Angioedema in a Patient with Underlying Lymphoproliferative Disorder

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Title Page

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Running Head: Angioedema in Patient with Lymphoproliferative Disorder

Angioedema in a 61-year-old Patient with Underlying Lymphoproliferative Disorder

To the editor

A 61-year-old female presented to the emergency department for sudden tongue swelling with difficulty talking and swallowing. She received epinephrine and was admitted to the intensive care unit (ICU). Swelling resolved within a few hours after treatment with diphenhydramine and steroids. The patient did not require intubation. Subsequent work-up showed reduced C1 esterase inhibitor (C1-INH) protein; 13 mg/dL (Reference range: 21-39 mg/dL), C1-INH functional 88% (Normal >=88%), C4c <3 mg/dL (Reference range: 15-57 mg/dL), and C1Q <3.6 mg/dL (Reference range 6.0-8.6 mg/dL). Low C1-INH protein levels, complement C4c and complement C1Q lead to the initial diagnosis of acquired angioedema from C1-INH deficiency. CT scans of chest and abdomen were normal. Comprehensive metabolic panel and complete blood count (CBC) were within normal limits. Coagulation screen showed PT 10.5 sec, International normalized ratio (INR) 0.9, and activated partial thromboplastin time (aPTT) 22.1 sec, fibrinogen 328 mg/dL, and D-Dimer 14,519, ng/mL FEU (fibrinogen equivalent unit). Paraprotein workup showed the presence of IgG lambda paraprotein. Bone marrow examination showed 20% monoclonal lambda plasma cells thus confirming a diagnosis of lymphoproliferative disorder. Such disorders range from monoclonal gammopathy of undetermined significance (MGUS) to non-Hodgkin lymphoma in patients with acquired angioedema.

Angioedema is a common presentation in the emergency department because airway angioedema could be fatal without timely intervention (1). Each year, angioedema or allergic reactions are associated with approximately one million emergency room visits. However, most of these

patients are diagnosed with allergic reactions (2). Therefore, it is important to investigate causes of angioedema because it can be associated with various conditions including drug induced, acquired, hereditary or idiopathic (Table 1).

Acquired angioedema due to C1-INH deficiency is a rare cause of adult-onset non-urticarial angioedema which could lead to life-threatening laryngeal edema and asphyxiation, similar to those observed in patients with hereditary forms of C1-INH deficiency, but without any family history (4). The classification of C-1-INH deficiency has been expanded due to discovery of many newly identified genetic variations, all of which appear to result in increased levels of bradykinin causing angioedema (5). Interestingly, hereditary angioedema, a rare disease, is due to deficiency of functional C1-INH where bradykinin is also the biologic mediator of swelling (5, 6).

Diagnostic criteria of acquired C1-INH deficiency has not been established but such disorder is typically observed in older patients (fourth decade of life or later) with underlying conditions such as malignancy (usually B cell in origin; 30-50%), monoclonal gammopathy (30-50%) and autoimmune disorder (5-10%) which are often undiagnosed during first presentation. Patients with an acquired deficiency produce immune complexes that consume large amounts of C1q and C1 esterase inhibitor, resulting in quantitative and functional deficiencies or both. C1-INH antigen may be low or normal in patients with acquired deficiency. Acquired C1-INH deficiency can be distinguished from inherited deficiency by measurement of C1q and C4 complement levels. Patients with the hereditary disease have normal levels of C1q, while those with the acquired form have low levels. Patients with active attacks of all forms of angioedema will have

low C2 and C4 levels due to C1 activation and complement consumption. Bowen et al presented a useful algorithm for diagnosis of acquired C1-INH deficiency (7). Treatment recommendation are available acute attack and prophylaxis of C1-INH deficiency which may also be applicable to acquired C1-INH deficiency. Recently, Busse et al published guidelines for treatment of angioedema (8). Avoidance recommendations exists for estrogen, tamoxifen and angiotensin-converting enzyme (ACE) inhibitors. Although our patient responded to antihistamine and steroid therapy, a common therapy is treatment with plasma-derived or recombinant C1-INH (4).

References

1. Bernstein JA, Cremonesi P, Hoffmann TK, Hollingsworth J. Angioedema in the emergency department: a practical guide to differential diagnosis and management. Int J Emerg Med. 2017; 10: 15.
2. Kelly M, Donnelly JP, McAnnally JR, Wang HE. National estimates of emergency department visits for angioedema and allergic reactions in the United States. Allergy Asthma Proc. 2013;34:150–154.
3. Bertazzoni G, Spina MT, Scarpellini MG, Buccelletti F, De Simone M, Gregori M, et al. Drug-induced angioedema: experience of Italian emergency departments. Intern Emerg Med. 2014;9:455–62.
4. Shi Y, Wang C. Where we are with acquired angioedema due to C1 inhibitor deficiency: A systematic literature review. Clin Immunol. 2021;230:108819.
5. Patel G, Pongracic JA. Hereditary and acquired angioedema. Allergy Asthma Proc. 2019;40:441-445

6. Busse PJ, Christiansen SC. Hereditary angioedema. N Engl J Med 2020;382:1136-1148
7. 7. Bowen T, Cicardi M, Farkas H, Bork K, Longhurst HJ, Zuraw B et al. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. Allergy Asthma Clin Immunol. 2010; 28;6:24.
8. 8. Busse PJ, Christiansen SC, Riedl MA, Banerji A, Bernstein JA, Castaldo AJ. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema. J Allergy Clin Immunol Pract 2021; 9: 132-150

Table 1. Various types of angioedema

Type of angioedema	Comments
Hereditary angioedema	Bradykinin mediated. Most cases are due to mutation of gene encoding C1-INH (Type I) or normal concentration of functionally impaired C1-INH (Type II). Both disorders are rare.
Drug induced angioedema	Most common with ACE inhibitors but other drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs) and oral antidiabetics, (gliptins), sirolimus, tacrolimus, everolimus may also cause angioedema.
Histamine mediated angioedema	This is also called allergic angioedema (including allergy to food), which is an immunoglobulin E mediated hypersensitivity immune response of mast cell

	degranulation (most common).
Acquired angioedema	Bradykinin mediated, a very rare condition; Type 1 is associated with increased catabolism of C1-INH (lymphoproliferative disorder, autoimmune) while Type II is associated with autoantibody to C1-INH. Presentation is similar to hereditary angioedema but develops at fourth decade of life or later. In hereditary angioedema, C1q levels are normal but C4 levels are decreased. In acquired angioedema, both levels are decreased.
Idiopathic	Usually, histaminergic