Case Report

Coincidence of Intracranial Myoepithelioma and Adrenocortical Carcinoma in a Young Man

Abstract

Myoepithelial tumors are rare neoplasms that develop from myoepithelial cells in glandular structures and soft tissues. Primary intracranial myoepithelial neoplasms are even rarer with around ten cases reported. On the other hand, adrenocortical carcinoma (ACC) is also uncommon with an annual incidence of 0.7–2 per million and carries a poor prognosis. It is known to have an association with certain familial cancer syndromes. Even in sporadic cases, a significant portion of them had other malignancies before and after diagnosis of ACC. We reported a 34-year-old gentleman who was diagnosed to have ACC without known familial cancer syndrome. After that, he was also found to have right occipital myoepithelioma that was confirmed by excisional biopsy. There was no known association between these two pathologies. This is the first report of coincidence of ACC and intracranial myoepithelioma.

Keywords: *Adrenocortical carcinoma, brain neoplasms, myoepithelioma*

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Introduction

Myoepithelial tumors are rare neoplasms that develop from myoepithelial cells in glandular structures such as salivary glands, mammary glands, and secretory glands in dermis. It may also arise from soft tissue, but these two subtypes may have different genetic profiles.[1] Based on the degree of cellular atypia and mitotic activity, it can be classified into myoepithelioma with a benign course or myoepithelial carcinoma that is highly malignant.[2-4] Primary intracranial myoepithelial neoplasms are even rarer with only around nine cases reported [Table 1].[1,3-9] Extra-axial tumors contributed to the majority in this cohort. Due to the rarity of such a condition, it has been considered as an independent disease without association with other diseases.

Adrenocortical carcinoma (ACC) is also uncommon with an annual incidence of 0.7–2 per million and carries a poor prognosis.[10,11] Sporadic cases are more common, but it is known to have an association with familial cancer syndromes such as Li-Fraumeni syndrome, multiple endocrine neoplasia type 1, Beckwith–Wiedemann syndrome, familial adenomatous polyposis, Lynch syndrome, Carney complex, and neurofibromatosis type 1.[10,12-17] These conditions are not typically associated with myoepithelial neoplasms. On the other hand, 11.5% of nonfamilial cancer syndromes patients with ACC had other malignancy before or after their diagnosis of ACC.[11]

Despite the low incidence of each disease, we encountered a patient with both intracranial myoepithelioma and ACC which is the first known case report in the English literature.

Case Report

Our patient is a 34-year-old gentleman who enjoyed good past health. His grandparents died of terminal malignancies that were common locally at the age of above sixties. His parents have remained healthy. There is no suspicion of familial cancer syndrome. Just more than 1 year ago, he complained of lower abdominal discomfort. Computer tomography (CT) of the abdomen showed a huge mass at the hepatorenal fossa that arose from the right adrenal gland [Figure 1a]. The hormonal profile was unremarkable. Laparotomy for tumor excision was performed, and histopathology confirmed that it was an ACC. The tumor

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Table 1: Summary of primary intracranial myoepithelioma reported in literature

	Age	Gender	Site	Positive markers	Negative markers
Gowripriya *et al*.[5]	43 years	Male	Left Meckel's cave	S-100, pancytokeratin, SMA, GFAP, vimentin, CK14, 34 betaE12, D240	NA
Hayward *et al*.[1]	17 years	Female	Right orbital apex	S-100, keratin, SMA, p63, EMA	Desmin
Erdogan *et al*.[6]	46 years	Female	Left frontal dura	S-100, keratin, SMA, calponin, GFAP	EMA, synaptophysin, chromogranin, p63, CD34
Hong *et al*.[7]	48 years	Female	Left cavernous sinus	S-100, SMA, GFAP, vimentin	Desmin, EMA, CK5/6, CD138, myosin, HMB45, CD79a, CD45
Vajtai *et al*.[4]	32 years	Male	Left cerebellopontine angle	S-100, SMA, actin, cytokeratin, GFAP, vimentin, INI1	EMA
Choy and Pytel[8]	13 years	Male	Interhemispheric	Desmin, EMA, cytokeratin CAM5.2, calponin, GLUT1, vimentin	S-100, GFAP, SMA, synaptophysin, cytokeratin AE1/AE3, p63, CD34, HMB45
Choy and Pytel[8]	10 month	Male	Right cerebral hemisphere	S-100, desmin, EMA, GFAP, cytokeratin CAM5.2, cytokeratin AE1/AE3, p63, calponin, GLUT1, CD34, vimentin	SMA, synaptophysin, FLI1, CD99/MIC2, CD20, myogenin
Nieder *et al*.[3]	34 years	Female	Sella	NA	NA
Gupta and Klimo[9]	2 years	Female	Left parieto-occipital	S-100, SMA, cytokeratin, CAM5.2, EMA	GFAP, PLAG-1, PLAP
Our patient	34 years	Male	Right occipital lobe	S-100, SMA, cytokeratins, GFAP	EMA, SSTR2A, p63, Olig2, SOX10, melan A, inhibin, SF-1, chromogranin, synaptophysin, calretinin, TTF-1

SMA - Smooth muscle actin; GFAP - Glial fibrillary acidic protein; CK - Cytokeratins; EMA - Epithelial membrane antigen; SSTR2A - Somatostatin receptor 2; TTF - Thyroid transcription factor; NA - Not available

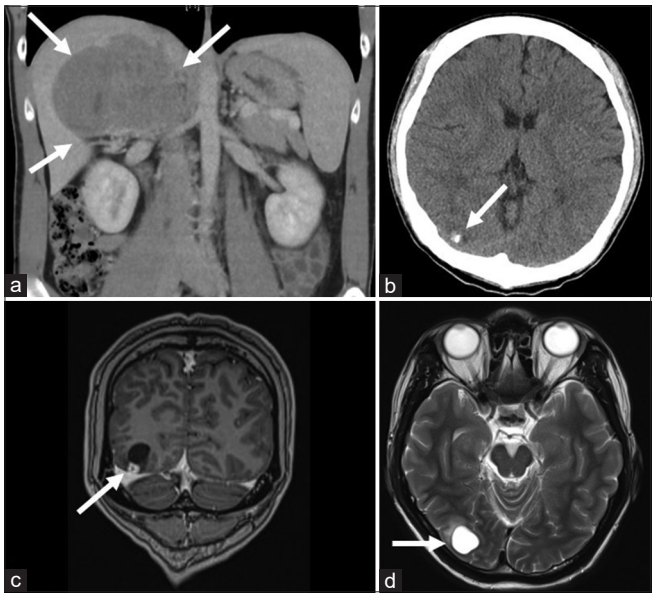

Figure 1: (a) Coronal image of computer tomography of the abdomen with contrast. Arrows marked the huge tumor in the hepatorenal fossa. (b) Axial plain computer tomography brain showed a hypodense lesion with calcification (arrow). (c) Coronal magnetic resonance imaging T1 sequence showed that the nodule had gadolinium contrast enhancement and was in contact with the tentorium (arrow). (d) Axial plain magnetic resonance imaging T2 sequence showed the cystic portion of the tumor (arrow)

also invaded into the diaphragm, which showed capsular and venous invasion. The resection margin was clear. He received adjuvant radiotherapy uneventfully followed by long-term mitotane with hydrocortisone replacement. Two positron-emission topographies (PETs)-CT using 14F-fluorodeoxyglucose were performed at 1 month and 6 month after surgery. Both the studies showed neither local recurrence nor distant metastasis.

He remained well till 12 months after operation when he complained of nonspecific headache associated with dizziness. The patient had no other symptoms and was neurologically intact. CT of the brain showed a hypodense lesion at the right occipital lobe with speckles of calcification [Figure 1b]. In retrospective review, the lesion had been present in prior PET-CTs without serial change. Magnetic resonance imaging (MRI) of the brain showed a right occipital cystic lesion with a gadolinium-enhancing mural nodule [Figure 1c and d]. Given the diagnosis of ACC, the preliminary diagnosis was brain metastasis and stereotactic radiosurgery was contemplated. However, his treating oncologist opinioned that a biopsy should be taken, as the lesion did not look like metastasis. Craniotomy for tumor excision was performed. The lesion was found to be rubbery in consistency, had a calcified nodule that adhered to the tentorial surface, and contained clear cystic fluid. A gross total excision was achieved. The patient remained well after surgery.

Histopathological examination showed a partially calcified and extensively fibrotic nodular lesion adhered to the superficial brain cortex [Figure 2a]. The lesion comprises

irregular nests and clusters of tumor cells in a hyalinized background, which focally (not extensively) infiltrates the cortex [Figure 2b-e]. There is no cellular whorl formation. The cells possess oval nuclei containing dispersed chromatin and pale eosinophilic cytoplasm with indistinct cell borders. Their nuclei are mildly pleomorphic with dispersed chromatin. Mitotic figures are not identified. Neither necrosis nor vascular invasion is seen. Occasional cells display pseudonuclear inclusions; these are reminiscent of those seen in meningiomas, although nonspecific. In view of the clinical history, immunohistochemistry was pursued, which revealed the absence of convincing expression of meningothelial markers such as epithelial membrane antigen (EMA) and SSTR2A [Figure 3a and b]. Instead, there are expressions of cytokeratins, glial fibrillary acidic protein (GFAP), S-100 protein, and focally smooth muscle actin [Figure 3c-f]. The nuclear expression of INI1 is retained [Figure 3g]. They are negative for p63, glial markers (Olig2 and SOX10), neuroendocrine markers (melan A, inhibin, SF-1, chromogranin, synaptophysin, and calretinin), and TTF-1 (not shown). The Ki-67 proliferative index is low (1%) [Figure 3h]. This tumor is therefore morphologically different from the previously excised ACC, and the combination of expression of cytokeratin, GFAP, S-100 protein, and SMA is supportive of myoepithelial differentiation. Morphologically, the tumor is bland looking and shows low proliferation. However, it is difficult to accurately predict the biological behavior of this tumor since there have been no specific histopathological criteria for malignant myoepithelioma in the central nervous system nonetheless except for the focal cortical infiltration.

This lesion had no alarming histological features; we therefore decided to observe without adjuvant treatment. CT of the abdomen performed 1 week after craniotomy showed no evidence of recurrent ACC. The patient was on his prior treatment for ACC with mitotane. MRI of

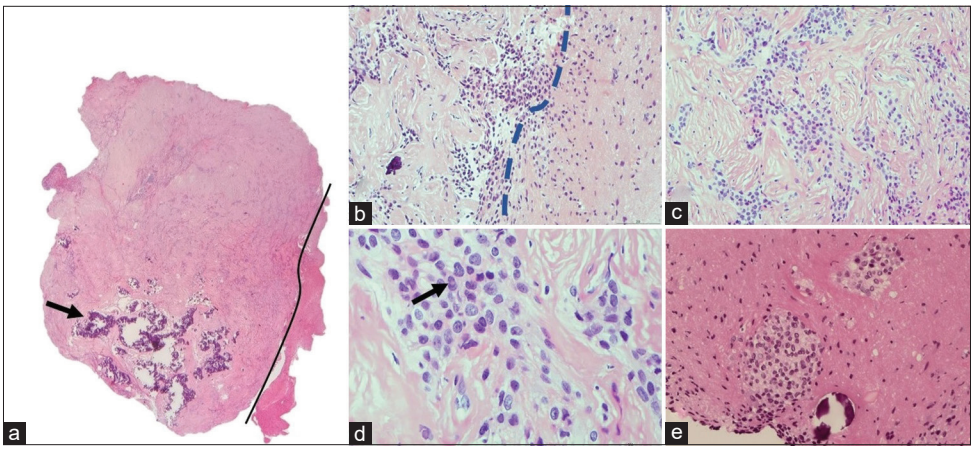

Figure 2: (a) The lesion displays a nodular configuration on low power, which is adhered to a rim of superficial brain cortex (to the right of the black line). Heavy calcification is focally noted (arrow) (H and E, ×20). (b and c) The tumor cells are arranged in irregular nests and clusters in a hyalinized background. They infiltrate into the superficial cortex in (b) (beyond the dotted line) (H and E, ×200). (d) Rare cells contain pseudonuclear inclusions (arrow; H and E, ×400). (e) Tumor nests in the brain cortex, associated with calcification (H and E, ×200)

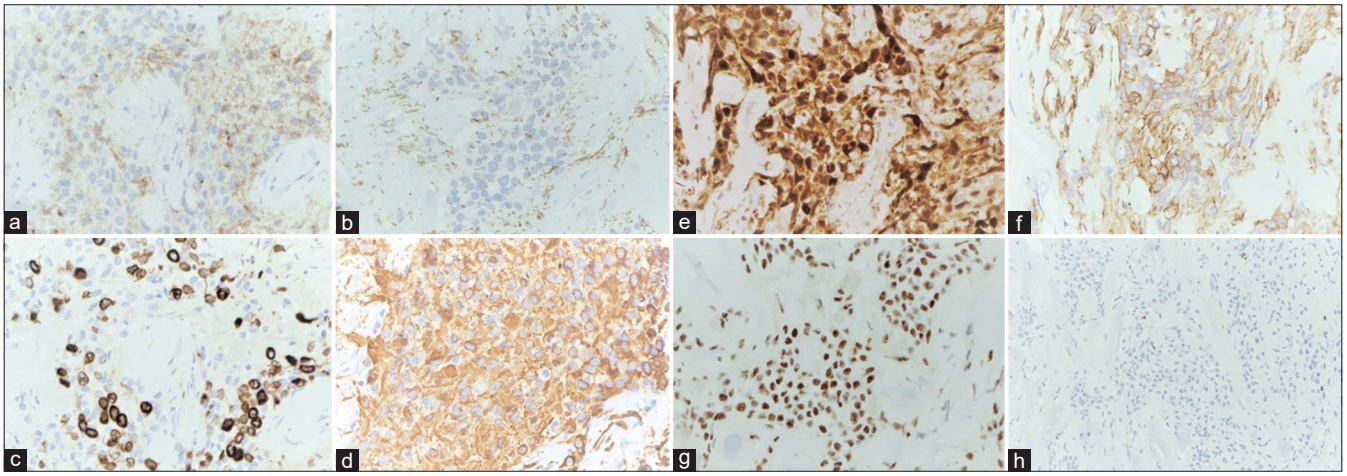

Figure 3: By immunohistochemistry, the tumor cells do not show genuine staining for meningothelial markers such as epithelial membrane antigen (a) and SSTR2A (b). Some of them express cytokeratin (MNF-116) (c). They are diffusely positive for GFAP (d). They express S-100 protein diffusely (e) and smooth muscle actin focally (f). INI1 expression is retained (g). Their Ki-67 proliferation index is very low (h) (immunoperoxidase method, ×400)

the brain performed 4months after craniotomy showed no recurrent tumor.

Discussion

The origin of intracranial myoepithelial neoplasms has remained unknown. They have been postulated to be developed from salivary gland rest in the sellar region, middle cranial fossa, and cerebellopontine angle during embryonic development.[1,4,18] While these proposed mechanisms may explain extra-axial myoepithelial neoplasms located at the skull base, they cannot readily explain those occurring in intra-axial location, falx, high convexity dura, and in our patient, the occipital lobe.[6,8] Apart from the heterogeneity in location, the reported cases had a variable spectrum of protein expression as shown by immunohistochemistry. The diagnoses, besides morphology, relied heavily on different combinations of cytokeratin, S-100 protein, EMA, SMA and GFAP, p63 and calponin expression.

The presence of focal cortical infiltration did raise some concern for its potential biological behavior despite the bland morphology and low proliferative index. However, an infiltrative border may not always herald an aggressive clinical course at least in the setting of soft-tissue myoepithelial tumors. In a study of 101 of such tumors in soft tissues, it was found that invasive growth cannot be relied upon as a useful prognostic finding since none of the infiltrative tumors recurred or metastasized.[19]

For a young patient like ours, the development of ACC and myoepithelioma, both being rare, led us to wonder if he had a germline predisposition to tumors or cancers. To the best of our knowledge, there has only been a single case report of myoepithelial carcinoma occurring in association with a hereditary cancer syndrome.[20] Although biallelic inactivation of the APC gene was demonstrated, myoepithelial carcinoma is not conventionally regarded as part of the tumor spectrum of FAP. On the other hand, most cases of ACC are sporadic, and as previously discussed, none of the associated hereditary syndromes are known to confer an increased risk of myoepithelial tumors.

Furthermore, the two tumors are not known to share common oncogenic pathways. Rearrangements of the EWSR1 gene have been reported to be associated with myoepithelial tumors in soft tissue and other nonsalivary gland locations.[2,5,21] A subset of skin and soft-tissue myoepithelial tumors display frequent PLAG1 gene rearrangements and therefore appear to be genetically linked to their salivary gland counterparts.[21,22] For sporadic ACC, several comprehensive genomic studies have identified IGF2 overexpression, WNT pathway perturbations (CTNNB1 and ZNRF3 mutations), TP53 mutations, copy-number alterations including massive DNA loss and whole-genome doubling, and decreased telomere length.[23-26] Overall, it appears that ACC and myoepithelial tumors show distinctly different mechanisms leading to their respectively genetic lesions.

With the available evidence, it is probably a coincidence that our unfortunate patient developed two rare tumors at a young age. Nonetheless, in the era of next-generation sequencing, whole-exome or whole-genome sequencing of germline and tumor DNA may hold the answer to our question of whether there is a hereditary predisposition to tumor development in this patient. Even so, it is anticipated that interpretation will not be straightforward, as this is the first known report of co-occurrence of two rare tumors and the complexities in demonstrating the pathogenicity of the many variants that will likely be identified.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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