CASE REPORTS

Warthin tumor: a curious entity – case reports and review of literature

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Abstract

Warthin tumor was first described in the American literature, by Aldred Warthin, in 1929, the pathologist who named this tumor papillary cystadenoma lymphomatosum, but since than it was also knew as adenolymphoma, cystadenolymphoma, and Warthin tumor. Because of its microscopically appearance and unknown origin, this tumor entity is still fascinating head and neck surgeons and pathologist. We evaluate the histopathological aspect of Warthin tumors using Hematoxylin–Eosin stain, and immunohistochemical and histological techniques. We reviewed the medical record of patients with salivary gland tumors diagnosed at County Hospital of Timisoara from 2002–2008. In six years, 22 cases with Warthin tumor were diagnosed and among them 17 men and five women, with average age 58.47. The analysis showed that 77.27% of Warthin tumors occurred in men, and the main histopathological aspect was with 50% epithelial component. The stromal component showed a prominent B-cell population by staining with CD20, and histological techniques for mucin were positive, and reticulin fibers were revealed while using Gordon–Sweets stain. The standard and the histological and immunohistochemical techniques highlighted the complex and variable microscopical appearance of Warthin tumor that the pathologist should consider when a diagnosis for this tumor is to be considered.

***Keywords*:** Warthin tumor, salivary gland tumor, cystadenolymphoma.

Introduction

The term "Warthin tumor", named after Aldred Warthin, the pathologist who published the first two reports in the American literature in 1929 [1], is the most commonly used term in order to avoid confusion with malignant lymphomas, but the tumor is also known as adenolymphoma or papillary cystadenoma lymphomatosum.

Warthin tumor is a controversial entity of benign salivary gland tumors because of its histopathological appearance and unknown origin. Histologically, is composed of bilayered oncocytic and basaloid epitelium forming cystic structures, papillae and glands that are accompanied by a dense lymphoid stroma. The lymphoid stroma becomes an issue when Warthin tumor's origin is been discussed. Some authors believe that this tumor develops from the epithelial cells restant within the intraparotid lymph nodes on heterotopic salivary gland [2–5]; other thinks that is an adenoma with lymphocytic infiltration [6, 7].

Recent molecular studies have shown that the epithelial component is polyclonal and does not exhibit clonal allelic losses, suggesting that this tumor is not a true neoplasm [8].

The most accepted hypothesis about the origin of Warthin tumor is that it develops from salivary ducts inclusions in the lymph nodes, after the embryonic development of the parotid gland the stromal component is the lymph node. This hypothesis is further supported by the frequent detection of salivary gland tissue in the peri- and intraparotidal lymph nodes; Warthin tumor is almost exclusively located in the parotid region. In the parotid region, lymph nodes were noted oncocityc and papillary changes, and the tumors presenting epithelial differentiations similar to those observed in Warthin tumors develops outside lymph nodes and has no lymphoid stromal component. With regard to luminal cells of the tumor lining the lymphoid stroma the cells reveal a similar aspect to the striated ducts of the normal salivary glands and have numerouse mitochondria. This cells, called oxifile or oncocytic cells are swollen epithelial cells, with abundant eosinophilic granular cytoplasm, rich in mitochondria and enzymes. An increased number of oncocytic cells are also observed in the normal salivary glands once the person is getting older. The diffuse proliferation of the oncocytes without other changes has no pathologic significance and is called oncocytosis or oncocytic metaplasia [9].

Clinically, Warthin tumors occur almost exclusively in the parotid glands, in its superficial lobe and rarely in the deeper lobe (10%). The tumor presents as a nodular, not painful mass, slow growing firm or fluctuant at palpation, multicentric (12–20%), bilateral (5–14%). The patients can be asymptomatic or can have facial pain-rarely, facial nerve palsy may be seen in tumors associated with inflammation and fibrosis, which can be

mistaken for malignant tumor. Ipsilateral earache, tinnitus and deafness are uncommon ear symptoms that might be seen at some patients [6, 10]. Warthin tumor is commonly present in the sixth or seventh decade of life and has a definite male predominance. There are studies that demonstrated that this tumor is associated with cigarette smoking, which may be due to irritation of the ductal epithelium by tobacco smoke that initiate the tumorigenesis [7, 11, 12]. An interesting fact that caught the attention of the pathologist was that a decline in the incidence in man and a concurrent increase incidence in women has been observed in recent years. The change is probably due to a decline in the smoking habit in man and a reverse trend in women [13]. Studies conducted among atomic bomb survivors suggest that radiation may also be implicated in the tumorigenesis [14]. An earlier claim of a strong association with Epstein–Barr virus (EBV), because of the EBV–DNA found in tumor cells in some studies has not been substantiated [15, 16].

Material and Methods

We retrospectively investigated specimens from 22 patients with Warthin tumor, age ranged from 46–71 years, mean age 58.47, from a total of 189 cases of salivary gland tumors, admitted in Timisoara City Hospital, in the period 2002–2008. From 22 cases with Warthin tumor, five females and 17 males were taken into study. The surgical technique performed in all patients was parotidectomy, and in each case specimens were taken from the tumor and the parotid salivary gland. Specimens were fixed in 10% formalin, paraffin-embedded, and slide sections were stained with Hematoxylin–Eosin (HE). Additional slides from tumors with predominant lymphoid stroma were immunohistochemically stained with CD20 (L26, Dako). In addition, we used histological techniques: Periodic Acid–Schiff (PAS) for mucin, and Gordon–Sweets technique for reticulin fibers.

Results

The HE sections revealed a variable pattern of the cases. We examined 18 cases of classic Warthin tumor (50% epithelial), two cases of subtype 2 (stroma poor) (Figure 1), two cases of subtype 3 (stroma rich) (Figure 2), and one case with squamous metaplasia (but only small foci) (Figure 3) (subtype 1, 2, 3 – after the classification made by Seifert).

We studied the stroma rich cases immunohistochemically and observed a prominent B-cell population which stained positive at CD20 (Figure 4).

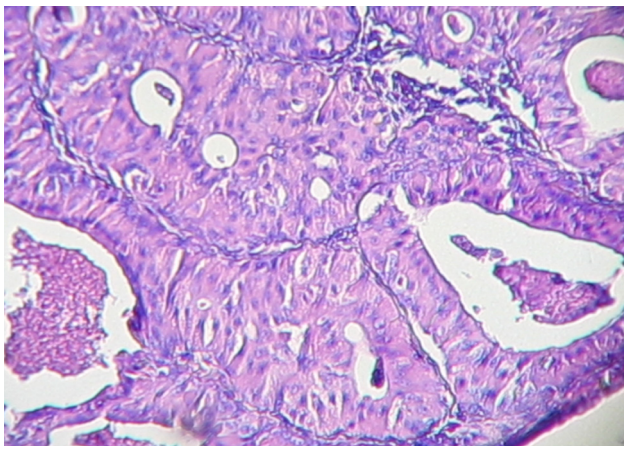

Figure 1 – ***Warthin tumor: prominent epithelial component with tall oncocytic luminal cells palisading of a basal cell layer (HE stain, ×200).***

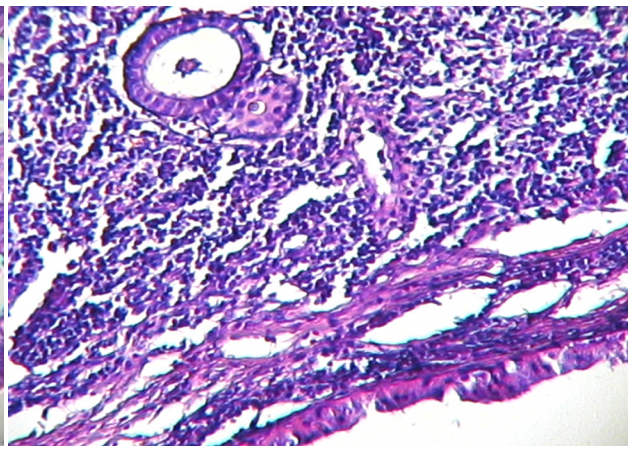

Figure 2 – ***Warthin tumor: rich in lymphoid component and two small salivary ducts (HE stain, ×200).***

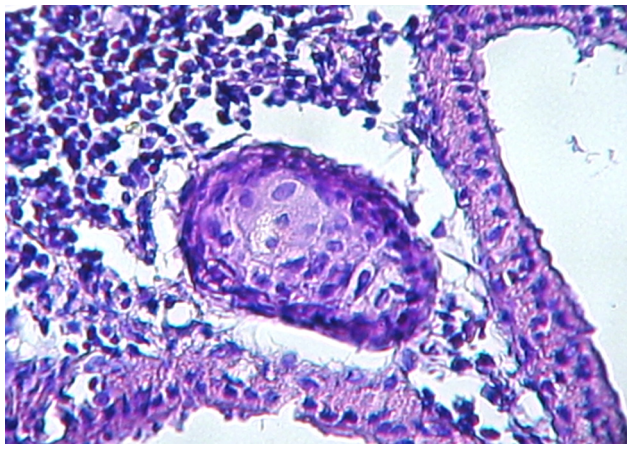

Figure 3 – ***Warthin tumor: small foci of squamous metaplasia, cystic areas and lymphoid stroma (HE stain, ×200).***

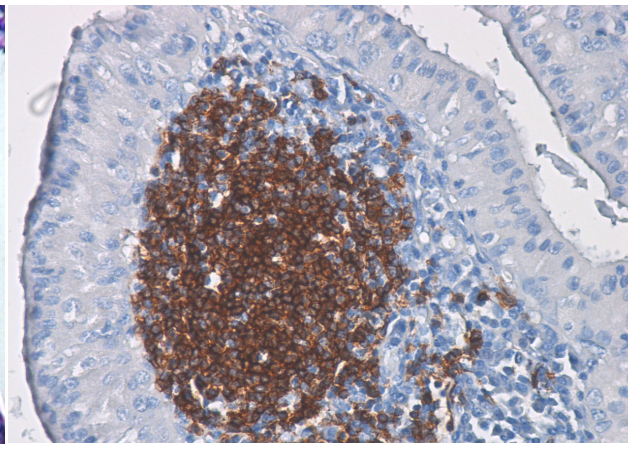

Figure 4 – ***Warthin tumor: lymphoid components positive at CD20.***

We also had a case associated with granulomatous inflammation (Figure 5), one with chronically sialadenitis, and a case with goblet cells (Figure 6), and another with squamous metaplasia (Figure 3).

We noted that the cystic spaces contain not only eosinophilic secretion, but also occasional crystal formation and in the case associated with chronic inflammation, we observed granulomas with cholesterol crystals, and caseous necrosis (lesions of tuberculosis) (Figure 5).

In one situation, a patient after two years from the first surgical intervention developed a relapse and it was proved to be again Warthin tumor – at this moment there is no indication of a new relapse.

In PAS technique we see the PAS-positive material in a magenta color, in this case the neutral mucins were revealed, the oncocytic cells nuclei are blue (Figure 7).

In the Gordon–Sweets technique the reticulin fibers stained black, the oncocytic cells nuclei are black or unstained and the collagen is yellow-brown (Figure 8).

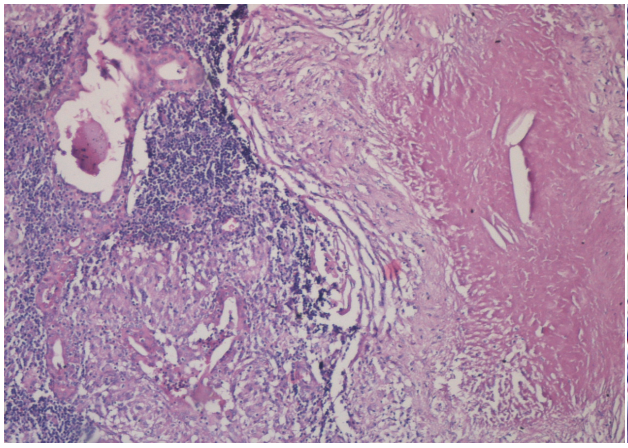

Figure 5 – ***Warthin tumor with granulomatous inflammation associated (HE stain, ×200).***

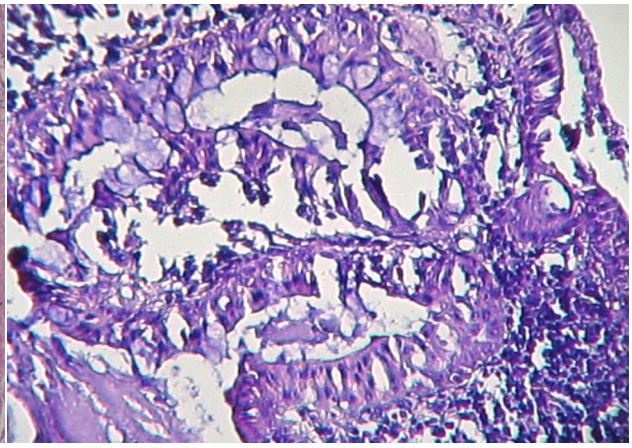

Figure 6 – ***Warthin tumor conspicuous mucus metaplasia (HE stain, ×200).***

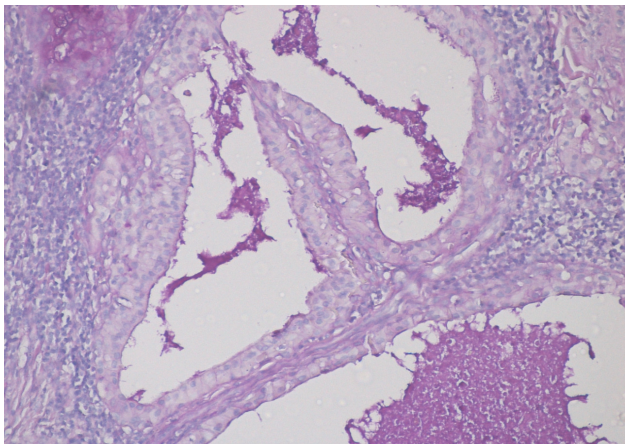

Figure 7 – ***Warthin tumor: goblet cells PAS-positive.***

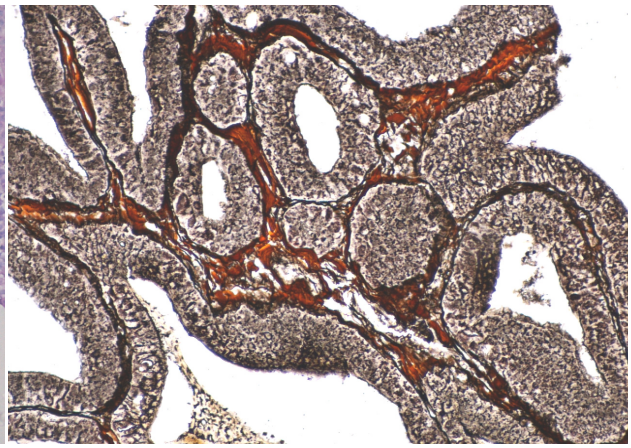

Figure 8 – ***Warthin tumor: reticulin fibers are black, the oncocytes cells nuclei are black or unstained, the collagen is yellow-brown (Gordon–Sweets technique).***

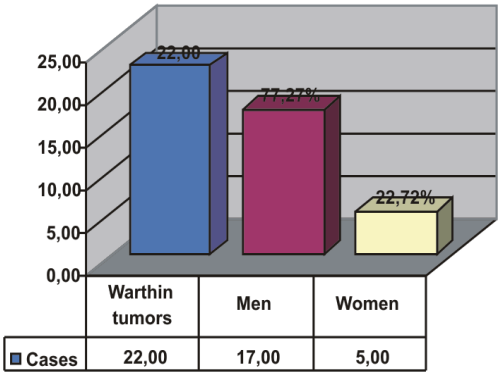

Figure 9 – ***Twenty-two patients were diagnosed with Warthin tumor: 17 males and five females. 77.27% of patients with Warthin tumor were men and 22.72% were women.***

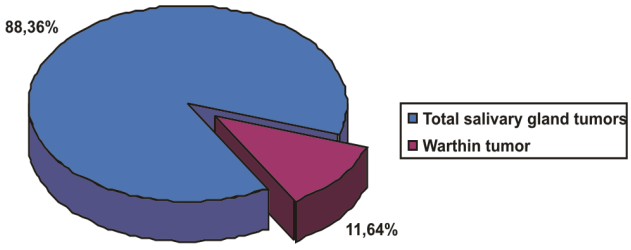

Figure 10 – ***From a total of 189 cases of salivary glands tumors, Warthin's tumor represented 11.64%.***

We notice that from a total of 189 cases of salivary gland tumors taken into study males are affected more frequently than females: 77.27% of all cases with Warthin tumor were men and 22.72% were women (Figure 9). Also, in our study, Warthin's tumor accounts for about 11.64% of all salivary neoplasms (Figure 10).

Discussion

Warthin tumor has an epithelial component and a lymphoid stroma. The epithelial cells, the oncocytes, are disposed on two layers, a luminal layer of oncocytic columnar cells, supported by a discontinuous layer of oncocytic basal cells. The nuclei of the luminal cells appear uniform and display palisading towards the free surface. The basal cells posses round to oval nuclei, centrally located, small, with conspicuous nucleoli. The oncocytes cytoplasm is granular and eosinophilic due to accumulation of mitochondria. The lumen of the cysts contains thick proteinaceous secretions, cellular debris, cholesterol crystals, and sometimes-laminated bodies that resemble corpora amylacea.

The epithelial component can undergo metaplastic change to squamous, mucous cells or even ciliated cells, especially in response to inflammation or infarction [17, 18]. Sometimes the tumor undergoes infarction, either spontaneously or following fine-needle aspiration, and the tumor cells can be obscured by necrosis, granulation tissue, inflammatory reaction, and fibrosis. Worse still, cellular atypia and a pseudoinfiltrative appearance of the metaplastic squamous epithelium in the residual tumor often invite an erroneous diagnosis of squamous cell or mucoepidermoid carcinoma. Lack of true infiltrative growth into the surrounding parenchyma and merging of the atypical squamous islands with oncocytic epithelium should point to the correct diagnosis [19, 20].

The lymphoid stroma, with germinal centers consist of small lymphocytes consisting especially in B-lymphocytes (it can also contain T-lymphocyte) and some plasma cells, histiocytes and mast cells. The lymphocyte population is polyclonal with predominance of the IgA producing cells. Lymphoid marker studies have shown B (CD20), NK (CD56) and T (CD3) cells, including helper (CD4) and suppressor (CD8) subtypes that is similar to that in normal or reactive lymph nodes [6].

Warthin tumors are described as having a monotonous aspect, but Seifert G observed a variable quantitative rapport between the stromal and epithelial component. The relative proportions of epithelial and lymphoid components in Warthin tumors vary. Seifert G recognizes four subtypes: subtype 1 (classic Warthin tumor) in 50% epithelial (77% of all Warthin tumors); subtype 2 (stoma poor) is 70–80% epithelial (14% cases); subtype 3 (stroma-rich) is only 20–30% epithelial (2%); and subtypes 4 is characterized by extensive squamous metaplasia [21].

With regard to the differential diagnosis, Warthin tumor, in general, has a highly distinctive morphology and poses no problem in diagnosis. It differs from oncocytoma in the presence of a prominent lymphoid component, papillae and glands rather than trabeculae and packets and conspicuous basal cells (which are inconspicuous in the latter tumor) [22, 23].

The epithelial component can undergo metaplastic change to squamous, mucous cells or even ciliated cells, especially in response to inflammation or infarction. Sometimes the tumor undergoes infarction, either spontaneously or following fine-needle aspiration, and the tumor cells can be obscured by necrosis, granulation tissue, inflammatory reaction, and fibrosis. Presence of cellular atypia and a pseudoinfiltrative appearance of the metaplastic squamous epithelium in the residual tumor often can be mistaken for squamous cell or mucoepidermoid carcinoma [20, 24, 25].

Squamous metaplasia of Warthin tumor usually lacks keratinization, which is seen in most squamous cell carcinoma. In contrast to low-grade mucoepidermoid carcinoma, there is no definite infiltrative growth and the tumor cells appear more frankly squamous. Lack of true infiltrative growth into the surrounding parenchyma and merging of the atypical squamous islands with oncocytic epithelium should point to the correct diagnosis [19].

A differential diagnosis must be made also with a variant of papillary thyroid carcinoma recently reported as "Warthin-like". The microscopic characteristic is a prominent lymphoid stroma and oncocytic metaplasia of the epithelium, but the nuclei have chromatin clearing, inclusion and groove-formation and the epithelial cells show immunohistochemical expression of thyroglobulin [6].

The elective treatment is surgical removal, which can be easily performed, due to the superficial location of the tumor. Some surgeons prefer a local resection with surrounding tissue; others choose the superficial parotidectomy in order to avoid the rupture of the tumoral capsule. Warthin tumor has a low recurrences rates (2–5%), and were explained through the existence of a second primary tumor, which has not been diagnosed during the first surgical exam, or as a expression of a multicentrical tumor [6, 17].

Rarely, either the epithelial of lymphoid component of Warthin tumor can undergo malignant transformation with an estimated incidence of less than 0.1% [18, 25]. In order of frequency, the commonest carcinomas are squamous cell carcinoma, oncocytic carcinoma, adenocarcinoma, undifferentiated carcinoma, mucoepidermoid carcinoma and Merkel cell carcinoma [17, 23–26]. From the literature, one third of patients have regional lymph node metastasis, and some may also develop distant metastasis.

Lymphoma arising from the lymphoid stroma is characterized by a relatively monomorphic infiltrate with distortion of the epithelial and lymphoid architecture. Various types of non-Hodgkin lymphoma and Hodgkin lymphoma have been reported [17]. This tumor is sometimes seen in association with other benign salivary gland tumors, especially pleomorphic adenoma [6, 17, 27].

Conclusions

Warthin tumor is more frequent to male gender.

The commonest histological aspect was the classical type-described by Seifert as subtype 1, in which the epithelial component represents almost 50% of the tumor.

The particular cases that we found were a case associated with granulomatous inflamation (tuberculosis), another had chronic sialadenitis also and two cases had revealed-one goblet cells and the other non-keratinizing squamous metaplasia.

All the tumors were located in the parotid gland.

Prominent epithelial component was present in 9.09% cases and the lymphoid stroma was more obvious in 9.09% cases.

There were two bilateral tumors and in one case was signaled a tumor relapse.

The frequency of Warthin tumor was 11.6%; a relatively low frequency compared to the rest of the salivary gland tumor taken into study.

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