A case report of necrotizing sialometaplasia with immunohistological findings and a review of the literature

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Abstract: We report a case of necrotizing sialometaplasia arising as bilateral ulcers in the palate of a 20-year-old Japanese female patient. Based on histopathological and immunohistochemical findings, we discuss how to distinguish the condition from neoplastic lesions such as squamous cell carcinoma or mucoepidermoid carcinoma. Histopathologically, the ulcer bed of granulation tissue contained hyperplastic capillary vessels, inflammatory cell infiltrates, necrotizing and degenerating palatal glands, and squamous metaplasia of ducts and acini leaving lobular structures of the mucous gland. Immunohistochemically, the epithelial islands were positive for pan-cytokeratin (CK), CK7 and S-100 protein, partially positive for α -smooth muscle actin, and not positive for periodic acid-Schiff reaction. We diagnosed the lesion as a necrotizing sialometaplasia. It healed spontaneously without treatment, and there was no recurrence. [Oral Med Pathol 2011; 15: 87-90 doi: 10.3353/omp.15.87]

Key words: bilateral ulcer, cytokeratin 7, literature review, necrotizing sialometaplasia, palate

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Introduction

Necrotizing sialometaplasia (NS) was first reported by Abrams *et al.* in 1973 (1). It is a relatively rare and benign condition of salivary gland metaplasia with necrosis and inflammation. The importance of this disease is that it resembles a malignant tumor both histopathologically and clinically, and the possibility of an incorrect diagnosis exists. Therefore, we should take NS into account when making a diagnosis. In this paper, a case of NS on both sides of the palate in a 20-year-old female is immunohistologically characterized and described.

Case Report

A 20-year-old Japanese female was admitted to the Department of Oral and Maxillofacial Surgery, Tokyo Dental College Suidobashi Hospital, with a chief complaint of a painful ulcer about 15 × 10 mm existing in her bilateral palate (Fig. 1a). The patient had a history of asthma. Two weeks before being admitted to the hospital, she had been conscious of a slight spontaneous pain and swelling in her palate, and had consulted an otolaryngologist, who prescribed a vitamin preparation. However, she then consulted a dentist because her symptoms had not improved.

At the initial visit, she received a blood test, a microorganism test, a histopathological test, and an X-ray examination; in addition, the wound was disinfected. There were no specific radiographic findings. At the second visit, she underwent a CT scan and the wound was disinfected again. Some bone resorption was evident in the CT image (Fig. 1b), and follow-up care was given. The histopathological diagnosis was reported as a NS. The reductive appearance of the ulcer on the palate is shown in Fig. 1c. This case of NS healed without treatment, and there was no recurrence.

Histopathological and immunohistochemical findings

The resected tissue was fixed in 20% neutral buffered formalin, embedded in paraffin, and processed for routine histological examination. Microscopically, fibrous connective tissue was covered with a parakeratotic stratified squamous epithelium with extensions of the epithelial legs. The epithelium had become ulcerated. The submucosa contained granulation tissue hyperplasia of capillary vessels, inflammatory cell infiltration such as neutrophils and lymph cells, necrotizing and degenerating palatine glands with mucus spillage and dissolution of the acinar structure, squamous metaplasia of ducts, and acini with preserved lobular structures (Figs. 2a & 2b). In addition, partially

Fig. 1. Necrotizing sialometaplasia arising in bilateral sides of the palate of a 20-year-old Japanese female patient. Intraoral views of the patient at the initial visit (a) and 17 days later (b). (c) Computed tomography finding of the palatal region. The patient had painful bilateral ulcers, measuring about 15 × 10 mm, on her palate (a). There was some bone resorption in the bilateral palate (b). Reductive appearance of the ulcer was found (c).

assembled neutrophils were observed. Squamous cells with weak nuclear atypia were seen in some areas; however, almost all areas displayed a bland, benign appearance of the squamous cells. The contents of salivary ducts and tissue surrounding the destroyed ducts were positive for periodic acid-Schiff reaction (Fig. 2c). Mucus seemed to be flowing from the ducts. Immunohistochemically, the metaplastic

epithelial islands and the salivary ducts were positive for pan-cytokeratin (Fig. 2d), S-100 protein, and cytokeratin7 (CK7) (Fig. 2e). Ducts and luminal trace parts of metaplastic epithelial islands were positive for α -smooth muscle actin (α -SMA).

Fig. 2. Histopathology of necrotizing sialometaplasia. (a, b) Hematoxylin and eosin stain; (c) periodic acid-Schiff (PAS) stain; immunoperoxidase stain for pan-cytokeratin (d) and cytokeratin 7 (CK7) (e). (a) × 40; (b, e) × 200; (c-d) × 100. The mucosa was partially ulcerated. The lamina propria space was replaced with fibrous granulation tissue, in which inflammatory cell infiltrates and squamous epithelial nests were pronounced (a). The epithelial nests were metaplastic changes of salivary ducts, around which necrotic or degenerative glandular lobules were observed (b). PAS-positive amorphous materials were retained in the salivary duct lumen and scattered around deformed or destroyed ducts (c). Most of the epithelial cells forming both the metaplastic epithelial islands and salivary ducts were positive for pancytokeratin (d), while CK7 was definitely positive in luminal cells of the ducts and faintly and occasionally positive in lumen-like traces within the metaplastic epithelial islands (e).

Discussion

It is said that NS is cured spontaneously within 6 to 12 weeks, and there is no need for surgery (2). However, since NS resembles a malignant tumor histopathologically and clinically (2-3), it is possible that it could be misdiagnosed as a squamous cell carcinoma (SCC) or a mucoepidermoid carcinoma (MEC). Therefore, care is needed to make an accurate diagnosis. NS is a relatively rare disease found in all age groups. Mesa *et al.* reported that it represents only 0.03% of all lesions biopsied during a 10-year period (4). Brannon *et al.* reported that the average age of a patient with NS is 45.9 years, and that NS occurs in men 1.86 times as frequently as women (2). Oda *et al.* reported an average age of 44.1 years and no gender gap in Japan (5). The most frequent site of NS is the palate, which accounts for 70% to 80% of all cases (2, 6). However, bilateral symmetrical affection occurs rarely and has been reported as a 12% incidence (2). Other sites reported include the parotid gland (2, 7), nasal cavity (2, 8-9), upper pharynx (10), gingiva (11), lip (2, 12-13), buccal mucosa (14-15), back of the molar (2, 11, 16), tongue (2, 17) and maxillary sinus (18).

The clinical finding of NS is the formation of an ulcer and a mass. The boundary of the undermined ulcer is comparatively clear. It has been reported that the size ranges from 0.5 cm to 4 cm, with an average of 2 cm (2), and that erythema is sometimes observed surrounding the ulcer (1). Oppressive or dull pain is noted in many cases. However, slight pain is often a clinical finding, and in some cases patients report a numb feeling. In one investigation, the authors thought that the numb feeling was caused by several factors, such as the influence of the greater palatine nerve surrounding the inflammatory stimulus and hematogenous disorder, infarction, and necrosis of the gland tissue (19).

There are various opinions about the cause of NS. The gland infarction theory proposed by Arguelles *et al.*, in which NS originates as a hematogenous disorder due to various causes is the most supported (20). The ischemic necrosis and the ulcer formation of the saliva gland are caused by the squamous metaplasia of glands regenerating epithelial tissue during the reparative process. NS was studied in short-term experiments by Standish *et al.* (21) and

Englander *et al.* (22), who ligated blood vessels of rat mandibular glands. They suggested that an ischemia change is related to the occurrence of NS. Smoking, chronic alcohol use, unsuitable dentures, local anesthesia, surgical treatment, external wounds, upper respiratory infections, tumors, operations, irradiation and frequent emesis are thought to be local causes of NS (2, 8, 23-26). Dominguez-Malagon *et al.* (24) and Yoshioka *et al.* (25) reported that T-cell lymphoma is considered as a causative condition of NS. Ylikontiola *et al.* reported that a girl's adenoidectomy may have affected branches of the palatine arteries in the soft palate, compromised the underlying vascular supply and likely caused infarction of the salivary gland tissue (26). In our case, the possible causes described above were not found. Disturbances of nutrition caused by eating disorder, hyperpiesia, diabetes or tuberculosis are thought to be whole body incitement (1, 19, 27-28).

The features of NS described by Abrams *et al.* include the following: i) lobular infarction or necrosis; ii) bland-appearing nuclear morphology of the squamous cells; iii) simultaneous metaplasia of ducts and mucous acini; iv) prominent granulation tissue and inflammatory components; and v) maintenance of the general lobular morphology in spite of fairly extensive inflammatory and metaplastic changes often involving more than one lobule (1). In the present case, necrotic and degenerating palatine glands and a bland-appearing nuclear morphology of the squamous cells were observed. Part of the lobular morphology was indistinct, but most of the cells preserved a lobular architecture. The preservation of normal lobular architecture of salivary glands seems to be a key feature that distinguishes NS from neoplasia (1). Anneroth and Hansen clarified the histopathogenesis of NS by suggesting it has five histopathologic stages: i) infarction, ii) sequestration, iii) ulceration, iv) reparation, and v) healed. Our case is considered to be at the ulceration or reparation stage (6).

The results of immunohistochemical findings have been reported (Table 1). Rizkalla *et al.* investigated the use of immunohistochemistry to distinguish NS from SCC and MEC by identifying residual myoepithelial cells and cytokeratin expression (29). Immunohistochemical staining showed that residual myoepithelial cells and CK7 expression

Table 1. Histochemical and immunohistochemical profiles of necrotizing sialometaplasia documented in the literature

staining	reports by (reference #)				present case
	Oda Y <i>et al.</i> (5)	Miki Y <i>et al.</i> (19)	Rizkalla H <i>et al.</i> (29)	Lee DJ <i>et al.</i> (30)	
periodic acid schiff (PAS)	(+)	(+)			(+)
pan-cytokeratin		(+)			(+)
cytokeratin 5, 6			(+)	(+)	
cytokeratin 7			(+)	(+)	(+)
cytokeratin 7, 8 (CAM 5.2)			(+)		
cytokeratin 18		(+)			
α -smooth muscle actin			(+)	(+)	(±)
calponin			(+)		
S-100 protein	(-)		(+)		(+)
p63			(+)	(+)	
Ki-67		(±)			

may help to distinguish NS from similar conditions. In general, squamous metaplasia is considered to occur in acinar and ductal components (23-24). S-100 protein and α -SMA, well known as myoepithelial cell markers, were found to be positive in solid epithelial islands, which meant they were myoepithelial characters. The solid epithelial islands were also considered to simultaneously obtain ductal characteristics, because moderate CK7 expression was occasionally found in the lumen of the epithelial islands with duct-like structures and the solid epithelial islands. These results indicated their epithelium metaplastic nature from salivary gland terminal cells. Considering the staining results, we diagnosed this NS from an ulcer in the bilateral palate.

In summary, the ability to distinguish NS from SCC and MEC relies on characterized morphological features. While hematoxylin-eosin staining remains the gold standard for making a diagnosis, the use of immunohistochemical staining to detect residual myoepithelial cells and CK7 expression is helpful as an adjunct in difficult cases. As shown in the case reported here, it is important to distinguish NS from malignant tumors and to employ treatment methods based on histopathological diagnosis at an early stage to avoid overtreatment.

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