

Selected presentations of lip enlargement: clinical manifestation and differentiation

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Abstract

Lip enlargement may be an important symptom of either systemic or local diseases. On the basis of selected age-matched clinical cases we present the possible causes of lip swelling. We describe the most representative symptoms and recommend treatment of these pathologies. We differentiate lip swelling in Miescher syndrome, monosymptomatic form of Melkersson-Rosenthal syndrome, lip swelling in erythema multiforme and Stevens-Johnson syndrome and lip hemangioma and mucous extravasation cyst. We compare different causes of lip edema and indicate the most helpful diagnostic and treatment methods.

Key words: Melkersson-Rosenthal syndrome, mucocele, Miescher syndrome, Stevens-Johnson syndrome.

Introduction

Lip enlargement may be an important symptom of either systemic or local diseases. It can be characterized by diffuse or well-localized, acute or chronic, persistent or recurrent swelling. Many allergies can be manifested by edema of the lips. The lower face, eyelids and lips are often involved in Quincke's edema. Lip edema may precede Stevens-Johnson syndrome or erythema multiforme. Chronic lip edema is an important sign of hypothyroidism and other endocrinopathies, liver or renal failure, amyloidosis and sarcoidosis. Accompanying symptoms, such as facial paralysis and lymphangitis, are helpful to distinguish and properly diagnose lip enlargement. Persistent or recurrent lip swelling is a typical sign of Melkersson-Rosenthal syndrome, and its localized monosymptomatic form is known as Miescher syndrome. Minor salivary gland abnormalities result in mucous retention cysts and mucous extravasation cysts. Lip enlargement may result from benign or malignant tumors and blood vessel abnormalities [1–3].

Aim

The aim of the study was to present and differentiate the possible causes of lip enlargement. The most repre-

sentative symptoms and diagnostic and treatment methods were described and indicators for their use specified.

The most important issue in the diagnosis and differentiation of lip swelling is the character of this enlargement and accompanying symptoms and lesions.

Granulomatous diseases

Recurrent or persistent lip swelling is typical of Melkersson-Rosenthal syndrome (MRS) or its monosymptomatic type. Melkersson-Rosenthal syndrome is a very rare clinical entity and is characterized by the following triad: recurrent facial nerve palsy, recurrent or permanent swelling of the lips and fissured tongue [1]. However, all three symptoms appear only in 8–25% of cases. Most commonly, one element of the triad precedes the development of the other symptoms [4]. According to Elias *et al.*, periodontal disease, a history of allergic disease, Crohn's disease, migraine headaches, and systemic lupus erythematosus can accompany the typical triad of symptoms [2]. The monosymptomatic or oligosymptomatic form is more common and ranges from 18% to 70%. Its typical manifestation is facial edema and/or enlargement of the lips. Gradually increasing edema of the lips

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Figure 1. Lip edema in Miescher syndrome [3–5]



Figure 2. Enlargement of the lower lip in Miescher syndrome [3, 6, 8]

and the opening of submandibular glands are the main symptoms (Figures 1, 2).

Excisional biopsy reveals granulomatous infiltrations. This monosymptomatic form is known as Miescher syndrome [1–3]. Both MRS and Miescher syndrome are classified as granulomatous diseases and an isolated form of orofacial granulomatosis (OFG). Orofacial granulomatosis is an uncommon disease, which usually presents as a persistent swelling of the soft tissues in the orofacial region and is characterized histologically by granulomatous inflammation. The term orofacial granulomatosis is used in the literature to describe nonspecific granulomatous inflammation. Oro-facial granulomatosis is a rare chronic inflammatory disorder, presenting characteristically with lip swelling but also affecting gingivae, buccal mucosa, the floor of the mouth, and a number of other sites in the oral cavity. A subset, cheilitis granulomatosa (CG), which presents clinically as persistent lip swelling, is a granulomatous inflammation of unknown origin of the lips [5–8]. Cheilitis granulomatosa may also be part of the triad of MRS and some consider it an oligosymptomatic form of MRS [3]. A thorough work-up to eliminate other etiologies of granulomatous disease is essential when a patient presents with granulomatous inflammation of the lip. In the case presented, facial paralysis and fissured tongue were excluded. The persistent character of this edema indicated Miescher syndrome and histopathological examination confirmed the preliminary diagnosis. Various conservative methods for the treatment of labial swelling in patients with cheilitis granulomatosa have been attempted, often with only moderate success and sometimes with persistent disfiguring lip swelling. Severe macrocheilia can produce an unaesthetic facial deformity associated with functional disturbances. In patients with persistent macrocheilia, reduction cheiloplasty with excision of excess tissue may be indicated when conservative treatment has proven ineffective in reducing swelling, but may be successful in stabilizing the dis-

ease [4]. Cheilitis granulomatosa seems to respond well to steroid treatment and the need for surgery is minimal and should be reserved for recalcitrant cases [3]. Recent studies have considered MRS a granulomatous disease, and possibly the initial presentation of Crohn's disease in the orofacial area of some patients [7]. Histologically, OFG resembles Crohn's disease (CD), and a number of patients with CD have oral involvement identical to OFG. In our case we excluded Crohn's disease, but we recommend confirming or excluding Crohn's disease in all cases of MRS, Miescher syndrome and OFG. However, the exact relationship between OFG and CD remains unknown [5]. According to Sanderson *et al.*, an intestinal abnormality was significantly more likely if the age of OFG onset was less than 30 years [7]. Those with more severe oral inflammation were also more likely to have intestinal inflammation, and there was also a correlation between the histologic severity of oral inflammation and the histologic severity of gut inflammation. Orofacial granulomatosis with associated intestinal inflammation may represent a separate entity in which granulomatous inflammation occurs throughout the gastrointestinal tract in response to an unknown antigen or antigens [7]. Melkersson-Rosenthal syndrome and Miescher syndrome patients should therefore be screened and monitored for gastrointestinal symptoms [8]. Patients with deterioration of lip swelling usually responded to intralesional injections with triamcinolone or to a short course of systemic glucocorticoids. Nonsteroidal systemic modalities, such as clofazimine, hydroxychloroquine, or sulfasalazine, are alternatives to glucocorticoid regimens, thus avoiding the long-term side effects of corticosteroids. Surgical intervention should only be performed in severely disfiguring cases [6]. Intralesional glucocorticoids remain the first-line treatment, but recurrences are common [7]. Intralesional injections with glucocorticoids were applied in the case presented and decreased lip swelling. The effectiveness of this method requires lon-



Figure 3. Erythema multiforme with accompanying severe mucositis and lip swelling [9, 10, 13]



Figure 4. Stevens-Johnson syndrome [9, 13, 14, 18]

ger observation. Intralesional injection of triamcinolone at 20 mg every 15 days associated with oral clofazimine at 50 mg/day for 3 months was described previously and was the recommended method of treatment [6]. Alternative treatment strategies include combination therapy with other anti-inflammatory agents and biologics, such as infliximab [4].

Erythema multiforme and Stevens-Johnson disease

Lip edema can be the prodromal symptom of Stevens-Johnson syndrome (SJS) and erythema multiforme (EM) (Figures 3, 4). This edema has got an acute and temporary character. Lip swelling has not been determined as an initial sign of SJS so far and severe mucositis usually precedes a painful generalized erythematous vesiculobullous rash. Widespread necrolysis involving the skin surface occurs in most patients, with a gradual onset over a period of 2–15 days. Involvement of the mucous membranes of the mouth and nose is usually an early feature and leads to erosive and hemorrhagic mucositis [9–17]. Erosive mucous membrane lesions and oral involvement were observed respectively in 97% and 93% of patients with SJS [18]. This is characterized by painful mucosal erythema with subsequent blistering and ulceration. Similar involvement of the vermillion of the lips progresses to hemorrhagic sloughing with the development of dark adherent crusts. The tongue and palate are frequently affected, while in severe cases, mucosal involvement may extend to the oropharynx, larynx, nasal cavity and respiratory tract. Mucositis may restrict mouth opening and cause difficulty with eating or speaking. A possible long-term complication of acute oral involvement is labial and intraoral scarring and sicca syndrome, caused by damage to the minor salivary glands. Stevens-Johnson syndrome most often represents a reac-

tion to systemic medications. More than 200 offending medications have been implicated as triggers of SJS. In the Asian population, carbamazepine, phenytoin, and allopurinol are the most common offending agents. Other reports detail SJS after ingestion of medicines for the common cold [10, 12, 13, 17]. Symptoms of SJS develop within the first 8 weeks after starting a new medication. Several medications, e.g. clobazam and phenytoin, and viruses, especially HIV, can increase susceptibility to SJS. No more than 70–80% of cases are drug-induced, with similar percentages for SJS, toxic epidermal necrolysis (TEN) and SJS/TEN overlap [12]. Bacteria and viruses are also treated as possible causes of SJS. Infection with *Mycoplasma pneumoniae* is a controversial cause, because it has been associated with erythema multiforme and can cause primary mucositis. Reactivation of herpes simplex predisposes to SJS recurrences. In the case presented here, infection of the upper respiratory tract or therapy with β -lactam antibiotics could have been a causative or predisposing factor of SJS. Causality implications are helpful in differentiating erythema multiforme major (EMM) from SJS. Erythema multiforme major is mostly related to herpes simplex virus reactivation and rarely to drugs. Stevens-Johnson syndrome is usually triggered by a drug, rarely by an infection. Erythema multiforme major differs from SJS in terms of demographics, associated diseases, causes and severity. Erythema multiforme major usually involves typical targets which have a round shape with well-defined borders and three different zones of color. Distribution of these lesions is acral and includes less than 1% of the body's surface area [12]. The case of SJS presented can be an example of rare, atypical form of SJS – *Mycoplasma pneumoniae*-associated mucositis, which is characterized by a phenotype of predominantly mucous membrane involvement with few or no cutaneous lesions [9]. There is currently insufficient evidence to recommend systemic corticoste-

roids for the treatment of the oral manifestations in acute SJS [9]. However, steroids are commonly used in a variety of doses for 5–7 days during acute illness [18]. In the cases presented corticosteroids were effective and reduced oral involvement. Usually, oral assessment reveals a complete remission of lesions 7–10 days after the onset of systemic corticosteroid treatment. Additionally, local regular emollients, topical analgesics and antiseptics are recommended in oral SJS. Topical corticosteroids are prescribed in oral SJS and they reduce oral inflammation [18]. Alternative treatment includes plasmapheresis, granulocyte colony stimulating factor, cyclosporine, TNF- α inhibitors and human intravenous immune globulin [9].

Infectious disease as a source of lip enlargement

Erysipelas is a common skin infection. Its clinical picture is characterized by an inflammatory reaction of the upper dermis with a sharp demarcation of the erythema. Occasionally, a primary lesion such as a wound or skin crack is present. According to Bläckberg *et al.*, group A streptococci (GAS) were identified in 15–22%, group G streptococci (GGS) in 3–12%, and *Staphylococcus aureus* in pure culture in 7–18% of cases with erysipelas [19]. The face is affected in 9% of all cases [19]. One of the possible consequence of erysipelas is elephantiasis [19]. Elephantiasis nostras (EN) is a rare condition that can result in persistent swelling of the lips secondary to recurrent attacks of lymphangitis caused by bacterial infection. Lymphangitis of bacterial origin causes fibrosis and thickening of both epidermal and connective tissue. A diagnosis of EN should be entertained in patients with chronically edematous, scaling lip lesions [20].

Lip enlargement in endocrinological disorder

Persistent lip edema requires a comprehensive endocrinological examination. None of the patients had endocrinopathies and liver or renal failure. Hypothyroidism, hypersecretion of growth hormone (GH) and endocrinopathies secondary to renal and liver failure may result in lip enlargement. In hypothyroidism lip edema usually accompanies eyelid and lower face edema. It is discrete, constant and diffuse and can be the first symptom of pathology. In renal and liver failure, lip swelling is usually isolated, discrete and less severe. It is difficult to diagnose without a comprehensive physical examination. Lip enlargement in these cases requires causative treatment. One of the most severe lip enlargements occurs in acromegaly. It is a rare and underdiagnosed disorder caused, in more than 95% of cases, by a growth hormone (GH)-secreting pituitary adenoma. Growth hormone hypersecretion leads to the overproduction of insulin-like growth factor 1 (IGF-1), which results in a multisystem disease characterized by somatic overgrowth, multiple comorbidities, physical dis-

figurement, and increased mortality. Acromegaly affects both males and females equally and the average age at diagnosis ranges from 40 to 50 years. The typical coarsening of the facial features includes furrowing of the forehead, pronounced brow protrusion, enlargement of the nose and the ears, thickening of the lips, skin wrinkles and nasolabial folds, and macroglossia, as well as mandibular prognathism that leads to dental malocclusion and increased interdental spacing. Gigantism accounts for up to 5% of cases and occurs when the excess of GH becomes manifest in the young before epiphyseal fusion. The disease also has rheumatologic, cardiovascular, respiratory, neoplastic, neurological and metabolic manifestations, which negatively impact its prognosis and patients' quality of life [21]. Treatment of acromegaly is based on the surgical removal of pituitary adenoma. Only the most severe clinical cases require surgical correction of lip enlargement.

Angioedema

Another possible cause of lip swelling is angioedema. Physical examination usually reveals localized swelling of both lips with no other significant findings. Angioedema is related to increased capillary permeability in the subcutaneous layer. It is usually idiopathic and often occurs when patients are in their 40s or 50s. There are hereditary, acquired, allergic, idiopathic, and medication-associated causes of lip swelling and angioedema-eosinophilia syndrome. The levels of complement C1 inhibitor, C4, C3, and C1q can help distinguish between hereditary, acquired and other causes of angioedema. Hereditary angioedema is characterized by low levels of the C4 and C1 inhibitor and normal serum levels of C1q and C3. Acquired angioedema is associated with low levels of C4, C3, C1q and C1 inhibitors. Other types of angioedema do not change the levels of complement. Hereditary angioedema usually begins in childhood and does not respond to antihistamines or steroids. The medication-associated type of angioedema results from nonsteroidal anti-inflammatory drugs (e.g., ibuprofen, naproxen) and angiotensin-converting enzyme inhibitors (e.g., lisinopril, captopril). Angiotensin-converting enzyme inhibitors are also known to increase flare-ups in those with hereditary angioedema. Angioedema in response to medication most commonly occurs within a week of starting the medication, but can develop months to years after use. The absence of family history, immunological disorders, or previous malignancy may also suggest acquired angioedema. Periodic attacks associated with urticaria and pruritus, high eosinophil counts and spontaneous recovery are typical of angioedema-eosinophilia syndrome. Serum interleukin-5 is elevated in angioedema-eosinophilia syndrome, which can be clinically established with severe bouts of urticaria and pruritus, as well as rapid elevation of serum eosinophils. Idiopathic angioedema is characterized by recurrent attacks and may be associated with



Figure 5. Mucocele of the lower lip [23, 24]



Figure 6. Hemangioma of the lower lip [25]

urticaria. It usually responds to steroids and antihistamines. Allergic angioedema is characterized by urticaria, pruritus and previous exposure to allergen. Serum tryptase and 24-hour urine histamine levels are useful markers in evaluating for allergic angioedema [22].

Abnormalities of minor salivary glands

Well-localized swelling of the lips, especially of the lower lip, should be distinguished from cysts of minor salivary glands. Oral mucocele is the most common benign lesion of the minor salivary gland caused by any form of mechanical trauma to the excretory duct of the gland. It is characterized by a well-localized, soft consistency, bluish, and transparent cystic swelling on the lower lip (Figure 5).

Mucosa of oral cavity usually does not present any lesions. The lesion develops for a few days. It may appear in two forms, mucous extravasation phenomenon and mucous retention type, of which the extravasation type is more common. Mucoceles can appear anywhere in the oral mucosa, such as the lips, cheeks and the floor of the mouth, but mainly appear on the lips. About 80% of all lesions occur on the lower lips. Diagnosis is mostly based on clinical findings. Occurrence on the upper lip requires differentiation from benign and malignant tumors of minor salivary glands. Mucoceles most frequently affect young patients but can affect all age groups. They may have a soft consistency, bluish, and transparent cystic swelling, and a history of bursting and collapsing due to which they resolve then refill, a process which may be repeated. The treatment of choice is surgical excision of the mucocele with the removal of the affected minor salivary glands. Alternative methods of treatment are cryosurgery and laser surgery [23, 24].

Tumors and blood vessel abnormalities

Possible causes of lip enlargement are malignant and benign tumors of the salivary glands, and blood and

lymph vessel abnormalities. Vascular lesions are classified based on anatomical and structural features and biological behaviour. It can be manifest such as a well-localized swollen lesion of the lower lip (Figure 6). Clinical examination shows easy bleeding and elevated lesion. Touch and trauma predisposes to bleeding. Difficulties eating and drinking are predominant complaints. They divide the lesions predominantly into hemangiomas and other vascular malformations. The term hemangioma encompasses a heterogeneous group of vascular lesions characterized by altered endothelial cell growth and proliferation. In contrast, vascular malformations are structural anomalies of blood vessels without endothelial cell proliferation. Hemangiomas are classified into superficial (capillary hemangioma), deep (cavernous hemangioma), and compound or mixed (capillary cavernous hemangiomas) types [25]. Hemangioma is the most ordinary benign tumour of vascular origin, occurring most frequently in newborns and during infancy and childhood, although some cases develop in adults [25]. The head and neck region is more commonly affected, especially the face, oral mucosa, lips and tongue. The lesions are clinically observed as an anemic spot, at times erythematous, or as a small cluster of deep red papules. It can be manifest such as a well-localized swollen lesion of the lower lip (Figure 6).

Clinical examination shows easy bleeding and elevated lesion. Touch and trauma predisposes to bleeding. Difficulties eating and drinking are predominant complaints.

Anemic hemangioma should be differentiated from lymph vessel abnormalities. Hemangioma is typically characterized by a rapid growth stage, a stagnation stage which lasts for several months and slow regression, usually before 10 years of age. In the case presented, there was no typical division into rapid growth, stagnation and regression stages. Slow growth progressed for 2 years and did not reveal any regression. Occasionally, hemangiomas may appear in a late form, especially those lesions located at deeper levels. The physiopathology of hemangiomas is unknown. Their appearance is prob-

ably attributed to genetic and cellular factors, mainly to monocytes, which are considered the potential ancestors of hemangioma endothelial cells. These lesions result from an imbalance in the angiogenesis, which causes uncontrolled proliferation of vascular elements. Vascular endothelial growth factor (VEGF), basic fibroblast growth factor (BFGF) and indoleamine 2,3-dioxygenase (IDO), which are found in large amounts during the proliferative stages, are involved in the physiopathology. It is estimated that 10–20% of hemangiomas require treatment. Lip

hemangiomas mainly cause deformities without severe complications. Therapy in hemangiomas depends on the anatomic location, accelerating growth, significant functional disturbances and unaesthetic markings. Systemic corticosteroid has been established as the most efficient medical therapy for common cutaneous infantile hemangiomas if started early in the proliferative phase. When there is no response to the systemic treatment or if there is an aesthetic complaint, surgical excision or lesion sclerosis using certain substances (5% sodium morrhuate,

Table 1. Summary of the most common causes of lip swelling. Comprehensive examination and accompanying symptoms are helpful in differentiation and diagnosis. Most lip pathologies can be treated by systemic or local conservative methods. Only limited lip enlargement is an indication of surgical correction

Disease	Onset and character of edema	Causes	Accompanying symptoms	Clinical presentation	Recommended treatment
EMM	Acute, frequent recurrences	Infections, idiopathic		Typical targets, acraly distributed, epidermal detachment < 1% body surface area	Steroids
SJS	Acute	Drug-induced, idiopathic	Systemic disturbances, skin, mucous, ocular and genital involvement	Widespread distribution, atypical targets, < 10% to 30%	Steroids, plasmapheresis, granulocyte colony stimulating factor, cyclosporine, TNF- α inhibitors and human intravenous immune globulin
Melkersson-Rosenthal/ Miescher syndrome	Recurrent, persistent	Unknown, oral granulomatosis	Facial paralysis, fissured tongue		Systemic or interlesional administration of steroids
Mucocele	Acute extravasation of minor salivary glands			Transparent, soft, limited lesion, usually lower lip	Surgical excision, marsupialization
Angioedema	Acute, recurrent	Hereditary, acquired, allergic, idiopathic, medication associated and angioedema-eosinophilia syndrome	Possible urticaria, pruritus, immunological disorders	Well-localized, possible without other symptoms	Dependant on origin
Acromegaly	Permanent	GH hypersecretion	Both internal and external abnormalities	Lip enlargement	Surgical excision of pituitary adenoma
Ascher syndrome	Recurrent, persistent		Blepharochalasis, non-toxic thyroid enlargement, upper eyelid edema	Double lip	Surgical excision
Hemangioma	Usually three stages of growth: Proliferative stage Involuting stage Involuting stage	Unknown		Anemic or erythematous spots or a small cluster of deep red papules	Systemic corticosteroids, intralesional injection of sclerosing agent, electrocoagulation, cryosurgery, laser therapy, embolization, and surgical excision
Minor salivary gland tumors	Undetermined onset, fast or slow growth	Unknown			Surgical excision

sodium psylliate, 5% ethanolamine oleate, 1% polidocanol, sodium tetradecyl sulfate and hypertonic saline) is indicated. Administration of systemic corticosteroids, intralesional injection of sclerosing agent, electrocoagulation, cryosurgery, laser therapy, embolization, and surgical excision are some of the treatment modalities practiced for hemangioma. Sclerotherapy and surgery are the most commonly used techniques for the treatment of oral hemangiomas [25]. Pleomorphic adenoma is the most common benign tumor of the salivary glands, usually occurring in major salivary glands (mostly in the parotid gland). It also affects the minor salivary glands present in the oral cavity [26]. Caliber-persistent labial artery (CPLA) is a vascular anomaly of the labial artery that penetrates into the submucosa of the lip without a reduction in diameter. It commonly presents as a bluish or normal-colored elevated mass and usually pulsates on manual palpation. It can resemble a mucocele or squamous cell carcinoma if surface ulceration presents. It can also be misdiagnosed as a varix, hemangioma, venous lake, mucocele or fibroma [27]. Caliber-persistent labial artery carries the risk of profuse bleeding if the artery undergoes transection during biopsy. The most frequently used method to confirm the diagnosis of CPLA is excisional biopsy, which carries the risk of profuse bleeding. Alternative diagnostic methods are angiography and Doppler ultrasonography. The recommended method of treatment is surgical excision. Hemostasis can be achieved either by application of surgical diathermy or ligation with deep sutures in the wound area [27, 28].

Ascher syndrome

Ascher syndrome is a disease of unknown etiology first described in 1920 by Ascher, an ophthalmologist from Prague. It presents with recurrent edema of the lip and upper eyelid resulting in double lip and blepharochalasis. In 10% of cases idiopathic nontoxic thyroid enlargement also occurs [29]. Double lip usually affects the upper lip and produces an unpleasant appearance on smiling. It rarely involves the lower lip or both lips. Double lip occurs due to lip maldevelopment. The lip normally develops during the second or third month of gestation from the pars glabrosa (outer cutaneous zone) and the pars villosa (inner mucosal zone) with the disappearance of the horizontal sulcus between them. Persistence of the horizontal sulcus with hypertrophy of the pars villosa leads to double upper lip. The recommended treatment is surgical excision, and this is indicated when it interferes with chewing, speaking or for aesthetic reasons. Blepharochalasis is present in more than 80% of cases of this syndrome. It starts at puberty and it presents with a form of localized angioedema with a decrease in dermal elastin. Indications for surgery are visual acuity disturbance or ocular complications [30].

Conclusions

Lip enlargement requires a comprehensive, multidisciplinary examination to assess the cause of abnormality. It can be a first symptom of systemic disease or it can be limited to the lip. Lip enlargement may precede other symptoms and can be helpful in the diagnostic process. Most cases can be effectively treated by conservative treatment, and surgical approaches are recommended only in malignant and benign tumors or tumor lesions. Table 1 summarizes the main differentiating symptoms and treatment recommendations.

Conflict of interest

The authors declare no conflict of interest.

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