Necrotizing Sialometaplasia
A Practical Approach to the Diagnosis

Diane L. Carlson, MD

• Context.—Necrotizing sialometaplasia is a benign, self-limited lesion of both major and minor salivary glands, although more commonly the latter. It can represent a diagnostic dilemma and may be mistaken for a malignant neoplasm, such as mucoepidermoid carcinoma, as well as invasive squamous cell carcinoma. A major causal relationship has been ascribed to ischemia. Bulimia, an eating disorder with increasing prevalence in our society, may also be an underlying underreported cause.

Objective.—To discuss the potential pathogenesis, diagnostic pitfalls, and the application of immunohistochemistry as an aid in the diagnosis of necrotizing sialometaplasia.

Data Sources.—This report uses a previously published case history for illustrative purposes and a review of the current literature.

The diagnosis of necrotizing sialometaplasia may be difficult and is reliant upon a well-oriented biopsy section and a complete clinical history. Diagnosis may be further supplemented via immunohistochemistry, demonstrating focal to absent immunoreactivity for p53, low immunoreactivity for MIB1 (Ki-67), and the presence of 4A4/p63- and calponin-positive myoepithelial cells. Interpreted in context collectively, these findings may be helpful adjuncts in the diagnosis of necrotizing sialometaplasia; nonetheless, to date, hematoxylin-eosin staining remains the gold standard. (Arch Pathol Lab Med. 2009;133:692–698)

Necrotizing sialometaplasia (NSM) is a benign, self-healing lesion of salivary glands, which represents less than 1% of biopsied oral lesions.1 It may arise in any area containing salivary gland tissue. Classically, it involves the mucous glands of the hard palate. Other sites where it has been reported include nasal cavity, trachea, parotid gland, sublingual gland, submandibular gland, larynx, buccal mucosa, maxillary sinus, tongue, tonsil, and retromolar trigone.2–5 Up to 10% of cases have been reported in major salivary glands.6 Collective examination of 184 cases reported in the literature reveals that the condition occurs in men in 65% of cases.3 Herein is a discussion of the clinical and pathologic findings, potential pathogenesis, and differential diagnosis of this entity.

CLINICAL PRESENTATION

The lesion is usually painful and presents as a sharply circumscribed ulcer, frequently 1 to 3 cm in diameter. Palate involvement usually appears as a single, unilateral ulcer on the posterior hard palate or at the junction of the hard and soft palates. The ulcer borders are often erythematos and may be raised. In some instances, the mucosal surface is intact and the lesion is raised and fluctuant, giving the false impression of an abscess.

There is a wide range in the age at presentation (1.5–83 years), although most patients are older than 40 years.3,7 The incidence appears to be 2 to 3 times greater in males than females.8 Patients commonly consult their dentist with fear for carcinoma and with a history of a noticeable lesion of a few weeks’ duration.

ETIOLOGY

The most commonly proposed and generally accepted etiology for NSM relates to ischemia. In 25 of 69 cases reported by the Armed Forces Institute of Pathology, the process was seen subsequent to a surgical procedure.3 Other traumatic injuries, such as dental injection, blunt force trauma, denture wear, alcohol and tobacco use, as well as upper respiratory infections, have been implicated as potential predisposing factors. Romagosa and colleagues9 reported 3 cases occurring in the trachea after intubation. Similarly, it has been described in the larynx secondary to atheromatous embolization.10

Anneroth and Hansen4 proposed 5 histologic stages in the development and evolution of necrotizing sialometaplasia: infarction, sequestration, ulceration, repair, and healing. They emphasized that these stages could overlap and would be dependent upon the extent and severity of damage.

An emerging associated etiology is that seen in the setting of bulimia, a history often difficult to elicit. Bulimia is a well-recognized eating disorder in which individuals binge eat unusually large quantities of food and induce vomiting by a mechanical gag reflex or by ingesting syrup...
of ipecac. According to the American Psychiatric Association, anorexia nervosa and bulimia nervosa affect as many as 3% of adolescent and young adult females, and the incidence of anorexia nervosa appears to have increased in recent decades. In a culture where “thin is in,” it would seem reasonable to conjecture that bulimia is most likely underreported and, hence, so is its correlation with NSM.

Necrotizing sialometaplasia in the context of bulimia was first reported in 1998 in 2 patients and has since been reported in 5 and possibly 6 cases. All patients were white women between the ages of 29 and 32 and the site of involvement for all was the palate (Table 1). Other oral complications frequently reported in association with bulimia include sialadenosis, which is hypertrophy of serous acinar cells, often with infiltration of adipocytes and without an inflammatory component. This is most commonly manifested in the parotid gland and is frequently bilateral. Xerostomia, dental caries, tooth erosion, and demineralization of enamel and dentin are additional consequences of repetitive, chronic vomiting.

A similar phenomenon to NSM has been described in the breast, lung, and skin. In the skin, it has been referred to as eccrine squamous syringometaplasia, where it has been reported in association with chronic ulcers, cytomegalovirus, herpesvirus, underlying neoplasia, and chemotherapeutic agents. The squamous metaplasia of minor salivary gland ducts and acini may contain apoptotic cells and areas of inflammation as well as mucin spillage. The preservation of the normal lobular architecture of the salivary glands is a key feature.

For illustrative purposes, a discussion of the characteristics of NSM follows that uses a previously published case, with additional immunohistochemistry results not previously reported.

**Case History**

A 32-year-old woman with a history of bulimia presented with a painful lesion on the left side of the hard palate of 12 weeks’ duration. On biopsy, this lesion was initially diagnosed as a mucoepidermoid carcinoma (Figure 1, a and b). The biopsy specimen was subsequently sent to a large tertiary cancer center where the diagnosis rendered was of a superficially invasive well-differentiated squamous cell carcinoma. The patient went to a third treatment center, where she underwent a conservative complete resection of the area. No lymph nodes were dissected. The slides from the initial biopsy and subsequent excision were then reviewed by another expert, who rendered a diagnosis of necrotizing sialometaplasia. A 6-month follow-up of the patient demonstrated complete resolution of any palatal lesion; however, the patient’s eating disorder remained uncontrolled.

Histologic features that help exclude the diagnosis of NSM include perineural invasion, the presence of apparently neoplastic goblet cells or proliferation thereof, and atypical mitoses. The extent of cellular necrosis must be evaluated in context. A few necrotic single cells are far less worrisome than islands of necrotic squamous cells. Similarly, while NSM may demonstrate cytologic atypia, marked nuclear pleomorphism in conjunction with high nuclear to cytoplasmic ratios should elicit concern for a malignant neoplasm (Figure 2, a and b).

**Differential Diagnosis**

The 2 most important differential diagnoses include squamous cell carcinoma and mucoepidermoid carcinoma. An entity described in the dental literature as nicotinic stomatitis, associated with cigar and pipe smoking, has a quite similar histologic and clinical presentation. It tends to be multifocal and grossly more punctate, with multiple
Figure 1.  a, Palate biopsy section demonstrating pseudoepitheliomatous hyperplasia in conjunction with necrotizing sialometaplasia. b, Higher magnification demonstrating atypia (hematoxylin-eosin, original magnifications ×20 [a] and ×400 [b]).

Figure 2.  a and b, Invasive squamous cell carcinoma of the palate in a 72-year-old man. Nuclear pleomorphism and abnormal mitotic figures are conspicuous (hematoxylin-eosin, original magnifications ×100 [a] and ×600 [b]).

Figure 3.  a and b, A parotidectomy for papillocytic acinic cell carcinoma demonstrates necrotizing sialometaplasia at the periphery of the gland, associated with a tissue culturelike proliferation of fibroblasts and granulation tissue (hematoxylin-eosin, original magnifications ×400 [a] and ×600 [b]).
Figure 4. Palate biopsy with necrotizing sialometaplasia demonstrating maintenance of the lobular architecture (hematoxylin-eosin, original magnification ×40).

Figure 5. Comparison of necrotizing sialometaplasia (NSM) and squamous cell carcinoma (SCC). Immunohistochemical staining with calponin highlights the presence of basal myoepithelial cells in NSM (a and b) and absence in SCC (c and d) (original magnifications ×100 [a and c] and ×200 [b and d]).

Foci localized to the palate. These latter lesions are not considered preneoplastic and resolve upon cessation of smoking.

Clinical history is helpful in recognizing NSM, although not all cases will be correlated with an obvious etiologic event. But when possible, it is of tremendous utility to interpret these lesions in the correct clinical context. Cytologic atypia can be severe with single-cell necrosis and hyperchromatic, angulated cells. In a major salivary gland, such as the parotid, an associated or nearby proliferation of tissue culturelike fibroblasts and granulation tissue may be present (Figure 3, a and b). It is the maintenance of lobular architecture, best seen at low power, which is the best histologic clue (Figure 4).

Reactive squamous epithelium can appear alarmingly atypical, with single-cell necrosis; hence, the application of immunohistochemistry has been attempted and proposed as an adjunct to diagnosis. The incorporation of an antibody panel including myoepithelial markers (smooth muscle antibody, p63, calponin), basement membrane markers (laminin, collagen type IV), E-cadherin, and various cytokeratins (CK5, CK6, CK7, CAM 5.2) has been suggested (Figure 5, a through d; Figure 6, a through d). These assays may be helpful when the basal layer sur-
Figure 6. Squamous cell carcinoma (SCC) is usually negative for cytokeratin (CK) 7, whereas benign and reactive salivary gland epithelium is CK7-positive. Mucoepidermoid carcinoma (MEC) is also positive for CK7. a, Necrotizing sialometaplasia, (CK7 immunostain, original magnification ×200). b, SCC (CK7 immunostain, original magnification ×200). c, MEC (hematoxylin-eosin, original magnification ×100). d, MEC (CK7 immunostain, original magnification ×100).

Figure 7. While necrotizing sialometaplasia is immunoreactive for MIB-1 (Ki-67) (a), the degree and intensity is far greater in squamous cell carcinoma (b) (original magnifications ×200 [a] and ×200 [b]).
malignancy, but, alone, neither is diagnostic (Figure 7, a and b; Figure 8, a through c). If a diagnosis of NSM is unclear on hematoxylin-eosin staining, the aforementioned antibodies may be supportive of a diagnosis but will not be pathognomonic. All test results must be interpreted in relation to each other, as well as within the clinical setting. Therefore, at present, multiple serial sections and a properly oriented tissue section remain the mainstay of diagnosis of NSM.

**TREATMENT AND PROGNOSIS**

The proposed etiology of NSM is vascular ischemia. Both physical and chemical trauma have been reported antecedent to the development of these lesions. Surgery, radiation, inflammation, and bulimia have all been associated with NSM. The treatment is symptomatic and lesions will undergo spontaneous healing within 2 to 3 months. Necrotizing sialometaplasia does not usually recur, and if it is properly diagnosed preoperatively, surgical excision is not necessary. Lesions that fail to resolve should be reassessed.

Interestingly, the Third National Health and Nutrition Examination Survey, conducted in the United States for a period of 6 years, revealed that of 17,235 adult patients, 25.9% had clinically detectable palate lesions on oral mucosal examination.25 These lesions ranged from infectious and benign to preneoplastic. Smokers had a higher prevalence of palatal lesions than did nonsmokers. Perhaps the palate is more sensitive to ischemia, in a variety of forms, more so than are other areas of the oral mucosa.

**SUMMARY**

The foremost characteristic histopathologic features of NSM are the overall preservation of lobular architecture and ductal squamous metaplasia. The differential diagnoses of greatest import include mucoepidermoid carcinoma and squamous cell carcinoma. The clinical scenario of a nonhealing palatal ulcer in an adolescent or young adult patient with clinical signs of bulimia should greatly increase suspicion for NSM, particularly because squamous cell carcinoma of the palate is uncommon in young females. While there is no definitive immunophenotype—and a properly oriented hematoxylin-eosin section remains the gold standard for diagnosis—use of MIB-1 (Ki-67), p53, calponin, and CK7 may be helpful, so long as they are interpreted in relation to each other. Avoidance of overtreatment of a nonneoplastic condition is the ultimate goal in maintaining the dictum *primum non nocere*.

**References**


Figure 8. Similar to the pattern of immunoreactivity with MIB-1 (Ki-67), p53 shows far greater positivity in squamous cell carcinoma (c), whereas in necrotizing sialometaplasia (a and b) it is faint and scant (original magnifications ×40 [a and c] and ×100 [b]).

Arch Pathol Lab Med—Vol 133, May 2009