Chapter 15

Pseudoangioedema

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Additional information is available at the end of the chapter

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Abstract

Angioedema is a rapid, localized and temporary subcutaneous edema, which targets the lips, eyelids, gastrointestinal and respiratory mucosa resulting in abdominal pain, asthma and even serious life-threatening conditions like airway obstruction. There are several other disorders such as allergic contact dermatitis, drug rash with eosinophilia and systemic symptoms (DRESS), superior vena cava syndrome (SVCS), orofacial granulomatosis and so on, which manifest with subcutaneous swelling and masquerade as angioedema and are known as 'pseudoangioedema' in the literature. Knowledge of pseudoangioedema for healthcare professionals is crucial to avoid potentially serious results of misdiagnosis such as further investigations, unnecessary applications and delayed diagnosis. We aim to discuss differential diagnosis of angioedema and help physicians recognize the typical features of angioedema and its differential diagnosis in this chapter.

Keywords: angioedema, pseudoangioedema, angioedematous, pseudoangioedematous, angioedema differential diagnosis, angioedema mimickers, swellings mimic angioedema, masquerading as angioedema, angioedema similar disease

1. Introduction

Angioedema is defined as a rapid, localized and temporary swelling of the skin and/or mucous membranes caused by increased endothelial permeability and extravasation of intravascular fluid into the interstitial tissues. It has predilection sites, including the lips, tongue, eyelids, gastrointestinal and respiratory mucosa [1, 2]. Angioedema represents one of the most common airway emergencies, so quick diagnosis and intervention mean the life of a patient. Although coexistence with urticaria is frequent (50%), angioedema without urticaria is defined

as a distinct disease. Angioedema without urticaria, called Quincke's edema/angioneurotic edema, is classified into two main categories: hereditary and acquired angioedema [1–3]. Hereditary angioedema is a severe and rare form caused by genetic mutations in the complement C1 inhibitor, factor XII gene or unknown etiology. Four types of acquired angioedema are identified: idiopathic histaminergic angioedema, idiopathic non-histaminergic angioedema, acquired angioedema related to angiotensin-converting enzyme inhibitors and acquired angioedema with C1 inhibitor deficiency [3]. Several disorders can cause subcutaneous swelling and are often misdiagnosed as angioedema. These conditions which mimic angioedema are known as 'pseudoangioedema' in the literature [2, 4]. Misdiagnosis may lead to life-threatening results because of ineffective management of these serious medical conditions. There are some clues help distinguish angioedema from other causes of swelling. Angioedema is characterized by asymetric and transient swelling, typically lasting 24–48 hours. It is essential to be aware of angioedema mimickers for healthcare professionals in both the emergency and outpatient setting [1, 2, 4].

2. Research design

This chapter based on a literature search in Pubmed using the keywords 'angioedema', 'pseudoangioedema', 'angioedematous', 'pseudoangioedematous', 'angioedema differential diagnosis', 'angioedema mimickers', 'swellings mimic angioedema', 'masquerading as angioedema' and 'angioedema similar disease'. Case reports, clinical trials, cohort studies, systematic reviews and meta-analyses associated with these keywords published up until now were evaluated.

3. Differential diagnosis for pseudoangioedematous disorders

The most common and important angioedema mimickers are discussed in this chapter.

3.1. Contact dermatitis

Contact dermatitis is an inflammatory skin disease due to delayed type hypersensitivity response after a direct contact with irritating or allergenic foreign substances. Contact dermatitis of the face frequently causes severe swelling of the facial and periorbital skin similar to angioedema [2, 4, 5], as in our case (**Figure 1**).

The first manifestation of contact dermatitis may be angioedema-like swelling but after a while, superficial erythema, vesicles or blisters and later eczematous dermatitis develop, whereas angioedema does not have these clinical signs [2, 4]. It can also be distinguished from angioedema by a history of exposure to chemical agents, especially cosmetic products. Facial contact dermatitis is becoming a common problem because of the increase in the use of cosmetic products, and the cosmetic market has grown progressively. Unlike angioedema, antihistamines are not effective, and causative agents can be identified by an epidermal patch test [5].

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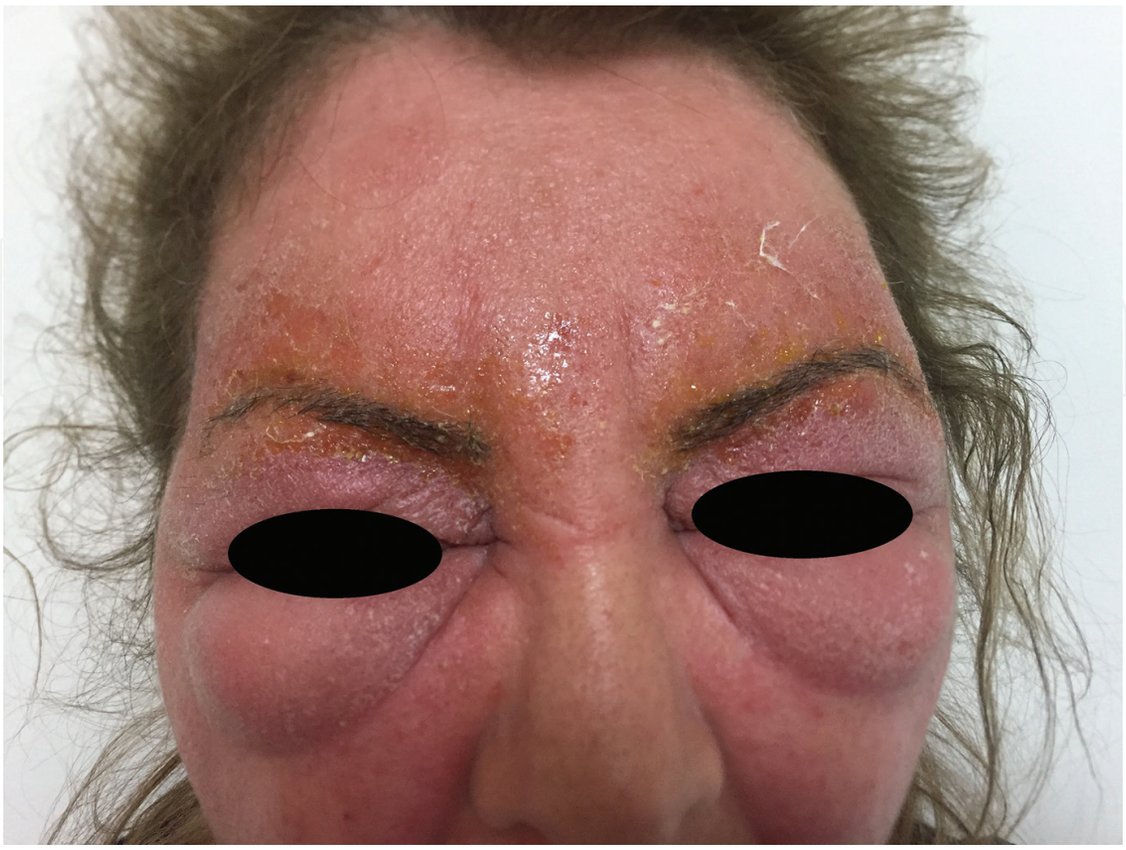

Figure 1. Contact dermatitis with severe facial swelling after hair dyeing.

3.2. Drug rash with eosinophilia and systemic symptoms (DRESS)

DRESS syndrome is a rare life-threatening cutaneous adverse drug-induced reaction associated with 10% mortality. Aromatic anticonvulsants, especially phenytoin, carbamazepine and phenobarbital, are the most common causes of DRESS [6–9]. Although there can be various manifestations, it usually starts as diffuse morbilliform rash later becoming indurated with associated edema. There is often aberrant facial edema, especially in the periorbital and midfacial region that can sometimes be mistaken for angioedema. 25% of patients have prominent facial swelling [6, 8]. History of medication, lymphadenopathy and other systemic findings and laboratory test results such as eosinophilia help differentiate this medical condition from angioedema. The onset of symptoms occurs 2–6 weeks after drug administration, longer than other drug reactions. There is no reliable standard for the diagnosis of DRESS, and management is the discontinuation of the causative drug [6, 9].

3.3. Dermatomyositis and lupus erythematosus

Dermatomyositis is an autoimmune inflammatory disorder, which affects the skin, muscles and blood vessels. Cutaneous manifestations are intense erythema and edema on the dorsum of the hands and periorbital region [10–13]. Heliotrope rash is a distinctive feature defined as periorbital erythema with symmetrically distributed edema. Gottron papules are

erythematous to violaceous plaques often on the extensor joints of hands [10, 12, 13]. Although it may mimic angioedema due to periorbital edema, accompanying symmetrical proximal muscle weakness, fatigue, weight loss and elevated serum creatine kinase levels distinguish the disease from angioedema [14]. Diagnosis is confirmed by typical, clinical electromyography patterns, elevated muscle enzymes and muscle biopsy [12, 13].

Angioedematous appearance of the periorbital area is also a rare presentation of systemic lupus erythematosus. A pathophysiological mechanism of this condition is explained by autoantibodies against C1 inhibitor causing acquired deficiency of C1 esterase inhibitor [15, 16]. Although periorbital edema as the sole presenting manifestation of cutaneous lupus erythematosus is extremely rare, it is very rarely associated with discoid lupus erythematosus and lupus erythematosus profundus [17, 18].

3.4. Morbihan disease

Rosacea is a common cutaneous disease that affects middle-aged individuals present with a variety of clinical manifestations. Morbus Morbihan is a rare complication of rosacea characterized by chronic erythematous edema of the face, exclusively in the forehead and periorbital region which mimics angioedema [19, 20]. There is no specific laboratory and histopathologic findings to verify diagnosis. The patient has no complaint. Furthermore, other clinical features of rosacea like telangiectases, inflammatory papules and pustules may not be present as well [19]. This disorder could be differentiated from angioedema by refractory, aberrant and solid edema without spontaneous involution [4]. Reported therapies include systemic corticosteroids, tetracyclines, isotretinoin, clofazimine and ketotifen. Excision of redundant edematous tissue is a surgical alternative treatment [21].

3.5. Superior vena cava syndrome

Superior vena cava syndrome (SVCS) is an obstruction or severe reduction in blood flow through the superior vena cava. SVCS has been associated with infections and malignancies but more recently, with the increased use of intravascular devices; as in our case (**Figure 2**), more cases have been associated with pacemaker implantations. Despite the increase in thrombus-related SVCS, malignancies remain the most common cause of SVCS. Facial and neck swelling which mimic angioedema is present in 82% of the patients [22, 23].

However, angioedema symptoms are often episodic, whereas SVCS is characteristically persistent and progressive. The other clue to differentiate SVCS from angioedema is increase of signs when the patient is in a supine position [23]. Diagnosis of SVCS is confirmed by a Doppler ultrasound and CT scan of the chest including thoracic inlet. Prognosis and treatment of SVCS depend on the underlying disease [22, 23].

3.6. Subcutaneous emphysema

Subcutaneous emphysema is a rare disease with the sudden onset of swelling as a result of air entrapment under the skin [24–27]. There are various causes including blunt or

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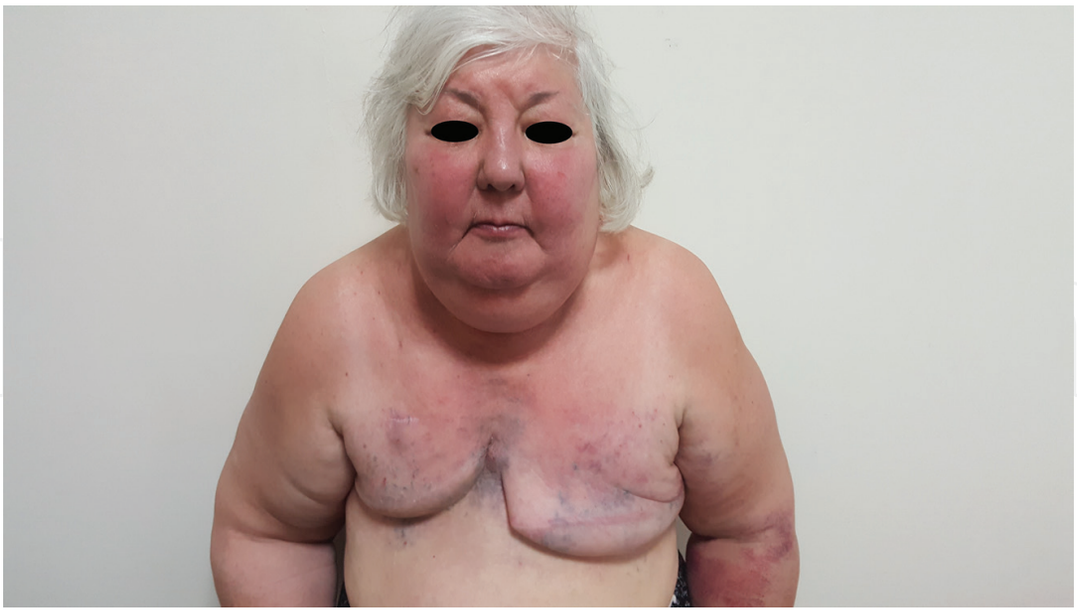

Figure 2. Facial and neck swelling with dilatation of pectoral veins in a patient with superior vena cava syndrome.

penetrating trauma to the chest or neck, following gastrointestinal perforation (corrosive burns of the esophagus, Boerhaave's syndrome, gas gangrene), diving injuries, endoscopy, tracheostomy, cryosurgery, dental surgery or skin biopsy [24]. The majority of the cases which mimic angioedema is reported after a dental surgery [24, 27]. The main clinical clue for differentiation from angioedema is a characteristic crackling sensation created as the gas is pushed through the tissue during palpation which is called crepitus [4, 24, 26]. In doubtful cases, an X-ray or a CT scan could be performed [25]. Severe subcutaneous emphysema can cause compression of the upper airway and jugular venous compression, which can lead to airway and cardiovascular compromise. Trauma-related causes may require emergent surgical intervention [27].

3.7. Hypothyroidism

Low levels of thyroid hormones cause symptoms including weight gain, constipation, dry skin, thinning of hair, hoarse voice, fatigue, lethargy, depression and cold intolerance. Eyelid swelling associated with hypothyroidism is uncommon and can occasionally mimic angioedema [28, 29]. Eyelid swelling is a clinical sign of severe acute hypothyroidism. Other more common dermatologic manifestations of hypothyroidism are thin, dry, rough, hyperkeratotic skin and rough, brittle hair [28]. In the case of sudden-onset, permanent, asymptomatic and bilateral soft swelling, hypothyroidism should be suspected. Diagnosis is confirmed with low levels of thyroid hormones, and treatment is hormone replacement [4, 28, 29].

3.8. Orofacial granulomatosis

Orofacial granulomatosis is a rare disease which presents as a swelling of the oral and maxillofacial region secondary to granulomatous reaction. The most common clinical presentation is

swelling of the lips [30–32]. Melkersson-Rosenthal syndrome is an idiopathic disorder involving persistent and recurrent painless swelling of the face and lips, classically associated with facial palsy and a fissured tongue. Cases of Melkersson-Rosenthal syndrome with only labial involvement is defined as granulomatous cheilitis, which masquerades as angioedema [29, 31, 33]. The etiology is unknown, some authors hypothesized it as a manifestation of sarcoidosis or Crohn's disease. Ano-genital granulomatosis may be regarded as the counterpart of orofacial granulomatosis [34]. It is also a rare chronic inflammatory condition that can present as diffuse penile, scrotal, vulvar or ano-perineal swelling which mimic angioedema [34, 35]. In addition, granulomatous reactions after cosmetic dermal filler injection reports, similar to our case (**Figure 3**), are increasing in the last decades due to the growing cosmetic market [36]. Although some clues like the chronic and persistent nature of edema persist, histopathological examination is obligated for differential diagnosis of orofacial granulomatosis from angioedema and other pseudoangioedematous disorders [30–36].

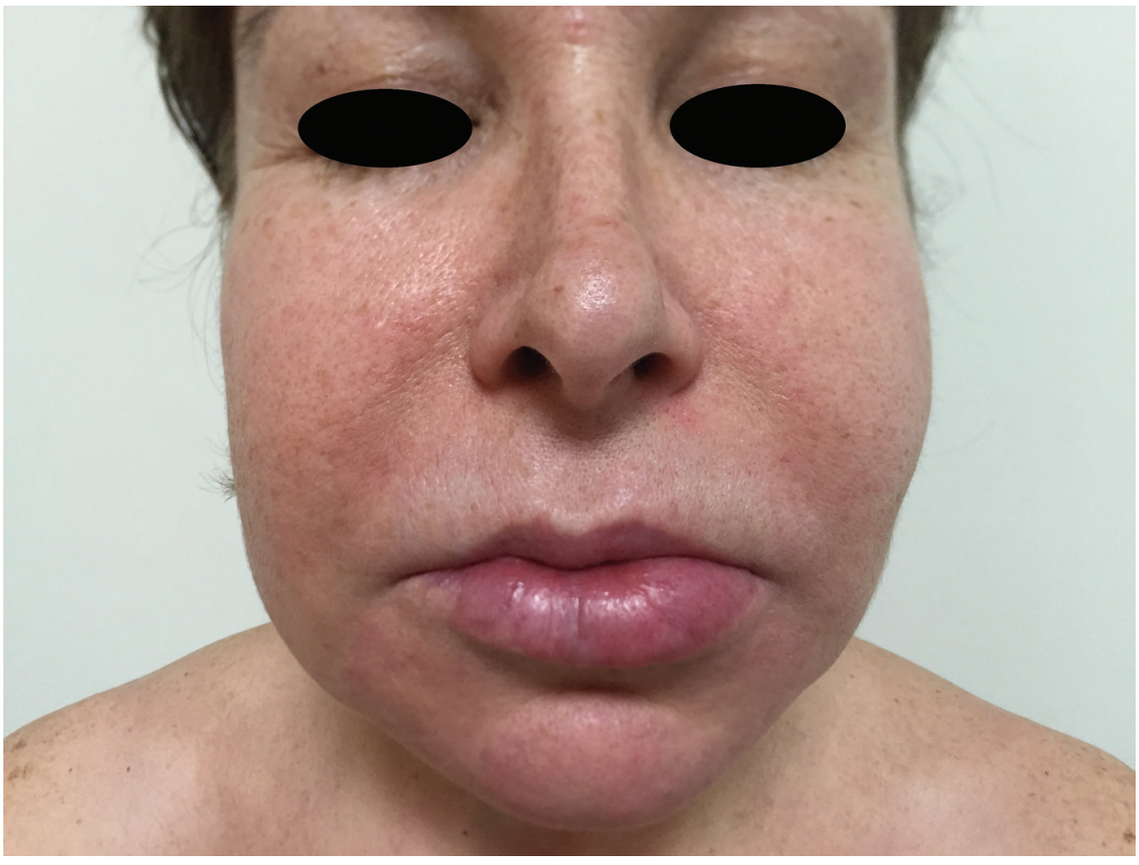

Figure 3. Granulomatous reaction on the lips and mandibular area 7 years after dermal filler injection.

Systemic steroid therapy is widely used for orofacial granulomatosis, Melkersson-Rosenthal syndrome and other granulomatous foreign body reaction such as cosmetic dermal fillers [30–36]. A combination of minocycline, clofazamine, non-steroidal anti-inflammatory drugs and thalidomide is reported as other therapies for Melkersson-Rosenthal syndrome [32, 33]. Surgical excision is another alternative option for Melkersson-Rosenthal syndrome and granulomatous foreign body reaction [32, 36].

3.9. Hypocomplementemic urticarial vasculitis syndrome

Urticarial vasculitis is characterized by recurrent urticarial lesions, angioedema and histologically with necrotizing venulitis. The patients have been categorized into two subgroups: those with hypocomplementemia and those with normal complement levels [37–39]. Hypocomplementemic urticarial vasculitis syndrome is a rare entity associated with urticaria and persistent acquired hypocomplementemia. It was identified as a systemic lupus erythematosus-related syndrome or hypocomplementemic cutaneous vasculitis [37]. Angioedema occurs in up to 50% of patients, frequently involving the lips, tongue, periorbital tissue and hands and can be the first sign of this syndrome. Characteristic cutaneous lesions of hypocomplementemic urticarial vasculitis syndrome are painful and usually resolve with postinflammatory hyperpigmentation. There are also systemic findings such as renal, pulmonary, gastrointestinal, neurologic, rheumatologic and ophthalmic. Treatment is determined by severity and systemic involvement of the disease, including systemic corticosteroids and immunosuppressants [37–39].

3.10. Weber-Christian disease

Weber-Christian disease (relapsing febrile panniculitis) is a very rare lobular panniculitis subtype associated with painful subcutaneous nodules, which are mainly present in the extremities and trunk, and systemic symptoms include fever, malaise, polyarthralgia and so on. [40]. Typically, lesions are distributed symmetrically on the legs and thighs. Furthermore, periorbital lesions which mimic angioedema can be detected in Weber-Christian disease, as well. Diagnosis is based on histological and clinical findings. Treatment of Weber-Christian disease includes systemic corticosteroid, non-steroidal anti-inflammatory drugs, anti-malarial drugs and immunosuppressive drugs in resistant cases [2, 40].

3.11. Infections

Infections localized in the tongue, lips and periorbital area cause swelling and masquerade as angioedema. Such infections persist until treated and thus must be differentiated from acute angioedema [2, 29]. It is important to consider infection as well as angioedema when confronted with lower lip swelling in the emergency department [41, 42]. Few cases of methicillin-resistant *Staphylococcus aureus*-related facial or lip infections mimicking angioedema are present in the literature [42]. Tongue abscess is also a very rare entity, causes enlargement of the tongue, and can be easily misdiagnosed as angioedema. Medical history of injury by foreign body, trauma or piercing of the tongue is helpful for differentiation from angioedema [42, 43].

Parasitic infections may be the reason for pseudoangioedema. Trichinosis and tropical filariasis can present as periorbital edema and be easily misdiagnosed as angioedema as well. Romana's sign is unilateral periorbital swelling detected in Chagas disease (also known as American trypanosomiasis) and mimics angioedema [2, 29].

3.12. Lymphoproliferative disorders

Lymphoproliferative diseases, B-cell lymphomas and monoclonal gammopathy of undetermined significance cause acquired angioedema secondary to C1 inhibitor deficiency.

Previously, a few rare cases of peripheral T-cell lymphoma presenting periorbital, upper and lower lip edema, initially mistaken for angioedema, are reported [44–46]. The clinical findings to differentiate from angioedema are progression and no resolution of these lesions. The final diagnosis is based on histopathologic examination [2, 45, 46].

3.13. Mucinosis and other infiltrating disorders

The most common pseudoangioedematous endocrinopathy is autoimmune thyroid disorder [1, 2]. Thyroid orbitopathy is a gradual swelling of the periorbital tissue related to severe hypothyroidism or Grave's disease. Both facial myxedema due to hypothyroidism and pretibial myxedema due to Grave's disease are caused by mucin deposition in the dermis [47, 48].

Scleromyxedema (papular mucinosis) is dermal mucin deposition without thyroid disease. It is frequently detected with paraproteinemia [1, 2, 49, 50]. The clinical features consist of forehead swelling and deep longitudinal furrows cause a lion-like face [49, 50].

The amyloidosis is a group of diseases, which is a result of extracellular deposition of amyloid fibrils. Pathognomonic clinical features of systemic amyloidosis include a combination of macroglossia and periorbital purpura [51]. Macroglossia could masquerade as angioedema which affects the tongue. Other systemic involvements (cardiac, renal and neurologic, etc.) and aberrant persistent edema are helpful to differentiate this clinical entity from angioedema. Diagnosis is confirmed by Congo red staining of amyloid fibrils in the histopathologic examination [2, 51].

3.14. Clarkson's disease (idiopathic systemic capillary leak syndrome)

Idiopathic systemic capillary leak syndrome, called Clarkson's disease, is a rare life-threatening disease manifested by recurrent episodes of sudden hypovolemic shock and massive edema due to the capillary leakage of plasma from the intravascular to the extravascular compartments. Approximately 79–82% of these patients have monoclonal gammopathy of unknown significance [1, 52, 53]. Angioedema should be considered upon the initial presentation of Clarkson's disease. Generalized symmetrical cutaneous swelling and a characteristic triad of hypotension, hemoconcentration and hypoalbuminemia in the absence of secondary causes of shock are helpful clinical features to differentiate from angioedema [1, 4]. Systemic corticosteroids and intravenous immunoglobulin are used in the treatment of this condition [52, 53].

3.15. Gleich's syndrome (episodic angioedema with eosinophilia)

Gleich's syndrome is a rare disorder characterized by episodes of angioedema, eosinophilia and resolves spontaneously without therapy. The etiology is unknown and typical clinical features are angioedema, fever, eosinophilia, elevated serum IgM, increased body weight and benign course without internal organ involvement [1, 4, 54]. The presence of specific laboratory features, together with the other characteristic clinical manifestations, should differentiate this entity from classical angioedema [4]. Systemic corticosteroids and imatinib have been reported beneficial for its treatment [1, 4].

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3.16. Idiopathic edema

Idiopathic edema is the persistent self-limited fluid retention in the gravitationally dependent areas, especially on the lower limbs. There is a female predominance and it is prominent in premenstrual periods, which is why the condition is also known as 'cyclical edema' [4, 55]. After a prolonged supine position, the facial and periorbital region may be included as well. It can be differentiated with symmetrical involvement and pitting edema from angioedema. Diagnosis is confirmed by exclusion of cardiac, hepatic, renal or thyroid disease, all well-known causes of edema [4].

3.17. Cluster headache

Cluster headache is a primary headache disorder typically characterized by severe recurrent attacks of unilateral pain with conjunctival injection, nasal congestion or rhinorrhea, ptosis or miosis and periorbital edema. Unilateral edema of the eyelid or the face is reported in 74% of the patients [4, 56]. Pain is intense and unresponsive to antihistamines and topical steroids. The characteristic headache with other clinical signs is helpful in the differential diagnosis of cluster headaches and angioedema [4].

4. Summary

Angioedema manifests with asymmetric, non-pitting and transient edema, which has predilection areas including the lips, tongue and periorbital region. Diagnosis and treatment of angioedema are crucial because it represents one of the most common airway emergencies. As a result, knowledge of typical clinical features and differential diagnosis for healthcare professionals are obligations. It is important to remember that not all swellings are angioedema in the clinical practice. Pseudoangioedematous disorders should be considered in patients presenting with long-lasting and resistant swellings. The most frequent diseases that mimic angioedema are acute contact dermatitis, DRESS syndrome, hypothyroidism, orofacial granulomatosis, idiopathic edema, vasculitis and panniculitis. These conditions do not respond to angioedema treatment and may cause serious life-threatening results. It is possible to recognize pseudoangioedema by detailed medical history and physical examination, but skin biopsy is required for resistant cases.

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