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Hereditary angioedema presenting as refractory urticaria: a case report

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Report

BACKGROUND: Hereditary angioedema (HAE) is a rare autosomal dominant genetic disorder characterized by localized or diffuse swelling of an affected patient's face, neck, larynx, visceral organs, extremities, and trunk. There is also an acquired form of angioedema that has been described in patients with malignancies (i.e., lymphocytic leukemia) or collagen vascular disease, or in those who have developed C1 esterase inhibitor (C1-INH) autoantibodies. However, HAE is rarely associated with urticaria.

CLINICAL CASE: A 19-year-old Caucasian woman was admitted to our hospital with five days of burning and pruritic whole-body erythematous rash, facial and eyelid swelling, sore throat, and abdominal pains. She was taking Yaz, an oral birth control pill (Bayer HealthCare Pharmaceuticals, Wayne, NJ). She was started on Benadryl 50 mg intravenously every six hours, famotidine 40 mg by mouth every 12 hours, doxepin 75 mg by mouth at bedtime as needed, and methylprednisolone 125 mg intravenously every six hours without clinical improvement. Extensive laboratory testing was performed and she had a low C4 level 15mg/dL (16-47 mg/dL), a low C1-INH level 6 mg/dL (10-25 mg/dL), and an elevated CRP level 1.6 mg/dL (0-0.9 mg/dL). Because of the relatively low levels of C4, low C1-INH levels, increased CRP, use of oral contraceptive pills, abdominal symptoms, and poor response to high dose steroid therapy, a provisional diagnosis of HAE was made and she was treated with intravenous infusion of C1-INH (Berinert, CSL Behring GmbH, Marburg, Germany) at a dose of 20 U/kg of body weight for one dose at a rate of 4 mL/min. Her symptoms completely resolved with this medication.

CONCLUSION: This is one of only a few case reports that demonstrates HAE presenting initially as refractory urticaria.

Hereditary angioedema (HAE) is a rare autosomal dominant genetic disorder characterized by localized or diffuse swelling of an affected patient's face, neck, larynx, visceral organs, extremities, and trunk.[1] There is also an acquired form of angioedema that has been described in patients with malignancies (i.e., lymphocytic leukemia) and collagen vascular disease, or in those who have developed C1 esterase inhibitor (C1-INH) autoantibodies.[2] HAE is rarely associated with urticaria but is most commonly associated with symptoms of swelling, laryngeal edema (which can compromise a patient's airway), and abdominal pain from visceral organ edema.[3] HAE is triggered by many different conditions including pregnancy, hormonal fluctuations (i.e., menses), medications (e.g., oral contraceptives, anti-androgen therapy), stress, and physical trauma, and in some instances the cause is idiopathic.[4]

The pathophysiology of HAE is complex. C1-INH is a protease structurally similar to alpha-one antitrypsin and anti-thrombin III. It is synthesized in the liver's hepatocytes and circulating monocytes. C1-INH circulates and

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binds to C1 esterase, which is a key component in the complement cascade, which structurally inactivates it. C1-INH also inactivates other proteins involved in the fibrinolytic, kinin, and clotting cascade (i.e., plasma thromboplastin antecendent, Factor VII, Factor XI, and kallikrein). In the presences of sufficient serum concentrations of C1-INH, this protease will antagonize the activation of C1 esterase and the reminder of the classical complement pathway. In the presence of insufficient serum concentrations of C1-INH there exists excessive activation of C1, C2, and C4 before other inhibitors, such as C4 binding protein (and others) that can block the cascade.[5] Specifically, it is the activation of the kinin pathway that leads to increased serum bradykinin levels. Bradykinin is an inflammatory mediator formed by the action of kallikrein on its substrate high-molecular-weight kininogen, which subsequently leads to neutrophil chemotaxis, capillary vasodilation, and smooth muscle relaxation. This is the major mechanism by which HAE causes symptoms of edema in affected patients.[6]

The C1-INH gene is located on chromosome 11 at locus p11-q13 (*SERPING1* gene). There are two types. Type I accounts for 85% of cases. Synthesis and/or excretion of C1-INH is blocked at the site of the mutated allele but occurs at the normal allele. Type II HAE accounts for 15% of cases and is related to normal production of an inactive form of the protease. A Type III HAE has been described in women, but is exceedingly rare.[7]

Urticaria is uncommonly associated with HAE. Urticaria most often involves only superficial layers of skin (dermis and epidermis) and its hallmark is a serpiginous erythematous rash with associated pruritus. On the other hand, angioedema (including HAE) typically involves deeper layers of the skin (i.e., the dermis and subcutaneous tissue), which results in localized edema sometimes associated with a burning-like sensation and, rarely, pruritus. Urticaria and angioedema rarely co-occur.[8] We describe the case of a 19-year-old white woman who was diagnosed with HAE after an initial presentation of urticaria and subtle facial and peri-orbital swelling.

Case report

Presentation

A 19-year-old white woman with no significant past medical history presented to our emergency department (ED) reporting five days of a burning and mildly pruritic whole-body rash and associated facial and eyelid swelling. She reported diarrhea preceding the onset of symptoms with some mild abdominal pain of two days' duration that resolved shortly after her presentation in our ED. She also complained of a sore throat and an occasional nonproductive cough.

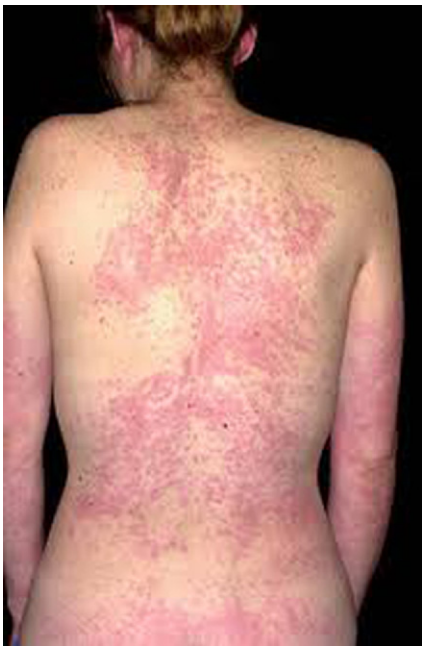

Figure 1 A 19-year-old Caucasian woman who presented with diffuse urticarial rash with very subtle facial and neck edema that was nonreponsive to typical urticarial treatment with H_2-blockers, antihistamines, and steroids. She was subsequently diagnosed with Type I hereditary angioedema.

History

The only medication the patient was taking was Yaz (an oral contraceptive pill; Bayer HealthCare Pharmaceuticals, Wayne, NJ) started by her primary care physician approximately two months before presentation. She worked at a nursing home and had come in contact with a latex-containing stethoscope, which she felt coincided with the development of her rash. She saw her primary care physician the day before her presentation to our facility and was prescribed 20 mg of prednisone as a taper for a suspected latex allergy. She had only taken one dose before arrival at our facility.

Presentation

Her vital signs were temperature 99.1°F, heart rate 109 beats/min, respiration rate 20 breaths/min, and blood pressure 122/78 mm Hg. Her examination consisted of a diffuse serpiginous erythematous pruritic rash involving her trunk, extremities (sparing the palms and soles), neck, face (sparing the nasolabial folds and oral mucosa), and head (Fig. 1). She also had a minimal amount of peri-orbital erythema.

She appeared anxious. Her oropharynx was without erythema or exudates and her neck was without lymphadenopathy. She was not jaundiced and there was no scleral icterus. Her thyroid was symmetric and not enlarged. The remainder of her physical examination was unremarkable. Antero-posterior chest film radiograph was unremarkable.

Electrocardiogram revealed sinus tachycardia with a rate of 110.

Laboratory work-up

The patient's urinanalysis showed trace to 1+ leukocyte esterase, 5-10 white blood cells (WBC), 2+ glucose, and rare red blood cells (RBCs) and epithelial cells. Urinanalysis with trace to 1+ leukocyte esterase, 5 to 10 white blood cell (WBC), 2+ glucose, and rare red blood cells (RBCs) and epithelial cells. Serum β-human chorionic gonadotropin was negative. Monospot was negative. Rapid *Streptococcus* antigen was negative. Serum Lyme IgM and IgG were negative. Thyroid-stimulating hormone was 2.88 mU/L (0.4-4.5). Liver function panel was: total bilirubin 0.44 mg/dL (0-1.5), albumin 3.6 g/dL (3.4-5.0), total protein 6.4 g/dL (6.4-8.2), alkaline phosphatase 53 u/L (20-115), aspartate aminotransferase 19 U/L (15-37), and alanine transaminase 42 U/L (30-65). WBC was 15.9×10^3/uL ($4.8\text{-}10.8 \times 10^3$), hemoglobin was 13.8 g/dL (12-16), hematocrit was 40.4% (36-47), platelets were 229×10^3/uL ($150\text{-}400 \times 10^3$). Differential revealed 87.9% segmented neutrophils and 2.2% basophils. Block 3 immunological profile revealed normal levels of immunoglobulins (IgA, IgG, IgM, and IgE), C3 of 143 mg/dL (90-180), C4 of 15 mg/dL (16-47), rheumatoid factor–negative, antinuclear antibody test $<$1:14 (negative). C-reactive protein (CRP) 1.6 mg/dL (0-0.9; on day 2 of hospitalization was 3.3 mg/dL). Erythrocyte sedimentation rate (ESR) was 5 mm/hr (0-20). C1-INH levels were 6 mg/dL (10-25).

Treatment

The patient was started on diphenhydramine 50 mg intravenous push every six hours, famotidine 40 mg by mouth every 12 hours, doxepin 75 mg by mouth at bedtime as needed, and methylprednisolone 125 mg every six hours. Her rash improved only slightly despite this aggressive regimen and the improvements were noted only in the hour preceding the next scheduled dose of methylprednisolone. After two days of treatment, the condition did not improve. At no time did the patient develop airway compromise and her oxygen saturation remained above 95% on room air. Because the presented at a rural hospital without subspecialists in allergy/immunology or dermatology, she was transferred to a nearby tertiary care facility for further care. Because of her relatively low levels of C4, low C1-INH levels, increased CRP, use of oral contraceptive pills, abdominal symptoms, and poor response to high-dose steroid therapy, a provisional diagnosis of HAE was made and treated with an intravenous infusion of C1-INH (Berinert, CSL Behring GmbH, Marburg, Germany) at a dose of 20 U/kg of body for one dose at a rate of 4 mL/min. Her symptoms completely resolved with this medication; the initial medications used at our facility were discontinued upon presentation at the tertiary care medical center. A skin biopsy was never preformed because of the positive response to this medication. After discharge from the hospital, she stopped taking her oral birth control pills and follow-up revealed that she has been asymptomatic from the time this article was submitted for publication. Our patient subsequently underwent genetic testing and was found to have Type I HAE with mutation in the C1-INH gene as evidenced by positive bands corresponding to the *SERPING1* gene located in the q12-q13.1 subregion of chromosome 11.

Discussion

HAE is an uncommon form of angioedema and is associated with stress, physical trauma, hormonal fluctuations, oral birth control, and anti-androgen medications. It can present in subtle ways. Our patient was initially believed to have an urticarial rash that was precipitated by recent exposure to a latex-containing stethoscope. After no response in 24 hours to 20 mg of oral prednisone, her condition worsened clinically and she sought treatment in our emergency department. She was presumed to have had poorly responsive urticaria when escalation of treatment did not seem to relieve her symptoms. Alternative diagnoses were then considered.

The differential diagnosis of urticarial rash is extensive and includes: (1) Physical urticaria caused by contact with heat, cold, excessive stress, pressure, vibration, and solar radiation; (2) hyperthyroidism (i.e., Hashimoto's thyroiditis); (3) liver disease (i.e., autoimmune liver disease, alcoholic hepatitis); (4) leukocytoclastic vasculitis, which is associated with fevers, arthralgias, weight loss, and elevated ESR; (5) connective tissue disorders (e.g., lupus); (6) ingestion of histamine-containing foods (i.e., strawberries, shrimp, cheese, spinach, eggplant); (7) direct mast cell degranulation mechanisms (i.e., aspirin, narcotics, vancomycin, nonsteroidal antiinflammatory drugs, skeletal muscle relaxants); (8) infections (group A beta-hemolytic *Streptococcus*, HIV, cytomegalovirus, Epstein-Barre virus, hepatitis B, hepatitis C); (9) emotional stress; (10) hypersensitivity reactions (i.e., airborne allergens, parasites, medications, serum sickness, and transfusion reactions).[9] The differential diagnosis of angioedema is very limited to obstruction of vascular or lymphatic channels by tumor, lymphadenopathy, or trauma. Most patients present with nonpitting edema of various body areas (i.e., head, neck, trunk, extremities, buttocks), a history of abdominal pain (from visceral organ swelling), and, rarely, urticaria. A thorough history can sometimes lend support for the diagnosis (i.e., a family member with intermittent episodes of unexplained swelling, a history of unexplained abdominal pain, urticarial rash of no known origin).

In patients suspected of having HAE, a complete work-up includes: (1) Careful history and physical examination; (2) review of the patient's medications; (3) Kidney-ureter-bladder or abdominal contrast computed tomography

Table 1 Acute treatment options for hereditary angioedema

Pharmacological agent	Dose
Synthetic C1-INH (Cinryze)	100 U IV infusion over 10 min repeated every 3-4 days until symptom resolution
C1-INH (Berinert)	20 U/kg continuous IV infusion at 4 mL/min until symptom resolution
Human plasma kallikrein inhibitor-Ecallantide (Kalbitor)	30 mg (3 mL) subcutaneously administered in 3 separate 10-mg (1 mL) injections into the thigh, abdomen, or upper arm (for persistent attacks, an additional 30-mg dose within 24 hours of the initial dose may be given)
Aminocaproid acid (Amicar)	7-8 g/day PO/IV every 6 hours until symptomatic improvement

PO = by mouth; IV = intravenous.

to evaluate for ileus or intraabdominal pathology; (4) laboratory testing that most commonly should include: complete blood count, liver function panel, amylase/lipase (if risk of pancreatitis or ongoing abdominal pain), pregnancy screening in sexually active women, thyroid function studies, Block 3, ESR, CRP, rapid *Streptococcus* test, monospot, HIV screening, and other laboratory testing based on the specific clinical situation. If laboratory testing and history points toward angioedema, further testing is indicated and this will include genetic testing and complement levels (i.e., C3, C4, C1-INH levels, and CH50). CH50 decreases during acute attacks only and has a low positive predictive value because all compliment levels decrease during acute attacks. Consideration should also be given to skin biopsy in difficult-to-diagnose cases. Histologically, HAE is indistinguishable from other types of angioedema. Perivascular mononuclear cell infiltrate and dermal/subdermal edema similar to that seen with chronic urticaria or angioedema of other types are observed. Therefore, a skin biopsy is only useful to rule out other conditions like leukocytoclastic vasculitis.

Our patient had an intensely burning rash with some mild pruritus. Pruritus is not typically associated with Type I HAE because it is not an IgE-mediated disease. A condition called *erythema marginata* sometimes occurs in patients with HAE and can resemble an urticarial rash but is rarely, if ever, described as pruritic and instead is most often described as "burning" or "painful." C1-INH deficiency of Type I HAE leads to unregulated inhibition of the first component of complement cascade and also the fibrinolytic enzyme plasmin, activated Hageman factor, and kallikrein. Through a series of complex biochemical reactions, this leads to the generation of vasoactive substances such as metabolites of arachidonic acid including prostaglandins and leukotrienes, which may be responsible for the pain and burning sensation associated with the rash our patient had. The cause of our patient's pruritus remains unexplained, but it may have been caused by IgE-mediated release of histamine from mast cells from localized tissue irritation as a result of the constant rubbing and pressure this patient applied to her skin in regions she described as "burning."

Treatments for HAE at one time were very limited, but they now encompass a variety of modalities. Clinicians must be aware that HAE is mostly mediated through bradykinin pathways and patients who present with urticaria, angioedema, or some combination of the two will be steroid-unresponsive. Steroids are not the treatment for this condition; selection of therapy depends on the nature and severity of the patient's symptoms.

Patients who have life-threatening laryngeal edema may require emergent advanced airway procedures (i.e., intubation, fiberoptic nasal intubation, cricothyrotomy). These patients (or those who do not improve after several days of ongoing severe or refractory symptoms) should be approached with one of the following treatments: synthetic C1-INH (Cinryze, ViroPharma Incorporated, Exton, PA); C1-INH (Berinert, CSL Behring GmbH); Ecallantide (Kalbitor, Dyax Corp., Cambridge, MA), a human plasma kallikrein inhibitor; or aminocaproid acid (Amicar, Xanodyne Pharmaceuticals, Newport, KY) (Table 1). Once the initial HAE attack has resolved, attention should shift toward modification of triggering mechanisms (i.e., discontinuation of oral contraceptives, prophylaxis with 2 U of intravenous fresh frozen plasma for dental procedures, long-term therapy with anti-androgens such as Danazol [Table 2]), and patient education.

Conclusion

In summary, we presented a rare case of hereditary angioedema (HAE) associated with urticaria in a young woman on oral contraceptives that was unresponsive to steroid therapy. She was successfully treated with C1-INH infusion

Table 2 Prophylactic androgen (Danazol) therapy in hereditary angioedema

Danazol taper
Initiation: 600 mg/day for one month
Taper: Reduce total daily dose by 100-mg at one month intervals
When at 200 mg/day, lower the dose by 50 mg every 2 months
When at 100 mg/day lower the dose by 50 mg every 3 months, then discontinue

once the diagnosis was determined. This article sheds light on HAE as a rare disorder than can present atypically. Clinicians must be aware of this type of atypical presentation of HAE and know how to respond in a timely fashion as this disorder can potentially be fatal and cause undue suffering from delayed treatment.

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