

Carcinoma ex pleomorphic adenoma: case report and options for systemic therapy

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ABSTRACT

The most common benign salivary tumour is a pleomorphic adenoma. Transformation to malignancy, carcinoma ex pleomorphic adenoma (CXPA), occurs in 6% of cases. Management focuses on surgical resection and radiotherapy; however, rare cases require systemic management. We present the case of a 60-year-old woman with a CXPA of the left parotid gland who required systemic therapy for locally recurrent disease. Treatment options were guided by the literature concerning malignant salivary gland tumour and by whole-genome and transcriptome sequencing of the tumour. The patient received multiple systemic agents during the course of her disease, with cyclophosphamide–doxorubicin–cisplatin providing the best control (partial response). Genome- and transcriptome-directed therapy, including sorafenib and vismodegib, were utilized with limited clinical benefit. Malignant transformation in CXPA is a complex process, and therapy directed at a single tumour pathway might not be sufficient to control disease.

Key Words Carcinoma ex pleomorphic adenoma, chemotherapy, cyclophosphamide, doxorubicin, cisplatin

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INTRODUCTION

Pleomorphic adenoma, also known as benign mixed tumour, is the most common benign salivary gland tumour. It has epithelial, myoepithelial, and mesenchymal components in varying quantities and histologies. It is found in the parotid gland approximately 80% of the time and occurs more commonly in women. Surgical resection is curative, but approximately 6% of these tumours transform into carcinoma ex pleomorphic adenoma (CXPA), also known as mixed malignant tumour¹.

Carcinoma ex pleomorphic adenoma can be classified as noninvasive, minimally invasive, or widely invasive². The first two types are generally treated with surgical resection and radiation, and carry a fair prognosis. However, widely invasive CXPA is extremely aggressive and has a high recurrence rate despite localized treatment. Given the rare incidence of CXPA, no standard systemic chemotherapy options have been established. The available literature consists mostly of case reports and limited phase II clinical trial data that deal mostly with malignant salivary tumours as a group. Only a few of the studies include CXPA patients, and as a group, they report widely varying response rates with the application of various chemotherapy combinations.

CASE DESCRIPTION

A 60-year-old Asian woman presented with a mass at the left angle of the jaw. She had been diagnosed as a child with pleomorphic adenoma and had undergone resection at 7 years of age and then again at 16 years of age. She had a 3rd recurrence and resection at the age of 30. Upon the 4th recurrence, she underwent total parotidectomy and primary repair of the facial nerve, followed by radiation delivered to the operative bed (60 Gy in 30 fractions over 6 weeks). Pathology for this resection specimen demonstrated features typical of a pleomorphic adenoma, with mixed epithelial and myoepithelial elements, together with chondromyxoid stroma [Figure 1(A)]. She had no evidence of recurrence for the next 12 years.

Computed tomography at the time of presentation showed a rounded peripherally enhancing 2.4 cm mass in the left parotid gland bed. Given the patient's history, the mass was felt to be a recurrent pleomorphic adenoma, although malignant transformation could not be ruled out. The feeling was that radiation would not provide further benefit, and after discussion with the patient, the decision was to monitor the lesion.

Eight months later, the woman developed significant pain, and repeat computed tomography imaging revealed

interval enlargement of the mass (now measuring 4.5 cm), with extension into the left internal jugular vein, causing occlusion from tumour thrombus, possibly secondary to malignant transformation of the known adenoma. Combined positron-emission tomography and computed tomography confirmed fluorodeoxyglucose avidity of the left parotid region mass, with central necrosis; no distant metastatic disease was revealed.

A core-needle biopsy showed a high-grade spindle-cell neoplasm with marked cytologic atypia and brisk mitotic activity [Figure 1(B)]. No residual evidence of pleomorphic adenoma was seen in the biopsy sample. Immunohistochemical analysis was negative for cytokeratins 5/6 and 14, myoepithelial markers p63 and muscle-specific actin, S100, HER2 (the human epidermal growth factor receptor), and estrogen receptor. Overall, the histologic features were supportive of malignant transformation of pleomorphic adenoma, most consistent with a diagnosis of CXPA, with the malignant component showing predominantly sarcomatoid features.

Literature review suggested a relatively high response rate of salivary tumours to the combination of cyclophosphamide, doxorubicin, and cisplatin. Our patient received 8 cycles, with an excellent clinical and radiologic response and minimal toxicity (Figure 2). After discontinuation of chemotherapy, her disease progressed after 3 months.

As part of an experimental protocol, a subsequent biopsy sample was analyzed by whole-genome sequencing and was compared with constitutive DNA from a blood sample to identify acquired somatic mutations in this woman's tumour³. Transcriptome data from the same biopsy sample was compared with the compendium of 19 normal libraries of various tissue types to find overexpressed and underexpressed genes. A *PLAG1-MEG3* fusion was found in the transcriptome, coupled with 2-copy gain and high expression of the *PLAG1* gene and its downstream target *IGF2*. Several other genes (*IGF1R*, *INSR*, *RET*, *NTRK1*, *FGF19*, *FGFR3*, *FGFR1*, *PGE*, *PDGFC*, and *PDGFRB*) were found to show high expression compared with the

compendium, potentially resulting in overexpression of both the MAPK and Akt/PI3K pathways. Multiple genes in the sonic hedgehog (SHH) pathway and its downstream target, the Wnt pathway, had gained extra copies in the tumour cell and were overexpressed compared with the normal compendium.

Based on potential targetable pathways identified through genome and transcriptome analysis, our patient was treated with a multi-targeted tyrosine kinase inhibitor, sorafenib. At the initial assessment, her disease appeared to have stabilized; however, she developed significant toxicity and discontinued the medication before radiographic response could be determined.

Whole-genome sequencing also identified upregulation of the SHH pathway, and using that rationale, a SHH pathway inhibitor, vismodegib, was identified as a possible targeted therapy. Treatment was started, but the patient's disease continued to progress. Subsequent treatments, including capecitabine and docetaxel, showed limited clinical benefit, and the patient died of locally progressive disease.

DISCUSSION

Carcinoma ex pleomorphic adenoma accounts for 11% of all salivary malignancies¹. Historical reports list 5-year survivals ranging from 30% to 70%⁴. The tumour often arises from the background of a recurrent pleomorphic adenoma and can be composed of various histologic subtypes, including high-grade salivary duct carcinoma, adenocarcinoma not otherwise specified, myoepithelial carcinoma, and sarcomatoid carcinoma, among others². Its pathogenesis is not fully understood, and the potential role of radiation therapy as a catalyst in causing secondary transformation of recurrent pleomorphic adenomas remains a source of controversy.

Data about the systemic management of CXPA is limited, because the primary management is surgical resection and radiotherapy. High expression of androgen

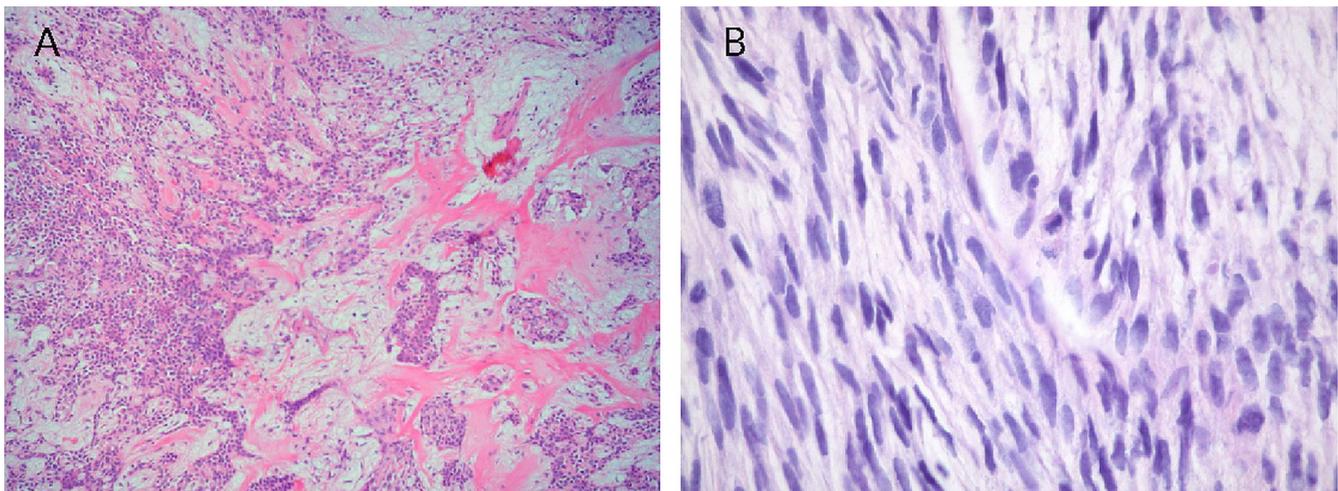


FIGURE 1 (A) Initial pathology, demonstrating a pleomorphic adenoma with mixed epithelial and myoepithelial elements, together with chondromyxoid stroma. (B) Biopsy taken at the time of malignant recurrence demonstrates a high-grade spindle-cell neoplasm, with marked cytologic atypia and brisk mitotic activity.

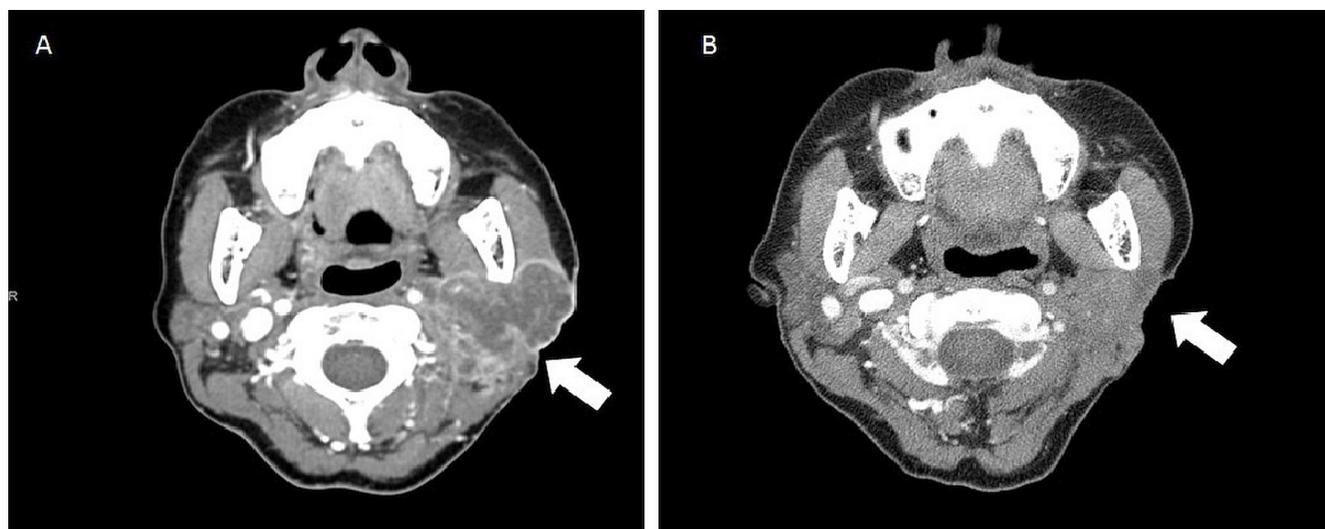


FIGURE 2 Axial computed tomography images obtained 6 months apart show the left parotid mass (arrow) (A) before and (B) after treatment with 6 cycles of cyclophosphamide–doxorubicin–cisplatin.

receptor has led to case reports describing responses to androgen deprivation therapy⁵. A potentially receptor-independent response to tamoxifen has also been demonstrated; however, more prospective data are needed to establish a role for hormonal therapy⁶. Given the overall limited treatment options, molecularly targeted therapies have also evoked interest. A case report using paclitaxel–trastuzumab in a patient with strong HER2 protein positivity and HER2 gene amplification described a complete response⁷. Similarly, Sharon *et al.*⁸ reported a long-term response with capecitabine–trastuzumab in a HER-positive patient. A third case report of CXPA reported progression on cisplatin–5-fluorouracil, stabilization with nedaplatin–docetaxel, and further stabilization on an experimental protocol with WT1 peptide vaccination⁹. That patient had WT1 expression in cancer tissue by immunohistochemistry. Systemic therapy in the foregoing cases relied on identification of predictive markers using protein expression and gene amplification.

In our patient, multi-agent chemotherapy with cyclophosphamide–doxorubicin–cisplatin resulted in an excellent response. The choice of therapy was based on several small phase II studies identifying that combination as active in the treatment of malignant salivary gland tumours, although with efficacy varying by histologic subtype^{10–12}. Newer combinations such as carboplatin–paclitaxel or cisplatin–gemcitabine have demonstrated moderate activity in small trials involving salivary gland tumours with a mix of histologies^{13,14}. Because of the absence of HER2 amplification, trastuzumab was not selected as therapy for our patient. Other single-agent therapies were selected based on limited data extrapolated from salivary tumour trials, but they were ineffective in controlling disease.

Studies have suggested that CXPA follows a multistep model of carcinogenesis, with progressive loss of heterozygosity at chromosomal arm 8q, and then arms 12q and 17p¹⁵. Alterations in *PLAG1* and *MYC*, coded on chromosome 8,

have been associated with CXPA^{16–18}. Potential drivers in 12q include *HMGA2* (formerly *HMGIC*) and *MDM2*^{18,19}. In salivary tumours, p53 mutations are commonly identified, and that identification is consistent in CXPA²⁰. Anomalies in cyclin-dependent kinases and inhibitors COX2 and FGF2 have also been identified in other studies^{21–23}. Although potential targets have been identified (*MYC*, *HMGA2*, *MDM2*, *COX2*, and *FGF2*) for which inhibitors are in development, none has been reported as attempted for patient management. Overexpression and amplification of HER2 remains the only target for which therapy has been applied in CXPA with efficacy^{24,25}.

Whole-genome and transcriptome sequencing was conducted to develop a better understanding of the biology of the tumour and to select therapeutic agents based on specific pathways. The systemic therapies selected based on the resulting data were sorafenib and vismodegib. Sorafenib is an agent that inhibits *KIT*, *VEGFR1–4*, *PDGFRB*, *RAF1*, *BRAF*, *RET*, *IGF1R*, and several other genes. Based on the molecular profile of our patient's disease that identified high expression of *IGF1R*, *INSR*, *RET*, *NTRK1*, *FGF19*, *FGFR3*, *FGFR1*, *PGF*, *PDGFC*, and *PDGFRB*, a multi-targeted tyrosine kinase inhibitor was a rational choice. Although her radiographic response to sorafenib was not evaluable because of cessation secondary to toxicity, stabilization was noted on clinical exam. Sequencing also showed that genes in the SHN and Wnt pathways had gained extra copies and were overexpressed compared with the normal compendium. Vismodegib was selected because it binds to and inhibits Smo to inhibit the SHN pathway, but the best response was progressive disease. The lack of efficacy of the foregoing agents speaks to the complexity of the disease and likely to its multiple drivers for malignancy.

Given the rare incidence and pathologic ambiguity of CXPA, no standard of care guides treatment. Extrapolation of data from salivary tumour clinical trials remains the basis for selection of systemic therapy.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare that we have none.

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