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CASE REPORT

Pituitary metastasis of Merkel cell carcinoma

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Abstract Merkel cell carcinoma (MCC) is a malignant neuroendocrine tumor of the skin that demonstrates a remarkable tendency to metastasize. However, only a few cases of MCC brain metastases have been reported in the literature. We here present a unique case of a pituitary metastasis of MCC in a 65-year-old patient with a history of pituitary adenoma. This case is particularly novel due to the fact that the primary site of the MCC is unknown.

Keywords Merkel cell carcinoma · Metastasis · Hypophysis · Brain · Unknown primary site

Introduction

Merkel cell carcinoma (MCC) is an uncommon, but aggressive cutaneous neuroendocrine tumor that usually occurs both in the head and neck region, and in the distal extremities of elderly patients. MCC is further characterized by a high propensity of recurrence, resulting in both lymph node and distant metastases. It was originally described by Toker in 1972 as "trabecular cancer" and was subsequently referred to as neuroendocrine carcinoma, apudoma and small cell neuroepithelial tumor of the skin [1]. MCC is believed to originate from Merkel cells, which are slowly adapting mechanoreceptors belonging to the amine precursor uptake and decarboxilation (APUD) system, located in the dermo-epidermal junction [2]. Morphologically, MCC consists of sheets of small cells having a sparse cytoplasmic volume, round-to-ovoid nuclei with finely dispersed chromatin, and either one or two small nucleoli. Mitotic activity is typically high, and necrosis is often present. In addition to neuroendocrine markers, MCC typically expresses cytokeratin 20 arranged in a characteristic "dot-like" paranuclear pattern [3]. Interestingly, tumors showing morphological, phenotypical and cytogenetic features identical to MCC of the skin have been described in unusual sites, including the lymph nodes [4, 5]. MCC tends to grow rapidly and metastasize at an early stage. It spreads into nearby lymph nodes, but then may localize to the liver, bone, lungs, brain or other parts of the body. Although brain metastases have been reported, our paper describes the first noted case of pituitary metastasis.

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Clinical history

A 65-year-old Caucasian male patient complaining of a progressive hemianopia was diagnosed for a sellar lesion compressing the optic chiasm. The neoplasm was radically removed through a transsphenoidal approach. The morphological features of the tumor were those of a pituitary adenoma (Fig. 1a). Synaptophysin was diffusely positive (Fig. 1b), whereas pituitary hormones were negative, supporting the diagnosis of null pituitary adenoma. The following postoperative course resulted in a partial visual recovery.

Seven years later, a mass was noted at the level of his left groin. Following an echotomography and CT scan examinations, a left inguinal lymphadenectomy was performed. The patient was diagnosed with a primary MCC of the lymph node. After extensive workup, no apparent primary

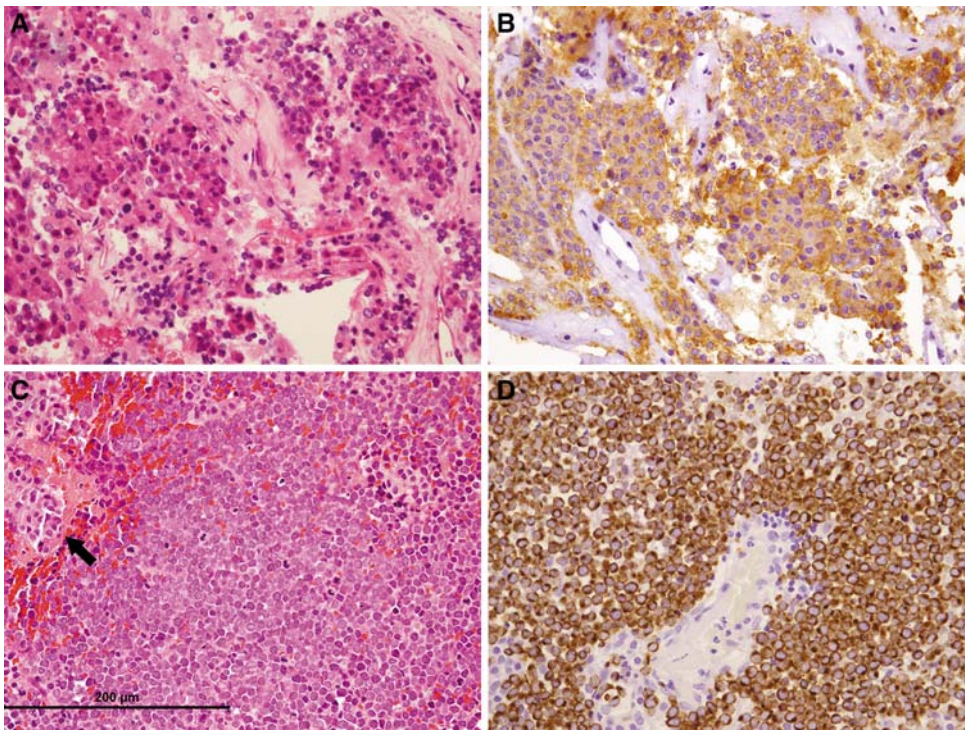

Fig. 1 Histological and immunophenotypical features of the pituitary masses resected at onset (**a**, **b**) and 10 years later (**c**, **d**). The first specimen showed a neoplasm composed of nests of acidophilic cells, consistent with pituitary adenoma (**a**, 40×, H&E). Synaptophysin immunostain was diffusely positive (**b**, 40×). The second specimen showed an undifferentiated small cell neoplasm characterized by round nuclei with granular chromatin and several mitoses. Residual pituitary gland was present (*arrow*) (**c**, 40×, H&E). The neoplastic cells were diffusely positive for cytokeratin 20 with a typical perinuclear dot-like pattern (**d**, 40×)

cutaneous lesions were detected. The patient was scheduled for a strict clinical and radiological follow-up, without any chemotherapy and radiotherapy treatment.

After 3 years, a 3.5-cm left inguinal lymph node was detected, and the patient underwent a left inguino-iliac-obturator lymphadenectomy with a regular postoperative course. Pathological examination confirmed the diagnosis of lymph nodal MCC. No chemotherapy was administered.

Six months later, the patient presented with visual deficits. Neurological examination revealed blindness in the left eye and severe visual impairment in the right eye (1/20). No other neurological deficits were noted. A cerebral MRI revealed a mass lesion (3.4 × 4.3 × 2.3 cm) at the level of the pituitary gland, interpreted as recurrence of the previous pituitary adenoma (Fig. 2a, b).

The tumor was partially removed by trans-sphenoidal endoscopy, followed by a transcranial approach, which allowed for the removal of the residual sovrasellar part of the tumor. The pituitary stalk was preserved, and a postoperative MRI showed a residual mass of <40% (Fig. 2c, f).

The histopathological examination displayed an undifferentiated small cell neoplasm, with extensive necrosis and brisk mitotic activity (Fig. 1c). The Ki67 labeling index was high (up to 70%). The neoplastic cells expressed cytocheratin CAM5.2 and cytokeratin 20 with a typical perinuclear dot-like pattern (Fig. 1d). Neuroendocrine markers, such as synaptophysin, chromogranin and CD56, were also expressed. Immunostains for pituitary hormones and TTF1 were negative, ruling out the possibility of small cell lung cancer. Based on the clinical history and the morphological and immunophenotypical findings, the patient was diagnosed with metastatic MCC.

Abdomen and thorax CT scans for tumor staging showed no pathological lesions.

The patient was scheduled for fractionated CyberKnife treatment for the pituitary metastasis (25 Gy, three fractions) combined with chemotherapy using cisplatin and VP16. The patient is still alive following 8 months of treatment, with his visual impairment being quo ante.

Discussion

This is a unique case of MCC metastasis in the pituitary gland. Based on the symptom of visual deficit and his previous history of pituitary adenoma, we suspected that the patient had a recurrent pituitary tumor. Also the imaging data seemed to support this hypothesis. However, the tumor morphology and the immunophenotype were those of MCC. The possibility of a sub-clinical small cell lung cancer-based metastasis was also considered in the differential diagnosis. However, the lack of TTF1 expression and the evidence of CK20 expression with the typical "dot-like" pattern ruled out this hypothesis. We also considered the possibility of a primary neuroendocrine small cell carcinoma; however, the patient's clinical history made this diagnosis unlikely, since the patient had had a diagnosis of MCC localized in the lymph node 4 years earlier.

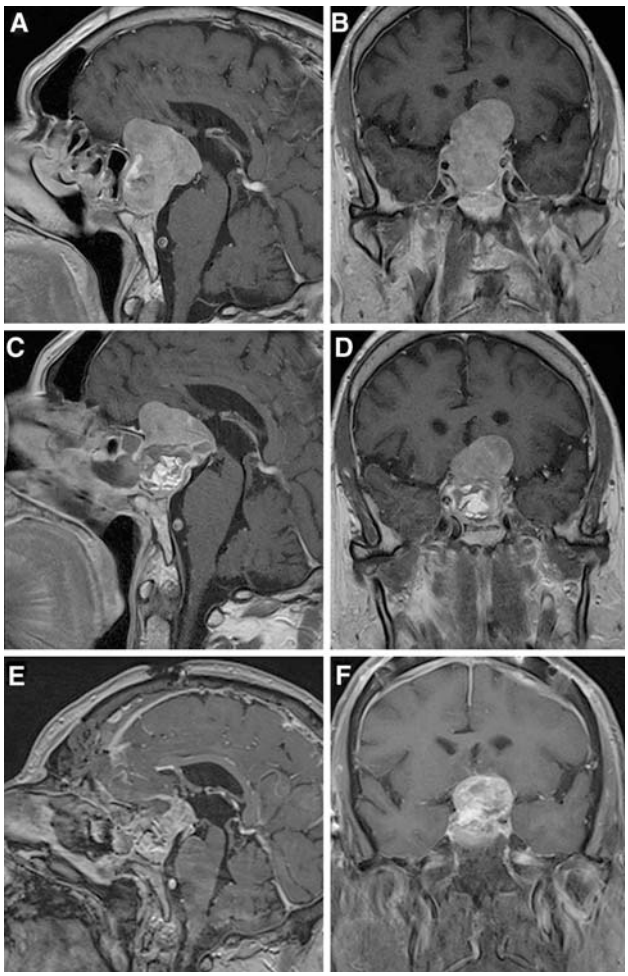

Fig. 2 Sagittal and coronal MR images. **a**, **b** A large sellar and sovrasellar lesion, initially interpreted as recurrence of the previously resected adenoma. **c**, **d** Partial removal after trans-sphenoidal approach. **e**, **f** Excision of sovrasellar remnant following craniotomy

It is worth noting that no skin tumor was detected. Lymph node localization of MCC from an unknown primary site has always been reported as a rare event, with some authors estimating its occurrence as being under 5% [6, 7]. Recent reviews suggest a higher incidence of between 10 and 20% [8]. We were able to find 89 published cases of MCC with an unknown primary site, the majority of which had proliferated into the lymph nodes. The reason underlying this phenomenon is still unclear, and at least three possible explanations have been suggested. One such explanation is that the primary skin tumor can spontaneously regress before clinical detection of the metastasis. This hypothesis is supported by the few reports of spontaneous regression of skin MCC [9]. Some authors assert that the MCC can grow primarily from a lymph node because of the malignant transformation of epithelial inclusions inside the node [10]; however, the presence of neuroendocrine cells in lymph nodes has never been proven. The hypothesis that MCC may originate from a pluripotent cell has gained recent support. This hypothesis could help to explain the origins of both skin and non-skin tumors, in addition to the cases of MCC in unexplained sites such as the parotid. Moreover, previous reports that the Merkel cell is pluripotent and localizes to the basal layer of the epidermis, whereas the MCC tumor usually affects the derma while sparing the epidermis, give strength to this third hypothesis [11].

To date, only 14 patients have been reported to have brain metastases from a MCC, and our patient represents the first one with a pituitary localization of the tumor (Table 1). MCC metastases generally spread following a hematic pathway, but a different spread pattern to the meninges and brain is represented by contiguous invasion by a scalp mass, as described in two cases [23, 28]. In the first case, a venous spread was suggested, in which the skull between the frontal scalp lesion and the invaded parenchyma remained intact. In the second case, however, the skull was clearly engaged.

It is interesting to note that the metastasizing cells reached a site where a surgical operation had been previously performed.

In our patient, it is possible that a previous surgical intervention can create a minor resistance site, which is more prone to develop a metastasis. Alternatively, we can also hypothesize that the postoperative fibrosis can create a more sheltered site for neoplastic cells. It has also been suggested that CNS tumors may provide a fertile substrate or an immunological haven for the metastases of additional tumors [29], and pituitary adenomas represent the second most frequent type of recipient tumor following meningiomas [30].

MCC brain metastases occur after a mean period of 19.7 ± 17.8 months (range 0–48 months) from the diagnosis of the primary lesion. In the reported case, pituitary metastasis appeared several years after the diagnosis of a nodal MCC, similar to published cases [15, 21]. Although the 5-year disease–specific survival ranges from 49% [26] to 64% [27], the mean survival time after the detection of a brain metastasis is only 6 ± 4 months (range 1–12 months), excluding the exceptional case of 3-year survival reported by Alexander et al. [17].

The metastases were surgically removed in only two reported patients [21, 23], with the remaining tumors always treated using the standard therapy consisting of palliative whole-brain radiotherapy and chemotherapy.

Our patient underwent surgery twice, with the objective of restoring visual acuity; the resection of the lesion was only partial due to the close adhesion of the tumor to the pituitary stalk. Then he underwent three sessions of radiosurgery (25 Gy) on the remaining pituitary metastasis; we did not find any other case of MCC metastasis treated with radiosurgery in the literature.

Table 1 Brain metastases from MCC: review of the literature

Case	Sex, age	Primary lesion	Brain metastasis	Therapy for brain metastasis	Other metastases	Period from first diagnosis	Survival time after brain metastasis
Wick et al. [12]	M, 62	Face	–	–	Liver	12 months	1 month, died
Goepfert et al. [13]	–	–	–	–	–	–	–
Giannone et al. [14]	F, 57	Scalp	Rt frontoparietal	RT (W), CT	Lung	2 months	4 months, survived
Knox and Kapp [15]	F, 75	Rt neck	Lt cerebellum	RT (W)	–	4 years	0 survived
Hitchcock et al. [16]	M, 52	Lt breast	–	RT (W), CT	Cutaneous, nodal	3 months	9 months, died
Alexander et al. [17]	M, 56	Lt face	Rt parietal	Biopsy, RT (W), CT	Lt Choroidal	0	3 years, survived
Yiengpruksawan et al. [18]	–	–	–	–	–	–	–
Snodgrass et al. [19]	M, 61	Forehead	Rt parietal, leptomeningeal carcinomatosis	RT (W), CT (intrathecal)	–	1 year	6 months, died
Straka and Straka [20]	F, 71	–	–	CT	Rt submaxillary lymph node	10 months	2 months
Ikawa et al. [21]	F, 49	Lt elbow	Rt cerebellum	Total removal, RT (W + L), CT	–	4 years	1 year, died
Eggers et al. [22]	M, 69	–	Pons and midbrain, leptomeningeal carcinomatosis	RT (W + L)	Inguinal and abdominal lymph nodes	10 months	6 months, died
Faye et al. [23]	M, 68	–	Rt parietal lobe	Surgery. Recurrence: RT + steroids	Axillary node	1 year	7 months, died
Chang et al. [24]	M, 45	Lt temporal skin	Cavernous sinus, left trigeminal cistern, bilateral internal acoustic meatus	CT, RT (W)	–	2 years	1 month, survived
De Cicco et al. [25]	M, 69	–	–	–	Lt axillary node	27 months	1 month, died
Present case	M, 65	–	Hypophysis	Surgery	Lung, abdominal and groin lymph nodes	4 years	8 months, survived

M male; *F* female; *Rt* right; *Lt* left; *RT* radiotherapy; *W* whole brain; *L* local; *CT* chemotherapy

Conclusion

Although MCC has a high tendency to metastasize, brain metastases are not a frequent occurrence. The diagnosis of a brain metastasis is usually associated with a poor prognosis. Surgical resection of the metastasis could probably increase survival, although substantial improvement resulting from this surgery cannot be predicted. We report for the first time a case of pituitary MCC metastasis that developed 11 years after the resection of a pituitary adenoma and 4 years after the diagnosis of lymph nodal localization of a MCC with unknown primary tumor origin. We believe that surgical manipulation could serve as a means to precondition a site to the spreading of neoplastic cells.

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