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Solid Tumour Section

Mini Review

Head and neck: Salivary gland: Warthin's Tumors

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Identity

Note

Warthin's tumor is the second most common benign salivary gland tumor, which is located almost exclusively in the parotid gland. Warthin's tumor accounts for about 15% of all epithelial tumors of the parotid gland.

The initial description of the tumor goes back to Hildebrand in 1895, who considered this disease a variant of congenital epithelial cyst of the neck. In 1910, Albrecht and Arzt reported two tumors of the upper neck region which they interpreted as "confused

and heterotopic salivary gland remnants entrapped in the parotideal lymph nodes. According to this theory, Warthin's tumors have their origin in these epithelial inclusions. This hypothesis is further supported by the occurrence of tuberculosis, metastases and malignant lymphomas in the lymphoid stroma of those tumors. The extraparotid location and multicentric nature of these tumors can be explained by the last-mentioned hypothesis.

Other studies discussed the importance of immunological reactions during the formation of Warthin's tumor. A number of immunohistochemical findings indicate that there is an immunological interaction between epithelium and lymphoid stroma. These results support the assumption that oncocytic cells represent the true tumor component and cause reactive hyperplasia of the lymphoid stroma. In this context, further similarities between the lymphoid components of the tumor and the lymphoid tissue of the intestinal mucosa were found.

The details of the pathogenesis of Warthin's tumor are still unclear. However, because of the arguments against a true neoplastic origin of this tumor, the author favour a hypothesis combining immunological interactions between tumor cells and lymphocytic infiltrations with heterotopia.

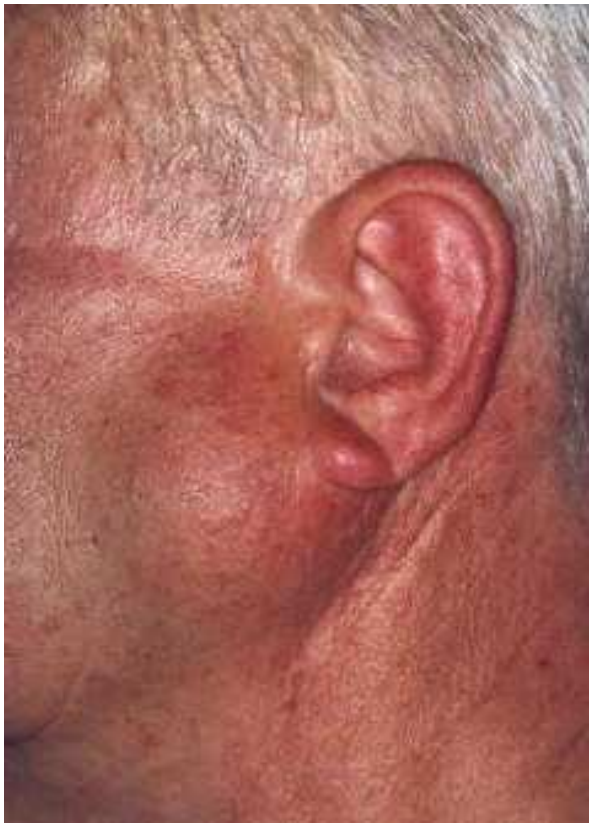
In the WHO classification of salivary gland tumors, certain diseases of the salivary glands are considered tumor-like lesions. Warthin's tumor may therefore also be classified in the group of tumor-like lesions, since both the epithelial and lymphoid tumor components are polyclonal in origin. The almost total lack of recurrence and malignant transformation of this tumor, similar to the situation in congenital lateral cervical cysts, further supports this view. Multicentricity at first excision and growth from a new focus seem to be responsible for the cases of recurrence reported in the literature. Malignant transformation of this tumor, if it ever occurs, is extremely rare. Most cases of reported malignancy can be attributed to a second tumor in association with Warthin's tumor.

Etiology

Several studies showed that a significant number of patients suffering from Warthin's tumor are smokers, in contrast to patients with other salivary gland tumors. The great majority of patients with Warthin's tumor had a history of over 20 years of smoking. The odds ratio for the incidence of Warthin's tumor among current smokers compared with never smokers was 8.3. Compared with never smokers, clearly higher odds of Warthin's tumor was observed in heavy smokers (more than 30 pack-years) (odds ratio=24.1) than patients who smoked less than 30 pack-years (odds ratio=4.9). Smoking was discussed as an important etiological factor.

Warthin's tumor consists of oncocytic cells containing numerous mitochondria frequently showing structural abnormalities and reduced metabolic function. Smoking can lead to damage to mitochondrial DNA due to the development of numerous reactive oxygen species. In this context, a high rate of deleted mitochondrial DNA has been detected in the oncocytic cells of Warthin's tumor.

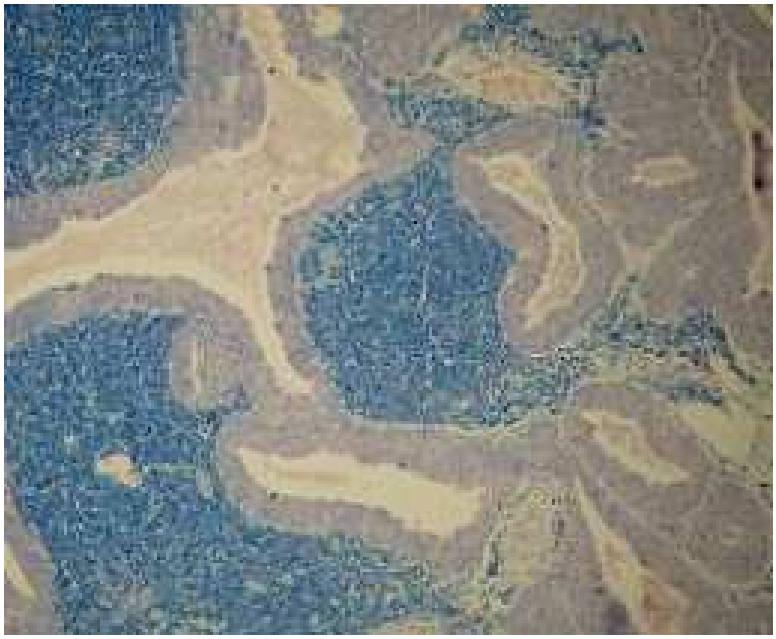
The role of hormones in the etiology of this disease has also been discussed. In some malignant salivary gland diseases and even in Warthin's tumor progesterone receptors have been found. A correlation with sex hormones could possibly play an important role in the development of those tumors and provide an explanation for the dominance of the male gender. However, it must be considered that more males than females used to smoke so that the role of the individual factors remains unclear and the intrinsic factor stimulating the development of Warthin's tumor is still unknown.



A sixty years old man with Warthin's tumor of the left parotid gland.

Pathology

These tumors are well encapsulated lesions with cystic and solid areas. These tumors consist of an oncocytic epithelial cell component arranged in double layers, which develops cysts and papillary



Warthin's tumor. Two histologic components are required for the diagnosis: the eosinophilic oncocytes and a lymphoid element.

projections, and a variable amount of lymphoid tissue often with germinal centers. The immunoprofile of the lymphocyte subsets is similar to that in normal or reactive lymph nodes. A few Warthin's tumors (about 8%) show areas of squamous cell metaplasia and regressive changes.

Treatment

On the basis of the clinical characteristics, a limited partial parotidectomy is recommended as an effective treatment of Warthin's tumor of the parotid gland.

Cytogenetics

Note

Few Studies have shown clonal genetic abnormalities at the cytogenetic level. However, other later studies showed a polyclonal pattern in Warthin's tumor. Other data demonstrated that Warthin's tumor do not have evidence of DNA mismatch repair defects at the genomic or protein expression level. These results argue against a general neoplastic origin.

The cytogenetic data available on this tumor are rather scare. However, analysis of cytogenetic findings revealed, beside normal karyotypes, also structural alterations and numerical deviations in some cases. t(11;19)(q21;p13) translocation with expression of chimeric genes CRTC1 - MAML2 is a very rare event in Warthin's tumor. Identification of cytogenetic subgroups in Warthin's tumor may suggest that it might be a pathogenetically heterogeneous group of lesions. When the fusion gene is present in this tumor type, it seems to be restricted in special cases with indeterminate morphology, especially involving necrosis and subsequent metaplasia.

Deletions of mitochondrial DNA is significantly higher in oncocytic tumor cells than parotid epithelia cells. In this context damage of mitochondrial DNA as a result of an increase in oxidative damage of cigarette smoke could be discussed.

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