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CASE REPORT

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An unusual case of acquired angioedema associated with monoclonal gammopathies of uncertain significance

Yun Liu[#], Guofeng Fan[#], Fei He, Hanwen Tong, Chenxiao Jiang, Peng Xu[*], Jun Wang[*]

Department of Emergency Medicine, Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Nanjing, China

[#]These authors contributed equally to this work

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Abstract
Acquired angioedema (AAE) is a rare disease due to the C1 esterase inhibitor (C1-INH) deficiency. Clinically, its symptoms are similar to hereditary angioedema (HAE) with hereditary C1-INH deficiency. Both conditions have the potential to cause upper airway obstruction, which can be fatal in clinical practice and thus require intense attention. Here, we'd like to discuss the clinical presentation, diagnosis and follow up of a special case of AAE associated with monoclonal gammopathies of unknown significance (MGUS) with recurrent upper airway obstruction. The patient was regularly followed up after being discharged from our ward. Measurements of C3-C4 levels were carried out by a hematological test. Due to the rarity of such a disease, especially in Chinese people, relevant diagnosis methods are missing in this patient, so the patient was only diagnosed with AAE-C1-INH associated with MGUS clinically. The latest follow up showed that he still underwent recurrent upper airway obstruction; thus, he remained in a tracheostomy state due to a lack of proper medication prophylaxis and died eventually. This unusual case reminds emergency physicians to pay attention to such disease during clinical practice, and relevant diagnosis method should be improved.

Introduction

Angioedema due to C1 esterase inhibitor (C1-INH) deficiency is a vascular reaction of the soft tissue or mucosa that leads to increased permeability of blood vessels, resulting in tissue swelling. There are two main types of angioedema: hereditary angioedema (HAE) and acquired angioedema (AAE). HAE is due to a gene mutation that leads to the lack of expression of C1-INH or the synthesis of a non-functional protein, while AAE is a rare case caused

***Corresponding authors:** Jun Wang, Department of Emergency Medicine, Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Nanjing 210008, China. *Email address*: wjgaogou@aliyun.com. Peng Xu, Department of Emergency Medicine, Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Nanjing 210008, China. *Email address*: exu_peng@163.com

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by decreased catabolism of C1-INH. HAE and AAE can be difficult to distinguish clinically. Usually, AAE may present a later onset of symptoms in the fourth or fifth decade of life.

First described in 1972, acquired C1-INH deficiency was first reported by Caldwell et al. in a patient with lymphoproliferative disorder.[1] It is usually associated with lymphoproliferative diseases, including monoclonal gammopathies of unknown significance (MGUS) and non-Hodgkin lymphoma (NHL), with no family history of angioedema. The main mechanism in angioedema is the consumption of C1-INH, which may lead to activation of the classical complement pathway and the contact activating system (CAS). It generates the vasoactive peptide bradykinin and leads to increased vascular permeability and angioedema. It is characterized by episodic swelling in the upper airways, bowel walls, and subcutaneous tissues,[2,3] while the laryngeal edema can be life-threatening. We report here a rare case with a recurrent upper airway obstruction and the hematological disorder of MGUS.

Case Presentation

A 68-year old male patient was transferred to our hospital with a recurrence episode of dyspnea. He was diagnosed with coma and respiratory failure in a local hospital. This is the second attack he has been through. In the first episode on October 6, 2021, he suffered from dyspnea without any underlying causes and he was intubated in a local hospital. After extubation, he presented with no abnormal symptoms. However, on December 17, 2021, he underwent endotracheal intubation because of another attack of dyspnea and was transferred to our hospital on December 18, 2021. Family history of angioedema was absent. He had a history of cerebral infraction as well as diabetes. The laboratory tests showed normal complete blood cell counts (CBC) with HB of 114 g/L, platelets at 96 × 10^9/L, and WBC of 7.4 × 10^9/L. Biochemistry showed no abnormalities. CT scan of the brain and chest showed no abnormalities. After a successful half-an-hour spontaneous breathing trial (SBT), we extubated the patient. He presented no discomfort in breathing and could communicate fluently; thus, a thorough physical examination was performed and it was all normal. But only a few hours later, he was reintubated because of another attack of dyspnea. The patient showed a sign of acute apnea. On room air, the arterial blood gas values were as follows: pH: 7.292, PO2: 54.8 mmHg, PCO2: 71 mmHg, base excess: 6.6 mmol/L with oxygen saturation of 82% indicating a hypercapnia respiratory failure. Though administrated with 5 mg of dexamethasone, the oxygen saturation of this patient still dropped to 80% and cannot be reversed by bag-mask ventilation. He presented with an obvious three concave sign, and was intubated immediately. Since we cannot find any causes for his suffocation and just in case of another attack of dyspnea, we performed the tracheostomy a few days later. The patient had negative family history of such illnesses. CT scan of the abdomen showed no abnormalities. He complained of dizziness and mild tiredness in 2020 and was diagnosed with MGUS in a local hospital. Thus, the diagnosis of AAE was suspected. The complement test was then performed, which revealed a relative lower plasma level of C4 (0.19 g/L, normal: 0.2–0.4 g/L) and normal plasma level of C3, supporting the diagnosis of AAE. Due to the rarity of this disease, further laboratory tests like plasma level of C1q and C1-INH antigen cannot be performed. Thus, the diagnosis can only be verified by the clinical presentation. We then consulted a hematologist to evaluate the current status of MGUS in our patient. Further test of MGUS was performed. It showed an IgG k isotype with the monoclonal(M)-protein in the serum reaching 29.8 g/L. Free kappa light chain was high at 34.8 mg/L (reference range = 3.3–19.4), free lambda light chain was high at 40.3 (reference range = 5.7–26.3), and the kappa-lambda light ratio was normal at 0.86. The patient showed no CRAB features (hypercalcemia, renal impairment, anemia and bone disease). Thus, the patient showed no progression in MGUS. The latest follow-up showed that the patient still underwent recurrent episodes of dyspnea, and since we have no experience treating such disease, he was recommended that he consult the top healthcare facility in our country. However, due to the frequent occurrences of COVID-19 outbreak, the patient could only stay in a local hospital and remained in a tracheostomy state until he died.

Discussion

The deficiency of C1-INH may be classified as hereditary or acquired. HAE is caused by a mutation in the C1-INH gene.[4] AAE, as in the case of our patient, resembles HAE and cannot be distinguished solely by symptoms with the exception that AAE has a late onset (on average, after the age of 40 years) and patients do not have a family history of angioedema. Laboratory analyses include a low level of C1-INH antigen and function, a reduced level of C4 and C1q (normally far below 50% of normal) and a normal level of C3. Low level of C4 may be the first test recommended to the patient suspected of having C1-INH deficiency. In our patient, we can see a relatively low level of C4 but a normal level of C3. The diagnosis of this patient was confirmed for AAE mainly from clinical symptoms since complement test of C1-INH and C1q level was not so easily available in our country. C1-INH-AAE is usually misdiagnosed as an allergy and therefore, most patients are treated with anti-allergic medication, but all proves to be ineffective.

AAE due to C1-inhibitor deficiency is recurrent, self-limiting and circumscribed edema that affects the subcutaneous tissue, the mucosa of gastrointestinal tract, and the upper respiratory airways and may resolve in 1–5 days without any damage. Thus, clinical presentation in the skin may involve urticarial eruptions and swelling in face, genitals, buttocks, and extremities. Abdominal attacks may involve vomiting, colicky abdominal pain, and diarrhea. Upper airway involvement may include dysphagia, voice change, and stridor that may precede to asphyxia, which is fatal and requires immediate emergency therapy. Apart from these clinical symptoms, the diagnosis of AAE should be confirmed by laboratory analyses. The tests show low level of C1-INH function and antigen, notably reduced C4 and C1q (far below 50% of normal) and normal C3. In emergency situation, low levels of C4 can be served as the first screening test to suspect C1-INH deficiency and help to rule out

histaminergic edema. Due to the rarity of this disease in our country, only a few specialized research laboratories can perform such tests. Thus, we cannot perform further testing of C1q and C1-INH in our hospital. The diagnosis of our patient is based on its clinical presentation and his past medical history. Though not fully confirmed by laboratory tests, we believe the diagnosis is correct, and we recommend that he go for further treatment in the top hospital in our country.

The characteristics of AAE involve an increased consumption of C1-INH and hyper activation of the classical human complement pathway. AAE can be divided into two types: Type I, which is associated with LPD and Type II, which is associated with autoimmunity.[1,5,6] But these two conditions may coexist in an AAE patient and make this classification meaningless. The most frequent LPDs associated with AAE are indolent lymphomas, including nodal and splenic marginal zone lymphomas and lymphoplasmocytic lymphomas, as well as Waldeström's disease. The autoimmune disease associated with AAE frequently involves cryoglobulinemia and rheumatoid arthritis. The pathological lymphatic tissue or the autoantibody consume the C1-INH and result in hyperactivation of the complement system or CAS, which leads to a further consumption of C1-INH and a generation of bradykinin, which results in increased vasopermeability that leads to angioedema. Gobert's study revealed a 38% occurrence of MGUS in C1-INH-AAE patients, while Bork et al. found a 53% occurrence of MGUS in AAE[7] patients. MGUS is characterized by the appearance of a serum monoclonal paraprotein derived from immunoglobulin (Ig). MGUS can be divided into IgM and non-IgM MGUS, which can progress to lymphoid malignancies such as Waldenström's macroglobulinemia (WM), chronic lymphocytic leukemia (CLL), and multiple myeloma (MM).[8,9] Most patients show no overt condition but suffer a shorter life expectancy (8.1 vs. 12.4 years) and are associated with a greater prevalence of recurrent infections, ischemic heart disease, peripheral neuropathy, and renal disease.[10] Patients with MGUS and autoantibodies to C1-INH frequently share the same heavy and light chain isotypes, but there is no increase in the frequency of MGUS progressing to MM was observed.[11]

Evidence revealing that the M components detected in these patients frequently correspond to anti-C1-INH antibodies, and that patients with auto-antibodies may develop lymphoproliferative diseases, suggests that a single B cell clonal disorder with different potential clinical evolutions underlies all cases of AAE. Thus, for all patients with angioedema due to acquired C1-inhibitor deficiency, we suggest an annual screening for lymphoproliferative disease.

Thus, according to his previous disease history, we suspected a diagnosis of AAE in this patient. The presence of MGUS can be regarded as a warning sign that may precede the onset of AAE,[7] and the patient we reported showed no signs of MGUS progression.

C1-INH-AAE is rare and life-threatening, especially in cases with acute upper airway edema. In the setting of the emergency room, when we encounter patients presenting with clinical features of edema, and not responding to epinephrine, glucocorticoids or antihistamines, especially if they proven to have a C4 consumption and a clinical history of LPDs, the diagnosis of C1-INH deficiency angioedema should be suspected. The therapy of AAE includes two aspects: (1) reversal of the symptoms of angioedema and (2) treatment of the associated disease. Moreover, patients should be aware of potential triggers of edema such as psychophysical stress and certain medications (angiotensin-converting enzyme inhibitors, tamoxifen, and estrogen-containing drugs). First-line therapy for treatment in severe attacks of AAE is the infusion of plasma-derived human C1-INH concentrate, which is available in several countries but not in ours. In this case, plasma (solvent/detergent treated plasma) should be promptly administered as a surrogate. Another useful alternative to plasma is Icarian, a synthetic selective bradykinin B2 receptor antagonist (available in the US and Europe) and is also available in our country recently. For long-term prophylaxis, antifibrinolytic agent that may reduce the peripheral consumption of C1-INH and attenuated androgens are commonly used. Antifibrinolytic agents such as tranexamic acid can lead to a decrease in the severity of an angioedema attack.[12] They are usually given orally with a starting dose of 3 g daily and should be preferred over androgen in children, women, and patients who do not tolerate androgen. Because it may increase the risk of thromboembolism, it should be administrated in association with warfarin. Attenuated androgens (such as danazol, stanozolol) are also effective in short- and long-term prevention. Infusions of C1-INHRP can be administered for prevention too, but it may induce resistance in some patients, thus it is normally applied in patients suffering from acute attacks.[13]

Conclusion

In this report, we try to remind physicians, especially emergency physicians, of the unique presentation of AAE accompanied by MGUS. The case is so rare and life-threatening that it shows recurrent obstruction in the upper airway without urticarial and pruritus as the first symptoms. Since dyspnea is an emergency situation in clinics and through our case, we'd like to remind clinicians of the possibility of angioedema in those patients if regular treatment is useless. Due to the rarity of the disease, corresponding drugs are still not available in practice. It is recommended that patients diagnosed with C1-INH deficiency should be carrying a note with cautions listing on it.

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