Intraparotid Classical and Nodular Lymphocyte-predominant Hodgkin Lymphoma

Pattern Analysis With Emphasis on Associated Lymphadenoma-like Proliferations

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Abstract: Most of the lymphoproliferative diseases involving the salivary glands represent indolent non-Hodgkin B-cell lymphoma (marginal zone lymphoma) related to chronic autoimmune sialadenitis (Sjögren disease). Other types of non-Hodgkin lymphomas involve the salivary glands less frequently. On rare occasions, classical Hodgkin lymphoma (CHL) and nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) present initially as a primary salivary gland mass. We analyzed a series of CHL (n = 3) and NLPHL (n = 6) presenting initially as parotid gland tumors concerning their pattern (parenchymal vs. intraparotid lymph node) and the presence of salivary inclusions and epithelial proliferations within the lymphoma infiltrate. The pattern of infiltration was determined on hematoxylin and eosin–stained slides assisted by immunostaining for pancytokeratin to highlight lobular salivary gland parenchyma. Patients included 6 male and 3 female individuals with a mean age of 62 years (range, 36 to 88 y). Lymphoma was localized within intraparotid lymph nodes in 8 cases and was limited to salivary parenchyma in 1 case. Parenchymal involvement in nodal-based cases was scored as absent (3) or minimal (5). Salivary inclusions (acini and ductules) within affected lymph nodes were noted in 6 cases (4/5 NLPHLs and 2/3 CHLs). In 3/6 NLPHL cases, salivary inclusions showed variable proliferative changes ranging from prominent lymphoepithelial lesions to cystic and oncocytic (Warthin-like) epithelial changes. Scanty small lymphoepithelial lesions were seen in 1 of the 3 CHL cases. One NLPHL in the intraparotid lymph node was accompanied by prominent lymphoepithelial sialadenitis in the absence of clinical signs of Sjögren disease. This study highlights that a majority of parotid gland Hodgkin lymphomas arise within intraparotid lymph nodes. Frequent entrapment and proliferation of salivary ducts and acini within the lymphoma infiltrate might mimic a variety of benign lymphoepithelial mass-forming lesions (nonsebaceous lymphadenoma, Warthin tumor, and autoimmune sialadenitis). Pancytokeratin stain is helpful for reliable assessment of the background architecture.

Key Word: parotid gland, Hodgkin lymphoma, nodular lymphocyte-predominant Hodgkin lymphoma, paragranuloma, lymphadenoma, salivary gland

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Careful analysis of the spatial arrangement of lymphoid infiltrates within salivary glands including related epithelial alterations (so-called pattern analysis) represents the mainstay in the assessment and classification of benign and malignant lymphoepithelial lesions of salivary glands.[1] Ideally, this histologic pattern analysis is substantiated by detailed clinical/radiologic information concerning the extent and distribution of the disease. Salivary lymphoepithelial lesions with a circumscribed, mass-forming presentation comprise cystadenolymphoma (Warthin tumor),[2] sebaceous and nonsebaceous lymphadenoma,[3,4] sporadic lymphoepithelial cyst,[1] benign and malignant epithelial neoplasms associated with prominent reactive lymphoid stroma,[5] and marginal zone B lymphoma arising in a background of chronic autoimmune sialadenitis.[6] In contrast, lymphoepithelial lesions with a diffuse multilobular pattern comprise autoimmune sialadenitis,[1,6] cystic lymphoepithelial lesions associated with human immunodeficiency virus infection,[7] and certain types of lymphoma.

The parotid glands are special within salivary glands as they harbor multiple intraparenchymal lymph nodes, which frequently contain embryologic salivary gland inclusions. Reactive, metaplastic, or neoplastic proliferations of these embryologic salivary inclusions within intraparotid lymph nodes may be the source of considerable diagnostic confusion. On the basis of the primary source of disease, malignant lymphomas within the parotid glands can show either a dominant diffuse parenchymal (extranodal) or a dominant nodal pattern of infiltration, or rarely a combination thereof. The nodal

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pattern can be further subdivided into primary (isolated) lymphoma of intraparotid lymph node/s and lymphomas secondarily involving the intraparotid nodes as part of a systemic disease.

The most frequent lymphoproliferative salivary gland disease with a parenchymal pattern of infiltration is marginal zone (MALT-) B-cell lymphoma, developing mostly secondary to long-standing autoimmune sialadenitis. Both autoimmune sialadenitis and related marginal zone lymphoma are characterized by numerous lymphoepithelial lesions, representing a characteristic hallmark of these diseases. The most frequent lymphoproliferative diseases with a dominant lymph node pattern of infiltration are follicular and diffuse large cell B lymphoma, both devoid of lymphoepithelial lesions.[1]

Classical Hodgkin lymphoma (CHL) and nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL; nodular paragranuloma) only very rarely initially present as a salivary gland mass.[8] Hence, their pattern of involvement of salivary glands has not been clarified yet. We recently have encountered parotid gland NLPHL associated with unusual epithelial proliferations mimicking autoimmune sialadenitis or lymphadenoma. This prompted us to study the pattern of salivary gland involvement by CHL and NLPHL. To our knowledge, there exists no detailed description of the histopathologic pattern of Hodgkin lymphoma in the salivary glands.

MATERIALS AND METHODS

We searched our routine surgical pathology files and files of the German National Consultation Centre/Registry for Malignant Lymphoma (University of Würzburg, Germany) for cases of Hodgkin lymphomas affecting the salivary glands. Prerequisite was a clinically and histologically proven location within (not adjacent to) salivary glands. All available slides were reviewed by 2 authors experienced in salivary gland pathology (A.A. and S.I.). Diagnosis and subtyping of lymphoma was based on the current World Health Organization classification of hematolymphoid neoplasms[9] and was confirmed in all cases by an experienced hematopathologist (A.R.). None of the cases has been published before.

The pattern of involvement (diffuse parenchymal vs. intraglandular lymph node with or without parenchymal extension) was assessed on hematoxylin and eosin–stained slides assisted by immunostaining for pancytokeratin. Thereby, multilobular architecture with organoid parenchymal remnants in the absence of a fibrous capsule around the lymphoma infiltrate was considered as parenchymal infiltration. Nodular configuration with the presence of peripheral encapsulation and the absence of multilobular architecture was considered evidence of nodal-based disease. In addition, surrounding salivary gland parenchyma was examined for the presence of inflammation and other

TABLE 1. CHL and NLPHL of Parotid Glands (n = 9)

No.	Age/Sex	Original Diagnosis	Diagnosis	Localization	Involvement of Parenchyma	Salivary Inclusions Within Lymphoma	Proliferative Lesions Within Lymphoma	Other Parenchymal Changes	Immunophenotype of Neoplastic Cells
1	55 M	NLPHL	NLPHL	Lymph node	Not involved	Present	Numerous LEL, partially cystic, focal oncocytic	—	$CD20^+$, $CD45^+$, $CD30^-$, $CD15^-$, $LMP1^-$
2	71 M	NLPHL in Warthin tumor	NLPHL	Lymph node	Not involved	Present	Numerous oncocytic lesions, partially cystic, few normal ducts	—	$CD20^+$, $CD45^+$, $CD30^-$, $CD15^-$, $LMP1^-$
3	42 M	Suspicion of marginal zone lymphoma	NLPHL	Limited to salivary lobules	Prominent involvement	Lobules involved	No	—	$CD20^+$, $CD45^+$, $CD30^-$, $CD15^-$, $LMP1^-$
4	67 M	Suspicion of lymphoma	NLPHL	Lymph node	Minimal involvement	Present	No	—	$CD20^+$, $CD45^+$, $CD30^-$, $CD15^-$, $LMP1^-$
5	36 M	Autoimmune sialadenitis vs. nonsebaceous lymphadenoma	NLPHL	Lymph node	Minimal involvement	Absent	No	Lymphoepithelial sialadenitis	$CD20^+$, $CD45^+$, $CD30^-$, $CD15^-$, $LMP1^-$
6	59 F	Suspicion of lymphoma	NLPHL	Lymph node	Minimal involvement	Present	Few LEL	—	$CD20^+$, $CD45^+$, $CD30^-$, $CD15^-$, $LMP1^-$
7	72 F	Suspicion of CHL	CHL, nodular sclerosis	Lymph node	Minimal involvement	Present	No	—	$CD30^+$, $CD15^+$, $CD20^-$, $PAX5^+$, $LMP1^-$
8	88 M	Suspicion of lymphoma	CHL, mixed cellularity	Lymph node	Not involved	Absent	No	—	$CD30^+$, $CD15^-$, $CD20^-$, $PAX5^+$, $LMP1^+$
9	74 F	Suspicion of CHL	CHL, nodular sclerosis	Lymph node	Minimal involvement	Present	Few LEL	—	$CD30^+$, $CD15^+$, $CD20^-$, $PAX5^+$, $LMP1^+$

LEL indicates lymphoepithelial lesion.

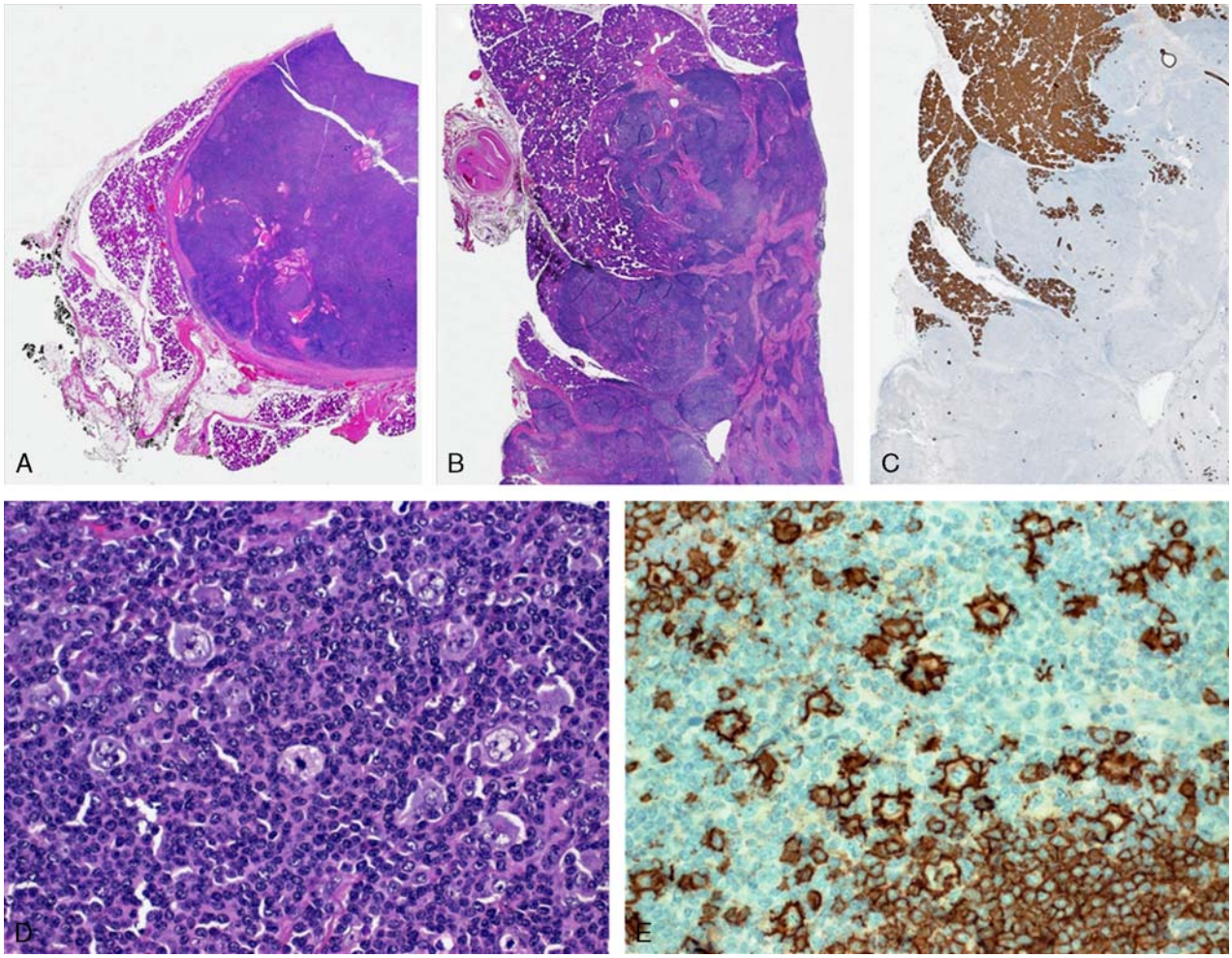

FIGURE 1. Architectural patterns of parotid gland Hodgkin lymphomas. A, This whole mount of an NLPHL shows clear demarcation from surrounding salivary parenchyma by a complete fibrous capsule. Note prominent oncocytic epithelial inclusions at this magnification (case 2). B, This example of NLPHL shows an exclusive parenchymal pattern with prominent lobular architecture (highlighted by pancytokeratin stain in C) and absence of a lymph node capsule at the periphery (case 3). D, LP cells with large folded nuclei, prominent nucleoli, and (E) strong membranous CD20 expression (case 4).

relevant findings. Epithelial inclusions within lymph nodes or within lymphoma were classified as acinar versus ductal, normal-looking versus proliferating/regenerative, including metaplastic (lymphoepithelial, oncocytic), cystic, or other changes. Immunohistochemical studies were performed on 3-µm-thick newly cut sections using the following antibodies: pancytokeratin (clone KL-1, 1:200; Immunotech), CD15 (clone Carb-3, 1:800; Dako), CD20 (clone L26, 1:500; Dako), CD23 (clone 1B12, 1:200; Novocastra), CD30 (BerH2, ready to use; Ventana), CD45 (clone 2B11 + PD7/26, 1:2000; Dako), PAX5 (clone 24, 1:1000; BD Biosciences), and LMP1 (L1-4, 1:400; Novocastra).

RESULTS

Nine cases (3 CHLs and 6 NLPHLs; Table 1) were retrieved. All cases presented clinically as a primary intraparotid mass and were initially treated surgically. No cases were identified in the other salivary glands. Patients included 6 male and 3 female individuals with a mean and median age of 62 and 67 years, respectively (range, 36 to 88 y). None was known to have autoimmune sialadenitis (Sjögren disease). According to the above defined criteria, lymphoma was localized predominantly within intraglandular lymph nodes in all but 1 case (Figs. 1A–C). Additional parenchymal involvement in the 8 nodal cases was judged as absent (3) or minimal (5). Among the 8 cases with intraparotid nodal disease, intratumoral epithelial inclusions (acini and ductules entrapped within the lymphoma infiltrate) were noted in 6 cases (4/5 NLPHLs and 2/3 CHLs).

The 6 NLPHL cases displayed the typical morphologic pattern of the disease. One case (case 3) showed a prominent involvement of the salivary gland parenchyma, whereas in all other cases a single intraparenchymal lymph node was extensively affected. The tumor infiltrates showed a predominantly nodular growth pattern of small lymphocytes and histiocytes with scattered large neoplastic cells with 1 large, folded nucleus and prominent nucleoli char-

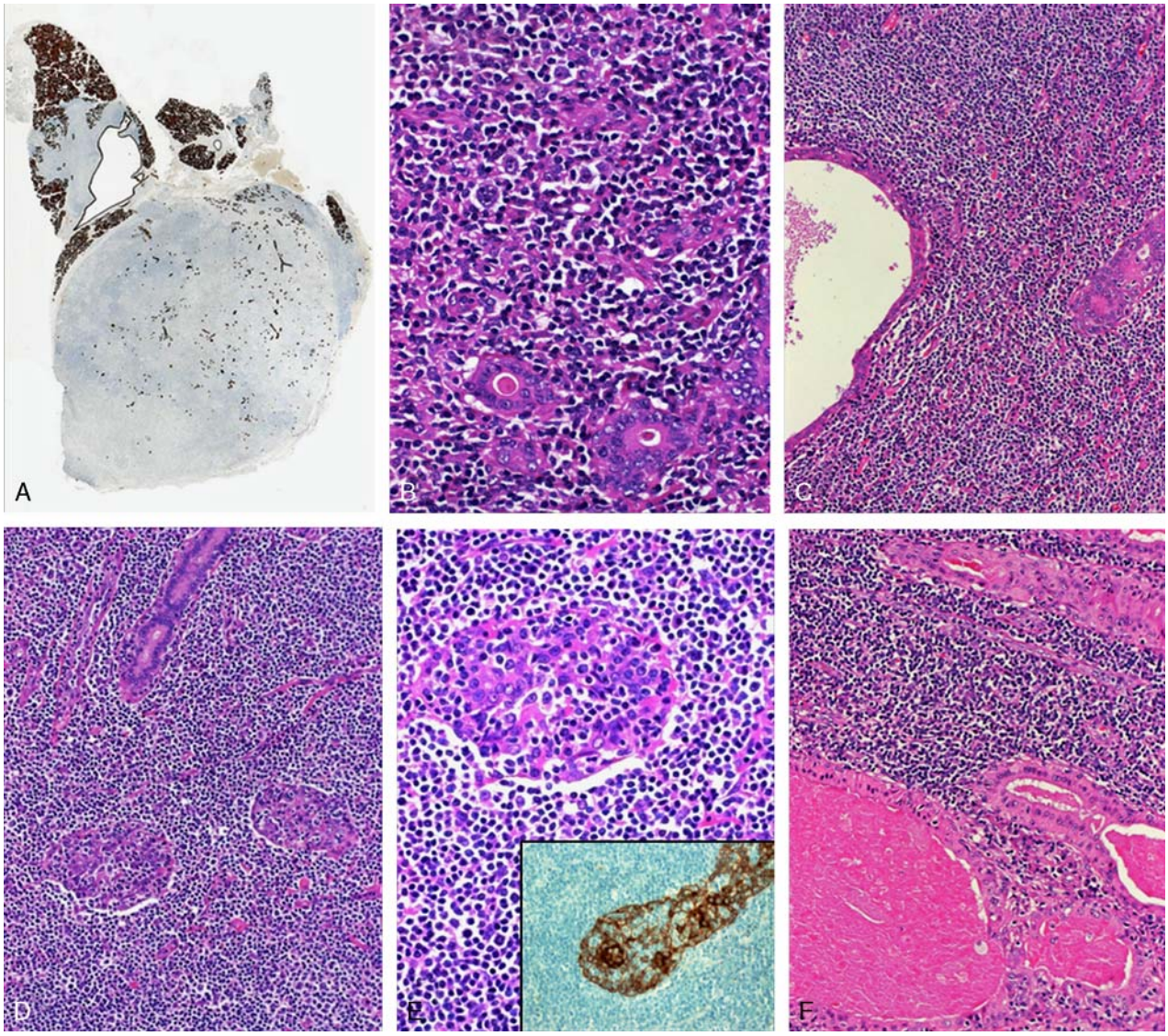

FIGURE 2. A, This example of NLPHL (case 1) shows a peripheral capsule and lacks a lobular pattern indicating intranodal disease, but contains diffusely distributed salivary inclusions (pancytokeratin, whole mount). B, Normal-looking salivary ducts within lymphoma with variable cyst formation (C; case 2). D and E, Prominent lymphoepithelial lesions (see normal-looking ducts above). E inset, Pancytokeratin highlighting lymphoepithelial lesions (case 5). F, Cystic salivary inclusions with Warthin-like oncocytic changes (case 2).

acteristic of LP cells (Fig. 1D). Immunophenotypically, the LP cells were positive for CD20 (Fig. 1E) and CD45 and negative for CD30 and CD15. All cases showed background meshworks of follicular dendritic cells, which stained positive for CD23.

Three of the 6 NLPHL cases showed variable features of proliferative changes within the intratumoral epithelial inclusions ranging from normal-looking serous acini (Figs. 2A, B) and bland cyst formation (Fig. 2C) to well-formed lymphoepithelial lesions (Figs. 2D, E). The lymphoepithelial lesions were prominent in case 1 and case 2. Multifocal oncocytic metaplasia in 1 of these cases strikingly mimicked origin within a Warthin tumor (case 2; Fig. 2F). However, the admixture of regular ductal structures with foci of oncocytic metaplasia favored secondary proliferative and metaplastic changes, probably in response to the lymphoma infiltration. One case of NLPHL (case 5) with pure nodal manifestation showed in addition a moderate degree of autoimmune-type sialadenitis in the surrounding salivary gland parenchyma without clinical or serological evidence of Sjögren syndrome.

All 3 cases of CHL showed infiltration of an intraparotid lymph node with absent or only minimal infiltration of the surrounding salivary gland parenchyma. In cases of the nodular sclerosis subtype (case 7, 9), the lymph node was completely replaced by nodular-arranged broad fibrous bands surrounding a mixed background infiltrate of small lymphocytes, histiocytes, and few eosinophils with loosely distributed Hodgkin and Reed Sternberg cells (HRS cells)

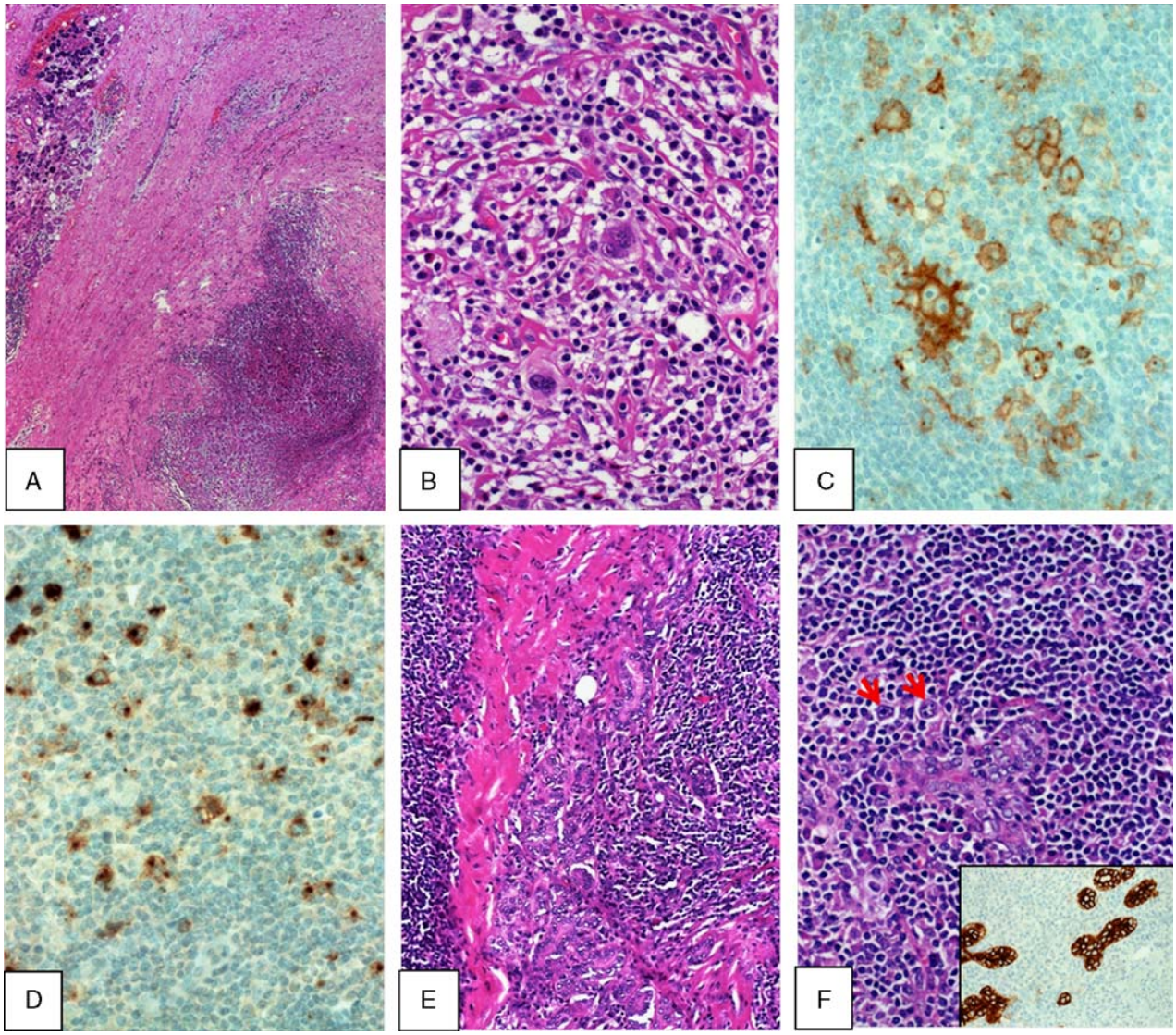

FIGURE 3. Pattern of CHL within intraparotid lymph nodes (A–E, Case 7; F, Case 9). A, This case of nodular sclerosis CHL showed a thick fibrous capsule separating the tumor from salivary tissue on the left. B, Higher magnification of the tumor cells. C, The neoplastic cells of CHL expressed CD30. D, CD15 from the same case. E, Numerous compact salivary acini were seen within the tumor in the same case. F, A few scattered acini and ducts were seen in this case. F inset, Pancytokeratin highlighted acinar salivary inclusions and absence of lymphoepithelial lesions in the same case. Arrows: HRS cells.

(Figs. 3A, B). In case 8, a large intraparenchymal lymph node showed subtotal involvement by an interfollicular mixed lymphoid infiltrate composed of small lymphocytes and focally pronounced epithelioid cells as well as some plasma cells and eosinophils admixed with loosely distributed HRS cells. In all cases of CHL, the HRS cells were positive for CD30 (Fig. 3C) with a weak positivity for PAX5 and negativity for CD20. In cases 7 and 9, the HRS cells stained positive for CD15 (Fig. 3D), whereas in case 8 the HRS cells remained CD15 negative. An Epstein-Barr virus association was found in cases 8 and 9 (LMP1), but not in case 7. Variable amounts of normal-looking serous acini were seen in cases 7 and 9 (Figs. 3E, F) and were associated with scanty small lymphoepithelial lesions in case 9.

DISCUSSION

Patients with lymphoma in salivary glands are treated initially by surgical resection because of suspicion of a primary salivary gland neoplasm.[10–12] Therefore, awareness of the specific pathologic appearance of CHL and NLPHL in the salivary glands and their distinction from different types of salivary lymphoepithelial lesions is mandatory for the pathologist. However, rarity of salivary gland Hodgkin lymphomas precluded the avail-

ability of detailed description of their histologic infiltration pattern within the salivary glands.

Our study illustrates that the majority of salivary gland Hodgkin lymphomas (8/9 cases) represent nodal disease of intraparotid lymph nodes. The presence of intrasalivary lymph nodes exclusively in the parotid glands and our observation that intraparotid Hodgkin lymphoma is a nodal-based disease explain the predominant (practically exclusive) occurrence in the parotid gland as opposed to the other salivary glands.

Extension of lymphoma into the surrounding salivary parenchyma was observed in 5/8 nodal-based cases (3/5 NLPHLs and 2/3 CHLs) but was usually of minimal degree. Extensive parenchymal infiltration was observed in only 1 case of NLPHL, which was limited to the salivary parenchyma without evidence of preexisting lymph node (case 3). Although extranodal (parenchymal or visceral) involvement by Hodgkin lymphoma is generally considered an adverse finding compared with disease limited to lymph nodes, the prognostic relevance of this distinction within the parotid glands is unclear.

Our results, in addition, show further important findings that merit detailed discussion: (1) overrepresentation of NLPHL over CHL; (2) frequent presence of unusual proliferative changes of embryological salivary gland inclusions within the lymphoma-infiltrated lymph nodes; and (3) as a consequence of point 2, the risk to misdiagnose intraparotid NLPHL or CHL as other types of benign lymphoepithelial lesions, especially as nonsebaceous lymphadenoma and autoimmune sialadenitis.

Regarding the first point, primary NLPHL in the parotid gland proved to be twice as common as CHL in our series. This is in sharp contrast with the fact that CHL in general is far more common than NLPHL.[9] However, there exist no epidemiological data on the frequency of salivary gland NLPHL versus CHL, and the low number of our cases does not allow for statistical conclusion regarding this aspect. Hodgkin lymphoma presenting as a primary parotid mass is rare, representing only 3.5% to 6% of primary parotid gland lymphomas and 0.3% of all Hodgkin lymphoma cases in general.[10,11,13] To date, <10 cases have been reported in the literature.[14,15] We are aware of only a single-case report of NLPHL involving the parotid gland.[8]

With regard to the second point, 3/5 NLPHLs and 1/3 CHLs were associated with unusual proliferation and metaplasia of salivary epithelial elements (salivary inclusions in intraparotid lymph nodes affected by the lymphoma). As a hallmark of autoimmune sialadenitis and of associated marginal zone B-cell lymphoma, lymphoepithelial lesions typically do not develop in other types of lymphomas manifesting in salivary glands.[1,6] Associated epithelial proliferations were intense in 2 cases of NLPHL in our study, in 1 case reminiscent of nonsebaceous lymphadenoma or autoimmune sialadenitis (case 5 in Table 1), and in the second case (case 2) with dominant oncocytic metaplasia mimicking lymphoma developing within a Warthin tumor.[16,17] In analogy to development of lymphoepithelial lesions in autoimmune sialadenitis,[1,6] the here presented findings suggest an inherent tendency especially of NLPHL to induce secondary lymphoepithelial and oncocytic proliferations of epithelial inclusions through a tendency for epitheliotropism or through not yet understood immunological mechanisms.

Concerning the third point, whereas CHL is usually a rather straightforward diagnosis due to the characteristic HRS cells, NLPHL may on occasion be a difficult diagnosis, given that the characteristic cellular elements of NLPHL (LP cells) might be sparse and the nodular architecture of NLPHL might be mistaken for a reactive process if this entity is not considered in the differential diagnosis. Associated prominent reactive epithelial proliferation and metaplasia in some of our cases highlight the potential for misdiagnosis of NLPHL in intraparotid lymph nodes especially as nonsebaceous lymphadenoma, Warthin tumor, or autoimmune sialadenitis.

In summary, this study represents the first detailed analysis of a series of NLPHL and CHL presenting as intraparotid mass with regard to the pattern of infiltration and associated proliferative lesions of epithelial salivary elements within the lymphoma. This series highlights the nodal origin of most of intraparotid Hodgkin lymphomas. The pattern analysis presented herein may be of great help in the differential diagnosis. Additional cytokeratin staining can greatly help in a first diagnostic step in highlighting the predominant pattern (intraparotid lymph node vs. diffuse lobular) of infiltration.

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