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Angioedema Masqueraders

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Abstract

Angioedema is a common reason for referral to immunology and allergy specialists. Not all cases are in fact angioedema. There are many conditions that may mimic its appearance, resulting in misdiagnosis. This may happen when a clinician is unfamiliar with conditions resembling angioedema or, when there is a low index of clinical suspicion. In this article, we explore a list of differential diagnoses based on body parts, including the lips, the limbs, periorbital tissues, the face, epiglottis and uvula, as well as the genitalia, that may pose as a masquerader even to an experienced eye.

Introduction

Angioedema is a common reason for referral to immunology and allergy teams. However not all patients presenting with swelling of a particular body part have angioedema.

It is estimated that every year in the United States there are more than 100,000 emergency room visits for angioedema.¹ Admissions to hospital for isolated angioedema were reportedly found to be relatively common in an Australian study, consistent with overseas research.² There is currently no available data on prevalence of diseases mimicking angioedema presenting for medical advice.

There are many conditions characterised by swelling that may masquerade as angioedema. The term *pseudoangioedema* has been used for these conditions. Delayed diagnosis of the correct condition or misdiagnosis of those presenting with swellings are well reported in the literature.^{3,4}

Angioedema is characterised by localised non-pitting oedema involving the subcutaneous, submucosal or deep dermal tissues due to increased vascular permeability and extravasation of intravascular fluid.⁵ The underlying pathomechanism of angioedema may be broadly categorised into either being histamine (mast cell-mediated) or bradykinin-mediated. Each pathomechanistic pathway has unique aetiology, immunopathological patterns and response to treatment.

Histamine- or mast cell-mediated angioedema may occur following exposure to an allergen which triggers the release of vasoactive mediators such as histamine via an immunoglobulin E (IgE)-mediated reaction, resulting in increased vascular permeability. Common allergens include food, medications and insect stings, and may represent a spectrum of anaphylaxis. Or, it may also occur in the form of a non-IgE mediated process, such as being a concomitant manifestation of chronic spontaneous urticaria that is usually treated with regular antihistamines. There are other, non-IgE-mediated forms of direct mast cell activation and histamine release, usually caused by drugs, that may result in angioedema. On the other hand, the entity of bradykinin-mediated angioedema includes Hereditary Angioedema (HAE), Acquired Angioedema caused by C1 esterase inhibitor (INH) deficiency and angiotensin-converting enzyme (ACE) inhibitor-induced angioedema.^{6,7}

Of note, novel genetic mutations causing HAE with normal C1-INH have been identified in recent years, shedding new light on the pathogenesis of these rare forms of HAE.^{8,9} Detailed description of pathogenesis of different subtypes of angioedema is beyond the scope of this article and key points are highlighted in Table 1.

Careful clinical evaluation, including detailed history taking, is important in excluding angioedema as the cause of a localised swelling as many symptoms may overlap. Establishing an accurate diagnosis may be challenging but is essential in management planning.

This review article aims to explore conditions mimicking angioedema that may be encountered in immunology, allergy, dermatology or general medical practice, hopefully raising awareness amongst

clinicians to consider differential diagnoses when standard treatments for angioedema fail to achieve desirable clinical outcomes.

For the purpose of this review article, we seek to discuss angioedema masqueraders based on organs or body parts involved. Characteristics of masqueraders are summarised in Table 2.

Lips

The lips and the eyes (periorbital region) are the most common sites where angioedema may occur.¹⁰

In authors' opinion, the most important condition that manifests with lip swelling other than angioedema is cheilitis granulomatosa (CG) or Miescher's cheilitis.

CG is a condition characterised by intermittent and painless lip swelling in the initial stage, followed by eventual, persistent swelling which may be cosmetically disfiguring when the disease progresses over time.¹¹ In many cases the upper lip seems to be the first site of involvement, followed by the lower lip.¹² (Figures 1 and 2) In authors' experience, an ACE inhibitor may be mistaken as the culprit of the lip swelling in some cases.

CG is regarded as part of the spectrum of orofacial granulomatosis, characterised by non-caseating granulomatous inflammation in the absence of a systemic inflammatory disease.^{13,14} It is therefore important to exclude underlying sarcoidosis, Crohn's disease or granulomatous polyangiitis (previously known as Wegener's granulomatosis). Oral ulceration and functional disability may occur, especially when both lips are involved. This uncommon condition mostly affects young adults without sex predilection. The exact cause remains poorly understood. Some studies speculated that food additives such as benzoate and cinnamon may be responsible given oral and lip inflammation appeared to be reduced following a benzoate- and cinnamon-free diet.^{15,16} A lip biopsy is necessary to establish the presence of non-caseating granulomas which may contain Langerhans giant cells.

CG is generally regarded as a monosymptomatic (or oligosymptomatic) form of Melkersson-Rosenthal syndrome (MRS).

MRS refers to a triad of orofacial oedema, facial palsy and fissured tongue (lingua plicata), with orofacial swelling being the most consistent and dominant feature.¹⁷ (Figures 3 and 4) This is a rare neuro-mucocutaneous granulomatous disease originally described by *Ernst Melkersson* in 1928.¹⁸

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Lingua plicata as an additional feature was added by *Curt Rosenthal* in 1931, following his description of three patients who had fissured or plicated tongue.¹⁹ Similar to CG, MRS has a recurrent and progressive course. Each recurring episode is more pronounced and lasts longer. The estimated incidence is 0.08%.²⁰ It may affect any age group, including children and preadolescents. *Rivera-Serrano CM et al* performed a retrospective review of patients diagnosed with MRS at a university-based facial nerve centre, analysing demographic and clinical features of 21 patients identified over 40 years. It was found that 14 patients who initially presented with unilateral paralysis subsequently developed metachronous contralateral paralysis, with the mean age of presentation being 44.1. Facial pain was the most commonly reported associated symptom, amongst taste changes, headache, migraine, dizziness and tinnitus. Of the 21 patients, 16 had a fissured tongue and 18 had facial swelling. It is worthwhile to note that patients with MRS may present to different specialties complaining of different symptoms, and not all the classic features of the triad will be present in all individuals.²¹

Treatment of CG is challenging. Various medical regimes have been explored with variable therapeutic outcomes. Importantly there has been no predictably successful model, and no single therapy has emerged as a leading intervention.²² Corticosteroids in topical and intralesional form have been tried and are often employed as first-line option in most cases. Intralesional triamcinolone injections have been found to demonstrate long-term effectiveness in controlling disfiguring lip swelling in a retrospective study of 22 patients with orofacial granulomatosis.²³ Other systemic medications either used as a single agent or in combination that have been found successful in individual case reports include antibiotics (minocycline, roxithromycin and metronidazole), methotrexate, clofazimine, lenalidomide, thalidomide and infliximab.²⁴⁻²⁹ Reduction cheiloplasty with excision of excess tissue may be considered to manage severe macrocheilia and to improve lip aesthetics when various conservative treatment options fail.³⁰

Limbs

Limb swelling may be seen in cellulitis, lymphoedema, thrombosis, and episodic angioedema with eosinophilia (EAE).

A diagnosis of cellulitis is usually easily established based on cardinal clinical features, including pain, redness and swelling, all of which are hallmarks of inflammation. In certain scenarios, especially in the background of specific risk factors, it is not uncommon to exclude underlying thromboembolic phenomenon as the cause for unilateral limb swelling, such as deep vein thrombosis of the lower limb. The gold standard investigation is ultrasound Doppler of the affected limb.

Lymphoedema (Figure 5) is caused by excessive lymphatic fluid retention in the interstitial compartment with underlying lymphatic drainage impairment. Primary lymphoedema is a recognised developmental anomaly seen in Turner syndrome.^{31,32} Secondary lymphoedema is acquired and may be related to surgery or a systemic disease. Diagnosis is often clinical. Lymphoscintigraphy has a role in assessing underlying lymphatic function of the affected limb.

EAE is a rare disorder characterised by cyclic episodes of fever, angioedema and urticaria. It was first reported by *Gleich GJ et al* in 1984, following the study of two children and two adults.³³ Weight gain (of up to 18 per cent) and dramatic eosinophilia during attacks are characteristic, which may resolve with diuresis with or without glucocorticosteroids. Though many clinicians regard this condition a variant of hypereosinophilia syndrome (HES), it presents a unique entity given its largely benign course. Production of interleukin-5 (IL-5) is believed to be a crucial determinant in the pathophysiology of the disease. Elevation of serum IL-5 for several days leading to peak eosinophilia and increased number of activated T lymphocytes preceding maximal eosinophilia had been demonstrated in early studies.^{33,34} Deposition of eosinophils with degranulation in angioedematous skin is a characteristic histological finding. Recent study confirmed an increase in aberrant CD3⁺CD4⁺ T lymphocytes.³⁵ Unlike other variants of HES, end organ involvement such as cardiac manifestations were thought to be unlikely until recent years. Development of eosinophilic endomyocardial disease with severe mitral insufficiency was recently described 16 years after initial presentation in one of the initially described subjects. This highlights the need for ongoing surveillance for cardiac disease in all patients with HES irrespective of clinical categorisation.³⁶

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Another variant with similar presentation was described in 33 Japanese subjects in 1998, known as non-episodic angioedema with eosinophilia (NEAE).³⁷ This subset of subjects was thought to have evolution of disease pattern different from classical Gleich's syndrome, including predominant involvement of young females, absence of recurrent attacks, localisation of the angioedema to the extremities and absence of an increase in serum IgM level. This unique variant of disease is reported predominantly in Japanese and Korean females. *Cho HJ et al* pioneered a study evaluating the clinical characteristics of angioedema with eosinophilia in a Korean population, including age, sex, eosinophil cationic protein, total immunoglobulin E, immunoglobulin M, C-reactive protein and erythrocyte sedimentation rate. Majority of the study subjects were female with the non-episodic type.³⁸ Small case series of NEAE with polyarthralgia have also been reported.^{39,40}

Well's syndrome, also known as eosinophilic cellulitis, may present with a swollen limb and a myriad of cutaneous lesions including plaques, papules, nodules and bullae, resembling bacterial cellulitis. Misdiagnosis may lead to inappropriate use of antibiotics. Skin biopsy is essential. Eosinophilia may be present. Corticosteroids are the treatment of choice for this eosinophil-driven disease.⁴¹

Periorbital tissues

Diseases involving dermal oedema of the eyelids include orbital cellulitis, thyroid eye disease, blepharitis, connective tissue diseases, lymphoproliferative diseases and immunoglobulin 4-related disease (IgG4-RD). Involvement may be unilateral or bilateral.

Orbital cellulitis is an inflammatory process involving the tissues posterior to the orbital septum within the bony orbit that typically originates from a sinus infection or an eyelid infection.⁴² Eyelid oedema, erythema and pain are the main manifestations, along with proptosis, fever and headache. Loss of vision is a complication.⁴³ Computed tomography (CT) imaging is required to establish the diagnosis.

Autoimmune hyperthyroidism such as Graves' disease may present with an array of ophthalmological features including chemosis (swelling of the conjunctiva), proptosis and exophthalmos. These orbital changes result from de novo adipogenesis, hyaluronan synthesis, interstitial oedema and extraocular muscle enlargement.⁴⁴ During the course of Graves' disease, glycosaminoglycan deposition and

fibrosis affecting the extraocular muscles and fat accumulation ultimately lead to exophthalmos.^{45,46}

Most often than not presenting patients may be clinically and biochemically hyperthyroid. Clinical features of thyrotoxicosis include atrial fibrillation (palpitations), sweatiness, diplopia, heat intolerance, increased bowel movements, increased deep tendon reflexes, clubbing (thyroid acropachy) and weight loss with increased appetite due to increased body metabolism.

On the contrary, autoimmune hypothyroidism such as Hashimoto's disease may present with marked periorbital swelling resembling angioedema of the eyes. This condition is characterised by weight gain, cold intolerance, constipation, lethargy, carotenemia, delayed deep tendon reflexes, hoarse and croaky voice, loss of lateral third eyebrows and mental obtundation. In severe cases, myxedema coma may ensue.

Diagnosis of thyroid disease is usually based on clinical recognition of features, supported essentially by biochemical findings such as thyroid-stimulating hormone (TSH) level, free thyroxine 4 level and presence of anti-thyroid antibodies such as anti-thyroid peroxidase, anti-TSH receptor and anti-thyroglobulin antibodies.^{47,48} A radioiodine uptake scan is useful. Depending on underlying thyroid activity, treatment options include suppressing a hyperthyroid state and correcting a hypothyroid condition.

Blepharitis is inflammation of the eyelids. It may cause loss of eye lashes.⁴⁹ Most cases are due to bacterial infections such as *Staphylococcus sp*, but ectoparasites which include head lice (*Demodex folliculorum* and *Demodex brevis*) can be responsible. The swelling associated with this may mimic angioedema of the eye lid.⁵⁰

Dermatomyositis and Sjögren's syndrome may present with periorbital swelling. In dermatomyositis, there are often other accompanying tell-tale cutaneous features that may help make a clinical diagnosis, including Gottron's papules (erythematous papules on the dorsum of the metacarpophalangeal and interphalangeal joints), photosensitivity (shawl sign of the neck) and heliotrope rash (a violaceous hue of the periorbital area). Periorbital swelling, mistaken as angioedema due to an allergic cause, may be unilateral in some cases.⁵¹ Other systemic features include muscle weakness due to myopathy, dysphagia due to oesophageal muscle involvement and exertional dyspnoea if pulmonary fibrosis complicates. Dermatomyositis may also be a paraneoplastic

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phenomenon and is associated with underlying breast, pulmonary, ovarian, nasopharyngeal, pancreatic, gastric, genitourinary and colorectal neoplasms.^{52,53}

Sjögren's syndrome is a systemic inflammatory disorder characterised by positive anti-SSA and anti-SSB antibodies. It typically occurs in the 4th to 6th decade of life, with a female predominance. The overall incidence of Sjögren's syndrome was estimated at approximately 7 per 100,000 people in a meta-analysis.⁵⁴ Xerophthalmia and xerostomia (sicca syndrome) are the main presenting features. Nontender enlargement of the lacrimal glands manifesting as swelling of the eyelids related to lymphocytic inflammation may also occur.⁵⁵ Concomittant parotid gland swelling caused by lymphocytic infiltration may be mistaken as facial angioedema.

Lymphoma of the eyelids may present with eyelid swelling.^{56,57} Lymphoma of the eyelids constitutes 5% of ocular adnexal lymphoma, with a slight predominance of B-cell origin.⁵⁸ Extranodal marginal zone lymphoma and diffuse large B-cell lymphoma are the most frequently encountered type, with majority of cases in elderly patients. T-cell lymphomas such as mycosis fungoides, extranodal natural killer cell and primary cutaneous anaplastic large-cell lymphoma are also well reported. Immunophenotyping and tissue biopsy are helpful investigations.

IgG4-RD is a unique systemic disease that is increasingly recognised. It is characterised by tumour-like swelling of the affected organs, histologically hallmarked by lymphoplasmacytic infiltrate enriched in IgG4-positive plasma cells and storiform fibrosis,^{59,60} and biochemically characterised by high serum immunoglobulin G4 (IgG4) levels. Major presentations that have been described include salivary gland disease presenting as salivary gland swelling, orbital pseudotumour or lacrimal gland disease presenting as eyelid swelling, autoimmune pancreatitis, retroperitoneal fibrosis, aortitis, sclerosing cholangitis and thyroiditis.⁶¹⁻⁷⁰ In the collective experience of *Takahira M et al*, IgG4-RD appears to account for approximately 25% of cases where patients present with eyelid swelling and proptosis.⁷¹ IgG4-related ophthalmic disease (IgG4-ROD) is characterised by bilateral lacrimal gland enlargement hallmarked by infraorbital nerve enlargement, extraocular myositis and compressive optic neuropathy.⁷² IgG4-RD being a systemic disease, may affect more than one organ.⁷³⁻⁷⁵ Hence further evaluation should be carried out to detect other systemic involvement. Complications include major organ damage leading to organ failure and lymphoma. As high as 40% of patients with IgG4-

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RD have allergic diseases including sinusitis, bronchial asthma, eczema and eosinophilia.⁷⁶ Tissue biopsy is recommended to confirm the diagnosis. Serum IgG4 level is a useful biochemical parameter. Circulating plasmablasts have been found to be elevated in active IgG4-RD.⁷⁷ Though potentially useful in diagnosis and disease activity monitoring, this test is not widely available. Isolated eyelid oedema as the first presentation of MRS has also been described. It highlights the importance of recognising atypical presentation of a rare disease.⁷⁸

Face

Contact dermatitis (Figure 6) may be misdiagnosed as facial angioedema in the setting of facial swelling. From authors' experience, these patients commonly present following application of a cosmetic product or following domestic or occupational exposure to hair dye. Dendritic epidermal T cells, natural killer cells, mast cells and neutrophils all play an important role in the pathogenesis of contact hypersensitivity.⁷⁹ Two distinct forms of contact dermatitis are recognised, i.e. irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD). ICD leads to a rapid response, typically within minutes or hours after exposure to the irritant, and is usually confined to the area of contact with the irritant. ACD may induce widespread to systemic hypersensitivity reactions, which often result from cross-reactivity of topically applied substances with implant materials.⁸⁰ A history of occupational contact dermatitis has been reported in up to 50% of hairdressers. Offending agents seen in hairdressers include ammonium persulfate, p-phenylenediamine, toluene-2,5-diamine, glycerol monothioglucolate and 2-nitro-4-phenylenediamine and they are well-reported in the literature, including in Australia.^{81,82} The most striking feature distinguishing contact dermatitis from angioedema is a history of exposure to a culprit agent and failure to respond to regular antihistamines. Initial clinical differentiation may be challenging as both may present with severe swelling, redness and pruritus. Patch testing is required to confirm underlying hypersensitivity.

Superior vena cava (SVC) syndrome results from obstruction of blood flow through the SVC, which may be caused by thrombosis within the SVC, or from external compression or invasion of the vessel from structural pathology within the mediastinum, including lymph nodes, the ascending aorta and the right lung.⁸³ By far intrathoracic neoplasms account for most cases of SVC syndrome. Diffuse

engorgement of the face and neck due to SVC obstruction may mimic angioedema. Certain tell-tale signs of SVC syndrome not present in angioedema include engorged blood vessels on the upper chest, dilated vessels underneath the tongue and oedema of the upper arm. The Pemberton's sign may be positive. CT thorax is essential in further evaluation.

Epiglottitis and uvula

Epiglottitis is a significant pathology seen in the Emergency Department and it carries a mortality risk.⁸⁴ It may be infectious in nature, caused by a variety of organisms, including *Haemophilus influenzae* type B and *Streptococcus pneumoniae*. It may also be caused by mechanical injury or inhalation of hot objects.⁸⁵ It may be misdiagnosed as angioedema given presence of particular symptoms and signs. Patients with epiglottitis may present with dysphagia, and if severe enough, drooling and stridor. Clinical examination may reveal diffuse aryepiglottic swelling. The uvula may appear swollen. Main differentiating characteristics from angioedema include presence of fever and exudates. Soft-tissue radiography of the neck and indirect laryngoscopy may be useful,⁸⁶ as well as biochemical makers supporting underlying infective or inflammatory process.

Genitalia

Scrotal swelling may be acute and painful, or chronic and painless. Whilst scrotal (and penile) swelling may be caused by gravity-dependent oedema, such as in the context of cardiac failure, there are other important causes that must be excluded. Of all, acute, painful scrotal swelling caused by torsion is a urologic emergency and should not be missed as early intervention may salvage the affected testes. From authors' experience, this is an important differential diagnosis to consider in juvenile males with known personal history or family history of hereditary angioedema as scrotal swelling may be attributed to an acute attack of angioedema.

Lymphatic filariasis caused by filarial nematodes *Wuchereria bancrofti*, *Brugia malayi* and *Brugia timori* may present with acute, recurrent adenolymphangitis manifesting with constitutional symptoms, as well as transient oedema and erythema of the scrotum when scrotal lymphatics are affected. Chronic infection may result in hydrocele, mimicking the appearance of angioedema. Whilst this

disease is endemic in tropical or subtropical regions, globalisation, convenience of travel and migration are important reasons why it is now seen in a non-endemic country, including Australia.⁸⁷

Conclusion

Not every swelling is angioedema. Careful evaluation including specific history taking, physical examination and investigations are essential to ascertain the cause of the presentation that mimics angioedema. When the stereotypical features of angioedema are absent or standard angioedema treatment fails, the clinician should consider alternative diagnoses.

This review article has highlighted common and rare conditions resembling angioedema according to the site of involvement, including useful clues in disease pattern recognition. Once a correct diagnosis has been established, appropriate management plans may be proposed for early treatment to reduce disease morbidity and in some cases, mortality.

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References

1. Kelly M, Donnelly JP, McAnnally JR, Wang HE. National estimates of emergency department visits for angioedema and allergic reactions in the United States. *Allergy Asthma Proc* 2013;34(2):150-154.
2. Mullins RJ, Wainstein BK, Barnes EH, Campbell DE. Angioedema in Australia: hospital admission rates and fatalities. *Med J Aust* 2018;208(7):308.
3. Makatsori M, Manson AL, Gurugamai P, Wakelin S, Seneviratne SL. Penile granulomatosis presenting as pseudoangioedema. *Eur Ann Allergy Clin Immunol* 2013;45(3):111-112.
4. Kakimoto C, Sparks C, White AA. Melkersson-Rosenthal syndrome: a form of pseudoangioedema. *Ann Allergy Asthma Immunol* 2007;99(2):185-189.

5. Cicardi M, Zanichelli A. Diagnosing angioedema. *Immunol Allergy Clin North Am* 2013;33:449-456.
6. Lang DM, Aberer W, Bernstein JA, Chng HH, Grumach AS, Hide M et al. International consensus on hereditary and acquired angioedema. *Ann Allergy Asthma Immunol* 2012;109:395-402.
7. Fok JS, Katelaris CH, Brown AF, Smith WB. Icatibant in angiotensin-converting enzyme (ACE) inhibitor-associated angioedema. *Intern Med J* 2015;45(8):821-827.
8. Gill P, Betschel SD. The clinical evaluation of angioedema. *Immunol Allergy Clin North Am* 2017;37(3):449-466.
9. Cicardi M, Zuraw BL. Angioedema due to bradykinin dysregulation. *J Allergy Clin Immunol Pract* 2018;6(4):1132-1141.
10. Kaplan AP. Angioedema. *World Allergy Organ J* 2008;1(6):103-113.
11. Critchlow WA, Chang D. Cheilitis granulomatosa. *Head Neck Pathol* 2014;8(2):209-213.
12. Worsaae N, Christensen KC, Schiødt M, Reibel J. Melkersson-Rosenthal syndrome and cheilitis granulomatosa. A clinicopathological study of thirty-three patients with special reference to their oral lesions. *Oral Surg Oral Med Oral Pathol* 1982;54(4):404-413.
13. Grave B, McCullough M, Wiesenfeld D. Orofacial granulomatosis – a 20-year review. *Oral Dis* 2009;15(1):46-51.
14. Al Johani KA, Moles DR, Hodgson TA, Porter SR, Fedeles S. Orofacial granulomatosis: clinical features and long-term outcome of therapy. *J Am Acad Dermatol* 2010;62(4):611-620.
15. Campbell HE, Escudier MP, Challacombe SJ, Sanderson JD, Lomer MC. Review article: cinnamon- and benzoate-free diet as a primary treatment for orofacial granulomatosis. *Aliment Pharmacol Ther* 2011;34(7):687-701.
16. White A, Nunes C, Escudier M, Lomer MC, Barnard K, Shirlaw P et al. *Inflamm Bowel Dis* 2006;12(6):508-514.
17. Zimmer WM, Rogers RS 3rd, Reeve CM, Sheridan PJ. Orofacial manifestations of Melkersson-Rosenthal syndrome. A study of 42 patients and review of 220 cases from the literature. *Oral Surg Oral Med Oral Pathol* 1992;74(5):610-619.
18. Melkersson E. Ett fall av recidiverande facialispares i samband med ett angioneurotiskt ødem.

Stockholm: Hygiea. 1928;90:737-741.

19. Rosenthal C. Klinisch-erbbiologischer Beitrag zur Konstitutionspathologie. Gemeinsames Auftreten von Facialislähmung, angioneurotischem Gesichtsoedem und Lingua plicata in Arthritismus-Familien. *Zeitschrift für die Gesamte Neurol Psychiatr* 1931;131:475-501.
20. Hornstein OP. Melkersson-Rosenthal syndrome. A neuro-cutaneous disease of complex origin. *Curr Probl Dermatol* 1973;5:117-56.
21. Rivera-Serrano CM, Man LX, Klein S, Schaitkin BM. Melkersson-Rosenthal syndrome: a facial nerve centre perspective. *J Plastic Reconstr Aesthet Surg* 2014;67(8):1050-1054.
22. Banks T, Gada S. A comprehensive review of current treatments for granulomatous cheilitis. *Br J Dermatol* 2012;166(5):934-93.
23. Fedele S, Fung PP, Bamashmous N, Petrie A, Porter S. Long-term effectiveness of intralesional triamcinolone acetonide therapy in orofacial granulomatosis: an observational cohort study. *Br J Dermatol* 2014;170(4):794-801.
24. Coskun B, Sarai Y, Cicek D, Akpolat N. Treatment and follow-up of persistent granulomatous cheilitis with intralesional steroid and metronidazole. *J Dermatolog Treat* 2004;15(5):333-335.
25. Veller Fornasa C, Catalano P, Peserico A. Minocycline in granulomatous cheilitis: experience with 6 cases. *Dermatology* 1992;185(3):220.
26. Inui S, Itami S, Katayama I. Granulomatous cheilitis successfully treated with roxithromycin. *J Dermatol* 2008;35(4):244-245.
27. Fdez-Freire LR, Serrano Gotarredona A, Bernabeu Wittel J, Pulpillo Ruiz A, Cabrera R, Navarrete Ortega M et al. Clofazimine as elective treatment for granulomatous cheilitis. *J Drugs Dermatol* 2005;4(3):374-377.
28. Medeiros M Jr, Araujo MI, Guimarães NS, Freitas LA, Silva TM, Carvalho EM. Therapeutic response to thalidomide in Melkersson-Rosenthal syndrome: a case report. *Ann Allergy Asthma Immunol* 2002;88(4):421-424.
29. Solimani F, Eming R, Juratli HA, Scarsella L, Gschenell M, Pfützner W. Successful treatment of cheilitis granulomatosa with lenolidomide. *J Eur Acad Dermatol Venereol* 2019 May 7. doi:10.1111/jdv.15654.

30. Kruse-Lösler B, Presser D, Metze D, Joos U. Surgical treatment of persistent macrocheilia in patients with Melkersson-Rosenthal syndrome and cheilitis granulomatosa. *Arch Dermatol* 2005;141(9):1085-1091.
31. Atton G, Gordon K, Brice G, Keeley V, Riches K, Ostergaard P *et al*. The lymphatic phenotype in Turner syndrome: an evaluation of nineteen patients and literature review. *Eur J Hum Genet* 2015;23(12):1634-1639.
32. Rothbauer J, Driver S, Callender L. Describing lymphedema in females with Turner syndrome. *Lymphology* 2015;48(3):139-152.
33. Gleich GJ, Schroeter AL, Marcoux JP, Sachs MI, O'Connell EJ, Kohler PF. Episodic angioedema associated with eosinophilia. *N Engl J Med* 1984;310(25):1621-1626.
34. Butterfield JH, Leiferman KM, Abrams J, Silver JE, Bower J, Gonchoroff N, Gleich GJ. Elevated serum levels of interleukin-5 in patients with the syndrome of episodic angioedema and eosinophilia. *Blood* 1992;79(3):688-692.
35. Khoury P, Herold J, Alpaugh A, Dinerman E, Holland-Thomas N, Stoddard J *et al*. Episodic angioedema with eosinophilia (Gleich syndrome) is a multilineage cell cycling disorder. *Haematologica* 2015;100(3):300-307.
36. Wright BL, Butterfield JH, Leiferman KM, Gleich GJ. Development of eosinophilic endomyocardial disease in a patient with episodic angioedema and eosinophilia. *J Allergy Clin Immunol Pract* 2016;4(2):336-337.
37. Chikama R, Hosokawa M, Miyazawa T, Miura R, Suzuki T, Tagami H. Nonepisodic angioedema associated with eosinophilia: report of 4 cases and review of 33 young females reported in Japan. *Dermatology* 1998;197(4):321-325.
38. Cho HJ, Yoo HS, Kim MA, Shin YS, Ye YM, Nahm DH *et al*. Clinical characteristics of angioedema with eosinophilia. *Allergy Asthma Immunol Res* 2014;6(4):362-365.
39. Matsuda M, Fushimi T, Nakamura A, Ikeda S. Nonepisodic angioedema with eosinophilia: a report of two cases and a review of the literature. *Clin Rheumatol* 2006;25(3):422-425.
40. Nagashima T, Matsumoto K, Yamamoto R, Iwamoto M, Minota S. Polyarthrititis induced by nonepisodic angioedema associated with eosinophilia. *Rheumatol Int* 2008;28(10):1065-1066.

41. Sinno H, Lacroix J, Lee J. Diagnosis and management of eosinophilic cellulitis (Well's syndrome): A case series and literature review. *Can J Plast Surg* 2012;20(2):91-97.
42. Tsirouki T, Dastiridou AI, Ibáñez Flores N, Cerpa JC, Moschos MM, Brazitikos P *et al.* Orbital cellulitis. *Surv Ophthalmol* 2018;63(4):534-553.
43. Hamed-Azzam S, Al-Hashash I, Briscoe D, Rose GE, Verity DH. Common orbital infections - state of the art - part 1. *J Ophthalmic Vis Res* 2018;13(2):175-182.
44. Khong JJ, McNab AA, Ebeling PR, Craig JE, Selva D. Pathogenesis of thyroid eye disease: review and update on molecular mechanisms. *Br J Ophthalmol* 2016;100(1):142-150.
45. Bahn RS, Heufelder AE. Pathogenesis of Graves' ophthalmopathy. *N Engl J Med* 1993;329(20):1468-1475.
46. Hatton MP, Rubin PA. The pathophysiology of thyroid-associated ophthalmopathy. *Ophthalmol Clin North Am* 2002;15(1):113-119.
47. Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JI *et al.* Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Endocr Pract* 2012;18(6):988-1028.
48. Fröhlich E, Wahl R. Thyroid autoimmunity: role of anti-thyroid antibodies in thyroid and extra-thyroidal diseases. *Front Immunol* 2017;8:521.
49. Kowalski RP, Dhaliwal DK. Ocular bacterial infections: current and future treatment options. *Expert Rev Anti-Infect Ther* 2005;3(1):131-139.
50. Escudero Pastor AI, Martínez Díaz F, Carbonell Martínez A, Miralles López JC, Martínez Navarro A, Fernánde Calvo E. Palpebral and periorbital edema in an immigrant woman. *J Investig Allergol Clin Immunol* 2013;23(6):439-440.
51. MacFarlane L, Osman N, Ritter S, Miller AL, Loscalzo J. Clinical problem-solving. Eye of the beholder. *N Engl J Med* 2016;374(18):1774-1779.
52. Hill CL, Zhang Y, Sigurgeirsson B, Pukkala E, Mellekjær L, Airio A *et al.* Frequency of specific cancer types in dermatomyositis and polymyositis: a population-based study. *Lancet* 2001;357(9250):96-100.

53. Udkoff J, Cohen PR. Amyopathic dermatomyositis: a concise review of clinical manifestations and associated malignancies. *Am J Clin Dermatol* 2016;17(5):509-518.
54. Qin B, Wang J, Yang Z, Yang M, Ma N, Huang F *et al*. Epidemiology of primary Sjögren's syndrome: a systematic review and meta-analysis. *Ann Rheum Dis* 2015;74(11):1983-1989.
55. Zhu JW, Wang JY. Images in clinical medicine. Eyelid swelling and primary Sjögren's syndrome. *N Engl J Med* 2013;368(26):2501.
56. Hashimoto R, Uchiyama M, Maeno T. Case report of subcutaneous panniculitis-like T-cell lymphoma complicated by eyelid swelling. *BMC Ophthalmol* 2016;16:117.
57. Pandya VB, Conway RM, Taylor SF. Primary cutaneous B cell lymphoma presenting as recurrent eyelid swelling. *Clin Exp Ophthalmol* 2008;36(7):672-674.
58. Svendsen FH, Heegaard S. Lymphoma of the eyelid. *Surv Ophthalmol* 2017;62(3):312-31.
59. Deshpande V, Zen Y, Chan JK, Yi EE, Sato Y, Yoshino T *et al*. Consensus statement on the pathology of IgG4-related disease. *Mod Pathol* 2012;25(9):1181-1192.
60. Khosroshahi A, Wallace ZS, Crowe JL, Akamizu T, Azumi A, Carruthers MN *et al*. International consensus guidance statement on the management and treatment of IgG4-related disease. *Arthritis Rheumatol* 2015;67(7):1688-1699.
61. Geyer JT, Deshpande V. IgG4-associated sialadenitis. *Curr Opin Rheumatol* 2011;23(1):95-101.
62. Stone JH, Caruso PA, Deshpande V. Case records of the Massachusetts General Hospital. Case 24-2009. A 26-year-old woman with painful swelling of the neck. *N Engl J Med* 2009;361(5):511-518.
63. Khosroshahi A, Stone JH. A clinical overview of IgG4-related systemic disease. *Curr Opin Rheumatol* 2011;23(1):57-66.
64. Cheuk W, Yuen HK, Chan JK. Chronic sclerosing dacroadenitis: part of the spectrum of IgG4-related sclerosing disease? *Am J Surg Pathol* 2007;31(4):643-645.
65. Zampeli V, Moutsopoulos HM. IgG4-related orbital disease presenting with unilateral eyelid swelling. *Arthritis Rheumatol* 2016;68(11):2824.
66. Sato Y, Ohshima K, Ichimura K, Sato M, Yamadori I, Tanaka T *et al*. Ocular adnexal IgG4-related disease has uniform clinicopathology. *Pathol Int* 2008;58(8):465-470.

67. Hamano H, Kawa S, Ochi Y, Unno H, Shiba N, Wajiki M *et al.* Hydronephrosis associated with retroperitoneal fibrosis and sclerosing pancreatitis. *Lancet* 2002;359(9315):1403-1404.
68. Stone JR. Aortitis, periaortitis, and retroperitoneal fibrosis, as manifestations of IgG4-related systemic disease. *Curr Opin Rheumatol* 2011;23(1):88-94.
69. Kasashima S, Zen Y, Kawashima A, Konishi K, Sasaki H, Endo M *et al.* Inflammatory abdominal aortic aneurysm: close relationship to IgG4-related periaortitis. *Am J Surg Pathol* 2008;32(2):197-204.
70. Li Y, Nishihara E, Kakudo K. Hashimoto's thyroiditis: old concepts and new insights. *Curr Opin Rheumatol* 2011;23(1):102-107.
71. Takahira M, Azumi A. IgG4-related disease. Springer;2014.77-84 p.
72. Kashii S. IgG4-related disease: a neuro-ophthalmological perspective. *J Neuroophthalmol* 2014;34(4):400-407.
73. 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):277-288.
74. Stone JH, Zen Y, Deshpande V. IgG4-related disease. *N Engl J Med* 2012;366(6):539-551.
75. Khosroshahi A, Stone JH. IgG4-related systemic disease: the age of discovery. *Curr Opin Rheumatol* 2011;23(1):72-73.
76. Kamisawa T, Anjiki H, Egawa N, Kubota N. Allergic manifestations in autoimmune pancreatitis. *Eur J Gastroenterol Hepatol* 2009;21(10):1136-1139.
77. Wallace ZS, Mattoo H, Carruthers M, Mahajan VS, Della Torre E, Lee H *et al.* Plasmablasts as a biomarker for IgG4-related disease, independent of serum IgG4 concentrations. *Ann Rheum Dis* 2015;74(1):190-195.
78. Rawlings NG, Valenzuela AA, Allen LH, Heathcote JG. Isolated eyelid edema in Melkersson-Rosenthal syndrome: a case series. *Eye (Lond)* 2012;26(1):163-166.
79. Martin SF. Immunological mechanisms in allergic contact dermatitis. *Curr Opin Immuno Allerg* 2015;15(2):124-130.
80. Esser PR, Martin SF. Pathomechanisms of contact sensitisation. *Curr Allergy Asthma Rep* 2017;17(12):83.

81. Lyons G, Roberts H, Palmer A, Matheson M, Nixon R. Hairdressers presenting to an occupational dermatology clinic in Melbourne, Australia. *Contact Dermatitis* 2013;68(5):300-306.
82. Frosch PJ, Burrows D, Camarasa JG, Doms-Goossens A, Ducombs G, Lahti A *et al.* Allergic reactions to a hairdressers' series: results from 9 European centres. The European Environmental and Contact Dermatitis Research Group (EECDRG). *Contact Dermatitis* 1993;28(3):180-183.
83. García Mónaco R, Bertoni H, Pallota G, Lastiri R, Varela M, Beveraggi EM *et al.* Use of self-expanding vascular endoprosthesis in superior vena cava syndrome. *Eur J Cardiothorac Surg* 2003;24(2):208-211.
84. Hanna J, Brauer PR, Berson E, Mehra S. Adult epiglottitis: Trends and predictors of mortality in over 30 thousand cases from 2007 to 2014. *Laryngoscope* 2019;129(5):1107-1112.
85. Mayo-Smith MF, Spinale J. Thermal epiglottitis in adults: a new complication of illicit drug use. *J Emerg Med* 1997;15(4):483-485.
86. Ames WA, Ward VM, Tranter RM, Street M. Adult epiglottitis: an under-recognised, life-threatening condition. *Br J Anaesth* 2000;85(5):795-797.
87. Jeremiah CJ, Aboltins CA, Stanley PA. Lymphatic filariasis in Australia: an update on presentation. Diagnosis and treatment. *Med J Aust* 2011;194(12):655-657.

Figure Legends

Figure 1 Upper lip swelling in cheilitis granulomatosa

Figure 2 Lower lip swelling in cheilitis granulomatosa

Figure 3 Unilateral facial nerve palsy and lip swelling in Melkersson-Rosenthal syndrome

Figure 4 Fissured tongue in Melkersson-Rosenthal syndrome

Figure 5 Unilateral lower limb swelling in lymphoedema

Figure 6 Eyelid (face) swelling in contact dermatitis

Table 1 Characteristics of different types of angioedema

	Mast cell (histamine) mediated	Bradykinin mediated
Pathomechanism	IgE-mediated <i>in response to allergen exposure</i> <i>release of vasoactive mediators</i> non-IgE-mediated <i>may be associated with chronic</i> <i>spontaneous urticaria</i> idiopathic <i>no identifiable cause</i> <i>recurrent, episodic in nature</i>	through complex interplay of the complement, coagulation and contact pathways HAE with C1-INH deficiency or defect due to SERPING1 gene mutations <i>HAE type 1</i> <i>HAE type 2</i> HAE with normal C1-INH <i>factor 12 gene mutation</i> <i>plasminogen (PLG) gene mutation</i> <i>angiopoietin-1 (ANGPT1) gene mutation</i> acquired angioedema with C1-INH deficiency ACE inhibitor-induced angioedema
Urticaria	frequent	absent
Symptom development	faster	slower
Useful investigations	serum tryptase levels <i>useful in the context of anaphylaxis/</i> <i>allergen trigger</i>	serum complement 4 C1-INH quantitative levels C1-INH antigenic levels <i>*all normal in ACE inhibitor-induced angioedema</i>

IgE immunoglobulin E

HAE hereditary angioedema

C1-INH C1 inhibitor

ACE angiotensin-converting enzyme

Table 2 Characteristics of angioedema masqueraders by body parts

	Salient features	Associated skin changes	Helpful investigations	Need for histology
Lip CG/ MRS	Painless, intermittent swelling initially Persistent swelling eventually (may be irreversible) *orofacial oedema, facial palsy, fissured tongue in MRS	No erythema	Exclude other CG mimics e.g. serum ACE level and ANCA	Essential (noncaseating granulomas)
Limb Cellulitis EAE	Unilateral involvement typically May have fever Cyclical, transient episodes of fever, angioedema, urticarial, weight gain, eosinophilia	Painful erythema Oedematous	Exclude deep vein thrombosis e.g. Doppler US Full blood count (eosinophils) C reactive protein Serum interleukin 5 level Echocardiogram (for end organ damage)	No Desirable (eosinophil deposition)
Periorbital tissues Orbital cellulitis Thyroid eye disease	Unilateral painful swelling Fever and headache Chemosis, proptosis, exophthalmos. Features of hyper- or hypothyroidism Constitutional symptoms Arthralgia/	Painful erythema Pretibial myxoedema	CT orbit/ head Thyroid function test Thyroid antibodies Radioiodine uptake scan	No No

Dermatomyositis	arthritis, myalgia/ myositis, dysphagia, lung fibrosis.	Gottron's papules Raynaud's phenomenon Heliotrope rash (purplish hues of upper eyelids) Photosensitivity	Serum creatinine kinase level Myositis immunoblot Exclude underlying malignancy	Muscle biopsy (e.g. quadriceps) in selected cases
Sjögren syndrome	Dry eyes, dry mouth, arthralgia/arthritis, parotid gland swelling. Constitutional symptoms	Eyelid swelling may be erythematous	Antinuclear antibodies Extractable nuclear antigens	No
Lymphoma		Associated erythroderma in mycosis fungoides (Sézary syndrome)	Immunophenotyping/ Flow cytometry Bone marrow biopsy	Essential (with immunochemistry staining)
IgG4-RD	Systemic disease. May have salivary gland swelling, pancreatitis, retroperitoneal fibrosis, cholangitis, aortitis, thyroiditis, eyelid swelling.	No	Serum IgG4 levels	Essential (lymphoplasmacytic infiltrate, IgG4-positive, storiform fibrosis)
Face				
Contact dermatitis	Crucial history of culprit exposure and specific occupation	Severe itchy and/ or painful erythematous facial swelling	Patch testing	No
SVC syndrome	Diffuse engorgement of face and neck. Pemberton's sign may be positive.	Engorged blood vessels on upper chest	CT thorax (exclude intrathoracic neoplasm)	Lung biopsy in selected cases
Epiglottis/ Uvula				
Epiglottitis	Fever and exudates	No	Radiography of neck Laryngoscopy Throat swab	No

Genitalia				
Testicular torsion	Acute, painful swelling	May be oedematous	Scrotal US	No
Filariasis	Painful when chronic, resembling hydrocele	May be oedematous	Filarial IgG EIA Blood film for microfilariae Scrotal US	No

CG chelitis granulomatosa

MRS Melkersson-Rosenthal syndrome

ACE angiotensin-converting enzyme

ANCA anti-neutrophil cytoplasmic antibodies

EAE eosinophilic angioedema with eosinophilia

US ultrasound

CT computer tomography

IgG4-RD Immunoglobulin G4 related disease

SVC superior vena cava

IgG immunoglobulin G

EIA enzyme immunoassay











