MENINGEAL MELANOCYTOMA ("MELANOTIC MENINGIOMA")

Its Melanocytic Origin as Revealed by Electron Microscopy

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A primary melanotic tumor of the leptomeninges with prolonged clinical course and benign histology was studied by light and electron microscopy. Similar tumors, referred to as "pigmented" or "melanotic" meningiomas, were reviewed. The cells of the tumor reported here lack the ultrastructural features of meningothelium and are characterized by the presence of numerous melanosomes and premelanosomes in their cytoplasm. Therefore, the term "meningeal melanocytoma" rather than "pigmented meningioma" appears appropriate. A benign histology and favorable clinical course distinguish meningeal melanocytoma from primary malignant melanomas of the leptomeninges. The histology, ultrastructure, and behavior of this tumor show similarities to melanocytic tumors of the dermis (cellular blue nevus) and of the uveal tract (spindle A melanoma). While cytologically and biologically benign, meningeal melanocytomas may cause neurologic deficits through their expanding growth; an early excision may be curative before neurologic complications become fatal.

MELANOCYTES ARE KNOWN TO EXIST NORmally in the human leptomeninges, being more abundant over the ventral surface of the medulla and the upper spinal cord. Primary meningeal neoplasms derived from these melanocytes are rare and, in most cases reported, malignant. Several publications[3,7,10,20,25] have been concerned with the primary meningeal malignant melanomas and have made pathologists aware of their histologic picture and ominous prognosis. In contrast, the existence of a benign variety of melanin-pigmented meningeal tumors has not been adequately recognized. A few such cases have been reported[1,2,8,21,24,26] under the term "melanotic or pigmented meningioma" although the cell of origin of these tumors remains obscure.

We present here the study of a melanin-pigmented meningeal tumor displaying the gross and light-microscopic features of the so-called "pigmented meningioma." Similar cases culled from the literature are reviewed, and the histogenesis of the tumor is discussed in the light of its ultrastructural characteristics.

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Received for publication June 12, 1972.

CASE REPORT

The patient was a 71-year-old Caucasian man whose clinical history dated back 6 years prior to his death, when he was hospitalized for headaches and motor weakness more pronounced in the left leg. Complete work-up at that time failed to reveal the cause of his symptoms. Three and a half years later, he was reevaluated for progression of his neurologic deficits. Marked weakness of all extremities, paresthesia of the legs, and a neurogenic bladder were present. Radiologic examination of the skull and spine, a brain scan, and a myelogram were interpreted as normal. Over the next 2½ years, the patient's condition deteriorated to the point that he became bedridden. He also developed difficulty in swallowing solid and liquid foods. Physical examination on his last admission revealed marked muscle atrophy (neurogenic by biopsy) of all extremities, absent abdominal reflexes, bilateral Babinski's reflex, profound diminution of pin-prick sensation extending to the level of C_2–C_3, and impaired proprioceptive and vibratory sensation in all extremities except for the right arm. Fundoscopy revealed no lesions; lumbar puncture yielded clear cerebros-

pinal fluid with an opening pressure of 150 mm H_2O and closing pressure 85 mm H_2O. The protein concentration was 83 mg/100 ml. Myelography demonstrated a normal subarachnoid space up to the level of C_2; a small amount of contrast medium entered the base of the middle cranial fossa but visualization of the atlantooccipital region remained unsatisfactory. Compression of the spinal cord at the level of the foramen magnum was suspected but could not be confirmed by myelography. The patient died 3 months later with extensive bronchopneumonia.

AUTOPSY FINDINGS

On removing the brain, a black, smooth-surfaced mass was noted protruding from the left anterolateral surface of the medulla at the level of the foramen magnum, lying partly in the posterior fossa and partly in the spinal canal (Fig. 1). The mass was not attached to the dura and appeared clearly defined. It compressed the medulla below the olivary nuclei and the C_1–C_2 neurotomes, reducing these structures to a thin rim of tissue covering the right lateral and posterior aspects of the tumor (Fig. 2). The tumor measured 4.5 × 3.5 × 2.7 cm, and was soft, rubbery, and uniformly black. Two 0.2-cm black speckles were seen in the leptomeninges over the left cerebral hemisphere. Very few similar spots were noted on the leptomeninges of the spinal cord. The rest of the brain, cranial cavity, cord and spinal canal were normal. The cerebral and spinal arteries showed mild focal atherosclerosis. No tumor was found in any of the other organs, and the skin showed no pigmented lesions. The eyes were not examined. The immediate cause of death was an extensive suppurative bronchopneumonia.

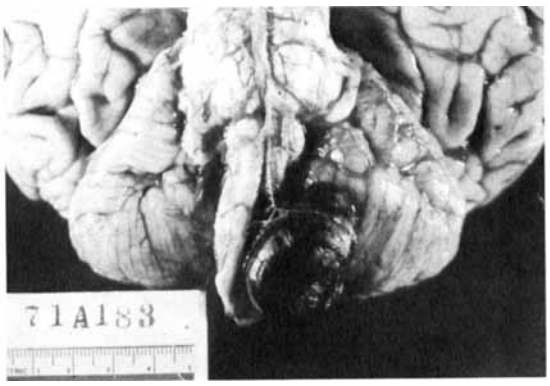

FIG. 1. Gross appearance of the tumor.

FIG. 2. Transverse section of the tumor at the level of C_1. The tumor is dumbbell-shaped and well circumscribed. There is marked distortion of the cord, especially on the left side; the right anterior horn is preserved. The darker-stained zone between the tumor mass and the cord is particularly vascular and rich in heavily pigmented macrophages (×2.3).

PREPARATION, STAINING, AND HISTOLOGIC FINDINGS OF THE TUMOR

Sections were routinely processed and stained with hematoxylin and eosin, Gomori's trichrome, Gomori's methenamine silver, and by the Prussian blue reaction. Some sections of the tumor were bleached in hydrogen peroxide before staining. For electron microscopy, the tissue was fixed in 2% buffered glutaraldehyde, post-fixed in phosphate-buffered 1% osmium tetroxide, dehydrated through graded concentrations of ethanol and propylene oxide, and embedded in Epon 812. Thin sections were stained with uranyl acetate and lead citrate and examined with a Siemens 101 electron microscope.

The tumor was cellular, consisting of closely packed, elongated spindle cells arranged in bundles which were disposed in different directions and showed a tendency to whorl (Fig. 3). Clusters of larger polygonal cells loaded with irregular clumps of dark-brown pigment were also present, especially around vessels. The spindle cells possessed a relatively large, elongated nucleus with a fine chromatin pattern. No nucleoli or mitoses were noted. The cytoplasm was sparse with occasional polar processes. Under high magnification, fine brown granules were seen scattered uniformly within the cytoplasm. These granules, as well as pigment in macropages, failed to stain for iron. The trichrome and methenamine silver stains brought out thin collagenous septa and a delicate lattice of fine

reticulum fibers enveloping small groups and individual cells (Fig. 4). Neither necrosis nor hemorrhage was seen. The free surface of the tumor was covered by a thin fibrous membrane. The compressed and distorted medullary and cord structures showed gliosis and degenerative changes. Melanophages were present in the perivascular spaces, but no neoplastic infiltration was noted. Atrophy and demyelinization were observed in the descending tracts at lower levels of the spinal cord. Spindle cells with melanin granules and polar processes made up the black speckles observed in the leptomeninges elsewhere (Fig. 5).

Ultrastructurally, the tumor consisted of melanocytes containing premelanosomes at varying stages of development and fully pigmented mature melanosomes (Fig. 6). Each of these organelles was limited by a unit membrane and varied in size from 300–600 mμ (Fig. 7). The premelanosome exhibited the characteristic lamellar internal structure (Fig. 8). The rough endoplasmic reticulum of the tumor cells was not extensive, and no cytoplasmic fibrils were observed. The Golgi apparatus and mitochondria were too poorly preserved to be evaluated. The nucleus was usually oval with a shallow indentation. Nucleoli were not prominent. In some areas, individual cells were partially surrounded by a basement membrane-like material. Occasionally, attachment sites were seen between tumor cells; in these sites, the adjoining cell membranes were parallel and closely interposed leaving an intercellular space of about 20 mμ. The material filling the intercellular space was homogeneous and of rather low density while the subjacent cytoplasmic matrix was conspicuously dense (Fig. 9). Intercellular attachments with these characteristics correspond to the zonula adherens or intermediate junction of Farquhar and Palade.[4] The interstitium contained fine (6 mμ) fibrils, fibrous long-spacing collagen (periodicity 76 mμ),

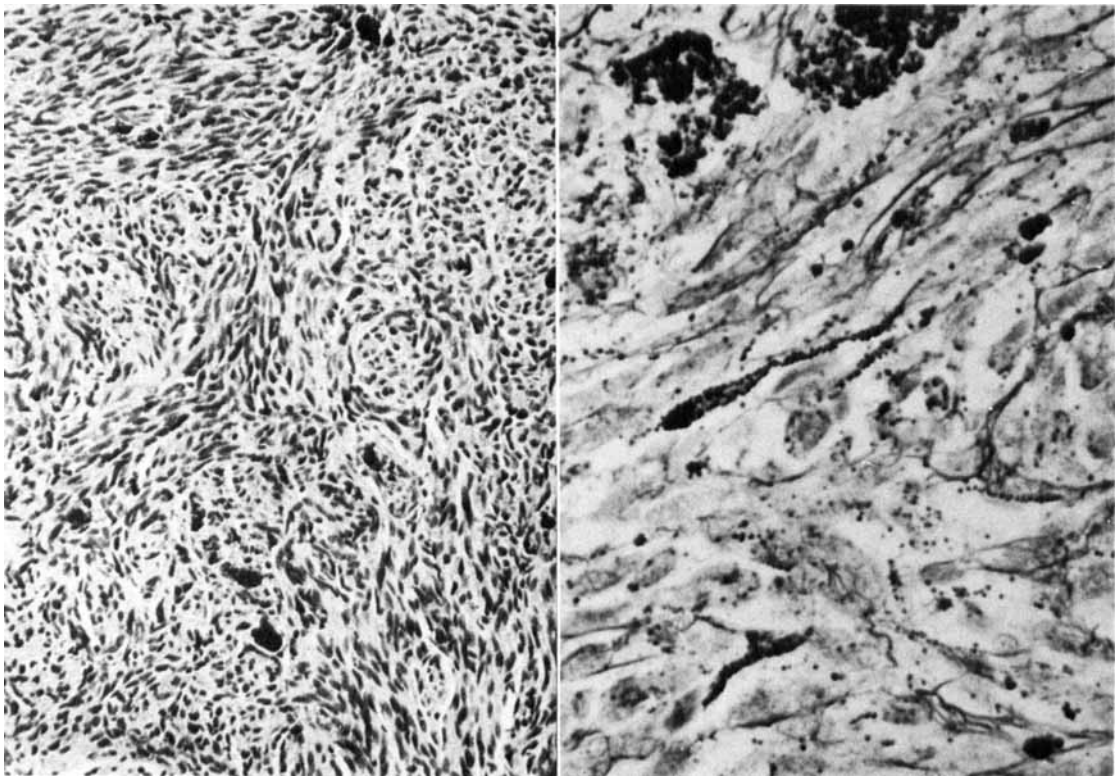

FIG. 3 (*left*). The tumor is composed of spindle-shaped cells arranged in fascicles showing a tendency to whorl. Note clusters of heavily pigmented melanophages (H and E, ×158).

FIG. 4 (*right*). Silver stain shows delicate reticulum fibers surrounding the small groups and individual cells. This stain also brings out the fine, uniform melanin granules within the cytoplasm of neoplastic cells which contrast with the irregular lumps of melanin in the macrophages (left side of the figure), Gomori's methenamine silver, ×710.

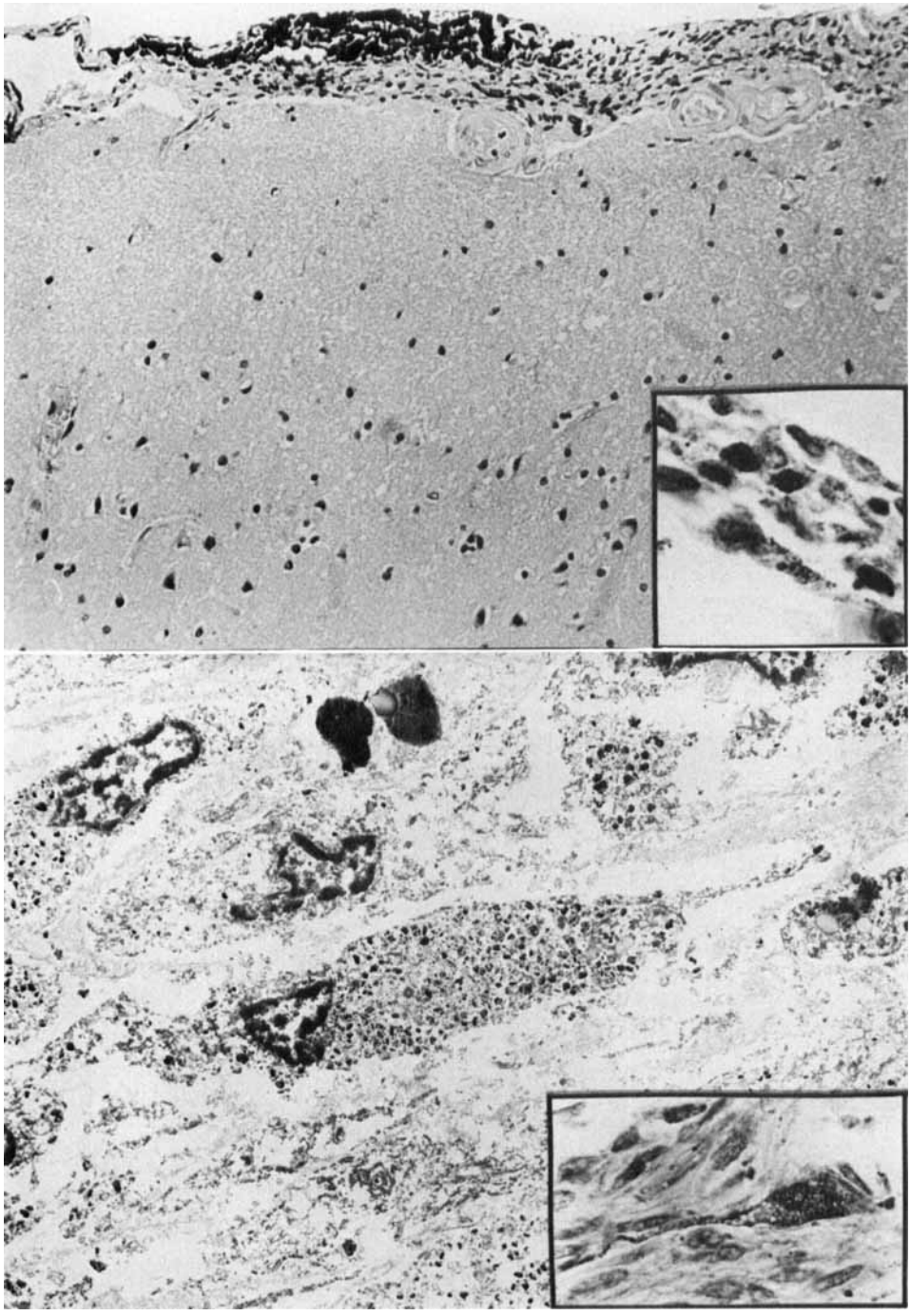

FIG. 5 (*top*).A small focus of leptomeningeal hyperpigmentation over the left cerebral hemisphere (H and E, ×201). The cellular composition of this focus is shown in the insert (H and E, ×1216).

FIG. 6 (*bottom*). Tumor cells are elongated with thin polar processes, numerous melanosomes and partially pigmented premelanosomes are seen as discrete units within the cytoplasm. The large irregular clusters of melanin (top middle) belong to a melanophage (×5600). The characteristic polar processes are also seen at the light microscopic level (insert, H and E, ×704).

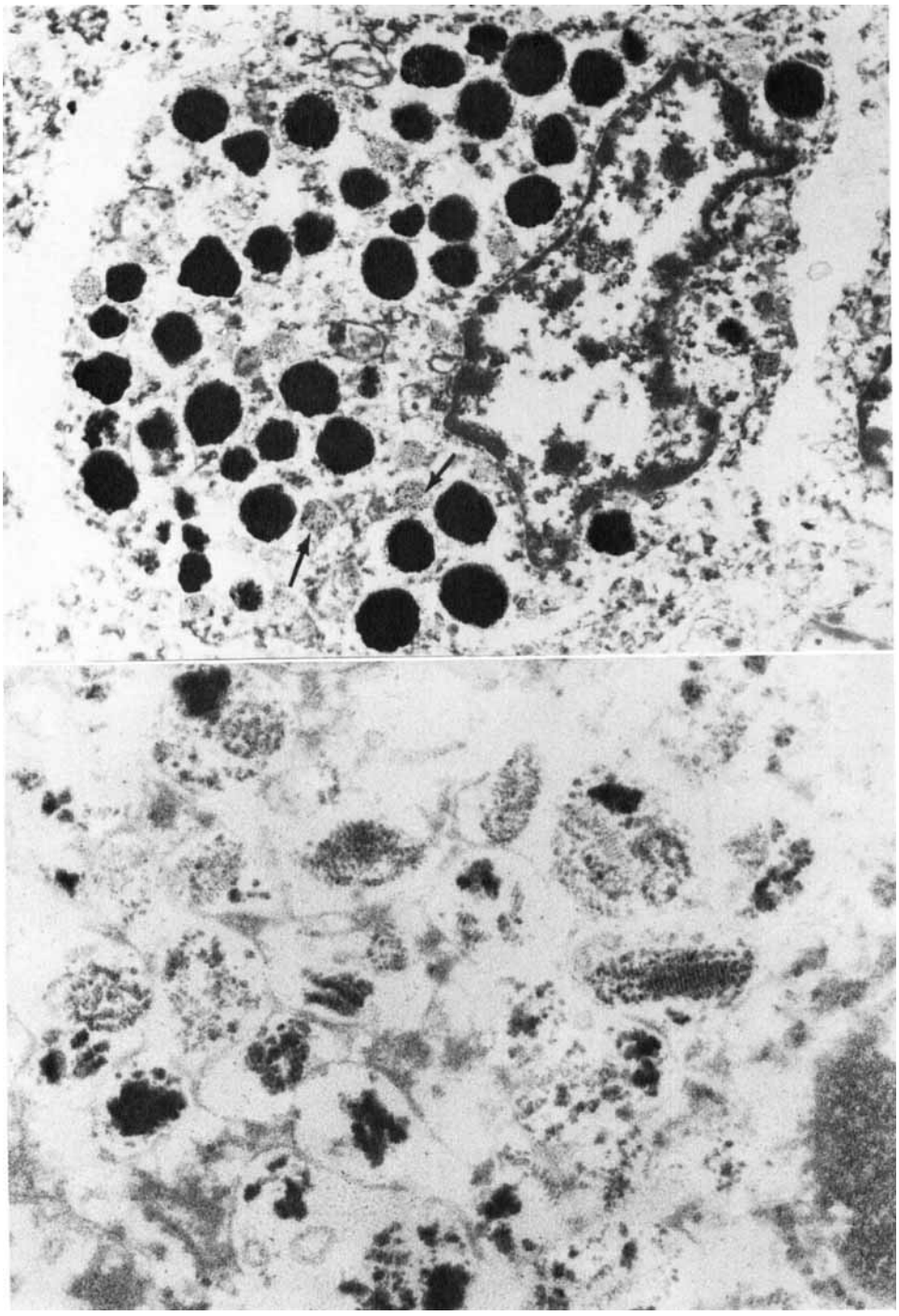

FIG. 7 (*top*). Ultrastructural detail of a tumor cell in cross section. Arrows indicate premelanosomes (×13,200).

FIG. 8 (*bottom*). Premelanosomes in various stages of melanization are seen within the cytoplasm of a tumor cell; each is surrounded by a unit membrane (×88,000).

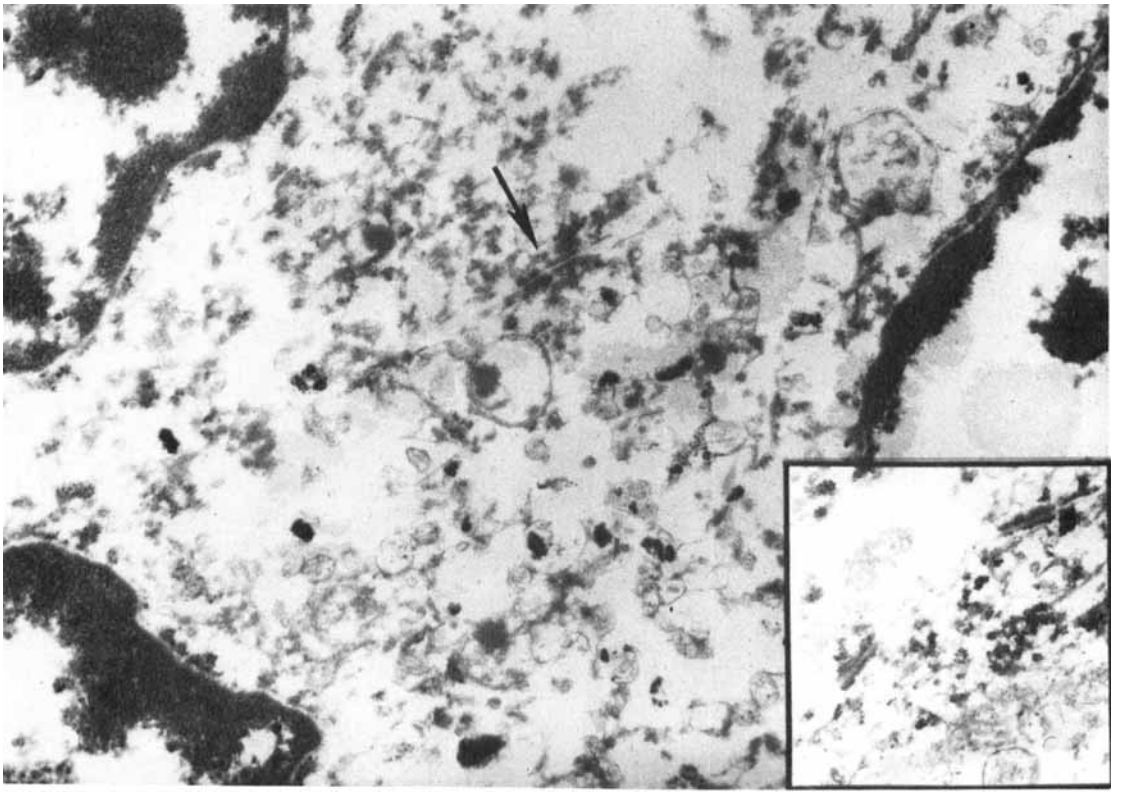

FIG. 9. Portions of three tumor cells. Intercellular attachment sites of the zonula adherens type (arrow) are seen between two of them (×25,900). Insert: similar junctions in more detail (×26,200).

and few collagen fibers (Fig. 10). The melanophages contained large, irregular melanosome complexes in varying states of degradation.

DISCUSSION

The scanty melanocytes normally existing in the leptomeninges are spindle-shaped with short, polar processes and contain few pigment granules.[16] Excessive pigmentation of the leptomeninges, so-called "meningeal melanocytosis," due to an increase in the number of melanocytes and the amount of melanin produced, is occasionally encountered and may be associated with pigmented cutaneous nevi.[22] Melanotic meningeal neoplasms can be classified as *metastatic,* which are by far the commonest since melanomas comprise 12–16% of all tumors metastatic to the central nervous system,[2] and *primary,* which are uncommon. The majority of the reported primary melanotic tumors are malignant in contrast to the rarity of malignant neoplasms originating from the meningothelium.

The pathology and clinical course of primary malignant meningeal melanomas are well recognized.[3,7,10,20,25] By the time of autopsy or surgical intervention, these tumors are usually diffuse or multifocal and may occur in any part of the central nervous system but predominantly involve the spinal cord and cerebral hemispheres. The cells display marked cellular pleomorphism, but spindle cells are encountered most consistently. Numerous mitoses, necrosis, and hemorrhage bespeak their malignant nature. A short history of neurologic symptoms usually correlates with rapid tumor growth, a poor prognosis, and death within a year from the onset of symptoms.[7]

One might expect that benign melanocytic tumors would occur in the leptomeninges as they do in other parts of the body where melanocytes are present. Indeed, meningeal tumors with melanin pigmentation, benign histologic features, and a favorable clinical course have been reported. The term "pigmented or melanotic meningioma" was coined

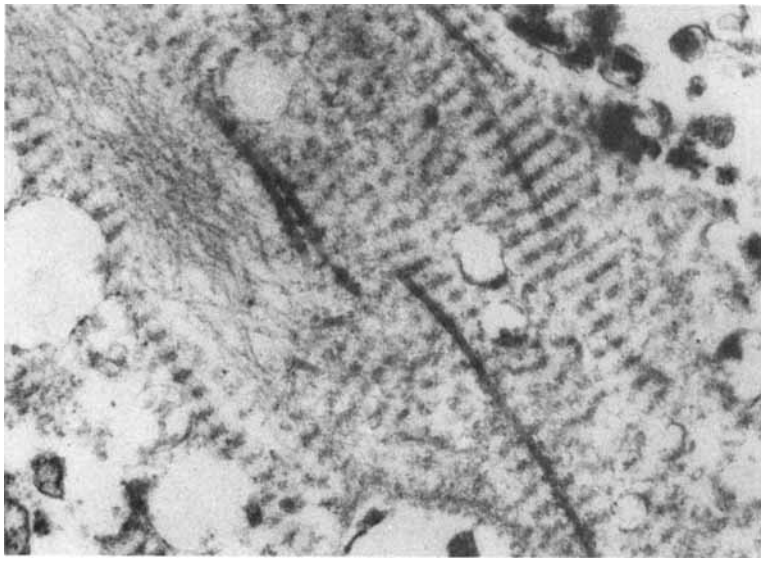

FIG. 10. Bands of long-spacing collagen with a periodicity of 76 mμ are seen in the interstitium of the tumor, in close apposition to the cell membrane. These bands are comprised of thin longitudinal filaments. Fine fibrils (6 mμ wide) are also present (×34,000).

by Ray and Foot[21] for histologically benign meningeal tumors with heavy melanin pigmentation in an attempt to distinguish them from malignant melanomas and to emphasize their resemblance to meningiomas. Table 1 summarizes the clinical and pathologic data of the eight cases reported since 1940, under this descriptive term. The tumors are reported as solitary, well-circumscribed, moderately firm, black or dark-brown 2- to 5-cm masses. They are most often located in the subdural space of the spinal canal and in the posterior cranial fossa. The tumors probably grow slowly as evidenced by the longstanding history of symptoms and their tendency to compress rather than infiltrate adjacent tissues. On occasion, they may become locally aggressive against bone (cases 2, 5). The presence of

TABLE 1.

Author(s)	Race and sex	Age (yrs.)	Duration of symptoms	Location of tumors	Size	Treatment	Survival (yrs.)
Ray & Foot[21]							
Case 1	W, F	29	5 yrs.	L_1-L_3	1.5 × 3.5 (cm)	Complete resection	25*
Case 2	F	45	1 yr.	Post. fossa	25 g	Complete resection and radiotherapy	11/2†
Bakody et al.[2]							
Case 3	W, M	45	2 yrs.	L_2-L_4	5 cm	Subtotal resection	8*
Keegan and Mullan[8]							
Case 4	W, M	51	6 yrs.	Pons	1.5 cm	Subtotal resection	3½*
Turnbull & Tom[26]							
Case 5	F	35	2 yrs.	Meckel's cave	5 cm	Partial resection and radiotherapy	19‡
Abbott et al.[1]							
Case 6	W, M	57	5 yrs.	T_4	2 cm	Complete resection	1*
Russell Rubinstein[24]							
Case 7	NS	NS	NS	Cervical cord	NS	NS	NS
Case 8	NS	NS	NS	Cerebellum	NS	NS	NS

Clinicopathologic data for previously reported cases of "pigmented meningioma." NS = not stated.
* Patient alive at the time of report.
† Patient died of unknown cause.
‡ Patient died of lymphosarcoma and residual tumor was found at autopsy.

melanophages in the Virchow-Robin spaces may give the false impression of invasiveness.

The histology of these tumors is very consistent and, in all instances, identical to that of our case. They are cellular and composed of spindle cells arranged in fascicles. Fine melanin granules are discernible in the cytoplasm of the spindle cells, but bulky pigment aggregates are only seen within macrophages. Cellular atypia, mitotic activity, necrosis, and hemorrhage are absent. The overall histology, therefore, is reminiscent of fibroblastic meningiomas. A tendency to whorl formation has been interpreted as a clue regarding this origin from the meningothelium. This belief is further enhanced by the presence of rare psammoma bodies (case 3) and focal calcification (cases 4, 6).

Electron microscopic studies have not been reported before the present case, and, on the basis of light microscopy, the presence of melanin pigment in these tumors has been considered as the result of transfer from non-neoplastic melanocytes rather than as a product of the neoplastic cells.[10] In the light of our studies, we believe that the tumors previously reported under the title "melanotic or pigmented meningioma" as well as our case are neoplasms of melanocytic rather than meningothelial origin.

Ultrastructurally, the tumor cells lack the characteristics of meningothelial tumors[9,19] such as numerous desmosomes, interdigitating cytoplasmic processes, and intracytoplasmic fibrils. By contrast, the tumor cells in our case have polar processes, few zonula adherens (intermediate junctions), and large numbers of premelanosomes and melanosomes.

Meningeal melanocytosis and an associated meningeal malignant melanoma have been studied electron microscopically by Kinoshita et al.[11] They described numerous melanosomes at different stages of differentiation, loosely arranged fine cytoplasmic fibrils, cytoplasmic dendritic processes, and few "desmosomes." Melanosomes or premelanosomes have never been described in either meningiomas or normal meningothelium. The suggestion[26] that melanin is produced by non-neoplastic melanocytes and is subsequently taken up by meningothelial tumor cells is not supported by our study. The tumor cells lacked the characteristics of meningothelium and contained numerous melanosomes and premelanosomes in the form of discrete units. Pigment granules occurring in non-melanocytic cells as a result of melanin transfer tend to form aggregates[6] (complex melanosomes) and only rarely[12,14] have isolated melanosomes been described in these cells.

Besides their resemblance to meningiomas, these benign, melanin-pigmented, meningeal tumors share many morphological characteristics with neoplasms derived from melanocytes of the uveal tract and dermis (uveal nevi, spindle A uveal melanomas, cellular blue nevi).[23,27] The normal leptomeningeal melanocytes are also morphologically and histochemically similar to those of the uveal tract and dermis.[16] It is reasonable to expect that tumors arising from these cells will exhibit similarities in histology and behavior. Cytologically, the neoplasm described in the present case corresponds most closely to the cellular blue nevus and spindle A melanoma. It shares some ultrastructural features with them in addition to the presence of premelanosomes and melanosomes. Occasional attachment sites referred to as "desmosome-like" have been described in spindle cell melanomas of the uvea[13] and in a malignant blue nevus.[17] Similar intercellular attachments were described in some detail in an electron microscopic study of experimentally induced cellular blue nevi[18] and, as in our case, appeared to be of the zonula adherens type.

The basement-membrane-like material seen in our case has also been described in melanotic tumors believed to originate from Schwann cells.[17,18] Schwannoma was the first tumor in which the peculiar form of collagen with long spaced periodicity was observed.[15] It has since been described[5] in a variety of other neoplasms (neurofibroma, astrocytoma, pinealoma, chromophobe adenoma) but never in meningiomas, melanomas, or benign melanocytic tumors. Its presence in our case is of uncertain significance for the interpretation of the histogenesis of the tumor.

In conclusion, meningeal neoplasms presenting the histology of the case studied here are most likely of melanocytic origin and deserve the designation "meningeal melanocytoma" rather than "pigmented meningioma." They closely resemble cellular blue nevi and spindle A uveal melanomas. Although the possibility of malignant transformation of an originally benign tumor can not be entirely

dismissed, this tumor of meningeal melanocytes does not seem to have an ominous prognosis. A thorough local excision may result in cure or at least suffice to assure the prolonged survival of the patient. Focal leptomeningeal hyperpigmentation may coexist and should be distinguished from metastasis. Although the tumor seems biologically benign, the neurologic consequences of its expanding growth may kill the patient as occurred in our case. In locations amenable to surgery, early excision may eliminate these complications.

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