

Malignant transformation of Warthin's tumor into squamous cell carcinoma: A case report

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Abstract. Malignant transformation of Warthin's tumor into squamous cell carcinoma is rare. The present study reported on a case of a 67-year-old male patient diagnosed with this condition. Microscopically, the tumor was mainly composed of squamous cell carcinoma and lymphoid stroma. Furthermore, the squamous cell carcinoma cells were arranged in a solid flake-like, papillary and cystic shape. Local bleeding was observed in the mass and a large number of lymphoid stroma-associated centers were observed between the cancer cells. The expression of cytokeratin (CK)5/6, P40, CK7, CK18, CK8 and MutS protein homolog 2 was detected by immunohistochemistry, in addition to Epstein-Barr encoding region *in situ* hybridization (-), Ki-67 (epithelial 25% +) and p53 (wild-type). The diagnosis of malignant transformation of Warthin's tumor into squamous cell carcinoma depends on the histopathology. The microscopic diagnosis is based on the dynamic process of scaling, atypical hyperplasia and cancerization of the eosinophilic columnar epithelium. Of note, it is also necessary to differentiate it from cervical malignant tumors such as lymphoepithelial carcinoma. The main clinical treatment is surgical resection with negative margins.

Introduction

Warthin's tumor is a type of benign tumor that develops with a membrane, which is frequently composed of cystic adenoid and papillary structures with lymphoid stroma (1). Malignant transformation may occur occasionally and the epithelial components may transform into squamous cell carcinoma, adenocarcinoma or mucoepidermoid carcinoma (2,3), of which transformation into squamous cell carcinoma is rarest (4,5).

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The main morphological features of the malignant transformation of Warthin's tumor into squamous cell carcinoma are a scaly eosinophilic columnar epithelium, atypical hyperplasia and cancerization. Immunohistochemistry frequently indicates cytokeratin (CK)5/6, P40, CK7, CK18 and CK8 positivity (5). The present study reports on a case of malignant transformation of Warthin's tumor to squamous cell carcinoma and in addition, the relevant literature was reviewed to explore the clinicopathological features, modes of diagnosis (and differential diagnoses), biological behavior and prognosis of this type of tumor.

Case report

Case presentation. A 67-year-old male patient was admitted to Xiaoshan Affiliated Hospital of Wenzhou Medical University (Hangzhou, China) in December 2021 due to a parotid gland mass that appeared 15 days previously. The left and right sides of the patient's face were asymmetrical and there was a lump below the right ear, with the absence of pain and numbness. On physical examination, a lump in the right parotid gland area with a clear boundary, medium hardness, slight mobility, no tenderness and no deviation of the mouth and other facial nerve injuries were noted. There was no redness or swelling at the parotid duct orifice and a clear fluid oozed out upon squeezing. B-ultrasound of the parotid gland indicated a low-echo light mass with a size of ~4.4x2.2 cm² in the right parotid gland, with a clear boundary and irregular shape; the internal echo was grid-shaped. Cystic dark areas and blood flow signals were observed in the light mass. Initially, these findings were assumed to resemble a Warthin's tumor. After two days, the mass of the right parotid gland and the superficial and deep lobes of the right parotid gland were excised under general anesthesia. During the operation, it was observed that the tumor was wrapped in the parotid gland tissue and the mass was removed together with the surrounding parotid gland tissue. The patient did not receive any postoperative treatment. At the last follow-up in February 2022, the patient was in a good postoperative condition, with good wound healing and no postoperative complications.

Pathological findings

Macro-examination. A piece of grayish-yellow parotid gland tissue, measuring 5x3x3.5 cm; a grayish-white multi-nodular

mass with a size of 4.8x2.5x3.0 cm was observed on the cut surface and the boundary with the surrounding parotid gland tissue was not clear. There was a local capsule and the mass was solid and hard, exhibiting local bleeding (Fig. 1). The tissue was fixed with 4% neutral formalin and embedded in paraffin, and 4- μ m serial sections were prepared that were subjected to H&E staining and envision immunohistochemical staining.

Microscopic observation. Histological analysis indicated that the tumor was mainly composed of squamous cell carcinoma and lymphoid stroma. The squamous cell carcinoma cells were arranged in a solid flake-like, papillary and cystic shape. The squamous cell carcinoma cells were clearly deemed to be heteromorphic and the mitotic images were easy to observe. The focal tumor cells were transparent and vacuolar. A large number of lymphoid stroma-associated centers were observed between the cancer cells. Germinal centers were also present and the remnants of benign Warthin's tumors were observed in certain areas. It was also noted that the eosinophilic columnar epithelium gradually underwent a dynamic process of scaling, atypical hyperplasia and carcinogenesis (Fig. 2). Immunohistochemical staining and specific staining provided the following results: CK5/6 (epithelial +), Ki-67 (epithelial 25% +), p53 (wild-type), P40 (epithelial +), CK7 (epithelial +), CK18 (epithelial +), CK8 (epithelial +), Epstein-Barr encoding region (EBER) *in situ* hybridization (-), MutS protein homolog 2 (MSH2) (+) and Alcian blue/periodic acid-Schiff staining (focal +) (Figs. 3-5).

Pathological diagnosis. The diagnosis was poorly differentiated squamous cell carcinoma (malignant transformation from Warthin's tumor).

Discussion

Warthin's tumor, also known as 'adenolymphoma' or 'papillary cystadenoma lymphomatosum', is the second most common type of salivary gland tumor. It frequently occurs in middle-aged and elderly individuals (age, 40-70 years) and the condition is also more prevalent among males. Patients frequently present with painless tumors of the parotid gland, which may occur frequently or symmetrically on both sides. The average size of the tumor is ~2-4 cm. Approximately 8% of Warthin's tumors occur in the cervical lymph nodes outside the parotid gland (6). Warthin's tumor frequently presents with a characteristic image through imaging techniques that are used for diagnosis (7). When it becomes malignant, imaging still retains the characteristics of Warthin's tumor. Therefore, it may be easily distinguished from other malignant tumor types of the parotid gland. In the present case, initial B-ultrasound of the parotid gland also indicated Warthin's tumor and malignant transformation was detected only through subsequent pathological examination.

Warthin's tumor is generally a well-defined round or oval mass with a smooth surface and capsule. The slices are grayish-brown, cystic and lobulated, and are also characterized by a sulfur granule paste. Its nuclei are oval and deeply stained, close to the cavity surface, with inverted polarity and palisade arrangement. The outer layers of bilateral structures are small flat or cubic basal cells, which express immunohistochemical

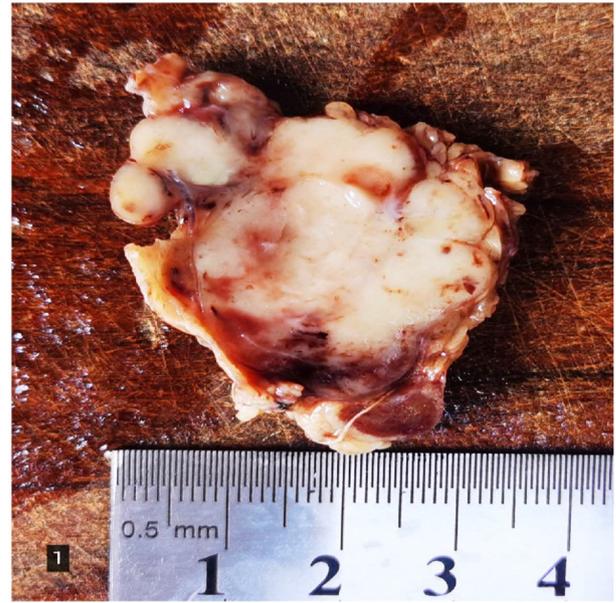


Figure 1. Gross image of parotid gland tumor (scale bar in cm).

markers such as CK5/6 and P40. The inner and outer cells are usually staggered and arranged in a pseudo-stratified structure (8). Mucinous metaplasia cells and sebaceous metaplasia cells may also be observed in the lesions (9). According to the number of tumor cells and lymphatic stroma, the tumors may be divided into four subtypes: Classic type, less stromal component type, more stromal component type and degenerative variant type.

Most scholars have reached a consensus on the pathogenesis of Warthin's tumor into squamous cell carcinoma and it is thought that squamous metaplasia occurs in the inner layer epithelium of eosinophilic hypercolumns. It occurs under the action of multiple factors such as ischemia, hyperplasia and cancerization, eventually developing into invasive squamous cell carcinoma (4,5,10). This dynamic process distinguishes this tumor from malignant tumors that metastasize from other sites (11,12). The lymphoid stroma frequently contains germinal centers, which may be due to the immune response of the immune system to tumor epithelial cells (13). Since the superficial lymph nodes of the parotid gland are located on the surface of the parotid gland, they drain the lymph nodes of the forehead, skull top, temporal area, auricle, external auditory canal, cheek and parotid gland; therefore, malignant tumors in the parotid gland should be excluded from the above-mentioned malignant tumors. In addition, malignant tumors with hematogenous metastasis from the lungs, breasts, kidneys, gastrointestinal tract and colon should also be excluded. In such circumstances, it is particularly important to combine information from the patient's clinical history.

Malignant transformation of Warthin's tumor to squamous cell carcinoma should be differentiated from the following diseases. First, lymphoepithelial carcinoma: It is a malignant tumor prone to occurring at the parotid gland, with a wide age distribution of 10-90 years and obvious ethnic and regional distribution characteristics. The occurrence of certain lymphoepithelial carcinomas is related to EB virus infection. Microscopically, the tumor usually has no capsule and invades

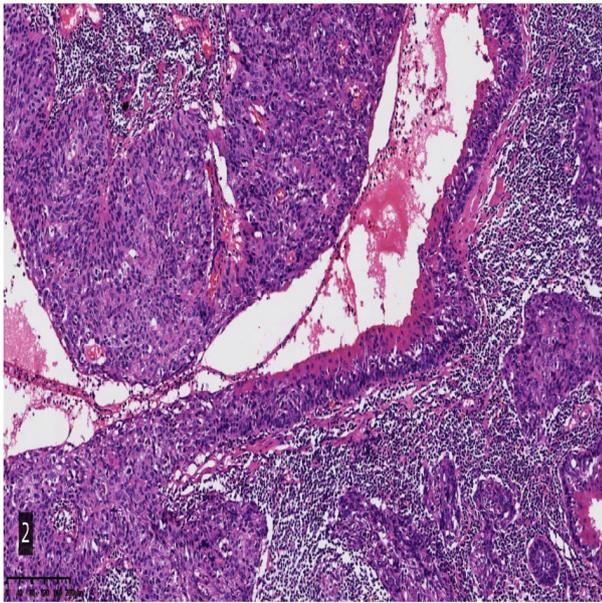


Figure 2. Morphological characteristics of tumor cells (magnification, x100; scale bar, 200 μm ; H&E staining).

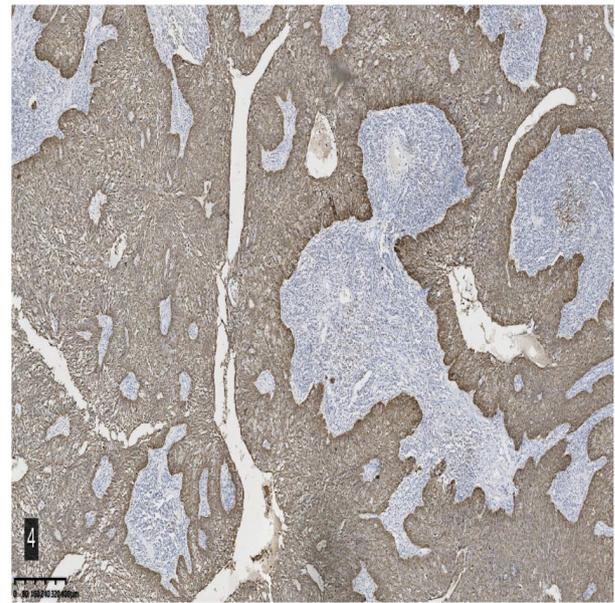


Figure 4. At low magnification, the staining for cytokeratin 5/6 in squamous cell carcinoma was brownish yellow (magnification, x50; scale bar, 400 μm).

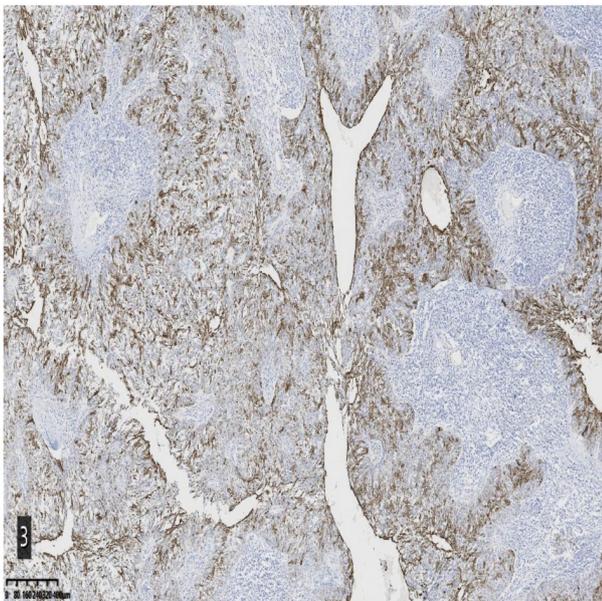


Figure 3. At low magnification, the staining for cytokeratin 7 in squamous cell carcinoma was brownish yellow (magnification, x50; scale bar, 400 μm).

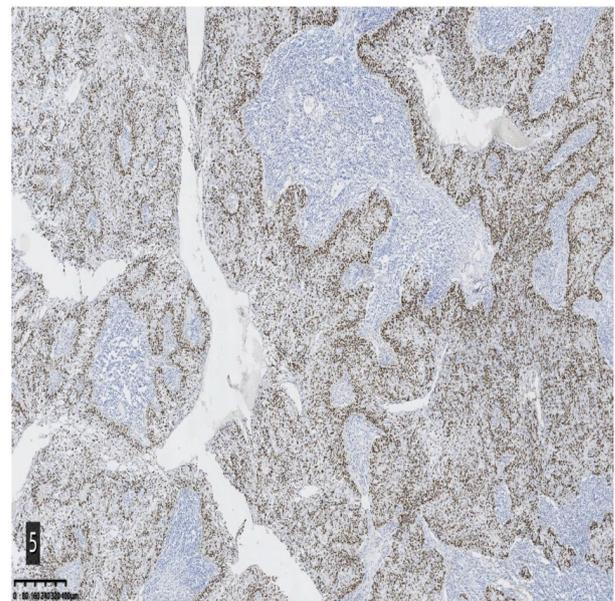


Figure 5. At low magnification, the staining for P40 in squamous cell carcinoma was brownish yellow (magnification, x50; scale bar, 400 μm).

the surrounding normal parotid gland tissue. Heterotypic neoplastic epithelial cells are arranged in flakes or nests or have a single scattered, infiltrating growth. The stroma is rich in lymphocytes and the formation of lymphoid follicles may be observed. Tumor cells are polygonal, with unclear cell borders; they are fused with each other; have a lightly stained cytoplasm, round vacuoles in the nucleus and obvious nucleoli; they also feature easy-to-observe pathological mitosis and necrosis. Tumor cells are frequently positive for expression of CKpan, CK5/6, P40 and Ki-67, and the positive index is usually high; EBER is positive in most tumors detected by *in situ* hybridization (14).

Second, the cyst wall epithelium in the parotid cleft cyst turning malignant into squamous cell carcinoma: The parotid cleft cyst is a developmental cyst, once known as the ‘lympho-epithelial cyst’, which primarily occurs before puberty. The mass is slow-growing, well-defined, mobile and cystic. The cyst contains an egg white-like liquid. The lining epithelium of the cyst wall contains stratified squamous epithelium without obvious keratosis, which may be mixed with stratified columnar epithelium and may be accompanied by incomplete keratosis. Furthermore, the epithelium is thin without the nail process. The fibrous capsule wall contains a large number of lymphoid tissues, which may form lymphoid follicles.

The stratified squamous epithelium of the capsule wall may produce atypical hyperplasia and cancerization under the stimulation of numerous factors. It differs from the malignant transformation of Warthin's tumor in that it does not have a double-layered cellular structure (15).

Third, sebaceous adenocarcinoma: It usually occurs in the elderly and is frequently located in areas rich in sebaceous glands, i.e., in the eyelids, ears, head and neck. Microscopically, it presents as irregular diffuse or solid nodular infiltrative growth and is composed of basal-like cells and sebaceous gland cells. It is frequently dominated by basal-like cells. Cells with less cytoplasm, obvious atypia and clear mitotic images may be observed without difficulty. Sebaceous gland cells are rich in cytoplasm, are bright or vacuolar and have common scaly and ductal structures; immunohistochemical characteristics are expression of CKpan and epithelial membrane antigen (16).

Fourth, benign lymphoepithelial lesion: It is an autoimmune disease that usually occurs in middle-aged and elderly females. The clinical features are unilateral or bilateral parotid or submandibular gland enlargement and diffusely enlarged salivary glands with unclear borders, and certain tumors may form tumor-like nodules. Patients occasionally experience symptoms of pain and dry mouth. The disease is closely related to Sjogren's syndrome. Clinically, almost all patients with Sjogren's syndrome suffer from lymphoepithelial sialadenitis; however, only 50% of patients with lymphoepithelial sialadenitis have manifestations of Sjogren's syndrome. The typical pathological changes are benign lymphoepithelial lesions formed by dense multifocal, progressive lymphocyte infiltration, acinar atrophy and residual ductal hyperplasia. Lymphoid follicles containing germinal centers may appear in dense lymphocyte infiltration areas (17).

The treatment of malignant transformation of Warthin's tumor to squamous cell carcinoma is surgical resection with negative margins. Postoperative radiotherapy or chemotherapy usually have no effect on prognosis (5). Malignant transformation of Warthin's tumor into squamous cell carcinoma may lead to local lymph node metastasis, but distant metastasis is rare. Small size, negative margins, no distant metastasis, low histological grade and early clinical stage are indicators of good prognosis. Patients with positive tumor margin and lymph node metastasis typically have poor prognosis (9). The patient of the present study was followed up for 6 months after complete resection of the mass and there was no recurrence or metastasis.

In summary, the present study reported a case of malignant transformation of Warthin's tumor into squamous cell carcinoma. Squamous cell carcinoma is the rarest type. The present case not only showcased that the squamous cell carcinoma cells are arranged in a solid flake-like, papillary and cystic shape but also emphasized the expression of CK5/6, P40, CK7, CK18, CK8 and MSH2 in the diagnosis of malignant transformation of Warthin's tumor into squamous cell carcinoma. The present study also explored the clinicopathological features, diagnosis and differential diagnosis, biological behavior and prognosis of this tumor type.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

LS and JY drafted the manuscript and conceived the study. XC was in charge of the case data collection. YJ revised the manuscript and interpreted the data. LS and YJ confirm the authenticity of all the raw data. All authors agreed on the journal to which the article has been submitted and agreed to be accountable for all aspects of the work. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient provided written informed consent for the case study to be published.

Competing interests

The authors declare that they have no competing interests.

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