ORIGINAL PAPER

Pathogenesis of Warthin's tumors

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Abstract: *Introduction:* Warthin's tumor, also known as papillary cystadenoma lymphomatosum, monomorphic adenoma, or adenolymphoma, is a benign cystic tumor of the salivary glands containing abundant lymphocytes and lymph node-like stroma. It is named after the pathologist Aldred Scott Warthin, who described two cases in 1929. *Objective:* The aim of this study is to analyze the pathogenesis of Warthin's tumor. *Methods:* A total of 15 patients with Warthin's tumor were studied. Hematoxylin and eosin stains, which have been used for at least a century and are still essential for recognizing various tissue types and the morphologic changes for cancer diagnosis, were used. Warthin's tumor was evaluated for the expression of MGMT, CD3, HSP90AA1, MMP-1, Bcl-2, CD79A, IgG, Ki-67, p53, IgM, OPN, S100, myeloperoxidase, and VEGF by immunohistochemistry. *Results:* Immunohistochemical staining confirmed that the immune cells within the follicles of Warthin's tumor were positive for MGMT ($10.0 \pm 0.34\%$), Ki-67 ($13.3 \pm 0.45\%$), Bcl-2 (42.6 ± 8.33), and p53 (11.6 ± 2.3). The immune cells associated with CD3 were present at the stroma of residual cells (47.3 ± 3.89); however, they were not present in the epithelium cell layers. B cells (CD79A) consistent with germinal centers were present within the immune cells and formed follicles ($43.2 \pm 13.5\%$). *Conclusions:* Histopathological analysis of the stroma and parenchyma revealed balanced distribution of epithelial and stromal component. Epithelial component of the Warthin's tumor is the trigger for the tumor process. This study indicates that the Warthin tumor is a consequence of inflammatory etiology.

Keywords: salivary gland, adenoma, lymphoma, Warthin's tumor, cystic papillary adenoma

Introduction

History

Papillary cyst adenolymphoma is the second most common benign cystic tumor of the salivary gland. This tumor was first described by Hilderbrand in 1895 as a form of congenital cyst of the neck. Historically, Hilderbrand's description was forgotten. In 1929, Warthin called this tumor as papillary cystadenoma lymphomatosum. Currently, this tumor is called as adenolymphoma, Warthin's tumor, and cystic papillary adenoma [1].

Clinical features

Warthin's tumors occur almost exclusively in the parotid glands, in its superficial lobe and rarely in the deeper lobe (10%). It presents as a slow growing node, firm or fluctuant at palpation, with indolent mass, multicentric (12%–20%), and bilateral (5%–14%) [2]. Ellis and Auclair, [3], has shown adenolymphoma incidence between 5% and 11% of all parotid gland tumors, and Eveson and Cawson, [4] has found 14%–30% of parotid tumors.

Etiology

There is no consensus regarding the origin of this tumor. However, the studies by Kotwall [5], Pinkston and Cole [6], and Yoo et al. [7] have demonstrated that these tumors are associated with cigarette smoking, which may be due to the irritation of the ductal epithelium by tobacco smoke that initiates the tumorigenesis.

Studies conducted among atomic bomb survivors suggest that radiation may also be implicated in the Warthin's tumorigenesis [8]. There is also an earlier view by Santucci et al. [9] of the strong association of the Epstein–Barr virus in the etiology of Warthin's tumors.

Papillary cystadenoma lymphomatosum (Warthin's tumor) is generally considered to be a benign tumor. However, only a few well-documented cases of malignant transformation have been reported [10].

Histogenesis

Warthin's tumor has incomprehensible histogenesis of lymphoid stroma [11]. According to the 2005 World Health Organization classification of tumors, Warthin's

tumor can be defined as a tumor composed of glandular and often cystic structures, sometimes with a papillary cystic arrangement, lined with characteristic bilayered epithelium, comprising inner columnar eosinophilic or oncocytic cells surrounded by smaller basal cells.

Lymphoid stroma often contains many germ centers, which may be the result of an immune response to neoplastic epithelium or may represent residual lymphoid tissue in the lymph nodes partially replaced by neoplastic epithelium [12]. van der Wal et al. [13] have shown that the lymph nodes near the gland may be present within the healthy tissue of salivary gland, and on the other hand, salivary gland tissue may be present in the structure of lymph nodes.

Expression of markers

Immunostain reactions for CD20cy and CD45RO in 21 cases with Warthin's tumor revealed a predominance of B lymphocytes specifically marked with CD20cy in five cases (23.8%) and T lymphocytes marked with CD45RO in four cases (19%) [14].

Studies by Barnes et al. [12, 15] have shown B (CD20), NK (CD56), and T (CD3) cells, including helper (CD4) and suppressor (CD8) subtypes, in Warthin's tumors lymphocyte population. The lymphocyte population is polyclonal, with a predominance of IgA-producing cells. CD9 has been reported to be present in every Warthin's tumor (18/18) [16].

Bcl-2 also plays a role in the development of adenomas [17]. Occult B-cell monoclonality as determined by IgH FISH/PCR and Bcl-2 FISH/PCR was not identified in the selected random cases of Warthin's tumor and did not establish the benign polyclonal nature of the lymphoid stroma in this neoplasm [18]. Results from the Genetzakis et al. [19] study suggest that Bcl-2 can be used to identify locally advanced or histologically aggressive tumors with a higher survival probability following the standard treatment modalities.

The epithelial malignancy was labeled with cytokeratin (CK) and epithelial membrane antigen (EMA). The immunohistochemical study of the bilayer epithelial component of Warthin's tumor has different immunostaining pattern of the two types of epithelia. CKs and EMA are the two most widely used markers (CK and EMA immunostain) for epithelial origin cells, and they usually do not show up in the Warthin's tumor after the malignant transformation [2].

In all the Warthin's tumor cases, the immunostaining for CK5/6 was positive in bilayer epithelial basal cells, both in the structure of the cysts and the papillae.

In the case of the immunostaining for p63, Dăguci et al. [20] noticed limited nuclear positivity in the basal cells, while the columnar cells' nucleus were negative. By reverse transcriptase and nested PCR, all tumors expressed p63 [21]. Neoplastic epithelial cells of Warthin's tumor showed slightly positive staining for S100 alpha in their cytoplasm, and there was a strong positive reaction in a limited number of lymphoid stroma [22].

Beta4-integrin is strongly expressed in all cell basement membrane and intercellular contacts of the epithelium. E-cadherin and desmoglein-2 are expressed in cell–cell contacts, but not in basal cell–basement membrane connections.

HCAM (CD44s) is expressed in intercellular contacts of both luminal basal cells and monocytic–lymphocytic stroma. ICAM-1 has weak expression in both luminal and basal epithelial cells and strong expression in the germinal lymphocytic centers. CAM is expressed in the ductal structure of bilayer secretory in the neoplastic epithelium of Warthin's tumor [23].

Wang et al. [24] have shown that PRDM1 is expressed only on the epithelial component but not on ectopic lymphoid tissue of the Warthin's tumor. IgG4 levels increased in 27% of Warthin's tumors [25], and 35.71% of Warthin's tumors expressed VEGF [26].

The etiology of Warthin's tumor is still not clearly investigated. In this study, we tried to evaluate some immunostaining marker expressions, focusing on the lymphocyte and epithelial population that were present in Warthin's tumor. The aim of this study is to find markers that can help understand the pathomechanism of Warthin's tumor.

Methods

Benign tumor of the salivary gland was used as the study material. Only patients with Warthin's tumor, who had undergone surgery during 2013–2015 in the Department of Oral and Maxillofacial Surgery of the Sumy Regional Hospital, took part in this study. A total of 15 patients with Warthin's tumor were included, and the Warthin's tumor without malignant metastasis was investigated. Hematoxylin and eosin staining, which have been used for at least a century and are still essential for recognizing various tissue types and the morphologic changes for cancer diagnosis, was performed.

Immunostaining for proteins was performed on formalin-fixed (pH 7.4), paraffin-embedded Warthin's tumor tissue sections using mouse monoclonal antibody *(Table I)*. Based on the manufacturer guidelines (Thermo Fisher Scientific), immunohistochemistry protocol was carried out [27].

Briefly, 4-μm thick tissue sections were dewaxed in xylene and were brought to water through graded alcohols. Antigen retrieval was performed by microwaving slides in 10 mM citrate buffer (pH 6.2) for 30 min at high power, according to the manufacturer's instructions.

To remove the endogenous peroxidase activity, sections were then treated with freshly prepared 1.0%

Table I Types of antibody dilution, clone, and level of the protein expression in Warthin's tumor

				Epithelium		
S. No	Antibody	Dilute	Clone	Oncocytic cells (%)	Basal cells (%)	Lymphoid tissue (%)
1	MGMT	1:50	MT 3.1	25.6 ± 0.59	59.3 ± 1.79	10.0 ± 0.34
2	CD3	1:150	SP7	–	–	47.3 ± 3.89
3	HSP90AA1	1:200	Poliklon	0.5 ± 0.15	0.41 ± 0.23	0.5 ± 0.26
4	MMP-1	1:50	Poliklon	0.41 ± 0.23	0.5 ± 0.15	0.36 ± 0.26
5	Bcl-2	1:100	100/D5	–	0.15 ± 0.03	42.6 ± 8.33
6	CD79A	1:200	SP18	–	–	43.2 ± 13.5
7	IgG	1:500	Poliklon	0.08 ± 0.05	0.08 ± 0.06	0.75 ± 0.15
8	Ki-67	1:100	SP6	–	30.0 ± 1.5	13.3 ± 0.45
9	p53	1:100	SP5	–	3.6 ± 2.3	11.6 ± 2.3
10	IgM	1:500	Poliklon	–	–	0.50 ± 0.15
11	OPN	1:100	Poliklon	0.66 ± 0.12	0.41 ± 0.32	–
12	S100	1:100	4C4.9	–	–	21.6 ± 8.2
13	Myeloperoxidase	1:100	Poliklon	–	–	–
14	VEGF	1:200	Poliklon	0.33 ± 0.15	0.50 ± 0.15	–
15	Glycophorin	1:100	Poliklon	–	–	5.6 ± 1.13
16	Chromogranin A	1:100	Poliklon	0.25 ± 0.12	0.41 ± 0.22	0.5 ± 0.15

hydrogen peroxide in the dark for 30 min at 37 °C. Nonspecific antibody binding was blocked using blocking serum. Sections were then incubated for 30 min at 37 °C, with the primary antibodies against protein diluted in phosphate-buffered saline (pH 7.2), by triple washing with PBS.

Anti-mouse IgG–horseradish peroxidase conjugate (1:40,000 dilution) was used for the detection of the primary antibodies. Then, the sections were incubated for 20 min at 37 °C and visualized by reacting with DAB (3,3'-diaminobenzidine).

The appearance of the positive factors was detected semiquantitatively by counting the intensity of positive staining in the visual field. Proteins in cytoplasmic region were determined by the intensity of DAB staining: 0, no; 0.25, weak; 0.5, average; 0.75, strong; and 1, very strong. Proteins in nucleus were determined by counting DAB-positive nuclei.

The data were analyzed using STATISTICA 8.0 (version STA862D175437Q), and the results were presented as mean (± SD). Cluster analysis was also carried out using STATISTICA 8.0.

Results

Warthin's tumor is sharply demarcated with a thin capsule. At the periphery of the lesions, there is extensive fibrosis, with dense hypocellular collagen and myofibroblastic spindle cell proliferation. There is a heavy mixed inflammatory infiltrate (Fig. 1D) composed of chronic inflammatory cells and sheets of macrophages.

The epithelium includes dual layers of cells: one layer shows the oncocytic luminal cells (Fig. 1A) with high and columnar structure and the other layer shows palisading of their bland single ovoid nuclei. Deep to this layer, lie smaller flattened or cuboidal basal cells (Fig. 1C). Their cytoplasm is similar, but less profuse. No significant nuclear atypical or mitotic activity is recognized. Small foci of squamous metaplasia, scanty goblet cells, and very occasional sebaceous cells are seen.

The stroma comprises lymphoid tissue displaying varying degrees of reactivity, and germinal centers are normal. Increased numbers of mast cells and plasma cells may also be seen. The cystic spaces comprise eosinophilic
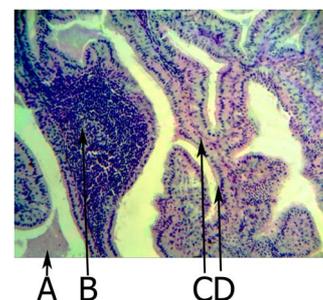

Fig. 1. Warthin tumor stained by hematoxylin and eosin. Magnification 150×. A – the oncocytic cells; B – the cystic spaces; C – the cuboidal basal cells; D – the mixed inflammatory infiltration

secretions with occasional crystal formation and laminated figures resembling corpora amylacea *(Fig. 1B)*. Atypical cells can be projected with several mitotic figures, but none is abnormal.

Immunohistochemical staining of the immune cells within the follicles of Warthin's tumor were positive for MGMT, Ki-67, Bcl-2, and p53 *(Fig. 2)*.

The immune cells were associated with a CD3+ residual cell meshwork *(Fig. 2)*, but they were not present in the epithelium cells. Some CD79A-B cells consistent with germinal centers were present within
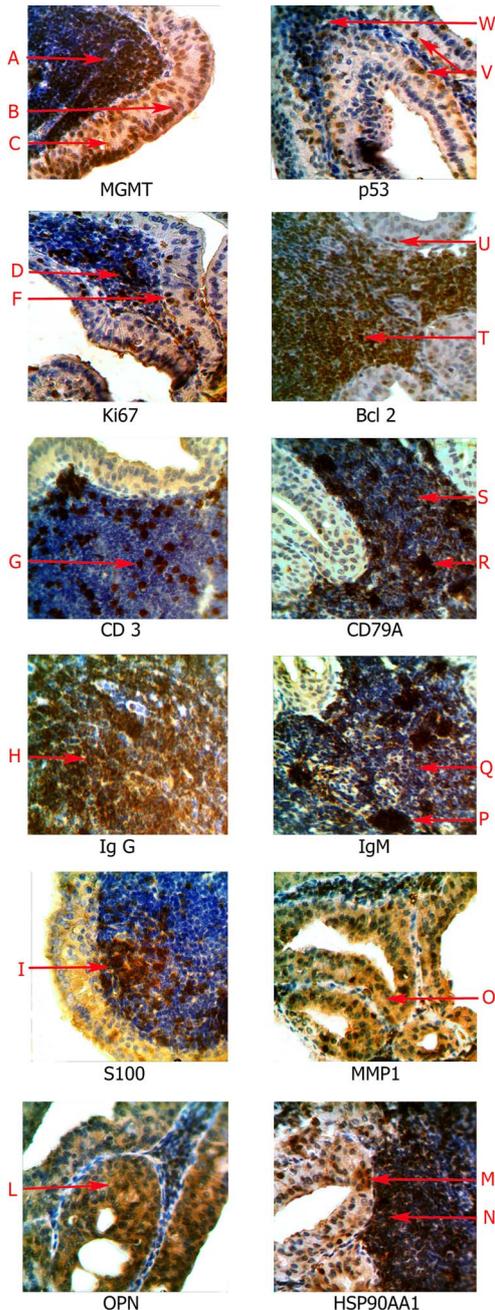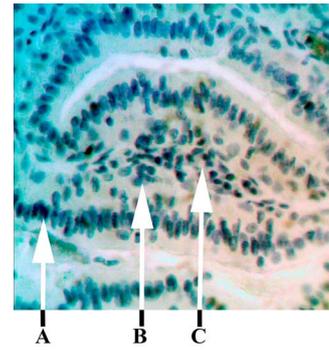

Fig. 3. Myeloperoxidase, negative expression in Warthin's tumor. Magnification 400×. A – negative expression in the oncocytic cells; B – negative expression in the cuboidal basal cells; C – negative expression in the mixed inflammatory infiltration

the immune cells. B cells formed follicles *(Fig. 2R)*, and the inflammatory infiltrate expressed IgG and IgM. Immunostaining performed on IgG showed diffuse expression. IgM was product of B cells-CD79A forming follicles *(Fig. 2P)*.

The inflammatory infiltrate was positive for S100 and negative for epithelial cells *(Fig. 2I)*. S100-positive immune cells had subepithelial localization. MMP-1 and OPN presence was negative in the immune cells of Warthin's tumor *(Fig. 2)*, but weakly positive for HSP90AA1 *(Fig. 2N)*. Epithelium in the oncocytic luminal cells and basal cells areas expressed OPN and MMP-1 *(Fig. 2L, O)*, respectively. Warthin's tumor was negative for myeloperoxidase *(Fig. 3)*.

Chromogranin A *(Fig. 4A, B)* and glycophorin expression in Warthin's tumor are shown in *Fig. 4*. Glycophorin expression was negative for epithelial cells. Glycophorin stains small areas of hemorrhage in the stroma of tumor. Warthin's tumor was positive for chromogranin A *(Fig. 4A, B)*. Epithelium and immune cells
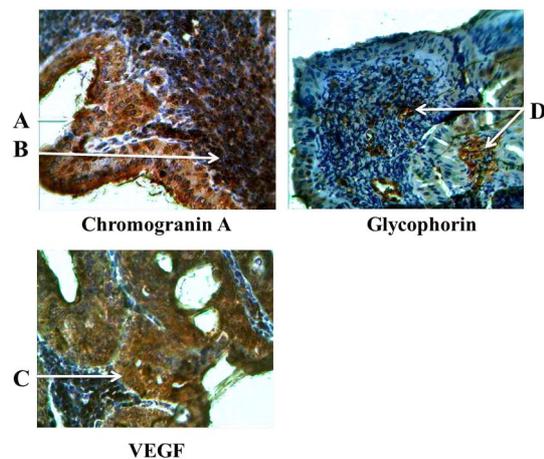

Fig. 2. Marker expressions in Warthin's tumor. Magnification 400×

Fig. 4. Chromogranin A, VEGF, and glycophorin expression in Warthin's tumor. Magnification 400×

expressed chromogranin A. Oncocytic luminal and basal cell areas expressed VEGF *(Fig. 4C)*. Different levels of the marker expressions were shown in *Table I*.

Cluster analysis combining a large number of parameters obtained from the analysis was disseminated on two objects, G and M clusters, so that each object G includes subclusters. Results from the cluster analysis of protein expression are shown in *Fig. 5*.

The horizontal axis represents proteins and the vertical axis represents the connection between the proteins. The first stage of the tumor–protein relationship was connection of the following proteins: HSP90AA1 in basal cells, CD3 and glycophorin in mixed inflammatory infiltrate, VEGF and Ki-67, IgG in basal cells.

The indicated proteins in oncocytic luminal cells have minimum distance and are characterized by epithelium, including dual layer stimulus on inflammatory infiltrate (*Fig. 5*, black line). The indicators are part of the second cluster that shows the influence of stroma in tumor epithelial component (*Fig. 5*, gray line).

Discussion

We have shown that expression of p53 may be associated with the regulation of MGMT expression in Warthin's tumors. Levels of MGMT and low level of p53 are predictors of Warthin's tumors.

Rolhion et al. [28] reported that MGMT gene expression was significantly lower in p53 benign tumors, and mutant p53 was clearly correlated with poor survival in tumor. Some of these tumors, such as those derived from the brain, lung, head and neck, and lymphomas, also have

hypermethylation-associated inactivation of MGMT. The Bcl-2 protein is a potent inhibitor of cell death, whereas the wild-type p53 protein activates the apoptotic pathway [29].

Mutated p53 loses this function and allows the proliferation of neoplastic cells. Bcl-2 also modulates the function of p53 and triggers cell proliferation and transformation [30]. We defined that manifestation of Bcl-2 in inflammatory infiltrate of Warthin's tumor showed good prognostic markers.

Expression of the Ki-67 proliferation marker, which detects all phases of the cell cycle except G0, is known to predict disease outcome in many human malignancies [31]. At the same time, Ki-67 and p53 were reported to be used in a parallel manner [32].

The positivity for Ki-67 on the basal layer may be explained by the presence of active proliferating cysts. Generally, the positive expression of Ki-67 in the cells of basal layer may indicate the grade of epithelial proliferation. Immunohistochemical expression of the proteins p53, Bcl-2, and Ki-67 in the Warthin's tumor may indicate the growth aspect of the proliferating epithelium and immune cells.

The expression of S100 has been detected as proinflammatory phagocytes cells at sites of intestinal inflammation [33, 34]. Systemic autoimmune diseases (dermatomyositis, systemic lupus erythematosus, Kawasaki disease, etc.) are associated with S100 expression of macrophages infiltrating with degeneration of tissue [35, 36].

Macrophages are versatile cells that play many roles. Along with dendritic cells, they are foremost among the cells that present antigens, and their crucial role is to initiate immune response. As secretory cells, monocytes
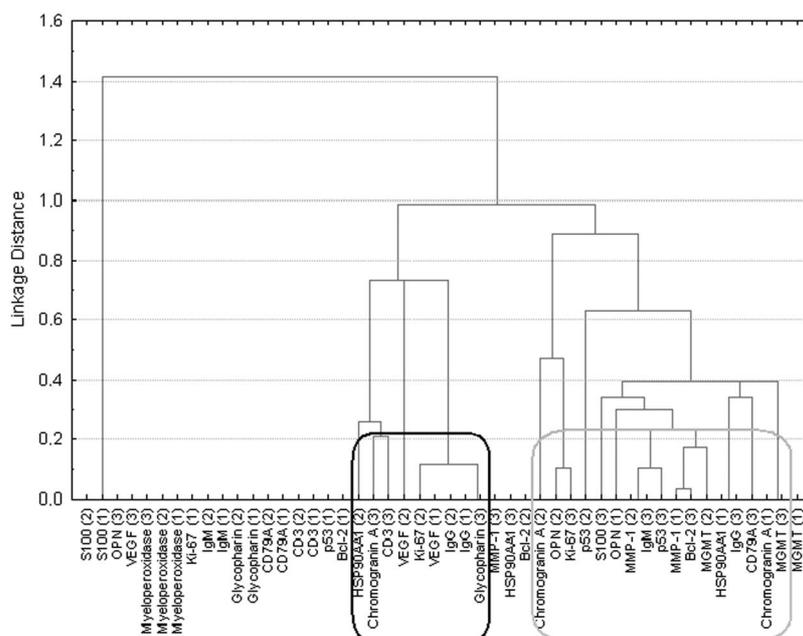

Fig. 5. Diagram of cluster analysis

and macrophages are vital to the regulation of immune responses and the development of inflammation [37]. We have supposed that the macrophages act as antigen-presenting cells in the Warthin's tumor: they activate helper T cells (CD3) and B cells (CD79A) by presenting them with antigens.

The question is: What is the antigen in the Warthin's tumor? We can offer a couple of options for the antigen: (a) epithelial cells infected by a virus or chemical such as tobacco smoke, and as a result of it, there is a mutation and immune response and (b) autoimmune response on its own duct cells.

IgG and IgM are basic antibodies that are produced by B cells. They act as antibodies through several mechanisms: IgG-mediated binding of pathogens causes their immobilization and binding together via agglutination, IgG coating of pathogen surfaces (known as opsonization) allows their recognition and ingestion by phagocytic immune cells, IgG activates the classical pathway of the complement system, a cascade of immune protein production that results in pathogen elimination, and IgG also binds and neutralizes toxins.

Because IgM is a large molecule, it cannot diffuse well and is found in the interstitium only in very low quantities. Due to its polymeric nature, IgM possesses high avidity and is particularly effective at complex activation. By itself, IgM is an ineffective opsonin; however, it contributes greatly to the opsonization by activating complement and causing C3b to bind to the antigen.

C3b is the larger of two elements formed by the cleavage of complement component 3. C3b covalently bonds to microbial cell surfaces within an organism's body. This leads to the production of surface-bound C3-convertase and accordingly more C3b components.

Bound C3b also aids in the opsonization of the microbe by macrophages [38].

The measurement of IgG can be a diagnostic tool for certain conditions, such as autoimmune diseases. Clinically, measured IgG antibody levels are generally considered to be indicative of an individual's immune status to particular pathogens. A common example of this practice are titers drawn to demonstrate serologic immunity to measles, mumps, and rubella, hepatitis B virus, and varicella, among others [39]. We obtained a strong reaction of IgG, and the above confirms our view of the viral etiology in the Warthin's tumor.

The other protein expression that confirms the viral etiology in the Warthin's tumor is the nonexpression of myeloperoxidase. Myeloperoxidase and glycophorin are expressed in neutrophils [40, 41], which are mainly present in inflammation caused by bacteria.

The chemoattractant property of OPN has been demonstrated in the migration of monocytic cells/macrophages, T cells, smooth muscle cells, endothelial cells, epithelial cells, and several malignant cells [42–44]. In addition, OPN is an important factor in immune system activation and virus resistance and was named by Patarca et al. [45] in 1989 as T-lymphocyte activation 1 protein (Eta-1). Today, this protein is designated as OPN and is known to be involved in wound repair, immune function, angiogenesis, and cell survival.

Both soluble OPN, which works as a cytokine, and immobilized OPN, which functions as an extracellular matrix protein, protect against apoptosis and induce survival and proliferation in several cell types. OPN has a prosurvival and/or proliferative function in adherent cell types, such as smooth muscle cells [46] and epithelial cells [47].
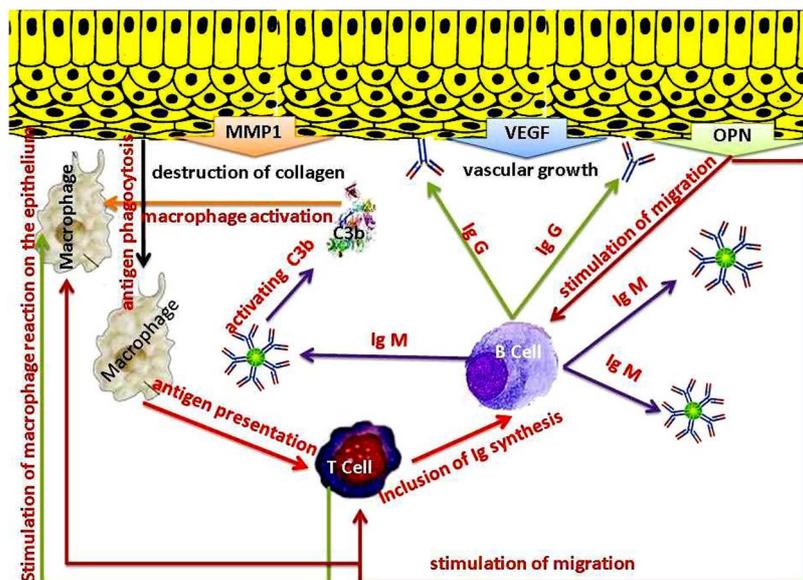

Fig. 6. Pathogenesis of Warthin's tumor

Our results suggest that as one of the most abundant proteins in tumor cells and a key factor that stabilizes tumor proteins involved in tumor growth and survival, increased HSP90 expression may play an important role in stimulating development of Warthin's tumor. In neoplasia, HSPs have been associated in multidrug resistance [48] and regulation of apoptosis [49], as well as modulators of p53 function [50]. Conversely, wild-type (but not mutant) p53 downregulates HSP90 expression [51].

Our data indicated that MMP-1 reduced cell proliferation, as demonstrated by the low Ki-67 expression in tumors epithelium. Probably, as a consequence of this, Warthin's tumor has also slow growth and reduction of collagen-1.

On the contrary, overexpression of MMP-1 (in conjunction with other genes) in human breast carcinoma cells increased xenograft growth rates [52] and facilitated the assembly of new tumor blood vessels that causes release of tumor cells into the circulation and the breaching of lung capillaries by circulating tumor cells to seed pulmonary metastasis.

Based on the results of the cluster analysis and studies of scientists, form of proteins rapport was established (*Fig. 6*).

Conclusions

1. Histopathological analysis of the stroma and parenchyma revealed balanced distribution of epithelial and stromal component. Epithelial component of the Warthin's tumor is the trigger for the tumor process. Reactive proliferation was present as a response to epithelial proliferation that modulates it, which caused active production of IgG and IgM. Epithelium proliferation also stimulated macrophage and T-cell infiltration.
2. Markers of this study showed inflammatory etymology of Warthin's tumor. The immunostaining of stromal component with Ki-67 markers showed lymphocytic proliferation in the stromal cells of the tumor with predominantly type B-plasmacytoid (CD79A immunostained). This study indicates that Warthin's tumor is a consequence of inflammatory etiology.

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Conflict of interest: None declared.

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