

CASE REPORT

MALIGNANT TRANSFORMATION OF THE EPITHELIAL COMPONENT OF A WARTHIN TUMOUR INTO ADENOCARCINOMAWENBIN GOU^{1,2}, BEIWEN SONG³, KEJIA TONG⁴, YONG QIANG YANG³¹Department of Pathology, The First Affiliated Hospital of Hainan Medical University, Haikou City, Hainan Province, China²Department of Pathology, People's Hospital of Wanning, Wanning, Hainan Province, China³Department of Endoscopy, People's Hospital of Wanning, Wanning, Hainan Province, China⁴Department of Stomatology, Hainan Medical College, Grade, China

To study the clinicopathological features of malignant transformation of the epithelial component of a Warthin tumour into adenocarcinoma. The histological and immunophenotypic features of the malignant transformation of the epithelial component of a Warthin tumour into adenocarcinoma were studied, and the literature was reviewed. The patient had a history of surgery for a Warthin tumour 3 years previously, and the typical histological manifestations of a Warthin tumour were observed under the microscope following biopsy. Scattered tumour tissue infiltration was observed in the lymphatic interstitium, and a transitional area of benign and malignant epithelial cells was observed locally. The tumour cells were solid, nested, and glandular and grew infiltratively in the salivary gland tissue. There was diffuse positive staining for CK7 and CK19 in the cytoplasm of tumour cells. CK5/6 was positively expressed in the cytoplasm of basal cells in the tumour tissue, and P63 was positively expressed in the basal cell nuclei. Ki-67 positivity reached approximately 10% in tumour tissues. The *MAML2* fracture probe result was negative. The final diagnosis was malignant transformation of a Warthin tumour, with malignant transformation of epithelial components into adenocarcinoma. Malignant transformation of a Warthin tumour is rare, and the intraoperative histopathological diagnosis based on frozen sectioning should be made with caution. The key to diagnosis is to determine whether there is migration between benign and malignant epithelium.

Key words: Warthin tumour, malignant transformation, adenocarcinoma.

Introduction

Warthin tumours occur almost exclusively in the parotid gland, mainly in the superficial lobe, with 10% affecting the deep lobe of the parotid gland [1]. Most of the tumours present as slow growing painless nodules, which are hard or fluctuating when palpated and are multicentric or bilateral [2]. It is generally considered a benign tumour with possible malignant changes in both epithelial and lymphatic

components, but its progression into cancer is rare (0.3%) [3, 4].

There are few literature reports on the malignant transformation of the epithelial component of a Warthin tumour into adenocarcinoma. This article reports a case of malignant transformation of the left parotid epithelial component into adenocarcinoma in our department, as follows. In addition, a retrospective review of 40 relevant literature reports on malignant transformation of Warthin tumours was conducted,

including 7 cases of malignant transformation into adenocarcinoma, to deepen the understanding of malignant transformation of Warthin tumours and improve the accuracy of diagnosis.

Case report

A 60-year-old male patient was admitted to our hospital due to recurrence of a left parotid Warthin tumour 3 years after surgery. Physical examination revealed an oval mass, $6 \times 5 \times 4$ cm in size, was found in the left superficial lobe of the parotid gland, with a clear boundary and poor activity. Recently, the mass had gradually increased, occasionally leading to a tingling sensation and headache, as well as nasal congestion, but no hearing impairment. During the operation, it could be observed that the parotid gland mass was closely connected with the anterior and inferior walls of the external auditory canal as well as the trunk of the temporofacial nerve. The tumour was completely resected and sent for intraoperative frozen sectioning and pathohistological examination, and the results showed local malignant transformation of the Warthin tumour. Consequently, a region II lymph node dissection was performed.

Gross examination revealed no plastic tissue, $7.2 \times 6.3 \times 5$ cm in size. The section showed a mass approximately $5 \times 4 \times 3.5$ cm in size, greyish-red fuscine, mainly solid areas, focal microcapsules, and unclear boundaries with surrounding tissue. Microscopic examination showed a typical Warthin tumour-like tissue visible in the cystic area, with transitional areas of benign and malignant tumour cells locally visible. Tumour cells were seen infiltrating the surrounding lymphoid tissue (Figures 1A–C). In the solid area, the tumour cells were nested and glandular, infiltrating the salivary gland and proliferative fibrous connective tissue. Red blood cells and neutrophils were seen in the central duct. The tumour cells had large nuclei and eosinophilic cytoplasm. Red blood cells and inflammatory necrosis was visible in the adenoid cavity (Figure 1D), and a large number of single mucoid cells were scattered among the tumour cells (Figures 1D–F). Periodic acid-Schiff (PAS) staining revealed the presence of mucous cells in the cancer cell nest (Figure 1G).

The tumour tissue samples were stained by enhance labelled polymer system (ELPS) immunohistochemistry. Staining for CK7 and CK19 was diffusely positive in the cytoplasm of tumour cells (Figures 2A, B). CK5/6 was positively expressed in the cytoplasm of basal cells in the tumour tissue (Figure 2C), and P63 was positively expressed in the basal cell nuclei (Figure 2D). Ki-67 was expressed in about 10% of tumour cells (Figure 2E).

FISH detection was performed on $5\text{-}\mu\text{m}$ -thick paraffin sections using a Guangzhou Ambipin *MAML2*

fracture probe. The *MAML2* fracture probe detection was performed using 2 different tumour tissue wax blocks, but both Fish tests were negative (Figure 2F).

During microscopic examination, scattered individual mucoid cells could be seen in the tumour tissue, and the cytoplasm of the tumour cells was eosinophilic. Therefore, it was necessary to rule out the possibility of a Warthin tumour transforming into eosinophilic mucoepidermoid carcinoma. However, P63 was positively expressed in the basal cell nuclei of tumour tissue, and the *MAML2* fracture probe test was negative.

Therefore, the final diagnosis was malignant transformation of parotid Warthin tumour – epithelial malignant transformation differentiated into adenocarcinoma.

According to 40 relevant literature reports, 55 cases of malignant transformation of Warthin tumours into other tumours were reported. Among them, there were 23 cases of mucoepidermoid carcinoma, 14 cases of lymphoma (5 cases of Hodgkin's lymphoma, 4 cases of diffuse large B-cell lymphoma, 2 cases of unclassified non-Hodgkin's lymphoma, 1 case of T-cell lymphoma, 1 case of B-cell lymphoma, and 1 case of follicular lymphoma), 7 cases of squamous cell carcinoma, 4 cases of poorly differentiated carcinoma, and 7 cases of adenocarcinoma. Among all cases of malignant tumours, the age of onset was 23–102 years, with a male:female ratio of 2.4 : 1 and left:right location ratio of 1 : 1.4. Most patients sought medical attention due to a painless lump in the neck, with a diameter ranging 1.3–13 cm. Among them, 9 patients had a history of progressive enlargement of the lump within a few months, which was mostly cystic and solid. The clinicopathological characteristics of the 7 reported cases of malignant transformation of Warthin tumours into adenocarcinoma are listed in Table 1.

Discussion

Warthin tumours are benign lymphoepithelial neoplasms, but their lymphatic and epithelial components can undergo malignant transformation. The transformation of lymphoid components into malignant lymphoma seems more common in Warthin tumours, whereby epithelial components often transform into squamous cell carcinoma and mucoepidermoid carcinoma, while adenocarcinoma is extremely rare [5]. Epithelial-derived malignancies within Warthin tumours can have three different histological sources:

- primary cancer inside the Warthin tumour,
- cancer that has metastasised inside the Warthin tumour,
- cancer co-occurring with a Warthin tumour.

Therefore, the differential diagnosis of malignant transformation of a Warthin tumour should take into account the possibility of extrinsic metastatic tu-

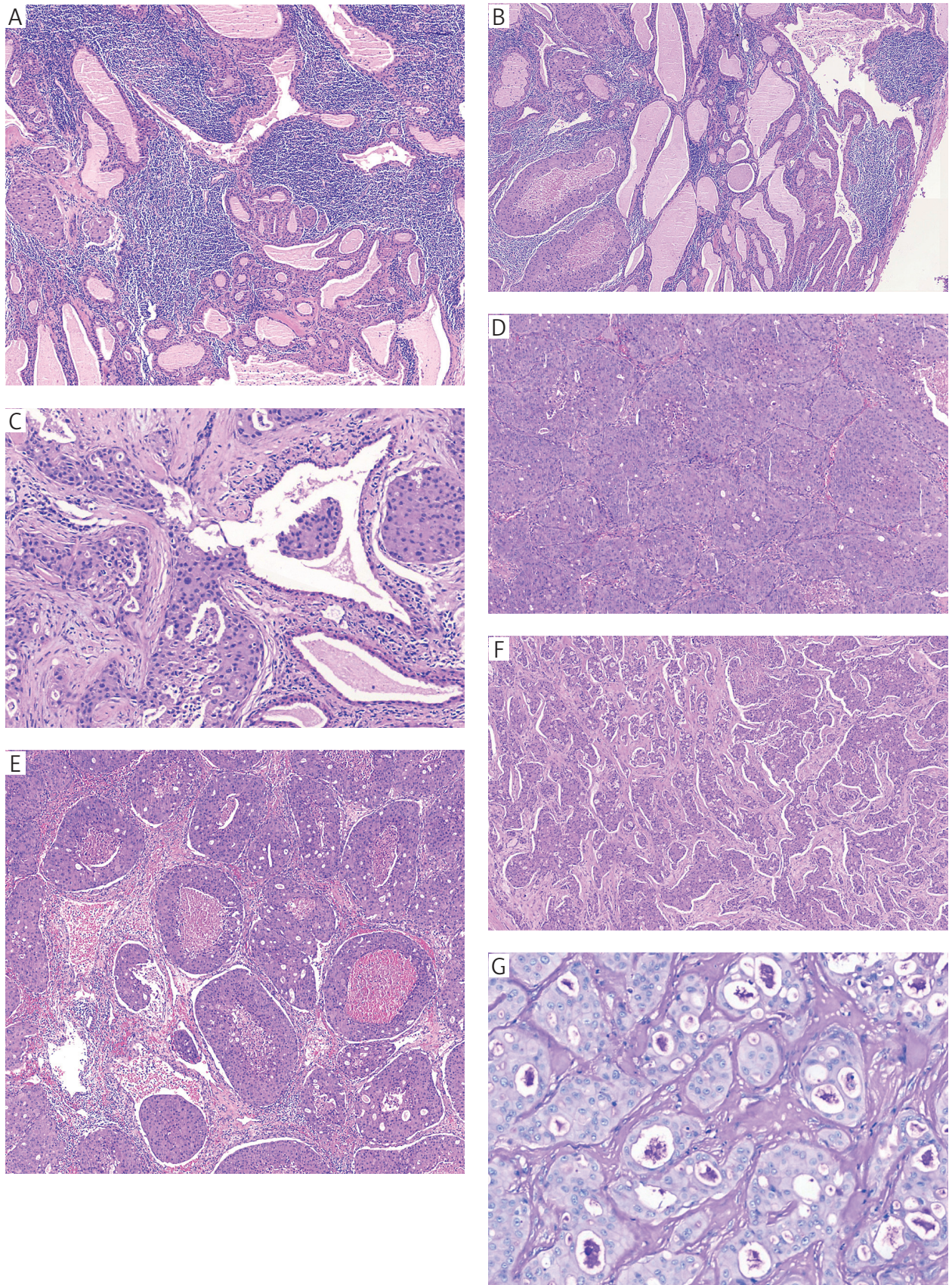


Fig. 1. Histological presentation of malignant transformation of epithelial components of Warthin tumour into adenocarcinoma (magnification 200×). **A, B, C)** Warthin tumour-like area and transitional area with benign and malignant tumour cells. **D)** Solid areas within tumour tissue. **F)** Solid nest-like agglomerations of tumour cells infiltrating and growing in fibrous connective tissue. **G)** Periodic acid-Schiff displaying mucinous cells within the tumour cell nests

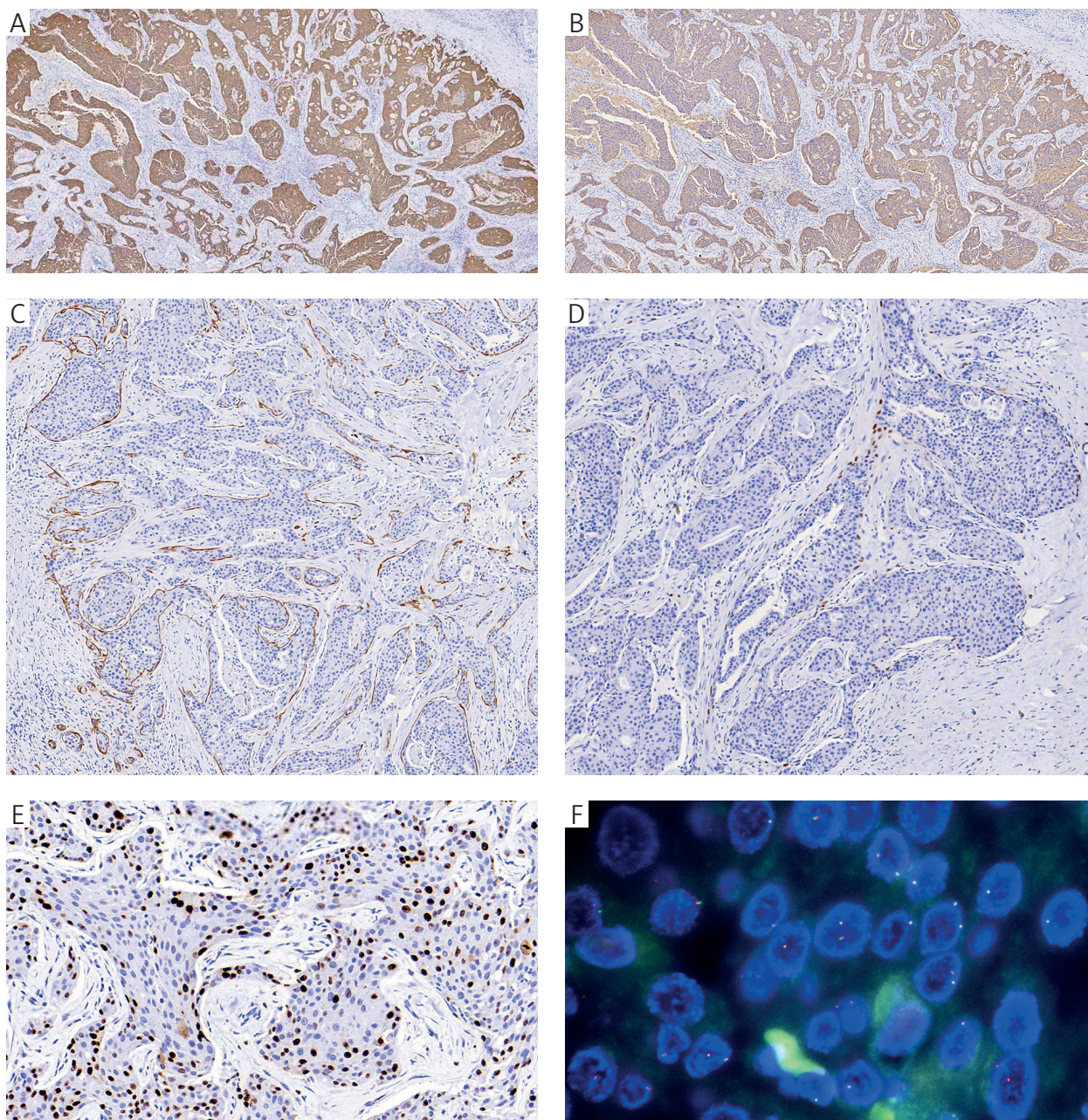


Fig. 2. Immunohistochemistry and FISH staining of tumour tissue. A) Diffuse positive expression of CK7 in the cytoplasm of tumour cells. B) Diffuse positive expression of CK19 in the cytoplasm of tumour cells. C) CK5/6 was positively expressed in the cytoplasm of basal cells of tumour tissue. D) P63 was positively expressed in the basal cell nuclei of tumour tissue. E) Ki-67 was positively expressed in the nuclei of tumour tissue. F) Negative *MAML2* fracture probe test

mours. The most common primary sites of metastatic squamous cell carcinoma and melanoma are the head and neck. Other primary sites include lung cancer, breast cancer, kidney cancer, gastrointestinal cancer, and colon cancer.

Seifert [6] proposed 4 criteria for the diagnosis of malignant transformation of Warthin tumours:

- history of benign Warthin tumours,
- the presence of a transitional zone from benign epithelium to malignant epithelium,
- invasive growth in peripheral lymphoid tissue,
- metastatic cancer at other sites was excluded.

The patient in this case report had undergone resection of the left parotid gland mass at Hainan Provincial People's Hospital 3 years prior. The postoperative pathological diagnosis was Warthin tumour of the left parotid gland. In this biopsy, intraocular transition zones of benign and malignant epithelial cells were observed, and tumour cell infiltration was observed in the lymphoid stroma. There was no apparent history of malignant tumours in other parts of the patient's body at the time of the examination, indicating a primary intratumoural cancer in a Warthin tumour.

Table I. Clinical and pathological characteristics of seven cases of malignant transformation from Warthin tumour to adenocarcinoma

AUTHOR	AGE	SEX	LOCATION	COURSE OF DISEASE (MONTHS)	TUMOUR SIZE [CM]	FOLLOW-UP
Brown <i>et al.</i>	68	Female	Left submandibular region	24	1.8 × 2.2 × 1.5	No recurrence in 24 months
Lee <i>et al.</i>	24	Female	Left parotid gland	3	2 × 2	Unclear
Deodhar <i>et al.</i>	75	Male	Right neck	34	3 × 3 × 2	No recurrence in 16 months
Kim <i>et al.</i>	79	Male	Left infraauricular	10	3.8	Recurrence after 7 months of surgery
Sayar <i>et al.</i>	63	Male	Right infraauricular area	6, rapidly increasing by 2	2 × 1 × 1	No recurrence in 12 months
Tonder <i>et al.</i>	77	Male	Left neck	2	3 × 1.5	No recurrence in 15 months
Perrotti <i>et al.</i>	49	Unclear	Left neck	Unclear	Unclear	7 years without recurrence

Based on the histological characteristics of the tumour, the considerations for morphology were as follows:

- Warthin tumour malignant transformation – epithelial component malignant transformation into adenocarcinoma,
- Warthin tumour malignant transformation, epithelial component malignant transformation into eosinophilic mucoepidermoid carcinoma.

However, in eosinophilic mucoepidermoid carcinoma, P63 often exhibits diffuse strong positive expression in tumour tissue [7]. In this case, P63 was positively expressed in the nuclei of the basal cells of the tumour tissue, which was inconsistent with literature reports. Approximately 70–80% of mucoepidermoid cancers contain detectable *MAML2* gene fractures [8], while in this case, the *MAML2* fracture probe test was negative on 2 embedded blocks. Therefore, the possibility of the malignant transformation of a Warthin tumour into eosinophilic mucoepidermoid carcinoma was ruled out, and the final diagnosis was malignant transformation of a Warthin tumour, more specifically epithelial malignant transformation into adenocarcinoma.

The pathogenesis of the malignant transformation of Warthin tumours remains unclear. A study by Nagao *et al.* [9] suggested that the malignant transformation of Warthin tumours might be caused by the presence of a salivary duct in the parotid gland or paraparotid lymphoid tissue. Seifert *et al.* [10] showed that about 7.5% of the epithelial components of Warthin tumours could undergo squamous cell or mucous cell metaplasia. When these metaplastic changes occur in the normal parotid duct, they may be related to the occurrence of cancer [9]. In this case, scattered individual mucinous-like cells

were visible in the tumour tissue, and PAS staining showed the presence of mucinous cells in the tumour cell nests.

Conclusions

The treatment for malignant transformation of a Warthin tumour is generally accomplished by complete resection of the tumour, with or without radical neck lymph node dissection. Cases of regional lymph node metastasis and distant hematogenous metastasis to the lungs and liver have been reported in the literature [6, 11]. The patient in this case was followed up for 10 months after surgery and had no recurrence or metastasis at the time of writing.

Disclosures

1. Institutional review board statement: Not applicable.
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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