The Pleomorphic Xanthoastrocytoma and Its Differential Diagnosis:

A Study of Five Cases

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Five brain tumors with the histopathologic features of pleomorphic xanthoastrocytomas (PXAs) are presented. Computed tomography scans showed a remarkable homology. Two cases had atypical localizations for a PXA, while one 46-year-old patient did not conform to the normal age distribution of this tumor. Nevertheless, in these cases, the histopathology was always characteristic for PXA, a remarkable pleomorphism, in addition to simultaneous expression of glial fibrillary acidic protein and histiocytic markers in the various tumor cells. In one of the presented tumors, however, clusters of neoplastic neuronal cells were also found. In this particular case, differential diagnostic criteria to distinguish between a PXA and a desmoplastic infantile ganglioglioma are lacking. HUM PATHOL 22: 1128–1135. Copyright © 1991 by W.B. Saunders Company

In 1979, Kepes et al described 12 young patients with superficial brain tumors with extensive involvement of the leptomeninges.[1] In spite of an impressive pleomorphism, necrosis was never found in these tumors, and mitoses were scanty. The presence of intracytoplasmic lipid droplets in part of the tumor cells, as well as a basal lamina around individual cells, supported the initial view that these highly pleomorphic neoplasms represented a variant of meningocerebral fibrous xanthomas.[2] Once the expression of glial fibrillary acidic protein (GFAP) was found in the tumor cells, however, these neoplasms were considered to be variants of astrocytomas and, subsequently, were termed "pleomorphic xanthoastrocytomas" (PXAs).[1] In contrast to their ominous histopathology, the clinical courses appeared to be relatively favorable.[1] Therefore, distinction of PXAs from other pleomorphic gliomas is important. The presence of necrosis in a pleomorphic intracerebral tumor should definitely exclude the diagnosis of PXA, since necrosis is invariably linked with malignancy.[3,4]

Several cases of PXA have been described.[5-19] Some of these had exceptional clinical features. In contrast with the typical young age of incidence of PXAs, a 62-year-old man was described by Mackenzie.[12] Unusual localizations of PXAs were the suprasellar region and the floor of the medial skull fossa.[8,17] Furthermore, PXAs with extensive recurrences after initial operation and rapid fatal outcomes have been reported.[19-21]

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Despite some atypical clinical features, the histopathology of the present five cases was compatible with the entity of PXA. However, in one of the presented tumors, neoplastic neuronal cells were found. The differential diagnosis of PXA and of this case, in particular, are discussed.

MATERIALS AND METHODS

Conventional Staining and Immunohistochemistry

Pleomorphic tumors with malignant appearance from patients with unexpected benign courses as well as from patients with a primary diagnosis of PXA were reviewed. The paraffin-embedded material from five selected cases was retrieved from the archives and new sections were made. The slides were stained with hematoxylin-eosin, periodic acid-Schiff for mucopolysaccharides and glycogen, Nissl stain for the Nissl substance, and Bodian stain for visualization of axon bundles.

For immunohistochemistry, the slides were incubated with antibodies against vimentin, keratin, desmin, epithelial membrane antigen, S100 protein, GFAP, neuron-specific enolase, lysozyme (muramidase), α-1-antitrypsin, α-1-antichymotrypsin, neurofilament (monoclonal reacting with 70- and 200-kd proteins), and synaptophysin. The primary antibodies were obtained from DAKO (Copenhagen, Denmark). Immunohistochemistry on 5 μm-thick sections of the paraffin-embedded material was done with the two-step indirect immunoperoxidase technique as described previously.[22] Final visualization was achieved by incubation with 0.02% diaminobenzidine in phosphate-buffered saline and 0.075% H_2O_2. Control slides, in which the primary antibody was replaced by phosphate-buffered saline, were always negative. The slides were slightly counterstained with hematoxylin to determine the cellular morphology. For keratin staining a mild proteolytic treatment with pronase (Sigma no. P5147, St Louis, MO) was performed (0.1% pronase for 15 minutes at room temperature) to demask the keratin epitopes.

RESULTS

Patients and Computed Tomography Scan Findings

The clinical data of the five cases are summarized in Table 1. One patient (case no. 4) was 46 years old. The tumor in this patient was located in the thalamus. The patient died after 3 years due to tumor progression. Although a stereotactic operation was performed, sufficient material for reliable diagnosis was available. Case no. 5 presented with a tumor located in the temporal lobe with extension into the thalamus.

On a computed tomography (CT) scan, the lesions showed uniform intense contrast enhancing (Fig 1). The

TABLE 1. Clinical Data of the Five Patients

Case No.	Sex	Age (yr)	Location	CT Scan	Angiogram	Treatment	Follow-up
1	M	10	Parietooccipital	Cystic	Avascular	Resection	Alive, 4 yr
2	F	15	Parietooccipital	Cystic	Moderately vascular	Small decompression	Alive, 3 yr
3	M	26	Temporal	Cystic	Poorly vascular	Debulking, radiation	Alive, 11 yr
4	M	46	Thalamus	Cystic	Avascular	Stereotactic operation	Dead, 3 yr
5	F	9	Temporal-thalamus	Cystic	Avascular	Debulking	Alive, 4 yr

lesions were sharply demarcated, with brain edema extending into the white matter. In three patients (nos. 1, 2, and 3) the tumors were located at the convexity, with brain edema extending centrally into the white matter. Two patients (nos. 4 and 5) had centrally located lesions, including the thalamus, with no or only mild development of brain edema (Fig 1).

Histopathologic Features

A marked pleomorphism was an invariable finding in all five patients (Fig 2A). Xanthomatous cells as well as polygonal cells with eosinophilic hyaline granules in the cytoplasm[9] were seen among irregular bundles of spindle-shaped cells (Fig 2A, C, D, E, and F). Furthermore, gemistocytic cells, giant cells (some of which were polynuclear), and nude nuclei without recognizable cytoplasm were seen (Fig 2A and G). Many periodic acid-Schiff–positive, diastase-resistant granules were present in part of the tumor cells (Fig 2E). Only sporadic mitoses were noted. In all five cases necrosis was definitely absent. Vascular proliferation was not obvious. Reticulin staining revealed a fiber network surrounding individual tumor cells (ie, both the polygonal cells and the spindle-shaped cells) (Fig 2F). Focal infiltrates of lymphocytes and plasma cells were found (Fig 2A).

In case no. 5 clusters of neuronal elements were seen dispersed between the other tumor elements (Fig 2H-L). The neoplastic nature of the neuronal elements was supported by their pleomorphism and random orientation; they sometimes formed clusters (Fig 2K). The true neuronal nature of these neoplastic cells was proven by the presence of Nissl substance in addition to immunohistochemical profiles (see below) (Fig 2I).

Immunohistochemistry

In all tumors a majority of the tumor cells stained positive for anti-GFAP antibody (Table 2; Fig 2B) and for anti-vimentin, as well as for the histiocytic markers α-1-antitrypsin and α-1- antichymotrypsin (Table 2; Fig 2C). Furthermore, the tumor cells expressed S100 protein and neuron-specific enolase (Table 2). In none of the cells was immunostaining acquired for anti-keratin and anti-lysozyme (Table 2).

In the neoplastic neuronal cells of case no. 5 the perikaryon and the cell processes were positive for neurofilament (Fig 2J). Intense positivity for anti-synapto-

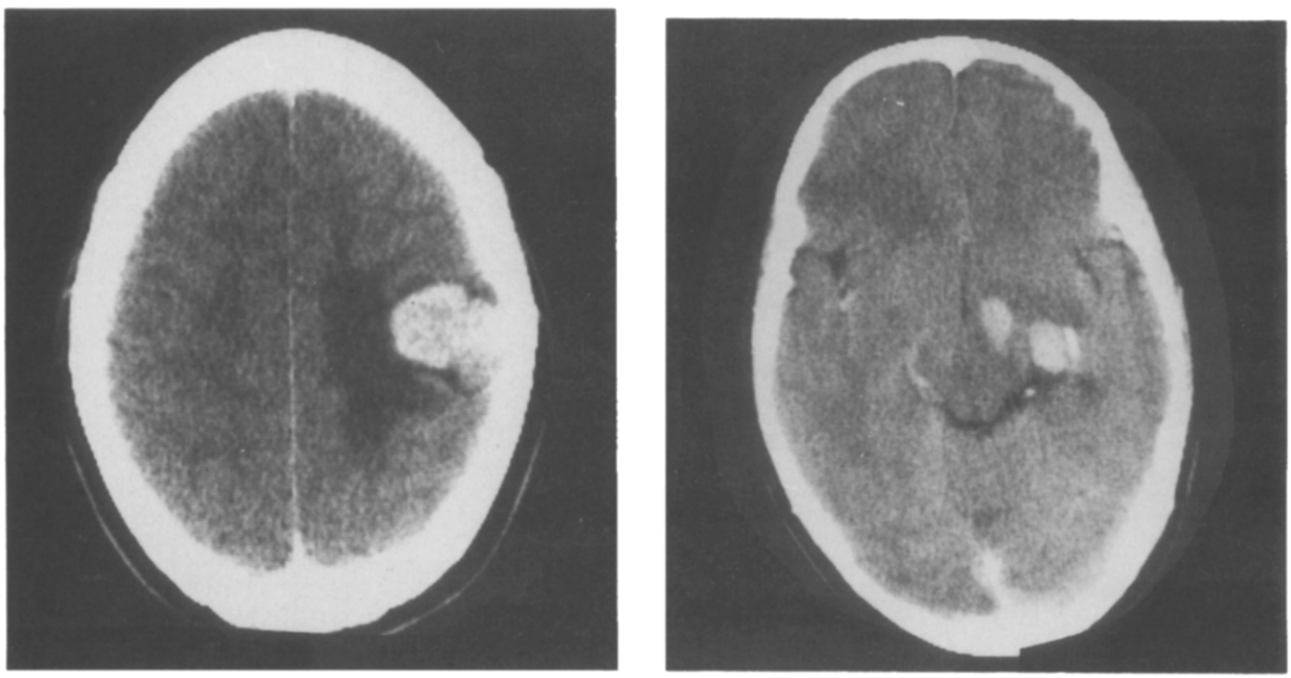

FIGURE 1. Computed tomography scan findings. (Left) Case no. 2. Computed tomography idiosyncrasies of a PXA: a parietal located, partly cystic tumor, firmly connected with the dura. (Right) Case no. 5. Cystic tumor with deep temporal location, extending into the thalamus. No connection with the dura is noted.

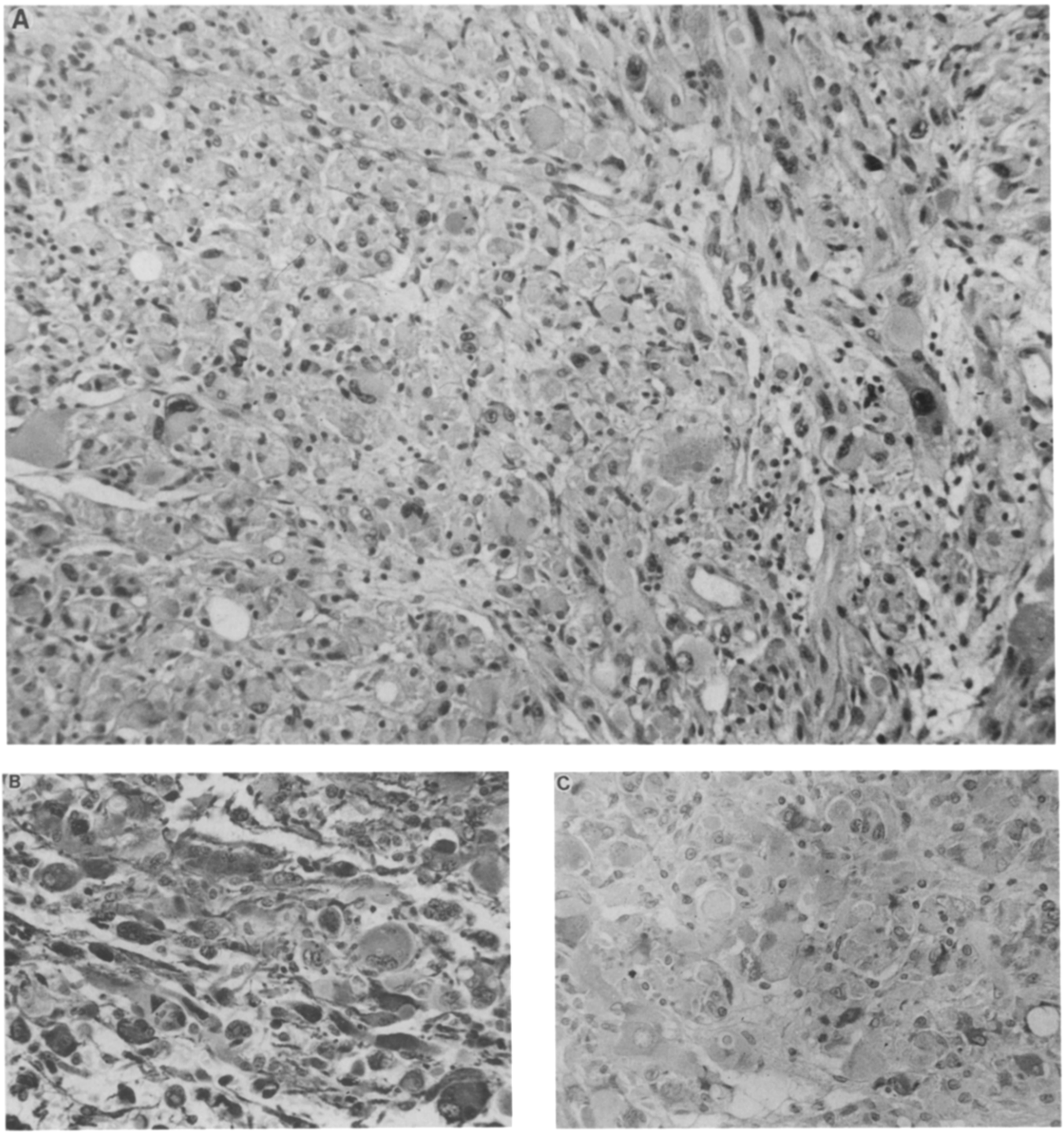

FIGURE 2. Histopathologic and immunohistochemical pictures. (A) Case no. 1. Low-power magnification of a typical PXA: a moderately cellular, marked pleomorphic tumor, without necrosis. (Hematoxylin-eosin stain; magnification ×9.) (B) Case no. 1. Immunopositivity for GFAP of the various tumor cells. Round cells as well as spindle-shaped cells are positive for GFAP. (Peroxidase antiperoxidase (PAP) stain for GFAP; magnification ×79.) (C) Case no. 1. Immunopositivity for α-1-antichymotrypsin in the PXA. The expression is variable. (PAP stain for α-1-antichymotrypsin; magnification ×79.) (D) Case no. 1. Xanthomatous cell ("lipid-laden cell"): polygonal cell with confluent vacuoles in the cytoplasm. (Hematoxylin-eosin stain; magnification ×264.) (E) Case no. 1. Eosinophilic hyaline granular cell: this cell was described in detail as a constituent of the PXAs by Iwaki et al.[9] Intracytoplasmatic eosinophilic granules are found, which stain strongly with periodic acid-Schiff. (Magnification ×264.) (F) Case no. 1. Spindle-shaped cell. Reticulin is not exclusively found around this cell type, but surrounds the lipid-laden cells as well. (Gomori stain; magnification ×264.) (G) Case no. 3. Multinuclear giant cell (Touton-like giant cell). A variety of larger cells are seen in the PXA, ranging from gemistocytic cells to monstrous cells. The nuclei of the Touton-like cells have an (almost) circular arrangement. (Hematoxylin-eosin stain; magnification ×264.) (H) Case no. 5. Neuronal cell (arrow) in a highly pleomorphic tumor indistinguishable from the PXA. (Hematoxylin-eosin stain; magnification ×115.) (I) Case no. 5. Among the neuronal cells in case no. 5, several binucleated cells were found. (Nissl stain; magnification ×264.) (J) Case no. 5. Neuronal cell (arrow) PAP stained for neurofilament. (Magnification ×264.) (K) Case no. 5. Cluster of neuronal cells (arrows). The random orientation and pleomorphism, in addition to strong positivity for synaptophysin, indicate the neoplastic nature of these cells. (PAP stain for synaptophysin; magnification ×79.) (L) Case no. 5. Higher magnification of neuronal cell, stained for synaptophysin. Immunostaining is seen in the perikaryon as well as in and around the cell processes. (PAP stain for synaptophysin; magnification ×264.)

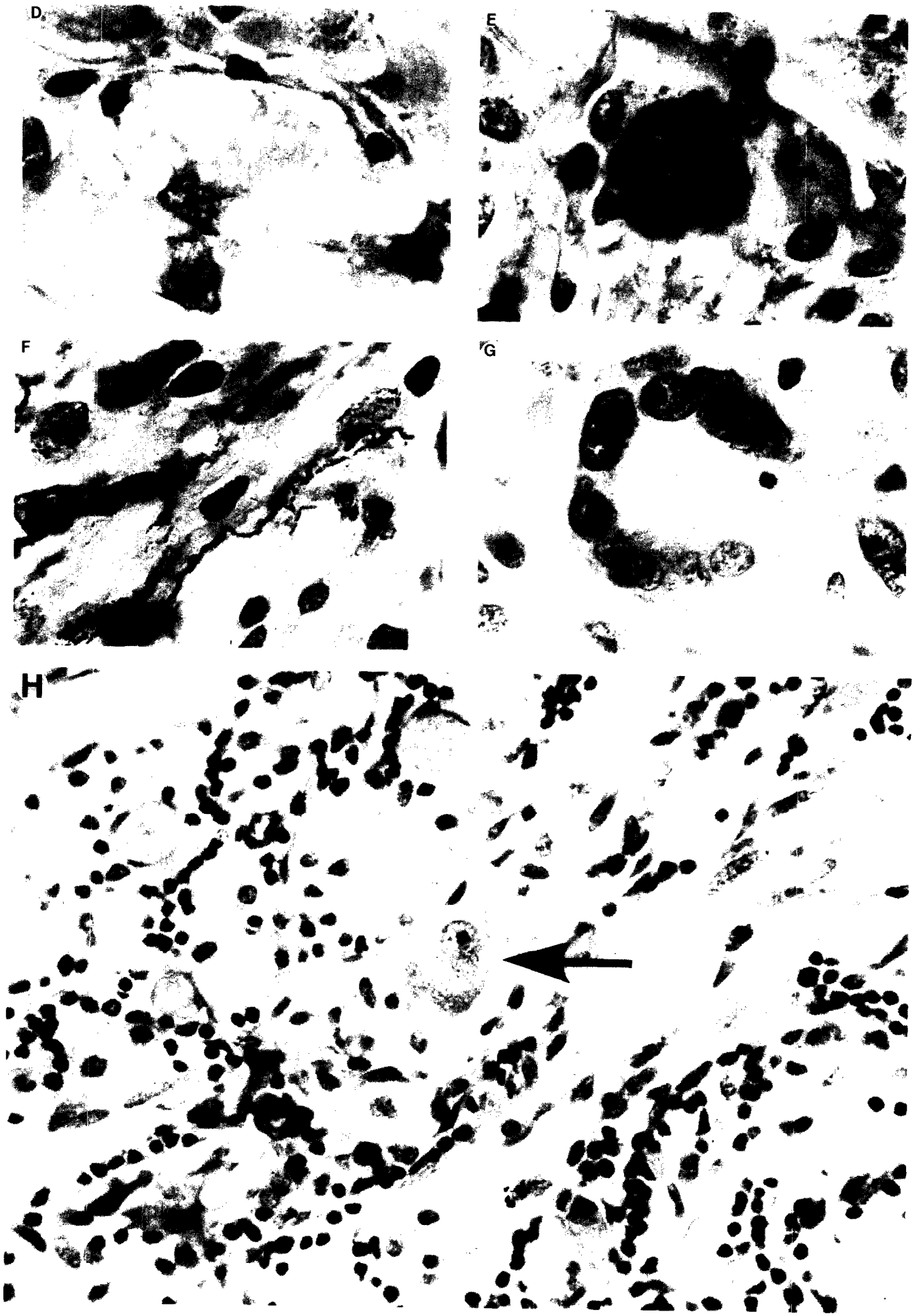

FIGURE 2. *(Continued)*

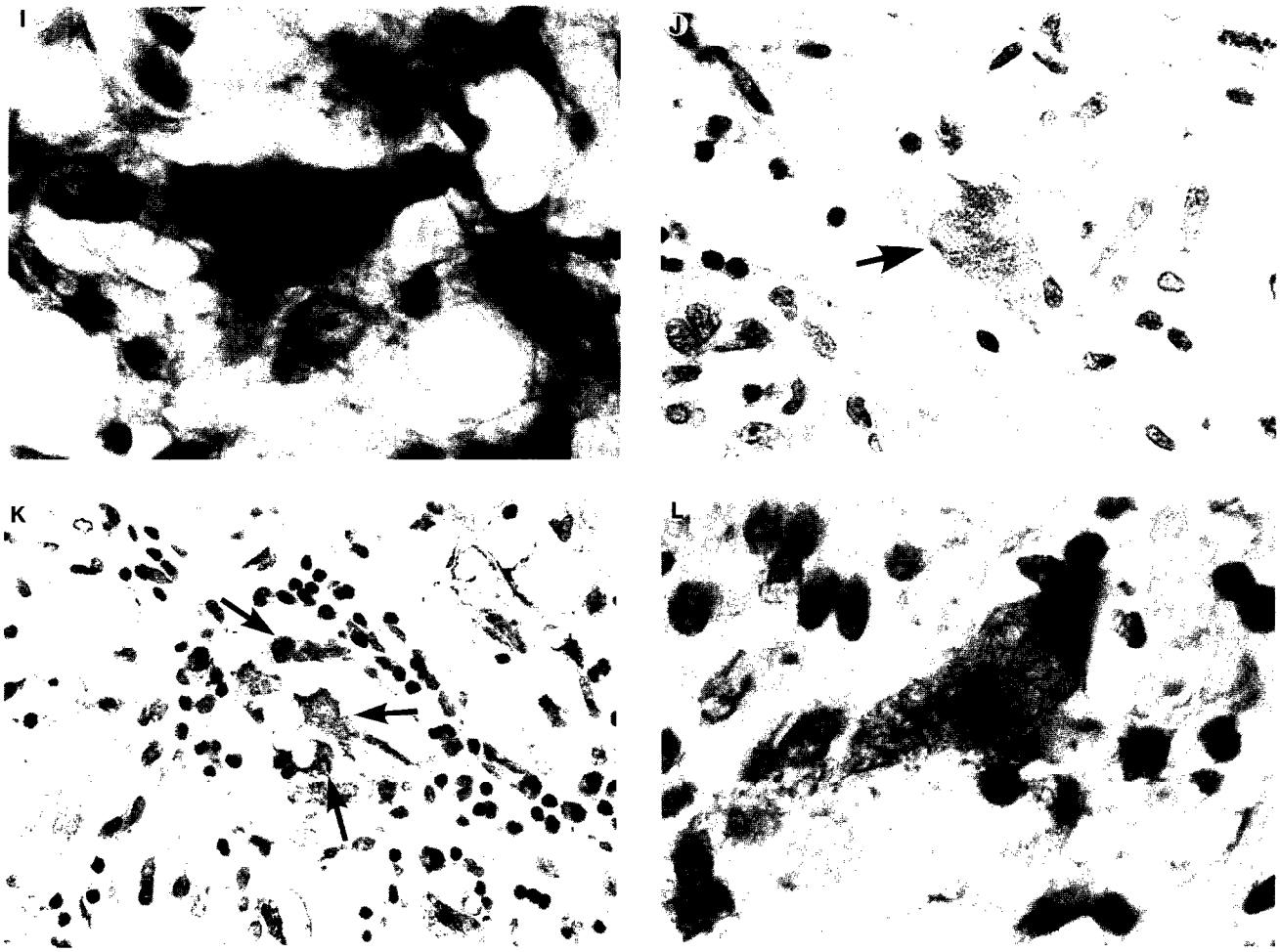

FIGURE 2. (*Continued*)

physin antibody was seen in the cytoplasm and in and around the cell processes (Fig 2K and L).

DISCUSSION

Comparison of the CT scans of the present five patients (Fig 1) with photomicrographs of CT scans in the literature[6,13,17,19,21] revealed a remarkable similarity. The lesions invariably showed distinct borders with the surrounding brain tissue, and contrast enhancement was a constant finding. Cysts were seen in all tumors. The CT scan findings are not specific for PXAs, however, since comparable scans are found in a variety of other benign as well as malignant brain tumors.[3,23,24]

Despite a similar histopathology, the presented cases had discrepant clinical data. Although one case of PXA has been described before in an elderly patient,[12] PXAs usually appear in young people. One of our patients was 46 years old. In this patient and in one other

TABLE 2. Immunohistochemical Results

	ker	vim	gfa	lys	trp	chy	nse	nf	S100	syn
Spindle-shaped cells	−	+	+	−	+	+	+	−	+	−
Xanthomatous cells	−	+	+	−	+	+	+	−	+	−
Cells with eosinophilic hyaline granules	−	+	+	−	+	+	+	−	+	−
Gemistocytic cells	−	+	+	−	+	+	+	−	+	−
Giant cells	−	+	−	−	+	+	±	−	+	−
Touton-type giant cells	−	−	−	−	+	−	+	−	+	−
Neuronal cells	−	−	−	−	−	−	+	+	−	+

Symbols: −, negative; +, positive; ±, faint immunostaining.

Abbreviations: ker, keratin; vim, vimentin; gfa, glial fibrillary acidic protein; lys, lysozyme (muraminidase); trp, a-1-trypsin; chy, a-1-chymotrypsin; nse, neuron-specific enolase; nf, neurofilament; S100, S100 protein; syn, synaptophysin.

(no. 5), the tumor was located in a deep region (ie, the thalamus) (Fig 1, right). These cases and a few others in the literature illustrate that PXAs may be found in sites without obvious meningeal contact.[8,17]

Almost all cell types simultaneously expressed GFAP as well as the histiocytic markers α-1-antitrypsin and α-1-antichymotrypsin (Table 2; Fig 2B and C). Although intracranial localized malignant fibrous histiocytomas may show pleomorphism as well, there is definitely no expression of GFAP in these tumors.[25-27] Despite morphologic and immunohistochemical similarities between PXAs and meningeal-derived fibrous histiocytomas, Kepes et al believe that PXAs represent primary glial, and not mesenchymal, neoplasms.[21] In spite of the presence of reticulin, collagen depositions, (hemi)desmosomes, and intracytoplasmic lipid droplets, the marked GFAP positivity of the tumor cells was seen as a definite sign of the true glial nature of this tumor.[21] Paulus and Peiffer, however, disputed its true glial nature because of the positivity of the tumor for monocytic-histiocytic markers, in addition to the distinct mesenchymal features.[28] According to their observations, the presence of GFAP-positive cells would be limited to areas of cortical infiltration and might be explained by endocytic processes of histiocytic cells or by migration of reactive astrocytes into the primary mesenchymal tumor.[28] If the PXA indeed represents a meningeal-derived tumor, the occurrence of this entity in nonsuperficial parts of the brain, such as the thalamus, is not easily explained. Moreover, in our cases, the expression of GFAP was not restricted to nonsuperficial tumor cells (Fig 2b). Whatever histogenesis PXAs may have, it should be kept in mind that expression of any marker could very well be the result of capricious behavior of the tumor cells rather than the indication of a supposed nonneoplastic cell of tumor origin.[29]

Necrosis has been identified as a histopathologic feature with independent prognostic significance in gliomas.[30] Based on the strict absence of this feature in PXAs, these tumors should be distinguished from gliomas with heavily lipidized tumor cells[3,4] (Table 3), as well as from monstrocellular brain tumors in which necrosis invariably heralds a bad prognosis.[14] Although the lengths of survival in monstrocellular glioblastomas are longer than those in less pleomorphic subtypes, they differ considerably from those recorded in cases of PXA.[1]

The presence of necrosis in two putative cases of PXA presented by Gaskill et al was linked with the rapid death of one of the patients,[20] while it was also the cause of criticism surrounding the accuracy of the histopathologic diagnosis.[31] However, some investigators have suggested that anaplastic evolution of PXAs, associated with necrosis, might occur.[19,21] Moreover, the transition of a PXA into a glioblastoma with necrosis as a genuine feature has been interpreted as further corroboration of the true glial nature of the former.[21]

TABLE 3. Clinicopathologic Findings

Group	Age	Localization	Macroscopic Findings	Prognosis	Main Histopathologic Features	Spindle-Shaped Cells	Xanthomatous Cells	Neuronal Cells	Necrosis	Mitoses	Pleomorphism
HLMG[4]	Adults	Frontal Temporal Cerebellar	Variable sizes No cysts Deep; no connection with dura	Bad; death within 1 yr	Majority of tumor cells characterized by vacuolated foamy cell bodies GFAP + cells	-	++	-	+*	++	++
SCA[23]	1.5–9 mo	Frontal Parietal (Temporal)	"Massive" Cystic Attached to dura	"Favorable"	Storiform pattern of spindle-shaped cells Marked desmoplasia (collagen, reticulin) Lipidization not prominent GFAP + cells	+	±+	-		±	+
PXA[1]	Young to various ages	Temporal Parietal Frontal (Thalamic) (Suprasellar)	Variable sizes Cystic Extensive leptomeningeal involvement	"Relatively favorable"	Marked pleomorphism Lipidized cells GFAP + cells α-1-Antitrypsin + cells α-1-Antichymotrypsin + cells	+	+			±	++‡
DIG[24]	3–18 mo	Frontal Parietal (Temporal)	"Huge" Cystic Variable dural attachment	"Relatively favorable"	Dense fibrous desmoplasia Neuronal cells in different degrees of maturation GFAP + cells NF + cells	-	−§	+‖	±¶	+	+

Abbreviations: HLMG, heavily lipidized malignant glioma; SCA, superficial cerebral astrocytoma; PXA, pleomorphic xanthoastrocytoma; DIG, desmoplastic infantile ganglioglioma; GFAP, glial fibrillary acidic protein; NF, neurofilament.

Symbols: −, absent; ±, scanty; +, present; ++, abundant.

* The presence of necrosis clearly distinguishes the HLMG from the other tumors.

† Lipidization is not a prominent feature of the SCA.

‡ In comparison with the other tumors, pleomorphism is most apparent in the PXA.

§ Xanthomatous cells are not found in the DIG.

‖ Variable numbers of pleomorphic neuroepithelial cells are (exclusively?) found in DIGs.

¶ In the 11 DIGs that were described by VandenBerg et al,[24] the feature of necrosis was present in one case.

The superficial cerebral astrocytomas that were found in some very young children by Taratuto et al[23] and Chadarévian et al[32] may be confused with PXAs, but clinical data and histopathology are distinct from the latter. Although superficial cerebral astrocytomas contain spindle-shaped cells and gemistocytic cells, lipidized cells are sporadic and the degree of pleomorphism is not as pronounced as in PXAs (Table 3). Because of GFAP positivity, the superficial cerebral astrocytomas are believed to be glial tumors as well.[23] Just as in the PXA, the subpial astrocytic subset has been considered as a possible ontogenic lineage for these superficial localized neoplasms.[23,32]

Our finding of neoplastic neuronal cells in an otherwise typical PXA (case no. 5) has not been reported previously. The neuronal cells presented with several degrees of maturation. Binucleated neuronal cells were frequently seen (Fig 2I). The presence of Nissl substance, in addition to the expression of neurofilament and synaptophysin, was a signpost for the true neuronal character of these cells[33,34] (Fig 2I-L), while the random orientations and clustering are indicative of their neoplastic status (Fig 2K). Their presence had, in this case, led to a primary diagnosis of ganglioglioma (ie, desmoplastic infantile ganglioglioma [DIG]).[24] Gangliogliomas and ganglioneuromas may very well be found in the floor of the third ventricle, although they might arise anywhere else in the brain,[33,35-37] whereas DIGs are only encountered in peripheral parts[24] (Table 3). Although pleomorphism may be present either in the glial or in the neuronal cell component of gangliogliomas, the glial part would be responsible for occasional malignant transformation of these tumors.[33] In exceptional cases, gangliogliomas transform into glioblastomas.[38-40] The variants of DIGs affect young children and usually present as huge tumors affecting more than one cerebral lobe[24] (Table 3).

Desmoplastic infantile ganglioglioma and PXA do share a number of clinical and histopathologic characteristics (Table 3). Both contain GFAP-positive cells, and both are preferentially associated with the leptomeninges. The distinction between PXAs and DIGs, however, is based on the finding of xanthomatous cells in the former, while neoplastic neuronal cells should be exclusively diagnostic for gangliogliomas (ie, DIGs).[1,24] Therefore, the presence of xanthomatous cells in addition to neoplastic ganglion cells in our case no. 5 causes difficulties in the differential diagnosis. Fortunately, the distinction between a PXA with a neoplastic neuronal component on the one hand and a DIG with xanthomatous cells on the other appears to be irrelevant with respect to the expected biologic behavior.

In conclusion, we believe that, due to its relatively favorable prognosis and characteristic histopathology, the pleomorphic xanthoastrocytoma definitely represents a separate entity. If neuronal elements are accepted as a possible constituent of this tumor, its distinction from DIGs may be impossible.

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