CASE REPORT

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ACUTE MULTIFOCAL SIALADENITIS WITH UNKNOWN ORIGIN: DIAGNOSTIC WORKUP AND VALUABLE KNOWLEDGE FROM AN UNUSUAL CLINICAL CASE

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Abstract. *Salivary gland swelling can be a challenge for clinicians, and there are various reasons why. Many diseases may affect salivary tissue, and it is important to be familiar with their symptoms and paraclinical findings. Knowing the most common etiologies of multifocal swelling of salivary glands and the precise use of different clinical and paraclinical modalities can improve diagnostic accuracy. The goal of our research is to present a rare clinical case of acute multifocal sialadenitis of major and minor salivary glands of unknown origin and to discuss the differential diagnostic options that can improve timely, accurate treatment and improve the result of the treatment.*

Key words: *salivary gland diseases, multifocal salivary gland infection, differential diagnosis, diagnostic workup*

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INTRODUCTION

Enlargement of salivary glands may have a different genesis and can be unifocal or multifocal [1, 2].

Acute, unifocal swelling of the salivary glands may be due to infection, obstruction (sialoliths or canal stricture), or postradiation. Bacterial unilateral infection could be caused by polymicrobial flora like aerobes: *Staphylococcal aureus, Hemophilus influenzae, Gram* – negative *aerobes* (e.g, *Enterobacteriaceae*), and anaerobes: *Prevotella, Fusobacterium, Peptostreptococcus*.

The patient's general health status could be affected: fever, increased CRP, leukocytosis, and left shift. Locally, soreness of the glands and purulent saliva coming out of the ductal opening can be observed. Assessing the clinical symptoms and their time of development can help to determine whether the bacterial infection is primary or secondary due to sialoliths. If there is an obstructive reason, it usually takes several days before an infection develops and intraorally

is detected as purulent discharge in the saliva flow from the affected gland. In some cases, saliva may be absent if the duct is completely blocked [1-3].

Chronic granulomatous infection can also affect the unilateral salivary glands, in cases of tuberculosis, actinomyces, Bartonella henselae infection, and sarcoidosis.

Acute, multifocal swelling of the salivary glands may be due to a **viral infection** (eg, mumps or other viruses), systemic radioactive iodine treatment, contrast-induced sialadenitis, juvenile relapsing parotitis (JRP), or as a side effect of medication [1, 4-6].

Sialadenitis due to viral infection (viral sialadenitis) can be due to various causes, such as paramyxovirus (causing mumps), human immunodeficiency virus (HIV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), human herpes simplex virus (HHSV-8), hepatitis C virus (HVC), human papilloma virus (HPV), coxsackie virus, influenza virus, echovirus, etc. The viral infections are associated with infection of the salivary glands bilaterally and must be differentiated from infection with the paramyxovirusq which causes parotitis. In pediatric patients, Epstein-Barr virus (EBV) and parainfluenza virus (PIV) have been found to be the most common causes of viral infections mimicking mumps. Infection with adenovirus, enterovirus, parvovirus, and herpes virus type 6 (HHV-6) has also been identified as affecting the salivary glands [5, 6].

Sialadenitis may also be an “early” symptom when it is associated with COVID-19 infection [7], as well as wich enlargement of the salivary parotid or submandibular gland due to intraparotid lymphadenitis [8].

Treatment with radioactive iodine (131-I) in the management of carcinoma of the thyroid gland or hyperthyroidism may also cause enlargement of the salivary glands. Acute, painful, multifocal swelling of the salivary glands is found after administration of radioiodine (131- I). Symptoms of inflammation of the salivary glands usually begin within a few hours of 131-I administration, and acute symptoms usually resolve within a few days [5].

The risk of developing **sialadenitis after contrast administration** is associated with high serum iodide levels (> 10 mg/100 mL) and is more likely to occur in impaired renal function due to reduced elimination of contrast material [5, 9].

The pathogenesis of **JRP (juvenile recurrent parotitis)** is unclear, with various causes hypothesized, including autoimmune disease, retrograde infection (bacterial or viral) through the ducts, genetic abnormality, and congenital ductal malformation.

Drug-induced parotitis is a relatively rare adverse drug reaction associated with taking l-asparaginase, clozapine, phenylbutazone, valproic acid, and thiourea [5, 10]. The mechanism is unknown and may be due to a spasm of the smooth muscles in the gland, a change in the sympathetic (vasoconstrictor effect) and the parasympathetic (anticholinergic effect) innervation.

Chronic enlargement of the parotid gland has also been described in patients with eating disorders, anorexia, and bulimia. Stopping the act of vomiting associated with **bulimia nervosa** [2] can lead to painful bilateral parotid ***swelling*** [11]. Symptoms are usually controlled with warm compresses, Non-steroidal anti-inflammatory drugs NSAIDs, and sialagogues.

In different articles, predisposing risk factors are divided into two categories: modifiable and non-modifiable [1-3].

- Modifiable risk factors: dehydration, malnutrition, sialolithiasis, recent surgery under general anesthesia, medication (anticholinergics, diuretics, and chemotherapy).
- Non-modifiable risk factors: age (elderly), eating disorders, cystic fibrosis, diabetes, HIV/AIDS, liver/kidney failure, and previous radiation [5].

Autoimmune sialadenitis is a non-infectious disease leading to chronic inflammation and subsequent fibrosis of the salivary glands. Two of the most common autoimmune diseases include Sjogren’s syndrome and sarcoidosis, and less common are IgG4-related Mikulicz disease and xanthogranulomatous sialadenitis [1, 2, 5, 11-15].

Our article aims to present a rare clinical case of acute multifocal sialadenitis of large and small salivary glands of unclear origin.

A 47-year old female patient was referred to the Department of Dental, Oral and Maxillofacial Surgery, FDM, MU – Sofia with enlargement of both major and minor salivary glands.

Clinical examination revealed general signs of inflammation – pyrexia, lymphadenopathy, and malaise.

Extraorally, a minor asymmetry was found due to enlargement of the submandibular glands. Intraorally, enlargement of the sublingual and minor glands of the labial mucosa was detected. (Fig. 1A, B and Fig. 2A, B).

Submandibular and sublingual glands were enlarged and painful. Bimanual palpation of the submandibular salivary glands was performed, whilst inspecting the oral cavities for the ductal orifices, and there was no purulent discharge from the duct, or any additional symptoms from any potential abscess formation. Erythema around the ostia of ducts of the affected

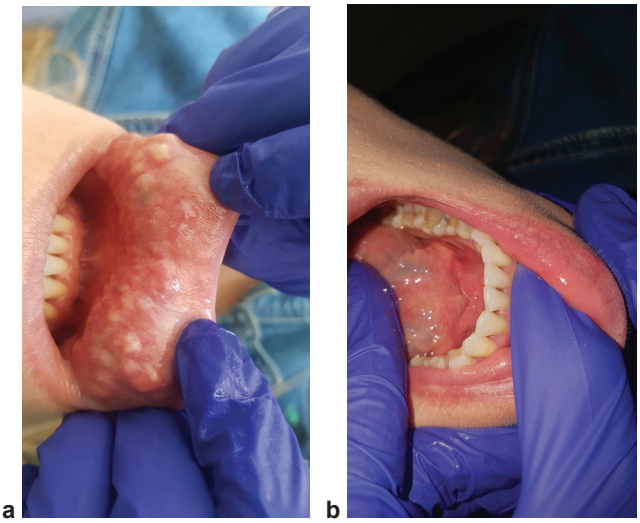

Fig. 1 A, B. Enlargement of the small salivary gland of the lower lip and the sublingual glands

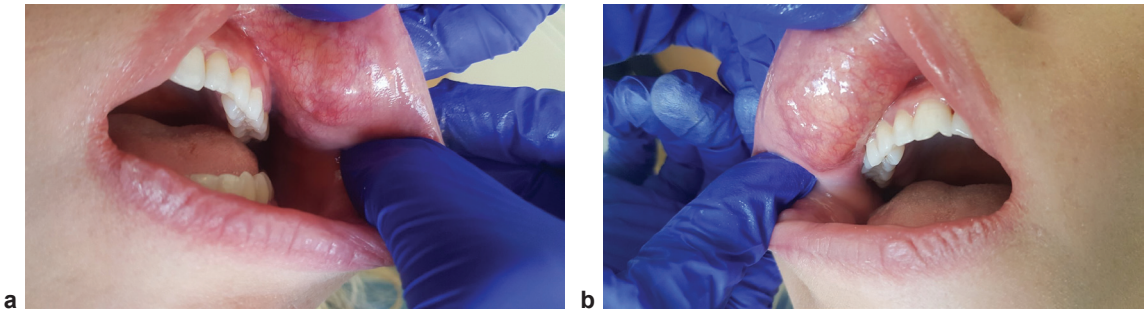

Fig. 2 A, B. Enlargement of the small salivary gland of the upper lip

glands (incl. major salivary glands) was detected, and reduced normal saliva was drained. Examination of the oral cavity showed enlarged minor salivary glands, which were detected in palpation in areal of the upper and lower lip and buccal mucosa.

After a thorough clinical examination, the following paraclinical investigations were performed: ultrasound examination, serological test, and blood test.

The clinical and paraclinical examination disclosed acute inflammation of major and minor salivary glands without data for autoimmune diseases.

- Blood test revealed elevation of neutrophils (74.6%) leucocytes (12.7 x 10^9/l), ESR(52), C-reactive protein (36.53 mg/l) and decreasing of lymphocytes (18.1%).
- Serological test showed elevated IgG (3.44) for mumps and negative IgM (0.37) (not current infection) and negative for other viral infections (cytomegalovirus, EBV, COVID, etc.).
- According to ultrasound examination – major salivary glands were enlarged bilaterally. Submandibular lymphadenitis as well as submandibular sialodochitis were detected.

The patient was diagnosed with acute inflammation of salivary glands and was treated with antibiotic Augmentin 2x1.0 g for 7 days), Sol. Kalii Iodati 5% (3 x 1 ml 2 times per day), Bromhexine (3 x 8 mg), Prednisolon cortico with decreasing dosage (first 3 days 40 mg; following 20 mg for 2 days and 10mg for 1 day). We suspected acute multifocal infection of salivary glands with abnormal immune response.

There was improvement of clinical symptoms in two days.

The patient was followed up, and there was no relapse of the symptoms for the next two years.

DISCUSSION

A thorough evaluation of the patient is essential for an accurate diagnosis [16, 17]. In the described case, the patient was observed carefully and in detail: chief complaint, duration of symptoms (acute or chronic inflammation), extraoral and intraoral clinical examination.

In case of sialadenitis tendered and enlarged minor and major salivary glands could be detected unilaterally or bilaterally; pain associated with eating or saliva stimulants (+/-), unpleasant taste in the mouth (+/-), systemic symptoms – fever, asthenodynamia, blood cell count, other general symptoms – joint pain, dry eyes and mouth, comorbidity: alcohol use, diabetes, eating

disorder, liver disease, autoimmune disease, has had radiation therapy or contrast imaging; data on current drug therapy. Correct diagnosis is established based on medical history, physical examination, and laboratory test, as in our case – ultrasound, blood test, and serology [1, 3, 9]. When a clinician suspects sialolithiasis, X-ray could be performed – axial and orthopantomography. If autoimmune disease of connective tissue disorders is suspected, a biopsy and other examinations are needed to rule out autoimmune etiology, such as SSA/anti-Ro, SSB/anti-La, ANA, and RF [1, 2, 5, 12-15].

In case of multifocal salivary gland swelling, the following paraclinical tests may be performed: complete blood count – for the presence of infections; ultrasonography – can be useful for positive sialoliths (> 1 mm) and inflammation or abscess, enlarged lymphatic nodes inside the gland [1, 2, 18, 19]. In our case, leukocytosis, increased ESR, and C-reactive protein were found. On the ultrasound examination, enlarged salivary glands – submandibular and sublingual with signs of inflammation were detected. CT scan and MRI could be appointed in case of diagnostic difficulties and in case when conventional figurative investigations are not informative. There was no indication for such an imaging method, as our patient was with acute symptoms. The scintigraphy can be used to establish the functional glandular activity [1], so we did not use it in our case.

Mumps sialadenitis or other viral infection should be suspected based on acute multifocal swelling of the salivary glands accompanied by systemic symptoms including fever, malaise, and asthenia. Laboratory tests can confirm the diagnosis.

A serological test to rule out a viral infection such as mumps, HSV, EBV, cytomegalovirus, etc., is of diagnostic significance. In our case, we received information about a past infection for promoted IgG for mumps and negative IgM and negative for other viral infections (cytomegalovirus, EBV, COVID, etc.). For our patient, we did not perform FNA cytology of the affected gland because there was no clinical evidence of chronic sclerosing sialadenitis, autoimmune or systemic granulomatous disease [12, 20-23], but lymphopenia and leukocytosis were detected.

The differential diagnosis in multifocal involvement of the salivary glands includes: systemic infection (viral, bacterial); granulomatous chronic infection, such as tuberculosis, sarcoidosis, cat scratch disease, actinomycosis; autoimmune genesis, endocrine and metabolic causes, and in our case, we excluded all but infection of a bacterial or viral origin [5, 11, 12].

According to medical history in the described case, the patient has not recent exposure to 131-I radioiodine therapy or administration of an intravenous iodinated contrast agent.

The risk of developing contrast-induced sialadenitis is associated with high serum iodide levels (>10 mg/100 mL) and is more likely to occur in impaired renal function due to reduced elimination of contrast material [5, 9, 11, 24, 25]. At a high concentration of iodine agent in the salivary glands, it can lead to local inflammation and edema, leading to blockage of the salivary ducts [9, 24]. Symptoms usually disappear quickly, within hours to a few days, and treatment includes hydration and, if necessary, non-steroidal anti-inflammatory drugs (NSAIDs) [24] or, in severe cases, systemic glucocorticoids [9, 24]. Dialysis treatment is another treatment option for patients with severe, persistent symptoms despite the above treatments.

Drug – induced parotitis is the other diagnosis that we had turned off. In the described case the patient had no accompanying diseases or current drug treatments. Medications that are related to adverse drug reaction and drug-induced parotitis are: α l-asparaginase, clozapine and phenylbutazone, Valproic acid and thiourea [25]. The mechanism of action of drug-induced salivary swelling is largely unknown, but may involve spasm of smooth muscle in the gland, as well as altered sympathetic and parasympathetic autonomic effects [5, 25].

Endocrine and metabolic causes such as alcoholism, hypothyroidism, diabetes mellitus, eating disorders, cirrhosis, vitamin deficiency, and malabsorption were rejected and were not in our field of differential diagnosis, as in our case, no comorbidity or long-term medical condition was detected [11, 26-37].

Most cases of acute multifocal sialadenitis can be managed conservatively by prescribing antibiotics, mucolytics, antiseptics, adequate hydration, and anti-inflammatory drugs and paracetamol. Corticosteroids can be prescribed, as in this case, when an abnormal immune response was suspected – oral corticosteroids in decreasing doses were administered.

CONCLUSION

The described clinical case shows that the correct approach to the diagnosis of multifocal salivary gland swelling in adults can be a challenge in clinical practice. Clinicians should be aware of the variety of diseases and long-term conditions which can affect the salivary glands. The correct diagnosis as a result of proper and accurate evaluation of clinical and paraclinical indicators is essential for adequate treatment and a successful outcome.

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Consent for publication: *Consent form for publication was signed by the patient and collected.*

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