Original Article

'Not All Swellings Are Angioedema' – An Overview And Systematic Approach For Acute Medical Physicians

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Abstract

Angioedema refers to a localised area of swelling affecting the subcutaneous and submucosal tissues due to release of vasoactive peptides, such as histamine or bradykinin. Despite being a relatively common presentation in the emergency room, the diagnosis can present a challenge to many healthcare professionals. Several conditions presenting with muco-cutaneous swellings may be misdiagnosed as angioedema. This article aims to provide an overview of the typical hallmarks of angioedema alongside its aetiology. We provide an overview of angioedema mimics that might potentially lead to misdiagnosis and highlight key features that help distinguish these conditions from angioedema. This is further illustrated with two interesting cases erroneously labelled as angioedema.

Keywords

Angioedema, Differential diagnoses, Swelling

Key points

1. The commonest cause of angioedema is spontaneous (idiopathic) urticaria and angioedema.
2. Angioedema is usually histamine-mediated, it is recommended to use a combination of antihistamines, corticosteroids and adrenaline (if indicated) in the acute phase unless the patient is known to have bradykinin-mediated angioedema (eg: hereditary angioedema) presenting with a typical attack.
3. A variety of conditions could be mistaken for angioedema. Systematic assessment of patients should enable clerking physician to distinguish these mimics from angioedema.

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Introduction

Angioedema is a relatively common presentation in the emergency room and primary care. The true incidence of angioedema remains elusive due to lack of high quality epidemiological data. The available data is largely extracted from surveys or national registers of hospitalised cases and is hampered by methodological short-comings. This is further limited as majority of angioedema episodes are managed in primary care.

Angioedema is commonly histamine-mediated and associated with urticaria. It has been reported that about 10-20% of the population will experience urticaria ± angioedema at some point in their lifetime. The worldwide prevalence of spontaneous (idiopathic) urticaria is estimated to be 0.5% to 2% and associated angioedema is present in 40-50% of these cases; this represents the commonest cause of angioedema in adults[1]. IgE-mediated allergic reactions may account for 0.2–1% of emergency admissions and the estimated incidence of anaphylaxis is 1–3 per 10 000 people; angioedema is present in about half of these cases[2]. There is some evidence of a worldwide rise in the incidence of spontaneous and allergic urticaria/angioedema[3]. On the other hand, bradykinin-mediated angioedema is uncommon. The most common cause of bradykinin-mediated angioedema is angiotensin-converting enzyme (ACE) inhibitor-induced angioedema (0.1% to 0.2%) as opposed to hereditary angioedema (HAE; 1 per 50,000)[4].

Several conditions presenting with muco-cutaneous swellings may be misdiagnosed as angioedema. This review aims to provide an overview of angioedema alongside its differential diagnoses, and highlights conditions that might masquerade as angioedema potentially leading to misdiagnosis.

What is angioedema?

Angioedema, previously known as angioneurotic oedema, was first described in the late 19th century[5]. It refers to a localised area of swelling affecting the deeper layers of the skin and/or mucous membranes (i.e. subcutaneous and submucosal tissues). It occurs due to release of vasoactive peptides, such as histamine and bradykinin, resulting in a rapid increase of microvascular permeability with extravasation of plasma into the interstitial tissue[6]. It is important to

recognise that angioedema is a physical sign and not a single disease entity.

Clinical presentation and aetiology

Clinically, angioedema manifests as a non-pitting swelling which can be associated with a tingling sensation or discomfort (Table 1). It is usually asymmetric and the overlying skin looks normal or slightly erythematous. Onset is usually subacute over hours, nevertheless, the symptoms may have a rapid onset (i.e., within minutes) when triggered by an allergic reaction (IgE mediated or type I hypersensitivity reaction). Angioedema is typically transient with complete resolution of symptoms within a few hours or days, without desquamation or any other residual skin changes. Furthermore, angioedema is not gravitationally dependent, and symptoms more frequently affect certain areas such as the lips, tongue, periorbital region, genitalia and extremities[7-9]. Acute attacks involving the pharynx and larynx can be potentially life-threatening and may require airway support.

Angioedema can be broadly classified into two main categories: histamine-mediated and bradykinin-mediated angioedema (Table 2).

Histaminergic angioedema

Is the most common and occurs as a consequence of mast cell degranulation releasing histamine and other vasoactive substances. This form of angioedema is therefore, usually associated with other signs and symptoms of mast cell-mediator release such as pruritus, erythema and/or urticaria, as well as bronchospasm, cardiovascular compromise, diarrhoea and vomiting in severe cases (anaphylaxis). Whilst the most common cause of histamine-mediated angioedema in children is an IgE mediated food allergy, the aetiology in adults is more commonly idiopathic or spontaneous, but can also occur due to an IgE-mediated hypersensitivity reaction to food, drugs or insect stings. Histamine-mediated angioedema responds to conventional treatment with antihistamines, corticosteroids and adrenaline[10,11]. Acute angioedema can often be erroneously labelled as anaphylaxis in emergency departments and medical admissions units. Angioedema may occur as a part of an anaphylactic reaction. However, the term 'anaphylaxis' should be used only to describe a specific combination of signs and symptoms involving respiratory/cardiovascular/gastrointestinal systems, usually with muco-cutaneous manifestations (i.e. urticaria and/or angioedema) but sometimes without.

Bradykinin-mediated (non-histaminergic) angioedema

Is non-pruritic and does not present with the histamine-mediated symptoms described above[12]. It is characterised by attacks of swelling due to uncontrolled activation of the Kallikrein-Kinin pathway and over-production of bradykinin[13]. This uncommon form of angioedema can be classified to three groups[14]:

Table 1. Typical characteristics of angioedema

- Non-pitting oedema
- asymmetric distribution
- Usually associated with urticaria
- Overlying skin is normal or slightly erythematous
- Transient (hours to few days)
- Non-gravitational, not position dependent
- A predilection for areas with loose connective tissue (lips, tongue, periorbital region, genitalia and extremities)

Hereditary angioedema (HAE)

Is a rare autosomal dominant disorder which can be sub-classified into 3 types. Type I is the commonest form of HAE caused by a loss of function mutation in the C1-inhibitor (C1-INH) gene resulting in deficient expression of this critical regulator of the complement, fibrinolytic and contact systems. HAE types II and III are very rare and occur as a result of dysfunctional C1-INH protein and factor XII mutation, respectively[15,16].

Acquired angioedema (AAE)

Is an uncommon complication of autoimmune or lymphoproliferative disorders due to overconsumption of C1-INH[17].

Drug-induced

Angioedema is a known non-immunologic side effect to angiotensin-converting enzyme (ACE) inhibitors. Unlike allergic reactions, ACE inhibitor-induced angioedema is unpredictable and the temporal association between administration of the drug and onset of symptoms is quite variable ranging from days to months or even years[6]. Other drugs associated with angioedema include Entresto (sacubitril/valsartan) and Gliptins.

Bradykinin-mediated angioedema may be life threatening (due to laryngeal obstruction) and

Table 2. Aetiology and classification of angioedema

Histaminergic*
• Spontaneous
• IgE-mediated hypersensitivity reaction
• Infection-induced
• Physical (inducible) urticaria and angioedema
Non-histaminergic
• Drug-induced (ACE inhibitors, nonsteroidal anti-inflammatory drugs)
• Hereditary angioedema
• Acquired angioedema due to C1-INH deficiency
• Idiopathic non-histaminergic angioedema

*usually associated with urticaria.

ACE: angiotensin converting enzyme. C1-INH: C1 esterase inhibitor.

Table 3. Angioedema mimics

Dermatological
• Cutaneous/soft tissue infections (cellulitis/erysipelas)
• Contact dermatitis
• Rosacea
• Morbihan disease
• Subcutaneous emphysema
Systemic
• Fluid retention secondary to renal, cardiac or hepatic impairment
• Drug rash with eosinophilia and systemic symptoms (DRESS)
• Superior vena cava syndrome
• Hypothyroidism
• Lupus/scleroderma
• Dermatomyositis
• IgG4-related disease
• Urticarial vasculitis
• Carcinoid syndrome
Miscellaneous
• Orofacial granulomatosis
• Melkersson-Rosenthal Syndrome
• Sarcoidosis
• Systemic capillary leak syndrome
• Gleich's Syndrome
• Idiopathic oedema
• Intermittent laryngeal obstruction (ILO)
Factitious angioedema

should be considered if no response to treatment for anaphylaxis. There are a number of targeted therapies for acute attacks of bradykinin-mediated angioedema (such as C1 inhibitor concentrate and Icatibant) and it is important to acknowledge that this form of angioedema does not respond to conventional treatment with antihistamines, corticosteroids or adrenaline[18].

Noteworthy, there is no point-of-care diagnostic test available to discriminate between bradykinin-mediated and histaminergic angioedema. It is therefore essential that clerking physicians are equipped with the adequate basic knowledge and clinical skills to help guide treatment decisions. Whilst it is important to ensure that the exact form of angioedema is diagnosed and treated, it is often difficult to differentiate between the two forms in an emergency setting when standard immediate interventions are put in place[19]. Since the majority of angioedema cases are histamine-mediated, it common clinical practice to use a combination of antihistamines, corticosteroids and adrenaline (if indicated) unless the patient is known to have bradykinin-mediated angioedema (eg: HAE) presenting with a typical attack[20].

Angioedema mimics

A variety of conditions could potentially be mistaken for angioedema (Table 3). In this section, we provide an overview of angioedema mimics and highlight key features that help distinguish these conditions from angioedema. This is further illustrated with two cases erroneously labelled as angioedema and referred to our service for further evaluation.

Dermatological conditions

Cutaneous and soft tissue infections, especially if affecting the face, can sometimes be mistaken for angioedema. Detailed history looking for other associated features and an accurate chronology of symptoms are key to diagnosis. Typical clinical manifestations of cellulitis/erysipelas, such as hot and tender erythema with or without blistering, should clearly differentiate this from angioedema. Furthermore, localised lymphadenopathy, elevated inflammatory markers and fever with other systemic symptoms are common features of infection[21]. One of the conditions that may masquerade as angioedema is contact dermatitis, which represents a delayed, type IV hypersensitivity reaction in response to a chemical agent such as cosmetics (allergic contact dermatitis). The presence of dermatitis, skin crusting/peeling and a history of skin contact with respective trigger and delayed onset of symptoms (usually 48-72 hours post-exposure) are suggestive of contact dermatitis rather than angioedema[22].

The periorbital oedema occasionally observed in patients with dermatomyositis can be erroneously labelled as angioedema[23]. However, presence of proximal myopathy and the cardinal cutaneous features, including the heliotrope rash and Gottron's papules, are the most distinctive clinical manifestations of dermatomyositis. The diagnosis of this idiopathic inflammatory myositis can be verified by elevation in serum creatine kinase and identification of typical myopathic features on magnetic resonance imaging (MRI), muscle biopsy and neurophysiological evaluation[24]. Another cause of non-pitting facial oedema is Morbihan disease which is regarded as a rare complication of rosacea; nonetheless it has been reported in the absence of clinical manifestations of rosacea. Unlike angioedema, the facial erythematous swelling caused by this disease is typically symmetrical, persistent and develops slowly over months. Morbihan disease is a clinical diagnosis and there are no characteristic histopathological findings specific to this condition, physical examination may demonstrate other signs of rosacea which would be helpful to reach a diagnosis[25,26]. Subcutaneous emphysema refers to accumulation of gas in the subcutaneous tissues resulting in a sudden onset of swelling in the affected area. It can occur as a complication of surgery, trauma, chest tube insertion, pneumothorax, necrotising infection or positive pressure ventilation. This condition is clinically distinguished from angioedema by the characteristic crepitus on palpation[27] and the clinical impression should be confirmed by an X-ray or CT scan.

Systemic conditions

Oedema of cardiac, renal or hepatic origin is characteristically pitting and symmetrical, unlike angioedema which is non-pitting and often asymmetric. Patients with congestive heart failure and liver disease can develop dependent (gravitational) oedema in the lower extremities which is unlikely to be confused with angioedema. On the other hand, particular attention should be paid to oedema of renal disease which typically starts as periorbital puffiness, is non-pruritic, more so in the morning with improvement as the day progresses and can resemble angioedema[28]. Superior vena cava (SVC) obstruction may mimic angioedema due to its clinical presentation[29]. SVC syndrome is caused by external compression by upper mediastinal tumors in most cases; however, a number of case reports have highlighted intrinsic SVC stenosis due to pacemakers (Case 1) or implantable defibrillators[30]. In contrast to angioedema, SVC syndrome is characterised by slowly progressive, non-pruritic and symmetrical oedema confined to the face and upper extremities. The puffiness of SVC syndrome is typically worse in supine position, more prominent early in the morning and usually associated with dyspnoea and cough. If this syndrome is suspected, physical examination should be performed looking for elevated jugular venous pressure (JVP) with dilated chest wall venous collaterals; a CT scan of the chest usually confirms the diagnosis[31].

Case 1.

A 70year old gentleman presented with a 6month history of worsening symmetrical facial uedema and flushing without associated urticaria or pruritus. His symptoms were particularly worse in morning with improvement as the day progressed, but the observed swelling never resolved completely. He also reported some breathlessness in the supine position. There were no identifiable triggers for his symptoms and he was treated for a suspected 'allergic reaction' in the emergency department on multiple occasions with intramuscular adrenaline, intravenous chlorpheniramine and corticosteroids. Physical examination revealed mild, diffuse symmetrical facial oedema and flushing. There was no evidence of urticaria, bronchospasm or hypotension. Laboratory studies showed mildly elevated urea and creatinine with no proteinuria, serum albumin and liver function test were normal. Complement C4, C1 esterase inhibitor level and function were within the reference range. An initial computed tomographic (CT) chest scan was normal.

Past medical history included antero-septal myocardial infarction with primary angioplasty; he had a permanent pacemaker implanted due to trifascicular block and chronotropic incompetence. Other comorbidities included hypertension and insulin dependent diabetes.

Due to high clinical index of suspicion, diagnosis of SVC syndrome was re-considered months later and a repeat contrast-enhanced CT scan of the chest demonstrated a 4mm stenosis of the superior vena cava with the pacemaker wires occupying most of the lumen. There was extensive venous collateralisation around the azygos system with no evidence of extrinsic compression. Following evaluation by vascular surgeons and Cardiologist, conservative management with life-long anticoagulation was recommended.

One of the complications of severe hypothyroidism is myxoedema (excessive deposition of glycosaminoglycans in the dermis resulting in non-pitting oedema) which can present with periorbital swelling that mimics angioedema[32]. Nonetheless, other systemic symptoms of hypothyroidism (such as extreme fatigue, cold intolerance, weight gain, constipation, poor concentration, dry/coarse skin, hoarse voice and depression) are usually obvious. Drug rash with eosinophilia and systemic symptoms (DRESS) is an uncommon, idiosyncratic drug-induced hypersensitivity reaction. This condition can cause a facial swelling which can be confused with angioedema; however, associated clinical features including fever, morbilliform rash, lymphadenopathy, hepatic/renal impairment and peripheral blood eosinophilia should point to the diagnosis of DRESS syndrome[33]. It is worth noting that signs and symptoms usually start 2 to 6 weeks after commencing therapy (eg: suphonamides, anticonvulsants, allopurinol, NSAIDs, dapsone etc,.). This has to be taken into consideration and a careful medication history should be obtained if there is a clinical index of suspicion for DRESS syndrome.

Cutaneous manifestations of some connective tissue diseases such as lupus and scleroderma may sometimes be mistaken as angioedema[34]. Detailed history, physical examination and the presence of typical systemic and laboratory features should distinguish these autoimmune disorders from angioedema. Immunoglobulin G4-related disease (IgG4-RD) is a rare disorder that was first described in the early 2000's with characteristic histopathological features including dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, storiform fibrosis and obliterative phlebitis[35]. IgG4-RD commonly affects the soft tissues of the head and neck resulting in mass-forming lesions (eg. orbital pseudo-tumour, salivary and lacrimal gland enlargement) which may possibly be misdiagnosed as angioedema upon the initial presentation. This fibro-inflammatory syndrome usually follows a chronic relapsing–remitting course and there is multi-organ involvement in 60-90% of the cases[36]. The diagnosis can only be confirmed by demonstration of the histologic findings typically observed in this condition and patients usually respond well to corticosteroid therapy[37]. Up to 50% of patients with urticarial vasculitis, a form of small vessel vasculitis, can present with facial oedema[38]. In distinction to typical urticaria and angioedema, the vasculitis rash is typically non-pruritic, painful, persists for >48 hours and may resolve with post-inflammatory bruising and hyperpigmentation. Moreover, systemic manifestations are common in vasculitis and include arthralgia/arthritis, pulmonary disease, gastrointestinal symptoms, ocular inflammation and glomerulonephritis. Diagnosis can be confirmed by combining the clinical presentation with complement studies (low levels of complements C3, C4 and C1q with detectable anti-C1q autoantibodies) and demonstration of leukocytoclastic vasculitis in skin

'Not All Swellings Are Angioedema' – An Overview And Systematic Approach For Acute Medical Physicians

Case 2.

A 19year old gentleman presented with a 2 month history of persistent swelling of his upper lip and peri-orbital region (Figure 1). He was treated with antihistamines and corticosteroids in the community with no effect; therefore he was referred to our service as a case of 'refractory angioedema'. During the consultation he was found to have a temperature of 39.50C and hypotension. Blood tests revealed pancytopaenia, deranged liver function test with grossly elevated ferritin level. Given this presentation, hemophagocytic lymphohistiocytosis (HLH) was suspected and bone marrow studies were undertaken which confirmed appearances of HLH. Despite comprehensive investigations, including infections and genetic causes, aetiology of HLH was unclear. He was commenced on dexamethasone, etoposide, ciclosporin and immunoglobulins for 12 weeks. He successfully completed the treatment with good clinical response and his haematological and biochemical markers were normalised. Moreover, the swelling of his eyes and lips improved with some residual swelling of upper lip.

Punch biopsy of upper lip showed a granulomatous infiltrate on a background of florid perivascular/perineural chronic inflammation in keeping with orofacial granulomatosis.

Interestingly, the patient developed bilateral 7th cranial nerve palsy. The combination of orofacial swelling and facial nerve palsy was consistent with Melkersson-Rosenthal Syndrome; a clinical subtype of orofacial granulomatosis. He had a recurrence of severe upper lip swelling few years later which was successfully treated with oral steroids.

biopsy samples[39]. Carcinoid syndrome can sometimes present with symptoms that resemble angioedema due to excessive release of biogenic amines from neuroendocrine tumours[40].

Miscellaneous conditions

Orofacial granulomatosis refers to a group of rare disorders of unknown aetiology characterised by granulomatous inflammation affecting the soft tissues of the face and lips in the absence of a systemic cause. Although, the orofacial swelling is asymmetrical and painless, the chronic nature of this disorder, together with the histopathological features, should discriminate the swelling from angioedema[41]. Melkersson-Rosenthal syndrome is a subtype of orofacial granulomatosis associated with lower motor neurone facial nerve palsy (Case 2); other clinical variants include granulomatous cheilitis and Miescher cheilitis[42-44]. Management often requires the use of corticosteroids (+/- other immunosuppressive drugs) and improvement can be observed in most cases. Head and neck involvement in sarcoidosis has only been reported in about 10% of patients and includes subcutaneous mass, parotid swelling and enlarged lymph nodes[45,46]. It is worth noting that isolated facial swelling is an exceedingly rare presentation of this idiopathic chronic granulomatous disease. The swelling is persistent and not transient like angioedema and the presence of compatible systemic features would direct the clinician to consider sarcoidosis. High index of clinical suspicion with typical radiological findings and *histological evidence* of non-caseating granulomas would confirm the diagnosis.

Gleich's syndrome is an uncommon disorder of poorly understood aetiology that presents with periodic episodes of oedema affecting head, trunk, and extremities. Contrary to classic angioedema, this condition is associated with fluid retention, fever, marked peripheral blood eosinophilia, elevated serum IgM and overproduction of interleukin-5. Gleich's syndrome is not known to cause any end-organ damage and the attacks usually resolve spontaneously; corticosteroids (and other immunomodulating agents) have been used with success to treat more severe flare ups[47,48]. Another possible angioedema mimic is systemic capillary leak syndrome (SCLS); a very rare disorder with less than 500 cases reported in the literature, since it was first described in 1960[49]. Affected patients suffer from episodic attacks of generalised, symmetrical oedema (mostly in extremities) due to leakage of fluids from the intravascular to the interstitial compartment. The presence of the characteristic triad of transient hypovolemia, haemoconcentration and hypoalbuminemia in the acute phase is indicative of SCLS rather than angioedema[50].

Fluid retention in the absence of cardiac, renal or liver disease can be due to idiopathic oedema. This condition typically affects females and causes swellings of limbs, abdomen and, occasionally, periorbital region. Idiopathic oedema can masquerade as angioedema nonetheless; the swelling is pitting, symmetrical and can result in weight gain. The pathophysiology underlying this condition is unclear and it remains a diagnosis of exclusion[51]. Patients with cluster headache can develop peri-orbital oedema; but the hallmark of this disorder is unilateral severe headache in contrast to angioedema. Other commonly associated features include facial sweating, nasal congestion, conjunctival injection, ptosis, pupil constriction and excessive watering of the eye and nose on the affected side[52]. Intermittent laryngeal obstruction (ILO) occurs due paradoxical vocal cord movement resulting in choking sensation, breathlessness and stridor. ILO is frequently mistaken for laryngeal angioedema resulting in unwarranted A&E admissions. Patients with ILO should be assessed and managed by Speech & Language Therapist[53].

Discussion

Clinical presentation of a wide range of dermatological, systemic and other miscellaneous conditions occasionally referred to as 'pseudo-angioedema', may lead to misdiagnosis. In addition to these mimics, Feldman et al published a small case series of factitious angioedema due to Münchausen syndrome, which is likely to be underreported in the literature[54]. Overreliance on a commonly encountered condition, such as angioedema, has been observed in clinical practice and can lead to inappropriate management and delayed diagnosis of conditions that resemble angioedema. Misdiagnosis

of angioedema may be attributed to lack of awareness of its typical manifestations amongst some healthcare professionals both in primary and secondary care[55-57]. Furthermore, some of the angioedema masqueraders are rare and misdiagnosis may occur due to unfamiliarity with presenting features of these conditions[58]. Figure 1shows a simplified diagnostic algorithm for evaluation of patients presenting with swelling.

Conclusion

This review highlights the importance of a careful and systematic assessment of patients presenting with muco-cutaneous swelling. Identifying atypical clinical features of angioedema should prompt healthcare professionals to consider angioedema mimics. It is important to bear in mind that not all swellings are angioedema.

Further research

Further research is required to identify the aetiology and pathogenesis of spontaneous angioedema, which are currently poorly understood. Investigation of the role of environmental factors, genetic associations and correlation with autoimmunity.

Studies designed to correlate clinical presentation of various types of angioedema with prognosis and response to treatment.

Defining disease endotypes and their biomarkers which will enable the identification of novel therapeutic targets.

Author contribution

OEM and MTK conceived this review. The review was undertaken by LM, KS, SA, OMA and AE. OEM led the drafting of the manuscript. All authors critically commented on the drafts and approved the final manuscript.

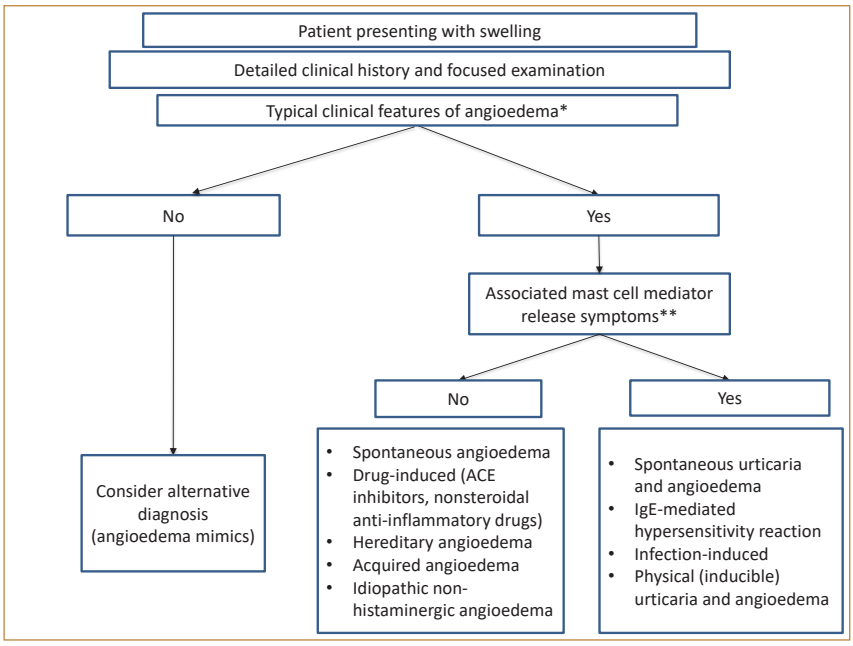

Figure 1. A simplified diagnostic approach for assessment of patients presenting with swelling.
*See Table 1 above.
**Pruritus, erythema and urticaria, as well as bronchospasm, hypotension, diarrhoea and vomiting in severe cases (i.e. anaphylaxis).

Declaration

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References

1. Sánchez-Borges M, Asero R, Ansotegui IJ, *et al.* Diagnosis and treatment of urticaria and angioedema: a worldwide perspective. *World Allergy Organ J.* 2012;**5(11)**:125-147.
2. Moneret-Vautrin DA, Morisset M, Flabbee J, Beaudouin E, Kanny G. Epidemiology of life-threatening and lethal anaphylaxis: a review. *Allergy.* 2005;**60**(4):443-451.
3. Turner PJ, Campbell DE, Motosue MS, Campbell RL. Global Trends in Anaphylaxis Epidemiology and Clinical Implications. *J Allergy Clin Immunol Pract.* 2020;**8**(4):1169-1176.
4. Hahn J, Hoffmann TK, Bock B, Nordmann-Kleiner M, Trainotti S, Greve J. Angioedema. *Dtsch Arztebl Int.* 2017;**114(29-30)**:489-496.
5. Quincke HI: Über akutes umschriebenes Hautödem. *Monatsh Prakt Dermatol* 1882; **1**:129–131.
6. Kaplan AP. Angioedema. *World Allergy Organ J.* 2008;**1(6)**:103-113.
7. Bernstein JA, Cremonesi P, Hoffmann TK, Hollingsworth J. Angioedema in the emergency department: a practical guide to differential diagnosis and management. *Int J Emerg Med.* 2017;**10(1)**:15.
8. Frigas E, Nzeako UC: Angioedema. *Clin Rev Allergy Immunol* 2002; **23**: 217–231.
9. Tai S, Mascaro M, Goldstein NA: Angioedema: a review of 367 episodes presenting to three tertiary care hospitals. *Ann Otol Rhinol Laryngol* 2010; **119**: 836–841.
10. Busse PJ, Smith T. Histaminergic Angioedema. *Immunol Allergy Clin North Am.* 2017;**37(3)**:467-481.
11. Hacard F, Nosbaum A, Bensaid B, *et al.* Angioedème histaminique et urticaire chronique [Histaminergic angioedema and chronic urticaria]. *Presse Med.* 2015;**44(1)**:37-42.
12. Busse PJ, Buckland MS. Non-histaminergic angioedema: focus on bradykinin-mediated angioedema. *Clin Exp Allergy.* 2013;**43**(4):385-394.
13. Kaplan AP, Joseph K. Pathogenic mechanisms of bradykinin mediated diseases: dysregulation of an innate inflammatory pathway. *Adv Immunol.* 2014;**121**:41-89.
14. Kaplan AP. Bradykinin-mediated diseases. Chem Immunol Allergy. 2014;**100**:140-147.
15. Banerji A. Hereditary angioedema: classification, pathogenesis, and diagnosis. *Allergy Asthma Proc.* 2011;**32(6)**:403-407.
16. Khan DA. Hereditary angioedema: Historical aspects, classification, pathophysiology, clinical presentation, and laboratory diagnosis. *Allergy Asthma Proc.* 2011;**32(1)**:1-10.
17. Cicardi M, Zanichelli A. Acquired angioedema. *Allergy Asthma Clin Immunol.* 2010;**6(1)**:14. Published 2010 Jul 28.
18. Zeerleder S, Levi M. Hereditary and acquired C1-inhibitor-dependent angioedema: from pathophysiology to treatment. *Ann Med.* 2016;**48**(4):256-267.

References

19. Moellman JJ, Bernstein JA, Lindsell C, *et al.* A consensus parameter for the evaluation and management of angioedema in the emergency department. *Acad Emerg Med.* 2014;**21**(4):469-484.
20. Craig TJ, Bernstein JA, Farkas H, Bouillet L, Boccon-Gibod I. Diagnosis and treatment of bradykinin-mediated angioedema: outcomes from an angioedema expert consensus meeting. *Int Arch Allergy Immunol.* 2014;**165**(2):119-127.
21. Clebak KT, Malone MA. Skin Infections. *Prim Care.* 2018;**45**(3):433-454.
22. Tan CH, Rasool S, Johnston GA: Contact dermatitis: allergic and irritant. *Clin Dermatol.* 2014; 32: 116–124.
23. Milisenda JC, Doti PI, Prieto-Gonzolez S, Grau JM: Dermatomyositis presenting with severe subcutaneous edema: five additional cases and review of the literature. *Semin Arthritis Rheum* 2014; 44: 228–233.
24. Muro Y, Sugiura K, Akiyama M: Cutaneous manifestations in dermatomyositis: key clinical and serological features – a comprehensive review. *Clin Rev Allergy Immunol.* 2016 Dec;51(3):293-302.
25. Nagasaka T, Koyama T, Matsumura K, Chen KR. Persistent lymphedema in Morbihan disease: formation of perilymphatic epithelioid granulomas as a possible pathogenesis. *Clin Exp Dermatol* 2008; 33: 764–7.
26. Wohlrab J, Lueftl M, Marsch WC. Persistent erythema and edema of the mid third and upper aspect of the face (morbus morbihan): evidence of hidden immunologic contact urticaria and impaired lymphatic drainage. *J Am Acad Dermatol* 2005; **52**: 595–602.
27. Çakmak SK, Gönül M, Gül Ü, Kiliç A, Demirel Ö: Subcutaneous emphysema mimicking angioedema. *J Dermatol* 2006; **33**: 902–903.
28. Diskin CJ, Stokes TJ, Dansby LM, Carter TB, Radcliff L, Thomas SG. Towards an understanding of oedema. *BMJ.* 1999;**318**(**7198**):1610-1613.
29. Burgdorff T, Douwes KE, Bogenrieder T, Szeimies RM, Hohenleutner U, Landthaler M, Stolz W: Superior vena cava syndrome: an important differential diagnosis in patients with facial edema. *Acta Derm Venereol* 2001; **81**: 205–206.
30. Chee CE, Bjarnason H, Prasad A. Superior vena cava syndrome: an increasingly frequent complication of cardiac procedures. *Nat Clin Pract Cardiovasc Med.* 2007 Apr;**4**(**4**):226-30.
31. Wan JF, Bezjak A: Superior vena cava syndrome. *Emerg Med Clin North Am* 2009; **27**: 243–255.
32. Swedlund HA. Iodide myxedema with facial swelling simulating angioneurotic edema. *J Allergy.* 1971 Jun;**47**(**6**):341-5.
33. Cacoub P, Musette P, Descamps V, Meyer O, Speirs C, Finzi L, Roujeau JC: The DRESS syndrome: a literature review. *Am J Med* 2011; **124**: 588–597.
34. Bertinotti L, Miniati I, Cerinic MM. Angioedema and systemic sclerosis. A review of the literature. *Scand J Rheumatol.* 2002;**31**(**3**):178-180.
35. Kamisawa T, Funata N, Hayashi Y, Eishi Y, Koike M, Tsuruta K, Okamoto A, Egawa N, Nakajima H. A new clinicopathological entity of IgG4-related autoimmune disease. *J Gastroenterol.* 2003;**38**(**10**):982.
36. Okazaki K, Uchida K, Koyabu M, Miyoshi H, Takaoka M. Recent advances in the concept and diagnosis of autoimmune pancreatitis and IgG4-related disease. *J Gastroenterol.* 2011;**46**(**3**):277.
37. Khosroshahi A, Stone JH. A clinical overview of IgG4-related systemic disease. *Curr Opin Rheumatol.* 2011;**23**(**1**):57.
38. Buck A, Christensen J, McCarty M: Hypocomplementemic urticarial vasculitis syndrome: a case report and literature review. *J Clin Aesthet Dermatol* 2012; **5**: 36–46.
39. Jara LJ, Navarro C, Medina G, Vera-Lastra O, Saavedra MA. Hypocomplementemic urticarial vasculitis syndrome. *Curr Rheumatol Rep.* 2009 Dec;**11**(**6**):410-5.
40. Bukhari S, Dirweesh A, Conaway H. Angioedema in a patient with neuroendocrine tumour. B*MJ Case Rep.* 2017 Jan 20;2017:bcr2016218961.
41. Celebi Z, Ozguclu S, Aydin O, Okcu A, Soyyigit S: A rare syndrome in the differential diagnosis for angioedema. *J Med Cases* 2014; **5**: 579–582.
42. Kakimoto C, Sparks C, White AA: Melkersson-Rosenthal syndrome: a form of pseudoangioedema. *Ann Allergy Asthma Immunol* 2007;**99**:185–189.
43. Miest R, Bruce A, Rogers RS. Orofacial granulomatosis. *Clin Dermatol.* 2016 Jul-Aug;**34**(**4**):505-13.
44. Magister MJ, Ghaffari G. Granulomatous cheilitis mimicking angioedema. *Cutis.* 2017 May;**99**(**5**):E16-E18.
45. Yates JM, Dickenson AJ. Sarcoidosis presenting as an isolated facial swelling--an unexpected diagnosis?. *Dent Update.* 2006;**33**(**2**):112-114.
46. Hanazawa T, Terada N, Konno A. *Nihon Rinsho.* 2002;**60**(**9**):1813-1817.
47. Khoury P, Herold J, Alpaugh A, Dinerman E, Holland-Thomas N, Stoddard J, Gurprasad S, Maric I, Simakova O, Schwartz LB, Fong J, Lee CC, Xi L, Wang Z, Raffeld M, Klion AD. Episodic angioedema with eosinophilia (Gleich syndrome) is a multilineage cell cycling disorder. *Haematologica.* 2015;**100**(**3**):300-307.
48. Abisror N, Mekinian A, Dechartres A, *et al.* Abnormal T-cell phenotype in episodic angioedema with hypereosinophilia (Gleich's syndrome): frequency, clinical implication and prognosis [published online ahead of print, 2019 Feb 6]. *J Am Acad Dermatol.* 2019;S0190-9622(19)30196-3.
49. Druey KM, Parikh SM. Idiopathic systemic capillary leak syndrome (Clarkson disease). *J Allergy Clin Immunol.* 2017 Sep;**140**(**3**):663-670.