CASE REPORT

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A diagnosis confused with hereditary angioedema: nephrotic syndrome

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ABSTRACT

Hereditary angioedema (HAE) is a rare, autosomal dominant disease that primarily affects the skin, upper respiratory tract, and gastrointestinal system. Nephrotic syndrome (NS) is defined by the presence of severe proteinuria, low serum albumin levels, and generalized edema. Periorbital edema seen in NS can be confused with allergic edema or HAE. Accurate differential diagnosis is essential for appropriate treatment. This report presents a case of NS initially misdiagnosed as HAE.

Introduction

Hereditary angioedema (HAE) is an uncommon autosomal dominant condition that mainly involves the skin, upper airways, and gastrointestinal tract. Impaired C1 inhibitor (C1-INH) function or deficiency leads to excessive bradykinin generation, which increases vascular permeability and causes angioedema (AE) (1). Bradykinin-mediated AE does not respond to antihistamines (AH), corticosteroids (CST), or adrenaline. Attacks of AE typically last 2-5 days. Unlike mast cell-mediated AE, HAE-related AE is usually not accompanied by urticaria (2).

Nephrotic syndrome (NS) is defined by the presence of severe proteinuria, low serum albumin levels, and generalized edema. NS should be considered in the differential diagnosis of newly developed periorbital edema, which can resemble AE caused by allergies or other conditions (3,4).

We present a case of NS misdiagnosed as HAE.

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Case Presentation

A 36-year-old male with a medical history of rheumatoid arthritis (RA) and chronic kidney disease presented to the emergency department with swelling in his hands and feet for one week, progressing to facial and periorbital edema over the past two days. He was taking upadacitinib for RA and had undergone the right nephrolithiasis surgery 30 years ago. There were no similar past episodes, no abdominal pain, and no family history.

On physical examination, asymmetric edema was observed in the eyes, lips, and face (Figure 1A). There was no uvular edema or urticaria. Vital signs and systemic examination were normal. He received intravenous pheniramine 45.5 mg and dexamethasone 8 mg, without improvement. Due to unresponsive AE, he was administered 1000 international units (IU) plasma-derived C1-INH, (pdC1-INH), followed by 30 mg icatibant without clinical improvement.

Laboratory tests revealed hypoalbuminemia, proteinuria, and low C3 and C4 levels. Liver and thyroid functions, and C-reactive protein were normal. Complete blood count showed anemia and leukocytosis (Table 1). Anemia of chronic disease was considered. Consumption-related hypocomplementemia was considered due to low C3, C4, and C1q levels. In this case, the low level of C3, along with C4, normal determination of C1-INH level and function (Table 1), and the presence of edema that does not respond to pdC1-INH and icatibant treatment exclude the diagnosis of HAE. Nephrology consultation was obtained, diuretics were initiated, and the edema regressed (Figure 1B). A kidney biopsy was planned for the patient to investigate the causes of NS and for treatment planning.

Rheumatology consultation revealed antinuclear antibody, anti-double-stranded deoxyribonucleic acid, anti-Smith D1, lupus anticoagulant positivity, and hypocomplementemia, consistent with systemic lupus erythematosus (SLE). Kidney biopsy confirmed class IV lupus nephritis (diffuse proliferative necrotizing glomerulonephritis). Upadacitinib was discontinued, and pulse steroid therapy was started. During the service follow-up, the patient was intubated due to a sudden loss of consciousness, and brain computed tomography revealed findings consistent with subarachnoid hemorrhage. The patient underwent endovascular treatment of the intracranial aneurysm. The patient was transferred to intensive care and was pronounced deceased during follow-up.

Discussion

Bradykinin-mediated AE in HAE is not associated with allergies or urticaria. It presents with recurrent, spontaneously resolving edema. Patients with HAE frequently experience skin swelling and abdominal pain, with laryngeal edema being a potentially life-threatening manifestation (5,6). HAE can be fatal if not treated, due to laryngeal involvement. In cases of AH, CST, and adrenaline-unresponsive AE, HAE should be considered, and treatment should be initiated immediately (7). First-line treatment in acute attacks includes pdC1-INH and icatibant. pdC1-INH is administered via slow intravenous infusion. If the body weight is less than 25 kg between the ages of 2-11, 500 IU is administered; if the body weight is more than 25 kg, 1000 IU is administered. In adults, 1000 IU is administered. Icatibant, a bradykinin B2 receptor antagonist, is delivered via subcutaneous injection at 30 mg/3 mL. It is a ready-to-use product that does not require dilution (8-10).

This is a case report of an NS patient who was misdiagnosed as having HAE. Although HAE may be confused with NS, clinicians have to keep in mind laboratory parameters and systemic edema. In patients with persistent, bilateral, pitting edema unresponsive to AH and CST, clinicians should consider NS, particularly when accompanied by proteinuria and hypoalbuminemia. NS-related edema is influenced by gravity, unlike HAE.

Figure 1. (A) There is bilateral asymmetric edema in the eyes, lips, and face. (B) It is seen that the patients edema regressed following diuretic treatment

Table 1. Blood parameters

	Laboratory results	Reference range
Blood biochemistry		
Glucose (mg/dL)	90	70-107
Urea (mg/dL)	144	19-44
Creatinine (mg/dL)	2.48	0.7-1.2
ALT (u/L)	40	0-40
AST (u/L)	36	0-40
Total protein (g/dL)	5.4	6-8.3
Albumin (g/dL)	2.6	3.5-5.2
CRP (mg/dL)	18.5	0-5
Complete blood count		
Hemoglobin (g/dL)	9.4	13.4-17.6
Leukocyte count (x10^3/mm^3)	13.28	4.01-9.75
Platelet count (x10^3/mm^3)	315	151-387
Hormones		
TSH (mU/L)	6.01	0.4-4.2
Free T4 (ng/dL)	1.01	0.8-1.7
Rheumatological markers		
Rheumatoid factor (u/mL)	24.1	0-14
Anti-CCP IgG (u/mL)	6.7	<20
C3 (mg/dL)	43	90-180
C4 (mg/dL)	5	10-40
C1 esterase inhibitor (mg/dL)	42.2	18-40
C1 esterase inhibitor function (%)	>130	70-130
Complement C1q (mg/dL)	2.13	15.7-30.6
IgG (mg/dL)	1604	700-1600
IgA (mg/dL)	20.3	70-400
IgM (mg/dL)	196.2	40-230
PR3-ANCA (u/mL)	2.6	<10
MPO-ANCA (u/mL)	1	<5
Anti-dsDNA (u/mL)	>200	<20
Lupus anticoagulant	54.4	31-44
Antinuclear antibody	++++ (1/10000) Nuclear speckles and a cytoplasmic dense fine speckle pattern	
Anti-SS-A	+++	
Anti-SS-B	Negative	
Anti-SCL	Negative	
Anti-Jo-1	Negative	
Anti-RNP	+++	
Anti-ribosomal P	+++	
Anti-histon	++	
Anti-Sm D1	+++	
Serum amyloid A (mg/dL)	>30	<1
Urine analysis		
Protein (full urinalysis)	+++	
Protein (spot urine) (mg/dL)	234.5	0-30
Creatinine (spot urine) (mg/dL)	71.9	22-392
Protein/creatinine (spot urine) (mg/g)	3261.47	0-150

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein, TSH: Thyroid stimulan hormone, Anti-CCP: Anti cyclic citrullinated peptide, C3: Complement 3, C4: Complement 4, IgG: Immunoglobulin G, IgA: Immunoglobulin A, IgM: Immunoglobulin M, PR3-ANCA: Proteinase 3 anti-neutrophil cytoplasm antibodies, MPO-ANCA: Myeloperoxiase anti-neutrophil cytoplasm antibodies, Anti-dsDNA: Anti-double stranded deoxyribonucleic acid, Anti-SS-A, Anti Sjogren's syndrome-A, Anti-SS-B: Anti Sjogren's syndrome-B, Anti-SCL: Anti-scleroderma antibody, Anti-RNP: Anti-ribonucleoprotein, Anti-Sm D1: Anti Smith antigen

A thorough clinical history is essential, including pruritus, urticaria, triggering factors (food, insect bites, medication, exercise, stress, infections), concomitant diseases, family history, previous attacks, and treatment responses. AE can be histamine- or bradykinin-mediated. Histamine-mediated AE responds to AH and CST treatments, is symmetrical, and is usually accompanied by urticaria (9). Our case does not have these features. It has the features of bradykinin-mediated AE. Bradykinin-mediated AE types include HAE, acquired C1-INH deficiency, and AE due to angiotensin-converting enzyme inhibitor use. Acquired C1-INH deficiency can arise in patients with underlying disorders, including lymphoproliferative or autoimmune diseases, or in conditions that either reduce C1-INH levels or trigger the production of antibodies that neutralize C1-INH (7,9).

The following diseases should be considered in the differential diagnosis of AE: autoimmune diseases, thyroid diseases, superior vena cava syndrome, subcutaneous emphysema, and hypocomplementemic urticarial vasculitis (7,9).

In our case, other causes were considered because of the lack of response to HAE treatment, and the C1-INH level and function were also found to be normal. Thyroid and liver function tests were normal. There was renal dysfunction and proteinuria. Low complement and positive lupus autoantibodies suggested the diagnosis of SLE, and a kidney biopsy was performed.

Moreover, multiple studies have reported a higher prevalence of autoimmune disorders, particularly SLE, in patients with HAE, likely due to the chronic activation of early components of the classical complement pathway. Acquired C1-INH deficiency, however, is more frequently linked to lymphoma or monoclonal gammopathy of undetermined significance than to autoimmune conditions, including SLE, even in the presence of anti-C1-INH antibodies (11). The mechanisms by which the C1-INH enzyme is depleted or autoantibodies against C1-INH play a role are still being investigated. The therapeutic approach for acquired C1-INH deficiency centers on treating the underlying disorder (9).

Conclusion

This case emphasizes the importance of distinguishing NS from HAE. Clinical judgment, response to treatment, and laboratory parameters are essential for correct diagnosis.

There are several limitations in our case report. In our case, the low levels of C3 together with C4, the presence of SLE autoantibodies, normal C1-INH level and function; and the lack of response to HAE treatment excluded the diagnosis of HAE. Genetic evaluation can be conducted to identify HAE. This was not needed because there was no response to HAE treatment in our case. Anti-C1 antibodies should be checked for the diagnosis of SLE-associated acquired C1-INH deficiency, but could not be tested because the test was not available in our hospital. However, the treatment remains focused on addressing the underlying disease, obviating the need for additional diagnostic procedures.

Ethics

Informed Consent:

Footnotes

Authorship Contributions

Surgical Medical Practices: Ö.Ü., E.Ç.B., B.H., Consept: Ö.Ü., S.Y., Ö.K., Design: Ö.Ü., S.Y., Ö.K., Data Collection or Processing: Ö.Ü., E.Ç.B., Analysis or Interpretation: Ö.Ü., Ö.K., Literature Search: Ö.Ü., E.Ç.B., Writing: Ö.Ü.

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