Lymphadenoma of parotid gland: Two additional cases and a literature review

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For classification purposes, proper identification of infrequent and unique salivary gland tumors requires the gradual accumulation of a sufficient number of cases. Lymphadenoma (i.e., an adenomatous, generally parotid-based lesion with an exaggerated lymphocytic infiltrate, but a lack of sebaceous differentiation) has approximately 9 reported cases. This report adds 2 additional cases occurring as a discrete, at least partially encapsulated nodule in the parotid gland. Embedded within the extensive lymphocytic component were isolated nests of solid or glandular epithelium, with 1 case displaying a few foci of chondrocytic differentiation. Immunohistochemical investigation of the latter case revealed the presence of both luminal and myoepithelial cells. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008;105:491-4)**

A lymphoid component is the norm for salivary gland lesions such as Warthin's tumor, sebaceous lymphadenoma and carcinoma, lymphoepithelial cyst, and lymphoepithelial carcinoma. With varying but considerably less frequency, tumor-associated lymphoid stroma also occurs in acinic cell carcinoma, mucoepidermoid carcinoma, oncocytoma, oncocytic carcinoma, primary squamous cell carcinoma, and cystadenocarcinoma.[1,2]

Lymphadenoma represents a relatively recent addition to the group of salivary gland lesions with a prominent tumor-associated lymphoid stroma, with perhaps 9 cases reported or illustrated in journals and texts—in a few instances, it is not possible to tell if the same cases are being illustrated.[1,3-8] Histologically, lymphadenomas are well-defined, generally encapsulated lesions with a predominant lymphoid background within which most often are embedded solid nondescript or squamous epithelial nests.[4,6-8] But occasionally, the epithelium is glandular,[5] mixed solid/glandular,[3] or cystic.[3-5] In all of these cases, what distinguishes these lesions from sebaceous lymphadenoma has been the absence of sebaceous differentiation. In addition, the arrangement and cellular makeup of the epithelium does not resemble any of the usual benign or malignant salivary gland tumors. This report describes 2 additional cases of lymphadenoma occurring in the parotid gland, 1 of which has some unique histological aspects.

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MATERIAL AND METHODS

Case 1 had been recently accessioned as a surgical pathology specimen in the Department of Laboratory Medicine at the Ottawa Hospital, Ottawa, Ontario, whereas Case 2, which in 1981 had originally been thought to represent a basal cell adenoma with extensive lymphocytic infiltrate, was retrieved from the files of the Canadian Reference Centre for Cancer Pathology, University of Ottawa, Ottawa, Ontario.

Following review of the hematoxylin-eosin sections, additional sections were cut and immunostained using routine immunoperoxidase techniques and antigen retrieval (except for S-100 protein) with the following antibodies: AE1/AE3 (Chemicon, Temecula, CA; 1:400 dilution), smooth muscle actin (Dako Canada, Mississauga, Ontario, Canada; 1:50 dilution), p63 (Dako Canada; 1:100 dilution), and S-100 protein (Biogenex Inc., San Ramon, CA; 1:200 dilution). Unfortunately, due to poor fixation of the material archived from Case 2 in 1981, meaningful immunostaining could not be obtained.

CASE REPORTS

Case 1

A 45-year-old man appeared with a right parotid mass approximately 2 cm in diameter. There was no cervical lymphadenopathy. The excised tumor was well defined and separated from the parotid gland by a capsule of variable thickness, below which there was no evidence of lymphatic sinusoids (Fig. 1, *A, B*). Histologically, the main feature was a dense lymphatic

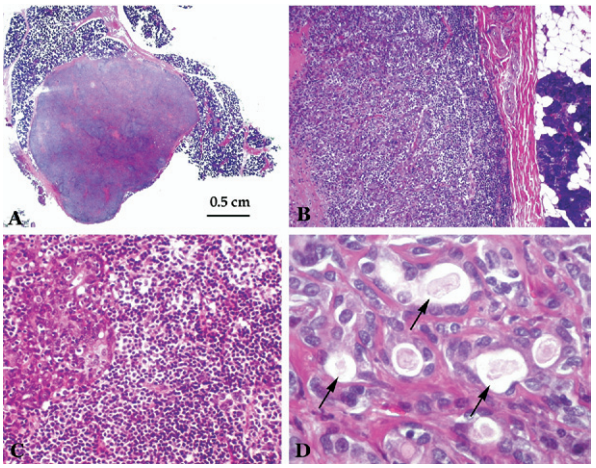

Fig. 1. Case 1. **A,** Intraparotid, discrete, thinly encapsulated tumor nodule. Note the extensive lymphocytic infiltrate (hematoxylin-eosin). **B,** A relatively thin capsule separates the tumor nodule from normal parotid gland (right; (hematoxylin-eosin, original magnification ×50). **C,** At this magnification, the ill-defined epithelium is distinguishable from the more numerous lymphocytes (hematoxylin-eosin, original magnification ×130). **D,** In this region, the epithelium consists of nests of regular epithelial cells forming variably sized, glandular, or ductlike lumens (*arrows*; (hematoxylin-eosin, original magnification ×325).

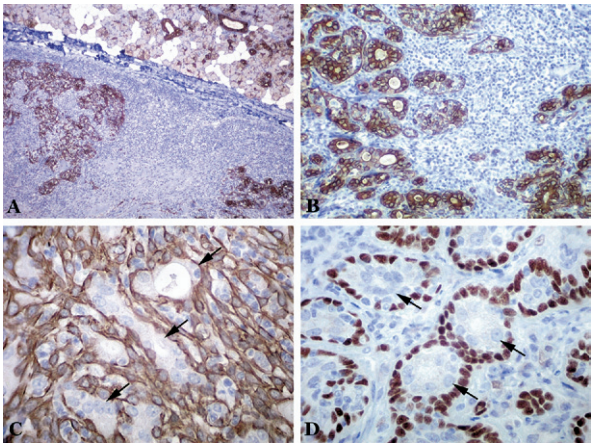

Fig. 2. Case 1. Immunohistochemical preparations. **A,** Low-power micrograph (×50) immunostained with anticytokeratin antibody AE1/AE3, showing the irregular clusters of epithelial cells within the predominant and unstained lymphocytic population. Note the preferential staining of ductal structures in the adjacent, normal parotid gland (top). **B,** Higher magnification of AE1/AE3 immunostained tumor (×130) showing the irregularly shaped and sized ductlike structures enclosed by lymphocytes. **C,** Immunostaining with anti–smooth-muscle actin antibody revealing polygonal to spindle-shaped abluminal tumor cells, some of which surround nonstaining luminal cells (*arrows*; ×325). **D,** In this region, antibody to p63 clearly defines the polygonal to slightly flattened abluminal cells surrounding unstained luminal cells (*arrows*; ×325).

infiltrate that tended to obscure an isolated epithelial component (Fig. 1, *A, B*). The latter consisted of irregularly sized and shaped sheets of tumor cells and collections of ductlike glandular structures (Fig. 1, *C, D*), both of which became more obvious in immunohistochemical preparations (Fig. 2, *A, B*). A few foci of collagenous and chondroid matrix, as well as epithelial nests with prominent basement membranes, were evident (Fig. 3, *A, B*). The numerous lymphocytes were small and uniform in appearance (Fig. 1, *B, C*; Fig. 2, *A, B*) and the epithelial component showed no evidence of cytological or nuclear abnormalities and a lack of mitotic activity (Fig. 1, *C, D*).

Immunohistochemistry for cytokeratins (AE1/AE3) confirmed the glandular differentiation of the epithelial portion of this tumor (Fig. 2, *A, B*), whereas antibodies to smooth muscle actin (Fig. 2, *C*), p63 (Fig. 2, *D*), and S-100 protein highlighted the neoplastic myoepithelial cell differentiation on the outer aspect of unstained luminal cells. There was no evidence of recurrence at 6-months follow-up.

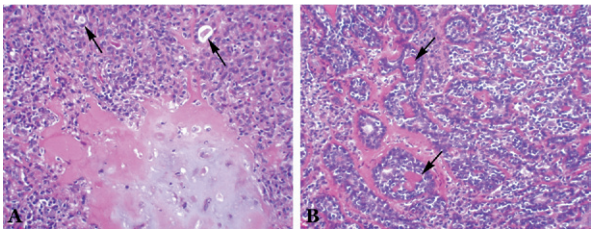

Fig. 3. Case1. **A,** Note the focus of chondrocytic differentiation among the epithelial cells, which in this region have a sheetlike distribution with an occasional ductlike lumen (*arrows*; hematoxylin-eosin, original magnification ×130). **B,** In another region of this lymphadenoma, tumor cell nests are partially to completely enclosed by relatively thick bands of hyaline material, some of which is also present within the cell groups (*arrows*; hematoxylin-eosin, original magnification ×130).

Case 2

The patient was a 52-year-old male with a 6-month history of a painless mass in the right parotid gland. A discrete, fleshy mass 20 mm in diameter was subsequently resected, together with a portion of a normal parotid gland. Histologically, the lymphocytic component of this well-defined tumor nodule tended to obscure the epithelial component (Fig. 4, *A*). A fibrotic capsule, lacking evidence for a subcapsular sinus, en-

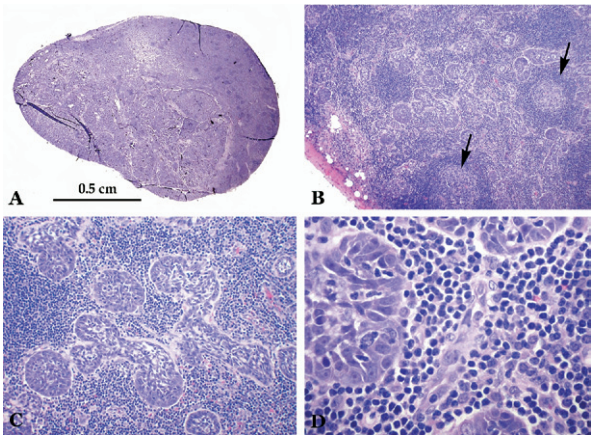

Fig. 4. Case 2. **A,** Circumscribed tumor nodule, part of which has a thin capsule, with an extensive lymphocytic infiltrate. **B** and **C,** At progressively higher magnification (**B,** ×50; **C,** ×130), the degree of separation of the discrete epithelial tumor cell nests by the germinal center-forming lymphocytes (*arrows*) becomes evident. Note the tumor-associated capsule (lower left in B; hematoxylin-eosin). **D,** The discrete nests of polygonal to irregularly shaped tumor cells, surrounded by normal lymphocytes, have regular nuclear features (hematoxylin-eosin, original magnification ×325).

closed the tumor (Fig. 4, *B*). Scattered among the lymphocytes were numerous, discrete, relatively small round to irregularly shaped nests of epithelial cells (Fig. 4, *B, C*). Tumor cells were polygonal to irregular in shape, with round-to-oval shaped nuclei and small-to-moderately sized nucleoli; mitotic figures were absent (Fig. 4, *D*). Glandular differentiation was absent (Fig. 4, *B-D*). Primarily small mature lymphocytes, with occasional plasma cells and germinal centers, separated the epithelial tumor cells (Fig. 4, *B-D*). The patient was well 3 years after surgical removal, with no evidence of local recurrence or metastases.

DISCUSSION

In this class of adenoma with tumor-associated lymphoid proliferation (i.e., lymphadenoma), the growth pattern of the epithelial component generally lacks resemblance to other benign salivary gland tumors such as pleomorphic adenoma, basal cell adenoma, canalicular adenoma, or myoepithelioma. Basic criteria for this entity are outlined in Table I. For practical purposes, lymphadenoma is thus a form of adenoma, not otherwise specified, with an absence of sebaceous differentiation but an obvious lymphocytic infiltrate.[1] This is especially evident in routinely stained histological preparations where the intensity of the lymphocytic cell population tends to obscure the epithelial portion. As noted by Ma and associates,[4] however, the growth pattern within some lymphadenomas resembles basal cell adenoma or cystadenoma. Epithelial growth patterns become more apparent with immunohistochemical techniques.[4,7] These features are apparent for the 2 cases included in this report.

Table I. Diagnostic criteria for lymphadenoma

No sebaceous differentiation
Nononcocytic epithelium
Predominant lymphocytic component with or without germinal centers (may be plasma cells)
Solid, glandular, or cystic epithelial nests
Well-defined tumor mass with a lack of nodal capsule or subcapsular sinusoids

As was indicated in the case reports, no histological features suggested either case arose from salivary gland rests within an intraparotid lymph node. No characteristic histology was initially noted in case 1 and the diagnosis was unclear, especially with the overriding lymphocytic component. A few foci of chondroid differentiation, however, together with the ductal elements and associated neoplastic myoepithelial cells (particularly evident with immunohistochemistry), made cellular pleomorphic adenoma a consideration. Pleomorphic adenoma with lymphocytic stroma is said to be extremely rare,[1] but we are not aware of a reported case. So, although this case might qualify as a pleomorphic adenoma with tumor-associated lymphocytic stroma, it is more practical to include such a case within the lymphadenoma category. A similar argument applies to case 2. This example and a number of the lymphadenoma cases reported in the literature have histological features of basal cell adenoma[4,7] but continue to be classified as lymphadenomas. Other lymphadenomas have the basic architecture of a cystadenoma.[4,5] At low-to-medium magnifications, however, the histology of both lesions in this report was comparable to that evident in other examples of lymphadenoma in the literature. Since all such lesions raise comparable differential diagnostic problems, grouping these serves a practical approach, particularly with the already diverse histopathology of lymphadenomas. One example of a lymphadenocarcinoma has been reported.[9]

The potential differential diagnoses for lymphadenoma are considerable (summarized in Table II) and have been previously well discussed.[1,4] Given the general histological features of lymphadenoma, metastatic carcinoma, mucoepidermoid, and acinic cell carcinomas with tumor-associated lymphocytic proliferation and sebaceous lymphadenoma or lymphadenocarcinoma are the main considerations. Warthin's tumor is ruled out by the absence of both a bilayered oncocytic epithelium and a papillary growth pattern.

Table II. Differential diagnoses for lymphadenoma

Metastatic carcinoma
Mucoepidermoid carcinoma with lymphoid stroma
Acinic cell carcinoma with lymphoid stroma
Sebaceous lymphadenoma and lymphadenocarcinoma
Warthin's tumor
Myoepithelial sialadenitis
Benign lymphoepithelial cyst and AIDS-related lymphoepithelial cyst
Lymphoepithelial carcinoma
Malignant lymphoma
Papillary cystadenocarcinoma with lymphoid stroma
Primary squamous cell carcinoma with lymphoid stroma
Primary salivary gland tumors arising within a lymph node

AIDS, acquired immunodeficiency syndrome.

Parotid gland involvement by metastatic carcinoma is likely to involve an intraglandular lymph node. Thus, the absence of subcapsular sinusoids and nuclear and cellular atypia, no increased mitotic activity, and lack of invasive tumor features all support a diagnosis of lymphadenoma. It should be noted, however, that one lymphadenoma had evidence of a subcapsular sinus but an absence of histological features of malignancy.[5] Although some lymphadenomas will be cystic,[3,4] such lesions lack the goblet and intermediate cell lining epithelium characteristic of mucoepidermoid carcinoma with tumor-associated lymphoid proliferation.[1] In addition, lymphadenomas lack the extravasation of mucus and invasive tendencies of mucoepidermoid carcinoma. The epithelial component of lymphadenoma does not demonstrate the microcystic and follicular growth patterns and acinar cell differentiation with its characteristic granular cytoplasm of acinic cell carcinoma with prominent lymphoid stroma.[2] Such histological features would also apply to primary mucoepidermoid and acinic cell carcinomas arising in intraparotid lymph nodes.[10] The absence of sebaceous differentiation is the key differential criteria eliminating sebaceous lymphadenoma and lymphadenocarcinoma. Thus, there would be good reason for referring to the current entity as nonsebaceous lymphadenoma.

REFERENCES

1. Auclair PL. Tumor-associated lymphoid proliferation in the parotid gland. A potential diagnostic pitfall. Oral Surg Oral Med Oral Pathol 1994;77:19-26.
2. Michal M, Skalova A, Simpson RHW, Leivo I, Ryska A, Starek I. Well-differentiated acinic cell carcinoma of salivary glands associated with lymphoid stroma. Hum Pathol 1997;28:595-600.
3. Ellis GL, Auclair PL. Tumors of the salivary glands, atlas of tumor pathology. 3rd series, Fascicle 17. Washington, DC: Armed Forces Institute of Pathology; 1996. p. 135-6.
4. Ma J, Chan JKC, Chow CW, Orell SR. Lymphadenoma. A report of three cases of an uncommon salivary gland neoplasm. Histopathology 2002;41:342-50.
5. Kwon GY, Kim EJ, Go JH. Lymphadenoma arising in the parotid gland. A case report. Yonsei Med J 2002;43:536-8.
6. Chang JY, Hsiao CH. Lymphadenoma lacking sebaceous differentiation in the parotid gland. J Formosa Med Assoc 2004;103:459-62.
7. Bos I, Meyer S, Merz H. Lymphadenoma of the parotid gland without sebaceous differentiation. Immunohistochemical investigations. Pathologe 2004;25:73-8.
8. Musthyala NB, Low SE, Seneviratne RH. Lymphadenoma of the salivary gland. A rare tumor. J Clin Pathol 2004;57:1007.
9. Hill DS, Ellis GL, Gatland DJ. A unique parotid adenocarcinoma. J Laryngol Otol 2000;114:402-4.
10. Seifert G. Primary salivary gland tumors in the lymph nodes of the parotid gland. Report of 3 cases and review of the literature. Pathologe 1997;18:141-6.

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