioedema.

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