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Nonsebaceous lymphadenoma of salivary glands: proposed development from intraparotid lymph nodes and risk of misdiagnosis

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Abstract Nonsebaceous lymphadenoma (NSLA) is a rare benign salivary gland tumor composed of lymphoid and epithelial components. By definition, the epithelial component lacks sebaceous differentiation and instead displays a wide range of histological differentiation. In this study, we have collected nine cases of NSLA to characterize their histological and immunohistochemical profiles. The samples were histologically reviewed and immunohistochemical stains for CK5/6, CK7, CK14, CK18, p63, and Ki67 performed. Patients were six males and three females (mean age, 50 years). All tumors were located in the parotid gland and showed intimate intermingling of lymphoid tissue with islands or strands of epithelium with a wide spectrum of histological differentiation. The immunohistochemical profiles mirrored the epithelial differentiation; hence, areas with basaloid or lymphoepithelial differentiation strongly expressed CK5/6, CK14, and p63, while areas with ductal differentiation showed strong positivity for CK18/CK7 and CK5/6/CK14/p63 in luminal and basal cell layers, respectively. A hilus structure with salivary inclusions or D2-40 (podoplanin)-positive marginal sinus was identifiable in four and nine of the cases, respectively, supporting origin within intra-/periparotid lymph nodes. Six cases were initially misdiagnosed as other benign (n=4) or malignant tumors (n=2). Our study on the second largest series of NSLA reported to date provides strong evidence that NSLA belongs to the group of salivary gland tumors that pathogenetically develop from embryonic salivary gland inclusions in intra-/periparotid lymph nodes. Knowledge of the wide histological spectrum of this rare and presumably underreported tumor is important in order to avoid misdiagnosis, particularly as malignant tumor.

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Introduction

Since the first description of a case designated as 'nonsebaceous lymphadenoma' (NSLA) in 1991 by Auclair et al. [1], a total of 17 cases of this rare entity have been described, mostly as single case reports or small case series [2–11]. NSLA was officially recognized as a separate tumor entity by the World Health Organization's (WHO) classification in 2005 [12], distinct from the more common sebaceous lymphadenoma. NSLA is defined as a benign salivary tumor,

composed of intimately intermingled lymphoid and epithelial components, the latter being devoid of sebaceous, oncocytic, clear cell, and mucinous differentiation [3, 7, 9, 10, 12, 13]. During the revision of this article, a large series of salivary gland lymphadenoma (n=33) including 11 cases of NSLA was published [13]. Thus, the nine cases described in our study represent the second largest series to date of this rare salivary gland tumor, increasing the total number of reported cases to 37 cases in the English literature.

Analogous to Warthin's tumor, a pathogenetic development of NSLA from intraparotid lymph nodes harboring embryonic salivary gland inclusions has been proposed [2, 8, 13] but refuted by the majority of authors [3, 4, 6, 7, 9–11]. The present findings represent arguments for a pathogenetic development of NSLA from intraparotid lymph nodes. Knowledge of this rare tumor entity is important, as misdiagnosis occurs frequently.

Material and methods

Material

Seven cases were retrieved from the records of the Institute of Pathology, Ludwig Maximilian University, Munich and the Institute of Pathology, University Hospital Erlangen and two cases from the consultation files of one of the authors (SI). The investigation was undertaken according to the guidelines of the local research ethics committee.

Methods

The specimens were fixed in 4% buffered formaldehyde, embedded in low melting point paraffin wax (Vogel, Germany) and cut into serial sections of 4 μm. Antibodies for p63 (BC4A4, Biocare Medical, USA/dilution 1:100), pancytokeratin (Lu-5, Biocare Medical, USA/dilution 1:500), cytokeratin (CK) subtype 7 (Ks7.18, Progen, Germany/dilution 1:500), CK14 (MCA890, Serotec, Germany/dilution 1:400), CK18 (Ks18.04, Progen, Germany/dilution 1:450), CK5/6 (D5/16 B4, Roche Tissue Diagnostics Basel, Switzerland/dilution 1:50), and the proliferation-associated antigen Ki67 (MIB1, Dako, Germany/dilution 1:50) were applied as described in previous investigations by our group [14, 15]. For MIB1, the alkaline phosphatase–antialkaline phosphatase (APAAP) method was used (APAAP-ChemMate, Dako, Germany). For the other antibodies, an avidin–biotin–peroxidase complex (ABC) method was applied (ABC kit, Vector, UK). Because of the high level of endogenous biotin, especially in eosinophilic cells of salivary glands, a biotin-blocking system (Biotin-Blocking System X0590, Dako, Germany) was added to the ABC method.

Results

Clinical and histological data are summarized in Table 1. The cases included six males and three females aged between 40 and 65 years with a mean age of 50 years. A parotid mass was the presenting symptom in all cases, and none of the patients had clinical evidence of Sjögren syndrome or human immunodeficiency virus (HIV) infection. In two cases, a positive and in three cases, a negative smoking history was found. However, in four cases (including two referral cases) information regarding smoking history was not available. All tumors were located in the region of parotid glands. Surgical excision was complete in all cases. There was no reported recurrence in any of the cases. The tumor size ranged from 1.2 to 3.5 cm with an average of 2.0 cm. All tumors were macroscopically and microscopically well circumscribed and surrounded by a thin fibrous capsule (Fig. 1). Histologically, they showed intimate intermingling of organoid lymphoid tissue with islands and strands of epithelium, the latter comprising 20% to 70% of the whole tumor area (Fig. 2a, b, d, e, f, g).

The lymphoid component showed characteristics of lymph nodes. A hilus structure with embryonic inclusion of salivary gland parenchyma was clearly identifiable in four cases, equivalent to a typical hilus structure of intraparotid lymph nodes (Fig. 2a, b, d, e, f, g). Although most lesions completely replaced the lymph nodelike structure (Fig. 2a, b), two tumors showed clear-cut residual lymphoid tissue adjacent to the tumor (Fig. 2d, e). Reactive-type lymphoid follicles were present with variable frequency in all cases. Marginal sinus structures with D2-40 (podoplanin)-positive lymph vessels consistent with a lymph node sinus were present in all cases (Fig. 2c).

Sebaceous, oncocytic, clear cell or mucinous differentiation of the epithelial component was lacking in all cases. Five of the nine cases showed multiple small- to medium-sized cysts of up to 8 mm in the epithelial islands (Fig. 1 and Fig. 2a, b, f, g). Both epithelial and lymphoid components showed no evidence of cytological atypia and a lack of increased mitotic or proliferative activity (Ki67 index <10%).

The epithelial component showed a wide variety of histological differentiation with dominant basaloid differentiation in three cases (Fig. 3a), diffuse intraepithelial distribution of lymphocytes equivalent to lymphoepithelial differentiation in four cases (Fig. 3d), and dominant ductal or cribriform differentiation in two cases (Fig. 3g). The type of epithelial differentiation correlated with the expression pattern of immunohistological markers: Tumors or areas with dominant basaloid or lymphoepithelial differentiation showed strong reaction to CK5/6, CK14, and p63 with absence or minor expression of CK18/CK7 in suprabasal layers (Fig. 3b, c, e, f). Tumors or areas with dominant ductal differentiation showed strong positivity for CK18/

Table 1 Clinical and histomorphological data of nine cases of nonsebaceous lymphadenoma

	Sex/age	Size (mm)	Histological differentiation	Suprabasal cell layers: CK5/6 (+CK14, p63)	Suprabasal cell layers: CK18/7	Cysts (mm)	Epithelial component in %	LN-hilus	Original diagnosis
1	f/40	12	Ductal	−	+	Yes (3)	50	Yes	Lymph node metastasis of adenocarcinoma
2	m/65	35	Basaloid	+	−	No	60	Yes	Nonsebaceous lymphadenoma
3	m/62	15	Basaloid/ductal	+	(+)	Yes (3)	50	Yes	Warthin's tumor
4	m/51	23	Lymphoepithelial	+	(+)	Yes (8)	20	No	Metaplastic Warthin's tumor
5	m/50	14	Lymphoepithelial	+	(+)	Yes (8)	70	No	Cystic benign lymphoepithelial lesion
6	m/62	35	Basaloid/lymphoepithelial	+	−	Yes (4)	50	No	Lymphoepithelial carcinoma
7	f/65	22	Ductal	−	+	No	70	No	Sebaceous lymphadenoma
8	f/51	17	Lymphoepithelial	+	−	No	30	No	Nonsebaceous lymphadenoma
9	m/47	15	Lymphoepithelial	(+)	(+)	No	40	Yes	Nonsebaceous lymphadenoma

f female, *m* male, *LN* lymph node

CK7 in suprabasal cell layers and positivity for CK5/6, CK14, and p63 restricted to the basal cell layer (Fig. 3h, i). The original diagnosis was NSLA in three cases. Six cases were initially mislabelled as other types of benign salivary tumors in three cases, cystic lymphoepithelial lesion in one case, and malignant salivary tumor in two cases (Table 1).

Discussion

This study, based on the second largest series of the recently recognized entity of NSLA reported to date, supports the previous notion that the epithelial component is characterized by a broad spectrum of histological differentiation, ranging from basaloid to lymphoepithelial and ductal [3, 4, 6, 7]. Presumably developing from a common basal cell component, this diverse epithelial differentiation seems to represent a neoplastic counterpart to diverse reactive metaplasias (such as lymphoepithelial metaplasia and basal cell hyperplasia), which develop from basal cells of regular striated ducts, as described by our group [14, 16]. Kang et al. [17] had suggested a separation of this rare entity into cases with ductal differentiation in sensu strictu 'Nonsebaceous lymphadenoma' and cases with basaloid or lymphoepithelial differentiation in 'nonsebaceous lymphoepithelioma'. Considering the rarity of this tumor entity and the broad and overlapping spectrum of the histological epithelial differentiation, we, however, strongly support to regard all cases as part of a common tumor entity comprising a heterogeneous spectrum of epithelial differentiation including a variable degree of cystic transformation.

Analogous to Warthin's tumor, pathogenetic development of NSLA from embryonic salivary inclusions in intra-/periparotid lymph nodes has been proposed [2, 8, 13]. However, this theory did not achieve wide acceptance and has been refuted by the majority of authors, who instead regard the lymphoid component as reactive tumor-associated lymphoid tissue [3, 4, 6, 7, 9–11]. Our finding of an unequivocal hilus structure with embryonic parenchymal inclusions in four of the nine cases (Fig. 2), in conjunction with frequent secondary follicles and lymph vessels within marginal sinus structures demonstrated in all cases (Fig. 2c), represent, in our view, strong arguments for a pathogenetic development of NSLA from embryonic salivary inclusions in intra- or periparotid lymph nodes.

Hilus structures were not detectable in five of the nine tumors, which can be attributed to incomplete tumor sampling and/or to effacement of hilus structures by the expanding tumor. A respective development of a Warthin's tumor

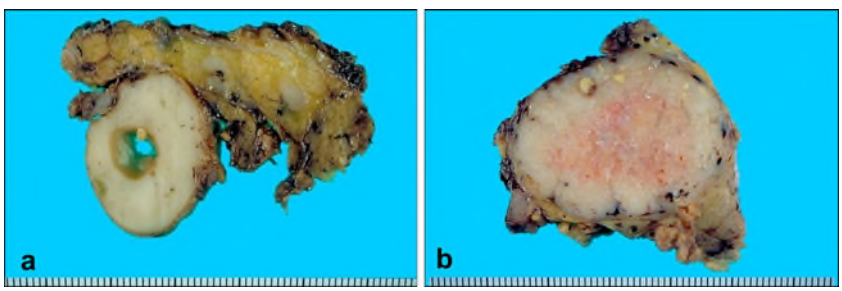

Fig. 1 Macroscopic image of two cases of nonsebaceous lymphadenoma (NSLA) with well delineated border and gray-whitish cut surface that displayed both solid areas and large (**a**) or small (**b**) cystic components

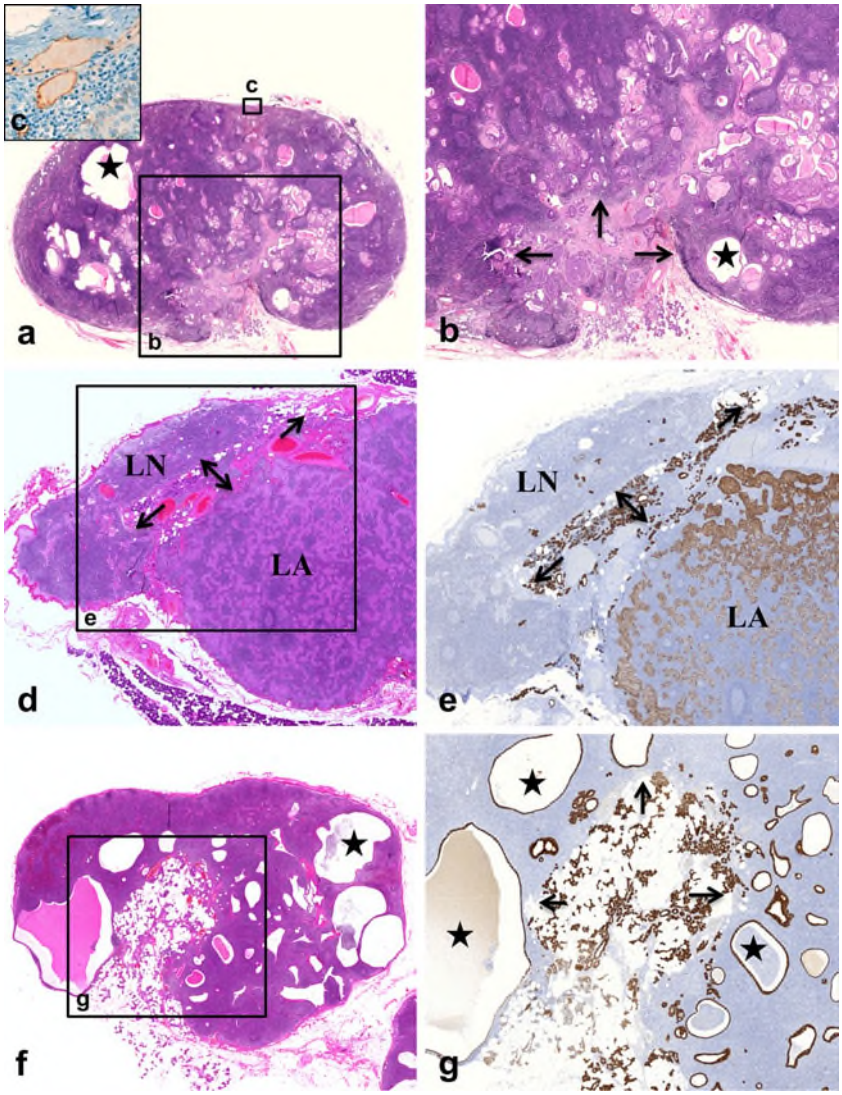

Fig. 2 **a**–**c** Case no. 1 with minor cystic component (*star*) and unequivocal preserved hilus structure (**a**) with inclusion of salivary parenchyma (**b**: *arrows*); podoplanin-positive lymph vessels in marginal sinus (**c**); **d**, **e** case no. 2 with a preserved portion of a lymph node (*LN*) on the left, adjacent hilus with inclusion of salivary parenchyma (*arrows*) and NSLA on the right; no cystic component (**e** pan-keratin); **f**, **g** case no. 3 with intense cystic components (*star*) and unequivocal hilus structure (*arrows*; **g**: pan-keratin); magnification: **a**×6, **b**×10, **c**×1,000, **d**×4, **e**×5, **f**×4.5, **g**×10

from intraparotid lymph nodes was first postulated by Bernier and Bhaskar in 1958 [18] and is now generally accepted [19, 20] even though hilus structures can be demonstrated in only a minority of mostly small and incipient Warthin's tumors. An analogous histogenetic pathogenesis has been proposed for sebaceous lympadenoma [21, 22]. The proposed development from intra- or periglandular lymph nodes is further supported by the fact that Warthin's tumor, sebaceous lymphadenoma, and NSLA are almost invariably restricted to parotid glands [12, 20], which exclusively harbor intra- and periglandular lymph nodes. However, this constellation presumably does not represent a pure intranodal epithelial tumor growth, but an intimate immunological relationship of the epithelial and lymphatic components within this combined lymphoepithelial type of tumor.

It is highly likely that this rare tumor entity is more frequent than the data suggest, as it is easily confused with a series of other benign and malignant tumor entities. In contrast to the usually straightforward diagnosis of sebaceous lymphadenoma, misdiagnosis of NSLA has been repeatedly reported [4, 7] and is attributable to a lack of familiarity with this rare tumor entity as well as to the heterogeneous spectrum of lymphoepithelial, basaloid, or ductal epithelial differentiation seen in NSLA, which results in an unusually wide spectrum of both benign and malignant differential diagnoses.

Six of our nine cases were initially misdiagnosed, with three cases having been misdiagnosed as other types of benign salivary tumors without clinical consequence, one case as reactive sialadenitis, and two cases as carcinoma (Table 1). Due to imprecise diagnostic criteria, so-called benign lymphoepithelial lesion represents one lesion that is at risk to be confused with NSLA, which occurred in one of our cases. The basaloid type of NSLA might be misinterpreted as basal cell adenoma within a lymph node. However, the basaloid nests of NSLA are loosely arranged within the lymphoid background and lack prominent PAS-positive basal membranelike material. A serious misinterpretation in our series was a lymph node

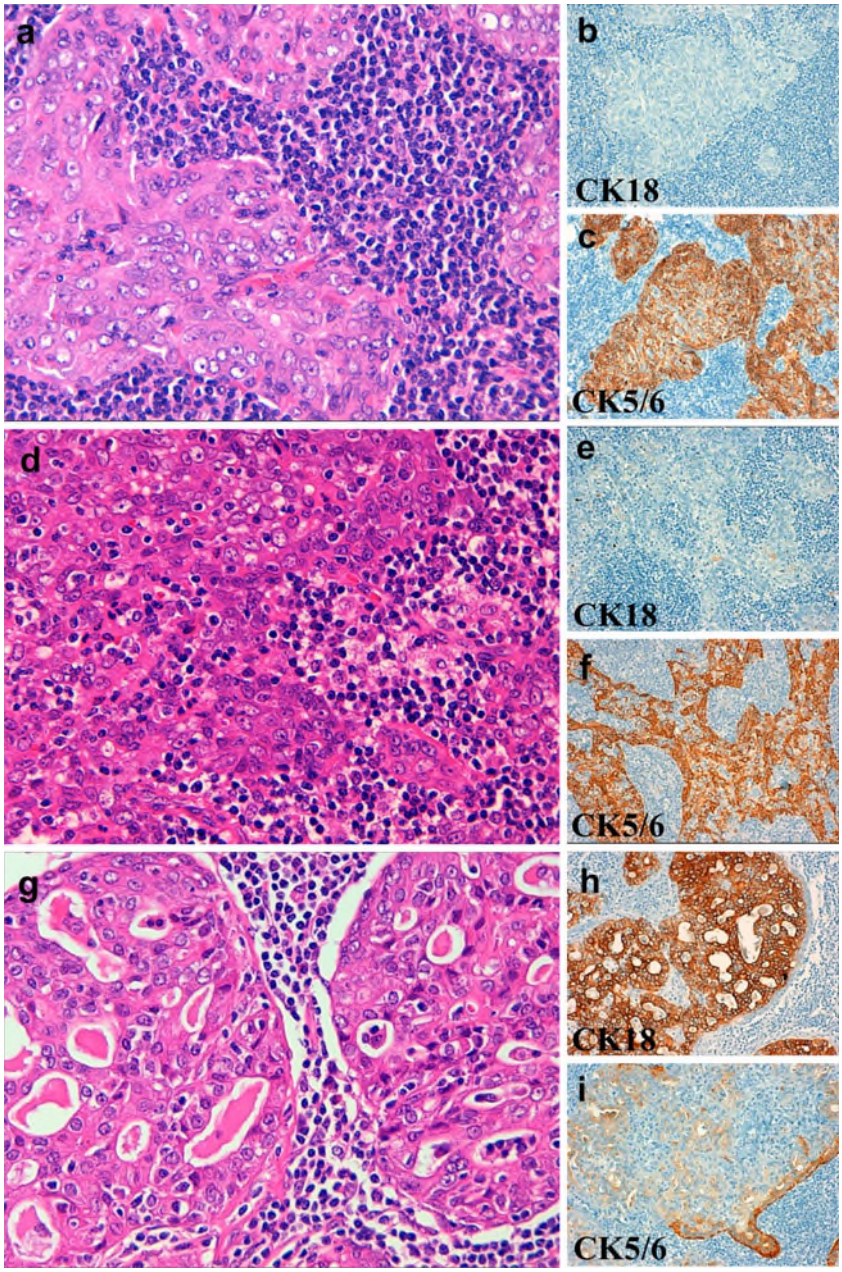

Fig. 3 **a**–**c** Case no. 2 with basaloid epithelial differentiation, corresponding to strong overall positivity for CK5/6 (**c**) and negativity for CK18 (**b**); **d**–**f** case no. 6 with lymphoepithelial differentiation with abundant intraepithelial lymphocytes and identical immunoreactive pattern as in **b** and **c** (**e**, **f**); **g**–**i** case no. 7 with ductal epithelial differentiation with positivity for CK18 in suprabasal layers (**h**) and positivity for CK5/6 restricted to basal cells (**i**); magnification: **a**, **d**, **g**×800; **b**, **c**, **e**, **f**, **h**, **i**×400

metastasis from a well-differentiated adenocarcinoma, which led to an uneventful search for a suspected primary carcinoma (Fig. 2a, b). Another serious misinterpretation was lymphoepithelial carcinoma, which, in contrast to NSLA, is characterized by blunt tumor infiltration, significant proliferation, and other features of frank malignancy. Finally, NSLA has to be distinguished from microscopic embryonal salivary tissue inclusions within intra- or periparotid lymph nodes, which may show a minor degree of reactive hyperplasia and cyst development.

During the revision of this article, another slightly larger series of 11 cases of NSLA was published [13]. Although their investigation and ours share many equivalent findings especially with regard to intranodal location in four cases, there are noteworthy differences: Two of their 11 cases showed focal keratinization, a feature that was absent in our cases. The mean age was one decade higher than in our series, and they found a dominant female predominance (4:1) in contrast to a male predominance (3:1) in our series. The findings in these two large series indicate that the clinicopathological features of NSLA are rather heterogeneous with wide variation with respect to histology, age, and gender distribution.

In summary, we report the second largest case series of NSLA illustrating that this rare lesion belongs to the group of salivary gland tumors that pathogenetically develop from embryonic salivary inclusions in intra- or periparotid lymph nodes. Similar to Warthin's tumor, the exact mechanisms driving the

tumorigenesis of NSLA from intranodal salivary inclusions remains currently obscure. The prognosis of NSLA is excellent with no reported recurrences. Knowledge of this rare and probably under-recognized lymphoepithelial tumor entity and familiarity with its heterogeneous spectrum of epithelial differentiation is important in order to avoid misdiagnosis, especially as malignant tumor with inappropriate overtreatment.

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