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# Adenoid cystic carcinoma of the labium oris with rare metastasis to the pleural cavity

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## SUMMARY

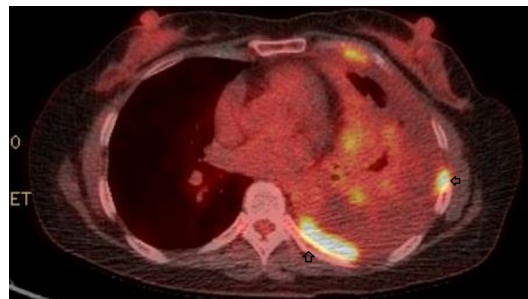
A 57-year-old Southeast Asian woman with a remote history of adenoid cystic carcinoma (ACC) of the right labium superius oris (upper lip) presented to the hospital with vague epigastric pain. On workup, she was found to have multiple pleural nodules. Histopathology confirmed the diagnosis of metastatic ACC. After 8 months of active surveillance, evidence of disease progression was found and the patient was started on pembrolizumab. Follow-up after starting pembrolizumab showed stable disease with no significant side effects.

## BACKGROUND

Adenoid cystic carcinoma (ACC) accounts for approximately 10%–15% of all salivary gland tumours and 1% of head and neck cancers.<sup>1</sup> ACC is generally characterised by its lengthy course, indolent behaviour, delayed and silent metastasis.<sup>1</sup> About 35%–50% of patients with this carcinoma develop distant metastases, usually to the lungs and less commonly to the liver and the bone.<sup>2</sup> ACC has a propensity for perineural invasion (PNI) and extension beyond surgical margins.<sup>2</sup> Pleural metastasis is extremely rare and has been reported only in a few case reports.<sup>3,4</sup> Despite being a slow-growing tumour, ACC is associated with a high risk of mortality and treatment is usually challenging.

## CASE PRESENTATION

The patient is a 57-year-old Southeast Asian woman with a history of ACC of the right labium superius oris (upper lip), status post surgical resection



**Figure 2** Positron emission tomography CT scan showing a large left pleural effusion with numerous hypermetabolic pleural-based nodules in the left hemithorax consistent with malignancy (arrows).

followed by reconstruction and then adjuvant radiation therapy 18 years ago in Singapore. The patient moved to the USA in 2010 and presented to the emergency department in August 2019 for evaluation of epigastric and left upper quadrant abdominal pain. The patient was in her usual state of good health until 12 hours before presentation when she started reporting of abdominal pain, nausea and vomiting. A review of systems was significant for intermittent dyspnoea on exertion. The patient vital signs were stable. Physical examination was significant for decreased breath sounds at the left lung base, with dullness on percussion. There was mild tenderness on palpation of the epigastric region but no guarding or rigidity.

## INVESTIGATIONS

Laboratory studies showed haemoglobin 134 g/L, white cell count  $5.4 \times 10^9/L$ , troponin 5 ng/mL, beta natriuretic peptide 50 pg/mL and lipase 40  $\mu\text{g/L}$ . ECG revealed sinus rhythm with no ST-segment changes. Chest X-ray revealed a large left side pleural effusion (figure 1). Echocardiography showed a normal ejection fraction of 55%–60% with mild left ventricular hypertrophy. Ultrasound of the abdomen was negative for cholecystitis or pancreatitis. A CT of the abdomen revealed numerous pleural-based lung nodules involving the left lung, associated with a moderate to large left pleural effusion. Due to the presence of pleural-based lung nodules on CT scan and the patient's remote history of malignancy, a positron emission tomography (PET) scan was ordered. This revealed a large left pleural effusion with numerous hypermetabolic pleural-based nodules (maximum standardised fluorodeoxyglucose (FDG) uptake value 7) in the left hemithorax consistent with malignancy (figure 2). A therapeutic and diagnostic

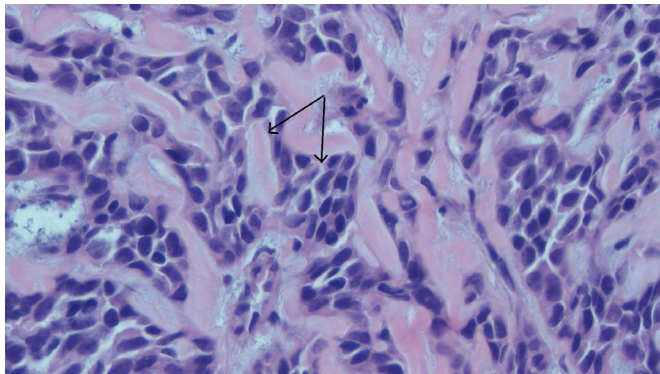


**Figure 1** Chest X-ray showing a large left side pleural effusion (arrow).



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**Figure 3** Pathology with microscopy showing infiltrating epithelioid neoplasm composed of columnar and cuboidal cells suggestive of large cell carcinoma (arrows).

thoracentesis of the left pleural effusion was negative for malignancy by cytological analysis. Due to the unclear aetiology of the pleural effusion, a video-assisted thoracoscopic surgery with biopsy of the pleural nodules, talc pleurodesis and placement of a pleural drainage catheter (PleurX) were done.

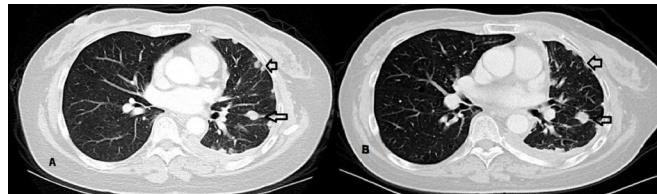
Biopsy showed an infiltrating epithelioid neoplasm composed of columnar and cuboidal cells consistent with metastatic large cell carcinoma (figure 3). Immunohistochemistry (IHC) staining demonstrated scattered immunoreactivity for pan-cytokeratin AE1/AE3 and CAM 5.2 with a rare cell demonstrating immunoreactivity for CK7. Diffuse strong immunoreactivity was noted for CK5/6, CD-117 and P63 with lesser immunoreactivity noted for p53. The neoplastic cells did not demonstrate immunoreactivity for keratin 20 (CK20), epithelial membrane antigen (EMA), thyroid transcription factor (TTF1) or calretinin, and the Ki-67 proliferation rate was >10%. Based on the presence of the Cytokeratin 7 (CK-7), anti-cytokeratin (CAM 5.2), CD117, p63 and pan-cytokeratin, this IHC staining pattern was suggestive of ACC. Cytogenetics and next-generation molecular sequencing of the tumour cells revealed chromosomal rearrangement for myeloblastosis viral oncogene homolog (MYB) and nuclear factor I/B (NFIB) (MYB-NFIB) and also copy number gain of mouse-double-minute 4 (MDM4). Microsatellite instability status was high (MSI-H), and programmed death-ligand 1 receptor status was negative.

### DIFFERENTIAL DIAGNOSIS

Our initial differential diagnosis for this patient presenting with epigastric and abdominal pain included cholecystitis, pancreatitis and myocardial infarction. These diagnoses were excluded based on the workup mentioned above. The presence of pleural effusion on CXR suggested the diagnosis of heart failure; however, it was ruled out when Brain natriuretic peptide (BNP) and echocardiogram were normal. The presence of pleural-based lung nodules on CT scan, in addition to the patient's remote history of malignancy, led us to believe that this could be a neoplastic process; hence the PET scan was ordered and again showed only the pleural nodules without any other lesions. At that point, our differential diagnosis was primary pleural malignancy versus metastasis of unknown origin. After taking biopsies of the nodules and pathological evaluation, the final diagnosis of metastatic ACC was made.

### TREATMENT

The case was reviewed at our multidisciplinary tumour board, and given that the patient was asymptomatic, the consensus



**Figure 4** (A) Pre-treatment CT of the chest in February 2020 showing progression of the left lung pleural-based nodules with the largest measuring 10×6 mm in dimension. (B) Repeat chest CT in June 2020 after pembrolizumab showing stable disease (arrows).

decision was active surveillance with periodic clinical evaluations and serial CT imaging to be done every 3–6 months. CT scans at 3 and 6 months showed stable disease.

### OUTCOME AND FOLLOW-UP

On the eighth month of follow-up, the patient developed worsening abdominal pain. A CT scan of the chest, abdomen and pelvis showed progression of the left pleural disease and a new right lung nodule (figure 4A). After a discussion with the family, and due to the progression of her disease, we decided to start treatment with pembrolizumab 200 mg intravenously every 3 weeks.

The patient received three treatments so far with her most recent imaging study (CT scan of the chest) at 2 and 4 months of follow-up showed stable appearance of the lung nodules (figure 4B). Clinically, she is doing well only with intermittent left-sided lower rib pain.

Case timeline appears in table 1.

### DISCUSSION

ACC comprises around 10%–15% of salivary gland tumours and approximately 1% of oral and maxillofacial tumours.<sup>1</sup> The usual primary site of ACC is in the parotid glands; other less common sites include secretory glands in the trachea, the lacrimal glands and the external auditory canal.<sup>1</sup> ACC is generally characterised by its lengthy course, indolent behaviour with delayed and silent metastasis.<sup>1</sup> ACC is similar to other head and neck cancers in that it has a propensity to PNI and extension beyond surgical margins.<sup>2</sup> The most common clinical presentation of ACC is an asymptomatic slowly growing mass in the head and neck, while pain and paresthesia may reflect PNI.

Distant metastasis of ACC is more frequent than locoregional spread with an incidence of approximately 35%–50%.<sup>2</sup> van Weert *et al* described 105 patients with ACC, of which 44 developed distant metastasis.<sup>5</sup> The lungs were the most common site of distant metastasis in 93%, followed by the liver and the bones.<sup>5</sup> Metastatic ACC to the pleural cavity with an isolated pleural effusion is exceedingly rare, and to the best of our knowledge it has been described in only two case reports.<sup>3,4</sup>

The majority of metastatic disease in ACC develops within 5 years of diagnosis.<sup>5</sup> The mechanism for the spread of ACC is believed to be related to positive tumour margins, PNI, the presence of nodal disease and advanced local disease.<sup>5,6</sup> Van Weert *et al* also reported that distant metastasis occurred in some cases despite reasonable locoregional control, suggesting unapparent micrometastasis at the time of surgical intervention.<sup>5</sup> Patients with lung metastasis have been found to have a more extended survival period compared with those with liver or bone metastasis.<sup>1</sup>

MYB translocations are the most frequent mutations found on chromosomal analysis of ACC.<sup>7</sup> The translocation t(6;9)

**Table 1** Case timeline

2002	Underwent surgical resection followed by reconstruction and then adjuvant radiation therapy of adenoid cystic carcinoma (ACC) of the right labium superius oris (upper lip)
August 2019	Presented with vague epigastric pain and was found to have a large left pleural effusion with numerous hypermetabolic pleural-based nodules. Underwent video-assisted thoracoscopic surgery with biopsy of the pleural nodules, talc pleurodesis and placement of a pleural drainage catheter (PleurX). Biopsy consistent with metastatic ACC.
September 2019–February 2020	Active surveillance with periodic clinical evaluations and serial imaging done every 3–6 months that showed stable disease.
February 2020	CT of the chest showed progression of the left pleural disease and a new right lung nodule.
March 2020	Treatment with pembrolizumab 200 mg every 3 weeks.
June 2020–till present	Repeat CT of the chest showed resolution of the right lung nodule and interval decrease in the size of the left pleural-based nodules.

(q22-23;p23-24) that results in a fusion of the two transcription factor genes MYB and NFIB is detectable in half of the ACC's cases.<sup>7</sup> The biological significance of MYB overexpression is an upregulation of many target genes, including vascular endothelial growth factor (VEGF) A, fibroblast growth factor receptor 2 and KIT compared with normal salivary glands.<sup>8</sup> Unlike other head and neck cancers where tumour suppressor p53 mutations are frequent, it has been identified only in approximately 5% of ACC cases.<sup>6,9</sup> Biomarkers, such as VEGF, p53 and KIT, have been associated with aggressive disease and poor prognosis.<sup>1</sup> Moreover, alterations of NOTCH signalling pathways have also been found to be associated with an unfavourable prognosis.<sup>7</sup> Our patient had the MYB-NFIB mutation as well as copy number gain of MDM4.

Metastatic ACC is usually incurable, and treatment is mostly directed towards palliation.<sup>10</sup> Due to the lack of effective treatment options for metastatic disease, active surveillance of the disease is recommended in asymptomatic patients with a slow rate of metastatic tumour progression.<sup>11,12</sup> Palliative chemotherapy for metastatic ACC can be given in the event of disease progression or the presence of physical symptoms.<sup>10</sup> A combination of cyclophosphamide, doxorubicin and cisplatin is the most commonly studied regimen with a response rate of up to 50%; however, this regimen is highly toxic.<sup>12</sup> For subsequent lines of treatment, targeted therapy may be considered. Lenvatinib, a VEGF tyrosine kinase inhibitor, is a promising treatment option for recurrent or metastatic ACC.<sup>8</sup> In a single-arm study of 33 patients with recurrent ACC, lenvatinib resulted in a partial response in 16% and stable disease in 75% of the patients.<sup>8</sup>

Initially, our patient underwent pleurodesis, and she was asymptomatic following the procedure. Therefore, we decided to observe her disease with serial CT scans. After evidence of disease progression and recurrence of symptoms, we started her on treatment with the immune checkpoint inhibitor pembrolizumab. Her tumour was MSI-H, and thereby, she was a candidate for treatment with pembrolizumab.

Pembrolizumab is a programmed cell death-ligand (PD-L1) monoclonal antibody that reverses T-cell suppression and induces an antitumour response.<sup>13</sup> Pembrolizumab was recently approved for the treatment of unresectable or metastatic solid tumours with MSI-H expression regardless of the histology of the tumour or the tumour site.<sup>13</sup> To the best of our knowledge, pembrolizumab has not been previously reported as a treatment for ACC.

Our patient received three treatments so far with pembrolizumab and her most recent CT imaging studies at 2 and 4 months of follow-up showed stable appearance of the size of the pleural-based nodules. Clinically, she is doing well only with intermittent left-sided lower rib pain.

## Learning points

- ▶ Adenoid cystic carcinoma is an indolent malignancy, and metastatic disease can present many years following the management of the primary tumour.
- ▶ Chromosomal analysis and examining for microsatellite instability are essential because they help to guide management on the progression of the disease.
- ▶ Pembrolizumab, a programmed death-ligand 1 checkpoint inhibitor, can be offered to patients with high microsatellite instability tumours regardless of tumour histology or origin.

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