

## Necrotizing sialometaplasia of the palate associated with angiocentric T-cell lymphoma

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### Abstract

In this article we present 2 cases of necrotizing sialometaplasia (NS) associated with angiocentric lymphoma of the midline. Immunohistochemical analysis confirmed a T-cell origin, and in situ hybridization in one case revealed its relationship to Epstein-Barr virus. These findings suggest that vascular occlusion by the neoplastic cells produces ischemia, which leads to local infarction contributing to the salivary gland lesion. To our knowledge, the association between angiocentric lymphoma and NS has been previously reported in only one instance, and we suggest that this particular type of lymphoma should be added to the list of related conditions for NS.

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### 1. Introduction

Necrotizing sialometaplasia (NS) is a benign inflammatory condition that may occur in any site containing salivary gland elements, although it most frequently involves the minor salivary glands of the hard palate [1,2]. Morphologically, NS is characterized by lobular necrosis with granulation tissue and inflammation. Typically, there is pseudoepitheliomatous hyperplasia of the surface epithelium and squamous metaplasia of ducts and acini with preservation of the lobular architecture. Most authors believe NS is the result of ischemia that leads to local infarction. The cause of this phenomenon is uncertain, but a number of potential predisposing factors have been implicated, mostly related to local trauma and injury, including dental injections, alcohol abuse, smoking, cocaine use, upper respiratory infections, prior surgery, and adjacent tumor growths [2-4].

Association of NS with neoplastic conditions is a relatively rare event; Brannon et al [2], in a detailed study of 69 cases obtained from the surgical pathology files of the Armed Forces Institute of Pathology and a review of 115 cases from the literature, found 8 instances of NS associated with an adjacent neoplasm or a cystic lesion, and only 4 of them occurred in the palate (1 mixed tumor, 1 monomorphic adenoma, 1 salivary gland hyperplasia, and 1 lymphoproliferative lesion). To our knowledge, there is only one case report of nasal natural killer (NK) cell/T lymphoma associated with pseudoepitheliomatous hyperplasia and NS [5].

The purpose of this article was to present 2 unusual cases of NS associated with angiocentric T-cell lymphoma of the midline, one arising in the palate and the other in the nasal cavity, and to discuss the possible pathogenic mechanisms, diagnostic difficulties, and salient pathologic findings.

### 2. Presentation of the cases

#### 2.1. Case 1

A 24-year-old man was referred to our hospital for evaluation and treatment of a rapidly growing palatal lesion discovered 2 months earlier. Physical examination

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revealed a 3 × 2-cm ulcerated and bleeding lesion extending from the hard palate to the oropharynx. There was no palpable lymphadenopathy.

By needle biopsy, the lesion was interpreted as a nonspecific inflammatory lesion. An incisional biopsy sample of the hard palate was taken, which produced persistent hemorrhage that lasted for several hours until it was controlled by constant gauze pressure. A diagnosis of NS associated with angiocentric T-cell lymphoma was established in the biopsy material.

Subsequent staging procedures, including a bone marrow biopsy, failed to identify any involvement by lymphoma. The patient received 5 cycles of chemotherapy consisting of cyclophosphamide, doxorubicin, vincristine, and prednisone. However, the response was poor and the lesion extended into the nasal mucosa, producing obstruction of the left side. During this period, the patient had intermittent fever but results of repeated cultures of the ulcer were negative for bacteria. Later he developed pancytopenia and persistent fever suggestive of virus-associated hemophagocytic syndrome, which was not corroborated. He finally died of acute hepatic failure 5 months after admission. No permission for autopsy was granted.

## 2.2. Case 2

A 39-year-old woman was admitted because of rhinorrhea, otalgia, and nasal obstruction accompanied by fever and weight loss of 20 kg. Computerized axial tomography scan disclosed a tumor involving all paranasal sinuses with a zone of osteolysis of the medial wall of the maxillary sinus. Results of a biopsy showed angiocentric T-cell lymphoma.

Treatment included radiotherapy (30 Gy) and 4 cycles of chemotherapy with a combination of cyclophosphamide, doxorubicin, vincristine, and prednisone. Complete clinical remission was obtained but the patient abandoned the treatment and was lost to follow-up at 7 months of treatment.

## 3. Materials and methods

Sections for histologic analysis were obtained from paraffin-embedded tissue and stained by routine hematoxylin-eosin method. Immunohistochemical studies were performed from the same paraffin blocks using primary antibodies to CD45 (LCA), CD43 (MTI), CD45RO (UCL-1), CD15 (LeuM-1), CD30 (BerH2), CD4, CD8 (Dako, Carpinteria, CA), CD57 (Biogenex, San Ramon, CA), Epstein-Barr latent membrane protein (LMP-1, Dako), CD20 (L26), CD3, CD56, granzyme, and TIA-1.

In situ hybridization for Epstein-Barr virus (EBV)-encoded RNA (EBER) was kindly performed by Dr John K. C. Chan at Queen Elizabeth Hospital in Hong Kong on sections obtained from paraffin-embedded tissue.

## 4. Histologic findings

Histologic examination of case 1 disclosed an ulcerated lesion characterized by abundant granulation tissue associated with pseudoepitheliomatous hyperplasia of the covering epithelium, acinar necrosis of the adjacent salivary glands, and squamous metaplasia of ducts and acini with preservation of the lobular architecture (Fig. 1A). A profuse lymphocytic infiltrate with a population of atypical cells

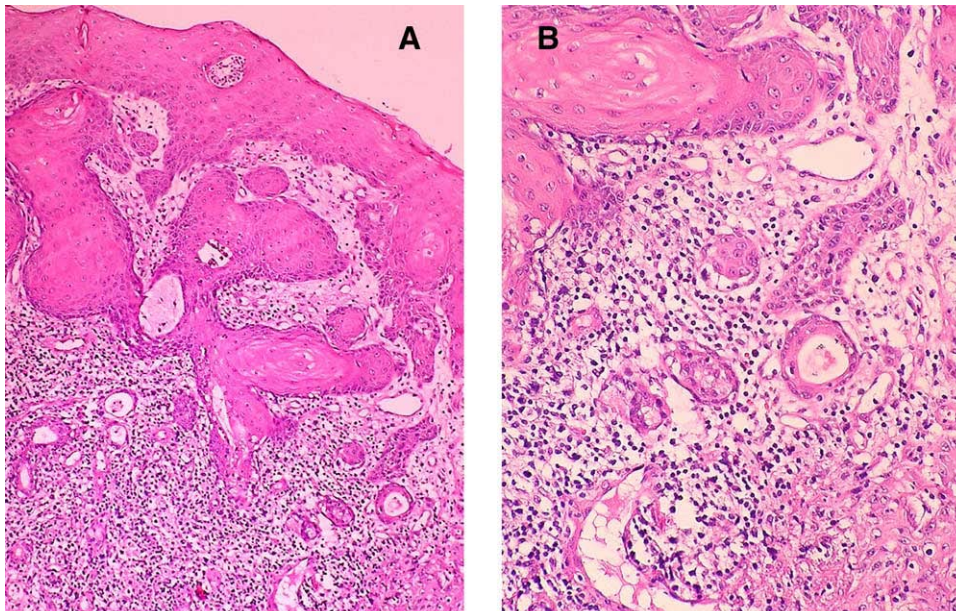


Fig. 1. Histologic appearance of palatal lesion in case 1. (A) Squamous metaplasia of salivary gland ducts and acini with lobular preservation. (B) Atypical lymphoid cells infiltrating the stroma adjacent to salivary ducts.

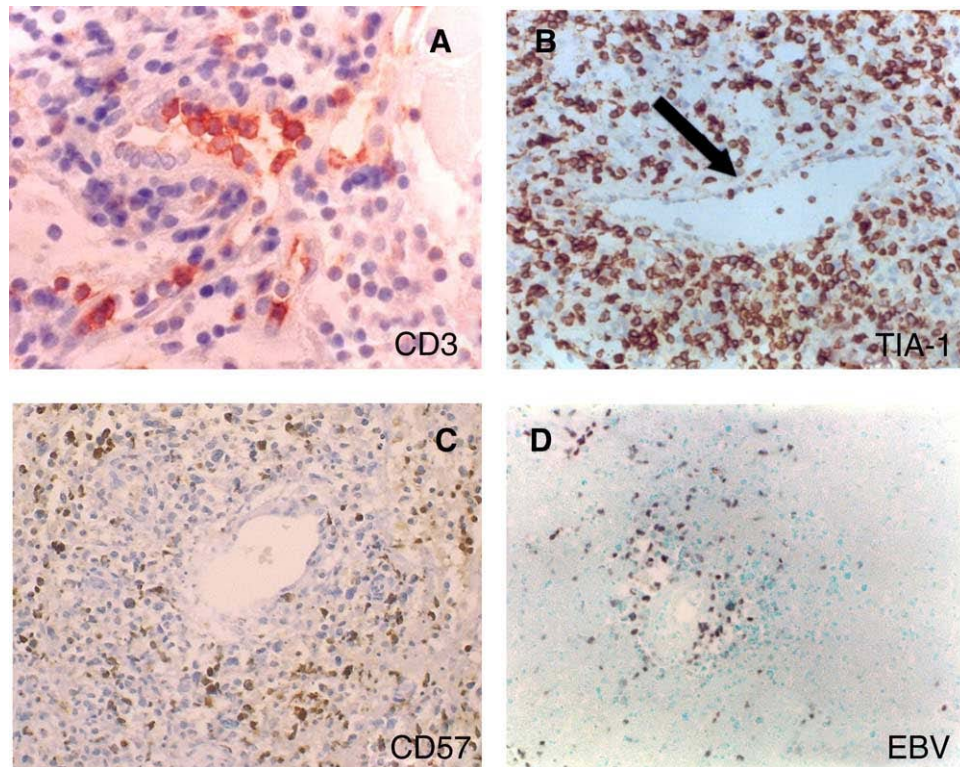


Fig. 2. Immunohistochemical and in situ hybridization studies of case 1: atypical lymphoid cells positive for CD3 infiltrate the endothelium of a vessel (A). TIA-1 is expressed in lymphoid cells infiltrating a vessel (arrow); granular staining is seen in the cytoplasm (B). CD57+ cells infiltrate the wall of a blood vessel (C). In situ hybridization for EBV shows strong signal in neoplastic cells (D).

surrounded the epithelial structures and extended downward to infiltrate adjacent glandular tissue (Fig. 1B) and skeletal muscle. The cell population showed a diffuse growth pattern with some patchy necrotic areas, and it was prominent around and within blood vessels. The lymphoid cells featured scarce pale cytoplasm and convoluted nuclei with finely dispersed chromatin and small to medium-sized nucleoli.

A nasal biopsy in case 2 showed respiratory epithelium with extensive areas of coagulative necrosis. The accessory mucous glands featured lobular necrosis and squamous metaplasia involving ducts and acini with preservation of the lobular architecture (Fig. 3A). A diffuse infiltrate with a population of large atypical lymphoid cells surrounded the epithelial structures and invaded the walls of some blood vessels (Fig. 3B). The atypical lymphoid cells featured scarce pale cytoplasm and ovoid nuclei with clumped chromatin and prominent nucleoli.

### 5. Immunohistochemical findings

In case 1, the atypical lymphoid infiltrate displayed a strong positivity for CD45, CD3 (Fig. 2A), CD57 (Fig. 2C), CD45-RO, and TIA-1 (Fig. 2B). Results for other markers including CD20, CD4, and CD8 were negative. In situ hybridization showed a strong nuclear signal for EBV in lymphoid cells (Fig. 2D).

The lymphoid cells of case 2 displayed a strong positivity for CD3 (Fig. 3C) and granzyme (Fig. 3D), and focal positivity for CD57. Results for other markers including C20, CD56, and CD34 were negative.

### 6. Discussion

More than 75% of the reported cases of NS occurred in the salivary glands of the palate. In this location it usually starts as a nonulcerated swelling, often associated with pain or paresthesia, which eventually breaks to produce a deep and well-demarcated ulcer that ranges from less than 1 to more than 5 cm in diameter and heals spontaneously after 4 to 6 weeks [2–4].

Necrotizing sialometaplasia is believed to be a lesion that results from local ischemia, secondary to blockage of blood supply to the salivary gland tissue. This hypothesis is based on histologic findings, which include necrosis of acini with preservation of the lobular architecture, squamous metaplasia of ductal epithelium, and, in some cases, marked pseudoepitheliomatous hyperplasia of the overlying epithelium [1–4]. Because of its clinical and microscopic features, it has been confused with squamous carcinoma and mucoepithelioid carcinoma [1,2,4,6].

The pathogenesis of NS has been a controversial issue, but most authors agree that local ischemia is an important mechanism. Morphologic evidence is provided by the

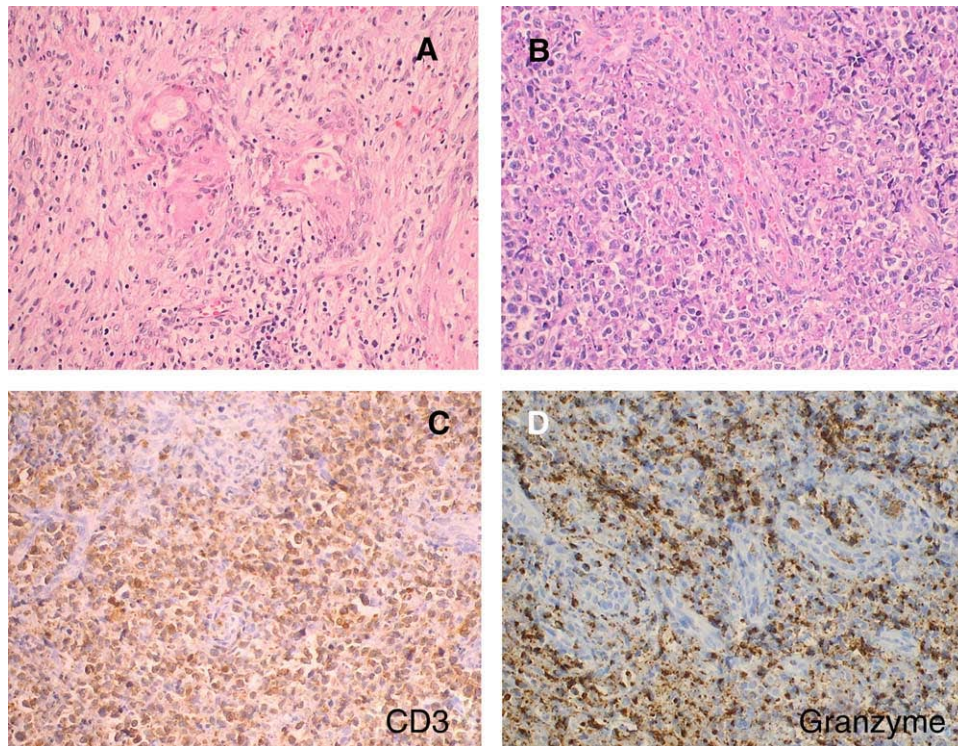


Fig. 3. Histologic and immunohistochemical appearance of case 2. Accessory glands show squamous metaplasia with preservation of lobular architecture (A). Angiocentric infiltrate by atypical lymphoid cells (B). The neoplastic lymphoid cells express CD3 (C) and granzyme (D).

presence of lobular infarction in the early phases of the disease, and support is given by experimental animal models, in which fastening of duct and artery of submandibular glands produces necrosis and subsequent replacement of the glandular tissue by scar tissue; there is reduction in mucus production and most acini degenerate, and consequently, there is replacement of the ductal columnar epithelium by squamous cells [7,8].

Necrotizing sialometaplasia has been described in association with several nonneoplastic conditions that may produce local vascular obliteration, such as atherosclerosis [8], local surgical trauma [2,9,10], allergy [2], thromboangiitis obliterans (Buerger disease) [11], dental injections, dental prosthesis, sickle cell anemia [12], and heavy alcohol and tobacco consumption [2]. Neoplasm including mixed tumor, monomorphic adenoma, Warthin tumor, and rhabdomyosarcoma have been published in association with NS [2,13]. One case of lymphoproliferative disease described associated with NS later proved to be an extension of a disseminated lymphoma [2].

Lymphoproliferative lesions that originate in the nasal cavity, paranasal sinuses, and hard palate constitute a diagnostically challenging group of diseases that have been included in the clinical spectrum of the so-called lethal midline granuloma syndrome [14]. Most of these lesions have proved to be malignant lymphomas, with a predominance of T/NK-cell lineage in Asian and some Latin-American populations [14,15]. Angiocentric T/NK

cell lymphomas in this anatomic region produce widespread necrosis, which is the result of vascular angioinvasion and angiodestruction by the cytotoxic cells and the surrounding inflammatory cell infiltrate. This produces large areas of ulceration on the overlying mucosa that may be confused clinically with various inflammatory and neoplastic diseases, and it is often necessary to perform several biopsies to reach a final diagnosis [16].

Necrotizing sialometaplasia had not been described in previous series of angiocentric lymphomas of the palate [15]. Recently, a case report appeared in the Indian literature on a nasal NK/T lymphoma associated with pseudoepitheliomatous hyperplasia and NS [5].

The unusual association of NS with T-cell lymphoma in the 2 cases presented here could be due to local ischemia of palatine salivary glands, possibly as a consequence of angioinvasion and angiodestruction by the neoplastic lymphocytes.

Although there is heterogeneity, most authors agree that most angiocentric lymphomas are derived from Epstein-Barr virus-infected cytotoxic lymphocytes of both NK- and T-cell lineages [17]. Most cases display a T/NK-cell phenotype characterized as CD2+, CD3+, CD56+, TIA-1+, and EBER+ [18,19]. In contrast, case 1 was characterized as CD56-, CD57+, CD3+, TIA-1+, CD4-, CD8+, and EBER+, and case 2 as CD3+, CD56-, and granzyme+. For these reasons, they are not considered of NK-cell lineage but better classifiable as cytotoxic T-cell lymphomas.

Both NK cells and cytotoxic T cells are characterized by the presence of cytoplasmic granules such as perforin, granzyme, and TIA-1, which are released in response to target cell recognition and play an important role in the induction of apoptosis and lysis of the target cell [20]. EBV is a significant and consistent finding among NK- and T-cell malignant lymphomas and, regardless of geographic origin, this infectious agent has been demonstrated in more than 95% of cases [18,21]. However, TIA-1 and granzyme are not limited to NK-cell lymphomas but are also seen in cytotoxic lymphomas of true T-cell lineage. In the series studied by Chan et al [22], there was a small group of tumors that were EBER+, TIA-1+, CD56-, CD2+, CD3+, CD4-/CD8-, or CD4-/CD8+. In the proposed World Health Organization classification, most angiocentric midline lymphomas would be grouped under the NK/T-cell lymphoma category; however, the question of how to classify EBER+, CD56-, and TIA-1+ angiocentric lymphomas of T-cell lineage occurring in similar sites with similar morphology still remains to be resolved.

In conclusion, we have described 2 cases of NS associated with midline angiocentric lymphomas. Based on these findings, we postulate that vascular occlusion by the neoplastic lymphoid cells produced ischemia and contributed to the development of the salivary gland lesion. To our knowledge, the association between NS and T-cell lymphoma has not been previously reported, and this particular type of lymphoma should be added to the list of conditions related to NS.

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