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CASE REPORT

Anaplastic pleomorphic xanthoastrocytoma

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Abstract A case of anaplastic pleomorphic xanthoastrocytoma (PXA) in a 9-year-old girl is reported. Histological features of PXAs are cellular pleomorphism of GFAP-positive cells, with intracytoplasmic lipidic vacuoles and a reticulin network, bizarre giant cells, low mitotic activity, and lack of necrosis and of endothelial vascular proliferations. These tumors are generally reported to have a favorable postoperative course. In our case, a poor clinical prognosis and spread of the illness through the CSF was observed. Immunohistochemical features of the tumor, which were histologically anaplastic in nature, were analyzed. There were small foci of necrosis in the sections of the material obtained at the first operation and extensive necrosis in that from the second operation, although the patient had not received radiotherapy between the operations. The presence of necrosis in PXA is an uncommon and significant feature. It predicts the poor prognosis seen in this case, and therefore this report strongly supports the notion that necrosis should automatically exclude a tumor from the PXA category. The histological grade was evaluated as grade 3 (according to the WHO classification).

Key words Pleomorphic xanthoastrocytoma · Brain neoplasm · Astrocytoma · Glial tumor · Metastasis

Introduction

Pleomorphic xanthoastrocytoma (PXA) is a kind of tumor that is usually seen in young adults and children. It was originally defined by Kepes et al. in 1979 [14] and is usually located superficially in the cerebrum, involving the leptomeninges but leaving the dura unaffected [5, 10, 14, 17, 23, 24, 32]. The tumor can be completely removed, since a gross cleavage plane between the tumor and the surrounding tissue is easily demarcated.

Initial reports of cases with PXA showed favorable outcomes, despite the cellular pleomorphism with bizarre nuclei of the tumor cells [3, 4, 9, 11, 14, 28, 29, 32, 33]. Some cases with poor prognosis have also been noted in the literature [1, 11, 13, 18, 24, 29, 33]. The latter differed from the others in that they contained necrosis. We report a case of an anaplastic tumor in a child, in which histological examination revealed necrosis and which had a poor clinical prognosis.

Case report

The patient was a 9-year-old female child who had had a generalized seizure 3 years before. On admission to hospital, she complained of headache, nausea and vomiting. A computed tomographic (CT) scan disclosed a partially cystic and partially solid mass of 3 cm in diameter in the temporal region. After contrast administration, the solid part of the tumor showed enhancement (Fig. 1). The tumor was evaluated histologically after the first operation, during which it was totally removed (14 October 1991), and was diagnosed as PXA

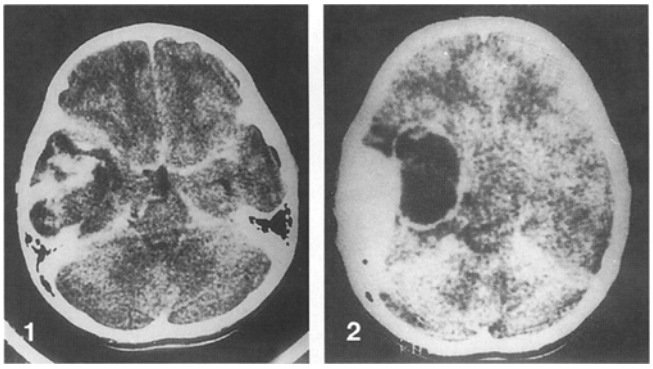
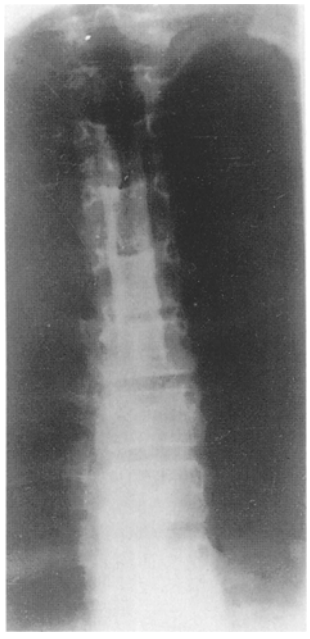


Fig. 1 CT scan showing an enhancing tumor in the right temporal lobe

Fig. 2 CT showing recurrent cystic tumor

Fig. 3 Myelogram showing a block between T5 and T8 levels



although necrosis was seen and explained as possibly suggesting anaplasia.

A CT scan 6 months after the operation revealed recurrence of the tumor in the same region (Fig. 2). As a result, a second operation was performed and the recurrent tumor was totally excised (20 May 1992). The anaplastic character of the tumor was confirmed by the recurrence of the tumor in a relatively short time, and the patient received radiotherapy postoperatively.

Four months later, the patient began to complain of weakness in her legs and was not able to walk. A myelogram was performed to rule out any spinal pathology; it showed a partial block within the thoracic spinal canal, extending from T5 to T8 (Fig. 3). The metastatic tumor mass causing the block was subtotally removed in a third operation (22 October 1992). The patient was paraplegic when she was discharged from the hospital.

On 27 March 1993, 10 months after the second operation, the patient underwent a final operation, since tumor regrowth was evident in the same location as the first recurrent tumor in the temporal region.

Histological sections of all the surgical specimens showed the same features although the necrosis was more extensive in the specimens obtained from the last operation. The patient died 10 days after the last operation. Autopsy could not be performed.

Histological examination

The formalin-fixed and paraffin-embedded material obtained from all four operations were processed for light microscopy and stained with hematoxylin and eosin and Gomori's method for reticular fibers and with Masson-Trichrome and modified Bielschowsky. Histological examination of the sections of the tumor tissues removed at the first operation demonstrated that the main structure was composed of clumps of fusiform tumor cells with distinct cytoplasmic projections. The nuclei were elongated and oval (Fig. 4). In some areas, some cells contained large eosinophilic and PAS-positive intracytoplasmic droplets and lipidic vacuoles. A few multinucleated giant cells were scattered between them (Fig. 5). Mitotic figures were sparse. There were small foci of necrosis (Fig. 6). Microcalcification zones were seen at the periphery of the excised tumor.

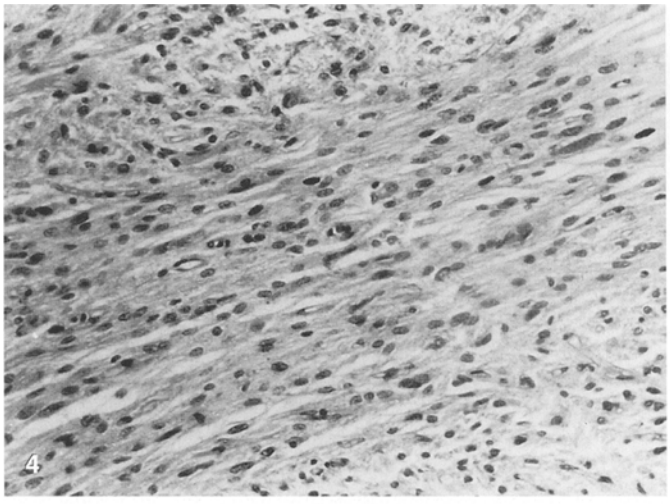
The same morphological patterns were seen in the paraffin-processed sections of the tumor from the second operation (Fig. 7a). In the second recurrent tumor, necrosis was more extensive than in the original tumor (Fig. 7b). Histological sections of the intraspinal intramedullary metastatic tumor showed that cells with lipid vacuoles in cytoplasm, multinuclear giant cells and very prominent endothelial vascular proliferations were evident in wide areas (Fig. 8).

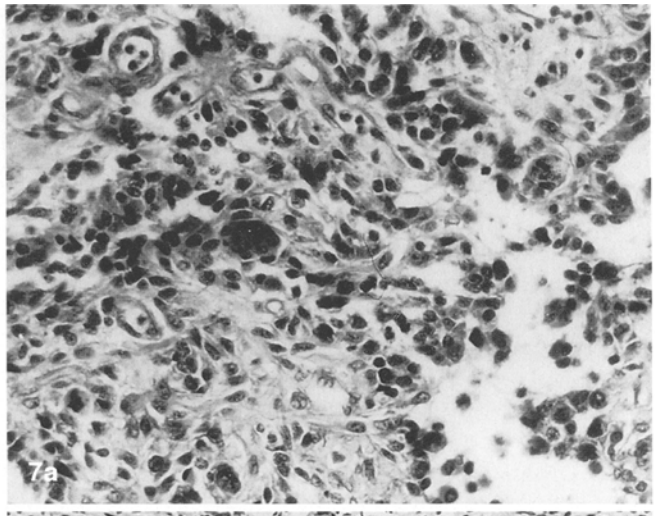
Histochemical reaction with Gomori's method for reticulin fibers was applied to the paraffin-processed sections prepared from the material obtained from all four operations, and reticular bands of fibers of varying thickness, which extended along the bundles and wrapped round the individual tumor cells, were detected (Fig. 9).

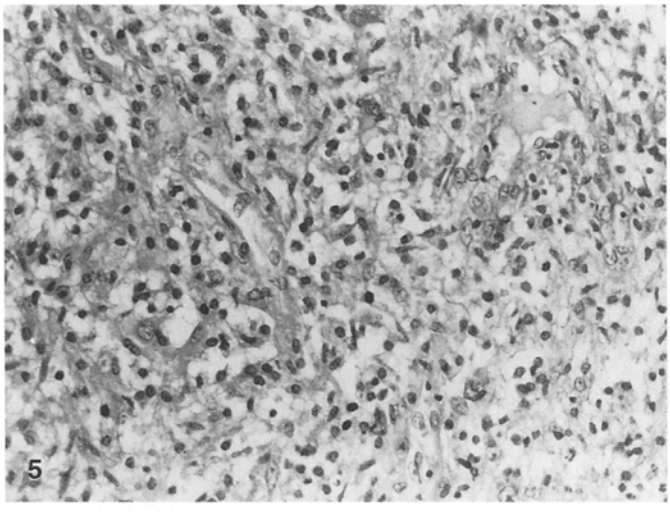
Masson-Trichrome stains disclosed a collagenous network entrapping individual or groups of glial cells. Bielschowsky staining did not show any axonal structures within the tumor.

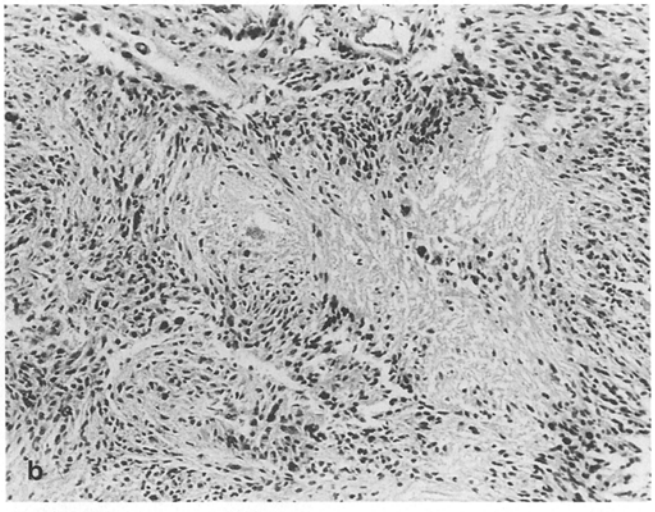
Immunohistochemical examination

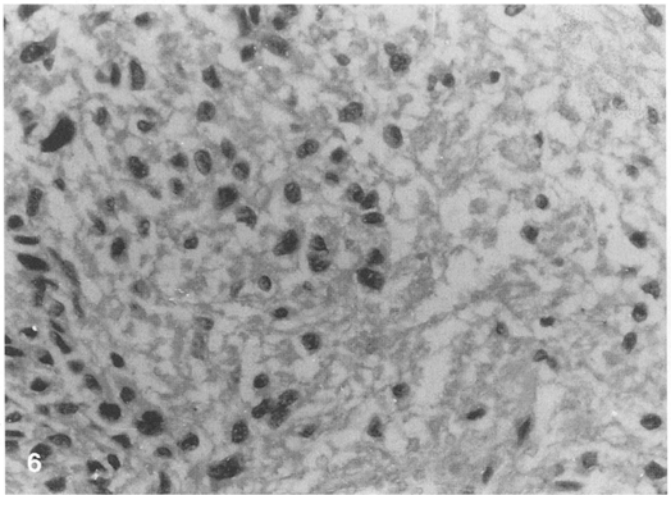
Immunohistochemical studies included staining for GFAP, neurofilament (68–200 kDa; NF) desmin, vimentin, S-100 protein and PCNA. The sections were deparaffinized, rehydrated, and washed in sodium citrate buffer. The endogenous peroxidase activity was terminated, and nonspecific binding sites were blocked with fetal calf serum and incubated for 18 h with the primary antibody. A standard strep-











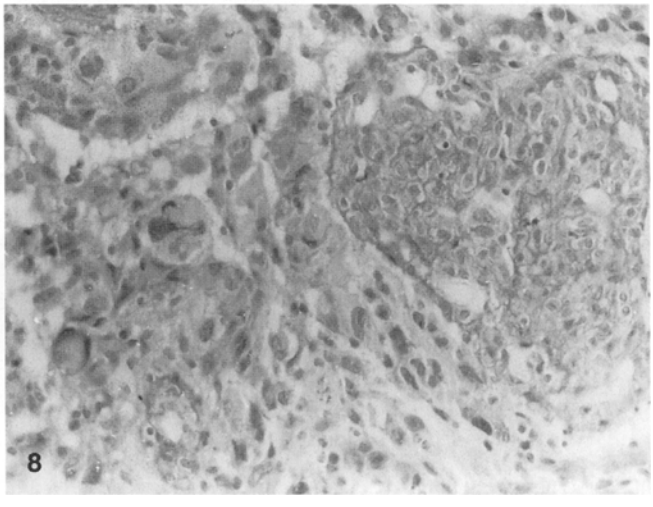


Fig. 4 Material from the first operation. Intersecting bundles of elongated cells in a densely fibrillated matrix. H&E, ×310

Fig. 5 Material from the first operation. Large plump eosinophilic cells with rounded outlines and eccentric nuclei. H&E, ×310

Fig. 6 Material from the first operation. Small foci of necrosis. H&E, ×500

Fig. 7 **a** Material from the first recurrent tumor. Cellular atypia, nuclear irregularity and hyperchromatism, multinucleated giant cell formation. H&E, ×310. **b** More extensive foci of necrosis than in the material from the first operation

Fig. 8 The spinal metastasis. The same histological appearance and vascular endothelial cell proliferation

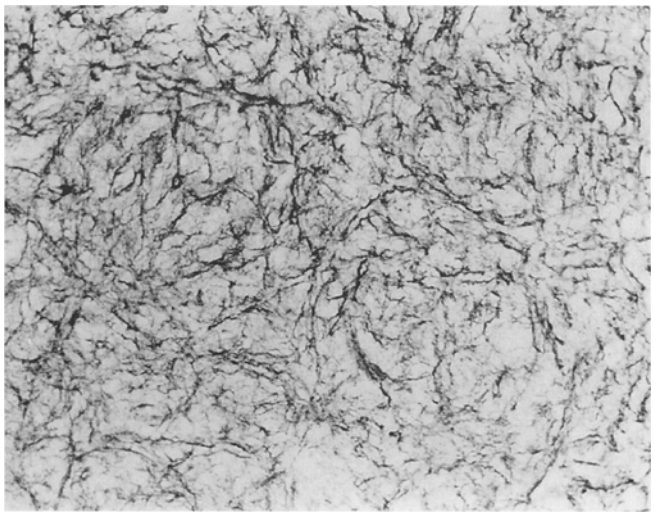


Fig. 9 Material from the first operation. Abundant reticulin network surrounding individual tumor cells. Gomori's method for reticular fibers, ×310

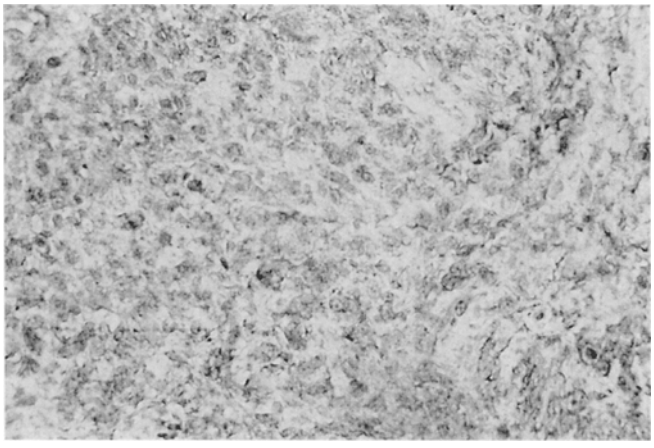


Fig. 10 Material from the first operation. Tumor cells are positive for GFA protein. GFAP, ×310

tavidin–biotin kit was used (Dako) followed by staining with diaminobenzidine and counterstaining with hematoxylin (Table 1).

The tumor cells reacted positively with antibodies to glial fibrillary acidic protein (Fig. 10) and S-100 protein. There was immunopositivity for vimentin in both fibroblasts and endothelial cells, as well as in tumor cells. NF was completely negative. Proliferative activity of tumor cells examined using PCNA indicated an average labeling index (31%, 10–45%). Positive immunoreactivity for alpha-1-antitrypsin and alpha-1-antichymotrypsin was found.

With due consideration for all the histochemical and immunohistochemical findings mentioned above, the tumor proved to be an anaplastic pleomorphic xanthoastrocytoma (WHO grade 3).

Table 1 Specificity and technical data of primary antibodies

	Source	Species	Dilution
GFAP	Dako	Mouse	1:100
S100 protein	Dako	Mouse	1:1000
Neurofilament	Dako	Rabbit	1:50
Desmin	Dako	Mouse	1:50
Vimentin	Dako	Mouse	1:30
PCNA	Dako	Mouse	1:25

Discussion

PXA is classified in a subgroup of astrocytomas in the tumor classification of the central nervous system listed according to the histological type of tumor [24]. It is usually seen in the second decade and more rarely in the first and third decades of life. There is no difference between the sexes in the frequency of PXA. These tumors are ordinarily located in cerebral hemispheres. Rarely, they may be seen in the cerebellum and spinal cord [7, 30]. In our case, the patient was a 9-year-old girl and the tumor was superficially located in the temporal lobe which is one of the most common sites of PXA.

PXA is one of the desmoplastic glial tumors of the brain. Microscopically, its most conspicuous properties are the pleomorphic, and in part xanthomatous, characteristics of the tumor cells that contain intracytoplasmic lipid. Monstrous giant cells, cell atypia, nuclear irregularity, hyperchromatism and mitotic activity can also be seen. Necrosis is absent. In contrast to their histological appearance, PXAs have a relatively favorable prognosis.

In our case we found all these features, but foci of necrosis were seen in the sections prepared from the material removed at the first operation. There were small foci of necrosis in the material from the first operation, and more extensive necrosis in the sections prepared from the first recurrent tumor. Radiation therapy was not given to the patient after the first operation. She received radiotherapy after the first recurrence, and diffuse necrosis was found in the second recurrent tumor after its removal.

In 1979, Kepes et al. reported increased anaplasia and some areas of necrosis in a recurrent tumor after surgery for PXA. This patient did not receive radiotherapy [14]. In 1981, Kepes et al. reported three cases of heavily lipidized malignant glioma with extensive xanthomatous changes [13]. These tumors contained necrosis, but all of them were situated deeply in the brain. All these patients died within 1 year of surgery. Kepes concluded that these tumors were glioblastomas. Weldon-Linne et al. described a case with

fatal outcome and extensive recurrent tumor at autopsy [31]. They pointed out that PXA may follow a less favorable course, culminating in malignant transformation even after a prolonged period of indolence. They also mentioned the absence of necrosis in the original tumor. They found numerous foci of necrosis in the recurrent tumor tissue. Their patient received radiotherapy after the first operation. Grant et al. reported three cases of PXA in 1986. One of these PXAs was mitotically active, contained areas of necrosis and vascular proliferation and progressed rapidly to the patient's death. They referred to this tumor as a "monstrocellular" or "heavily lipidized" variant of astrocytoma [6].

The histological differential diagnosis of PXA against malignant gliomas, which display the same features as PXA and contain necrosis and intracellular lipid, is important. In PXA, there is a reticulin network that surrounds the individual cells and extends along the bundles. The connective tissues seen in PXA are partly the result of leptomeningeal spread of the tumor, and the reticulin network is the basal lamina that surrounds the tumor cells. The basal lamina has been shown by electron microscopic studies [14]. The subpial astrocytes have been considered to be the cell origin of desmoplastic gliomas based on their basal lamina formation and superficial cortical localization [2]. There are authors who think that the abundant reticulin and collagen deposition may be a result of exophytic growth of ordinary low-grade astrocytoma into the subarachnoid space [11]. However, the presence of basal lamina should suggest a subpial origin.

In glioblastoma, the reticulin network is seen around necrosis. These reticular fibers do not wrap round the tumor cells. Development of glioblastoma has been reported in some patients with PXA [24, 28].

Anaplastic PXA shares several clinical and histologic features with other desmoplastic neuroepithelial neoplasms, such as gliofibroma [28], gliosarcoma [8], desmoplastic infantile ganglioglioma and desmoplastic cerebral astrocytoma of infancy [2, 16, 19].

Histologically, the glial component and fibromatous component of gliofibroma and the glial component and sarcomatous component of gliosarcoma are in general very distinct, with the former staining positive for GFAP and the latter positive for reticulin fibers [8, 20]. In desmoplastic infantile ganglioglioma, some zones that have glial components similar to PXA can be seen [4, 18]. The existence of cells that react positively with antibodies for NSE distinguishes them from PXA.

PXA should be differentiated from desmoplastic cerebral astrocytomas of infancy, which are of congenital origin and are thought to be a variant of the same entity as PXA and resemble mesenchymal tumors [8, 20]. Reticulin and Masson-Trichrome stains disclosed the rich reticulin and collagenous network entrapping the individual or groups of glial cells. Several large islands composed of undifferentiated, small hyperchromatic cells were seen [2].

Some authors have mentioned the significance of immunopositivity for alpha-1-antichymotrypsin and alpha-1-antitrypsin in suggesting histiocytic histiogenesis, thus allowing differentiation from PXA [9]. In our case, positive immunoreactivity for these enzymes was demonstrated. However, recent evidence has demonstrated that a positive immunoreaction for alpha-1-antichymotrypsin and alpha-1-antitrypsin can also be obtained in neoplastic astrocytes and even in normal brain tissue [25, 34]. Fortunately, the tumor cells of histiocytic or meningeal origin do not give an immunopositive reaction for GFAP. Thus, the differential diagnosis between these tumors and PXA can be made easier [6, 9, 10, 21].

Tien et al. mentioned that nonresected leptomeningeal invasion could account for tumor recurrence and peritumoral edema might be a prognostic factor for tumor recurrence and anaplastic evolution [29]. There was only one recurrent tumor in their series and it showed the histological features of anaplastic astrocytoma in a small region. However, they did not find any evidence of mitotic activity, necrosis and vascular proliferation in most of the tumor. They believed that the identification of peritumoral edema on MR images could suggest a more aggressive lesion. We suggest that it may be possible to predict the patients with PXA who have a poor prognosis by searching for foci of necrosis in the material removed at the first operation. In our case we found the foci of necrosis in the tumor removed at the first operation, when the patient had not yet received irradiation.

However, it must be remembered that transformation of PXA into a malignant astrocytoma or glioblastoma can occur many years after the initial diagnosis [1, 15]. In 1989, Kepes et al. reported three cases with changes from classic PXA to malignant glioblastoma-like tumors [15]. The cases described in their report showed evolution into classic examples of small-cell glioblastoma.

Some authors suggest that DNA ploidy pattern may explain why PXA carry a relatively favorable prognosis as long as they show no necrotic areas [9]. Genetic alterations are known to lead to tumor progression with the selection of variant subclones [26, 27]. Telomeric associations were observed in an untreated PXA [26]. Özek et al. reported a case of PXA associated with von Recklinghausen neurofibromatosis, in which there is a chromosome 17 abnormality [22].

An increased possibility of recurrence and poor prognosis should be assumed if necrosis is revealed, unless cytogenetic studies are performed. Therefore, when the PXAs are assessed histologically, the existence of necrosis is a significant peculiarity. Kepes expressed the view that the finding of necrosis should be regarded as a firm sign of malignancy and that the presence of necrosis should exclude a given tumor from the PXA category [12]. However, there is a problem when categorizing such a tumor as our case. Although this tumor behaved clinically as a malignant neoplasm with three recurrences, metastasis to the

spinal canal and fatal outcome 18 months after the first operation, the clinical, gross and histological features of the tumor removed at the first operation are more typical of PXAs (young age, superficial hemispheric cystic lesion, pleomorphism and lipidization of neoplastic astrocytes with reticulin formation within the tumor) rather than glioblastomas (advanced age, vascular endothelial proliferation, obvious necrosis, high mitotic activity, lack of diffuse desmoplasia). Consequently, we prefer to designate our case anaplastic PXA. On the other hand, metastasis to the spinal cord, as seen in our case, is not frequent in the case of PXAs, although a superficial location of the tumor may suggest spread of the tumor through the CSF pathway.

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EDITORIAL COMMENT

This article opens a new horizon on the repeatedly asked question of how frequently pleomorphic xanthoastrocytomas (PXAs) dedifferentiate and show biologically aggressive behavior by metastasizing. Although this exciting and enigmatic tumor of adolescents and young adults, first described by Kepes et al., is frequently seen most commonly in cerebral leptomeninges without attacking dura, and shows a favorable prognosis. Unfortunately, it might not be somehow biologically innocent, as discussed in this particular article. Nonetheless, most patients with PXA survive for many years, but some die quickly following one or more recurrences. As described in this case, recurrent tumors often exhibit malignant transformation to an overtly anaplastic tumor composed of small, more uniform cells exhibiting brisk mitotic activity, conspicuous necrosis and loss of intercellular reticulin staining. The frequency of malignant transformation is estimated at 10–25%. One of the features of this particular case that makes it perplexing is the coexistence of developing spinal drop metastasis and necrosis in its first presentation. Nevertheless, any attempt to explain these surprising findings would obviously raise new questions as to whether a PXA could express itself as a malignant tumor ab initio, i.e., so-called anaplastic PXA de novo, or whether it is a dedifferentiating anaplastic PXA after each recurrence. If the former explanation is true, why not designate it a glioblastoma although histopathological criteria are more likely to favor the features of PXA, i.e., pericellular reticulin, perivascular lymphocytic infiltration and cytoplasmic vacuolization due to accumulation of lipid droplets? If the second suggested explanation is true, these tumors could be designated anaplastic PXAs. The potential to metastasize is an extremely uncommon phenomenon in the natural history of this tumor, which is clearly documented by leptomeningeal seeding in this particular case.

In conclusion, the authors of this article evidently support the notion that a PXA could appear as a malignant tumor documented not only by its histological features, i.e., presence of necrosis and brisk mitotic activity, but also by its biological behavior, i.e., leptomeningeal seeding. All the evidence extracted from the data presented ensures that some pleomorphic xanthoastrocytomas should be regarded as high-grade tumors of the central nervous system.

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