ORIGINAL ARTICLE

Metastatic Melanoma to the Pituitary Gland

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ABSTRACT: ***Background:*** Metastasis to the pituitary gland is unusual, and occurs most often in patients with carcinomas of the breast or lung. Despite its propensity for spread to the brain, metastatic melanoma has rarely been described within the sella. ***Methods:*** We report two cases of malignant melanoma pathologically confirmed within the pituitary, both metastatic from a primary site on the chest wall. In each patient, transsphenoidal resection of the tumor was incomplete and each received local radiotherapy after surgery. ***Results:*** One patient recurred quickly and developed brain metastasis as well. He died four months after resection of the pituitary metastasis, but the second patient survived six months without recurrence. As intrasellar metastasis portends widespread systemic disease and may be synchronous with parenchymal brain metastasis, survival in such patients is limited regardless of adjunctive therapy. ***Conclusions:*** Such cases are likely to arise more commonly in future due to the increasing incidence of melanoma. Identifying them by imaging alone is difficult due to inconsistent signal characteristics on MRI (as shown by these cases) and the confusion introduced by any associated intratumoral hemorrhage.

RÉSUMÉ: Métastase pituitaire d'un mélanome. Les métastases à l'hypophyse sont rares et surviennent la plupart du temps chez des patients porteurs d'un cancer du sein ou du poumon. Bien que le mélanome ait tendance à métastaser au cerveau, une métastase à la selle turcique a rarement été décrite. ***Méthodes :*** Nous rapportons deux observations cliniques de mélanome malin dans l'hypophyse, confirmés en anatomopathologie. La tumeur primitive dans les deux cas était située sur le thorax. La résection transsphénoïdale a été incomplète chez les deux patients et ils ont reçu de la radiothérapie locale après la chirurgie. ***Résultats :*** Un patient a eu une récidive peu de temps après et il a présenté également des métastases cérébrales. Il est décédé quatre mois après la résection de la métastase pituitaire. Le deuxième patient a survécu six mois sans récidive. Étant donné qu'une métastase intrasellaire laisse présager une maladie systémique disséminée et peut coïncider avec des métastases cérébrales parenchymateuses, la survie de ces patients est limitée, quel que soit le traitement d'appoint. ***Conclusions :*** Comme l'incidence du mélanome augmente, ces cas seront de plus en plus fréquents. Il est difficile de les identifier seulement par l'imagerie à cause de caractéristiques variables du signal à l'IRM, ce qui était le cas chez nos patients, et de l'association possible d'une hémorragie intratumorale, ce qui introduit un facteur de confusion.

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Due to the increasing incidence of melanoma, patients with metastasis to all systemic sites (including unaccustomed or uncommon locations) are now more frequently seen. Among these, metastasis to the pituitary has occurred in only a handful of cases.[1-6] We report two patients with melanoma involving the pituitary, both with prior melanoma already established in extrapituitary locations. Because pituitary adenomas are common in the population at large, oncologists often assume that a sellar tumor in a patient with melanoma is a pituitary adenoma. The autopsy series of Max et al[7] showed that in patients with metastatic cancer a sellar lesion is actually twice as likely to be a benign pituitary adenoma as a metastasis. The characteristic MRI features of melanin, if present, would allow a sellar tumor to be identified as a melanocytic neoplasm, but they are not infallible and surgery may still be needed for biopsy and decompression. Although the assumption of a pituitary adenoma may often be correct, these two cases are presented to emphasize

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that patients who carry both systemic melanoma and a sellar tumor may harbor melanoma within the sella; and that melanoma may present as a sellar tumor even without a history of systemic melanoma.

Case Reports

Case 1

A 77-year-old male had wide local excision of melanoma (Clark level IV, Breslow's thickness 1.2 mm) of the anterior chest wall, without lymph node sampling. Thirty-three months later he developed ptosis and diplopia and had by exam oculomotor and abducens palsies on the left. Endocrine workup showed low levels of gonadotrophic hormones but other pituitary hormonal axes were intact. Ophthalmological exam showed full visual fields and visual acuity of 20/30 in the right eye and 20/70 in the left. On MRI a tumor centered on the sella was present which extended into both cavernous sinuses and the upper clivus [Figure 1]. After transsphenoidal surgery, during which subtotal resection of a fleshy, vascular, pigmented tumor was achieved, the cranial neuropathies did not improve and visual acuity was stable. Invasion of the adenohypophysis by tumor was noted at surgery. Pathological examination revealed a poorly differentiated melanoma (staining positive for HMB-45 and for S-100 protein) with bone invasion. Staging workup failed to reveal any other areas of metastasis. Intensity-modulated radiotherapy was given to the sella and parasellar area to control residual tumor within the cavernous sinuses and clivus. The patient was alive six months after surgery with no further growth of tumor evident, and no other intracranial metastases.

Figure 1: *MRI of sella, Case 1, coronal view: (A) T1-weighted image, post-contrast and (B) T2-weighted image. Bilateral cavernous sinus invasion is present, but no suprasellar extension, and the pituitary stalk appears intact. As hypointensity on T2-weighted imaging is typical for melanoma, the opposite signal displayed in this patient confounded the diagnosis prior to surgery.*

Case 2

A 42-year-old male presented with melanoma (Clark level IV, Breslow's thickness 3 mm) of the anterior chest wall, and was treated with wide local excision and axillary node dissection that revealed 0/15 nodes positive for tumor. He was free of disease for 77 months, and then developed two new subcutaneous nodules on his chest representing metastatic melanoma. Staging workup showed cervical and hilar lymphadenopathy and metastasis to lung and to retroperitoneum. Magnetic resonance imaging revealed an intrasellar tumor, 2.5 cm in maximum

Figure 2: *MRI of sella, Case 2,. (A) Coronal view, T1-weighted, post-contrast (B) Sagittal view, T1-weighted, post-contrast. (C) Coronal view, T2-weighted. The tumor shows a dumb-bell shape and significant chiasmal compression, together with possible invasion of the left cavernous sinus. The normal pituitary gland is not distinguishable from tumor. The low to isointense T2 signal is more consistent with melanoma than with pituitary adenoma.*

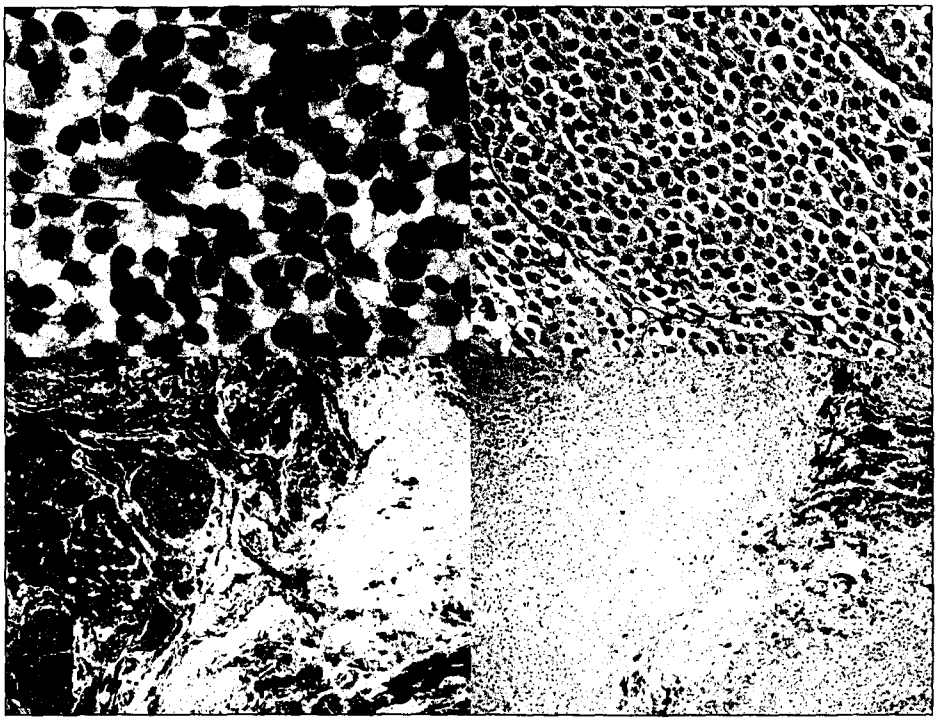

Figure 3: Smear preparation (upper left panel) shows an epithelioid round cell neoplasm with moderate pleomorphism. In the corresponding tissue section (upper right panel), the tumor is organized in sheets and lobules. Immunohistochemical staining for melanoma antigens (bottom left panel) shows strong tumor cell reactivity (left half of panel), with lack of staining in entrapped pituitary acini (right half of panel). In contrast, a serial section immunostained for synaptophysin (bottom right panel) shows strong positivity in normal pituitary acini (right half of panel), with no reactivity in the metastatic melanoma (left half of panel). Upper left panel, H&E, x 400; upper right panel, H&E, x 200; bottom left panel, melanoma antigen cocktail immunostain with hematoxylin counterstain, x 40; bottom left panel, synaptophysin immunostain with hematoxylin counterstain, x 40. The melanoma antigen cocktail comprises antibodies against Mart 1 (clone Ab3), dilution 1:100; HMB-45, dilution 1:50; and tyrosinase (clone T311), dilution 1:20.

diameter, with suprasellar extension and chiasmal compression [Figure 2]. As in Case 1, the radiological interpretation considered the history of melanoma and raised the possibility of metastasis, but considered pituitary adenoma more likely. Symptoms of central hypocortisolism and hypogonadism were present, as well as diabetes insipidus, but formal endocrine workup was not completed due to the urgent need to achieve decompression of the optic apparatus. Ophthalmological examination showed an incomplete right temporal hemianopia with visual acuity of 20/400 OD and 20/60 OS. At transsphenoidal surgery, the dura of the sellar floor was grossly invaded by tumor. Within the sella, hypervascular, friable, pigmented tissue was encountered and subtotally resected to achieve decompression of the optic apparatus. Pathological examination of the tumor showed melanoma; tumor cells were synaptophysin-negative, but stained positive for HMB-45 [Figure 3]. No necrosis was seen, but occasional mitotic figures were seen. After surgery, deficiencies of thyrotropin, adrenocorticotropin, gonadotropins, and vasopressin were confirmed. After initial improvement in vision, it relapsed to the preoperative level and he received whole-brain radiotherapy (30 Gy in 10 fractions). He was treated with thalidomide and temozolomide with resulting decrease in the size of the pituitary and lung metastases. However, new brain metastasis developed two months after surgery, and he died of widespread metastasis four months after that.

Discussion

Metastasis to the pituitary gland is uncommon overall, with the majority occurring in patients with carcinomas of the lung or breast. Many such tumors produce no symptoms during life, but metastatic deposits are found at autopsy in the pituitary glands of up to 5% of subjects with systemic cancer.[8] Premortem diagnosis typically follows the development of hypopituitarism, visual loss, or diplopia from cavernous sinus involvement, but can be difficult as the constitutional symptoms of systemic cancer can mimic those of anterior pituitary dysfunction.[9] Diabetes insipidus is seen at presentation in 45-70% of these patients, with others developing it later in the course of the disease.[8,9] Although both of the patients reported here had symptoms of parasellar compression and partial anterior hypopituitarism, only Case 2 reported polyuria and polydipsia on diagnosis.

Table: Patients with melanocytic tumors within the sella

	Age/sex	Extrasellar primary	Preop endocrine deficits	DI	Brain mets	Surgery	XRT	Chemo	HMB-45/MIB-1	Follow-up/mos
Primary sellar melanocytoma / benign										
Neilson et al 1963[16]	62/M	none	TSH, ACTH, FSH/LH	no	no	no	no	no		D/36
Scholtz and Siu 1976[17]	54/M	none	?	?	no	yes	no	no		D/0.5
Kasumova and Imauri 1980[18]	36/M	none	?	?	no	yes	no	no		A/72
Chappell et al 1990[19]	35/F	none	?	no	no	yes	no	no		A/3
Rousseau et al 2005[20]	25/F	none	ACTH	no	no	yes	no	no	positive / 3%	A/24
Primary sellar melanoma / malignant										
Roos 1963[23]	44/F	none	TSH, ACTH	yes	no	yes	no	no		D/15
Copeland et al 1980*[24]	37/F	none	?	no	LMD	yes	no	yes		D/41
Aubin et al 1997**[25]	47/M	none	TSH, FSH/LH, ACTH	SIADH	no	yes	yes	no	positive	D/16
Tutenberg et al 2004[26]	37/F	none	TSH, FSH/LH	no	no	yes	yes	no	positive / 15-30%	A/24
Jacob et al 2006[27]	63/F	none	none	no	no	yes	yes	no	positive	D/"weeks"
Metastatic melanoma										
Cox and Sloan 1924[1]	54/M	jejunum	?	yes	yes	no	no	no		D/6
Girdwood 1928[2]	42/F	skin (multiple)	?	yes	yes	no	no	no		D/1
Schurmeyer and Bettmann 1956[3]	31/F	skin (back)	?	no	no	no	no	no		D/unknown
Clifford et al 1968[4]	64/M	spinal cord (unproven)***	?	?	yes	no	no	no		D/unknown
Mayr et al 1993[5]	25/M	?	TSH	no	yes	?	?	?		A/unknown
Leung et al 2004[6]	46/M	skin (neck)	TSH, FSH/LH	yes	no	yes	yes	no	positive	A/7
McCutcheon et al 2006 (case 1)	79/M	skin (chest)	FSH/LH	no	no	yes	yes	no	positive	A/6
McCutcheon et al 2006 (case 2)	49/M	skin (chest)	TSH, FSH/LH, ACTH	no	yes	yes	yes	yes	positive	D/6
Non-melanocytic tumors showing melanin production		Tumor type								
Harris et al 1999[14]		craniopharyngioma (2 cases)								
Tobo et al 1981[15]		teratoma containing melanotic prognoma (1 case)								

*Tumor originated above the sella but on recurrence was intrasellar

**Marked necrosis and mitotic activity; at autopsy had liver metastasis and leptomeningeal involvement by tumor

***Multiple skin nevi were incompletely examined

Because melanoma so rarely appears in the sella, tumors found there during oncologic staging (or after scans prompted by headache or visual loss) are most commonly coincidental pituitary adenomas rather than metastases. Distinguishing an adenoma from a melanoma is uncertain at best, as both can invade the cavernous sinus, sphenoid bone, or clivus, and both can show intratumoral hemorrhage. Melanotic melanomas by MRI show high signal on T1-weighted images and low signal on T2, but interpretation of images may be confounded by the presence of intratumoral or peritumoral hemorrhage of varying ages, and intracellular methemoglobin shows similar characteristics to melanin.[10] Our Case 1 showed hyperintensity on T2, which confounded the preoperative diagnosis [Figure 1], but Case 2 did show low signal on such sequences [Figure 2]. In the absence of hemorrhage or cyst fluid within the tumor, pituitary adenomas theoretically differ from melanoma by showing mild hyperintensity on T2 (80%) and hypointense signal on T1.[11] As these proportions vary by secretory subtype, and by melanin or methemoglobin content, general statistics may be misleading in individual patients.[12,13] An MRI can suggest that an intrasellar tumor is melanocytic in nature, but only pathological examination can prove it.

Melanocytic tumors within the sella have been infrequently reported, and significant confusion exists in the terminology and classification of such neoplasms. We propose that they most logically divide into four categories: (1) melanocytomas, which follow a benign and indolent clinical course, much like many pituitary adenomas; (2) primary malignant melanomas, associated with no identifiable extrapituitary site of origin, displaying a tendency to enlarge more rapidly, and capable of metastasis; (3) malignant melanomas metastatic to the sella, with a known primary site in the skin, eye, or elsewhere; and (4) non-melanocytic tumors showing melanin production. This last category is very rarely seen, but craniopharyngiomas containing melanin have been reported,[14] as has a case of teratoma containing melanotic prognoma (a tumor usually seen in the infant maxilla).[15] Our analysis excludes tumors arising in parasellar locations like the cavernous sinus, and focuses exclusively on those that involve the pituitary gland.

Although melanocytomas occasionally occur in the intracranial compartment, typically in association with the leptomeninges, only five cases (Table) have been reported which arose unequivocally within the sella.[16-20] These tend not to be associated with diabetes insipidus, but anterior pituitary deficits are sometimes seen, and extended survival is possible. Melanocytes exist most densely over the ventrolateral medulla, but small clusters can be found anywhere along the leptomeninges.[21] Despite a report of melanocyte clusters within the pars intermedia in Zucker rats, the pattern of leptomeningeal distribution of such clusters differs from that seen in man, and intrapituitary melanocytes have yet to be detected in the human pituitary.[22] Thus, the cell of origin of intrasellar melanocytomas is uncertain.

Malignant melanomas have five times been reported in the sella without a known primary site.[23-27] It is impossible to say whether such tumors are truly primary to the sella, whether they represent instances in which a melanoma elsewhere flourished long enough to metastasize before undergoing involution, or whether the search for an extrasellar primary tumor was simply inadequate. These tumors show such hallmarks of malignancy as marked necrosis, high MIB-1 labeling indices, and frequent mitotic figures, and lead to the patient's demise in spite of aggressive treatment with surgery, local irradiation, and/or chemotherapy. None of the cases in the literature was associated with diabetes insipidus, but again anterior pituitary deficits are seen. The cells of these tumors stain positively for the HMB-45 antigen, as do those of melanocytomas and metastatic melanomas. In this category, only the case reported by Aubin et al had extracerebral metastasis, a hepatic nodule that did not appear until ten months after the initial surgery.[25]

Our patients both present a clear example of melanoma metastatic to the sella from a primary extrapituitary location. Six such cases have previously been reported with clinical detail, and only two within the past 25 years.[1-6] Such patients are also extremely rare at autopsy. In the series of Hagerstrand and Schonebeck encompassing 763 autopsy patients with cancer, 29 had metastasis to the pituitary of which two were melanomas.[28] In another such series compiled by Schreiber et al, 737 autopsy patients gave rise to 26 pituitary metastases, none of which were melanomas.[29] Melanoma metastases are mentioned in very small numbers and without description by other authors,[7,9,30] and in the largest surgical series of metastases to the sella published to date by Morita et al, none of the resected tumors was a melanoma.[31]

The metastasis may originate in any of the typical locations for melanoma (skin, gut) and here, as with other metastatic histologies, diabetes insipidus is common. In the only other case to have undergone surgery (followed by adjuvant radiotherapy), the patient was alive and well seven months later;[6] earlier untreated cases imply a natural history similar to that seen for untreated cases of cerebral metastasis. This is not surprising, as concomitant brain metastasis was observed in half the extant cases and occurred synchronously in our Case 2. In our patients, a transsphenoidal approach allowed subtotal excision, as the tumor was intimately adherent and invasive to the normal pituitary and the adjacent dura. Accordingly, we followed with limited-field radiotherapy (which was unsuccessful in shrinking the tumor) and in our second case, with chemotherapy designed to achieve some measure of penetration through the blood-brain barrier. The chemotherapy did cause tumor shrinkage but failed to prevent new brain metastases or further spread of his already widely scattered systemic disease. Stereotactic radiosurgery was not feasible given the close proximity of the tumor to the optic apparatus, but might have given better local control had the situation permitted its use.

An aggressive attempt at resection is advisable in these difficult neoplasms. If melanoma is suspected preoperatively from MRI signal characteristics, conclusions before surgery as to the malignancy of the lesion are premature; the tumor may prove to be an indolent melanocytoma requiring no further therapy, or an anaplastic melanoma needing strenuous further effort at local and systemic control. A careful search for concomitant brain metastasis may disclose lesions implying a malignant phenotype within the sella. However, it is always possible for a patient to harbor both a brain metastasis and a pituitary adenoma.

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