

Differential Diagnosis of Angioedema

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Angioedema is defined as transient swelling of defined areas in the deep dermis or subcutaneous tissue resulting from vascular leakage. Angioedematous lesions tend to be large, pale, nonpruritic (although they may be painful or burning), and occur anywhere on the body. While the duration of swelling in angioedema is sometimes short like urticaria (that often accompanies angioedema), the swelling of angioedema typically persists for a day or more and occasionally can last for multiple days before remitting.

A variety of other pathophysiologic processes may cause swelling that superficially resemble angioedema. Although the majority of these conditions do not respond to antihistamines or other medications used to treat urticaria and angioedema, they nonetheless may be mistakenly called “angioedema,” and frequently are treated with parenteral or oral glucocorticoids. Because the management of these disorders is generally distinct from the management of angioedema, it is important to carefully distinguish angioedema from other causes of swelling. Based on the patient’s recollection of the onset and duration of swelling together with key signs and symptoms, the astute clinician can generally distinguish angioedema from those conditions that resemble angioedema. This article will briefly review the major causes of angioedema, then discuss other non-angioedematous conditions that may masquerade as and be mistaken for angioedema.

Angioedema

Angioedema is a result of interstitial edema from mediators affecting capillary and venule permeability. The swelling due to angioedema involves tissues deeper than the dermis and thus appears and feels different than urticaria. Upwards of 50% of patients with urticaria may have angioedema concurrently [1]. The mechanisms responsible for the swelling in both

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urticaria and angioedema are generally similar. A major exception to this, however, is the angioedema associated with C-1 esterase inhibitor deficiency, which is caused by a distinct pathophysiologic mechanism (see the article by Davis elsewhere in this issue) and is not accompanied by urticaria [2].

Several clinical clues help distinguish angioedema from other causes of swelling. In most instances, the involvement is in highly vascular areas (eg, lips, oropharynx, peri-orbital region). The region involved is not symmetric (eg, only one side of the face involved) and typically does not favor dependent areas. Angioedema is also transient, a given lesion typically lasting 24 to 48 hours then resolving. Unlike urticaria, the sensation associated with angioedema is more painful or burning than pruritic.

Allergic angioedema

An allergic (IgE-mediated) etiology is typically considered first when patients present for evaluation of acute angioedema. Possible allergic basis of the angioedema is often suggested by a careful history that uncovers a relationship between the onset of swelling and exposure to foods, stinging insects, latex, medications, or aeroallergens (as in the case of angioedema seen with allergic conjunctivitis). Cutaneous contact with some allergens has also been shown to cause angioedema. Angioedema frequently accompanies anaphylaxis, which is a systemic allergic reaction typically including hypotension, urticaria, or difficulty breathing.

Nonallergic angioedema

Chronic recurrent angioedema

Chronic recurrent idiopathic angioedema is most commonly seen in the presence of concomitant chronic idiopathic urticaria, but can also occur without urticaria (see the article by Frigas and Park elsewhere in this issue). In addition, some of the physical urticarias can be mistaken for angioedema. Depending on the surface area involved, patients with acquired cold-induced urticaria may have extensive involvement mimicking angioedema of an extremity. Patients with vibration-induced urticaria/angioedema have angioedema as the most likely presenting symptom [3]. Patients with vibratory angioedema may have swelling of their hands as their chief complaint. Delayed pressure urticaria typically presents with subcutaneous discomfort and swelling that is more consistent with angioedema than urticaria [4]. Typically patients complain of discomfort in areas of pressure (eg, beltline, backs of legs, feet) yet often this diagnosis is difficult to confirm even with a properly performed challenge.

Pharmaceuticals causing angioedema on a non-IgE-mediated basis

Some pharmaceutical agents may promote angioedema from non-IgE-mediated mechanisms. Angiotensin-converting enzyme (ACE) inhibitors can cause angioedema, presumably through their ability to interfere with

the degradation of bradykinin (see the article by Byrd and colleagues elsewhere in this issue) [5]. Angioedema as a result of ACE inhibitors typically occurs shortly after starting the medication [6], although some cases have been reported to be delayed months after initiation of the medication [7]. Although there are rare reports of angioedema associated with angiotensin receptor blockers (ARB) [8], most patients with ACE inhibitor-induced angioedema are able to successfully switch to an ARB without recurrence of their angioedema [9]. Ionic radiocontrast material agents can promote anaphylactoid reactions including angioedema, presumably because of changes in serum osmolality (see the article by Greenberger elsewhere in this issue) [10]. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) can induce angioedema by their ability to inhibit cyclo-oxygenase 1 (COX-1) and thus presumably favoring cysteinyl leukotriene production [11]. Angioedema can be provoked in an estrogen-dependent manner in some individuals, and this appears to be transmitted in a hereditary manner (see the article by Bork elsewhere in this issue) [12].

Angioedema associated with eosinophilia

Hypereosinophilic syndrome (HES) is characterized by a blood eosinophilia of greater than 1500/ μ L for longer than 6 months, evidence of end-organ (cardiac, pulmonary, neurologic) dysfunction, and no other medical reason for the eosinophilia [13]. Angioedema or urticaria may occur with HES and patients are more likely to have a benign course if HES presents only with angioedema [14]. Patients presenting with weight gain (upwards of 18% of their total body weight), along with fever and marked peripheral eosinophilia with elevated IgM may have episodic angioedema with eosinophilia (Gleich's syndrome) (see the article by Banerji and colleagues elsewhere in this issue). This condition is differentiated from HES because of central organ involvement found in HES [15]. A nonepisodic version of angioedema with eosinophilia has been reported that is characterized by absence of recurrent attacks of angioedema, occurring in females, without an elevation in IgM. In contrast to Gleich's syndrome, the nonepisodic version affects the extremities and has a more benign course [16].

Angioedema associated with C1 inhibitor deficiency

As mentioned above, C1 inhibitor deficiency is associated with recurrent angioedema not accompanied by urticaria. This can occur both on a hereditary basis (hereditary angioedema, see the article by Frank elsewhere in this issue) as well as on an acquired basis (see the article by Zingale and colleagues elsewhere in this issue).

Masqueraders of angioedema

The causes of angioedema discussed above are all well known to allergists and to most clinicians. However, other cutaneous reactions that mimic

angioedema should be considered in the differential diagnoses. The majority of these reactions are rare but serve to demonstrate that not everything that causes swelling should be treated with antihistamines or corticosteroids. **Box 1** lists many conditions that present with swelling that may be mistaken for angioedema.

Contact dermatitis

Patients with contact dermatitis due to exposure to antigens eliciting delayed-type hypersensitivity responses often present with angioedema of the face and periorbital region. Rhus dermatitis from contact with poison ivy is notorious for producing isolated swelling affecting one eye and especially in children. Although angioedema-like swelling may be the first manifestation of contact dermatitis, the reaction usually declares itself with the production of vesicles or blisters, and later an eczematous dermatitis that lasts for days to weeks.

Box 1. Conditions that mimic angioedema

Contact dermatitis
Rhus (Poison ivy, oak)
Trauma or burns
Acute idiopathic scrotal edema
Autoantibodies (hypocomplementemic urticarial vasculitis syndrome)
Weber-Christian disease
Tumor necrosis factor receptor-associated periodic syndrome
Thyroid orbitopathy
Well's syndrome
Schulman's syndrome
Blepharochalasis
Clarkson syndrome
Dependent edema
Marasmus, hypoproteinemia
Superior vena cava syndrome
Infections
Viral (Parvo, herpes)
Bacterial (cellulitis)
Parasite (*Loa loa*, *Trichenella*)
Scleromyxedema
Systemic amyloidosis
Melkersson-Rosenthal syndrome
Crohn's disease
Acquired C1-inhibitor deficiency syndrome

Dependent edema

Patients with underlying medical conditions that cause dependent edema may have areas that are misconstrued as angioedema. Most likely, edema that develops in the lower legs in an older patient with underlying heart disease would be appropriately ascribed to vascular insufficiency or underlying congestive heart failure. Decreased plasma oncotic pressure is also associated with edema. However, more persistent edema may be related to vascular malformations that may especially involve the lymphatic system. Acute exacerbations of chronic edema may develop blisters (stasis blisters or hydrostatic bullae) that can sometimes be confused with an immune-mediated reaction [17].

In some instances, the obstruction may be central with edema that becomes noticeable only when the patient is dependent. Superior vena cava obstruction due to tumors may present with edema when the patient is supine or prone, yet the edema gradually resolves when the patient is upright. Cough and dyspnea are usually associated with this and the patient usually has swelling involving the upper (but not the lower) extremities as well as the face and neck [18].

Trauma may result in angioedema. Burns (especially superficial sunburns) may be associated with mild angioedema. Quincke's disease may result from thermal injury as in the case of a patient who had inhaled cocaine smoke and developed marked swelling of his uvula [19]. Acute idiopathic scrotal edema in young boys occurs in children from ages 2 to 10 years of age. Patients present with painful unilateral scrotal swelling due to thickening of the scrotal sac but without hydrocele. Erythema also accompanies the swelling, with demarcation that may extend to the perineum, abdomen, or penis and mimics cellulitis. However, the patient is afebrile and the condition resolves within days without antibiotics [20].

Infections

Some infections may present with swelling that can be diagnosed as angioedema. Such infections persist until treated and thus must be differentiated from acute angioedema. Parasite infections can cause angioedema around the eyes. Romana's sign is unilateral angioedema of one eye that occurs with American trypanosomiasis. Trichinosis can also cause periorbital edema with peripheral eosinophilia. Tropical filariasis can cause lymphatic obstruction with resultant swelling of the affected limb or can cause swelling of the eyeball (*Loa loa*) [21].

Bacterial infections may also mimic angioedema. Cellulitis (especially facial) is associated with erythema, swelling, and fever and is usually differentiated from angioedema. Rosacea may also present with swelling of the face and be mistaken for angioedema of the eyes or cheeks. In some instances, acne vulgaris may be extensive and involve swelling of the area [21].

Viral infections are frequently associated with urticaria in children. Parvovirus B19 has been described as a cause of angioedema in neonates [22]. In some instances, edema may precede the appearance of herpes infections including herpetic zoster.

Vasculitis and panniculitis

Autoantibodies are also found commonly in systemic lupus erythematosus (SLE). This can promote both urticaria and angioedema due to consumption of complement from autoantibodies to the collagen-like fragment of C1q [23]. Hypocomplementemic urticarial vasculitis syndrome has also been noted to cause angioedema in patients with SLE. Although this condition responds to immunosuppressants, rarely are monoclonal antibodies such as rituximab required [24].

Weber-Christian disease is a panniculitis with fever and swelling that may mimic angioedema [25]. This condition is characterized by fever, subcutaneous nodules, and involvement of subcutaneous fat. Two patients have been described with panniculitis and a mutation of the tumor necrosis receptor super family known as tumor necrosis factor receptor-associated periodic syndrome (TRAPS). Both patients responded to etanercept [26].

Mucinoses and other infiltrating disorders

Perhaps the most commonly considered endocrinopathy associated with edema that simulates angioedema is autoimmune thyroid disease. Thyroid orbitopathy is a condition characterized by gradual swelling of the periorbital area. It is usually associated with hypothyroidism and resolves after treatment with thyroid hormone supplement. Graves' disease may also present with orbitopathy. Other edematous manifestations of thyroid disease include myxedema of the face with severe hypothyroidism and pretibial myxedema seen in Graves' disease. The latter is characterized by waxy indurated nodules or plaques that may have a *peau d'orange* appearance [27]. Both conditions are a result of the accumulation of mucin within the dermis. In pretibial myxedema, perivascular lymphocytic infiltrate with mast cells may be similar to the pathology of urticaria except that large stellate fibroblasts are also seen in addition to the mucin amidst collagen bundles [28].

Scleromyxedema can present with swelling of the forehead along with small, waxy papules. Long and deep longitudinal furrows across the forehead may give the patient a lionoid appearance. Induration of other areas (especially the forearm) may simulate swelling. Scleromyxedema is most often associated with a paraproteinemia (most often IgG with λ light chains) and in 10% of affected patients, progresses to multiple myeloma [29].

Macroglossia can be mistaken for angioedema of the tongue. Most often, macroglossia is associated with systemic amyloidosis. Dental impressions on

the tongue that do not fade are a clue of the infiltration by AL protein in the area. Other signs such as periorbital ecchymoses and waxy, translucent facial papules may also be present. Primary systemic amyloidosis is usually associated with a plasma cell dyscrasia [30].

Eosinophilic dermatoses

Infiltrative disorders with eosinophils may present with large erythematous plaques or induration of subcutaneous tissue that may be mistaken for angioedema. Wells' syndrome presents as recurrent and often painful plaques that resemble cellulitis. Fever, peripheral eosinophilia, and malaise accompany the onset of the plaques. Biopsy reveals dense infiltration by eosinophils with characteristic flame figures from collagen fibers coated with eosinophil granules [31]. Shulman's syndrome (eosinophilic fasciitis) may present with edema, pain, and tenderness of the affected extremities. An elevated sedimentation rate, marked peripheral eosinophilia, elevated aldolase, and hyperglobulinemia are seen. Early diagnosis is important to prevent muscle contractures and loss of mobility [32]. A similar condition has been reported to occur with contaminants in tryptophan causing eosinophilic myalgia syndrome [33].

Orofacial swelling alone

Melkersson Rosenthal syndrome is a condition characterized by persistent swelling of the lips due to noncaseating granulomatous infiltration of the lips. It is typically associated with a fissured tongue (lingua plicata), orofacial edema, and facial nerve palsy. However, the classic triad is seen in a minority of cases [34]. Other areas of the face (eyelids, periorbital region) may present with persistent swelling as a variation of this syndrome [35]. Crohn's disease and sarcoidosis may also present with cheilitis granulomatosa but without facial paralysis or fissured tongue [36,37]. Rarely, a contact dermatitis may mimic cheilitis granulomatosa. Fig. 1 shows a young woman



Fig. 1. Lower lip swelling in a patient simulating cheilitis granulomatosa.

with Crohn's disease who had persistent angioedema of her lower lip that proved to be due to blistering delayed hypersensitivity to *Saccharomyces sp* after percutaneous testing.

Parotid gland involvement by sarcoidosis occurs in 6% of sarcoidosis patients and may cause swelling of the cheek confused with persistent angioedema. Likewise, a ranula is obstruction of a sublingual gland that may mimic angioedema [38].

Cheilitis glandularis is a rare condition that affects older men. It is characterized by hypertrophy of the lower lip that can mimic persistent (yet mild) angioedema and stinging of the lower lip. Close examination reveals secretory ducts that are inflamed with resultant red mucosal macules [39]. Scleredema adultorum of Buschke is a very rare infiltrative condition characterized by increased collagen and glycosaminoglycans that may present with persistent periorbital edema [40].

Blepharochalasis is a condition of the eyelids characterized by recurrent episodes of nonpruritic swelling that eventually causes visual field impairment and warrants surgical correction. Unlike festoons, which develop under the eyes, blepharochalasis involves both upper and lower eyelids [41].

Lymphoproliferative and autoimmune disorders

Acquired C1 inhibitor deficiency and angioedema (described earlier in this article) occurs as a consequence of lymphoproliferative disorders in some cases [42]. Clarkson syndrome from a capillary leak syndrome due to monoclonal gammopathy can precipitate angioedema and lymphedema [43].

In children, angioedema associated with a subsequent erythematopapular rash may be a presenting sign of autoimmune lymphoproliferative syndrome (ALPS) [44]. This entity is a result of a disorder in lymphocyte apoptosis involving the Fas-dependent pathway [45]. Facial edema precedes the onset of acute hemorrhagic edema, which is a leukocytoclastic vasculitis that is characterized by large annular or purpuric lesions on the extremities of a febrile child [46].

Dermatomyositis has been considered by some authors to be in the differential diagnosis of angioedema, possibly related to the poikiloderma of the face and the persistent edema of the eyelids [47].

Summary

There are many conditions that may present with swelling that mimics angioedema. When swelling persists for greater than a few days or is unresponsive to treatment for urticaria/angioedema, other etiologies should be considered. In most instances, a thorough history and physical examination will define other etiologies. However, for more persistent conditions, further laboratory evaluation and a biopsy may be required to define the diagnosis. Rarely is a more aggressive approach required to make the diagnosis.

Clinicians should remember that if the swelling does not act like angioedema, it more than likely is not angioedema.

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