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Histopathological features of recurrent pleomorphic xanthoastrocytomas: further corroboration of the glial nature of this neoplasm

A study of 3 cases

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Summary. Pleomorphic xanthoastrocytoma (PXA), a tumor most often presenting superficially over the cerebral hemisphere of young subjects, has certain morphological similarities to fibrous histiocytoma (or fibrous xanthoma) of the meninges and brain, namely the occurrence of lipid-laden neoplastic cells and, frequently, a dense reticulin fiber network. The detection of glial fibrillary acidic (GFA) protein in the tumor cells helped to establish its astrocytic derivation, but it has been advanced that, in spite of this agreed observation, the tumor should still be regarded as a fibrous xanthoma of meningeal origin. Although many patients have a long symptom-free postoperative survival, local recurrences at varying intervals after surgery have been noted in some instances. Weldon-Linne et al. first reported that such a recurrence had the morphology of a small-cell glioblastoma. We are reporting three further examples of locally recurrent neoplasms in patients whose original meningocerebral tumors had the typical features of PXA; the recurrences (developing 7 months, 7 years and 15 years, respectively, after surgery) were small-cell glioblastomas. The rich reticulin network present in the initial tumor was mostly lost in the recurrences. This anaplastic evolution further confirms the astrocytic nature of the PXA.

Key words: Pleomorphic xanthoastrocytoma – Recurrence – GFA protein – Fibrous xanthoma

Pleomorphic xanthoastrocytomas (PXA) present most often, although not exclusively [40], in the cerebral hemisphere of young subjects. These solid or cystic masses are close to the surface and extensively involve the leptomeninges. Despite their pleomorphic population that may include bizarre hyperchromatic, mono- or multinucleated giant cells, they carry a relatively favorable prognosis as long as they show no necrotic areas. Many patients enjoy many years or even decades of symptom-free postoperative survival [15, 19, 23, 32, 45, 46, 60], although recurrences have sometimes been noted at various time intervals after operation [2, 19, 23, 32, 46, 63].

The possibility of local recurrence was implied in the original definition of these tumors: they were not regarded as entirely benign, but only as having a relatively favorable biological behavior, particularly when contrasted to the degree of pleomorphism of the cells [30, 32].

Since our original description, typical cases have been reported from different countries [2, 15, 17, 19, 21, 23, 34, 40, 41, 45, 46, 53, 59, 60, 63]. There are certain morphological similarities between PXA and fibrous histiocytomas (fibrous xanthomas). These include the presence of multinucleated giant cells that contain lipid droplets and an often-dense reticulin network in which individual tumor cells may be entirely surrounded by argyrophilic fibers. Because of these features Kepes et al. [29] in 1973 originally reported some of these meningocerebral neoplasms as fibrous xanthomas. The application of glial fibrillary acidic (GFA) protein immunohistochemistry to astrocytes [7–10] helped to identify these tumors as variants of astrocytoma. Nevertheless, fibrous xanthomas or fibrous histiocytomas of the meninges and brain occur separately either spontaneously [38] or as a complication of radiation [16]. Reported cases have been

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summarized [4], whereas the histological and immunocytochemical criteria that help to distinguish PXA from fibrous histiocytomas have been laid down [17].

A suggestion has, however, recently been made [47] that all cases diagnosed as PXA should be regarded as fibrous xanthomas of the meninges. This view was based on the presence of α-1-antitrypsin and of α-1-antichymotrypsin in the tumor cells and, conversely, on the observation that GFA protein is also demonstrable in a number of normal and neoplastic cells other than astrocytes, among others in Schwann cells [43], stromal cells of capillary hemangioblastomas [6, 31] and in chondrocytes of the elastic cartilage of the human epiglottis [27].

The purpose of this paper is to report on the histological features of three recurrent examples of PXA in which the recurrences presented 7 years, 15 years and 7 months respectively, after the initial operation. In all three cases progressive anaplasia occurred and, although some of the original pleomorphic features were still present, transitions to typical glioblastoma multiforme, mostly of the parvicellular and isomorphic type, were easily demonstrated. The typical glial morphology of the neoplastic cells, the pattern of reticulin network (mostly absent from the tumor cell clusters and restricted to the blood vessel walls) and the immunohistochemical features clearly confirmed the glial nature of the tumors in question.

Case reports

Case 1

This patient, originally case 9 reported by us [32], was a 16-year-old girl in 1976 with a 2-year history of seizures. Electroencephalogram (EEG), radionuclide scan and a left carotid angiogram indicated a left posterior temporal mass, which at operation was a 2 × 2 cm nonencapsulated pink-purple tumor, containing a small cyst. It largely involved the leptomeninges and was only partially demarcated from the underlying brain, into which it extended superficially. Gross total removal was accomplished. A total dose of 3,000 rad was delivered to the right and left lateral ports on the skull. The patient remained asymptomatic and with normal annual computed tomography (CT) scans, until May 1982, when the first signs of a local recurrence were detected. The mass grew rapidly and in March 1983 a second operation was performed so as to remove as much of the recurrence as possible. The patient was given postoperative steroids and died a few months after surgery. Autopsy was not performed.

Microscopic findings. The original tumor consisted of rounded and spindle-shaped cells, many of the former containing large amounts of lipid and being variable in size and shape (Fig. 1). Necrosis was absent, but infiltrates of lymphocytes, small macrophages and occasional plasma cells were seen. A dense network of reticulin fibers was present, often surrounding the individual cells, including some of the large foamy cells (Fig. 2). A number of these large round cells, including their processes, were immunopositive for GFA protein (Fig. 3). Some of the elongated spindle cells were also GFA protein-positive.

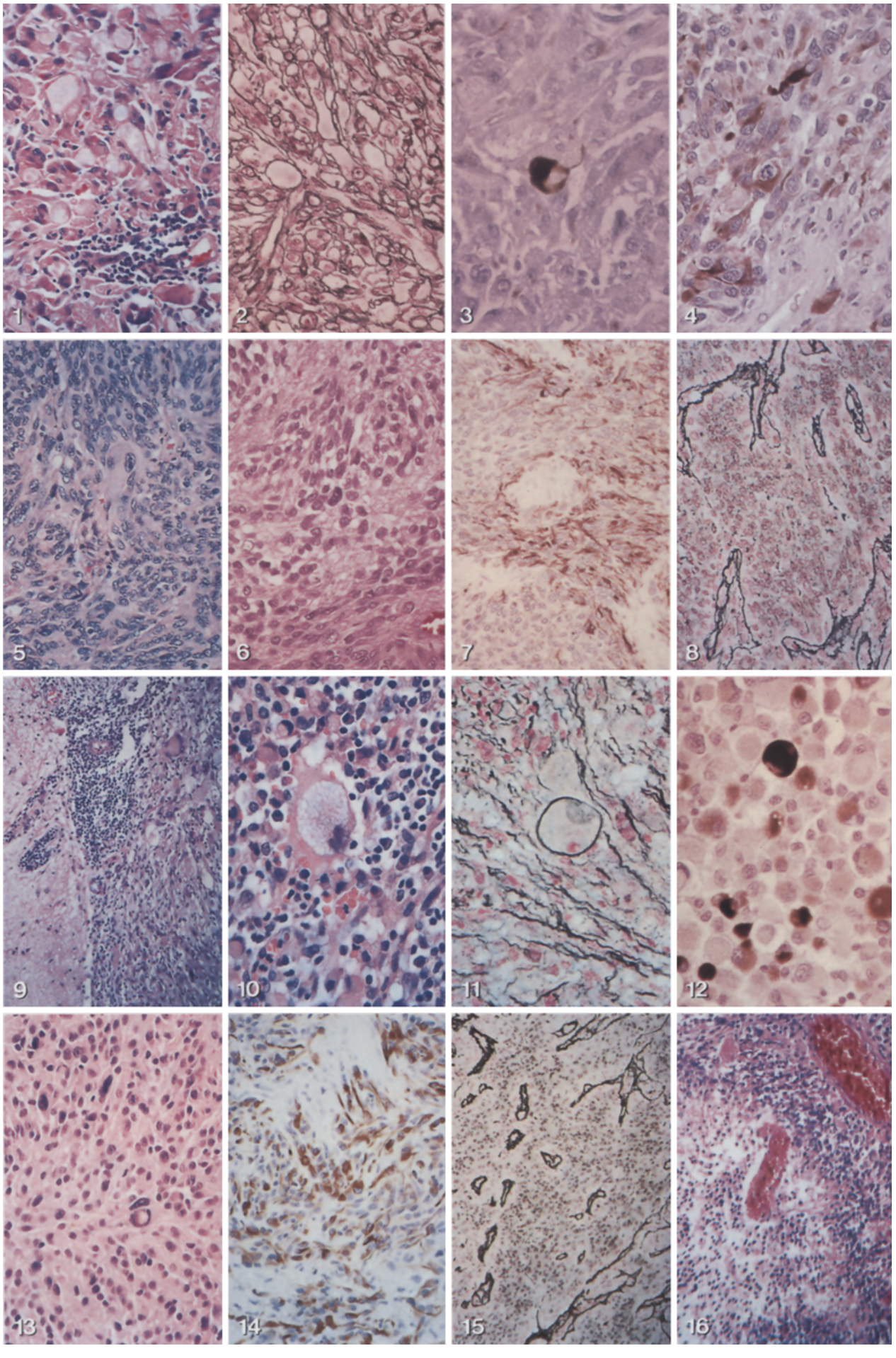
In the recurrent tumor, areas with cells closely resembling those of the initial neoplasm were seen mostly at the margin of the growth. Many of these cells contained GFA protein in their processes. Their morphology was not that of reactive astrocytes, and some of the immunopositive cells were in mitosis (Fig. 4, center). More deeply, only occasional large foamy cells were found, the majority of the cells being small, spindle-shaped, closely packed and with little pleomorphism (Fig. 5), but showing fairly numerous mitotic figures. Deeper still, small cells with fine fibrillary processes predominated (Fig. 6). These were often immunopositive for GFA protein (Fig. 7). In contrast to the original lesion (Fig. 2), only the blood vessel walls stained positively for reticulin (Fig. 8).

Case 2

This patient was a 16-year-old girl with a superficially located, right occipital tumor involving the leptomeninges, removed in 1964. She did well for 15 years, when in 1979 clinical and radiological signs of a local recurrence necessitated another occipitoparietal craniotomy. Multiple hemorrhagic, gelatinous gray-tan fragments were removed, some of them being bright yellow. The patient died 3 months later at home. No autopsy was performed.

Figs. 1–8. *Case 1.* **1** Original tumor, composed of large round cells, many with foamy lipid-laden cytoplasm, and a few spindle cells. The stroma has aggregates of reactive lymphocytes and plasma cells. H&E, × 200. **2** Individual tumor cells surrounded by reticulin fibers. Wilder's silver impregnation, × 200. **3** Round tumor cell in center, with slender cytoplasmic process at its base: much of the cytoplasm stains positively for glial fibrillary acidic (GFA) protein. Peroxidase-antiperoxidase (PAP) stain for GFA protein, × 260. **4** Recurrent tumor. Large tumor cells, including one in mitosis (*center*), staining positively for GFA protein. PAP stain for GFA protein, × 160. **5** Close to center of recurrence, small spindle-shaped cells predominate, with a rare large foamy cell. H&E, × 140. **6** Elongated cells with fine cytoplasmic processes showing the picture of a cellular pilocytic astrocytoma. H&E, × 140. **7** Same area as in Fig. 6. Many spindle-shaped tumor cells stain positively for GFA protein. PAP stain for GFA protein, × 120. **8** In striking contrast to the reticulin pattern of the original tumor (Fig. 2), reticulin fibers in the recurrence are restricted to the blood vessel walls. Wilder's silver impregnation, × 120

Figs. 9–16. *Case 2.* **9** Original tumor. Most of the tumor infiltrates the leptomeninges, (*right*) but it also extends into the superficial cortex (*left*). H&E, × 80. **10** Area of tumor consisting of small and large round cells, many of the latter being lipidized, as well as lymphocytes and plasma cells. H&E, × 220. **11** Reticulin-rich area with large lipidized tumor cell in center completely surrounded by reticulin fiber. Wilder's silver impregnation, × 220. **12** Same area as in Fig. 10. Round tumor cells showing various degrees of positivity for GFA protein. PAP stain for GFA protein, × 240. **13** Recurrence. Most tumor cells are small and dark, but a few larger irregular cells with hyperchromatic nuclei are seen. H&E, × 120. **14** Immunopositivity of many tumor cells for GFA protein. PAP stain for GFA protein, × 120. **15** Same areas as in Figs. 13 and 14. Reticulin fibers are entirely confined to the blood vessel walls. Wilder's silver impregnation, × 100. **16** Typical pattern of glioblastoma, with necrosis and pseudopalisading. H&E, × 80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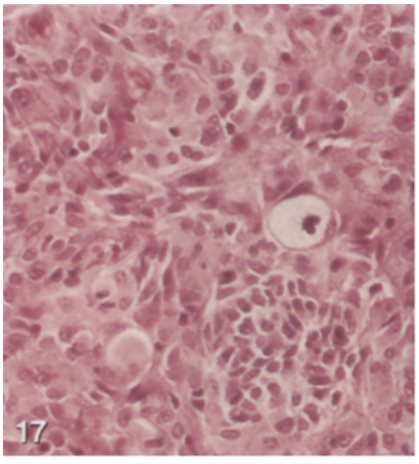
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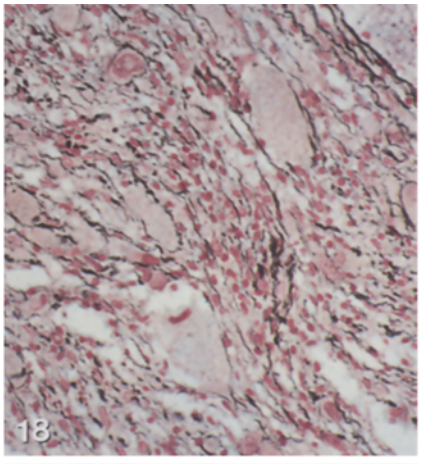
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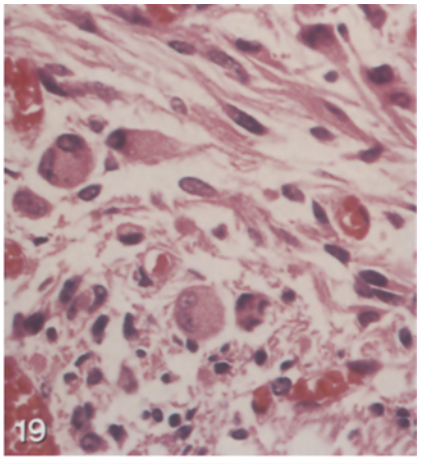
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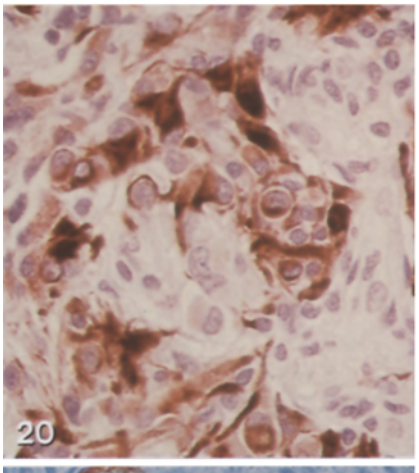
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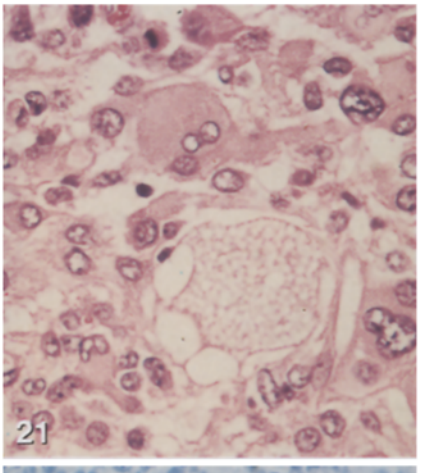
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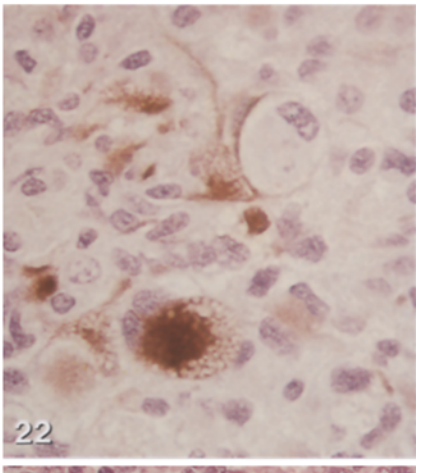
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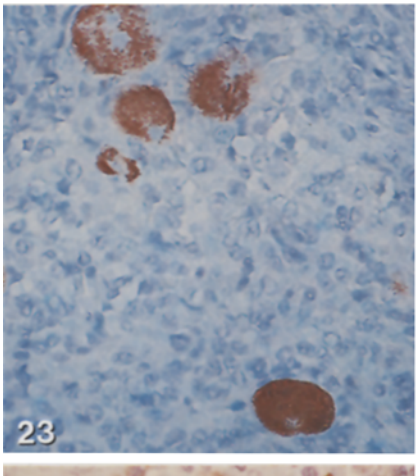
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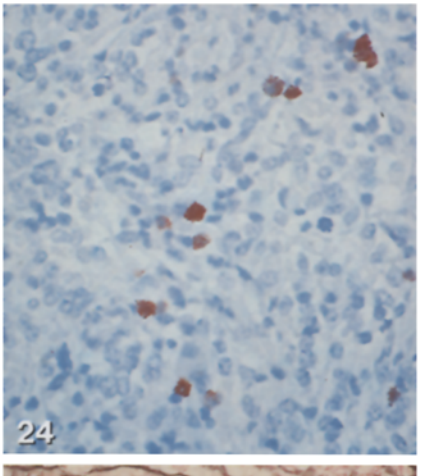
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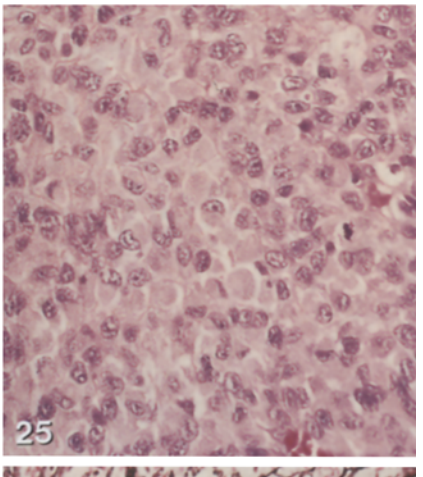
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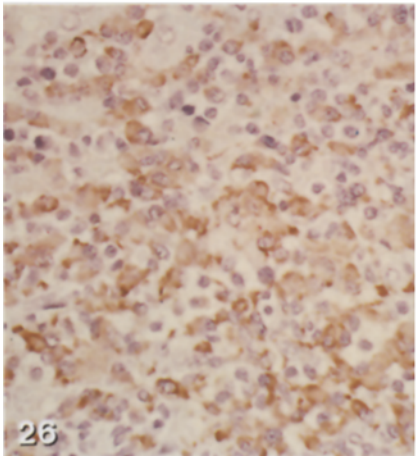
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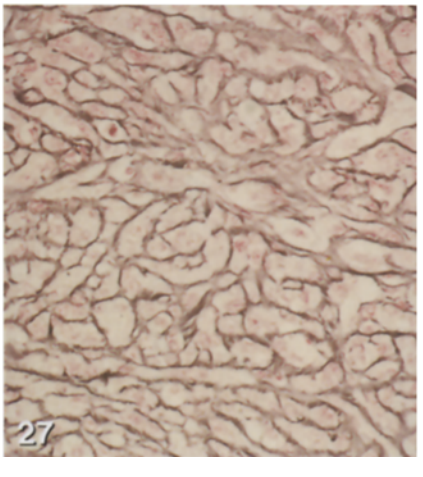
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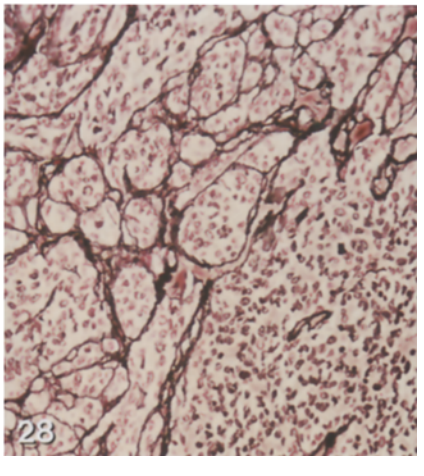
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Microscopic findings. In the initial specimen, a moderately cellular and very pleomorphic tumor consisting of spindle-shaped cells as well as mono- and multinucleated giant cells occupied the leptomeninges. It focally extended into the superficial cortex, mostly along the perivascular spaces (Fig. 9). A significant number of the large multinucleated cells had a foamy cytoplasm apparently caused by lipid deposits (Fig. 10). There was a rich reticulin network in some areas, some of the parallel fibers possibly representing the original leptomeningeal framework or an increased desmoplastic reaction, but with some of the tumor cells being completely surrounded by reticulin fibers (Fig. 11). A large number of these round cells stained positively for GFA protein (Fig. 12). Their outlines ruled out their identification as reactive cortical astrocytes. The fields in which these cells predominated lacked reticulin fibers.

In the recurrent tumor, some large bizarre cells with vacuolated nuclei were still present, but foamy cells were absent. Spindle cells were smaller and shorter, and more closely packed (Fig. 13). They were immunopositive for GFA protein (Fig. 14). Unlike the reticulin pattern of the original tumor (Fig. 11), the recurrent tumor showed reticulin fibers only in the walls of the blood vessels (Fig. 15). In some areas, the typical pattern of necrosis bordered by pseudopalisading, characteristic of glioblastoma, was seen (Fig. 16).

Case 3

The patient was a 7-year-old girl, operated in January, 1988 for a large right parietotemporal tumor that presented on the surface of the brain, but also penetrated the ventricle. Gross total removal was accomplished, followed by radiation. Tumor recurrence was evident by CT scan in early summer of that year and its growth was rapid, necessitating emergency reoperation.

Microscopic findings. The original neoplasm had the usual mixture of spindle-shaped elements, foamy giant cells and the collections of lymphocytes and plasma cells (Fig. 17). A rich reticulin network was present, often surrounding individual tumor cells, especially large foamy giant cells (Fig. 18). In some areas the astrocytic character of the tumor cells, both pilocytic and rounded, was obvious on H&E stain, and uni- and bipolar glial processes were seen (Fig. 19). The cytoplasm of many of these cells was immunopositive for GFA protein (Fig. 20). Some zones were entirely composed of slender, closely packed cells that were GFA protein-positive. Some of the giant cells were almost completely filled with fat droplets (Fig. 21), but in those areas where some non-lipidized cytoplasm were discernible, GFA protein-positivity was evident (Fig. 22). Immunostaining for α-1-antichymotrypsin was strongly positive in a large number of foamy giant cells (Fig. 23). Staining with the MAC 387 histiocyte-macrophage marker was negative in the giant cells and in the spindle-shaped tumor cells; however, small mononuclear cells within the lymphohistiocytic reactive infiltrates were immunopositive (Fig. 24).

In the recurrent tumor, giant cells were very rare, but small, round, slightly granular cells were present (Fig. 25). In many areas the tumor cells stained positively for GFA protein (Fig. 26). In parts of the recurrence, small groups of cells or individual cells were surrounded by a reticulin fiber network (Fig. 27), similar to that seen in the original lesion. In other areas, a transition was seen between that pattern and that of a typical glioma, in which only the blood vessel walls showed reticulin fibers (Fig. 28). In large areas of the recurrence, the reticulin pattern was entirely that of a glioma.

Figs. 17–28. *Case 3.* **17** Original tumor composed of pleomorphic cells; some of the larger tumor cells are heavily lipidized. H&E, ×180. **18** Original tumor, showing dense network of reticulin fibers, with some of the larger tumor cells enveloped by them. Wilder's silver impregnation, ×180. **19** In some areas, plump eosinophilic tumor cells with long slender wavy processes, fulfill morphological criteria for glial cells. H&E, ×240. **20** Immunopositivity of many tumor cells for GFA protein. PAP stain for GFA protein, ×260. **21** Large, plump tumor cells with foamy cytoplasm, H&E, ×240. **22** Varying amounts of GFA protein in the cytoplasm of foamy tumor cells. PAP stain for GFA protein, ×240. **23** Large foamy cells staining positively for α-1-antichymotrypsin. PAP stain for α-1-antichymotrypsin, ×120. **24** Scattered macrophages within the tumor, staining positively for the histiocyte marker MAC 387. Tumor cells, including foamy giant cells, are negative. PAP for MAC 387, ×120. **25** Recurrence. Tumor cells are smaller and less pleomorphic than in the original neoplasm. H&E, × 140. **26** Same area as in Fig. 25. Immunopositivity of many tumor cells for GFA protein. PAP stain for GFA protein, ×120. **27** The original reticulin-rich fiber network is still present in parts of the recurrence. Wilder's silver impregnation, ×100. **28** In this area of the recurrence, less reticulin is seen than in Fig. 27. Note transition to gliomatous pattern in right lower corner. Wilder's silver impregnation, ×80

Discussion

Each one of the above three cases represents a local recurrence of a presumably incompletely removed meningocerebral neoplasm. The original tumor in all three had the classic features of PXA, including some similarities to fibrous histiocytoma (fibrous xanthoma), but also morphological characteristics, at least in some areas, that even on routine stains labeled it as astrocytic. The histological appearances of the recurrences were clearly those of malignant astrocytic gliomas, in which confusion with tumors of a fibrous xanthomatous nature was no longer possible.

Similar differential diagnostic difficulties between neuroepithelial and mesenchymal neoplasms of the central nervous system (CNS) have been seen in other contexts. In the desmoplastic cerebellar medulloblastoma, sometimes designated in the past as "sarcoma", "circumscribed arachnoidal sarcoma" or "cerebellar sarcoma" [3, 11, 65], the sarcoma-like zones are due to reticulin and collagen fiber formation in the leptomeninges as a response to the invading tumor cells, whereas the desmoplasia is absent in the deeper portions of the neoplasm, in the reticulin-free cellular groups away from the meninges [51]. Some forms of giant cell glioblastoma with numerous blood vessels and abundant interstitial connective tissue have also been labeled "monstrocellular sarcomas" [66]. The presence of reticulin and collagen fibers deep within a brain tumor is susceptible of different interpretations. In some cases, it forms part of a post-necrotic scar in a malignant glioma (one of Scherer's "tertiary struc-

tures"). In others, it is an indication of the mesenchymal derivation of the tumor in question. In still others, it is due to a secondary sarcomatous change in the supporting vascular stroma of a glioma.

However, it is also known that both normal and neoplastic glial cells are in certain circumstances capable of producing a basement membrane (seen as basal lamina by electron microscopy): its presence on the outer surface of normal subpial astrocytes in the human brain has been documented [49]. Collagen secretion by neuroepithelial elements has also been observed in the embryo [5]. The parenchyma of the mature CNS contains an intercellular matrix [42, 52] that is related to substances of which basal laminae are normally composed. The latter in turn contain at least one type of collagen (type IV). Since astrocytes are capable of producing basement membranes in tissue culture [35], more complex structures ordinarily considered to be mesenchymal derivatives, i.e., collagen fibers, may surround neoplastic astrocytes, as reported in glioblastomas [33], in ependymomas [57] and, in its most striking form, in gliofibromas [12, 50]. Paulus, in a recent paper with Roggendorf and Schuppan [48], suggests (with minor reservations) that in some glioblastomas certain GFA protein-positive cells are collagen IV-producing glial cells.

By electron microscopy, uninterrupted basal laminae closely surrounding and following the cytoplasmic plasma membranes are, by contrast, *not* seen around fibroblasts or histiocytes, and this feature is also absent in well-documented cases of fibrous histicytoma, both extracranial or in the meninges or brain [1, 4, 13, 20, 24, 37, 39, 55, 56, 61, 62]. Instead, young collagen may be attached to the cell surface, and the cytoplasm often shows myofibroblastic differentiation, with closely packed filamentous plaques of the smooth muscle type [4]. This feature is never displayed in the cells of PXA. Its absence, as well as the presence of closely apposed basal laminae surrounding the tumor cells [25, 32, 34, 60], provide additional indirect support to our interpretation of a glial neoplasm.

The presence of large amounts of lipid droplets in foamy multinucleated tumor cells, while typical of mesenchymal tumors such as fibrous xanthomas, has also been noted in neoplastic astrocytes, not only in pleomorphic astrocytomas, but in otherwise typical glioblastomas, including those situated deeply within the parenchyma [14, 26, 28].

Lipidization of tumor cells, admittedly, creates additional diagnostic difficulties because fat droplets occupying most of the cytoplasm often obscure many of the identifying cytological features of the cell. Distention of these cells leads to a uniformly rounded appearance and to the blurring of histological differences, as may be seen in both the lipidized astrocytes and the stromal cells of capillary hemangioblastomas [6, 31]. In a different context, the cytoplasmic enlargement caused by large numbers of amassed mitochondria will make oncocytes of different tissue derivation resemble each other closely. Hamperl used the term "convergent differentiation" [18] for this phenomenon, meaning the loss of distinctive cellular features resulting in normal and neoplastic salivary gland ducts, thyroid, parathyroid, pituitary, kidney, and choroid plexus being capable of forming oncocytes with seemingly identical morphology. The deposition of large numbers of cytoplasmic fat droplets may likewise create similarities between the lipid-laden tumor cells of a fibrous xanthoma and those of a PXA. Nevertheless, as shown in our Figs. 3 and 22, and as previously illustrated ([32], Fig. 7 and Fig. 9, inset), such lipidized cells often clearly demonstrate GFA protein-positive cytoplasmic processes.

Astrocytes may also at times mimic cells of mesenchymal origin by their ability to act as macrophages, particularly in tissue culture [36]. Related to this is the finding that some presumed markers of mesenchymal macrophages such as α-1-antitrypsin (α-1-proteinase inhibitor) and α-1-chymotrypsin are regularly found in tumor astrocytes, both of low-grade astrocytomas and of glioblastomas, as well as in many other diverse neoplasms [44, 54, 58, 64]. These markers are, therefore, of no value in establishing the mesenchymal nature of tumors. Thus, in our case 3, many large lipid-laden tumor cells contained immunologically stainable α-1-chymotrypsin, whereas MAC 387, a histiocyte marker recognized for its much higher degree of specificity [22], was entirely absent from those cells. MAC 387 was, however, easily demonstrable in small non-neoplastic, reactive histiocytes that, together with lymphocytes, formed an inflammatory infiltrate (the latter being a regular feature of PXA). All this corresponds quite well to the observation – though not to the inference – of Paulus and Peiffer [47], according to whom all the giant cells and most of the spindle-shaped cells in their case expressed α-1-antitrypsin and α-1-antichymotrypsin, but no staining for lysozyme was found within the tumor, save for some intravascular monocytes. The same enzyme lysozyme was, however, found in those workers' material in two cases of cutaneous fibrous histiocytoma and in one example of extracerebral malignant fibrous histiocytoma. It was absent in all the glioblastomas and astrocytomas they studied.

Our observation of stainable GFA protein in the lipidized as well as the nonlipidized members of the original tumor cell population in our three cases, as well as in the typical glioblastoma-like recurrences, renders untenable the argument [47] that GFA protein positivity could be due to the phagocytosis, by mes-

enchymal tumor cells, of GFA protein released by astrocytes in areas of local tissue destruction. The GFA protein-positive cells are in fact often found a great distance away from the neural parenchyma. Moreover, necrosis is not a feature of PXA in their nonmalignant stage.

It should also be stressed that in all three of the original tumors reported here, as well as in many of those described previously, there were a multitude of cells that not only were GFA protein-positive, but also had the general morphology of process-bearing astrocytes rather than of histiocytes or macrophages.

Thus, while the demonstration of GFA protein in the tumor cells has proved decisive in establishing the astrocytic nature of the PXA, this interpretation is not based solely on the immunohistochemical data. It is also founded on other morphological and topographical observations that collectively characterize this tumor as a superficial cortical astrocytoma with massive leptomeningeal invasion, probably originating from the subpial astrocytes and in which the immunohistochemical findings are highly reliable for its identification. In many instances, typical infiltrative astrocytoma is found in a small rim of superficial cortex, although the bulk of the tumor is located in the subarachnoid space. This feature is also shown in the tumor reported by Paulus and Peiffer ([47], Figs. 1, 2c). Other examples of largely exophytic growths from the CNS include the desmoplastic cerebellar medulloblastoma, the desmoplastic infantile ganglioglioma and some optic nerve gliomas. Furthermore, none of the non-glial cells in which GFA protein has been demonstrated is remotely likely to be the cell of origin of the PXA. Therefore, collectively with the other evidence, the immunoreactivity for GFA protein constitutes a trustworthy signpost that clearly indicates the astrocytic direction of differentiation.

Finally, the development of typical astrocytoma, as seen in the present three cases, is not solely a late phenomenon in PXA. The reverse may also occur. In case 1 reported by us in 1979 [32], part of the initial growth was a classic pilocytic astrocytoma, whereas the picture of PXA predominated in the rest of the tumor and in its recurrences.

In summary, in our 12 previously reported cases [30, 32], in cases seen by others and in more than 40 examples that we have examined since our original publications, the astrocytic nature of the PXA could be well established on histological, immunocytological and electron microscopical grounds. Together with a few similar instances in the literature [21, 63], the evolution of three of our cases, described in this report, into classic examples of small-cell glioblastoma provides further evidence of the PXA as being a neoplasm of astrocytic origin.

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