Salivary Gland Lymphoproliferative Disorders: A Canadian Tertiary Center Experience

A. Paliga · J. Farmer · I. Bence-Bruckler ·
M. Lamba

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Abstract Salivary gland lymphoproliferative disorders (SGLD) are very rare tumors and clinicopathological data is sparse. In a Canadian series of 30 cases, extracted from the surgical pathology files of The Ottawa Hospital between 1990 and 2010, a clinical, histopathological, and immunophenotypic analysis was conducted. Tumors were staged using the Ann Arbor staging and classified using the World Health Organization 2008 classification. There were 15 salivary gland (SG) primary lymphomas with localized disease, predominantly mucosa associated lymphoid tissue type marginal zone lymphoma (MALT-L), but with a significant incidence of low grade follicular lymphoma (FL) and diffuse large B cell phenotype as well. There were 7 systemic SG lymphomas and 5 patients were diagnosed with lymphoproliferative disorders originating from intra-parotid lymph nodes. Finally, the remaining 3 cases represented reactive sialadenitis. A literature review was conducted and our primary lymphoma group was compared to those from other countries. SGLDs are predominantly B cell lymphomas that develop in older adults. Primary tumors, which have MALT-L and low grade FL characteristics, have a favorable survival, however MALT-L have a high rate of relapse. A minority of SG lesions are excised secondary to lymphomas that definitely arose from intra-parotid lymph nodes.

Keywords Salivary gland · Parotid · Lymphoma · Malt · Head and neck · Immunohistochemistry

Introduction

Salivary glands (SG) are tubuloacinar exocrine glands with the ability to acquire mucosa associated lymphoid tissue as a result of chronic stimulation [1]. SG enlargement can be secondary to a very diverse group of pathological processes, including many benign and malignant neoplasms, either epithelial or non-epithelial in origin. Among the malignant conditions, carcinomas are most common, but lymphomas do occur. Salivary gland lymphoproliferative disorders (SGLD) include a spectrum of disorders ranging from benign lymphoepithelial lesions to aggressive lymphomas. Reactive lesions can mimic malignancy, a distinction which may be difficult. Fortunately, primary lymphomas of the SG are rare tumors, representing 1.7–3 % of all SG neoplasms [2, 3], although the incidence may be on the rise [3–5].

Primary lymphomas of the salivary gland are almost exclusively extranodal non Hodgkin's lymphomas (NHLs) [6, 7]. Extranodal lymphomas can be clinically distinct from nodal lymphomas [8]. True primary extranodal lymphomas of the SG must be differentiated from nodal lymphomas that can arise from one of the many closely associated lymph nodes, or intra-parenchymal nodes [7, 9]. Furthermore, the SG can be a secondary extranodal site of involvement for patients with systemic lymphoma. Primary salivary gland lymphomas usually occur in the parotid gland, can be bilateral, and most are classified as extranodal marginal-zone B-cell lymphoma, MALT-type (MALT-L) [2, 10–13]. Sjogren's syndrome, a chronic immune mediated disease

A. Paliga (✉) · J. Farmer · M. Lamba
Department of Pathology, The Ottawa Hospital, University
of Ottawa, General Campus Critical Care Wing, 4th Floor,
Rm 4115, 501 Smyth Road, Ottawa, ON K1H 8L6, Canada
e-mail: apaliga@toh.on.ca

I. Bence-Bruckler
Department of Hematology, The Ottawa Hospital,
University of Ottawa, Ottawa, ON K1H 8L6, Canada

localized to the exocrine glands that produce tears and saliva, is a well accepted risk factor for acquiring salivary gland lymphoma [14, 15].

Due to the rarity of primary salivary lymphomas, histologic subtypes have been poorly characterized. Furthermore, there have been significant recent changes to the nomenclature and classification of lymphomas. This has been spurred by advancement in molecular diagnostic techniques, and a greater understanding of the underlying pathophysiology of lymphomas. These changes make it difficult to compare data with papers written before the release of the third edition of the World Health Organization (WHO) Classification of Lymphoid Neoplasms in July 2001, which represented the first true international consensus on classification of hematologic neoplasms [16]. Many types of extranodal NHLs demonstrate remarkable geographic variability in frequency of presentation, associated infectious agents, and clinical behavior [5, 17]. Case series of primary SG lymphomas since publication of the WHO Classification are few, the majority being from Northeast Asian countries. Little is reported from North American institutions. Furthermore, many group SG lymphoma patients with extranodal NHLs of the head and neck, rather than reporting them separately [18–20]. Finally, data on the clinical course of these rare neoplasms is sparse. Using the 2008 World Health Organization Classification of Lymphoid Tumors we conducted this study to determine the clinicopathologic profiles of SG lymphoproliferative disorders, with particular attention to primary SG lymphomas, in our Canadian patient population [21].

Methods

The surgical pathology files of the Ottawa Hospital for the years 1990 through 2010 were reviewed, and all cases involving lymphoproliferative disorders of the SG were selected. The study was reviewed and approved by the Ottawa Hospital Research Ethics Board.

All patients had SG enlargement as the primary presentation. Clinical information recorded included date of birth, age at diagnosis, laterality, signs and symptoms, medical history, evidence of systemic disease, and first line treatment, if any.

The cases were classified as follows: primary SG lymphoma, systemic SG lymphoma, reactive SG lymphoproliferative lesions, and lymphoproliferative disorders originating from an intraparotid lymph node. Histologic diagnosis of primary or systemic SG lymphoma required parenchymal involvement, and criteria as proposed by Schmid et al. [22] were used to indicate true extranodal

lymphomas of the SG: (1) The lesion contained no lymph nodes and (2) none of the lesions were demarcated by a capsule-like structure. Lesions that were classified as originating from an intraparotid lymph node consisted of the neoplastic component in continuity with benign intraparotid lymph node tissue that was identified by the presence of a capsule-like structure. This category included both patients with systemic and localized disease. Reactive SG lesions were diagnosed as per their accepted criteria.

Available computed tomography (CT) scans were reviewed to determine extent of disease. Ann Arbor staging was used. For lymphoma cases with no histologic evidence of lymph node involvement, patients with stage IE or IIE disease (i.e., localized disease) were designated as primary SG lymphomas. Patients who presented with advanced stage lymphomas (stage IIIE and IVE), or were found to have advanced stage disease within 6 months of initial diagnosis, and patients with a past history of NHL, were designated as having systemic lymphomas with secondary involvement of SG parenchyma as is the standard practice at our institution. Follow-up information recorded included first line treatment response and occurrence of other medical events (subsequent cancers or major illness). Overall survival (OS) and relapse free survival (RFS) was calculated using this data. All patients with a primary or systemic SG lymphoma diagnosis were seen by lymphoma specialists at a single institution.

For all cases, we reviewed tissue sections stained with hematoxylin–eosin and conducted immunophenotyping. The histological classifications were based on 2008 WHO Classification of Lymphoid Tumors [21]. Only one diagnosis required revision from an original diagnosis of low grade lymphoproliferative disorder, NOS to a follicular lymphoma (FL) grade 1/2. The basis for the revision was positive CD10 staining, as the immunohistochemical stain was not available at the original time of diagnosis. Immunohistologic analysis was performed on paraffin-embedded tissue with use of the avidin–biotin technique for staining (Vector Laboratories, Inc., Burlingame, Calif.) and primary antibodies for the following antigens: CD20 (Dako [DakoCytomation Inc., Mississauga, Ont.] MO755), CD45RO (Dako MO742), CD23 (Vector NCL-CD23-1B12), CD5 (Vector NCL-CD5-4C7), CD10 (Vector NCL-CD10-270), bcl-2 (Dako MO887) and cyclin D (Vector NCL-Cyclin D). In 10 cases we performed 2 colour flow cytometry, using a panel of antibodies, to further support the diagnosis of lymphoma.

The data were statistically analyzed using SPSS software for Windows (Version 20, SPSS, Chicago, IL, USA). OS and RFS differences were examined using the log-rank (Mantel–Cox) test to calculate the *p* values. Statistical significance was defined as $p \leq 0.05$.

Results

Of thirty SGLD cases, twenty-two patients presented with enlargement of the parotid gland (PG), seven presented with submandibular gland (SMG) enlargement, and one had a mass of the hard palate. No lesions were bilateral, and no patients had a history of Hepatitis C, transplant, previous radiation to the head and neck area, or HIV infection. No patients with a diagnosis of primary or systemic SG lymphoma were lost to follow-up. Figure 1 shows the distribution of SGLD in excised lesions in patients presenting with enlarged salivary glands.

There were fifteen primary lymphomas with lesions confined to parotid gland (eleven) and submandibular gland (four). Table 1 demonstrates histological classifications and patient demographics. Two patients had a history of Sjogren's syndrome (one diffuse large B cell lymphoma [DLBCL] & one MALT-L) and one had a history of Ulcerative Colitis (FL). All primary lymphomas were stage IE and all were treated with excision. All FL where grade 1/2. Six patients received radiation (four MALT-L and two FL), one FL patient received Rituximab, and all aggressive NHLs patients received CHOP chemotherapy plus radiation or Rituximab. Follow-up varied from 27 to 264 months (median 56). Six patients developed recurrent disease at 9–108 months time (median 42), two of which died of lymphoma related deaths (one DLBCL and one FL). The remaining four patients with recurrent disease remain alive with no evidence of disease after second line therapy. Figures 2, 3 and 4 show representative images demonstrating the histological features of the predominant types of primary SG lymphomas encountered.

Seven systemic SG lymphomas were identified; five parotid gland and two submandibular. Please refer to Table 1 for histological classifications and patient demographics. All FL where grade 1/2. All patients presented

Fig. 1 Distribution of SGLD in excised lesions in patients presenting with enlarged salivary glands

with stage IV disease, but one who had stage III disease. Most received chemotherapy with Rituximab. Two patients were not treated due to comorbidity (one SLL/CLL and FL 1/2). Three patients relapsed, two treated, one untreated, within 25–120 months of diagnosis (median 36) within a follow-up of 30–159 months (median 111). All relapsed patients responded to second line therapy; two are now disease free, and one continues to live with disease 159 months from diagnosis. One patient died of disease during the first cycle of chemo, one untreated patient died of unrelated disease within a year of diagnosis, and the remaining two patients are disease free.

Five of thirty SGLD patients were diagnosed with lymphoproliferative disorders originating from intra-parotid lymph nodes. Two of these patients were external consult cases, with a diagnosis of nodular lymphocyte predominant Hodgkin lymphoma and FL respectively, and no follow-up is available. Two of the three remaining patients were diagnosed with FL grade 3 (stage III) and grade 1/2 (stage Ia), and remain disease free 74 and 88 months post diagnosis, respectively. The patient with FL grade 3 was treated with Rituximab and CHOP, while the patient with FL grade 1–2 received no additional treatment after surgical excision of the

Table 1 Comparison of primary versus systemic salivary gland lymphoma

	Primary (15 total)	Systemic (7 total)
Sex (male:female)	1:1.5	1:1.3
Age (median)	63	57
Bilateral	None	None
Site of tumor (PG:SMG)	11:4	5:2
History of autoimmune disorder	3	0
<i>Histology</i>		
MALT	6/15 (40 %)	–
Follicular ^a	5/15 (33 %)	2/7 (30 %)
DLBCL	4/15 (27 %)	3/7 (40 %)
SLL	–	2/7 (30 %)
<i>Survival</i>		
Alive, NED at last follow-up	11 (73 %)	4 (57 %)
Alive with disease	0	1 (14 %)
Recurrence after first line tx	6 (40 %)	2 (40 %) ^b
Dead of disease	2 (14 %)	1 (14 %)
Dead of other cause	2 (14 %)	1 (14 %) ^c
OS	11/15 (73 %)	5/7 (71 %)
RFS	8/15 (53 %)	2/5 (40 %) ^b

PG parotid gland, SMG submandibular gland

^a Grade 1/2

^b Patient/patients who did not receive therapy at time of diagnosis were excluded from this number

^c This patient did not receive any therapy

Fig. 2 Histological features of primary malt lymphoma of the SG. **a** A low power view of a diffuse lymphocytic process infiltrating into a salivary gland ($\times 40$, H&E). **b** A high power view demonstrating typical lymphoepithelial lesion ($\times 400$, H&E). **c** Positive CD20

staining of the lymphocytes invading into the salivary glands, confirming the B-cell nature of the neoplasm ($\times 400$). **d** Diffuse kappa staining supporting the monoclonal nature of the neoplasm as well as perineural invasion ($\times 200$)

parotid. One patient was diagnosed with having an intra-parotid lymph node with progressive transformation of germinal center and he remains disease free 34 months later.

Finally, two of thirty cases had SG enlargement secondary to chronic sialadenitis. The last patient in our series had a mass of the hard palate secondary to a benign lympho-epithelial lesion within a SG.

Discussion

The SG is the anatomic site of 6–26 % of extranodal NHL in the head and neck (H&N), with Taiwan having the lowest incidence, and Iran reporting the highest incidence [20, 23–26]. Within the limited literature, there is some variability in the reported histological distribution of primary SG lymphomas (Table 3), but on the whole, low grade B-cell lymphomas predominate [10–13, 27, 28]. The majority of SG lymphomas are reported to originate in the parotid gland, which is consistent with our results [2, 7, 12, 29]. As expected, all our primary lymphomas were B-cell lymphomas. 40 % of our primary SG lymphomas were

MALT-L, with FL and DLBCL each representing about 30 % of cases.

The high incidence of primary DLBCL of the SG was surprising. Although several studies have reported primary DLBCL of the SG, most of these studies included patients with systemic disease in their definition of primary SG lymphoma (see Table 3, column 4). Of the studies that had stricter definitions of primary SG lymphoma, only one reported a significant incidence of DLBCL that is comparable to ours and three quarters of their DLBCLs represented transformed cases in a background of MALT-L [12]. None of our DLBCL cases had an identifiable background of MALT-L.

The high incidence of FL was also unexpected. Although primary extranodal FL is very rare, it has been described by other groups in the SG [9, 11, 27]. Kojima et al. [9] looked at primary SG FL and suggested a differing BCL-2 staining pattern between nodal and extranodal FL. Their reported extranodal SG FL cases were predominantly Bcl-2 negative, however most of the SG FL cases described by Kojima et al. were in patients with advanced stage disease. In our study these patients would

Fig. 3 Histological features of primary follicular lymphoma of the SG. **a** A low power view of a nodular lymphocytic process infiltrating into a salivary gland ($\times 40$, H&E). **b** A higher power view demonstrating

lymphocytes admixed with salivary gland ducts ($\times 200$, H&E). **c**, **d**, and **e** Bcl-2, CD10, and CD20 immunohistochemical staining confirming the diagnosis of follicular lymphoma ($\times 100$)

have been classified as systemic lymphomas. All of our early stage primary SG FL cases were Bcl-2 positive. Likewise, Nakamura et al. [11] also reported all early stage primary FL of the SG as Bcl-2 positive.

When comparing the MALT-L to non-MALT-L primary lymphomas, as demonstrated in Table 2, the non-MALT-L patient group had a younger median age and showed a higher proportion of females compared to the MALT-L group. The MALT-L group had a more frequent incidence of relapse, although this did not meet statistical significance.

High rates of local recurrence in early stage MALT-L have been previously described [29, 30]. The largest and most recent multicentre trial, conducted by thirteen member centers of the Rare Cancer Network, noted local recurrence in 15 of 46 (33 %) stage I and II primary SG MALT-L patients [29]. However the group argued that 5 year overall survival (OS), reported as 89 % in stage I and II primary SG MALT-L patients, was not affected by the rate of local recurrence. Likewise, half of our primary lymphomas recurred, however none died of their disease. We report an OS of 73 % for all primary SG lymphomas, and 83 % for the primary MALT-L. A high OS in primary

SG lymphoma is in keeping with other reports (see Table 3). Still, some studies have shown a statistically improved OS for MALT-L versus other primary NHL of the SG [13]. Roh et al. [13] evaluated 20 Korean patients with NHL of the SG. 12/20 of their patients had MALT-L, and compared to the non-MALT types, had significantly greater 5-year relapse-free (91.7 vs. 37.5 %, $p < 0.05$) and disease-free (90.9 vs. 35.0 %, $p < 0.05$) survival. However, all 8 of their non-MALT lymphomas were aggressive lymphomas, while in our series only 4 out of 9 patients had aggressive primary non-MALT NHL.

Only one of six primary MALT lymphoma patients had a history of Sjogren's syndrome. This is in keeping with other studies that have reported a rate of 8–46 % of primary SG MALT-L patients with Sjogren's syndrome [10–13]. None of our lesions were bilateral. This was unexpected as several series report 10–30 % bilateral lesions in primary SG lymphomas [11, 13], however it should be noted that these studies also included patients with systemic disease.

There were seven SG lymphomas that presented with advanced disease or with a past history of lymphoma and

Fig. 4 Histological features of primary diffuse large B-cell lymphoma of the SG. **a** A low power view of a diffuse lymphocytic process infiltrating into a salivary gland (×100, HPS). **b** A higher power view demonstrating sheets of large lymphocytes (×400, HPS).

c High ki67 immunohistochemical staining, indicating a highly proliferative process (×400). **d** Positive CD20 immunohistochemical staining confirming the B-cell nature of the neoplasm (×400)

Table 2 Comparison of primary SG lymphomas with MALT-L versus non-MALT-L histology

	MALT-L (6 total)	Non-MALT-L NHL (9 total)
Sex (male:female)	1:1	1:2
Age (median)	76	59
Site of tumor (PG:SMG)	5:1	2:1
Associated autoimmune disease	Sjogren's syndrome X 1	Sjogren's syndrome X 1 Ulcerative Colitis X 1
<i>Survival</i>		
Alive, NED at last follow up	5 (83 %)	6 (66 %)
Recurrence after first line tx	3 (50 %)	3 (11 %)
Dead of disease	–	2 (22 %)
Dead of other cause	1 (11 %)	1 (11 %)
OS	5/6 (83 %)	6/9 (67 %)
RFS	2/6 (33 %)	5/9 (56 %)

PG parotid gland, SMG submandibular gland

were thus designated as systemic lymphomas. They surprisingly had similar OS and RFS rates as the primary lymphomas, and there was no statistical significant difference between the two. Also, as a group, the patients with systemic lymphoma were younger.

Five patients had lymphoproliferative disorders originating from intra-parotid lymph nodes. Thus, in our institution, a minority of SG lesions are excised secondary to lymphoproliferative disorders that definitely arose from intra-parotid lymph nodes. It is important to distinguish these cases from true extranodal SG NHL as the accurate classification of these lesions is necessary to guide future investigative studies and patient care.

Limitations in this study include a small sample size and short follow-up time for a few patients, thus the results must be interpreted with caution. However with such a rare lymphoma, these limitations are difficult to overcome. There may be some geographic variability in histologic and clinical characteristics of SG lymphomas, but comparisons to other countries are challenging as there is no uniform definition for primary lymphoma of the SG. We believe

Table 3 Review of literature addressing clinico-histologic data for primary SG lymphoma using WHO classification

Source	Country	Number of patients	Stage III/IV patients	Age (mean/median)	Male/female	MALT	FL	DLBCL	Other	Overall survival calculated in study	Overall relapse free survival calculated from study
Dunn et al. [10]	Taiwan	23	13	NR/61	1.3:1	19/23 (83 %)	1/23 (4 %)	3/23 (13 %)	–	94.7 %	51.4 %
MacDermid et al. [27]	USA	10	0	NR	NR	8/10 (80 %)	1/10 (10 %)	–	1/10 ^a	90 %	70 %
Nakamura et al. [11]	Japan	27	4	(61.6/NR)	1:1.7	19/27 (70 %)	6/27 (22 %)	2/27 (7 %)	–	76 %	NR
Kojima et al. [12]	Japan	30	0	(NR/57)	1:1.7	15/30 (50 %)	7/30 (23 %)	8/30 (27 %)	–	96 %	77 %
Roh et al. [13]	Korea	20	6	(50.2/NR)	1:1	12/20 (60 %)	0	5/20 (25 %)	3/20 ^b	5 year	5 year
Triantafyllidou et al. [28]	Greece	24	0	(49/50)	1.3:1.1	15/24 (63 %)	1/24 (4 %)	0	8/24 ^c	83 %	71.5 %
Paliga et al. (2013, this study)	Canada	15	0	(65/63)	1:1.5	6/15 (40 %)	5/15 (33 %)	4/15 (27 %)	–	5 year	5 year
										79 %	NR
										73 %	53 %

Primary as defined by each paper, some groups included patients with advanced stage (III–IV)/systemic disease (column 4)

^a 1/10 SLL/CLL

^b 1/20 Mantle cell lymphoma, 1/20 peripheral T-cell lymphoma and 1/20 lymphoblastic cell lymphoma

^c 3/24 Mantle cell lymphomas and 5/24 CLL, NR not reported

that systemic lymphomas, and lymphomas originating from intraparenchymal lymph nodes, should be excluded from studies examining primary SG lymphomas. Overall our experience confirms that SGLD's are predominantly B-cell lymphomas that develop in older adults. Primary tumors, which have MALT-L and low grade FL characteristics, have a favorable survival, however MALT-L have a high rate of relapse.

Conflict of interest The authors declare that they have no conflict of interest.

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