Follicular Lymphoma Diagnosed in Warthin Tumor: A Case Report and Review of the Literature

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Abstract

Warthin tumor is one of the most common benign salivary gland tumors. It is unusual and difficult to diagnose follicular lymphoma within the lymphoid tissue of Warthin tumor. We present a rare case of a 69-year-old man with systemic follicular lymphoma initially diagnosed in a Warthin tumor. Lymphomas occurring within Warthin tumors are rare, however, follicular lymphoma is most commonly reported. Because these patients require further treatment depending on the stage of a disease, it is important for a pathologist to review the histology of Warthin tumors diligently to identify occult lymphomas.

Keywords Parotid gland · Lymph node · Warthin tumor · Hodgkin lymphoma · Non-Hodgkin lymphoma · Follicular lymphoma

Background

Warthin tumor, previously described as cystadenoma lymphomatosum papilliferum, is found exclusively in the parotid gland and peri-parotid lymph nodes [1]. It is a benign adenoma composed of varying component of bilayer columnar and basaloid oncocytic epithelium associated with an underlying lymphoid stroma that often contains prominent lymphoid follicles with reactive germinal centers [2]. Warthin tumor rarely undergoes malignant transformation. The epithelial component may evolve into adenocarcinoma, mucoepidermoid carcinoma, squamous cell carcinoma, oncocytic carcinoma, Warthin adenocarcinoma [3–7], while the lymphoid component may be involved by malignant lymphoma [2, 8–11]. Only a few cases of Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) associated with Warthin tumor have been reported in the

literature. Interestingly, among the NHL associated with Warthin tumor, the most commonly reported type of NHL was follicular lymphoma [2, 8, 10–18]. We report the 14th case (in the English literature) of follicular lymphoma first detected within Warthin tumor in a 69-year-old gentleman. This case highlights the utmost importance of careful light microscopic evaluation of the lymphoid follicles within Warthin tumors to identify occult lymphoma.

Materials and Methods

The patient's clinical history, laboratory data and follow up were obtained from the hospital's electronic medical records and patient's physician. The patient's specimen was received at Methodist University Hospital, Memphis. The hematoxylin and eosin slide was prepared using paraffin block 4 um section and stained by a standard method. Immunohistochemistry (IHC) studies using paraffin embedded tissue sections were performed on a fully automated IHC stainer, Leica BOND-III (Ventana). The details of antibody clones, retrieval method, RT and dilution are summarized in Table 1. Flow cytometry study on patient's specimen was performed using four color Beckman Coulter Cytomics FC500 Flow cytometer analyzer (software, CXP Cytometry, V 2.3).

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Table 1 Details of immunohistochemistry details of antibodies and their clones

	CD 3	CD 20/L26	BCL-2	BCL-6	CD 10	CD 5	Cyclin D1	Ki-67/MIB1	CD 21
Manufacture	Leica	Cell Marque	Leica	Leica	Leica	Leica	Cell Marque	Cell Marque	Cell Marque
Ab Clone	LN10	SP32	Bcl-2/100/DS	LN22	56CL	4C7	SP4	SP6	2G9
Retrieval method	HIER	ER1	ER2	ER2	ER2	ER2	ER2	CC1	CC1
	10 min	10 min	20 min	30 min	20 min	20 min	20 min	8 min	8 min
	100°	100°	100°	100°	100°	100°	100°	95°	95°
RT/dilution	RT4	1:100	RT4	RT4	RT4	RT4	1:50	1:100	RT4

Case

A 69-year-old male presented with a left neck painless mass for 3 months with a recent onset of right sided neck swelling for 2 weeks. The patient denied any fever, night sweats, or weight loss (B symptoms). His past medical history was significant for chronic smoking (55 pack year), atrial fibrillation, pacemaker placement, and cholecystectomy. The family history was significant for colon cancer. On complete physical examination, there were two palpable swellings, a 4 cm and a 1 cm below and inferior to the left parotid gland, and along with multiple sub-centimeter lymph nodes were palpated on the contralateral side. A computed tomography (CT) scan confirmed the presence of bilateral lymphadenopathy. Fine needle aspiration of the left neck mass performed at an outside facility displayed oncocytic epithelial cells with eosinophilic cytoplasm characteristic of Warthin tumor along with a population of lymphoid cells which raised concern for lymphoma.

The parotid mass on the left side was surgically excised and sent to the hematopathology section for evaluation.

Flow cytometric immunophenotypic studies performed on the left neck mass demonstrated 50% B-cells that included a population of CD20 positive, CD5 negative, CD10 positive, surface immunoglobulin negative B-cells. The remaining B-cells had polytypic surface light chain expression. T-cells were 43% of the total cells and did not show loss of pan T cell antigens. The CD4:CD8 ratio was 5:1.

The surgically excised specimen received in formalin consisted of two tan-pink portions of soft tissue measuring $2.0 \times 0.5 \times 0.5 \text{ cm}^3$ and $1.6 \times 1.5 \times 1.0 \text{ cm}^3$. Examination of the histologic sections revealed a peri-parotid lymph node. The lymph node was replaced by a tumor comprising of cystic structure lined by oncocytic luminal tall columnar cells with eosinophilic cytoplasm and a basal layer of bland cuboidal cells. The basal cells had round to oval nuclei and small but conspicuous nucleoli. The lumina of the cysts contained eosinophilic secretions admixed with

Fig. 1 Warthin tumor and follicle center lymphoma, follicular, grade 1–2. **a, b** Warthin tumor epithelium and many neoplastic follicles (H&E, $\times 2$ and $\times 4$). **c, d** Neoplastic follicles are composed of small cleaved lymphoid cells (H&E, $\times 10$ and $\times 20$)

cell debris. These findings were diagnostic of Warthin tumor (Fig. 1a, b). The sub-epithelial lymphoid stroma was composed of numerous uniform sized lymphoid follicles with germinal centers (Fig. 1c, d). The follicles exhibited loss of polarity with a monotonous population of centrocytes. Immunohistochemical studies were performed. The cells within the follicles were strongly positive for CD20, CD10, and BCL-6. The monotonous germinal centers were BCL-2 positive. Ki-67 displayed scattered positivity within the germinal centers (Fig. 2). These findings were diagnostic of grade 1–2 follicular lymphoma with a follicular growth pattern. Complete blood profile, liver function test, metabolic panel, and LDH were normal while beta-2 microglobulin was 2.4 mg/L (normal range 0.8–2.2 mg/L). Positron emission tomography (PET) scan showed 11 mm hypermetabolic nodule in the superficial left parotid with lymphomatous involvement of bilateral cervical, left axillary, and likely involvement of inguinal lymph nodes. There were multifocal lesions in the spine and bony pelvis likely representing osseous lymphoma with no signs of the fractures. The patient's disease was staged as stage IV lymphoma. At the time of the patient's most recent visit, he gained weight and remained asymptomatic, and therefore no treatment was initiated. The patient was closely followed up for 3 months without any symptoms. He has been prescribed Denosumab 120 mg SQ q28d with Citracel 1200 mg for bony lesions.

Table 2 Summary of malignant lymphoma associated with Warthin tumor

	Frequency (n)
Hodgkin lymphoma (n=6, 18.2%)	
CHL, mixed cellularity	2 [19, 20]
CHL, lymphocyte rich	1 [21]
CHL (Not distinguished)	2 [22, 34]
NLPHL	1 [23]
Non-Hodgkin Lymphoma (n=27, 82.8%)	
Follicular lymphoma	13 [2, 8, 10–18]
DLBCL	5 [14, 24–27]
Small lymphocytic lymphoma	3 [9, 28, 29]
Mantle cell lymphoma	2 [2, 30]
MALT-type lymphoma	1 [31]
Peripheral T cell lymphoma	1 [32]
T cell-lymphoblastic lymphoma	1 [33]
Unclassified	1 [17]

Discussion

Detection of a malignancy concurrently in Warthin tumor was first documented in 1954 [10]. Review of the English language literature revealed rare reports of lymphoma diagnosed within Warthin tumor. Thirty-four cases (including the present case) of lymphoma have been reported in association with Warthin tumor of which 28 were NHL and 6 were HL. Follicular lymphoma was most commonly reported

Fig. 2 Warthin tumor and follicle center lymphoma, follicular, grade 1–2. **a** CD 20 positive B cell follicles. **b** Inter follicular area CD 3 positive T cells. **c, d** Strongly positive follicles with CD 10, and BCL-2

(Table 2). Due to the rarity of follicular lymphoma in association with Warthin tumor, the pathogenic relationship is uncertain, and the occurrence of both entities simultaneously may be coincidence.

Including the present case, follicular lymphoma represented 14 out of 28 (50%) of the reported NHL cases. The follicular lymphomas were predominantly low grade (grade 1–2 of 3) [2, 8, 10–18]. The overall incidence of follicular lymphoma among all type of lymphoma associated with Warthin tumor is 41.2% (14/34) making follicular lymphoma the most common type of NHL detected in Warthin tumor. The age distribution ranged from 49 to 83 years with a mean age of 66.6 years and standard deviation (SD) of 10.6 years [11]. Our patient falls within

the age range of one SD of mean age. Warthin and follicular lymphoma association are far more frequent in males (77%, $n = 10$) than females (23%, $n = 3$). The recognized patterns of involvement by follicular lymphoma included follicular (63%, $n = 7$), diffuse pattern (10%, $n = 1$) and mixed follicular and diffuse (27%, $n = 3$). The present case was low-grade (grade 1–2/3) with a follicular growth pattern. The most common site for follicular lymphoma in Warthin tumor is a parotid gland. Giardini et al. reported bilateral parotid gland Warthin tumor involvement with follicular lymphoma [12]. Reiner et al. reported a case of large cell lymphoma in association with Warthin tumor, in a patient having preexisting Sjogren syndrome [19]. Generally, a bone marrow biopsy for these patients may

Table 3 Summary of follicular lymphoma detected in association with Warthin tumor

Study	Year	Age	Sex	Location	Pattern	Grade	Stage	Other organs involved at diagnosis/treatment	Follow up
Colby et al. [17]	1979	NA	NA	Parotid	F	1	NA	Regional LNs	NA
Seifert et al. [2]	1980	83	M	Parotid	NA	NA	NA	Regional LNs	NA
Miller et al. [16]	1982	49	M	Angle of mandible	NA	1	IA	None	3 months later surgical excision of regional LNs had NHL
Banik et al. [8]	1984	75	M	Left parotid	D	2	NA	None	NA
		76	M	Right parotid	F + D	2	IIIA	Generalized LNs (CT: chlorambucil and prednisone)	NHL in neck LNs 1 year later
Hall et al. [15]	1985	64	M	Right parotid	F + D	2	IA	None	Generalized NHL 7 months later
Griesser et al. [14]	1986	64	F	Palate	F	2	NA	NA	NA
Medeiros et al. [13]	1990	71	M	Left parotid	F + D	2	IIIA	Periaortic LNs (CT: V-16; adriamycin, cyclophosphamide, vincristine, prednisone, bleomycin)	NED 48 months later
Giardini et al. [12]	1990	57	M	Right and left parotid	F	1	IIA	Regional LNs (CT: endoxan, vincristine, prednisone)	NED 3 years later
Shikhani et al. [10]	1993	56	M	Right Parotid	NA	NA	IA	None (RT: 4500 rads)	Axillary LN recurrence 4 years 4 months later. Died of generalized NHL 7 years after initial diagnosis
Park et al. [11]	2000	68	F	Right peri-parotid LN	F	1	IA	None (RT: unknown dose)	4.5 years later inguinal LN NHL, complete clinical remission after combination CT
		55	M	Right parotid	F	1	IIA	Axillary LN	NA
Romero et al. [18]	2016	82	F	Right Parotid	F	Low	IV	None (CT: 4 cycles of Rituximab)	Improved thrombocytopenia
Present case	2018	69	M	Right neck LN	F	1–2	IV	Generalized LNs, Spine and Pelvic bone (No CT or RT given)	Recent study

Diagnosis translated into terminology according to World Health Organization Classification of Tumors when possible

F follicular; D diffuse; LN lymph node; NHL non-Hodgkin lymphoma; NA not available; NED no evidence of disease; CT chemotherapy; RT radiation therapy

show involvement by small clonal B cell population. Most of the patients have either nodal or visceral organ involvement by follicular lymphoma at the time of diagnosis [2, 8, 11–13, 17]. PET scan in our patient showed a disseminated lymphoma involving generalized lymph nodes above and below the diaphragm, with lesions in the spine and pelvic bones. The patient is currently being followed up in the outpatient department setting with regular clinical check-ups and laboratory workup as necessary. Table 3 summarizes all the Warthin tumor associated follicular lymphoma cases found in the literature including tumor grading, stage and follow up.

In summary, Warthin tumor can predispose to an epithelial malignancy or malignant lymphoma. We report a case of an initial diagnosis of low-grade follicular lymphoma associated with Warthin tumor in a peri-parotid lymph node. Although rare, this finding demonstrates that patients in 4th to 8th decade of life could have first time diagnosis of lymphoma in association with a benign tumor, like Warthin tumor. Therefore, it is crucial for pathologists to be aware of this potential presentation and carefully examine on light microscopy the lymphoid follicles of Warthin tumor and make judicious use of ancillary studies to rule out occult lymphoma.

Compliance with Ethical Standards

Conflict of interest All authors have no conflicts of interest to disclose.

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