Warthin's tumour: Aetiopathogenesis dilemma, ten years of our experience

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Abstract

Despite the volume of studies written after the initial report by Hildebrand (1895) on Warthin's tumour (WT), its aetiopathogenesis continues to be an unresolved and controversial question. Many different genetic and/or environmental aetiological factors seem to act on heterotopic ductal inclusions and may give rise to WT following an unknown tumorigenic event. Recent studies discussed the importance of immunological reactions during the formation of the tumour. A hypersensitive/allergic reaction may play a role in epithelial proliferation and may stimulate the reactivity of the germinal centres in the lymphoid stroma as showed at histological examination. The aim of this study was to inform readers of the current understanding of possible risk factors with a suggested aetiological role in Warthin's tumorigenesis. From 2001 to 2011, a total of 342 patients with benign salivary neoplasm were admitted in the Department of Maxillofacial Surgery of the University of Naples “Federico II”. A histological diagnosis of WT was made in 115 of the patients (33.6%); these were retrospectively investigated in our study. Correlation between the onset of WT and positivity for autoimmune diseases and smoking habits was calculated. The incidence rate of autoimmune thyroiditis in our series (9.5%) was significantly greater than that of the general population (0.58%) (p < 0.001). Analysis of our series and review of the literature support the hypothesis that this tumour is the result of an autoimmune reaction. Further studies and larger series are required to confirm this hypothesis and investigate the role of other aetiological factors in WT genesis.

1. Introduction

Warthin's tumour (WT), also known as papillary cystadenoma lymphomatosum is a fairly common tumour. It was first described by Hildebrand in 1895, when he described this disease as a variant of a lateral cyst of the neck. In 1910, Albrecht and Arzt reported two tumours of the upper neck region which they described as 'confused tissue' of the entodermal pharyngeal anlage, particularly that of salivary glands in the lymph nodes (Albrecht and Arzt, 1910). They called them papillary cystadenomas in lymph nodes. In 1929, Warthin described similar cases and they were renamed after him. Warthin's tumours make up 14–30% of parotid tumours. Yoo et al. in their series, found 90% within the parotid, 7.6% in cervical lymph nodes, and 2.3% in the submandibular gland (Yoo et al., 1994). Histologically, they are composed of bilayered oncocytic and basaloid epithelium-forming cystic structures, papillae and glands, accompanied by a dense lymphoid stroma. Recent studies have shown that the epithelial component is polyclonal and does not exhibit clonal allelic losses, suggesting that this tumour is not a true neoplasm (Arida et al., 2005). These tumours have a male propensity and are more frequently multicentric than other salivary
gland tumours; in fact, about 12% of patients develop multiple tumours. They can occur unilaterally or bilaterally, metachronously or synchronously (Laane et al., 2002). About a century after its first description, the aetiology of this tumour is still mostly unknown. In most surveys, the assumption prevails that this tumour has its origin in heterotopic salivary parenchymal or ductal inclusions in the intraglandular lymph nodes during the embryonic development of the parotid gland (Thompson and Bryant, 1950; Azzopardi and Hou, 1964). Many different genetic and/or environmental aetiopathological factors seem to act on these epithelial inclusions and may give rise to Warthin’s tumour following an unknown tumorigenic event. Other studies have discussed the importance of immunological reactions during the formation of the tumour (Allegra, 1971; Ogawa et al., 1990; Gallo and Bocciolini, 1997). It is possible that some hypersensitive/allergic reaction may play a role in epithelial proliferation and may stimulate the reactivity of the germinal centres in the lymphoid stroma as seen on histological examination. The aim of this study was to inform readers of the current understanding of possible risk factors with a suggested aetiological role in Warthin’s tumorigenesis.

2. Material and methods

From 2001 to 2011, a total of 342 patients with benign major salivary gland neoplasm were admitted to the Department of Maxillofacial Surgery of the University of Naples “Federico II”. One hundred and fifteen patients (33.6%) were histologically diagnosed as Warthin’s tumour and retrospectively investigated in our study (Fig. 1). All the data was inserted into our clinic database and analysed. The Patients’ age range was 38–79 years (mean age 58.47); and the male/female ratio was 2.5:1, with 33 females (28.9%) and 82 males (71.1%) included in the study.

All patients included in the study initially presented with a swelling in the parotid region which was diagnosed as WT and surgically removed. Patient data was reviewed and any history of smoking and/or autoimmune diseases was noted. In all the cases bilateral parotid ultrasonography (US) or computed tomography (CT) and fine needle aspiration cytology (FNAC) were performed in order to confirm the suspected clinical diagnosis. In 110 cases (82.7%), the surgery performed was extracapsular dissection (ECD); in 6 cases (4.5%) total parotidectomy; and in 17 cases (12.8%) superficial parotidectomy. The choice of the surgical strategy was based on the radiographic evidence of depth of the lesion, a second occurrence/recurrence after ECD, or presence of homolateral synchronous lesions. Warthin’s ECD was carried out with meticulous dissection immediately outside the tumour capsule. The tumour was removed with a few millimetres of normal glandular parenchyma; facial nerve preservation was obtained in all cases. Data for the preoperative cytology and the definitive histological diagnosis was reviewed. Patients were followed-up for a minimum of 28 months, and a maximum of 60 months (mean 44) in order to evaluate facial nerve function and determine the recurrence rate. Correlation between WT onset and positivity for autoimmune diseases and smoking habits was calculated. Univariate analysis was performed using Chi-Square test with the SPSS base system, version 12.0 (SPSS, Chicago, IL, USA). The test used to compare scientific results with the outcome research, was the parametric hypothesis test for one proportion where the null hypothesis foresees no difference between results of the two groups of research; the opposing hypothesis, an alternative hypothesis, represents the significant difference between the two groups (Eurodiab Ace Study Group, 2000; McGrogan et al., 2008).

3. Results

In our series unilateral or bilateral multifocal lesions were detected in 22 cases (19.1%). A total of 133 parotid operations were performed in 115 patients. Eighteen (13.5%) patients had further surgery after metachronous (tumours diagnosed at different times) homolateral, or contralateral tumour occurrence; four (3.5%) patients were treated for synchronous lesions (tumours diagnosed at the same time). In our series a second tumour occurrence/recurrence on the same side as the first operation (metachronous homolateral) was observed in two patients (1.7%) (Fig. 2); these tumours were detected 3 years and 5 years (median 4 years) after the first operation. A sudden partial facial nerve dysfunction due to surgical treatment was seen in nine cases (6.8%). Among these patients, eight (6%) had an isolated weakness of the marginal mandibular branch, and one (0.7%) reported a transient facial paresis. In all cases facial nerve function recovered within 3 months.

Evaluation of risk factors revealed that 86 (74.8%) patients were smokers. During the follow-up period 18 patients (15.7%) developed a metachronous lesion not previously diagnosed, and all of these (100%) were smokers. Retrospective clinical history analysis revealed that 11 patients (9.6%) were affected by common autoimmune diseases; three patients (2.6%) had a story of insulin-dependent diabetes mellitus; eight (6.9%) patients were affected by autoimmune thyroiditis. Levels of TSH, thyroid hormones and anti-thyroid Ab, were abnormal in six cases of hypothyroidism and in two of hyperthyroidism (Table 1).
Comparing the cases affected by insulin-dependent diabetes mellitus, second tumour occurrence/recurrence was observed in three of the 115 patients (2.6%). Although this percentage is higher than previous research, the hypothesis test showed no statistical difference ($p = 0.3015$).

There were significant differences when comparing patients affected by autoimmune hypothyroidism and hyperthyroidism. In the first case, 2 patients out of 115 (1.7%), compared with 430 out of 100,000 (0.43%) of the general population, had autoimmune hypothyroidism ($p = 0.0162$). In the second case, 9 patients out of 115 (7.8%), compared with 88 out of 100,000 (0.088%) of the general population, had autoimmune hyperthyroidism ($p < 0.001$). Overall, analysing all the pathologies (autoimmune hypothyroidism and hyperthyroidism) the percentage of cases (9.5%) is significantly different than the referenced study (McGrogan et al., 2008) (0.43% + 0.088% = 0.52%) with $p < 0.001$.

### Table 1

Autoimmune diseases in our series.

<table>
<thead>
<tr>
<th>Autoimmune diseases</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin-dependent diabetes mellitus</td>
<td>3</td>
<td>2.6</td>
</tr>
<tr>
<td>Autoimmune thyroiditis</td>
<td>8</td>
<td>6.9</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>6</td>
<td>5.2</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>2</td>
<td>1.7</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>9.6</td>
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Cystadenolymphomas consist of two components; an epithelial component, composed of bilayered oncocytic and basaloid epithelium-forming cystic structures, papillae and glands; and a variable stroma component, with lymphoid tissue similar to that of a lymph node. The lymphoid stroma, with germinal centres, consists of small lymphocytes, especially B-lymphocytes. Seifert et al. (Seifert et al.,1980; Satko et al., 2000; Tarsitano et al., 2014) observed a variable quantitative proportion between stromal and epithelial component. They recognized four subtypes: classic Warthin’s tumour (subtype 1); Stroma poor (subtype 2); Stroma rich (subtype 3); and squamous metaplasia (subtype 4).

Despite the volume of studies written after the initial report by Hildebrand (1895) on WT, its pathogenesis continues to be an unresolved and controversial question. The favourite theory is that it arises from proliferative salivary gland ductal cells, which were entrapped in parotid lymph nodes (Teymoortash and Werner, 2005). The ductal metaplasia, which is another unique feature of this pathologic lesion, would be induced by some aetiological factors but the tumorgenesis mechanisms are still unknown.

Carcinogens in tobacco smoke seem to be an important risk factor for the onset of Warthin’s tumour. Kotwall stated that the risk of smokers developing Warthin’s tumour is eight times higher than that of non-smokers (Kotwall, 1992). A strong association with smoking has been reported for both synchronous and metachronous bilateral lesions: smoking would act by the direct action of carcinogenic substances that are mixed in the saliva passing in a retrograde fashion into the salivary duct and leading to ductal metaplasia (Peter Klussmann et al., 2006;Giannone et al., 2008; Jia et al., 2012; Deveer et al., 2013). Our series confirms the increased risk. From 2001 to 2011, 86 patients (74.8%) with Warthin’s tumour were smokers and 15 of the patients (13.04%) requiring reoperation for multiple bilateral lesion were heavy smokers. The close correlation between this neoplasm and smoking could explain the progressive increase in its incidence in females, indisputably linked to the increase in modern society of women smokers.

Batori et al. (2002) noticed that ionizing radiation represents a decisive factor in the appearance of this tumour. This theory is confirmed by the high incidence of this tumour among the Japanese people who survived the atomic bomb explosions and among subjects irradiated at young age for treatment of ringworm.

Teymoortash et al. (2001) performed immunohistochemical analysis on tissue samples of cystadenolymphoma, pleomorphic adenoma and normal samples of the parotid gland, searching for oestrogen and progesterone receptors. Positivity for progesterone receptors was found in six out of nine samples tested. The presence of progesterone receptors in the salivary duct system of the normal parotid gland is expected to influence the regulation of water and electrolyte transport. The detection of sex hormone receptors in cystadenolymphoma might give evidence of a hormone dependence of this tumour that could explain the higher proportion of men affected by the disease.

The role of virus infection as a risk factor for Warthin’s tumour development was studied in detail by many of the authors. The presence of RNA or DNA viral genome in saliva, suggests that non-sexual transmission may be associated with latent infection of the salivary gland.

Dalpa et al. (2008) investigated the presence of human herpes virus 8 (HHV-8) in a series of 43 Warthin’s tumours of the salivary gland. HHV-8 DNA was detected in 19 out of 43 (44%) salivary gland tumour samples, suggesting a significant role of the virus in the aetiopathogenesis of the disease. Teymoortash et al. (2013) investigated 40 Warthin’s specimens by PCR followed by in situ hybridization but no relationship between human papilloma virus and Warthin’s tumour was found. Laane et al. (2002) found that none of the 13 Warthin’s specimens tested for the presence of
Epstein–Barr virus and cytomegalovirus by PCR-based assay were positive. All these authors have shown varying strengths of association between several factors and Warthin’s tumour, but what is not yet clear is the pathogenic mechanism underlying its origin. The lymphoid stroma could be the key to answering this question. The reactive nature of lymphoid stroma in WT and its possible activation and modulation by epithelial cells, have suggested the involvement of autoimmune reactions in the mechanisms responsible for tumour growth.

The association between WT and autoimmune disease was first hypothesized by Allegra in 1971 (1971). On the basis of morphological analogies between the histological features of WT and those observed in several organ-specific immune disorders, particularly in Hashimoto’s thyroiditis and autoimmune disease involving salivary and lacrimal glands (that is, Sjogren syndrome), Allegra postulated the involvement of cell-mediated immune mechanisms of the delayed hypersensitivity type in its pathogenesis.

In 1984 Nikai and Schroeder, using stereologic point-counting methods at the electron microscopic level, analysed the composition of lymphoid stroma in two specimens. They found that areas corresponding to the mantle zone of lymphoid follicles contain 83.6% small, and 15.8% medium/large lymphocytes. Authors suggested the present data seems to be in accordance with the speculation that the lymphoid stroma of adenolymphoma represents an immune reaction.

In 1990, Ogawa et al. used immunohistochemical methods to demonstrate the expression of MHC class II antigens on the epithelial component of WT, suggesting that these cells possess the potential to act as antigen-presenting cells with the capability of activating lymphoid stroma in WT (Ogawa et al., 1990). Moreover, Gallo and Bocciolini have tried to clarify the possible role of immune mechanisms in the pathogenesis of WT, searching for a possible association with autoimmune pathologies (Gallo and Bocciolini, 1997). They retrospectively investigated clinical records of 140 patients affected by Warthin’s tumour, compared with those of 380 patients affected by pleomorphic adenoma, and found a higher incidence of autoimmune disorders, particularly organ-specific disease (i.e. insulin-dependent diabetes mellitus, Hashimoto’s thyroiditis, autoimmune hyperthyroidism and hypothyroidism) in Warthin’s tumour patients than in pleomorphic adenoma patients (23% vs 3%; relative risk: 8.69; p < 0.0001).

Recently, in 2013, Aга et al., on the basis of the same aetiopathogenic hypothesis, indicated a possible involvement of Warthin’s tumour with immunoglobulin G4-related diseases (IgG4-RDs) (Aга et al., 2013). IgG4-RDs comprises a recently recognized group of diseases (autoimmune pancreatitis, sclerosing dacyroadenitis and cholangitis, salalenditis, lymphadenopathy, retroperitoneal fibrosis, tubulointerstitial nephritis, and abdominal aortic aneurysms) characterized by elevated serum IgG4 levels and prominent lymphoplasmacytic infiltration by IgG4-positive cells into multiple organs. These data could be further evidence suggesting that an immune reaction with an unknown inflammatory background may be involved in the aetiopathogenesis of Warthin’s tumour.

5. Conclusions

Analysis of our results and the review of the literature support the hypothesis that this tumour is the result of an autoimmune reaction. Histopathological similarities and close clinical correlation with other organ-specific autoimmune diseases are the strongest evidence in support of this hypothesis. Lymphatic-rich stroma appears to play a key role in the genesis of WT. The tumour seems to originate from interactions between the germinal centres in the lymphoid stroma and the epithelial component of the salivary ducts. There is scientific evidence demonstrating that these cells, following chemical insult from tobacco and viral (EBV) insults, act as antigen-presenting cells expressing MHC class II antigens on surfaces. In this way these cells would act as activators and modulators of the autoimmune response in the germinal centres of the lymphatic-rich stroma.

Further studies and larger series are required to confirm this hypothesis and to investigate the role of the other aetiologic factors in the development or progression of the lesion.

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