How Not to Be Misled by Disorders Mimicking Angioedema

A Review of Pseudoangioedema

Andersen, Michelle Fog; Longhurst, Hilary J; Rasmussen, Eva Rye; Bygum, Anette

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Title page

TITLE

How not to be misled by disorders mimicking angioedema: A review of pseudoangioedema.

AUTHORS

Michelle Fog Andersen
Department of Otorhinolaryngology, Head and Neck Surgery, University Hospital of Sjaelland, Lykkebaekvej 1
4600 Koege, Denmark

Hilary J. Longhurst
Department of Immunology, Barts Health NHS Trust
80 Newark Street, London E1 2ES, England

Eva Rye Rasmussen
Department of Otorhinolaryngology, Head and Neck Surgery, University Hospital of Copenhagen, Blegdamsvej 9
2100 Copenhagen, Denmark

Anette Bygum
HAE Centre Denmark, Department of Dermatology and Allergy Centre, Odense University Hospital, Sdr. Boulevard 29
5000 Odense C, Denmark

Corresponding author
Michelle Fog Andersen
Department of Otorhinolaryngology, Head and Neck Surgery, University Hospital of Sjaelland, Lykkebaekvej 1
4600 Koege, Denmark
E-mail: michellefog@yahoo.com
Phone number: +452193 0075
Fax number: +454732 9692

KEYWORDS

Angioedema, Pseudoangioedema, Differential diagnoses, Angioedema mimickers.

ABSTRACT

Background: Angioedema is a vascular reaction involving the lower dermis, subcutis and/or submucosal tissue causing a temporary localized swelling in any part of the body. For many health care professionals, the diagnosis presents an ongoing challenge; several disorders may manifest with subcutaneous or submucosal swelling and falsely be assumed to be angioedema. The clinicians at the emergency department and in the immunology/allergy clinics must be skilled at recognizing features of angioedema and its differential diagnosis.

Methods: The review is based on a literature search with specific indexing terms in PubMed, a review of bibliographies and the authors' clinical experience.

Results: The most essential diseases that mimic angioedema, the so-called pseudoangioedema, will be discussed and each illustrated by clinical photos, pointing out key features that help clarify the diagnoses and differentiate these from classic angioedema.

Conclusions: A variety of dermatologic conditions can cause swelling that resembles angioedema, some with potentially fatal outcome if misdiagnosed. Knowledge of pseudoangioedema is fundamental in the emergency setting when handling patients with edema and should be kept in mind when assessing an atypical angioedema case.

INTRODUCTION

Angioedema, synonyms *angioneurotic oedema* or *Quincke's edema*, was originally described in 1882 by the German internist and surgeon Heinrich Quincke [1]. The condition is characterized by swelling just below the surface of the skin and/or mucosa, caused by a sudden increase in endothelial permeability with extravasation of intravascular fluid into the interstitial tissues. A variety of mechanisms can trigger the process, causing angioedema to be classified into two main categories: hereditary and acquired angioedema [2–4]. Hereditary angioedema (HAE) is a rare form of severe angioedema caused by genetic mutations in the complement C1 inhibitor (C1-INH) gene, *Serping1*, leading to a decrease in C1-INH (C1-INH-HAE). This leads to recurrent episodes of uncontrolled spontaneous activation of the contact system resulting in the release of a potent vasoactive peptide named bradykinin. Hereditary angioedema with normal C1-INH was primarily discovered in women [5–7], and has been described with factor XII mutations (FXII-HAE) [6,8] and of unknown origin (U-HAE). Acquired angioedema (AAE) can be related to C1-INH deficiency as well (CI-INH-AAE), but is most commonly mediated by excess of local histamine and other vasoactive mediators released by mast cells and basophils. The cause is often idiopathic (IH-AAE) but can be immunologic, such as allergic reactions initiated by immunoglobulin E-mediated hypersensitivity to foods or drugs. AAE can also occur as a non-immunologic side effect to certain drugs, the most common being the cardiovascular drug Angiotensin Converting-Enzyme (ACE) inhibitors (ACEI-AAE), which interferes with bradykinin degradation. Cytokine-mediated angioedema is a relatively common complication of treatment with biological treatments, particularly monoclonal antibodies.

When working in the clinical setting, it is essential to remember that not *all* swellings are angioedema. A number of medical conditions can cause swelling that resemble angioedema and are often erroneously labeled as such, due to low awareness of their typical hallmarks amongst medical staff in both the emergency and out-patient setting [9,10]. Misdiagnosis may lead to ineffective management of these potentially serious conditions, as the majority do not respond to conventional angioedema treatment, making a correct determination of the root causes of symptoms essential and in some cases even lifesaving. An understanding of clinical features unique to angioedema, as well as its differential diagnosis, is therefore of great importance and will help the physician to target the correct underlying pathophysiology. Syndromes that masquerade as angioedema are referred to as pseudoangioedema in the literature and should be considered in any patient presenting with atypical manifestations [10]. In this review, we focus on the most common and serious differential diagnoses of angioedema supported by illustrating clinical photos.

MATERIAL AND METHODS

Studies on angioedema and its differential diagnoses were found by conducting a systematic literature search in PubMed (Medline), using the search words "angioedema", "differential diagnosis", "pseudoangioedema", "angioedema mimickers", "acute contact dermatitis", "drug rash with eosinophilia and systemic symptoms", "dermatomyositis", "morbus morbihan", "superior vena cava syndrome", "hypothyroidism", "subcutaneous emphysema", "orofacial granulomatosis", "hypocomplementemic urticarial vasculitis", "clarkson's disease", "gleich's syndrome", "cluster headache", "idiopathic edema" and combinations of these search words. Only articles in English published since the year 2005 were included in the initial search. The total search produced 14.331 hits, thus proving the need for a more relevant search strategy. The search was limited to full text articles, which were systematic reviews, meta-analyses, multicenter studies, clinical trials, randomized clinical trials or case reports. Using this approach, 1342 articles were found. In order to

find the original articles and identify additional pertinent reports, selected reviews were then screened for relevant cross-references and examined with the result of 4 new original publications. A total of 42 articles were yielded from these search results. The search was terminated on the 1st of September 2015.

RESULTS

WHAT IS ANGIOEDEMA?

Angioedema is a clinical symptom defined by local swelling of the deeper layers of the skin, mucous membranes, or both, including the gastrointestinal tract and upper airway. Although the swelling can affect any part of the body, it has a predilection for areas with more loose connective tissue, including the face (especially the lips, tongue and periorbital area), pharynx, larynx, abdomen, genitalia and extremities [11–13]. The swellings manifest as recurrent episodes of pronounced localized edema with ill-defined margins. Unlike other forms of edema, angioedema is non-pitting, often asymmetric and has a tendency not to involve gravitationally dependent areas. The skin is usually normal in color, but can be slightly erythematous. The majority of patients with angioedema describe a tingling, slightly numb or even burning sensation of the affected site, while itching is not a typical symptom. The swelling is typically of slow onset over several hours and lasts less than 72 hours, resolving spontaneously without staining or desquamation of the skin. However, angioedema can have a very rapid onset when it occurs due to anaphylaxis. Over half of the patients have concomitant urticaria [11,12].

PSEUDOANGIOEDEMA

There are several conditions presenting with subcutaneous swelling that superficially resemble angioedema. Based on key signs and symptoms (Table 1), these so-called pseudoangioedemas can clinically be distinguished from true angioedema. The most common and important diseases that can mimic angioedema are listed below.

Acute contact dermatitis

Acute contact dermatitis is an inflammatory response of the skin induced by contact with a foreign substance. The reaction can be triggered by direct interaction with an irritating agent (irritant contact dermatitis) or allergenic chemical substance (allergic contact dermatitis) causing a type IV allergic reaction [14]. Acute contact dermatitis of the face is often misdiagnosed as angioedema, as it can cause severe swelling of the facial and periorbital skin, especially after contact with hair dye (Figure 1) [14,15]. The reaction can become so severe, that intubation may be necessary. It can be distinguished from angioedema and other pseudoangioedemas by demonstration of superficial erythema, dermatitis, prominent pain or pruritus, and a history of exposure to a foreign substance. Finally, the skin will often peel as swelling resolves, in contrast to patients with angioedema [14]. Antihistamines are ineffective, but symptoms respond to corticosteroids given topically or systemically. Diagnosis is verified by patch testing and the management involves strict avoidance of any contact allergens identified, along with withdrawal of corticosteroids once symptoms are well controlled.

Drug rash with eosinophilia and systemic symptoms (DRESS)

DRESS refers to an uncommon but rather severe adverse drug-induced skin reaction. Among a wide list of drugs associated with this reaction, aromatic anticonvulsants (phenytoin, phenobarbital

and carbamazepine) are the most common [(16)]. DRESS may mimic angioedema due to its clinical manifestation with facial or more widespread edema, which is accompanied by a diffuse, morbilliform rash (Figure 2) [17]. Other characteristic findings include fever, eosinophilia, lymphadenopathy and internal organ involvement, mainly liver and kidneys, which differentiate this condition from angioedema. The onset of the disease is usually seen within six weeks after the initiation of drug exposure and DRESS has a longer duration than most allergic drug reactions [16,18]. In fact, the symptoms can even exacerbate despite discontinuation of the drug. A history of the patients' medication together with objective findings and blood tests are therefore of utmost importance. Traditional patch testing cannot be used to confirm the diagnosis, which has to be clinical. Management consists of discontinuation of the causative drug. Most patient recover completely after drug withdrawal, but treatment regimens with corticosteroid are commonly used as well [18].

Dermatomyositis

Dermatomyositis is a common idiopathic inflammatory myopathy that affects both skeletal muscle and skin [19]. Although the etiology is poorly understood, an immunological pathogenesis has been suggested. The disease is characterized by proximal muscle weakness and cutaneous eruption in the form of erythema. The most common cutaneous features include the heliotrope rash: a distinctive reddish-purple erythematous rash around the eyes and Gottrons sign or papules [19,20]. It may present with periorbital edema, which can resemble that of angioedema (Figure 3). However, the presence of symmetrical proximal myositis, the cardinal muscular feature, along with characteristic cutaneous lesions, fatigue, weight loss and fever, distinguish this disease from angioedema [11]. Clinical suspicion is confirmed by biochemical, electromyographic and histological evidence of inflammation, with raised serum creatine kinase, anti-synthetase antibodies, myopathic features on electromyography and Magnetic Resonance Imaging, and typical muscle or skin biopsy features which may be patchy. Management, usually within a specialist centre, involves immunosuppression [21].

Morbus Morbihan

An uncommon cutaneous disorder called morbus Morbihan, also known as persistent edema of rosacea, is a skin condition which can be confused with angioedema [22]. It is considered a rare complication of rosacea and is characterized by persistent erythematous edema restricted to the forehead, glabella, upper eyelids, and cheeks (Figure 4). The edema worsens gradually over months to years with a solid consistency. The patient has no other symptomatic complaints and neither specific laboratory nor histopathologic findings have been observed [23]. The chronic nature of the skin condition together with the restricted location should differentiate this from angioedema. There is no guideline for the management. However, reported therapy includes long-term systemic corticosteroids and/or oral antibiotics such as doxycycline and isotretinoin [24].

Superior vena cava syndrome

Superior vena cava syndrome is a group of symptoms caused by obstruction and thereby impaired blood flow through the superior vena cava into the right atrium. In most cases, the obstruction is caused by a malignant tumor within the thorax. The clinical manifestations of Superior vena cava syndrome usually develop slowly and include dyspnea, cough and hoarseness. Because the drainage of blood to the heart is obstructed, the syndrome can in the early stages masquerade as angioedema due to a gradual development of edema in the face and upper extremities (Figure 5) [25,26]. Clues to differentiate the two diagnoses include vein distension across the chest and neck as well as increase in signs when the patient is in a supine position [11,27]. X-ray or CT scan of chest

including thoracic inlet usually confirms the diagnosis and further management is undertaken by the thoracic oncology team.

Hypothyroidism

Insufficient production of thyroid hormones by the thyroid gland causes hypothyroidism, which is most often autoimmune [28]. The condition presents with a wide array of symptoms including weight gain, constipation, dry skin, thinning of hair, hoarse voice, fatigue, lethargy, depression and cold intolerance. Severe hypothyroidism can manifest with puffiness of the face and lips very similar to angioedema (Figure 6). When generalized nonpitting edema (myxedema) becomes a manifestation, periorbital edema is often seen as a symptom. Nonetheless, it is not transient like angioedema [10,17]. Identification of the diagnosis is based on the clinical features and low levels of thyroid hormones. The treatment of choice for hypothyroidism is thyroxine replacement [28].

Subcutaneous emphysema

Air bubbles or other gases trapped in the subcutaneous tissues, namely subcutaneous emphysema, cause sudden onset of swelling in the affected area [29]. Air can migrate through the various fascial planes to involve the thorax, abdominal wall, perineal region, extremities, and most often neck or face (Figure 7), causing the condition to mimic angioedema. The air may become trapped as a result of surgery or trauma, or can occasionally develop spontaneously. Subcutaneous emphysema can usually be diagnosed clinically by crepitus, a characteristic crackling sensation created as the gas is pushed through the tissue during palpation [29,30]. In patients with this significant finding, the differential diagnosis of angioedema is ruled out. In doubtful cases, an X-ray or CT scan could be performed to illustrate the air beneath the skin surface and to identify the source of the emphysema.

Orofacial granulomatosis

Orofacial granulomatosis represents a group of chronic diseases affecting the soft tissues of the oral and maxillofacial region secondary to an underlying granulomatous inflammation [31]. The clinical presentation commonly shows persistent swelling of the lips (Figure 8). The group includes Melkersson-Rosenthal syndrome, an idiopathic disorder represented by a classic triad of persisting lip or facial swelling, facial nerve paralysis and fissured dorsal tongue (lingua plicata). Monosymptomatic cases with labial involvement alone are referred to as cheilitis granulomatosa. The orofacial edema is painless and asymmetrical, most often affecting the upper lip. Clinically, it is similar to angioedema and plays an essential role as differential diagnosis [10,31,32]. However, the chronic nature should distinguish it from typical angioedema. The etiology remains unclear, but has been linked to an abnormal immune reaction. Diagnosis is confirmed by histology. The management often requires use of corticosteroids or immunosuppression [32].

Hypocomplementemic urticarial vasculitis syndrome (HUVS)

HUVS is a form of severe cutaneous small-vessel vasculitis characterized by urticaria and abnormally low levels of complement C1q, C3 and C4 with C1q antibodies [33,34]. The most distinctive manifestation of this rare disease is the recurrent episodes of chronic, nonpruritic, urticarial skin lesions (Figure 9) associated with a variety of systemic involvement, including pulmonary disease, abdominal pain, leukocytoclastic vasculitis, arthritis, arthralgia, and glomerulonephritis. Underlying malignancy, infection or connective tissue disease should be excluded. In addition, angioedema is the initial clinical presentation in over half of the patients, often involving the facial area and upper extremities – a clinical picture found to misguide less experienced physicians [33,35]. However, the characteristic lesions in HUVS are typically painful and often resolve with post-inflammatory hyperpigmentation or purpura upon their resolution.

These characteristics, including the extra-cutaneous and systemic involvement, are all uncommon for typical angioedema. The appropriate management is determined by the severity of the disease, and may include combinations of antihistamines, hydroxychloroquine, corticosteroids and immunosuppression [36].

Clarkson's disease

Systemic capillary leak syndrome (SCLS), also called Clarkson's disease, is a life-threatening condition characterized by recurrent episodes of sudden hypovolemic shock and massive edema due to capillary leakage of plasma from the intravascular to the extravascular compartments [37,38]. The pathogenesis is still unclear, but immune dysregulation may play an essential role. SCLS is diagnosed clinically after exclusion of other diseases caused by systemic capillary leak. Among many, the diagnosis of angioedema should be considered upon the initial presentation. Nonetheless, unlike angioedema the cutaneous swelling of SCLS is generalized and symmetrical (Figure 10). Moreover, the rapid shift results also in hypovolemia, hemoconcentration and reduced serum albumin – a triad not characteristic of angioedema. Acute treatment is supportive. Corticosteroids and intravenous immunoglobulin have been reported as beneficial in some cases [37]. No clear strategies for prophylaxis have been defined [38].

Gleich's syndrome

The syndrome of episodic angioedema with eosinophilia, also known as Gleich's syndrome, is a rare disorder of unclear etiology characterized by recurrent episodes of idiopathic angioedema, eosinophilia and elevation of serum immunoglobulin lasting up to a few months [39]. The clinical picture also demonstrates weight gain caused by fluid retention, fever, pruritus and, in some cases, urticaria. It is characteristic for the syndrome, that there is no systemic organ involvement. Presence of specific laboratory features together with the other characteristic clinical manifestations should differentiate this entity from classical angioedema. Although debate surrounds the pathophysiology, increased serum levels of interleukins 5 and 6 has been described [39,40]. Systemic corticosteroids are used when treatment is required.

Cluster headache

Cluster headache, also known as histamine headache, is a rare cause of unilateral head or facial pain and periorbital edema, often associated with autonomic features such as conjunctival injection, ptosis, pupil constriction, watering of the eye or rhinitis (Figure 11). Untreated, symptoms last up to a few hours and may recur. Pain is typically intense and resistant to antihistamines and topical steroids. Oral steroids provide relief. Treatment of episodes is usually with a rapid acting tryptan or high flow oxygen. Verapamil is the drug of choice for prophylaxis [41]. Presence of characteristic headache together with the other clinical manifestations should differentiate these entities from classical angioedema.

Idiopathic edema

Idiopathic edema is a self-limited condition of persistent fluid retention, primarily in women [3]. The fluid retention is typically most prominent in premenstrual periods, which is why the condition is also known as "cyclical edema". It is most prominent on the extremities or abdomen after prolonged upright position and in the facial area, including pronounced periorbital edema, after recumbency overnight (Figure 12). This distinctive alteration over time, combined with an excessive weight gain from morning to evening and pitting edema, is very uncharacteristic for angioedema. Also, the edema is pitting in contrast to the non-pitting nature of angioedema. The diagnosis is one of exclusion and should only be considered when there is no evidence of cardiac,

hepatic, renal or thyroid diseases; all well-known causes of edema. Patients with idiopathic edema often become dependent on diuretics when trying to minimize the fluid retention. It is therefore important to avoiding diuretics and instead consider ACE inhibitor when treating these patients [42].

DISCUSSION

A variety of dermatologic conditions can cause swelling that resembles the diagnosis of angioedema. This review has discussed the most essential diseases that mimic angioedema: so-called pseudoangioedema, pointing out key features that help clarify the diagnoses and differentiate these from classic angioedema. Working knowledge of this kind is fundamental in the emergency setting when handling patients with edema and the list of diseases should be kept in mind when assessing an atypical angioedema case. In this way, determination of the root cause of symptoms can be made, leading to more effective and appropriate management of sometimes life-threatening conditions.

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FIGURE TEXT

Figure 1. Acute contact dermatitis with severe facial swelling after hair dyeing.

Figure 2. Generalized edematous swelling and morbilliform rash in a patient with drug rash with eosinophilia and systemic symptoms.

Figure 3. Heliotrope rash and edema and rash in the shawl area in a patient with dermatomyositis.

Figure 4. Persistent swelling of the forehead, cheeks and upper eyelids in a patient with morbus Morbihan.

Figure 5. Facial and neck swelling accompanied by dilatation of veins and cyanosis in a patient with superior vena cava syndrome. Photo credit: Tarec Christoffer El-Galaly, MD and Nina Keldsen, MD. Reprinted with permission from *Ugeskrift for Læger* (Ugeskr Læger 2007;169(37)).

Figure 6. Severe manifestation of periorbital edema in a patient with hypothyroidism.

Figure 7. Subcutaneous emphysema with severe swelling of the left chin, eyelids and neck after simple dental procedure.

Figure 8. Persistent swelling of the lower lip in a patient with orofacial granulomatosis.

Figure 9. Edematous urticarial plaques in a patient with hypocomplementemic urticarial vasculitis syndrome.

Figure 10. Generalized edematous swelling in a patient with Clarkson's disease. Photo credit: Knud Bonnet Yderstræde, MD.

Figure 11. Characteristic left periorbital edema and partial ptosis, with left conjunctival injection and tear formation during a cluster headache attack. Photo credit: Horton Hovedpineforening (the Danish association for patients with Cluster headache), www.hortonforeningen.dk.

Figure 12. Fluid retention of the face in a patient with idiopathic edema.

TABLE

Table 1

Characteristics of pseudoangioedema	
Acute contact dermatitis	• A history of exposure to a foreign substance • Superficial erythema (can cause severe swelling of the facial and periorbital skin). The skin will often peel as swelling resolves • Dermatitis, prominent pain or pruritus
Drug rash with eosinophilia and systemic symptoms (DRESS)	• A history of drug exposure (within six weeks) • Facial or more widespread edema, which is accompanied by a diffuse, morbilliform rash • Fever, eosinophilia, lymphadenopathy and internal organ involvement, mainly liver and kidneys
Dermatomyositis	• Symmetrical proximal muscle weakness • Cutaneous erythema, periorbital edema • Heliotrope rash, Gottrons sign and papules • Fatigue, weight loss and fever
Morbus Morbihan	• Persistent erythematous edema restricted to the forehead, glabella, upper eyelids, and cheeks • Worsens gradually over months to years with a solid consistency
Superior vena cava syndrome	• Dyspnea, cough and hoarseness • Vein distension across the chest and neck • Edema in the face and upper extremities • Worsening of signs when the patient is in a supine position
Hypothyroidism	• Wide array of symptoms including weight gain, constipation, dry skin, thinning of hair, hoarse voice, fatigue, lethargy, depression and cold intolerance • Puffiness of the face and lips
Subcutaneous emphysema	• Air bubbles trapped in the subcutaneous tissue, causing sudden swelling of the thorax, abdominal wall, perineal region, extremities, and most often neck or face • Crepitus
Orofacial granulomatosis	• Chronic, painless and asymmetrical swelling of the lips • *Cheilitis granulomatosa*: monosymptomatic involvement of lips • *Melkersson-Rosenthal syndrome*: triad of persisting lip or facial swelling, facial nerve paralysis and fissured tongue (lingua plicata)
Hypocomplementemic urticarial vasculitis syndrome (HUVS)	• Chronic, nonpruritic, painful urticarial skin lesions which resolve with post-inflammatory hyperpigmentation or purpura • Systemic involvement includes pulmonary disease, abdominal pain, leukocytoclastic vasculitis, arthritis, arthralgia, and glomerulonephritis. • Angioedema is the initial clinical presentation in over 50% of these patients
Clarkson's disease	• Sudden hypovolemic shock and massive generalized edema (symmetrical) • Hypovolemia, hemoconcentration and reduced serum albumin

Gleich's syndrome	• Recurrent episodes of idiopathic angioedema, eosinophilia and elevation of serum immunoglobulin • Weight gain caused by fluid retention, fever, pruritus and in some cases urticaria • No systemic organ involvement
Cluster headache	• Sudden unilateral head or facial pain and periorbital edema • Often associated with autonomic features such as conjunctival injection, ptosis, pupil constriction, watering of the eye or rhinitis
Idiopathic edema	• Pitting edema most prominent on the extremities or abdomen after prolonged upright position and in the facial area after recumbency overnight • The diagnosis is one of exclusion

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