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CASE REPORT - BRAIN TUMORS

Genomic profile of a primary squamous cell carcinoma arising from malignant transformation of a pineal epidermoid cyst

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Abstract

Malignant transformation of intracranial epidermoid cysts is a rare occurrence. We present the second case of such an event occurring in the pineal region and the first case sent for detailed genomic profiling. MRI demonstrated two lesions: a cyst in a quadrigeminal cistern with restricted diffusion on DWI-weighted images and an adjacent, peripherally enhancing tumor with cerebellar infiltration. Both the lesions were completely resected with a small residual of the epidermoid cyst. The final pathology of both lesions was consistent with epidermoid cyst and squamous cell carcinoma (SCC), respectively. The tumor specimen was sent for comprehensive genomic profiling which revealed stable microsatellite status and loss of CDKN2A/B, MTAP (exons 2–8), and PTEN (exons 6–9). Although reports of primary SCC originating from the epidermoid cyst have been previously described, this is the first description of the genomic profile of such a tumor.

Keywords Primary SCC · Malignant transformation · Pineal · Epidermoid cyst

Introduction

In the context of normal embryological development, the human brain is devoid of any epithelial structures. Thus, the vast majority of intracranial squamous cell carcinomas (SCCs) occur secondary to distant metastasis or direct invasion of primary head and neck malignancies. Although exceptionally rare, primary intracranial SCC may occur due to malignant transformation of epithelioid cystic lesions (e.g., epidermoid cyst, dermoid cyst, Rathke's cleft cyst) [2].

Epidermoid cysts are slow-growing, benign lesions, which are typically asymptomatic for many years. The lesions comprise approximately 1% of all intracranial pathologies and are most commonly localized to the cerebellopontine (CP) angle and sylvian fissure [6]. Malignant transformation of these cysts is extremely rare. Here, we present the first ever case

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of malignant transformation of a pineal epidermoid cyst in the USA and the second case worldwide and the first such case sent for detailed genomic profiling.

Case report

History and examination

A 65-year-old female with a history of palpitations presented to her primary care physician with new-onset of gait and visual disturbances described as "veering to the right while running." Her symptoms were not relieved with meclizine. She underwent CT head w/o contrast and was subsequently referred to the neurosurgery department for further management. MRI brain revealed two adjacent mass lesions in the posterior fossa (Fig. 1). The first mass was a multi-lobular and non-enhancing mass with restricted diffusion centered in the quadrigeminal cistern. The second mass (3.9 × 2.5 × 3.2 cm) was solid, non-restricted diffusion pattern, peripherally enhancing, and centered in the left cerebellar vermis with suggestive compression of the left dorsal pons and 4th ventricle without hydrocephalus. It was unclear from the initial scan if these two lesions were contiguous or immediately adjacent with a small bridge of connecting tissue. Based on these findings, surgical resection of the lesion was recommended.

Operation

The patient was positioned in the lateral position, and lumbar drain was inserted. An occipital transtentorial approach to the quadrigeminal cistern and superior cerebellum was performed. Microdissection was utilized to access the quadrigeminal cistern. Frozen section from the quadrigeminal cistern tumor confirmed the diagnosis of an epidermoid cyst. Endoscope assistance was utilized to visualize the contralateral quadrigeminal cistern (see Operative Video). The adjacent cerebellar tumor was attached to the epidermoid cyst with a thin bridge of tissue but had a completely different appearance. The tumor had a thick fibrous capsule with milky fluid in the center. This mass was completely resected. Frozen

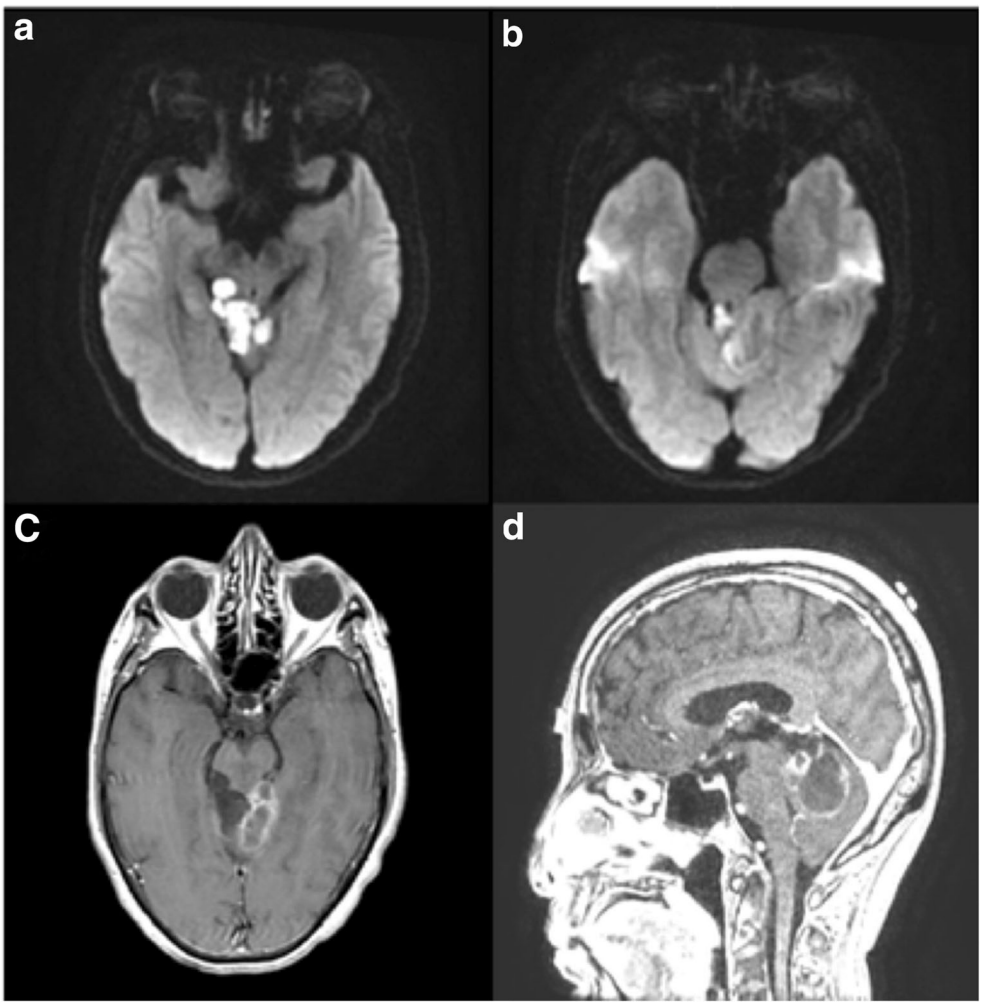

Fig. 1 Preoperative MRI imaging. **a** DWI axial cut showing restricted diffusion of the mass in the pineal region occupying the quadrigeminal cistern and extending to the right ambient cistern. **b** DWI axial cut showing the differentiation between the restricted diffusion of the cyst and the non-restricted pattern in the adjacent mass extending into the cerebellum. **c**, **d** Post contrast studies axial and sagittal respectively showing a non-enhancing pineal cyst with an adjacent peripherally enhancing mass at the pineal area with extension into the left cerebellar vermis

section of the cerebellar lesion revealed squamous cell carcinoma.

Pathological findings

Histopathological examination of the quadrigeminal cistern lesion was consistent with the epidermoid cyst. The cerebellar lesion was consistent with squamous cell carcinoma with moderately-differentiated squamous morphology, including keratin pearls (Fig. 2). Thus, malignant transformation of the epidermoid cyst was a consideration.

The malignant specimen was sent for comprehensive genomic profiling including an in-house clinically validated whole exome sequencing test, as well as a to Foundation One (Cambridge, MA), a commercially available targeted sequencing panel results from the targeted panel showed a low mutational burden (1 Muts/Mb), stable microsatellite status, and loss of CDKN2A/B, MTAP (exons 2–8), and PTEN (exons 6–9). Whole exome sequencing analysis revealed large copy number losses involving several chromosomes, raising the possibility of chromothripsis as an instigating event in the malignant component, as well as several variants of unknown significance (Tables 1 and 2).

Postoperative course

The early postoperative course was unremarkable. The patient's neurological symptoms of diplopia and gait disturbance remained stable. Postoperative MRI confirmed gross total resection of the cerebellar mass with the minimal epidermoid cystic residual in the right quadrigeminal plate cistern (Fig. 3). The patient was referred to neuro-oncology and radiation oncology. A full-body PET/CT was unremarkable for the primary neoplastic process. Adjunctive partial brain radiation therapy was initiated. At 6-week follow-up, her preoperative symptoms of diplopia and gait disturbance were markedly improved. MRI brain with contrast at this time revealed no recurrence with stable epidermoid cystic residual.

Discussion

To our knowledge, our patient represents the second-ever case of malignant transformation localized to the pineal region [11] reported in literature and the first with genomic profiling. Although uncommon, malignant transformation of epidermoid cysts has been reported previously in the literature [8]. Clinically, findings concerning malignant transformation include rapid development of symptoms [14], aseptic meningitis [13], and recurrence following resection [5]. Radiologically, restricted diffusion is the hallmark of epidermoid cysts. Furthermore, features suggestive of malignant transformation include marked rapid growth, tissue edema, and contrast-enhancement in areas adjacent or within the cystic lesion. However, it is important to recognize that contrast-enhancement is not specific for malignancy and may represent

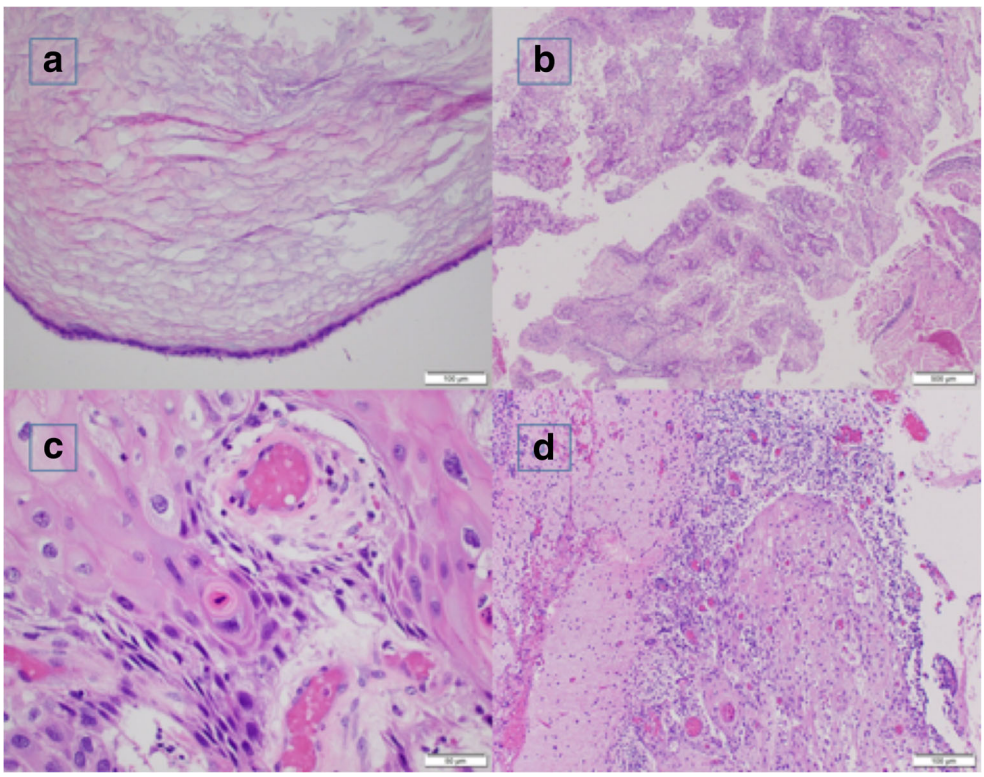

Fig. 2 Histology of each lesion. **a** In the tumor in the quadrigeminal region, the tumor consists predominantly of anucleated keratinous material, lined by a flat layer of cytologically benign squamous cells, characteristic of an epidermoid cyst (H&E × 20). **b** Sections of the cerebellar tumor demonstrate a moderately to poorly differentiated squamous cell carcinoma (H&E × 4). **c** At high power, keratin pearls and intercellular bridges are identified, characteristic of squamous cell carcinomas (H&E × 40). **d** The tumor invades the cerebellar parenchyma, here involving the internal granular layer (H&E × 10)

Table 1 Genomic alterations

Gene name (coordinates)	Classification	Tumor (normal) read depth	Tumor VAF	Protein change/notes
ABCB5 7:20,795,063	Missense	37 (89)	37.8%	p.Ala1197Val (c.3590C>T)
HUS1 7:48,018,102	Missense	49 (129)	34.7%	p.Glu199Lys (c.595G>A)
RFTN2 2:198,498,695	Missense	39 (124)	25.6%	p.Met155Ile (c.465G>C)
ACKR3 2:237,489,664	Missense	36 (112)	11.1%	p.Val186Ile (c.556G>A)
POLQ 3:121,251,934	Missense	420 (213)	29.8%	p.Arg288His (c.863G>A)
ZNF639 3:179,051,089	Missense	95 (67)	30.5%	p.Glu113Lys (c.337G>A)
TERT 5:1,268,636	Missense	38 (143)	10.5%	p.Gly861Arg (c.2581G>A)
ANKRA2 5:72,853,412	Missense	14 (31)	28.6%	p.Arg168Cys (c.502C>T)
ABCB5 7:20,795,063	Missense	37 (89)	37.8%	p.Ala1197Val (c.3590C>T)
HUS1 7:48,018,102	Missense	179 (203)	36.9%	p.Arg90Gln (c.269G>A)
USP20 9:132,630,492	Missense	41 (63)	29.3%	p.Arg300His (c.899G>A)
KRT84 12:52,779,185	Missense	252 (200)	32.9%	p.Ser62Leu (c.185C>T)
TRIM16 17:15,554,552	Missense	50 (44)	40.0%	p.Lys124Asn (c.372G>T)
ACTN4 19:39,191,662	Missense	173 (142)	41.0%	p.Glu100Lys (c.298G>A)
PRDM15 21:43,274,845	Missense	82 (38)	32.9%	p.Ala489Val (c.1466C>T)
PAGE1 X:49,454,072	Missense	90 (69)	30.0%	p.Val123Phe (c.367G>T)
AR X:66,765,985	Missense	25 (65)	16.0%	p.Ala333Thr (c.997G>A)

an alternative inflammatory process with foreign giant cell reaction [15].

The intuitive differential of a contrast-enhancing pineal mass with cerebellar encroachment and rapid neurological deterioration in an adult is high-grade glioma or metastasis. However, in the presence of an adjacent epidermoid cyst, it is important to consider malignant transformation as a differential. Garcia et al. [3] have previously described criteria for distinguishing primary from secondary SCC as follows: (1) tumor restricted to the intracranial and intradural compartments; (2) no extension beyond dura or cranial bones, (3) no communication with middle ear, air sinuses, or sella turcica; and (4) no evidence of a nasopharyngeal tumor. Hamlat et al. [4] further refined these criteria with the following addendum: (1) presence of benign squamous cell epithelium within or adjacent to the malignant tumor and (2) exclusion of metastatic carcinoma. Our patient meets all

Table 2 Other genomic alterations in cancer genes

Altered region (location)	Classification of SCNA	Number of cancer genes	Cancer genes
4:53,382-190,905,996	Focal loss	14	WHSC1 SLC34A2 RHOH PHOX2B FIP1L1 CHIC2 PDGFRA KIT KDR AFF1 RAP1GDS1 TET2 IL2 FBXW7
7:2,985,520-2,998,135	Focal deletion	1	CARD11
9:17,055-141,111,416	Focal loss	29	JAK2 CD274 PDCD1LG2 NFIB PSIP1 MLLT3 CDKN2A CDKN2B FANCG PAX5 GNAQ SYK OMD FANCC PTCH1 XPA NR4A3 TAL2 KLF4 CNTRL PPP6C SET FNBP1 ABL1 NUP214 TSC1 RALGDS BRD3 NOTCH1
0:93,416-135,440,129	Focal loss	24	KLF6 GATA3 MLLT10 ABI1 KIF5B RET NCOA4 CCDC6 TET1 PRF1 KAT6B NUTM2B BMPR1A NUTM2A PTEN FAS TLX1 NFKB2 SUFU NT5C2 VTI1A TCF7L2 KIAA1598 FGFR2
13:19,606,692-115,090,782	Focal loss	9	ZMYM2 CDX2 FLT3 BRCA2 LHFP FOXO1 LCP1 RB1 ERCC5
X:200,916-155,239,525	Focal loss	27	CRLF2 P2RY8 ZRSR2 BCOR KDM6A SSX1 SSX4 WAS GATA1 TFE3 SSX2 KDM5C AMER1 MSN AR FOXO4 MED12 NONO ATRX SEPT6 STAG2 ELF4 GPC3 PHF6 ATP2B3 RPL10 MTCP1

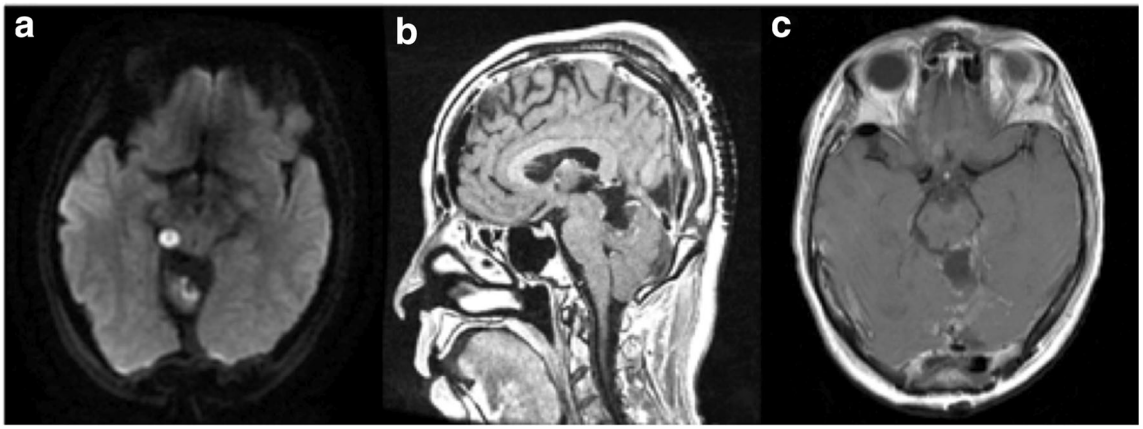

Fig. 3 Postoperative MRI imaging. **a** DWI axial cut showing minimal residual of the epidermoid cyst at the right quadrigeminal plate. **b**, **c** Post contrast studies sagittal and coronal respectively showing gross total resection of the squamous cell carcinoma

criteria described by prior authors to support the diagnosis of primary intracranial SCC and excludes the possibility of secondary SCC.

Surgical intervention with histopathological examination is imperative in the setting of both clinical and radiological deterioration for such lesions, as seen in our patient. Pineal region is a particularly complex region to approach surgically. Thus, preoperative presumptive diagnosis plays a crucial role in patient counseling and surgical decision-making. Yasirgil has previously described two surgical approaches, including supracerebellar infratentorial approach and occipital transtentorial approach. In the present case, we utilized the occipital transtentorial approach with endoscopic assistance to maximize visualization and surgical resection to both lesions [7]. Radiosurgery, while useful as adjunctive therapy, is not recommended as first-line treatment [10].

Development of intracranial epidermoid cyst is theoretically attributed to aberrantly trapped ectodermal remnant during neural tube formation in early embryogenesis [1]. Carcinomatous changes in ectodermal tissue can be caused by chronic inflammatory conditions, immunosuppression, and exposure to radiation. These factors may also play a role in malignant transformation of the ectodermal intracranial benign cystic lesions, especially when its content spilled out by rupture or subtotal resection. However, idiopathic carcinoma in situ is an alternative hypothesis, which is the likely etiology in our case [12].

Identifying molecular alterations associated with SCC development and developing assays which use these molecular alterations as markers of malignancy are of paramount importance. Ideally, such assays would significantly increase the diagnostic yield and/or serve as prognostic biomarkers or therapeutic targets. In this case, stable microsatellite status indicated intact DNA mismatch repair and intact expression of all related proteins. Loss of CDKN2A/B indicates downregulation of tumor suppressor p16(INK4A) and the p14(ARF) proteins and p15(INK4B). Loss of PTEN also impairs tumor suppression, and MTAP encodes an enzyme that plays a major role in polyamine metabolism and is important for the salvage of both adenine and methionine. The encoded enzyme is deficient in many cancers because this gene and the tumor suppressor p16 gene are co-deleted [9]. Although these are not actionable mutations, comparison with future malignant transformation cases may shed light on the etiology of this rare tumor.

Conclusion

Although reports of primary SCC originating from the epidermoid cyst have been previously described, this is the first description of the genomic profile of such a tumor.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from the patient.

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