

Intranodal extraparotid Warthin's tumors : clinicopathological study.

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Five patients in whom Warthin's tumor occurred in the neck nodes are described. Only 25 cases of such intranodal extraparotid neoplasm have been found in the literature. The tumors were most frequent in men, and most commonly occurred in the seventh decade of life. About three-fourths of the patients had clinical symptoms of non-tender slow growing neck mass, the remainders were discovered incidentally. This tumor should be listed in the differential diagnosis of neck masses. The definite diagnosis requires tissue examination.

Key words: *Warthin's tumor, Papillary cystadenoma lymphomatosum.*

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ได้รายงานผู้ป่วยด้วยเนื้ออกของวาร์ธิน ที่ต่อมหน้าเหลืองบริเวณ คอ จำนวน 5 ราย จากการทบทวนวารสารการแพทย์ พบผู้ป่วยด้วยเนื้ออกบริเวณดังกล่าวเพียง 25 ราย ผู้ป่วยส่วนใหญ่เป็นเพศชาย และอยู่ในช่วงอายุ 70-80 ปี ประมาณ 3 ใน 4 ของผู้ป่วยมีก้อนที่บริเวณคอ เนื้ออกของผู้ป่วยอื่นที่เหลือ พบโดยบังเอิญ ดังนั้นเนื้ออกชนิดนี้ควรรวม อยู่ในการวินิจฉัยแยกโรคของก้อนท่อมบริเวณคอ การตรวจชิ้นเนื้อทางพยาธิวิทยา เป็นสิ่งจำเป็นในการวินิจฉัยโรค

Warthin's tumor or papillary cystadenoma lymphomatosum (PCL) is a well recognized benign tumor of the parotid gland. The incidence varies from 2% to 24% of all parotid tumors.^(1,2) The occurrence of intranodal extraparotid PCL is exceptional. Only 25 cases of Warthin's tumor presenting in the neck nodes have been described.⁽³⁻⁹⁾ We here analyze the clinical and pathological findings in 5 additional cases of intranodal extraparotid Warthin's tumors and review the literature concerning this tumor in such unusual location.

Materials and Methods.

A total of 43 patients seen in the Department of Pathology, Chulalongkorn Hospital from 1984 to 1994 had the diagnosis of PCL. Of these 36 (83.7%) had lesions in the parotid gland, five (11.6%) in the neck nodes, and two (4.7%) unavailable location. The clinical records and pathological data of cases with this tumor in the neck nodes region were studied after review of the microscopic materials. The surgical specimens were fixed in 10% formalin and embedded in paraffin. Hemato-

xilin and eosin (H&E) stain was used routinely. Sections of the paraffin embedded tissue were further processed by immunohistochemical method (avidin-biotin technique) using unlabelled antibodies to keratin, epithelial membrane antigen (EMA), vimentin, CD-26 and UCHL-1. For electron microscopy, small tissues were cut from the paraffin block and were deparaffinized, rehydrated and transferred to 2.5% glutaraldehyde, post-fixed with osmium tetroxide, dehydrated and embedded in Epon. Ultrathin sections were cut and stained with lead citrate and uranyl acetate, and examined in a JEOL 1210 microscope.

Results

The clinical features and pathological data in the five cases are given in Table. All patients were men. The youngest patient was 60 years; the oldest being 84 years. The average age was 74 years. Most patients had progressive growing non-tender neck masses. The length of symptoms ranged from 8 months to 20 years.

Table 1. Clinical and Pathological Features.

Case No.	Age	Sex	Location	Size(cm)	Duration(yr)	Clinical Manifestations
1	60	M	R. cervical	1x0.8	-	Hematemesis with abdominal mass, cervical node enlargement.
2	65	M	R. cervical	2x1.5	8/12	Cervical mass
3	80	M	L. neck	7x4	15	Progressive growing mass
4	81	M	L. cervical	3x1.5	2	Cervical mass
5	84	M	R. neck	8x5	20	Slow growing mass

M = Male; yr = year; L = left; R = right.

The tumors were well circumscribed and encapsulated firm in consistency with gray-white cut surface. Irregular cystic spaces were noted in two cases (cases 3 and 5). The size of the tumors ranged from 1 cm to 8 cm. Microscopically, the tumors were composed of two components : epithelium and lymphoid tissue. (Fig 1.) The epithe-

lium was made up of tubulopapillary cystic structure. It often had two rows of cells. Goblet cells were occasionally present. The delicate basement membrane separated the epithelium from the lymphoid stroma which formed the core of the papillary configuration of the tumor. The lymphoid tissue often contained germinal centers.

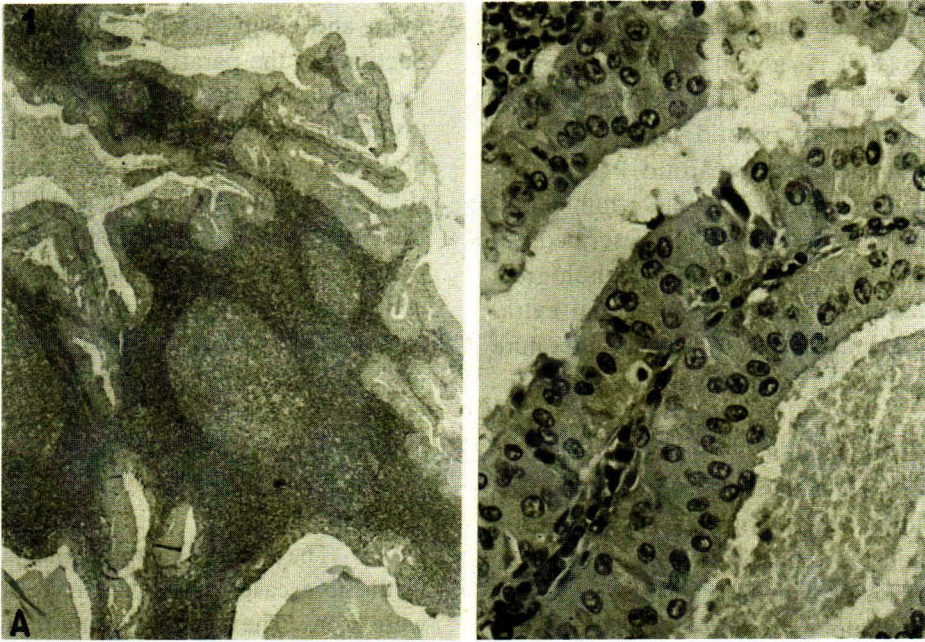


Figure 1. A. The characteristic epithelial and lymphoid component of Warthin's tumor. Note germinal centers are clearly demonstrated (H&E $\times 100$)
 B. Higher power view showing two row's of ciliated epithelium (H&E $\times 400$)

Using immunohistochemistry, the epithelial cells were positive for keratin, EMA but were negative for vimentin (Fig 2). The lymphoid tissue showed reactivity with T-cell and B-cell markers (Fig 3). B-cells were clustered in germinal centers

while T-cells were in area between the follicles. Ultrastructurally, the epithelial cells were packed with numerous mitochondrias, few ribosomes and lysosomes(Fig 4).

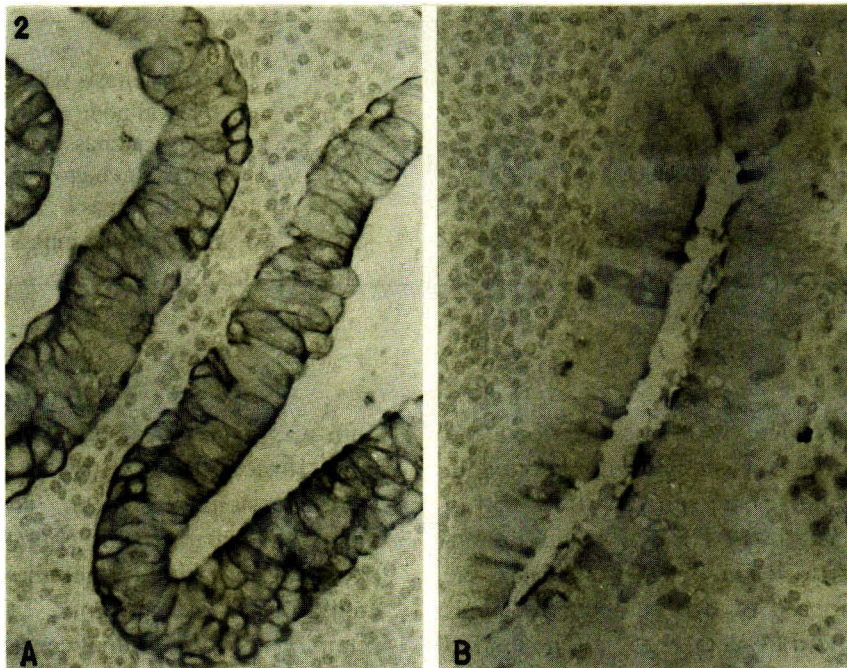


Figure 2. Immunostains with antibodies to epithelial cells.
 A. Positive reaction to EMA (avidin-biotin $\times 400$)
 B. Reactivity to keratin (avidin-biotin $\times 400$)

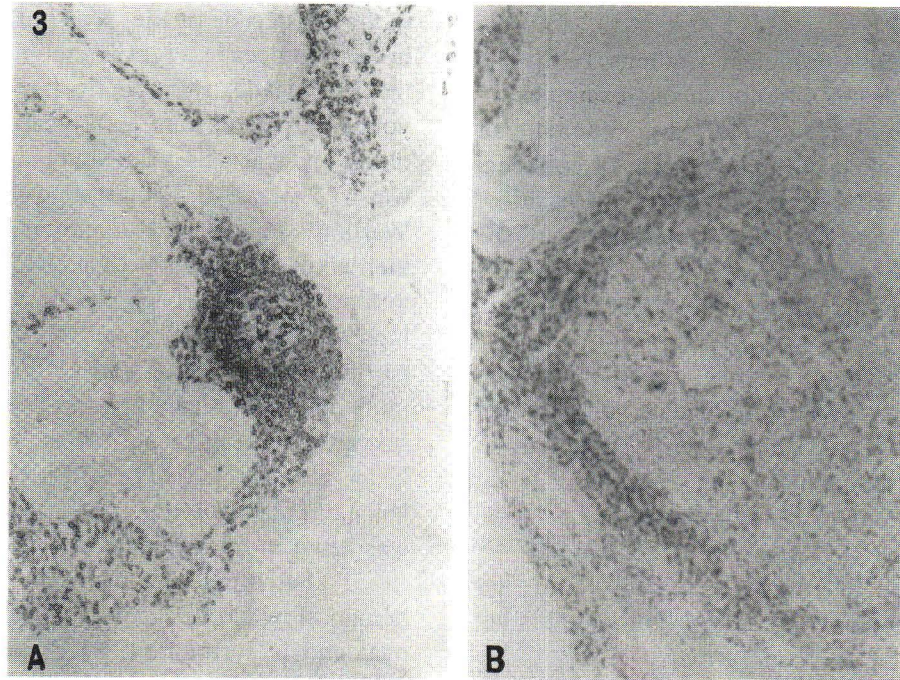


Figure 3. Warthin's tumor treated with antibodies for lymphocytes.
A. Positive L-26 for B-cells which are clustered in germinal center (avidin-biotin $\times 100$)
B. Positivity for UCHL-1, the antibody for T-cells which are distributed between the follicles. (avidin-biotin $\times 100$)

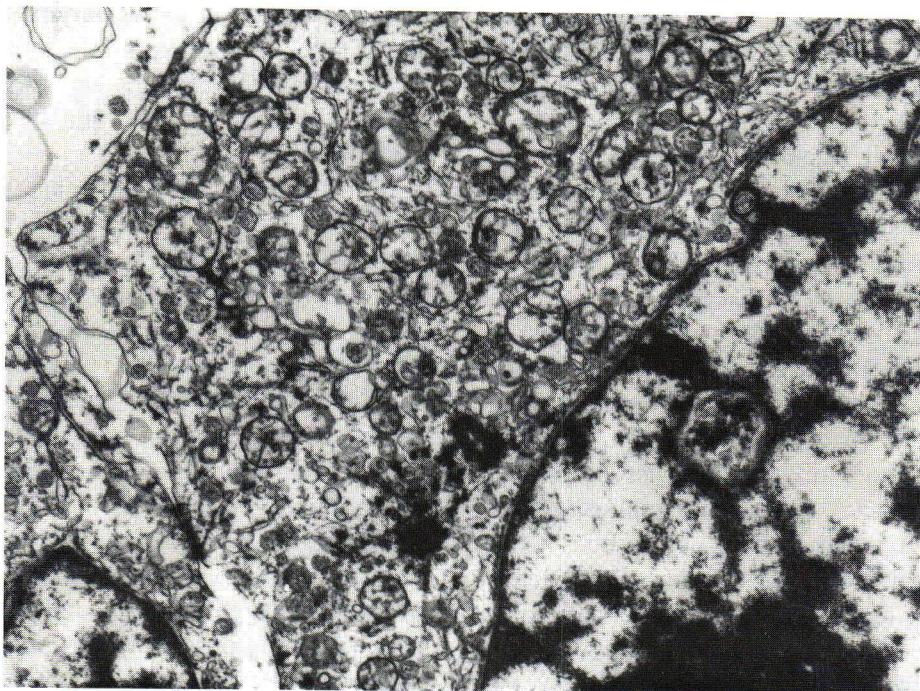


Figure 4. Ultrastructure showing numerous mitochondrias packed in the cytoplasm ($\times 13,200$)

Discussion

The histopathological findings fulfill the diagnosis of Warthin's tumor in our examples.⁽¹⁰⁾ The ultrastructural features of large numbers of mitochondria packed in the cytoplasm of epithelial cells were similar to the oncocytes.^(2,11) Results of immunohistochemistry also indicated that the lymphoid tissue consisted of T-cells and B-cells similar to that found in normal or reactive lymph nodes.⁽²⁾

PCL is a tumor which primarily involved the parotid gland as seen in our data and accounts for 6 to 10% of all parotid tumors.⁽¹⁰⁾ Extraparotid Warthin's tumors have been described in several locations such as submandibular gland,⁽¹²⁾ oral cavity,^(13,14) nasopharynx,⁽¹⁵⁾ and neck nodes.^(8,9) The incidence of intranodal extraparotid PCL has been reported to be 8% of all Warthin's tumors but was 11% in our series.^(5,9)

The pathogenesis of intranodal extraparotid Warthin's tumor is still debated though several theories have been postulated including a tissue immune reaction,⁽¹⁶⁾ the remnants of branchial arches,⁽¹⁷⁾ and heterotopic salivary gland tissue in lymph nodes.^(18,19) Results of immunohistochemical studies including ours have suggested that lymphoid tissue in Warthin's tumor is in a pattern similar to a normal lymph node distribution. Furthermore, in a delayed-type hypersensitivity, one often sees induration, erythema and sudden onset, clinically. Such clinical features are absent in patients with Warthin's tumor. Moreover lacked of circulating autoantibodies, and repeated affirmation of origin from enclaved salivary tissue within the parotid, periparotid nodes and lymphoid tissue are evidence against this contention. Hence the possibility of a immune response is unlikely. The concept of heterotopic salivary gland tissue in lymph node appears to be a more widely accepted theory for intranodal extraparotid PCL. It should be noted that salivary gland tissue and the early stage of PCL formation have been observed in lymph nodes in which the remainder of lymphoid tissue still has nodal characteristic.⁽¹⁸⁾ Although the salivary gland tissue is most frequent in periparotid node, it has also been found in other nodes of the neck.⁽⁹⁾ Hence it is not surprising to encounter intranodal extraparotid Warthin's tumors in the neck nodes.

A review of the literature disclosed 30 case reports including the current series of intranodal extraparotid PCL.⁽³⁻⁹⁾ There were 19 men and 11 women; a ratio of 1.7 : 1. Of these patients one was

in the 4th decade of life; four in the 5th decade; six in the 6th decade; eight in the 7th decade; seven in the 8th decade; and four in the 9th decade. The youngest patient was a 32-year-old man and the oldest one was a 84-year-old man. The average age was 67.2 years. It is interesting to note that parotid Warthin's tumors most commonly occur in men in their sixth and seventh decades of life and the male to female ratio has been reported as ranging from a high of 15.5:1 to a low of 1.5:1. Therefore either parotid PCL or intranodal extraparotid PCL, men more commonly have this tumor than women. The sex difference in recent series, however, may not be as great as reported previously. The peak prevalence in patients with extraparotid Warthin's tumor was between the sixth and eighth decades.

Pathologically, the tumor is considered as a benign slow growing mass. It is often round or oval and is surrounded by fibrous capsule. The surface of small lesion is smooth or lobulated while the large mass may contain irregular cystic spaces. Four instances (13%) developed tumor multicentricity.^(3,9) None of the cases in this review showed malignancy. However malignant transformation has been described in parotid Warthin's tumors such as squamous cell carcinoma, anaplastic carcinoma, mucoepidermoid carcinoma, as well as lymphoma.⁽²⁰⁻²²⁾ Additionally cases of intranodal extraparotid PCL have been reported with unrelated malignancy such as carcinoma of the larynx, oral cavity, and breast.^(8,9) Hence Warthin's tumor can undergo malignant alteration or another malignancy can arise independently of the Warthin's tumors and grow synchronously.

Clinically, most patients present with symptoms of neck mass. In this review, about three-fourths of the patients had progressive slow growing neck mass which was painless and non-tender. Only six tumors (27.3%) were disclosed incidentally.^(6,8,9) One was found at the time of elective carotid thromboendectomy and five were detected on pathological examination of neck nodes dissection for other primary malignancies. Therefore Warthin's tumor should be included in the differential diagnosis of the neck masses. The definite diagnosis requires tissue examination of the excised tumor. We would suggest that in diagnosing a lesion of neck mass, the possibility of tumor multicentricity or intranodal extraparotid Warthin's tumors should be considered before a decision on "metastatic carcinoma" is made particularly in patients who have malignancies of other organs such as adenocar-

cinoma of breast or papillary carcinoma of thyroid gland.⁽⁹⁾

Complete surgical excision of Warthin's tumor is usually curative. The tumor is radioresistant.⁽⁷⁾ Hence in the light of the intrinsic hazard of radiation and the benign nature of the disease, there is no medical justification for radiotherapy. However either radiation or chemotherapy may be useful for the rare malignant forms of this disease.^(20,21)

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