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Late intracranial metastasis from adenoid-cystic carcinoma of the parotid gland: Imaging, histologic and molecular features

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A B S T R A C T

We describe the neuroradiologic, histologic, and genetic features of a very unusual intracranial dural metastasis from adenoid cystic carcinoma of the parotid gland detected 27 years after the initial diagnosis.

A R T I C L E I N F O

Keywords: Dural metastasis; Adenoid cystic carcinoma (ACC); Imaging; genetic profile.

Introduction

Adenoid cystic carcinoma (ACC) has an estimated incidence of 3-4.5 cases per million individuals/year accounting for 10%-12% of all salivary gland tumours.[1] The tumor is characterized

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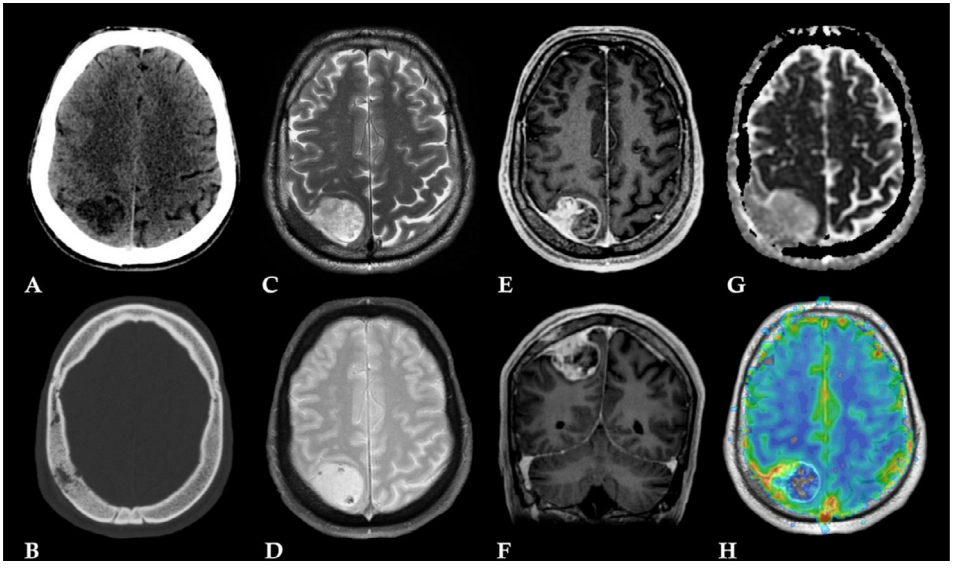

Fig. 1. CT (A-B) and MR (C-F) images of the mass. CT images demonstrated an extra-axial mass in the right parietal region predominantly hypodense with an isodense peripheral rim (A) associated with focal area of calvarial osteolysis (B). At MR the mass was the heterogeneously hyperintense in T2 (C) with few intralesional hypointense foci on T2* GRE images (D); the mass showed intense but heterogeneous enhancement with distinct "dural tail" (E-F). Calvarial involvement was indicated by evident signal alteration of the parietal bone in T2 (C) and DWI (G) with an area of focal enhancement (F). PWI image demonstrating increased rCBV at the level of dural attachment (H).

by numerous local recurrences and perineural spread, while distant metastases most commonly involve the lungs.[1] Only a few cases of intracranial ACCs of hematogenous origin have been reported. Herein, we present the very rare case of a parietal convexity dural metastasis detected 27 years after the initial diagnosis of a parotid gland ACC.

Case presentation

A 52-year-old man arrived in the emergency department complaining of palpitations, atypical chest pain, and paraesthesias of the left upper limb. Cardiological evaluation showed no abnormalities. A few days later, the patient returned to the emergency department due to the worsening of paraesthesias occurring in the left lower limb as well.

Computed tomography (CT) examination demonstrated an extra-axial mass (3.9×3.2 cm on the axial plane) involving the dura in the parietal region on the right side, predominantly hypodense with an isodense peripheral rim (Fig. 1A). A focal area of parietal bone osteolysis was noted (Fig. 1B). On magnetic resonance imaging (MRI), the mass was isohypointense on T1-weighted images and isohyperintense on T2-weigthed images (Fig. 1C) with a few hypointense foci on T2* GRE images related to intralesional bleeds (Fig. 1D). The mass showed intense but heterogeneous enhancement (Fig. 1E-F). Perfusion weighted imaging demonstrated increased relative cerebral blood volume at the level of the dural attachment due to increased vascularity (Fig. 1H). Prominent perilesional dural thickening and enhancement were also detected ("dural tail"). No perilesional edema was noted. The parietal bone at the level of the mass was hypointense both on T1- and T2-weighted images (Fig. 1C) with altered signal on diffusion-weighted imaging (Fig. 1G) and an area of contrast enhancement (Fig. 1F) due to infiltration. Diagnostic hypotheses were metastatic lesion or, less probably, meningioma variant or hemangiopericytoma.

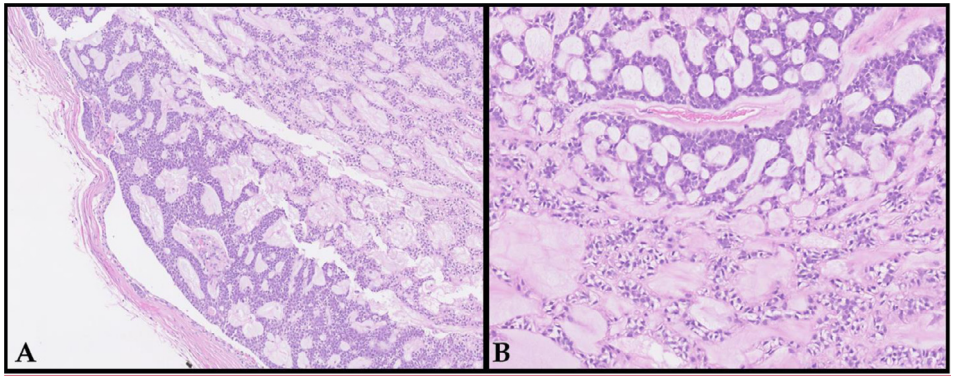

Fig. 2. Hematoxylin and eosin stain at 10x (A) and 20x (B) magnification. The image at lower magnification shows the neoplastic tissue based on the dura; higher magnification image demonstrates a detail of the neoplastic architecture and cytology.

In 1992, at the age of 25, the patient presented with a unilobar hardened lesion posterior to the mandibular angle on the right side. Ultrasound examination demonstrated an ovoid lesion measuring approximately $2.5 \times 1.4 \times 1.2$ cm with heterogeneous hypoechogenic structure and well-defined margins. Based on fine-needle aspiration, the initial suggested diagnosis was pleomorphic adenoma. The patient underwent right superficial parotidectomy with sparing of the ipsilateral facial nerve. The final histopathological diagnosis was adenoid cystic carcinoma with metastasis to one intraparotid lymph node. A right supraomohyoid neck dissection was subsequently performed but no evidence of cervical nodal metastasis was detected. Follow-up visits during a period of approximately 10 years were normal.

In the current episode, the patient underwent excision of the intracranial tumor through a right parietal craniotomy. The bone flap presented a small area of macroscopically evident neoplastic infiltration on its internal surface that was removed by drilling. A small portion of the tumor emerging above the dural layer was directly removed. A dural rim around the neoplasm was removed and sent for histologic analysis. The tumor had yellowish-brown appearance and elastic consistency, with a central gelatinous core and a good cleavage plane from the cerebral tissue. The features observed were suggestive for a meningeal tumor.

Histopathological examination of the resected mass revealed a dura-based neoplasm (Fig. 2A) of epithelial-myoepithelial origin with relatively monomorphous neoplastic cells characterized by rounded-ovoid nucleus and arranged in a mixed pattern of tubuloductular and cribriform areas with pseudocystic spaces (pseudolumina) (Fig. 2B) containing alcianophilic material or with interposed connective tissue. No solid pattern of basaloid cells was detected. Nine mitotic figures were noted per 10 HPF with focal necrosis. Full thickness meningeal infiltration was detected. On immunohistochemistry, the tumor cells were positive for p40, p63 and CD117. These findings were consistent with an intracranial metastasis of ACC.

The lesion was further characterized by next generation sequencing based on DNA extracted from formalin-fixed, paraffin-embedded tumor sample, employing methods previously described in literature.[2,3] Genetic analysis revealed a stable microsatellite status (MSS) and low tumor mutational burden (TMB) as well as the presence of the rearrangement *MYB* (ex1-14 NM_005375)-*NFIB* (ex8-9 NM_005596), and alterations of the following genes: *KDR* (R1032*), *MLL2* (E1571*), *MUTYH* (Y165C), *NOTCH3* (R592S), *PBRM1*(N398T), *PDGFRB* (Y249H), *PIK3C2G* (R1034H), *RPTOR* (R1012K).

Following the histopathological confirmation, a whole-body [18F] fluorodeoxyglucose positron emission tomography (18F-FDG PET) in combination with CT, ^{68}Ga-DOTA-TOC PET, and magnetic resonance imaging of the neck were performed. These examinations did not demonstrate alterations referable to local recurrence, lymphadenopathies nor perineural spread along

the facial nerve or other cranial nerves. The patient was treated with postoperative hypofractionated stereotactic radiotherapy in 5 fractions (total of 30 Gray) directed to the surgical bed.

Discussion

ACC is considered as a slow growing yet aggressive tumor with a protracted disease course characterized by frequent local recurrences and/or metastases, which often occurs years after initial diagnosis, even if locoregional control has been adequate.[4] ACC metastases usually occur in the lungs, bones, and liver, due to hematogenous spread, with a reported incidence varying from 17% to 40%.[5,6] Intracranial metastases of ACC are located primarily at the skull base, usually resulting from direct extension and/or perineural spread along the cranial nerves innervating structures adjacent to the primary lesions (lacrimal or salivary glands, paranasal sinuses, and nasopharynx). Despite the lower incidences of intracranial invasion, perineural spread, and/or microscopic perineural invasion are typical of ACC, occurring in 22%-46% of cases.[7,8] Cases of skull base ACC metastases due to perineural spread with imaging features indistinguishable from those of meningioma have been reported.[9,10] However, only a few cases of brain hematogenous metastases from ACC originating from different sites (submandibular gland, lung, breast, and parotid gland) have been described.[11-15] Among these reports, only 2 primary ACCs were located in the parotid gland.[11,12] In both cases, multiple intra-axial lesions were found with concomitant metastases in other sites (lung, bone) occurring from 1.3 to 10 years since the initial tumor presentation. Additionally, there were 14 reports of intracranial ACCs with unknown primary origin occurring in various sites,[16] including one case involving the posterior fossa with meningioma-like appearance and "dural-tail."[17] Kaur et al[18] described 2 cases of ACCs involving the lacrimal gland and the hard palate characterized by widespread dural involvement with both "en plaque" and mass lesion morphology, occurring respectively 2 and 12 years since disease presentation. According to the authors, ACC metastases may have occurred via direct extension and/or hematogenous spread; they also suggested an affinity of ACC for the dura, but this possibility has not subsequently been further investigated. In our case, the absence of clinico-radiological signs of cranial nerves involvement and the localization of the mass in the parietal dura are consistent with a hematogenous origin of the mass.

The parietal dural mass discussed here had imaging features reminiscent of some meningioma variants. Although meningiomas are most commonly isohyperdense compared to the normal brain tissue at noncontrast CT, some rare variants (cystic/microcystic) are hypodense on CT[19] like the mass herein discussed. Low density at CT has already been reported in ACC metastases[12,15,20] and may be correlated with the numerous pseudocystic spaces of the cribriform pattern. Focal areas of osteolysis also occur in atypical/ malignant meningeal tumors.[21] Thus, in the present case, the hypothesis of a metastatic lesion was based primarily on patient's anamnesis.

Jones et al[22] stated that ACC primary site recurrence rate is of 100% at 30 years follow-up and Coupland et al[23] recently described a submandibular ACC with local recurrence and liver metastasis which was detected more than 30 years from the original presentation. In the case discussed here, ACC intracranial metastasis was detected nearly 3 decades after the initial presentation without signs of local recurrence. However, since ACC is a slow growing tumor, it is possible that the tumor had metastasized much earlier than 27 years and was indolently growing for a long period of time.

In regard to genetic findings, the dural localization of ACC here discussed was characterized by a stable microsatellite status (MSS). The frequency and prognostic significance of microsatellite instability in salivary glands tumors have not been evaluated. MSS status indicates proficiency of DNA mismatch repair with intact expression of all MMR family proteins and suggests poor response to immune checkpoints inhibitors. A low TMB had been found in this metastasis (1 muts/Mb). Literature data indicate that salivary glands carcinomas harbor a median TMB of 3.6 mutations per megabase and 6.3% of cases have high TMB (more than 20 muts/Mb).[2] However, published data investigating the prognostic implications of TMB in salivary gland

carcinoma are limited. Available data from other tumor types indicate that, compared to patients with tumors harboring higher TMB levels, patients with tumors harboring low TMB levels have experienced lower rates of clinical benefit from treatment with immune checkpoints inhibitors.

The lesion showed *MYB-NFIB* fusion which has a high specificity for ACC.[24] The rearrangement results in a loss of *MYB* C-terminus leading to over-activation of *MYB* and over-expression of IGF2, an endogenous factor that interacts with IGF1R driving ACC cells proliferation through AKT and MAPK signaling. Recent findings suggest that IGF2-IGF1R-MYB-NFYB autocrine loop may represent a target for therapy. Partial results in single cases treated with IGF1R antibody figitumumab alone or in combination with other drugs have been reported in literature.[25] A clinical trial using a *MYB* vaccine combined with anti-PD1 immune checkpoint inhibitor is currently opened.[26] Literature data suggest high prevalence of mutations in genes encoding chromatin-state regulators[27] suggesting a role for epigenetic regulation of gene expression in ACC oncogenesis. Genes mutated in the present case were *MLL2* and *PBRM1*. Somatic mutation of *MLL2* has been previously observed in various solid tumors (especially prevalent in squamous cell lung carcinoma and small cell lung carcinoma),[28] including ACC.[29] Findings from this case demonstrate agreement with the data published by Rettig et al[29] who reported high proportion of truncating mutations in *MLL2*. The gene *PBRM1* is required for the stability of the SWI/SNF chromatin remodeling complex SWI/SNF-B (PBAF) and acts as a negative regulator of cell proliferation. The significance of the *PBRM1* mutation in ACC is unknown. Missense mutations of *PIK3C2G* and *RPTOR* have been found, both involved in PI3K/AKT1/mTOR tyrosine kinase signaling pathway. *PIK3C2G* mutation has been reported in 1.6% of tumors analyzed in COSMIC including melanoma, CRC and hematologic malignancies.[28] Mutation of *RPTOR* has been reported in less than 2% of ACC cases in AACR project GENIE registry.[30] The gene *PDGFRB* encodes a tyrosine kinase receptor for proteins in the platelet-derived growth factor family and is mutated in less than 1% of ACCs.[30] A further finding is *KDR* (*VEGFR2*) nonsense mutation R1032* resulting in a premature truncation of the *KDR* (*VEGFR2*) protein which represents one of the 2 receptors of *VEGF*. This mutation has been already reported in ACC as well as in numerous other neoplasms, but its significance is uncertain.[28,30] Mutation of *MUTYH*, a gene involved in DNA damage repair, was noted in this ACC. The role of *MUTYH* in mutagenesis and promotion of tumorigenesis is well recognized in colorectal cancer whereas in the context of other cancer types, including ACC is not established. *NOTCH1* mutation has been reported in 12% of tumors studied by Rettig et al.[29] The dural lesion here discussed was *NOTCH1* wild type whereas missense mutation was detected in *NOTCH3* gene. Regulation via *NOTCH3* signaling was first implicated in vasculogenesis but recent findings suggest that it may play an important role in oncogenesis and resistance to chemotherapy.[31] However, both *NOTCH1* and *NOTCH3* alterations can result in either tumor suppression or oncogenesis depending on the tumor type.[31]

In conclusion, genetic alterations found in this ACC dural metastasis were rearrangement of the gene *MYB* and alterations of the genes involved in chromatin remodeling, DNA damage, and tyrosine kinase signaling. However, most of the mutations detected in our patient have not been adequately characterized in literature and their significance is presently undefined.

Due to the limited number of cases reported, the optimal treatment of ACC intracranial metastases is unknown. In the present case, the patient was treated with surgery combined with postoperative hypofractionated stereotactic radiotherapy on the surgical bed, following the currently accepted treatment for disease control in the primary tumoral site.[1]

Conclusion

Because of its low incidence and prolonged clinical course, the timing and pattern of hematogenous metastases of ACC are only partially known. In particular, data on hematogenous dural metastases of ACC are very limited. We report a parietal convexity dural localization of a parotid gland ACC detected 27 years since primary disease presentation. This unpredictable clinical course of ACC represents a major challenge for the definition of the optimal treatment and clinical follow-up.

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