CASE REPORT

Postangioedema attack skin blisters: an unusual presentation of hereditary angioedema

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SUMMARY

Hereditary angioedema (HAE) is an autosomal dominant disorder characterised by attacks of self-limited swelling affecting extremities, face and intra-abdominal organs, most often caused by mutations in the C1-inhibitor gene with secondary Bradykinin-mediated increased vascular permeability. We describe a 36-year-old man with a history of HAE who presented with painful interdigital bullae secondary to an acute oedema exacerbation. Biopsy and cultures of the lesions were negative and they resolved spontaneously. It is important to highlight and recognise the development of oedema blisters after resolution of a flare of HAE (only 1 previous case report), and hence avoid unnecessary dermatological diagnostic workup and treatment.

BACKGROUND

Hereditary angioedema (HAE) is an autosomal dominant disease caused by a deficiency in functional C1 inhibitor.¹ Patients have spontaneous episodic attacks of non-pitting and non-pruritic subcutaneous or submucosal oedema most commonly affecting the hands or feet, though the genitalia, trunk or face may be involved as well.^{2 3} Abdominal pain secondary to mucosal oedema is another frequent manifestation.^{1 3} The most feared complication is laryngeal oedema that may require emergency intubation to ensure adequate airway protection. Attacks may start at any age, and are often associated with trauma or emotional stress.¹

The most common skin manifestation of the disease is oedema, which occurs in over 90% of all acute episodes.² One-third of patients present with a non-pruritic, erythema marginatum rash that usually appears before an attack.³ Presentation with oedematous blisters is rare, with only one reported case in the literature.⁴

CASE PRESENTATION

A 36-year-old man with a known history of HAE developed a sudden onset of left orbital oedema after recent accidental trauma during exercise. Over the next 24 h his oedema worsened complicated by progressive dysphagia and hoarseness. The patient presented to an emergency room with acute respiratory failure requiring endotracheal intubation. He received two units of fresh frozen plasma (FFP) after intubation and was subsequently transferred to our hospital. His previous angioedema episodes involved his face (figure 1), hands, feet and genitalia; in 2002 he had an episode of secondary small bowel obstruction; all episodes generally occurred after physical trauma and would never develop

Figure 1 Facial angioedema.

blisters with his attacks. The patient had been prescribed prophylactic danazol 100 mg twice a day, but had gradually been reducing the dosage due to concerns of secondary hypogonadism; at the time of presentation he had already tapered himself down to 100 mg danazol three times per week.

INVESTIGATIONS

Laboratory studies revealed a C4 level of 10 mg/dL and C1 esterase-inhibitor level of 10 mg/dL (both were low). After resolution of the orofacial swelling, he developed bullous eruptions in the interdigital spaces of both hands (figure 2) that were

Figure 2 Postangioedema interdigital blisters.

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noted 1 day after extubation. The vesicles were painful and clear. A dermatology consultation was sought, with an unrevealing biopsy, including negative cultures and stains for infectious causes.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for oropharyngeal and laryngeal oedema includes tonsillitis, peritonsillar or retropharyngeal abscess, glossitis and pharyngeal foreign body.

The differential diagnosis for local bullae includes bullous tinea pedis, fixed drug eruption, erythema multiforme, friction blisters, coma blisters, bullous insect bites, bullous diabeticorum and transient acantholytic dermatosis. Virtually all require a skin biopsy to confirm the diagnosis.

TREATMENT

The patient was extubated 3 days into his mobile intensive care unit course after resuming danazol as previously prescribed and receiving six additional units of FFP.

OUTCOME AND FOLLOW-UP

The lesions resolved spontaneously. It was thought that the lesions represented acute oedema blisters secondary to the angioedema episode. The patient is currently doing well on danazol.

DISCUSSION

HAE is a rare hereditary disease which causes swelling of the extremities, face and abdominal organs, secondary to a mutation in the C1-inhibitor gene.³ There are two main types, which are categorised by their respective genetic mutations but are indistinguishable clinically: type I with low detectable C1-INH serum protein (85% of cases) and type II with normal to high protein levels but low C1-INH function (15% of cases). Studies demonstrate that Bradykinin is the main mediator of increased vascular permeability during attacks,³ and large amounts of Kallikrein have been isolated from blister fluid in patients with HAE blisters.⁵ Fluid accumulation in HAE occurs over several hours and resolves spontaneously within the next few days. This cutaneous oedema is described as non-pitting and non-pruritic subcutaneous or submucosal oedema most commonly of the hand or foot.³ During acute attacks one-third of patients present with a non-pruritic, erythema marginatum rash, the most common dermatological manifestation.³ Current management of HAE includes treatment of acute attacks, short-term

prophylaxis to prevent an attack and long-term prophylaxis to minimise the frequency of recurrent attacks.³ FFP has been shown to be beneficial in treating acute attacks.⁶ In the USA, the FDA has recently approved a C1 esterase-inhibitor replacement therapy (Cinize) for treatment of acute attacks, though similar formulations have been available in other countries for over a decade.^{3 7 8} Steroids and antihistamines have no utility in acute events.⁷ The mainstay of prophylactic treatment includes 17 α -alkylated androgens and antifibrinolytic drugs, both of which significantly reduce the frequency of attacks.³

Learning points

- ▶ Blisters may have several aetiologies including secondary to oedema from fluid overload.
- ▶ Steroids and antihistamines have no utility in acute events.
- ▶ Treatment of this disease includes fresh frozen plasma and C1 esterase-inhibitor replacement therapy for acute attacks.
- ▶ Prophylactic treatment includes 17 α -alkylated androgens and antifibrinolytic drugs

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Frank M M, Complement disorders and hereditary angioedema. *J Allergy Clin Immunol* 2010;125:S262–71.
- 2 Bork K, Meng G, Staubach P, *et al.* Hereditary angioedema: new findings concerning symptoms, affected organs, and course. *Am J Med* 2006;119:267–74.
- 3 Zuraw B L. Clinical practice. Hereditary angioedema. *N Engl J Med* 2008;359:1027–36.
- 4 Fernandez Romero D, Di Marco P, Malbran A. Acute edema blisters in a hereditary angioedema cutaneous attack. *Allergol Immunopathol (Madr)* 2008;36:182–3.
- 5 Curd J G, Prograis L J Jr, Cochrane C G. Detection of active kallikrein in induced blister fluids of hereditary angioedema patients. *J Exp Med* 1980;152:742–7.
- 6 Prematta M, Gibbs J G, Pratt E L, *et al.* Fresh frozen plasma for the treatment of hereditary angioedema. *Ann Allergy Asthma Immunol* 2007;98:383–8.
- 7 Zuraw B L, Busse P J, White M, *et al.* Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. *N Engl J Med* 2010;363:513–22.
- 8 Zuraw B, Cicardi M, Levy R J, *et al.* Recombinant human C1-inhibitor for the treatment of acute angioedema attacks in patients with hereditary angioedema. *J Allergy Clin Immunol* 2010;126:821–7.e14.

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