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Clear Cell Meningioma

A Clinicopathologic Study of a Potentially Aggressive Variant of Meningioma

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Since clear cell meningioma has only recently been recognized as a morphologic entity, its pathobiology has not been studied. Fourteen examples occurring in seven females and six males, ages 9 to 82 years (mean 29 years), were examined; one was associated with type 2 neurofibromatosis. Of these cases, seven (50%) were spinal-intradural (six lumbar, one thoracic), three (21%) arose in the posterior fossa (cerebellopontine angle), three (21%) were supratentorial, and one (7%) was centered upon the foramen magnum. In one case (8%), two tumors were considered to be independent primaries. One tumor (8%) appeared to show no dural attachment. Thirteen tumors were subject to complete study. All were composed of sheets of clear, glycogen-rich, polygonal cells forming only a few vague whorls. Hyalinization, both stromal and perivascular, was often extensive. Mitoses were rare in primary tumors. Immunohistochemistry showed vimentin and epithelial membrane antigen staining to be reactive in 100%. Stains for S-100 protein and CAM 5.2 were negative. Progesterone and estrogen receptor staining was observed in 77% and 0%, respectively. Ultrastructural study showed abundant cytoplasmic glycogen, a few cytoplasmic lumina, intermediate filaments, interdigitation of cell membranes, and desmosomal junctions. The means, medians, and ranges of proliferating cell nuclear antigen (PCNA) and MIB-1 antigen labeling indices for nonrecurring and recurring tumors were 10.4%, 8.8%, 0.8–23.4% and 11%, 1.4%, 0.1–50.3%, as compared with 7.4%, 6.7%, 2.9–17.2% and 13.3%, 13.4%, 3.3–25.7%, respectively. Twelve successful DNA ploidy studies showed that 11 tumors (85%) were diploid and one was tetraploid; percentage S-phase determinations varied from 4 to 9% (mean 6.0%). Recurrence was noted in eight patients (61%) (five of whom had multiple recurrences); there was local discontinuous spread in two cases (15%) and widespread cranial to spinal metastasis in one case (8%). Three patients (23%) are dead of disease. In summary, clear cell meningiomas are morphologically unique, show no sex predilection, affect primarily the lumbar region and cerebellopontine angle, and despite their benign appearance, may be inordinately aggressive, particularly intracranial examples. No close association was noted between recurrence or clinical outcome and such factors as mitotic activity, PCNA proliferation indices, percent S-phase determination, or DNA ploidy status. In contrast, MIB-1 proliferation indices were appreciably higher among recurring tumors.

Key Words: Clear cell meningioma—Proliferative markers—Flow cytometry—Electron microscopy.

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No tumors affecting the central nervous system show more morphologic diversity than do meningiomas (4,18,21,26,28,29,36,37). Their gross appearance varies considerably, from globular to en-plaque, solid to cystic, and solitary to multifocal (2). Indeed, the diagnostic challenge it poses in surgical pathology is comparable to that of melanoma.

The new World Health Organization (WHO) classification of tumors of the central nervous system (22) recognizes a broad spectrum of meningioma variants (Table 1); the clear cell meningioma is among them. Only a few examples of such glycogen-rich meningiomas have been reported to date (4,22,32,37,40). No comprehensive clinicopathologic study of this lesion has been published. In an effort to characterize the lesion, particularly with regard to its aggressive potential, we undertook a histologic, immunohistochemical, ultrastructural, DNA flow cytometric, steroid hormone receptor, and proliferation marker study of 13 examples of this unique form of meningioma.

MATERIALS AND METHODS

Thirteen cases of clear cell meningioma were studied. Of these 13, six were encountered in a his-

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TABLE 1. *World Health Organization classification of tumors of the meninges*[a]

Tumors of meningothelial cells	3.1
Meningioma	3.1.1
Variants	
Meningothelial	3.1.1.1
Fibrous (fibroblastic)	3.1.1.2
Transitional (mixed)	3.1.1.3
Psammomatous	3.1.1.4
Angiomatous	3.1.1.5
Microcystic	3.1.1.6
Secretory	3.1.1.7
Clear cell	3.1.1.8
Chordoid	3.1.1.9
Lymphoplasmacyte-rich	3.1.1.10
Metaplastic	3.1.1.11
Atypical meningioma	3.1.2
Papillary meningioma	3.1.3
Anaplastic (malignant) meningioma	3.1.4

[a] See Jellinger and Slowik (19).

tologic review of 2,989 meningiomas accessioned to the files of the Mayo Clinic Tissue Registry between the years 1956 and 1992. The remaining seven were derived from the consultation files of one of us (B.W.S.).

Clinical information was obtained by chart review and by direct contact with referring physicians or patients. Information specifically sought included age, sex, initial symptoms, neurologic findings on admission, clinical course, computed tomography (CT) and magnetic resonance imaging (MRI) data, operative descriptions, radiotherapeutic data where applicable, and patients' follow-up.

For the purpose of histological examination, tissue obtained at surgery was fixed in neutral buffered formalin, routinely processed, and paraffin embedded. All were stained by the hematoxylin-eosin (H&E) and the periodic acid–Schiff (PAS) methods with and without diastase digestion. Immunohistochemical stains were performed using the avidin-biotin peroxidase complex (ABC) method of Hsu et al. (15). Primary antibodies were directed toward the following: vimentin (monoclonal; DAKO, Carpinteria, CA, U.S.A.; dilution 1:1,000), epithelial membrane antigen (EMA) (monoclonal; DAKO; dilution 1:40), cytokeratin (monoclonal; Boehringer Mannheim, Indianapolis, IN, U.S.A.; dilution 1:100), CAM 5.2 (monoclonal; Becton Dickinson, San Jose, CA, U.S.A.; dilution 1:25), S-100 protein (polyclonal; NSC, Toronto, Canada; dilution 1:800), proliferating cell nuclear antigen (PCNA) (monoclonal; DAKO; dilution 1:500); MIB-1 antigen (monoclonal; AMAC Inc., Westbrook, ME, U.S.A.; dilution 1:400), estrogen receptor protein (monoclonal; AMAC Inc.; dilution, 1:20), progesterone receptor protein (monoclonal; Novacastro, Burlingame, CA, U.S.A.; dilution 1:100).

The percentages of PCNA- and MIB-1-positive cells, expressed as the percentages of nuclear area, were determined by automated cell counting (Cell Analysis Systems, Chicago, IL, U.S.A.). Computations were based upon the assessment of 10 high-power (×400) microscopic fields in a representative area of the biopsy.

For the purpose of ultrastructural study, four tumors were promptly fixed in Trumps' solution (phosphate buffered, 4% formalin and 1% gluteraldehyde), postfixed in osmium tetroxide, stained en bloc with uranyl acetate, and embedded in Spurr. Thin sections were stained with lead citrate and examined with a JEOL 1200 electron microscope.

Flow cytometric analyses were performed upon the same paraffin-embedded tissue block from which microsections had been prepared. Cell nuclei were extracted from the paraffin block by a modification of the technique of Hedley et al. (14). As described in a previous report (11), the extracted nuclei were stained for DNA content by a modification of the method of Vindelov et al. (42). After analysis of DNA content on a FACS analyzer (Becton Dickinson), all specimens were sonicated for 2 minutes in order to decrease nuclear clumping. After sonication, DNA content was reanalyzed and compared with the previous result. Cell cycle analyses were performed on a Consort 30 computer (Becton Dickinson). If more than one G0/G1 peak was detected, the tumor was considered aneuploid, whereas if the percentage in G_2M was >9%, it was classified as tetraploid.

RESULTS

The following data, individually summarized by case in Table 2, is based upon a critical review of 13 cases.

Epidemiology

Of the 13 cases, six patients were operated on at the Mayo Clinic. Clear cell meningiomas represented 0.2% of all meningiomas in the institution's experience. Seven patients were female, and six were male. Patients' ages at the time of surgery ranged from 9 to 82 years (mean 29 years). One patient had type 2 neurofibromatosis.

Location

Of the 13 patients, one (case 1) had multiple (two) tumors. All but one of the seven spinal tumors were entirely intradural; five were situated in the lumbar region, one at the lumbosacral level, and one at the

TABLE 2. *Clinical data of the patients of C.C.M.*

Case	Age	Sex	Location	Therapy	Follow-Up
1	32	F	Tumor 1—right jugular foramen, cerebellopontine angle	Total removal	
			1st recurrence	Total removal	
			2nd recurrence	Radiosurgery	
			Tumor 2—T-1 to T-2 (?2nd primary)	Total removal	Alive, no evidence of tumor regrowth (7 yrs)
2	23	F	L-5	Total removal	No recurrence (3 yrs)
3	36	F	L-2 to L-5	Total removal	No recurrences (1 yr)
4	17	F	L-4 to L-5	Total removal	No recurrence (3 yrs)
5	82	M	Left frontotemporal	Subtotal removal	Dead (1 month)
6	11	M	Tumor 1—right frontal	Total removal	
			Recurrence and second tumor (?surgical implant or local metastasis) on ipsilateral sphenoid wing	Total removal and radiation (5,000 rad)	No evidence of disease (18 months)
7	34	M	L-4 to S-1	Total removal	
			1st recurrence	Total removal	
			2nd recurrence	Total removal	Alive with disease (13 yrs)
8	9	F	L-3 to L-5	Total removal	
			Recurrence	Total removal	No evidence of disease (2 yrs)
9	16	M	Left cerebellopontine angle	Total removal	
			1st recurrence	Total removal and RT (4,500 rad)	
			2nd recurrence with spinal (thoracic, lumbar, and sacral) metastases	Total removal of CP angle tumor + spinal RT (C-2 to T-10: 3,404 rad, T-10 to S-3: 3,420 rad)	Dead (27 months)
10	12	F	Left tentorial notch and posterior clinoid	Total removal	Third nerve paresis, no recurrence (2 yrs)
11	34	M	Foramen magnum	Total removal	PICA was damaged, alive with disease (8 yrs)
			Recurrence	Gamma knife therapy, twice	
12	47	M	L-3 to L-4	Total removal	
			L-5	Total removal	
			T-12 to L-1 and cauda equina metastases	Total removal	
			Right cavernous sinus lesion, unbiopsied	Craniospinal RT	Alive with tumor, RT is ongoing
13	21	F	Cerebellum; pons; V, VII, VIII cranial nerves; no dural attachment	Subtotal removal and RT (5,600 rad)	
			Recurrence with extension into cervical spinal space	Subtotal removal and RT (cerebellum: 3,000 rad, cervical spinal cord: 6,000 rad)	
			Recurrence	Total removal	Multiple right side cranial nerve palsies, dead (12 yrs)

RT, radiotherapy; PICA, posterior-inferior cerebellar artery.

thoracic level. Three tumors occurred in the cerebellopontine angle, one was in the tentorium-clinoid region, and one centered upon the foramen magnum. Of supratentorial lesions, one each was frontal and frontotemporal. In the case of one posterior fossa tumor affecting the cerebellum and pons as well as cranial nerves V, VII, and VIII (case 13), no mention of a dural attachment was made. The neuroimaging features of three cases are illustrated in Fig. 1.

Gross Appearance

Most tumors were well delimited, exhibiting a smooth, bosselated external surface. On cut section they appeared solid, gray-pink to tan-red. Their texture was usually soft, but some were described as firm. Neither cyst formation nor necrosis was noted.

Light Microscopy

All lesions were moderately cellular and with the exception of stromal hyalinization, showed a similar appearance from one low-power field to another. They consisted largely of a sheetlike or somewhat lobulated proliferation of polygonal cells, the cytoplasm of which was clear (Fig. 2). The formation of vague whorls was noted in most cases (Fig. 3). As a rule, nuclei were uniform and round with delicate

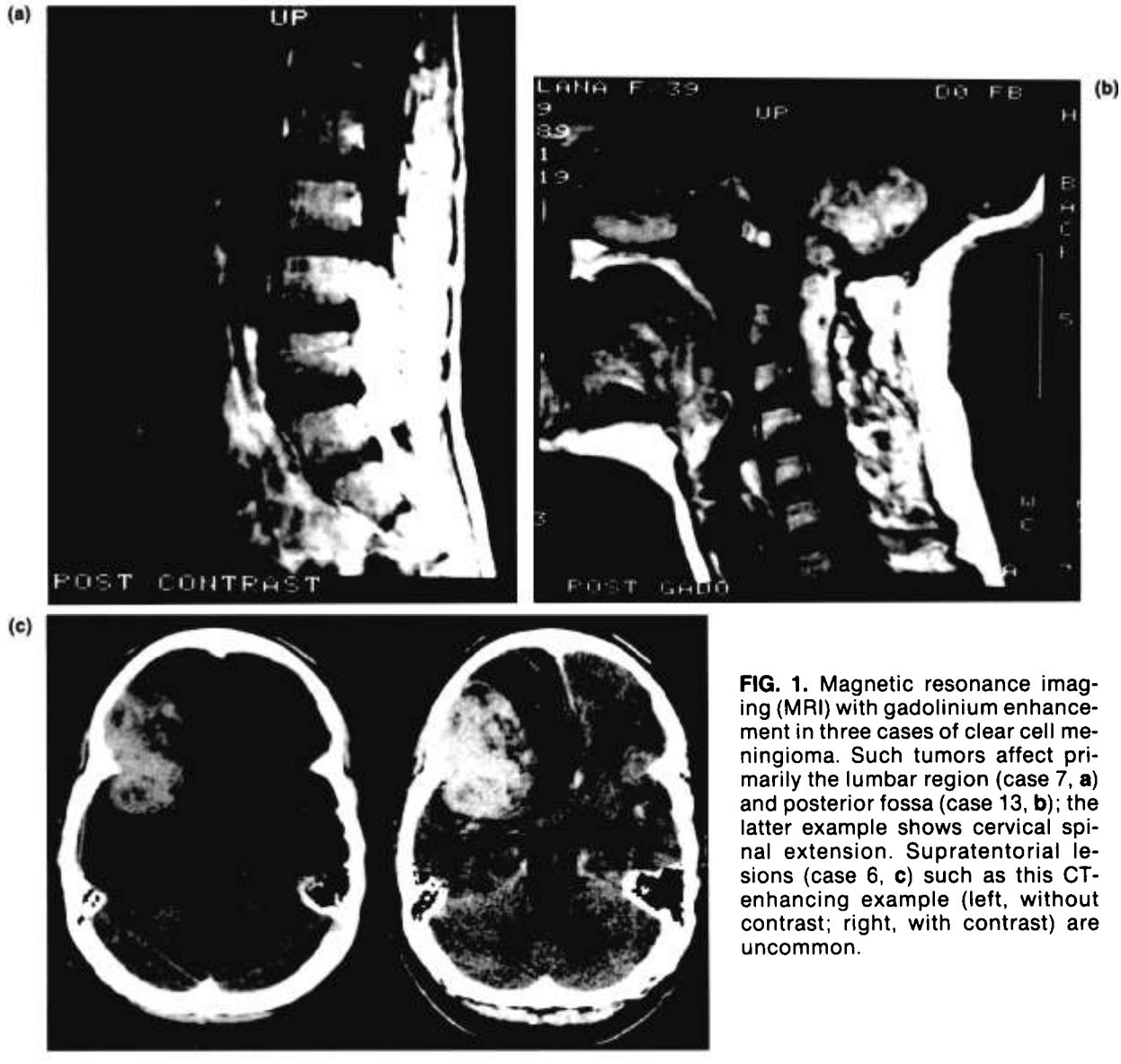

FIG. 1. Magnetic resonance imaging (MRI) with gadolinium enhancement in three cases of clear cell meningioma. Such tumors affect primarily the lumbar region (case 7, **a**) and posterior fossa (case 13, **b**); the latter example shows cervical spinal extension. Supratentorial lesions (case 6, **c**) such as this CT-enhancing example (left, without contrast; right, with contrast) are uncommon.

chromatin and inconspicuous nucleoli. Nuclear inclusions of cytoplasm were very uncommon. All tumor cells contained abundant cytoplasmic glycogen, the PAS stain being strongly positive (Fig. 4) and the reaction diastase labile. No xanthomatous change was seen. Although there was no evidence of a microcystic or of a secretory pattern as defined by the WHO (22), focal formation of microcysts, nearly all <1 mm in size, was an occasional finding (Fig. 4). As previously noted, no macroscopically apparent cysts were encountered. Nests of cytologically typical meningothelial cells were a focal feature in three cases (cases 9, 12, and 13) (Fig. 5).

To a varying extent, hyaline connective tissue often interrupted sheets of tumor cells and was concentrated around the blood vessels. In some instances, hyalinization was so extensive as to entrap cells and obliterate the architecture of the tumor (Fig. 6). Mitoses were rarely encountered in specimens obtained at first surgery, although five tumors showed a few mitotic figures (cases 3, 6, 9, 12, and 13). In two instances (cases 9 and 13) mitoses were easily identified in the second and third surgical specimens, respectively. Small foci of necrosis were seen in three lesions (cases 6, 9, and 13). Microscopic inspection of the surfaces of tumor fragments showed no evidence of brain invasion.

Immunohistochemistry

Of the 13 tumors studied, all lesions showed vimentin reactivity as well as a membranous pattern of staining for EMA (Fig. 7). In two instances, the reaction was strong, whereas in others it was gen-

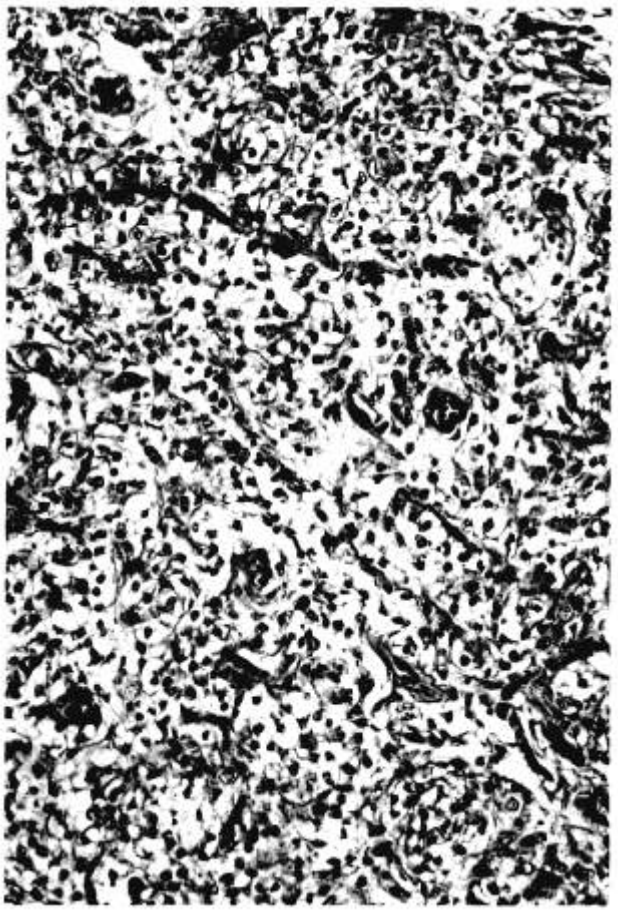

FIG. 2. The architectural pattern of clear cell meningioma varies from diffuse to somewhat lobular.

erally weak. The CAM 5.2 and S-100 protein stains were negative throughout. All tumors were ER negative, but immunoreactivity for PR was observed in 10 cases (77%).

The means, medians, and ranges of PCNA indices for nonrecurrent and recurrent tumors were 10.4%, 8.8%, and 0.8–23.4% and 11.0%, 1.4%, and 0.1–50.3%, respectively. For comparison, the means, medians, and ranges of MIB-1 indices for nonrecurrent and recurrent tumors were 7.4%, 6.7%, and 2.9–17.2% and 13.3%, 13.4%, and 3.3–25.7%, respectively.

Electron Microscopy

The four tumors showed similar ultrastructural features and were characterized by moderately abundant cytoplasm literally filled with glycogen particles and, to a lesser extent, by varying numbers of intermediate filaments (Figs. 8 and 9). The former either were present throughout the cytoplasm or aggregated among displaced organelles. Glycogen content varied between the cells of any one tumor. Glycogen "lake" formation was observed in specimens stained en bloc with uranyl acetate. Scattered tumor cells contained densely aligned intermediate filaments (Fig. 9), some arrayed in whorls. Tonofilaments were not identified. Aside from glycogen and intermediate filaments, other organelles were few but included lamellar mitochondria, short segments of rough endoplasmic reticulum, Golgi complexes, and free ribosomes. A few small lipid droplets were often noted, especially in association with glycogen lakes. Intracytoplasmic lumens without microvilli were occasionally identified.

Whereas most tumor cells exhibited interdigitation of cell membranes, cell processes were few. The cells were joined by junctional complexes, most often well-formed desmosomes (Fig. 9). Some pinocytotic and coated vesicles were present along the cell membrane. Cytoplasm abutting stroma often exhibited an interrupted basal lamina. The density of subplasmalemmal cytoplasm was greater in areas wherein such basal lamina was noted. The nuclei of tumor cells were ovoid and regular in

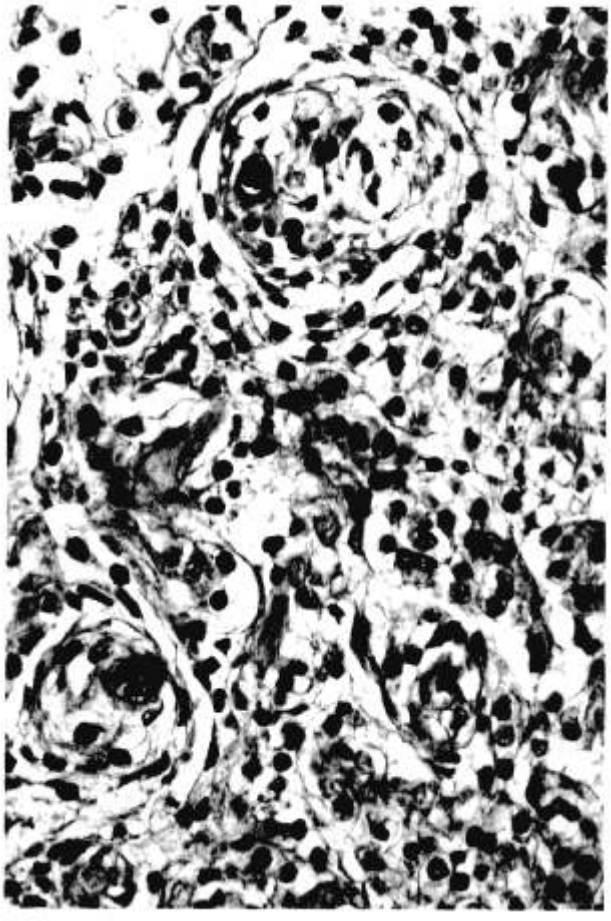

FIG. 3. Cytologic features of clear cell meningioma include vague whorl formation, polygonal to somewhat elongate cells, cytoplasmic clearing, and round nuclei that are uniform and may be eccentric.

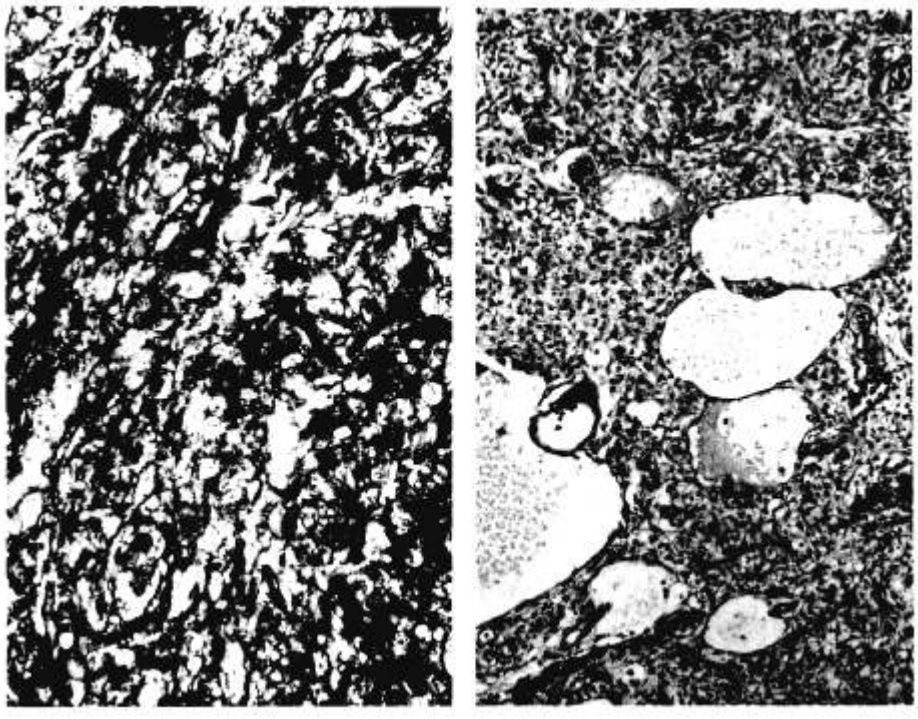

FIG. 4. A conspicuous feature of all tumors was strong PAS positivity due to cytoplasmic glycogen accumulation **(a)**. A minority of tumors showed microcyst formation **(b)**.

shape and contained finely dispersed euchromatin as well as a distinct nucleolus. Nuclear invaginations of cytoplasm corresponded to the small cytoplasmic nuclear inclusions occasionally noted at the light microscopic level. The stroma, primarily perivascular in location, contained variable amounts of collagen, some of which appeared to be amianthoid (giant collagen fibrils), as well as finely granular material.

Flow Cytometry

Of the 12 tumors in which DNA ploidy determinations were successful, 11 (91%) were found to be diploid and one (9%) tetraploid. One study was uninterpretable. S-phase fractions of diploid tumors ranged from 2 to 5%, whereas that of the tetraploid tumor was 4%. The G_2M fractions of diploid tumors ranged from 6 to 8%, whereas that of the tetraploid tumor was 9%.

CASE REPORTS

Case 1

A 32-year-old woman complained of chronic frontal headache and progressive right-sided hearing loss. On admission, a neurologic examination was unremarkable aside from the finding of diminished hearing on the right. A large right cerebellopontine angle tumor was evident on CT scan. A right posterior fossa craniotomy was performed,

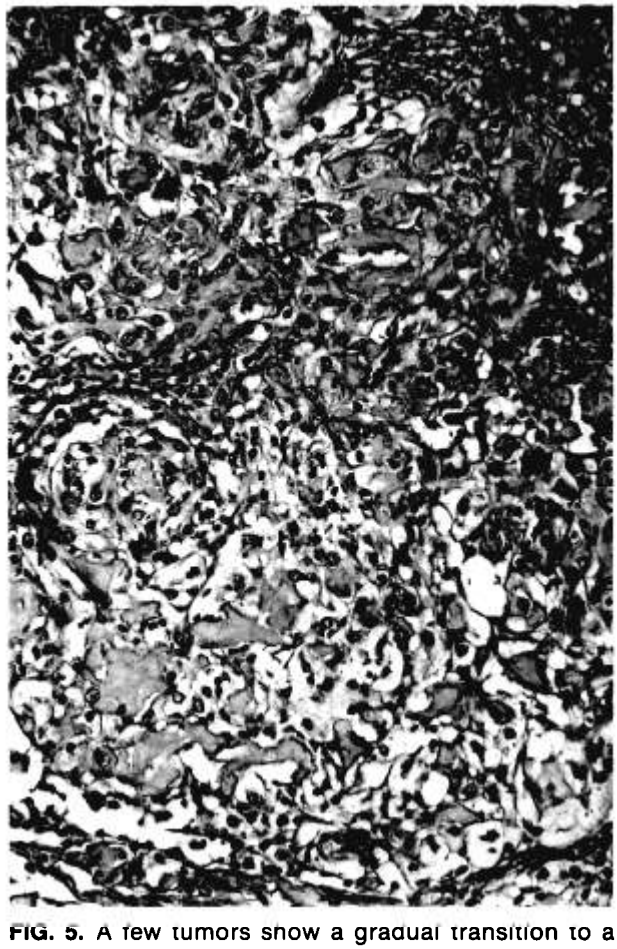

FIG. 5. A few tumors show a gradual transition to a more obviously meningothelial pattern (top).

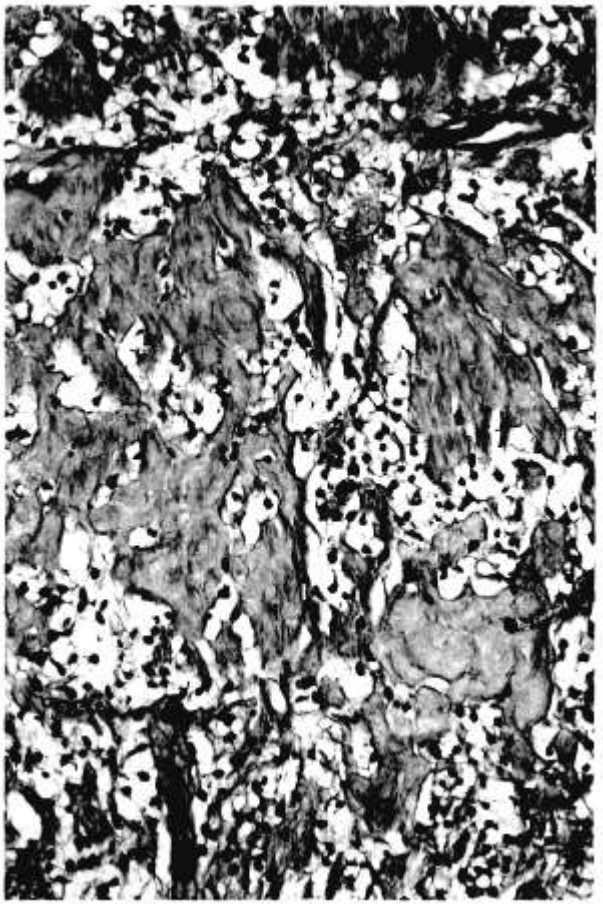

FIG. 6. Although it is usually focal, hyalinized "blocky" collagen deposition was a prominent feature of many tumors.

which found a large tumor mass centered upon the jugular foramen. A gross total removal was achieved. Although the seventh, eighth, 10th, and 11th cranial nerves were preserved, the ninth cranial nerve on the right was sacrificed to attain a complete resection.

Five months thereafter, the patient was involved in a boating accident. Although a CT scan showed negative results, seizure activity was observed and prompted dilantin therapy (400 mg a day). Three months later, she experienced chest and back pain. A chest radiograph was normal, and a CT scan of the head with and without contrast demonstrated no evidence of residual or recurrent tumor. A CT scan of the spine, however, showed a partially intradural extramedullary mass, one located on the right and extending from the superior aspect of T-1 to the inferior aspect of T-2. The mass, clinically considered a second primary rather than a metastasis, also had an extraspinal, retropleural component. A laminectomy was performed; the mass, a clear cell meningioma, was totally removed. Three years after the posterior fossa operation, an MRI scan showed a recurrence in the area of the jugular foramen. A gross total removal was again achieved. Two years thereafter an MRI scan showed a second recurrence. The patient then underwent radiosurgery. Seven years later, she is doing well with no evidence of tumor regrowth.

The occurrence of both a posterior fossa and a solitary thoracic tumor suggests the possibility of central neurofibromatosis. Although she has no external manifestations of a phakomatosis, it is noteworthy that her father had undergone several neurosurgical procedures at ages 7 and 14 years. Two different tumor masses were removed, one from his posterior fossa and another from the lumbar spine; both were diagnosed as ependymoma and were considered independent lesions. A subsequent operation was performed at age 24 for removal of a benign peripheral nerve sheath tumor from the thoracic spine at the T-5 level. He had no manifestation of peripheral neurofibromatosis but is considered to have central neurofibromatosis.

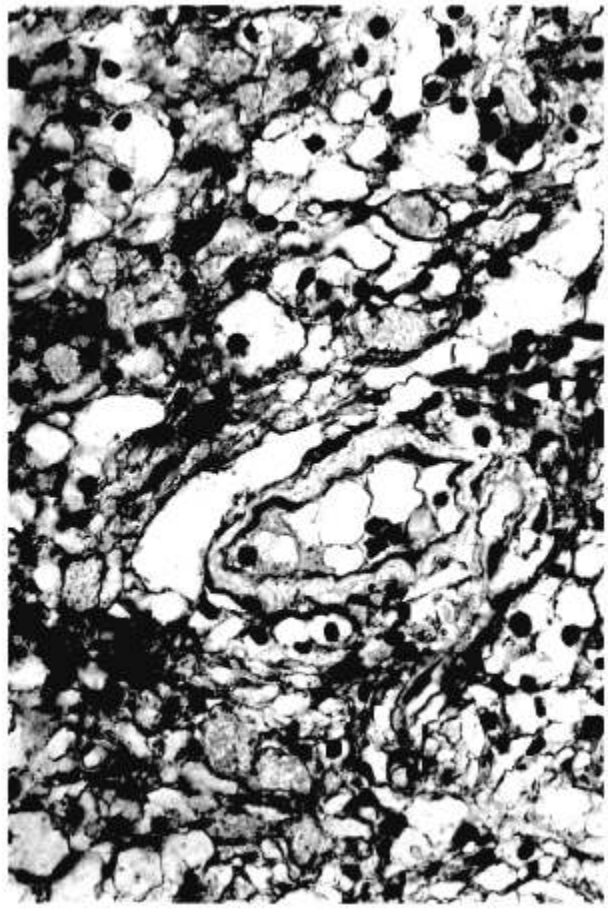

FIG. 7. Epithelial membrane antigen reactivity is a regular feature of clear cell meningioma, as seen by immunostaining.

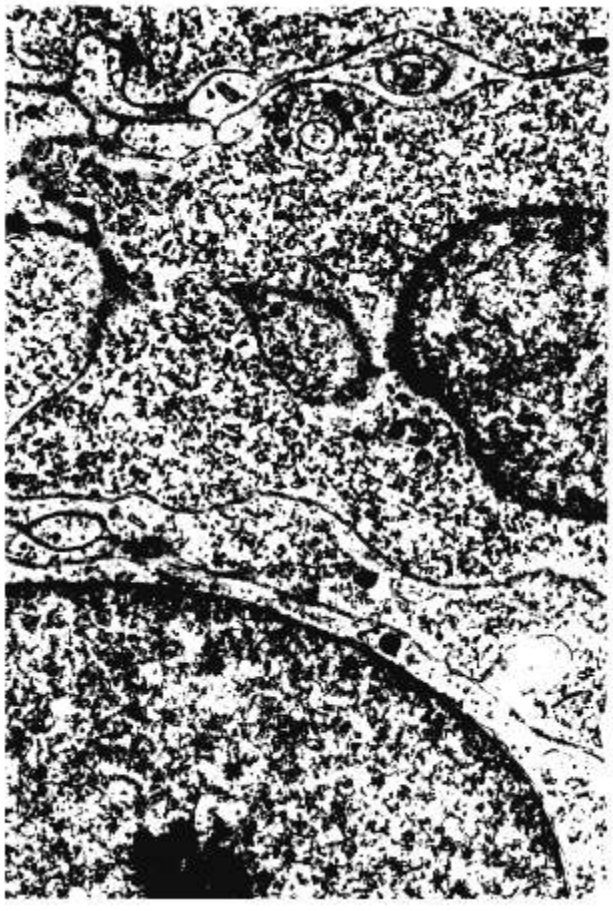

FIG. 8. Aside from remarkable cytoplasmic glycogen deposition, ultrastructural features typical of meningioma are also noted, including variable intermediate filament accumulation, imbrication of cell membranes, and well-formed desmosomal junctions.

Case 2

A 23-year-old woman had had a 3-month history of bilateral hip pain. At presentation, a neurologic examination found bowel and bladder function to be intact. A myelogram showed an intradural lesion at the upper margin of L-5. At surgery, the tumor was seen to arise from the dura. Nerve roots were displaced but not infiltrated. A gross total removal was achieved. Six months later a follow-up myelogram showed only a small posterior pseudomeningocele at the operative site as well as some evidence of "arachnoiditis." One year thereafter, when the patient was seen for left shoulder pain, a myelogram and CT scan were performed but showed no evidence of a recurrence.

Case 3

A 36-year-old woman had a 1-year history of progressively worsening left-sided groin pain radiating to the back. A variety of analgesics were unsuccessful in alleviating the pain, which not only persisted but after an additional year also became associated with bilateral leg weakness. An MRI scan of the lumbar spine demonstrated a large intradural mass, extending from the lower margin of the L-2 to the upper margin of the L-5 vertebra. At surgery, a sausage-shaped mass was seen to anteriorly and posteriorly displace cauda equina and nerve roots. In that the latter were intact and separable from the lesion, a gross total resection was achieved. At 1-year follow-up, a myelogram and a CT scan showed only scarring and "arachnoiditis." No evidence of residual or recurrent tumor was noted.

Case 4

A 17-year-old girl had a 3-month history of lower back and right leg pain. A neurologic examination was normal. An MRI scan showed a spinal intradural, contrast-enhancing mass at the L-4 to L-5 level. At surgery, an intradural mass was found to be attached to spinal nerve roots, one of which was splayed over the surface of the lesion. The roots were dissected free of the tumor, and a gross total removal was achieved. A follow-up MRI scan was unremarkable. Three years after surgery the patient is free of recurrence and is asymptomatic.

Case 5

An 82-year-old man was admitted to the hospital after having suddenly become unresponsive and aphasic. A CT scan of the head showed a mass in the left frontotemporal area, associated with significant midline shift and brain edema. At surgery the dural-based tumor was partially resected. Two days thereafter he again became lethargic and aphasic, although a second CT scan showed no significant change. The patient died 1 week after surgery.

Case 6

An 11-year-old boy had a history of progressive headaches. A CT scan showed an enhancing, dura-based mass in the right frontal region. At surgery, no brain invasion was noted. The tumor was totally resected, and a dural graft was placed. Thirteen months after surgery the patient was seen for severe headaches and papilledema. A CT scan showed two tumors, one at the site of previous excision, the other on the ipsilateral sphenoid wing. Both lesions were contrast-enhancing, appeared to be attached to the dura, and compressed the brain. No brain invasion was noted. Both tumors were successfully

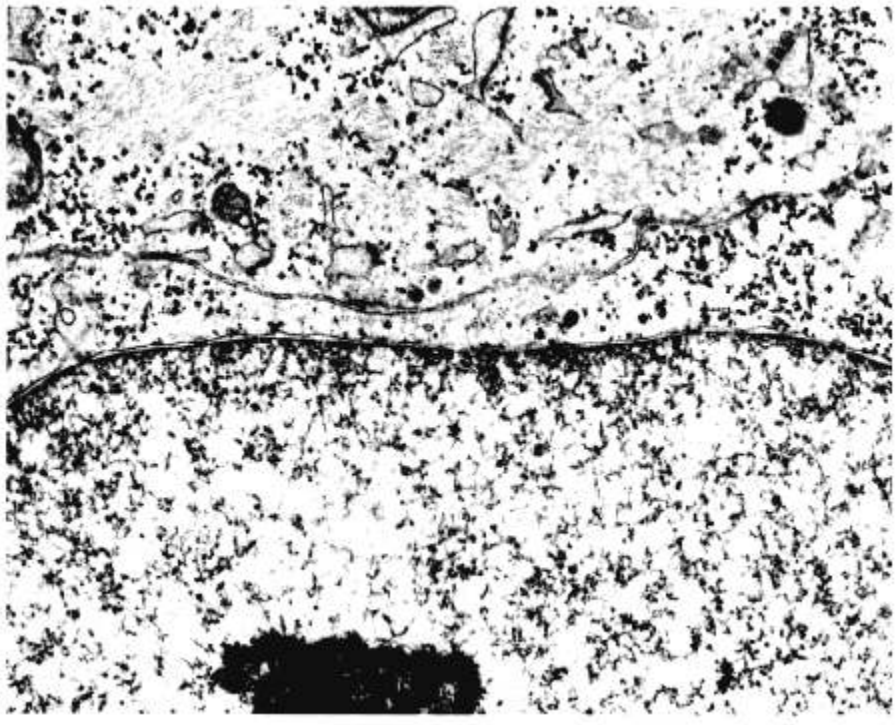

FIG. 9. Intermediate filament accumulation (top) may also be seen at the ultrastructural level.

resected in toto. Postsurgery, the patient received radiotherapy (5,000 rad). Five months after the second surgery he is well on tegretol therapy alone.

Case 7

A 34-year-old man had a long history of steadily worsening back stiffness, which had recently become continuous as well as associated with difficulty in urination and perianal hypesthesia. A CT scan of the spine showed a sacral mass that had grown through bone and into surrounding muscle. A myelogram demonstrated obstruction at the L-5 level. Two diagnostic surgical procedures were undertaken, but the tumor was considered unresectable. Two months thereafter the patient was transferred to the Mayo Clinic, where he underwent gross total removal of the tumor. Three weeks later he was pain free and could walk. One year after surgery an MRI scan showed recurrence of the tumor. Another gross total resection was achieved. Four months later, at which time pain and a sensation of pressure recurred, the area of postoperative sensory loss increased. The tumor involved bone and dura at the L-4 to L-5 level. A gross total tumor removal was again performed. One year later he again noted recurrence of lower back pressure. A follow-up MRI scan showed further recurrence. The patient has received no chemo- or radiation therapy.

Case 8

A 9-year-old girl had a 10-month history of lower back and leg pain that worsened at night and was particularly severe in the early morning. A neurological examination found only mild bilateral lower extremity weakness. Bowel and bladder functions were intact. An MRI scan of the spine showed an enhancing, smooth-contoured extraaxial mass at the L-4 level. At surgery the lesion was noted to be dura based and encompassed surrounding nerve roots. A gross total removal was achieved. Six months thereafter the patient had recurrent lower back pain. An MRI scan disclosed only matted nerve roots; the dura appeared to be unaffected. Two months after resection of this recurrence, the patient again experienced lower back pain, but an MRI scan showed no evidence of a neoplasm.

Case 9

A 16-year-old boy had experienced the recent onset of headaches, nausea, and vomiting. A CT scan of the head showed a large enhancing mass in the left cerebellopontine angle. At surgery a large, multilobulated, yellow-gray, dura-based mass was removed. Postsurgery, the patient did well, but 6 months later symptoms recurred. A CT scan of the head showed a huge, recurrent posterior fossa tumor with extension into Meckel's cave. A second surgery was undertaken. The entire cerebellopon-

tine angle was found to be filled by a multinodular tumor. The eighth nerve was totally infiltrated by tumor, as were lower cranial nerves. The tumor was subtotally resected, and the patient underwent radiotherapy (4,500 rad to the brain).

Seven months after this second surgery, the patient was seen for lower back pain. A myelogram showed a large intradural mass in the lower lumbar and sacral area as well as multiple smaller intradural lesions at the thoracic levels. A T-10–L-5 decompression laminectomy was performed. The tumor implants were removed, and radiation therapy was administered, levels C-2 to S-3 receiving 3,420 rad. At subsequent follow-up a CT scan showed an enlarging mass in the left-middle fossa with extension into the left sphenoid sinus, left nasopharynx, and retrobulbar area. In view of developing proptosis, a palliative orbital exenteration was performed. The patient died of tumor 1 month later. At autopsy, extensive tumor was found to involve the left-middle and posterior fossa as well as the sphenoid sinuses and left orbit.

Case 10

A 12-year-old girl had a 6-week history of headaches. A CT scan of the head showed an extraaxial, enhancing, 2-cm mass affecting the left portion of the interpeduncular cistern. At left temporal craniectomy, the tumor was seen to arise from the region of the tentorial notch. The tumor completely encased the third nerve, a structure sacrificed during resection. Although thereafter the patient underwent multiple surgical procedures related to third nerve paresis, follow-up CT scans have shown no evidence of tumor recurrence.

Case 11

A 34-year-old man had gait disturbance, nystagmus, and difficulty swallowing. An MRI scan of the head showed an enhancing, dura-based mass at the level of the foramen magnum. At suboccipital craniectomy and C-1 laminectomy, the tumor was seen to originate from the region of the hypoglossal canal on the left. A gross total removal was achieved. During resection, the posterior-inferior cerebellar artery was damaged, resulting in Wallenberg's syndrome. Two years thereafter a follow-up MRI scan confirmed local recurrence. Gait disturbance was apparent, as were problems with swallowing. One year later an MRI scan showed two separate lesions, one in the right cerebellopontine (CP) angle, the other in the area of Meckel's cave. The patient underwent two courses of gamma knife therapy. At present he still has multiple enhancing lesions, including one at Meckel's cave extending into the prepontine space with associated brain stem compression, and a 5-cm lesion extending superiorly to the right cavernous sinus. The patient is being considered for additional gamma knife therapy. No spinal metastases have been documented.

Case 12

A 47-year-old man had back pain intermittently radiating to the legs. A general and neurologic examination was normal. Myelography demonstrated an intradural mass at the L-3 to L-4 level. At laminectomy, the dura-based tumor was grossly totally resected. The patient did well until 3 years after surgery, when he experienced acute back pain with lateral leg radiation as well as subsequent severe headaches. An MRI scan showed a new intradural tumor at the L-5 level. At surgery, two separate tumors were found to be attached to spinal nerve roots. They were dissected free of the lesions, both of which were totally resected. One year thereafter he was seen for recurrent back pain radiating to the legs. No neurologic abnormality was noted. An MRI scan showed two new tumors, a 1-cm lesion at the L-1 level intimately adherent to several nerve roots and a 7-mm lesion at the T-12 level. Both tumors, apparently local metastases, were completely removed.

One year later a follow-up spinal MRI scan found three small enhancing nodules in the cauda equina region, and an MRI scan of the head showed a right cavernous sinus lesion. The previous lumbar incision was reopened, and the tumors were microsurgically removed. The patient is undergoing radiation therapy to the unbiopsied cavernous sinus lesion. It is noteworthy that he had a family history of colon cancer; one brother had had colon cancer at age 59, and his mother has had multiple colorectal polyps. On colonoscopy the patient was found to have two adenomatous polyps.

Case 13

A 21-year-old woman had a 10-month history of occipital headaches, as well as ataxia, dysphagia, and visual disturbance of 8 months' duration. An MRI scan of the head showed a right cerebellar tumor. A suboccipital craniectomy was performed, at which time the tumor was found to be demarcated from the cerebellum. It was, however, wrapped around the fifth, seventh, and eighth cranial nerves and also affected the pons and cerebellar peduncles. No mention was made of a dural attachment. The

lesion was excised, and radiotherapy (5,600 rad) was administered.

The patient did well until 13 years later, when she developed incoordination. An MRI scan showed extensive tumor in the cerebellum and extension into the cervical region. A subtotal tumor resection and decompressive cervical laminectomy were performed. Radiation therapy was again undertaken; the cerebellum and cervical spinal cord were given 3,000 and 6,000 rad, respectively. One year later she developed headaches, rapidly progressive ataxia, and right hemiparesis. Imaging studies found a 5-cm recurrence in the lateral recess, one filling the fourth ventricle and paramedian cerebellum as well as extending into the cervical canal with displacement of the brain stem and proximal cervical spinal cord. The patient underwent a third resection, at which time total removal of both the cerebellar and spinal portions of the neoplasm was achieved. Thereafter she developed multiple right-sided cranial nerve palsies, ataxia, and nystagmus. One year later she died of tumor.

DISCUSSION

As is apparent in Table 1, a summary of the new World Health Organization classification of tumors of the central nervous system (22), the morphologic spectrum of meningiomas is highly varied. Their broad spectrum of differentiation reflects the pluripotential nature of the arachnoid cap cells from which meningiomas are thought to originate. Such tumors not only are capable of differentiating along mesenchymal lines, but may also show remarkable epithelial differentiation as well. Examples with predominantly epithelial features include meningotheliomatous, microcystic, secretory, and clear cell meningiomas, whereas the mesenchymal end of the spectrum includes fibrous meningioma and a majority of the metaplastic variants.

Clear cell meningioma has recently gained recognition as a unique morphological variant of meningioma (4,22,37). Although only a few examples have been reported as such (4,22,32,37,40), no in-depth clinicopathologic study of this rare form of meningioma has been published.

Much confusion surrounds what has been termed the "humid" form of meningioma, a descriptive term introduced by Masson (26). The line drawings of this author clearly show features of what has subsequently come to be more aptly called microcystic meningioma (6,7,9,23,29,30,31). This unique meningioma variant, which on cut section often has a wet or glistening appearance, is the subject of numerous case reports and series reviews, most of which clearly equate the tumor with Masson's humid meningioma (23,29,31). It is characterized by the accumulation of fluid within extracellular spaces surrounded by elongate meningothelial cell processes. Masson (26) suggested that these minute lacunae and slits were the result of penetration of cerebrospinal fluid into the tumor, thus recreating a picture similar to that of leptomeninges.

Such microcystic meningiomas are highly distinctive and in no way resemble the clear cell meningiomas reported herein. Indeed, no transitional tumors exhibiting features of both variants were encountered in the present series. Confusion between microcystic and clear cell meningioma can readily be avoided. Their distinction is based upon recognition of the pale fluid lying between tumor cells in microcystic meningiomas and its lack, coupled with remarkable intracytoplasmic glycogen accumulation, in clear cell meningioma. It is surprising, therefore, that at least one example has appeared in a series report under the humid meningioma umbrella (29). The same is true of our case 2, which is illustrated in two well-known texts; the tumor was represented as a microcystic meningioma in one instance (20) and both a microcystic and a transitional meningioma in the other (34).

In clinical as well as pathologic terms, clear cell meningiomas differ significantly from more ordinary variants. It is noteworthy that they exhibit no sex predilection and that the broad age range of affected patients is skewed toward the young and includes the first decade. Their anatomic distribution also differs in that most tumors are spinal or affect the cerebellopontine angle. Last, two tumors in the present series (14%) were multifocal. One tumor (case 13) showed no apparent dural attachment.

One case was associated with type 2 neurofibromatosis, an abnormality localized to chromosome 22. Meningiomas are known to be associated with neurofibromatosis (NF) of both types 1 and 2. The genetic abnormalities underlying these conditions have recently been localized to chromosomes 17 and 22, respectively (28,39). Although cytogenetic studies have regularly shown meningiomas to be associated with an abnormality of chromosome 22, to date no clear cell meningiomas have been subject to cytogenetic analysis.

Clear cell meningiomas exhibit highly distinctive histologic features, consisting of a sheetlike or lobular proliferation of often polygonal cells with clear cytoplasm. Meningothelial features are inapparent and, at most, consist of vague whorl formation. Nuclei, sometimes eccentric, are generally small and round, showing little tendency to cytoplasmic nuclear inclusion formation or degenerative atypia.

Widespread cytoplasmic clearing, the hallmark of the lesion, is due to abundant glycogen accumulation, a feature readily apparent on PAS stain with diastase digestion. There is no evidence that clear cell change is degenerative in nature, since it is not associated with fibrosis or necrosis. This unique characteristic may therefore reflect an abnormality of glycogen metabolism. Stromal and perivascular deposition of blocky, hyaline collagen is a conspicuous, presumably degenerative feature of many clear cell meningiomas. Its tendency to confluence differs from the bandlike collagen distribution seen in more ordinary meningiomas.

Aside from conspicuous glycogen deposition, tumor cells showed typical ultrastructural features of meningioma, including cytoplasmic intermediate filaments, interdigitation of plasma membranes, and well-developed desmosomes. In addition to variable quantities of stromal collagen, one of our tumors contained "giant" collagen fibrils of the amianthoid type. This unique form of collagen has been identified in a variety of neoplasms, including benign and malignant schwannoma, such soft-tissue tumors as fibrous histiocytoma and chondrosarcoma, and neuroendocrine tumors (10,16). Although Harkin and Leonard (13) recently described amianthoid fibers in a meningioma said to be composed of clear cells, there is no apparent explanation for its appearance in the uncommon variant described herein.

The immunophenotype of clear cell meningiomas is similar to that of other meningioma subtypes. Apparently arising from cells of the arachnoid membrane, such tumors show distinctly epithelial properties, including interdigitating cell membranes and desmosomes (20). A dual mesenchymal-epithelial immunotype is reflected in their staining for both vimentin and EMA, a property exhibited by nearly all meningiomas as well as by normal arachnoidal cells (38,43). Staining for both antigens in our series of clear cell meningiomas supports Kepes' concept that all meningiomas, regardless of histological subtype, are derived from arachnoidal cells (21). Reactivity for S-100 protein, a feature of 20% of meningiomas as a whole (38), was evident in a few clear cell tumors, whereas keratin staining, a much less common (6%) finding (38), was not seen in our series.

The female "gender bias" exhibited by meningiomas, as well as their known association with estrogen-dependent tumors such as breast and endometrial carcinoma, has been well documented (18, 20,24). Nonetheless, studies of the presence of estrogen receptors yield conflicting results. Immunochemical, dextran-coated charcoal, and nuclear binding assay studies indicate that they are present in only a minority of meningiomas (12). Furthermore, our own series as well as previous reports are virtually unanimous in finding the presence of progesterone receptors in the great majority (3,41). Their clinical and therapeutic significance remains to be determined.

The biologic behavior of meningiomas is highly variable. Clinicopathologic correlation is required in assessing their aggressive potential in that clinical factors, radiologic data, operative features such as invasiveness, multifocality, and extent of resection, as well as histologic parameters all contribute to a patients' prognosis. With regard to the latter, it is important to note that features of atypia associated with recurrence and aggressive behavior in ordinary meningiomas, e.g., hypercellularity, brisk mitotic activity, a high nuclear cytoplasmic ratio, nuclear atypia, nucleolar prominance, uninterrupted patternless growth, and the presence of zonal necrosis (1,4,5,8,17,19), were largely lacking in primary tumors in the present series.

Proliferation markers are known to be of some utility in distinguishing benign from atypical and malignant meningiomas (25,33,35). Although most clear cell meningiomas were diploid and showed relatively low percentage S-phase fractions, variation was noted in G_2M fractions, as well as in PCNA and MIB-1 indices. In our series, recurrence was noted in 61% of cases, local discontinuous spread in 15%, and widespread cranial to spinal metastasis in 8%; three patients (23%) are dead of disease. We could find no close association between tumor recurrence and clinical outcome on the one hand, and mitotic activity, PCNA proliferation indices, percentage S-phase, DNA ploidy status, or histologic features of anaplasia, on the other. It is important, however, that MIB-1 indices were appreciably higher among tumors that recurred than in those that did not.

In summary, clear cell meningiomas are morphologically unique, show no sex predilection, and affect primarily the lumbar region and cerebellopontine angle. Although not all clear cell meningiomas are clinically malignant, on the whole they are more aggressive than other variants of meningioma. Clinical outcome appears to be relatively unassociated with conventional histologic indicators of aggressive behavior.

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