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CASE REPORT

Case Report: Hereditary Angioedema Accompanied by Chronic Spontaneous Urticaria

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Purpose: Hereditary angioedema (HAE) is a rare genetic disorder characterized by recurrent edema of the skin and tissues. Chronic spontaneous urticaria (CSU) is recurrent urticaria that lasts for more than 6 weeks without an apparent cause. It has long been believed that HAE does not occur with CSU.

Patient and Case Description: Herein, we report a case of definite HAE with CSU. The patient was diagnosed with CSU due to recurrent clinical symptoms. After treatment with omalizumab, the symptoms of CSU improved, but there were still unpredictable recurrent episodes of edema. For further diagnosis, genetic testing and other laboratory examinations were performed, and it was confirmed that the patient also had HAE.

Results: After treatment with omalizumab, the pruritus and erythema improved, confirming the diagnosis of CSU. The diagnosis of HAE (C1-INH deficiency, type 1) was established by WES, C1-INH concentration (0.08 g/L) and C4 level (25 mg/L) measurements, which explained the recurrent edema.

Conclusion: We report a case with both HAE and CSU, suggesting that doctors should consider the possibility of co-existence of diseases in diagnosis, and attention should be paid to the timing of different treatment options such as omalizumab in the course of treatment.

Keywords: chronic spontaneous urticaria, CSU, hereditary angioedema, HAE, omalizumab, case report

Introduction

Hereditary angioedema (HAE) is a recurrent genetic disease characterized by angioedema. HAE was first accurately described by Osler in 1888.[1] Traditionally, HAE is mainly classified into C1 esterase inhibitor (C1-INH) deficiency type (HAE-C1-INH) and non-C1-INH deficiency type (HAE-nC1-INH). HAE-C1INH is caused by mutations in the *SERPING1* gene, and diagnosis is often made by measuring the plasma levels of antigenic or functional C1 inhibitors. Considering that some HAE patients have no clear family history, abnormal C1-INH function caused by sporadic *SERPING1* mutations may also be one of the potential etiologies. In recent years, pathogenic variants in several genes (*F12, PLG, ANGPT1, KNG1, MYOF, HS3ST6, CPN1*, and *DAB2IP*) have been identified to be associated with HAE-nC1INH.[2] The pathophysiological mechanism of HAE-nC1-INH is closely related to the abnormal activation of the bradykinin signaling pathway. The *F12* gene mutation is one of its main pathogenic causes, this mutation can lead to abnormal activation of factor XII, which in turn activates the contact coagulation system, promotes excessive bradykinin production, causes an increase in vascular endothelial cell permeability, and ultimately leads to the occurrence of angioedema.[3] Some patients with HAE may have prodromal manifestations such as erythema and wheals, which can be easily confused with urticaria in the clinic. Chronic spontaneous urticaria (CSU) refers to recurrent urticaria that lasts for more than six weeks without an obvious trigger, and the pathogenesis of CSU may be related to both autoimmunity (IgG-mediated disease) and autoallergy (IgE-mediated disease).[4] Classic HAE subtypes are not accompanied by urticaria, and it is generally believed that the two conditions do not coexist. However, pathogenic variants in two genes (*CPN1* and *DAB2IP*) have been confirmed to be associated with hereditary angioedema (non-C1 inhibitor deficiency type) in families

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with urticaria,[5,6] which has broken the traditional understanding of the phenotypic characteristics of the disease and also provided new insights into the pathogenesis and clinical diagnosis of HAE. Herein, we report a rare case of confirmed diagnosis of HAE (HAE-C1-INH) combined with CSU in a young female patient. After treatment with omalizumab, some symptoms improved, confirming the diagnosis of CSU. The diagnosis of HAE was established by genetic testing and complement C4 level testing. This case suggests that Clinicians should be alert to the possibility of HAE when facing intractable recurrent edema in patients with CSU to avoid delayed diagnosis and treatment. We provide practical reference for improving the differential diagnosis of such edema, helping readers grasp its clinical characteristics.

Case Presentation

The patient was a 26-year-old woman who visited the doctor for recurrent erythema and pruritus of the trunk and limbs for over 1 year. The patient had multiple erythema and wheals on the trunk and limbs without obvious induction, which were obvious after scratching, and the rash resolved by itself. There was no significant family or allergic history. During the course of treatment, the patient was considered to have refractory chronic spontaneous urticaria, and first-line drugs, such as antihistamines, were ineffective. Since August 2022, the patient has regularly received 300 mg of omalizumab once a month. The drug was stopped for two months during the period of infection with COVID-19, and the illness was repeated during this time. The follow-up results showed that erythema, wheals, and pruritus were controlled. The Urticaria Control Test (UCT) score changed from 7 to 16 and remained stable. The Dermatology Life Quality Index (DLQI) scores improved to 5 points at follow-up during treatment. Omalizumab is indicated for patients with chronic spontaneous urticaria who still have symptoms after treatment with H1 antihistamines, but it is ineffective for the treatment of HAE. Considering the efficacy of omalizumab treatment combined with the clinical manifestations of the patient, the diagnosis of CSU was clear. However, during the course of the disease, the patient had recurrent mild lip and facial edema without obvious causes, which mostly occured after actions such as yawning, without wheals or itching, and often resolves on its own in about 30–40 minutes. It should be noted that the onset of this edema is not correlated with the activity of urticaria. Therefore, we advised further laboratory tests for detailed analysis of the conditions. The thyroglobulin and antinuclear antibody test results were negative. The concentration of complement C4 was 25 mg/L (reference interval: 100 mg/L–400 mg/L) and that of C1-INH was 0.08 g/L (reference interval: 0.21 g/L–0.39 g/L). In addition, a heterozygous mutation of *SERPING1* gene c.991C>A (p.P331T) was detected by whole exome gene assay, which showed an association with angioedema types 1 and 2 or partial deficiency of complement component C4. Combined with the patient's clinical manifestations, C1-INH concentration, and genetic test results, a diagnosis of HAE was confirmed. Considering that the patient's edema is mild and can resolve on its own, and the patient feels that her quality of life is not significantly affected, she did not receive treatment based on HAE.

Discussion

HAE is an autosomal dominant disease characterized by recurrent skin and/or submucosal soft tissue edema with certain disabling characteristics.[7] Recent studies have confirmed the molecular genetic basis of HAE as a deficiency of functional C1-inhibitor due to a mutation in *SERPING1*, and bradykinin is believed to be the biological mediator of swelling.[7,8] Deficiency (type 1) or dysfunction (type 2) of C1-INH caused by mutations in *SERPING1* can lead to overproduction of bradykinin and activation of the bradykinin b2 receptor, thereby increasing vascular permeability and leading to the onset of angioedema.[9,10] In vitro experiments have demonstrated that the bradykinin B1 receptor may be expressed during angioedema episodes, which likely explains the prolonged duration of swelling episodes.[11] HAE with normal C1-INH (HAE-nc1-INH) is a rare disease. The mechanism of swelling of HAe-nC1-INH is not clear, and it may be related to the mutation of factor XII, gene *F12*, and the enhancement of bradykinin signaling.[12] Early diagnosis and treatment are important for disease management, and HAE should be suspected in patients with recurrent skin swelling, prodromal symptoms, and treatment failure with antihistamines, glucocorticoids, omalizumab, or epinephrine.[10]

Erythema marginatum (EM) is a reticular and serpiginous, usually non-pruritic erythema and a specific prodromal symptom of HAE. It may precede or accompany angioedema or may occur independently. EM is considered a unique rash of HAE and a clinical manifestation that is easily confused with urticaria, which may lead to delayed diagnosis of HAE. The incidence of urticaria and prodromal symptoms (including EM) in a cohort of HAE patients was reported in

a Danish retrospective study and showed that 50% of HAE patients with EM had a rash that was misdiagnosed as urticaria, and 25% of HAE patients experienced prodromal symptoms of urticaria.[12,13] However, this study did not explicitly mention cases of HAE combined with CSU. Previously, the condition of HAE complicated with CSU was only mentioned in isolated case reports.[14]

CSU, as an important differential diagnosis of HAE, has long been considered non-concurrent with HAE.[3] This is a clinical dogma. Therefore, when urticaria rash and angioedema are present together or when patients have a history of urticaria, doctors often rule out the diagnosis of HAE in advance. Here, we report a case of HAE with CSU. According to the clinical manifestations of the patient and the improvement in erythema, wheals, and pruritus after omalizumab treatment, the diagnosis of CSU was clear. Simultaneously, a clear diagnosis of HAE was established through laboratory examination and clinical manifestations.

Recent studies have revealed a possible role of subclinical mast cell activation in the initiation of HAE attacks. This could potentially predispose patients to urticarial eruptions and vice versa; however, further investigations are required.[12] In the pathogenesis of HAE, the deficiency or functional abnormality of C1-INH leads to excessive activation of the complement system. The resulting vasoactive substances not only directly cause angioedema but also form a positive feedback loop by activating factor XII (FXII) and plasminogen in the coagulation system, intensifying bradykinin release and causing increased vascular permeability.[15–17] Recent studies have found abnormal activation of the complement alternative pathway in CSU. Elevated serum levels of C3a and C5a can induce mast cell degranulation, releasing inflammatory mediators such as histamine.[18] Meanwhile, in CSU patients, alternative pathway activation interacts with the coagulation system: thrombin enhances alternative pathway activity by activating factor B, while C5a promotes thrombin generation by upregulating tissue factor (TF). This positive feedback loop leads to increased vascular permeability and inflammatory amplification,[19] which forms a cross-correlation with the pathophysiology of vascular edema in HAE. In summary, complement system activation may be involved in the concurrent occurrence of HAE and CSU. However, the pathophysiological mechanisms still need further verification.

Previous studies have also suggested an increased likelihood of autoimmune diseases in patients with HAE.[20]

Conclusion

In this case, the patient with definite diagnosis of HAE showed clinical characteristics of CSU, and the urticaria manifestations were controlled after omalizumab treatment, which further suggested that the patient with HAE was complicated with CSU. This case report suggests that doctors should consider the possibility of co-existence of diseases in diagnosis, which is favorable for clearer diagnosis, reduction of misdiagnosis, and improvement of patients' quality of life. It should be noted that this study, as a single case report, has limitations, and it is necessary to conduct more clinical studies in the future. In addition, clinicians should re-evaluate the angioedema symptoms in patients with CSU to avoid missed diagnosis of concurrent HAE.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Zhejiang University. We confirmed all methods were carried out according to relevant guidelines and regulations.

Informed Consent

Informed consent was obtained from the patient for publication of this case report details.

Consent for Publication

Consent for publication was obtained.

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Disclosure

The authors declare that they have no competing interests in this work.

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