Sialadenosis

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Key Points

1. Sialadenosis (sialosis) is a chronic, noninflammatory, nonneoplastic, bilateral, often painless enlargement of the salivary glands, most frequently affecting the parotid glands, with no sex predilection and frequently affecting the third to seventh decade.
2. Approximately 50% of cases are associated with an underlying disease process, most commonly diabetes, alcoholism, cirrhosis, anorexia/bulimia, malnutrition, metabolic syndromes, and medications.
3. The pathogenesis of sialadenosis is unknown, but the current weight of evidence supports the theory that it arises from an autonomic neuropathy.
4. Initial clinical evaluation consists of a thorough history and physical examination to direct further investigation that may include blood testing to narrow the large differential diagnosis characterizing bilateral parotid swelling.
5. Diagnostic imaging is useful in supporting the diagnosis of sialadenosis and includes ultrasound, CT, and sialography.
6. Fine-needle aspiration (FNA) and open biopsy may be useful in selected cases. The histologic finding of acinar enlargement supports the diagnosis of sialadenosis.
7. Management involves addressing the associated medical conditions with the recognition that sialadenosis is not always reversed despite successful treatment of the underlying medical abnormality. Conservative symptomatic management can also be started at the same time, which can include heat application and sialogogues.
8. More invasive management is reserved for refractory cases to treat pain and/or aesthetic concerns, which includes botulinum neurotoxin injection, pilocarpine, steroid insufflation, tympanic neurectomy, and parotidectomy.

Introduction

Sialadenosis (sialosis) is considered a rare condition that was initially described in the early 1900s. It is defined as noninflammatory, nonneoplastic, bilateral, parenchymatous enlargement of the salivary glands [1–8]. Involvement most often affects the parotid gland but may also involve the submandibular gland or other minor salivary glands (Fig. 13.1). Sialadenosis is characterized by chronic swelling that, unlike obstructive sialadenitis, is not closely associated to the stimulus of eating. Sialadenosis originally was considered as a painless disorder, but more recently it has

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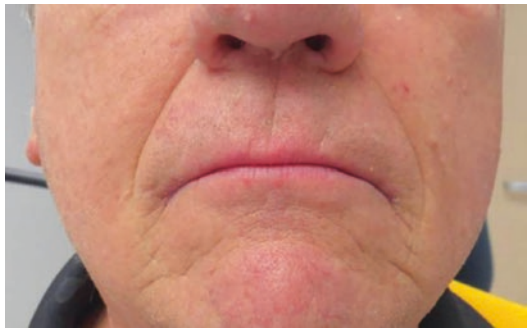

Fig. 13.1 Image of a patient with sialadenosis. This image shows the bilateral parotid enlargement present in sialadenosis [26]

been accepted that pain can be present [4]. Sialadenosis has no sex predilection and typically affects patients between the third and seventh decade [3–8]. Half of all cases of sialadenosis are associated with a recognized endocrine, metabolic, neurogenic, or nutritional disorder [8].

Anatomy

An understanding of sialadenosis and its management requires knowledge of the salivary secretory unit and its autonomic innervation. The secretory unit of the parotid gland consists of an acinus with an intercalated duct that are both surrounded by contractile myoepithelial cells [4]. The intercalated ducts condense progressively from proximal (acinar structures) to distal (Stensen's duct) as they progress from striated and then subsequently to excretory ducts. The main parotid duct, also known as Stensen's duct, has its orifice at the second maxillary molar.

The parotid gland receives equal autonomic innervation from both the sympathetic and parasympathetic systems. The gland receives parasympathetic innervation via the glossopharyngeal nerve which has its preganglionic fibers in the inferior salivary nucleus. These fibers join the glossopharyngeal nerve in which it synapses with the postganglionic cells at the otic ganglion. The postganglionic fibers join with the auriculotemporal branch of mandibular division of the trigeminal nerve. The parasympathetic innervation to the parotid regulates fluid and electrolyte secretions. The sympathetic innervation to the parotid gland has its preganglionic fibers that originate from the thoracic spine and travel up the sympathetic trunk to synapse at the superior cervical ganglion, in which the postganglionic fibers exit and travel through the external carotid artery plexuses to connect with the parotid gland. The sympathetic innervation is responsible for stimulating production and secretion of secretory granules [5–7, 9].

Pathophysiology

Sialadenosis was first identified nearly a century ago. Despite this extensive history, its diverse association with a wide range of disease processes has not permitted identification of a direct correlation with a single inciting cause. Donath and Seifert [10] presented a morphometric analysis of sialadenosis of the parotid gland in which they found enlargement of acinar cells when compared to controls. Histologically, they identified a granular pattern to the cytoplasm attributed to an increased number of secretory granules. They also noticed degenerative changes of the myoepithelial cells and postganglionic sympathetic nerves.

The above observations led to the hypothesis that sialadenosis arises from an autonomic neuropathy associated with dysfunctional protein secretion and/or synthesis which causes acinar enlargement [1, 4, 10]. This neuropathy of the sympathetic nervous system leads to the buildup of secretory granules seen in the acinar cells and the subsequent acinar enlargement causing the overall hypertrophic glandular structure. This neuropathy can be accounted for by the number of disease processes, such as diabetes and alcoholism, associated with sialadenosis that are known to cause peripheral autonomic neuropathies [5, 7, 11].

A second hypothesis of the pathogenesis of sialadenosis implicates dysfunctional aquaporin channels as a cause for the glandular swelling. Support for this hypothesis came from a patient with central diabetes insipidus treated with exogenous antidiuretic hormone (ADH), who

subsequently developed sialadenosis. ADH is known to upregulate the synthesis of aquaporin channels; therefore, when this patient's parotid biopsy was stained for aquaporin-5, which is found on the apical surface of salivary cells and is involved in saliva production and cell volume regulation, it was found to be upregulated when compared to control. This was confirmed by the same group in a case series of nine patients who had sialadenosis, in which they concluded that aquaporins may play a role in the pathogenesis of sialadenosis [12, 13].

Evaluation

Sialadenosis is characterized by a chronic, bilateral, primarily parotid swelling that cannot be accounted for by inflammatory or neoplastic causes. Although the history and physical examination may lead to sialadenosis as the most likely diagnosis, other causes of salivary swelling may either mimic sialadenosis or coexist with it in a way that usually requires further testing.

Clinical

The etiology of bilateral parotid enlargement includes a large and diverse differential diagnosis. Sialadenosis patients complain of chronic, bilateral parotid swelling occasionally accompanied by concern about aesthetic disfigurement that may be the chief complaint leading to consultation. Xerostomia and pain have also been reported to accompany sialadenosis, although it should be noted these could arise for a number of different reasons [4, 11]. Among the recognized causes of sialadenosis, malnutrition, liver disease (often alcohol related), and diabetes are prominent. The main causes are discussed.

Malnutrition disorders, such as bulimia and anorexia nervosa, were identified as a cause for sialadenosis in 1969 [14]. It has been estimated that 10–66% of all bulimics have sialadenosis [15]. The pathogenesis for sialadenosis resulting from bulimia is uncertain, but some theories have been proposed [15]:

1. Intense, repetitive autonomic stimulation to the gland causing enlargement.
2. Possible humoral connection between the pancreas and the parotid gland.
3. Chronic regurgitation of gastric acid contents is responsible for glandular change.

Regardless of pathogenesis, many bulimics suffer from sialadenosis, which in this patient population is of special concern due to their self-esteem and body image issues. Bulimics tend to have swelling 3–6 days after a binge-purge episode. Another symptom that bulimics experience is tooth enamel erosion and dental caries ascribed to acidic contents of their regurgitation. Interestingly, the degree of enamel erosion correlates with the size of the parotid glands [15].

Alcoholism and alcoholic cirrhosis are well-known causes of sialadenosis, and much of what we know about sialadenosis result from study of these disease processes. Studies have shown that 30–80% of alcoholic cirrhotics and 26–86% of alcoholics have sialadenosis [5, 7, 16]. It is well established that alcoholism is associated with autonomic polyneuropathy. There is controversy regarding an association between sialadenosis and nonalcoholic liver disease. A study of 28 liver transplant patients with sialadenosis showed that 17 had nonalcohol-related liver disease. It has been hypothesized that an underlying nutritional deficit occurring both in alcoholic and in nonalcoholic liver disease is responsible for sialadenosis [16].

The association between diabetes and sialadenosis is well established. The rising epidemic of diabetes would be expected to be accompanied with a parallel increase in the prevalence of sialadenosis. One case series showed that 49% of patients with sialadenosis had diabetes [17]. Diabetes also presents a potential confounder in patient populations with cirrhosis and sialadenosis, since a large portion of cirrhotics have diabetes as well. The liver plays essential roles in glucose and glycogen metabolism, and with liver disease, metabolic derangements can be seen with subsequent hyperglycemia and insulin resistance. This makes it difficult to establish whether cirrhosis or the subsequent diabetes is

the major underlying factor [16]. It is important to note that along with diabetes, the rising epidemics of obesity and subsequent metabolic syndrome are known causes of sialadenosis. A significant, almost linear, correlation has been noted between BMI and parotid size due to fat cell hypertrophy [18].

Sialadenosis has also been reported in association with hypothyroidism, diabetes insipidus, acromegaly, pregnancy, use of medications especially antihypertensives, and exposure to heavy metals. The work-up should start with a comprehensive history and physical examination looking for any underlying cause of bilateral parotid enlargement [19–21]. On physical examination, the parotid enlargement associated with sialadenosis commonly results in obliteration of the groove between the ramus of the mandible and mastoid process causing a trapezoid appearance [17]. Blood testing may be done to rule out other causes of bilateral parotid enlargement when supported by clinical findings to address possible Sjögren's syndrome. Unusual presentation may warrant a more detailed serum analysis to potentially include assessment for borreliosis, toxoplasmosis, syphilis, HIV, and brucellosis. If suspected, testing for specific nutritional deficiencies could be considered to rule out pellagra, beriberi, and kwashiorkor [20].

Radiologic

Radiologic imaging can be an important tool to help narrow the differential diagnosis of bilateral parotid enlargement and support the diagnosis of sialadenosis. Ultrasound, CT, and sialography are the most common imaging modalities when investigating sialadenosis.

Ultrasound of the salivary glands is an effective imaging modality that may be helpful, but usually not definitive, in ruling out other causes of salivary swelling. Ultrasound tends to be the first imaging modality of choice due to its widespread availability and its low cost and is becoming increasingly more common to conduct in-clinic ultrasound examinations, which allows the clinician to have immediate results with less user-dependent variability. Specifically in sialadenosis, it is important to confirm that the bilateral swelling is not of inflammatory or neoplastic origins. Sonography allows for this, by showing hyperechogenicity of the gland with no focal lesions present. In cases of sialadenosis, it is rare to see the deep lobes of the parotid gland on sonography due to the hyperechogenicity [22].

CT is more specific than other modalities and, in some cases, can serve as the only other radiographic imaging needed to confirm the diagnosis of sialadenosis. Initially in sialadenosis, acinar cell hypertrophy occurs, which on CT represents a diffuse glandular enlargement, but it is a similar density to the native parenchyma. As sialadenosis progresses, glandular parenchyma gives way to fatty infiltration, which decreases the glands attenuation, and the fat shows up as soft tissue masses (Fig. 13.2) [7, 23, 24]. This glandular enlargement is observed in the absence of other causes of glandular enlargement such as stone, tumor, or duct obstruction.

The first radiographical depiction of the salivary glands was in 1913 by Arcelin, and the term "sialographie" was coined in 1926 by Jacobovici to describe the radiographical demonstration of

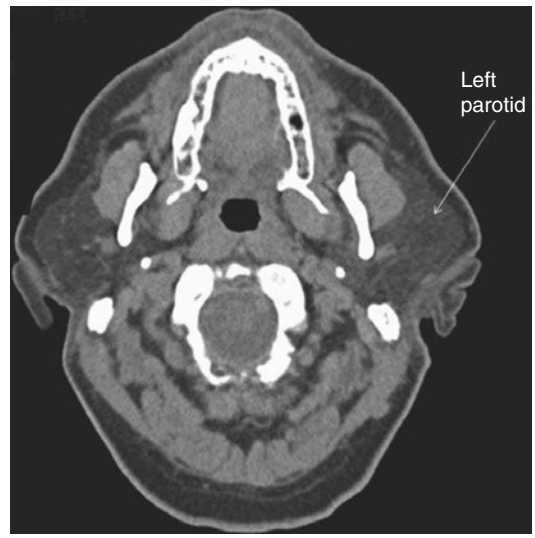

Fig. 13.2 CT scan of a patient with sialadenosis showing characteristic bilateral parotid gland enlargement with fatty infiltration. In this case, the left parotid appears to be slightly larger than the right and also enhancing more as well [26]

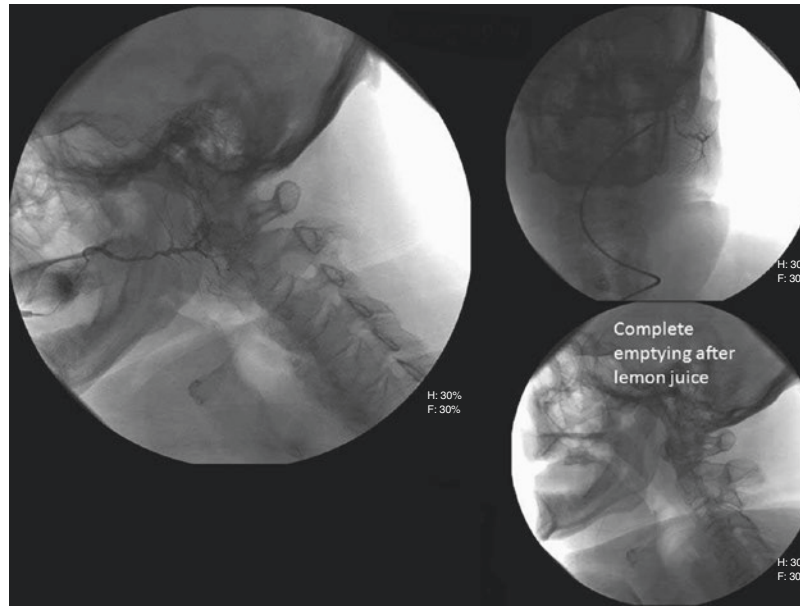

Fig. 13.3 Sialography on a patient with sialadenosis. This sialogram shows characteristic findings of a "leafless tree pattern" or of a thin, hairline salivary ductal system secondary to external compression seen in sialadenosis on sialography [26]

the salivary glands and ducts. Sialography is the modality of choice for visualizing ductal anatomy but has had a controversial role in sialadenosis [21]. In the early stages of sialadenosis, there may be little to no changes visualized on sialography due to the lesser degree of glandular swelling. Sialography in the latter stages of sialadenosis can be of important diagnostic utility because of a characteristic appearance of a thin, hairline salivary duct system, secondary to extrinsic pressure of the parenchymal swelling. In cases where the swelling is particularly pronounced, there may be no visualization of the proximal ductal system [24]. This classic sialography finding in sialadenosis is coined as a "leafless tree pattern" (Fig. 13.3) [3]. Contraindications to sialography are sensitivity to iodine-based compounds or presence of acute inflammation [24].

Pathologic

Pathologic analysis is not as frequently used for diagnosis of sialadenosis but in certain cases can be of important diagnostic utility because of its characteristic findings (Fig. 13.4). As described previously, Donath and Seifert were the first to do a morphometric analysis of sialadenosis, and

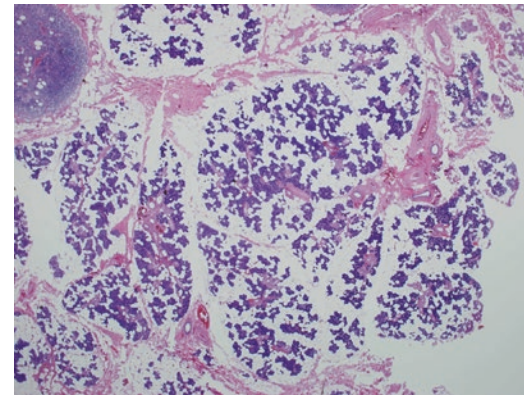

Fig. 13.4 Parotid specimen with sialadenosis. Patient with sialadenosis underwent a parotidectomy and his subsequent parotid specimen slide showing glandular structure with fatty infiltration [26]

they found enlargement of acinar cells when compared to controls, and histologically there was a granular pattern to the cytoplasm, secondary to the increased number of secretory granules [10]. This has been confirmed numerous times by others. FNA of glands with sialadenosis can show acinar enlargement up to 100um, with average control gland sizes between 30 and 40 μm [2, 5]. It has been determined by one group that a mean acinar diameter of greater than 62 μm is diagnostic of sialadenosis [24]. Donath and Seifert also

showed that there was degeneration of myoepithelial cells in sialadenosis. One study showed a diffuse decrease in alpha-actin staining, a contractile myofilament in myoepithelial cells, when compared to controls, which confirms the degeneration of myoepithelial cells. Also, when glands with sialadenosis were stained for Ki67, a marker of proliferation, there were lower levels when compared to the already low levels of controls, showing that the glandular swelling arises from hypertrophy [4].

Management

Treatment of sialadenosis initially starts with identification and treatment of the underlying disease process causing the sialadenosis, although resolution of the swelling is variable [3, 15]. Concurrently, patients can undergo symptomatic treatment including heat management, massage, and sialogogues. Salivary substitutes can also be used in patients who have sialadenosis and xerostomia. Pilocarpine, which is a nonselective muscarinic agonist with a mild B-adrenergic, has been shown to increase salivary flow in patients with sialadenosis and xerostomia and in some cases resolved the swelling that was present [25].

Surgical management is held for refractory cases when the aesthetic appearance of the glandular swelling is unacceptable. Tympanic neurectomy involves denervating the parotid gland of parasympathetic innervation which causes subsequent glandular atrophy. Patients initially have good results with decreased glandular swelling, but in some cases swelling came back after 3 years, likely secondary to parasympathetic reinnervation [24]. Botulinum neurotoxin injection has been used in cases of parotid swelling/hypertrophy to cause atrophy to the gland, but this procedure has to be repeated periodically to obtain consistent results. Parotidectomy is deemed a last resort, especially in patients with bulimia or anorexia, due to their severe body image issues and the potential of morbidity and poor aesthetic results with the surgery [15].

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