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A Salivary Gland Lymphoma Involving Contralateral Parotid Gland and Submaxillary Gland with a Review of the Literature*)

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ABSTRACT

A 75-year-old male was pointed out the right submandibular swelling followed by the left pre-auricular swelling, about half-year apart. Parenchyma of the left parotid gland was infiltrated by lymphoid growth, and the right submaxillary gland had a discrete lymphoid growth at a pole of the gland. Inside and outside these lymphoid growths, lymphocytes infiltrated between ducts, acini, adipose tissue, blood vessels and nerves. Patho-immunologically, the case was a follicular lymphoma of medium-sized (or small cleaved) cell type with no cytoplasmic immunoglobulin production, although a B-cell type of the malignant lymphoma was suggested because of a prominent nodular pattern. The patient has been in a complete remission for six months subsequent to chemotherapy. The major literature concerning malignant lymphoma primarily in parotid or submaxillary gland reported since 1959 was reviewed. The criteria for possible primary malignant lymphoma of the salivary gland, its pathogenesis and its differential diagnosis from other lymphoid and epithelial lesions were discussed.

INTRODUCTION

Foote and Frazell[7] wrote "As yet we have not had an unequivocal case of primary malignant lymphoma of a major salivary gland. When such a claim is made, it should be accompanied by proof that the salivary gland was not secondarily involved. This is difficult. There is, of course, no theoretical objection to the existence of a great many mesenchymal tumors of salivary glands, but vast patience is required to accumulate acceptable data. Publication of single case reports of convincing material of this sort should be encouraged." Although the head and neck is one of the most common place for malignant lymphoma, the salivary gland per se is rarely involved. We report an elderly man, who started the right submandibular swelling followed by the left pre-auricular swelling, about half-year apart; the pathologic findings confirmed their salivary gland origin.

CASE PRESENTATION

This is an elderly man born in December 1906. In April 1981, he was pointed out the

*) 田仲俊雄，杉浦友昭，渡辺周一，斎藤龍介，小倉義郎，林　恭一，大熨泰亮：対側の耳下腺および顎下腺を侵襲した悪性リンパ腫

Table 1. Pertinent Laboratory Data on Admission

Blood picture	
RBC	$4.69\times10^6/\mu l$
Hg	15.7 g/dl
Ht	43.7%
WBC	$7.0\times10^3/\mu l$
Differentials (%)	
Seg	68
Band	2
Lympho	22
Mono	8
Platelet	$22.7\times10^4/\mu l$
Serum protein (%)	
Albumin	59.1
Globulin	
alpha 1	2.9
alpha 2	11.4
beta	10.2
gamma	16.3
A/G	1.45
Immunoglobulin (mg/dl)	
IgA	349
IgG	1644
IgM	355
Peripheral blood (%)	
T cell	85
B cell	11
Serology (syphilis)	
Ogata	(++)
VDRL	(++)
TPHA	(+)
Mantaux reaction	
$\frac{10\times10}{10\times10}$	(±)
CH50	46.3 U/ml
LDH	217 IU/l

right submandibular swelling, followed by the left pre-auricular swelling in September of the same year. He then was referred to the Oto-laryngology Department, Okayama University Hospital, in November. On admission, physical examinations including lymphography indicated the clinical stage, IIE. Laboratory data (Table 1) showed increased IgM (normal ranges, 60–250 mg/dl), slightly elevated CH50 (normal ranges, 30.0–40.0 U/ml) and positive serology of syphilis; other pertinent data were not contributory. The right submandibular tumor measured approximately 3.0×2.5 cm and was entirely removed in the mid-November. The left pre-auricular tumor measured approximately 4.0×3.5 cm and the superficial part of the parotid gland was excised in the mid-December.

Postoperatively, three courses of a combination chemotherapy consisting of cyclophosphamide, adriamycin, vincristine and prednisolone was given and followed by 4,000 rads of Linac x-rays to the whole neck including Waldeyer's ring. The following three courses of the same combination chemotherapy as above was terminated because of its toxicity. In June 1983, relapse appeared at bilateral cervical, axillary and inguinal regions. He is currently in a complete remission with peroral administration of etopocide (VP-16-213)[22], 150 mg for five consecutive days and fourth-weekly.

PATHOLOGIC FINDINGS

The specimen from the left pre-auricular region consisted of a portion of parotid gland measuring approximately 1.7×1.7 cm. The specimen from the right submandibular region consisted of submaxillary gland measuring 3.0×2.0 cm in the largest dimensions, and two lymph nodes which were adjacent to the submaxillary gland and measured 3.0×2.0 cm and 2.0×1.0 cm, respectively.

As to parotid gland, nodular lymphoid growth circumscribed normal salivary gland which appeared like a few islands (Fig. 1a). In a different cut surface, a discrete nodule was embedded in the gland, whereas another nodule invaded to glandular parenchyma (Fig. 1b). In the periphery of nodules, lymphocytes infiltrated between ducts, acini and adipose tissue (Fig. 2). There was capsular thickening with perineural growth of lymphocytes (Fig. 3). Inside nodules, glandular architecture was entirely effaced due to intense lymphocyte infiltration with periductal, perivascular and perineural growths (Fig. 4). The tumor cells consisted of medium-sized, cleaved lymphocytes and very occasional

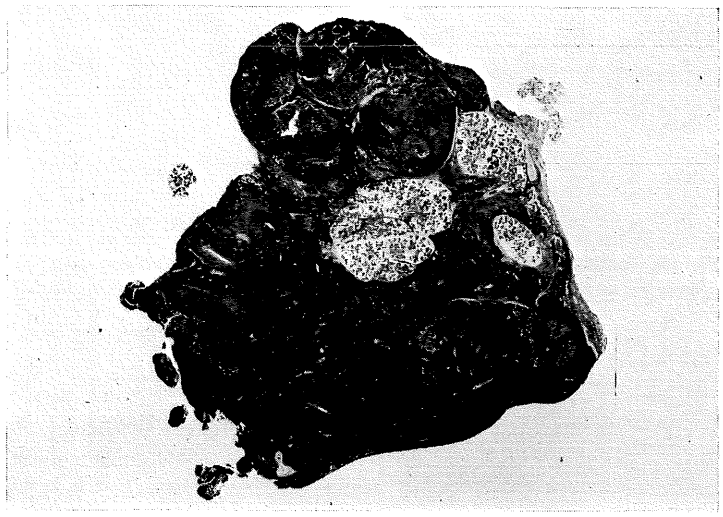

Fig. 1a. Panoramic view of parotid gland with lymphoid growths circumscribing normal salivary gland.

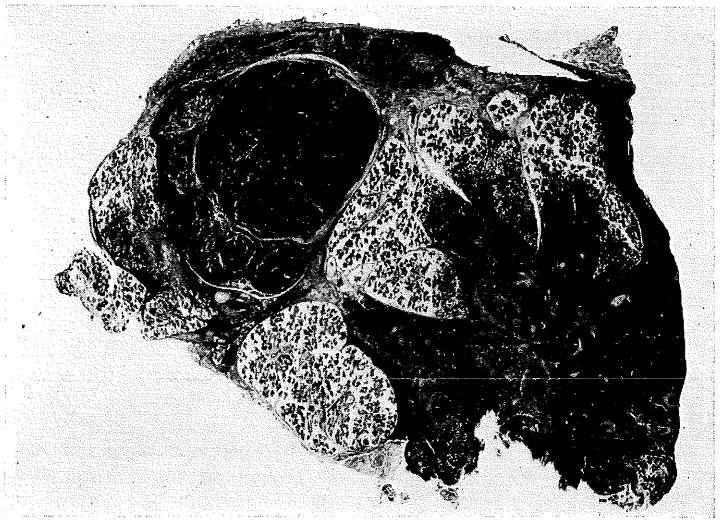

Fig. 1b. Panoramic view of another cut surface showing a discrete nodule in one side of the gland and another nodule infiltrating to glandular parenchyma.

large cells (Figs. 5, 6 and 7). Submaxillary gland had a discrete lymphoid growth at a pole of the gland, was surrounded by normal glandular tissue, and showed very prominent follicular pattern (Figs. 8 and 9). The periphery of the nodule was essentially identical to that of parotid gland with diffuse infiltration of lymphocytes around ducts, acini, blood vessels and nerves (Fig. 10). A normal lobular, glandular pattern was well preserved in more than half of the gland. The two lymph nodes adjacent to submaxillary gland showed also a prominent follicular pattern of lymphoid involvement as seen in parotid and submaxillary glands.

Peroxidase-antiperoxidase method demonstrated neither kappa and rhambda light chains nor IgA, IgG and IgM heavy chains in the lymphoid growth of parotid and submaxillary glands and two lymph nodes. This case, therefore, belonged to a follicular lymphoma of medium-sized (Lymphoma Study Group of Japan) or small cleaved (Working Formulation) cell type with no cytoplasmic immunoglobulin production, although a B-cell type of the malignant lymphoma was suggested because of a prominent nodular pattern.

DISCUSSION

According to Rauch[19], five cases of primary lymphosarcoma of the salivary gland were reported before 1959. In addition, Wheelock

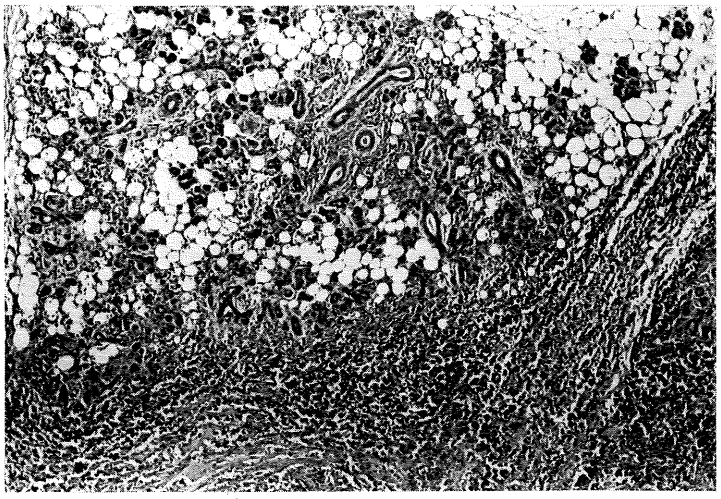

Fig. 2 The periphery of nodules showing lymphocytes infiltrating to ducts, acini and adipose tissue. H & E, ×40.

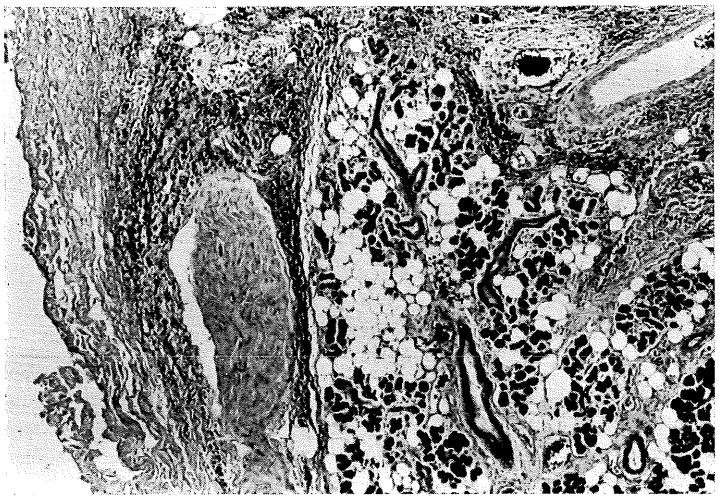

Fig. 3. Capsular thickening with perineural growth of lymphocytes. H & E, ×40.

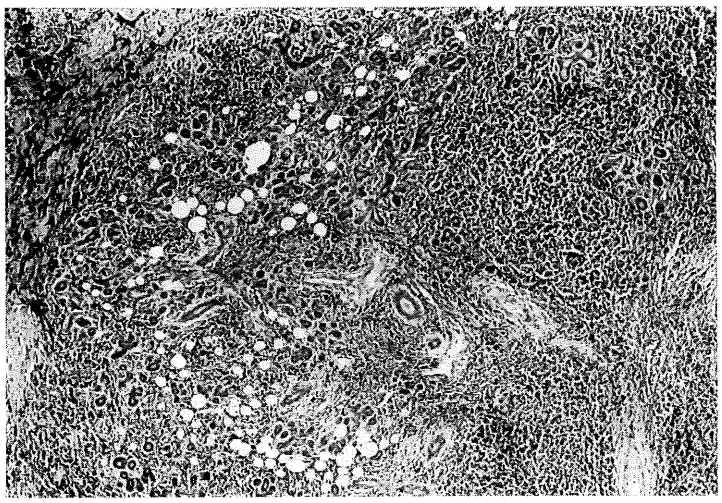

Fig. 4. The detail of nodules showing entirely effaced glandular architecture due to intense lymphocyte infiltration. H & E, ×40.

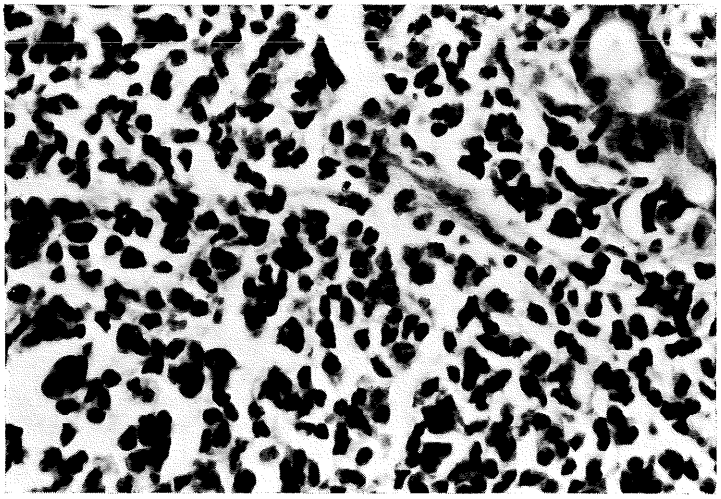

Fig. 5. The tumor cells consisting mainly of medium-sized, cleaved lymphocytes; a few residual ducts present at the right upper corner. H & E, ×400.

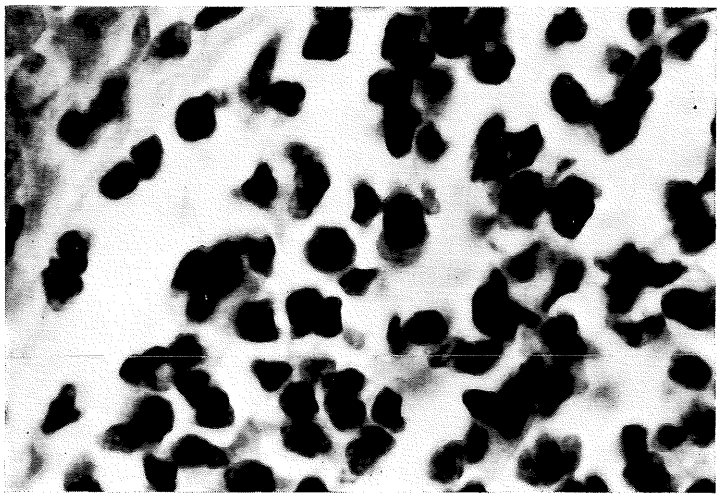

Fig. 6. Higher magnification of Fig. 5; a part of a residual duct present at the left upper corner. H & E, × 1,000.

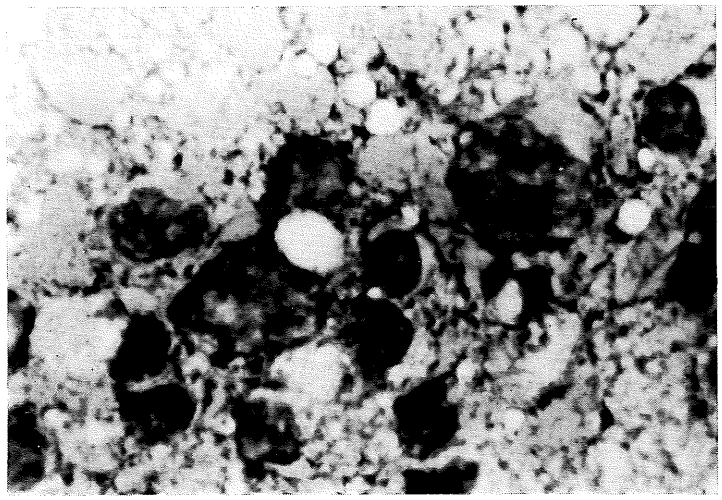

Fig. 7. Imprint smear from a nodular part of parotid gland showing two large cells in the center and several medium-sized cells. May-Grünwald-Giemsa, ×1,000.

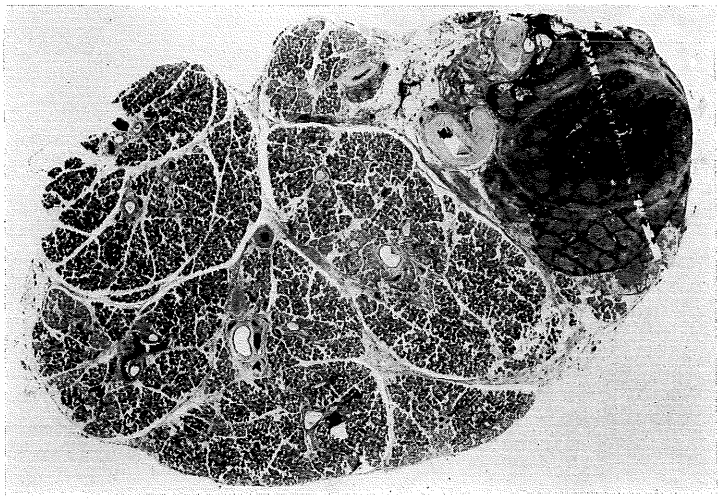

Fig. 8. Panoramic view ot submaxillary gland showing a discrete lymphoid growth, surrounded by normal glandular tissue, at a pole of the gland.

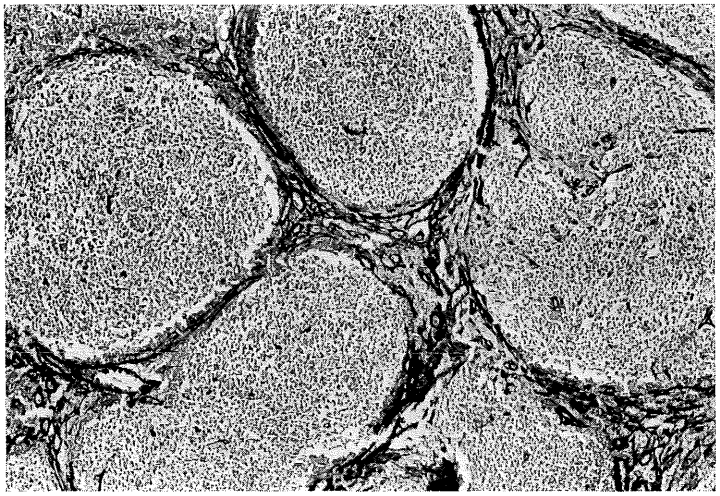

Fig. 9. The detail of the lymphoid growth showing several, very prominent follicular patterns. Silver, ×40.

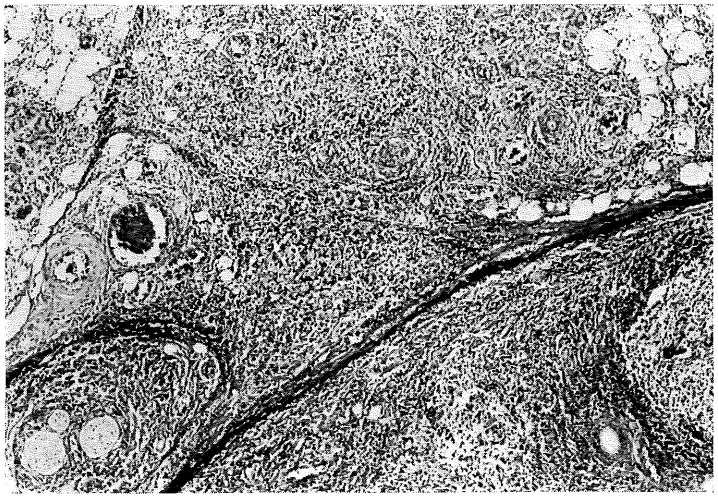

Fig. 10. The periphery of the nodule with lymphocytes infiltrating between ducts, blood vessels, nerves (at the left lower corner) and adipose tissue. H & E, ×40.

Table 2. Survey of Major Literature Concerning Malignant Lymphoma Primarily in the Parotid or Submaxillary Gland Reported Since 1959

Authors (Year reported)	Age Sex	Site involved[a)]	Histology[b)]	Nodular or Diffuse
Grage & Lober	1. 35 M	R Parotid	Giant follicular lymphoblastoma	
(1962)	2. 77 F	L Submaxilla	Hodgkin	
	3. 31 M	L Parotid	LSA	
	4. 64 M	L Parotid	Lymphoblastoma, intermediate type	
	5. 55 F	R Parotid	Lymphoblastoma, unclassified	
Hatziotis & Asprides (1964)	6. 60 M	L Submaxilla	LSA	Diffuse
Simons et al.	7. —	Submaxilla	LSA	
(1964)	8. —	Submaxilla	LSA	
	9. —	Submaxilla	LSA	
VandenBerg et al.	10. —	Parotid	ML	
(1964)	11. —	Parotid	ML	
	12. —	Submaxilla	ML	
Patey et al.	13. 46 F	Parotid*	ML	
(1965)	14. 66 F	Parotid*	LSA	
	15. 63 F	Parotid	LSA	
	16. 73 F	Parotid	RCS	
Sumangala Amma (1969)	17. 55 M	R Parotid	LSA	
Berdal et al.	18. —	Parotid	ML	
(1970)	19. —	Parotid	ML	
	20. —	Parotid	ML	
Leegaard &	21. —	Parotid	RCS	
Lindeman	22. —	Parotid	RCS	
(1970)				
Freedman	23. 54 F	R Parotid	LSA	
(1971)	24. 50 M	L Parotid	LSA	
	25. 32 F	L Parotid	Lymphoma	Nodular
	26. 50 M	R Parotid	Lymphoma	Nodular
	27. 71 F	R Parotid	Lymphoma	
	28. 77 F	R Parotid	RCS	
	29. 37 F	R Submaxilla	LSA	
	30. 62 F	R Parotid & R Submaxilla	LSA	Diffuse
	31. 43 M	R Parotid	LSA	
	32. 77 F	R Parotid	LSA	
Lipton & Lee	33. —	R Parotid	LSA	
(1971)	34. —	R Parotid	LSA	
	35. —	R Parotid	RCS	
Seligman et al. (1974)	36. 20 M	R Parotid	LSA	

Table 2. Continued

Authors (Year reported)	Age Sex	Site involved[a)]	Histology[b)]	Nodular or Diffuse
Eguchi et al. (1976)	37. 65 M	R Parotid	RCS	Diffuse
Emanuel (1976)	38. 74 M	L Parotid	ML, poorly differentiated	
	39. 55 F	L Parotid	ML, well differentiated	Diffuse
	40. 75 F	L Parotid	ML, undifferentiated	Diffuse
Hyman & Wolff (1976)	41. 37 M	R Parotid	Lymphocytic LSA	Nodular
	42. 78 F	R Parotid	Lymphocytic LSA	Nodular
	43. 65 F	L Parotid	Histiocytic LSA	Diffuse
	44. 38 M	Submaxilla*	Lymphocytic LSA	Nodular
	45. 60 F	L Parotid	Histocytic LSA	Nodular
	46. 36 F	R Parotid	Hodgkin, lymphocyte depleted	
	47. 46 F	L Parotid	Lymphocytic LSA	Nodular
	48. 24 F	R Parotid	Histiocytic LSA	Diffuse
	49. 56 M	L Parotid	Histiocytic LSA	Diffuse
	50. 55 F	R Parotid	LSA, mixed L-H	Nodular
	51. 58 F	R Parotid	Lymphocytic LSA	Nodular
	52. 21 M	R Parotid	LSA, mixed L-H	Nodular
	53. 62 M	L Parotid	LSA, mixed L-H	Diffuse
	54. 50 M	R Parotid	Histiocytic LSA	Nodular
	55. 73 F	L Submaxilla	Histiocytic LSA	Nodular
	56. 66 M	L Parotid	Lymphocytic LSA	Nodular
	57. 43 F	L Parotid	Histiocytic LSA	Nodular
	58. —	Parotid	LSA, mixed L-H	Nodular
	59. 60 F	Parotid	LSA, mixed L-H	Nodular
	60. 33 F	Submaxilla	Histiocytic LSA	Diffuse
	61. 36 M	R Parotid	Histiocytic LSA	Nodular
	62. 82 F	L Parotid	Histiocytic LSA	Nodular
	63. —	—	Histiocytic LSA	Diffuse
	64. 68 M	Parotid	LSA, mixed L-H	Nodular
	65. 46 F	—*	Histiocytic LSA	Diffuse
	66. 53 F	L Parotid*	Histiocytic LSA	Nodular
	67. 62 F	L Parotid	Histiocytic LSA	Diffuse
	68. 34 M	R Parotid	Histiocytic LSA	Diffuse
	69. 62 M	R Parotid	Lymphocytic LSA	Nodular
	70. 68 F	L Parotid	Histiocytic LSA	Nodular
	71. 57 M	R Parotid*	Histiocytic LSA	Diffuse
	72. 57 F	R Parotid	Histiocytic LSA	Diffuse
	73. 50 F	Parotid	Lymphocytic LSA	Nodular
Nime et al. (1976)	74. 15 F	L Parotid	Hodgkin, lymphocyte predominant	
	75. 51 M	L Parotid	Lymphocytic LSA	Diffuse
	76. 51 F	L Parotid*	LSA, mixed L-H	Diffuse
	77. 84 F	R Parotid	LSA, mixed L-H	Diffuse
Webber (1976)	78. 49 M	R Parotid	ML	

Table 2. Continued

Authors (Year reported)	Age Sex	Site involved[a)]	Histology[b)]	Nodular or Diffuse
Roth et al. (1978)	79. 29 M	L Parotid	Lymphocytic LSA, poorly differentiated	Nodular
	80. 70 F	Bilat Parotids	Lymphocytic LSA, moderately to poorly differentiated	Diffuse
	81. 52 M	R Parotid	Hodgkin	
Podoshin et al.	82. 74 F	R Parotid	ML, poorly differentiated	Diffuse
(1979)	83. 80 F	R Parotid	ML, poorly differentiated, mixed L-H	Diffuse
Furukawa et al. (1982)	84. 15 M	R Parotid	LSA, prolymphocytic	Nodular
Tsujimoto et al. (1982)	85. 35 M	R Parotid	ML, small cleaved	Nodular

a) * indicates a case associated with lymphoepithelial lesions.

b) ML: malignant lymphoma; LSA: lymphosarcoma; RCS: reticulum cell sarcoma; and L-H:lympho-histiocytic

and Madden[29] in 1948 reported two cases with lymphosarcoma and malignant lymphocytoma of parotid gland and one case with Hodgkin's disease of submaxillary gland. Our survey of the major literature since 1959 revealed approximately 70 and 10 cases, respectively, possibly originating either in parotid or submaxillary gland (Table 2). Of interest is one patient who developed diffuse lymphosarcoma of both parotid and submaxillary glands of the same side[8]. Other reports include 16 cases of parotid gland lymphoma and 5 cases of submaxillary gland lymphoma by Catlin[3], and 69 cases of salivary gland lymphoma by Freeman et al.[9] Among these, about 15 reports[4,5,8,10-13,16-18,20,21,24,26,28] are reasonably well documented as to clinical history, pathology, clinical staging, therapy or subsequent clinical course. Concerning a proliferating pattern of lymphoma, 26 cases (30.6%) were apparently nodular, whereas 22 cases (25.9%) diffuse. Thirty-three cases experienced by Hyman and Wolff[13] were also predominated by a nodular pattern, that is, 21 cases (64%) of a nodular versus 12 cases (36%) of a diffuse pattern.

Concerning the salivary gland to be primary site of lymphoma or secondary or simultaneous involvement, Hyman and Wolff[13] proposed the following criteria for its possible primary malignant lymphoma: i) clinically, salivary gland is involved first; ii) histologically, salivary gland parenchyma per se is involved by lymphoma rather than periglandular soft tissue or adjacent lymph nodes, that is, "when only an intraglandular lymph node was involved, without lymphomatous infiltration of salivary gland tissue itself, the case was considered to represent nodal lymphoma"; and iii) architecture and cytology of lymphoid infiltrate are compatible with the malignant nature. As described above, our case certainly safisfies these three conditions.

Regarding the pathogenesis of primary salivary gland lymphoma, Thompson and Bryant[25] observed "lymph nodes" with the histologically characteristic features or encapsulated lymphoid aggregates or small, ill-defined, periductal aggregates of lymphocytes frequently in parotid gland in contrast to in submaxillary gland of not only embryos but also of adults. Feind[6] noted 20 intraglandular lymph nodes in an average to as many as 32 in the adult parotid gland. In fact, 30% of salivary gland lymphoma were reported to arise from the intraglandular nodes[8]. Therefore, malignant lymphoma can

occasionally originate in these intraglandular lymphoid tissue, and may account for much frequent incidence of the lymphoma in parotid gland than in submaxillary gland. Based on the mode of intraglandular involvement by lymphoma as shown before (Figs. 1a, b and 8), our case may have begun first in parotid gland and further extended to contralateral submaxillary gland. Case 4 of Nime et al.[16] had "questionable latent syphilis". Our case had also the latent syphilis (Table 1); the patient received antiluetic therapy about 52 years ago. This may be one of coincidental findings not relating to the present malignant lymphoma.

Finally, we must differentiate genuine salivary gland lymphoma from nonspecific sialadenitis, pseudolymphoma, benign lymphoepithelial lesion or poorly differentiated epithelial tumor. Lymphoma arising in the lymphoepithelial lesion with or without Sjögren's syndrome have a quite different histogenesis[1]. Table 2 indicates at least seven cases associated with certain degrees of lymphoepithelial lesion. In fact, Nime et al.[16] concluded 12 cases to be well-documented primary salivary gland lymphoma not associated with benign lymphoepithelial lesion or Sjögren's syndrome out of 43 possible cases in the literature. Our case had neither Mikulicz's disease nor Sjögren's syndrome, so that, the possible occurrence of malignant lymphoma in this respect can be ruled out. In any event, as Foote and Frazell[7] emphasized, we need to accumulate more cases with convincing clinical and pathologic data to elucidate the pathogenesis of primary salivary gland lymphoma.

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