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Case Report

Metastatic Adenoid Cystic Carcinoma with Signet Ring Morphology in the Liver: Detection of MYB Translocation in Adenoid Cystic Carcinoma

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Abstract

Adenoid cystic carcinoma (ACC) is a relatively rare salivary gland malignancy. Approximately 25-55% of patients with ACC develop distant metastases. We present the case of a 65-year-old female who was incidentally found to have a hepatic lesion while undergoing monitoring for an intraductal papillary mucinous neoplasm of the pancreas. Significant background history included a previously resected ACC of the right sublingual gland with adjuvant radiotherapy seven years prior and Hepatitis B positive serology. Radiology review at the hepatobiliary oncology multidisciplinary meeting favoured a cholangiocarcinoma and a hemi-hepatectomy was performed. Macroscopic examination of the left hemi-hepatectomy specimen demonstrated a well-defined firm pale lesion in segment 2/4a. The histologic examination of this area showed a relatively well-demarcated lesion comprising of tubules and cords with a biphasic basaloid appearance and basement membrane matrix production. Large areas with signet ring morphology were also seen. The morphologic features and the presence of myoepithelial cells as demonstrated by immunohistochemical staining for S100, p63 and SMMHC were suggestive of a metastatic salivary gland tumour. Cribriform architecture typical of adenoid cystic cell carcinoma was not present. The histologic sections of the primary sublingual lesion were reviewed. These demonstrated typical cribriform architecture of adenoid cystic carcinoma with focal signet ring morphology. Fluorescent in situ hybridization (FISH) studies performed on both the primary and the metastatic lesion demonstrated MYB translocation, confirming the diagnosis and thus further augmenting the diagnostic accuracy. This case highlights the value of recent advances in molecular testing and their role in diagnosis of cases with unusual morphologic features.

ABBREVIATIONS

ACC: Adenoid Cystic Carcinoma

INTRODUCTION

Adenoid cystic carcinoma (ACC), while rare, is the 2nd most common primary salivary gland neoplasm. Metastases of ACC are rarely present at initial presentation, however, over the course of the disease, they occur in 25-55% of patients [1,2]. While most ACCs retain their usual morphologic features at metastatic sites, occasional tumours may show unusual architectural and cytological features causing a diagnostic dilemma. Recent advances in adenoid cystic carcinoma have centered around the identification of reciprocal translocation t(6;9)(q22-23;p23-24) resulting in the formation of MYB-NFIB fusion oncogene in 49% of ACCs [3]. MYB a leucine zipper transcription factor regulates cell proliferation, differentiation and apoptosis. MYB-NFIB fusion leads to overexpression of MYB and acts as an oncogenic driver. Fluorescent in situ hybridization probes for MYB rearrangement have recently become commercially available and their diagnostic utility is under investigation [4].

CASE PRESENTATION

We present the case of a 65-year-old female who was found to have a lesion in segment 2/4a of her liver while undergoing

monitoring for intraductal papillary mucinous neoplasm of the pancreas. The patient was otherwise well. She ceased smoking ten years prior and consumed minimal alcohol. An initial FNA at another center did not show any evidence of malignancy but a repeat MRI scan showed an increase in size from 13mm to 24mm in diameter over a period of 13 months. The MRI showed a single T1 hypointense, mildly T2 hyperintense liver lesion with some delayed enhancement as well as capsular retraction (Figure 1 and 2). Differentials included a peripheral cholangiocarcinoma or hepatic haemangio-endothelioma.

Significant background history included an ACC of the right sublingual gland which was resected seven years prior. Following surgery, and noting the close excision margins and the presence of extensive perineural invasion, the patient proceeded to wide field ipsilateral adjuvant radiotherapy directed to the surgical bed and neck with the aim of decreasing her risk of locoregional recurrence. The patient received a total of 60Gy in 30 fractions using CT planned 3D conformal megavoltage radiotherapy over six weeks. She tolerated her treatment well and experienced only the expected mucocutaneous side effects, which resolved shortly after completion of treatment. At the last follow up she remained clinically disease free within the head and neck.

A left hemihepatectomy was performed and the hepatic lesion was resected. Macroscopic examination of the specimen showed a well defined firm pale lesion 28 x 24 x 16mm in segment 2/4a (Figure 3). Sections showed a relatively well-demarcated lesion comprising of tubules and cords of epithelial cells with associated eosinophilic basement membrane like material (Figure 4). The nests and cords showed biphasic appearance in several areas. The central luminal cells showed scanty to moderate amounts of eosinophilic cytoplasm. Multiple large areas showed signet ring cell morphology both of the luminal cells of the tubules as well as in the cords (Figure 5). The abluminal cells appeared flattened and spindle shaped. Minimal typical cribriform architecture with intraluminal amphophilic material was observed at the periphery after extensive sampling of the specimen.

Immunohistochemistry with CK7, p63 and SMMHC highlighted the biphasic nature of the lesion (Figure 6 and 7). The morphologic features and the immunohistochemical profile were in keeping with a biphasic salivary gland. A differential diagnosis of an adenoid cystic carcinoma and an epithelial myoepithelial carcinoma were considered. The slides of the sublingual gland resection were retrieved for comparison and showed ACC with

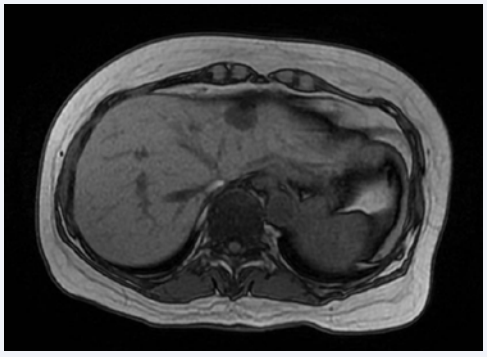

Figure 1 Axial MRI images of lesion in segment 2/4a.

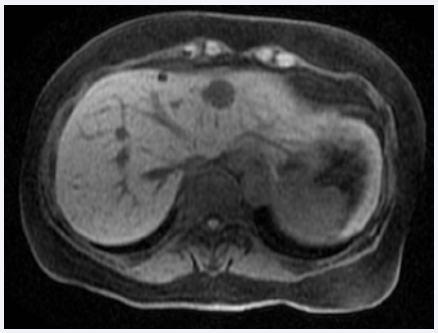

Figure 2 Axial MRI images of lesion in segment 2/4a.

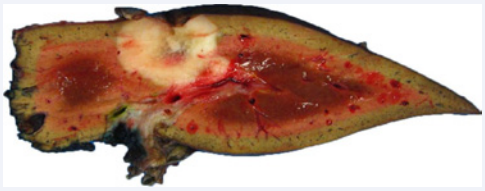

Figure 3 A subcapsular well demarcated grey white firm lesion.

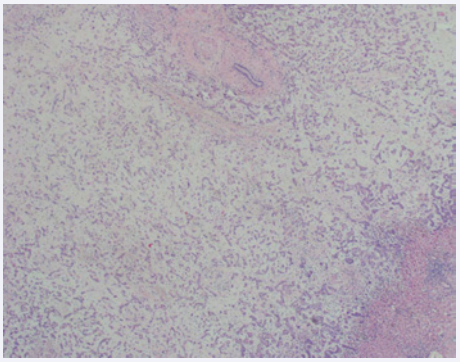

Figure 4 Tumour showing tubules and cords of epithelial cells and grey chondromyxoid matrix with normal hepatic tissue at the periphery. Typical cribriform morphology of adenoid cystic carcinoma is not seen. (Haematoxylin and Eosin x 40).

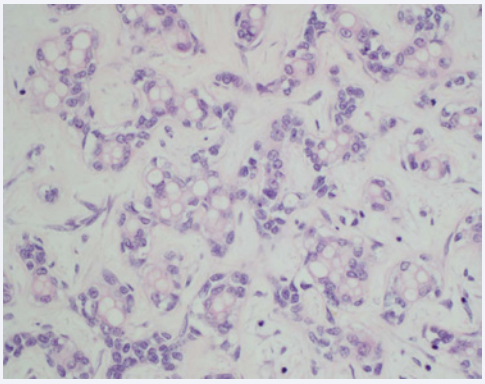

Figure 5 Tumour showing tubules and cords. A large number of signet ring cells are seen. The cells show an eccentric round vesicular nucleus and an intracytoplasmic vacuole. (Haematoxylin and Eosin x200).

predominantly typical histologic features and minimal signet ring cell morphology (Figure 8).

Interphase FISH for ZytoLight SPEC MYB Dual Color Break Apart Probe (ZytoVision) were performed on both the primary sublingual lesion as well as the metastases (Figure 9). Both showed MYB rearrangement in 40% of tumour nuclei, thus supporting the diagnosis of metastatic adenoid cystic carcinoma.

A decision was made post surgery for review at six months with a PET scan, followed by a MRI at one-year post resection.

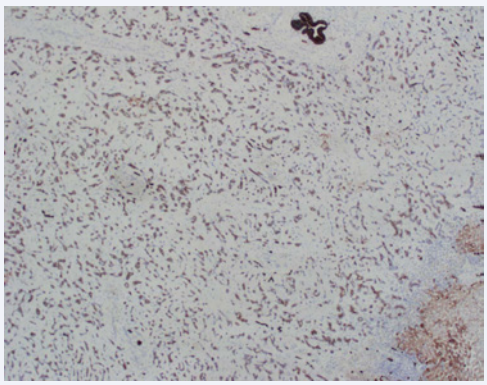

Figure 6 Metastatic ACC with CK staining of tumor cell cytoplasm.

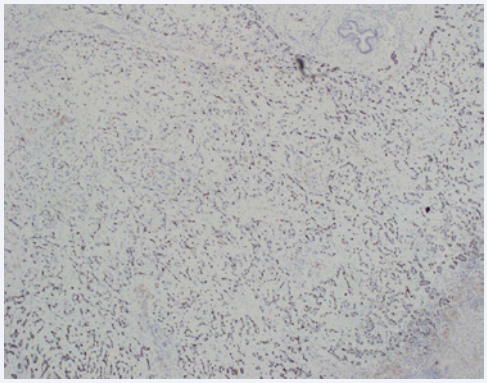

Figure 7 Metastatic ACC with p63 staining of myoepithelial cells.

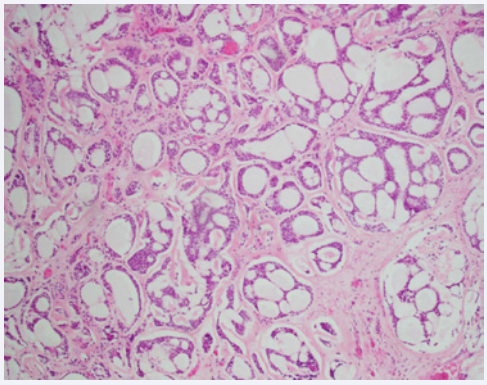

Figure 8 Sublingual ACC with predominantly typical histological features (Haematoxylin and Eosin x100).

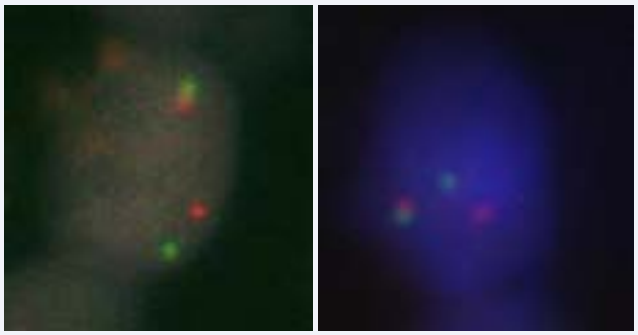

Figure 9 FISH for MYB rearrangement using a break apart probe (A) – Sublingual ACC (B) – Metastatic ACC. Green probe corresponds to centromeric 5' locus and red probe corresponds to telomeric 3' locus of the MYB breakpoint region.

DISCUSSION

Adenoid cystic carcinomas have significant likelihood of late distant metastases, even when adequate primary locoregional surgery and radiotherapy has been performed. The presence of late metastasis often means that the patients require long-term follow up. It also means that the complete medical history is not readily available to the pathologist while examining the tissue from the metastatic site. An additional confounding factor, particular to this case, was the presence of signet ring morphology. Signet ring cell morphology is extremely rare in adenoid cystic carcinoma and was only first described in the literature in 2013 by Altemani et al [5]. They described four cases involving the sinonasal, lip and submandibular ACC and noted that although this rare cellular modification in ACC causes significant diagnostic problems it does not appear to change the biological behavior of the tumor [3].

Detection of MYB-NFIB translocation is gaining ground as an ancillary diagnostic test in adenoid cystic carcinomas [6]. The presence of MYB rearrangement is highly specific for adenoid cystic carcinomas as it has not been described in other primary salivary gland neoplasms such as epithelial myopeithelial carcinoma, polymorphous low grade adenocarcinoma and canalicular adenomas. However, the sensitivity is relatively low as it is present in only 49% of the cases [3]. Detection of MYB rearrangement can also be a useful prognostic tool as demonstrated by Mitani et al, who identified age greater than sixty, solid phenotype and high MYB expression as adverse prognostic factors in adenoid cystic carcinoma [7].

Currently there are limited treatment options for metastatic ACC. In patients with advanced disease, first-line therapy is still conventional chemotherapy. Combination chemotherapy such as cisplatin and 5-FU or CAP (cisplatin, doxorubicin, and cyclophosphamide) can be used, however these regimens typically show a low response rate and median survival time after distant metastasis is only 36 months [8,9]. Targeted therapies such as Sorafenib, an oral multikinase inhibitor, have also been investigated in clinical trials with limited success [10]. While the diagnostic and prognostic utility of MYB is being increasingly understood, currently drugs targeting the MYB pathway in ACC are not available.

In conclusion, we describe another case of adenoid cystic carcinoma with signet ring morphology, at a metastatic site. Awareness of this rare morphologic variation of an adenoid cystic carcinoma is essential to prevent misclassification as an epithelial-myoepithelial carcinoma, a low-grade carcinoma with an indolent biologic course. Detection of MYB rearrangement, a test with high specificity though low sensitivity, can augment diagnostic accuracy in problematic cases of adenoid cystic carcinoma with variant morphologic features or small specimens with procedural artifacts.

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