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Original article

Tumor biology

Warthin tumors – risk factors, diagnostics, treatment

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Introduction. Warthin tumors are the second most common benign tumor of the salivary gland, located mainly in the parotid glands, sometimes bilaterally. The main risk factor is nicotine addiction. The aim of the study was to present our own experience in the diagnosis and treatment of salivary gland neoplasm, and to analyze the risk factors for the development of Warthin tumors.

Materials and methods. The study group consisted of 55 patients operated on with Warthin tumors (between 2009 and 2023). 55 control individuals with no Warthin tumors were recruited. The patients underwent a retrospective analysis of risk factors for head and neck cancer.

Results. Warthin tumor patients reported salivary gland diseases, such as urolithiasis, inflammation, dry mouth, nicotine addiction, and chronic diseases, such as hypercholesterolemia. In 83% of cases of fine-needle aspiration biopsy (FNAB) of Warthin tumors, results were confirmed by postoperative histopathological diagnosis. The therapy included extracapsular tumor removal, partial parotidectomy with preservation of the facial nerve, and removal of the submandibular gland. Postoperative complications were a cutaneous fistula and paresis of the marginal branch of the facial nerve.

Conclusions. The study confirmed that nicotine addiction (smoking duration and number of cigarettes smoked per day) was the main risk factor for developing Warthin tumors. An increase in body-mass index (BMI), hypercholesterolemia, salivary gland diseases, and dry mouth symptoms manifested Warthin tumors. FNAB, ultrasonography (USG) and computer tomography (CT) or magnetic resonance imaging (MRI) with contrast were essential in the diagnostics and planning therapeutic strategy. The main treatment used in the clinic was extracapsular tumor removal.

Key words: Warthin tumors, salivary gland neoplasm, diagnostic, surgery treatment

Introduction

Salivary gland neoplasm account for 6% of all head and neck neoplasm. More than 80% of large salivary gland tumors are benign [1]. After pleomorphic adenoma (PA), the second most common is Warthin tumors (WT) [2]. In recent years, a predominance of Warthin tumors has been observed in certain regions of Germany, 44.9–48% compared to 17.3–23% pleomorphic adenomas [3]. In Poland, according to the Registry of Non-Malignant Tumors of Major Salivary Glands, Warthin tumors (37.1%) rank second after pleomorphic adenoma (217/585) [4]. Warthin tumors were first described in 1895 by Hildebrand. It is located mainly in the parotid glands (it accounts for 2–15% of parotid tumors), rarely in the submandibular glands. Isolated cases of Warthin tumors were described in the oral cavity, larynx, nasopharynx, eyelids and perisalivary lymph nodes [5].

One of the theories of the pathogenesis of tumors is their development from the cells of the salivary gland ducts present in the intra- and peri-parotid lymph nodes [6]. Another theory suggests it is an active process based on an inflammatory reaction leading to neoplasm proliferation [7]. Warthin tumors grow slowly and are not painful whereas large tumors may cause discomfort and distort facial features. It is estimated

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that approximately 0.3% of tumors undergo transformation into malignancy [8]. Diagnostics is based on an interview, physical examination, fine-needle aspiration biopsy (FANB) under ultrasound guidance, computer tomography (CT) or magnetic resonance imaging (MRI) with contrast. Treatment involves surgical removal of the tumor – depending on the location of the lesion: extracapsular removal of the tumor along with a margin of healthy tissue or partial parotidectomy with preservation of the facial nerve. These methods are usually chosen to protect the facial nerve [9].

The aim of the study was to present our own experience in the diagnosis and treatment of salivary gland neoplasm, and to analyze the risk factors for the development of Warthin tumors.

Materials and methods

One hundred and ten individuals were recruited for the study. They were divided into 2 groups, the study group and the control group. The study group consisted of 55 patients, 24 (44%) females aged 27–85 years (mean age 60.1 years) and 31 (56%) males aged 40–78 years (mean age 52 years) treated for Warthin tumors of the salivary glands at the Department of Otolaryngology and Laryngological Oncology, Audiology and Phoniatrics, Medical University of Lodz. Pre-operative diagnosis involved a history and physical examination, laboratory tests (morphology, creatinine, CRP) and additional tests: ultrasound guided FNAB examination, CT or MRI with contrast. In all cases, surgical treatment was performed – extracapsular tumor removal or partial parotidectomy with preservation of the facial nerve. Post-operative care included: suction drainage (24 h), postoperative wound care (changing the dressing, rinsing with Octenisept), check-up and removal of stitches 7 days after the procedure, also a conservative lifestyle was recommended (2 weeks).

The control group consisted of 55 individuals, the so-called healthy volunteers (the criterion for inclusion was the absence of a salivary gland tumor confirmed by imaging; the patients and the controls were matched according to gender and age). The comparison group consisted of 24 females aged 27–75 years (mean age 58.2 years) and 31 males aged 24–71 years (mean age 53.4 years). The patients completed a questionnaire regarding the risk of head and neck cancer. The study was granted the consent of the bioethics committee of the Medical University of Lodz (RAN/222/17/KE).

Statistical analysis: for statistical analysis STATISTICA 12.0 software, the chi-square test was used and the V-Cramer coefficient was calculated. $P < 0.05$ was considered statistically significant.

Results

Statistical analysis ($p < 0.05$) showed that patients with Warthin tumors had a higher BMI, tendency to obesity, suffered from hypercholesterolemia, reported symptoms in the salivary glands (i.e. stones, inflammation) and dry mouth. They were also addicted to smoking, they smoked more cigarettes per day for a longer time than the control group (tab. I). Among smokers, more than half (52%) have been smoking more than 10 cigarettes a day for 10 years.

No statistically significant differences between the groups were found in: gender, thyroid disease, diabetes, hypertension, education, alcohol consumption, number of sexual partners, exposure to ionizing factors, UV, radiotherapy, exposure to the automotive industry, rubber industry, exposure to nickel, chromium, cement dust, asbestos dust, work in a hairdressing salon, treatment for cancer, head and neck cancer, and the incidence of Epstein-Barr virus. A physical examination revealed a tumor with a soft or taut consistency, movable in relation to the ground. Facial expressions were preserved. No cervical lymphadenopathy was observed. In most patients, tumor growth was painless (49/55), 6 individuals reported pain within the tumor. The lesions were located in the parotid (52/55) and in the submandibular glands (3/55) (tab. II). Synchronous tumors were observed in 6 and metachronous in 2 patients. Multiple tumors in a single salivary gland were present in 6 cases. The average time of tumor growth was 2.2 years. Based on neck CT with contrast or USG, the average tumor volume was estimated at 5.97 cm^3 [4], and the mean tumor size was 2.56 cm. A history of autoimmune diseases revealed hypothyroidism (13/55) and hyperthyroidism (2/55). The FNAB results were confirmed in postoperative histopathological diagnosis in 49 patients (83%). The following surgical procedures were performed: extracapsular removal of the tumor (50/55), superficial parotidectomy with preservation of the facial nerve (2/55) – parotidectomy II according to the ESGS classification and removal of the submandibular gland (3/55). Postoperative complications included, cutaneous fistula (2/7) and paresis of the marginal branch of the facial nerve (5/7). In patients with a cutaneous fistula, a strip dressing was applied, in those with paresis of the VII^{th} nerve, galantamine injections (Nivalin) and rehabilitation were recommended. All subjects regained normal facial nerve function. Recurrence of Warthin tumor was observed in two patients.

Discussion

Warthin tumors constitute approximately 17% of all salivary gland tumors. It is a benign, encapsulated tumor composed of oncocytic epithelium surrounded by lymphoid stroma with active germinal centers [10]. The risk of malignancy in case of the epithelial component is 0.3%; mucoepidermoid carcinoma, squamous-cell carcinoma, adenocarcinoma, oncocytic carcinoma were observed; the lymphatic component may undergo transformation towards malignant lymphoma [11]. Cases of coexistence of Hodgkin's lymphoma or non-Hodgkin's lymphoma with Warthin tumors are also known [12]. In the examined material, Warthin tumors and Hodgkin's lymphoma of the parotid gland were detected in one patient.

Table I. Characteristic elements of the physical examination of patients in the study groups

Analyzed trait	Study group n = 55	Control group n = 55	p < 0.05*
	number (SD)	number (SD)	
gender: female male	 24 31	 24 31	1
age in years – mean	58.64	56.22	0.6572
education: primary secondary higher	 13/55 27/55 15/55	 7/55 31/55 17/55	0.3853
BMI – mean	28.5	25.4	0.0451*
normal weight (BMI 18–25) overweight (BMI 25–30) obesity (BMI > 30) metabolic syndrome	12 29 12 2	24 28 3 0	0.0533
smoking status "yes"	41/55	17/55	6.231e-08*
duration smoking – in years	15.1	7.3	1.882e-04*
number of cigarettes per day – mean	12.1	8.2	1.424e-11*
alcohol consumption: never <30 U/week >30 U/week	 21/55 33/55 1/55	 24/55 30/55 1/55	0.733
thyroid disease: hyperthyroidism hypothyroidism	 2/55 13/55	 2/55 3/55	0.0887
diabetes: diabetes 1 diabetes 2	0/55 6/55	1/55 3/55	0.6214
hypercholesterolemia	16/55	4/55	0.0055*
hypertension artery	11/55	6/55	0.1531
number of sexual partners: 1–3 3–7 >7	 36/55 13/55 6/55	 35/55 15/55 5/55	0.2565
oral sexual activity	19/55	22/55	0.4321
salivary gland disease (inflammation, stones)	29/55	4/55	4.26e-05*
dry mouth	28/55	6/55	0.003145*
oncological treatment among patient's family (parents, grandparents, siblings)	12/55	4/55	0.08482
treatment for head and neck neoplasm among patient's family (parents, grandparents, siblings)	7/55	3/55	0.2998
oncological treatment in the past	7/55	2/55	0.05661
treatment of head and neck neoplasm in the past	1/55	1/55	1
exposure to: radiotherapy UV ionizing factors	 4/55 10/55 3/55	 1/55 9/55 1/55	0.2166 0.2773 0.1457
Epstein-Barr virus infection	2/55	1/55	0.4652
exposure to: the automotive industry, rubber industry, exposure to nickel, chromium, dust cement, asbestos dust, work in a hairdressing salon	14/55	3/55	0.0642

Table II. Clinical features of Warthin tumors in the study group

Tumor location										Features of tumors		
parotid gland*								submandibular gland		soft consistency	taut consistency	movable in relation to the surround tissue
right				left				right	left	38	17	49
I	II	III	IV	I	II	III	IV	0	3			
9	11	4	–	10	17	1	–					

* Region of parotid gland according to the ESGS classification I, II, III, IV

Epstein-Barr virus infection was found to cause multiple occurrences of Warthin tumors [13]. The main risk factor is nicotine addiction. Other risk factors comprise autoimmune diseases, inflammatory diseases and ionizing radiation [14] as well as an increase in BMI (average value 29.1), obesity and diseases related to the metabolic syndrome (hypertension, diabetes, coronary heart disease). Based on a database of smoking addiction in Austria (from 23.5% in 1972 to 24.3% in 2014) and the occurrence of Warthin tumors (from 1970 to 2015, a 3.9-fold increase in tumors was observed) it was concluded that other factors including increased BMI may influence the development of tumors [15]. *Mycobacterium tuberculosis* infections were detected in a Warthin tumor in one patient. In tobacco smokers, the occurrence of Warthin tumors was 8 times more frequent than mixed tumors, exacerbating factors include: benzopyrene, arsenic, and N-nitrosoguanidines present in tobacco smoke that affect the transformation of gland tissue [16].

The neoplasm develops mainly in men in the 5th and 6th decade of life. There has been an increase in Warthin tumor cases in women. The male to female Warthin tumor patient ratio ranged from 2.3:1, 1.8:1 to 12.6:1 [3, 17]. In our study, Warthin tumors were found in 56% of men aged 27–75 years (mean age was 54.3 years) and the male to female ratio was 1.3:1.

The first symptoms of Warthin's tumor are changes in the shape of the face – a palpable tumor in the area of the salivary gland. These lesions are oval, soft [18], and usually grow asymptomatically. It was found that approximately 7% of tumors may be painful, then malignant growth should be ruled out. Warthin tumors tend to be multifocal (12–20% of cases) and bilateral (5–14% of cases) [19]. The tumors are most often located in the superficial lobe, in the lower part, the so-called tail of the parotid gland (level II according to the European Classification of Salivary Glands), where intrasalivary lymph nodes are present. WT recurrences are observed in 5–10% patients [20].

In the diagnosis of monomorphic adenoma, additional tests are recommended: FNAB, ultrasound. According to the Milan Classification it is category IV.A – "benign tumor" or category IV.B "salivary gland tumor with uncertain malignant potential (SUMP)" [21]. Cells characteristic of Warthin tumors are lymphocytes and oncocytic cells. The FNAB results were consistent with the postoperative diagnosis at 95% to 74% [22]. In our study it was 83%. Although no statistically significant differences were observed between CT with contrast and MRI, due to the benefits for the patient (no radiation, no contrast containing iodine), magnetic resonance imaging is recommended [23].

The first choice treatment is surgical removal of the tumor. Depending on the location of the tumor, different techniques are recommended: partial parotidectomy is when the tumor is in the lower part of the salivary gland (tail), superficial parotidectomy when it affects the superficial lobe or, in the case of tumors located in the deep lobe, total paratidectomy with preservation of the facial nerve [24]. Based on meta-analysis, Quer et al. proposed parotidectomy II (partial parotidectomy) or extracapsular tumor removal (extracapsular dissection – ECD) when a single tumor is located in area I or II; parotidectomy depending on the size of the lesion when a single tumor is in area II or IV or intrasalivary; parotidectomy II (partial lateral parotidectomy) or ECD when a single lesion is larger than 3 cm and is located in the tail of the salivary gland; in the case of multifocal lesions in the superficial lobe, parotidectomy I or II (lateral or superficial parotidectomy), when multifocal lesions affecting the superficial and deep lobe are present, parotidectomy I, II, III, IV (total parotidectomy) are indicated [8]. Wierzbicka et al. described surgery for salivary gland tumors using new technologies such as VITOM 3D [28] and also emphasized the importance of synoptic reporting in the surgery of recurrent salivary gland tumors [29]. Mantsopoulos et al. recommend ECD using neuromonitoring as a procedure with the lowest risk of complications (including Frey syndrome) [25]. Postoperative complications include facial nerve damage, sialocele, postoperative hematoma, cutaneous fistula, Frey syndrome and scarring [31]. It is recommended to describe procedures for benign salivary gland tumors according to the ESGS classification [32]. Patients who do not decide to undergo the procedure or those with contraindications for general anesthesia should be observed and development of the tumor monitored by imaging tests [28].

In recent years, minimally invasive treatment procedures were used. There are isolated cases of treatment of Warthin tumors by ethanol sclerotherapy under ultrasound guidance with satisfactory results (reduction of tumor size, patient satisfaction

resulting from changes in appearance) [29] and ablation of tumors using radiofrequency [30] or microwaves [31].

Conclusions

In the operated patients, nicotine addiction (duration of smoking and number of cigarettes smoked per day) was the main risk factor for Warthin tumors. Increased BMI (including obesity), hypercholesterolemia, salivary gland diseases, and the presence of dry mouth were observed (statistically significant) in the group of patients with Warthin tumors. FNAB, USG and neck CT/MRI with contrast are essential in diagnosing and planning the therapy. The main treatment method was extracapsular tumor removal (according to the ESGS classification).

Article information and declarations

Author contributions

Katarzyna Kolary-Siekierska – conceptualization, formal analysis, funding acquisition, investigation, methodology, writing – original draft, writing – review and editing.
Anna Jałocha-Kaczka – methodology, writing – review and editing.
Piotr Niewiadomski – formal analysis, writing – review and editing.
Jarosław Miłoński – conceptualization, formal analysis, funding acquisition, investigation, methodology, writing – original draft, writing – review and editing.

Data availability statement

Data were collected from a questionnaire, a retrospective analysis was conducted.

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of the Medical University of Lodz (protocol code RNN / 222/17/KE).

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Conflicts of Interest

None declared

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