

CASE REPORT

Radziszław Kordek · Wojciech Biernat · Wojciech Sapieja
Janusz Alwasiak · Paweł P. Liberski

Pleomorphic xanthoastrocytoma with a gangliomatous component: an immunohistochemical and ultrastructural study

Received: 26 April 1994 / Revised: 29 July 1994 / Revised, accepted: 8 September 1994

Abstract We report a case of a 24-year-old woman with left temporal pleomorphic xanthoastrocytoma (PXA) with atypical neuronal cells. Many neoplastic cells, otherwise typical of PXA, expressed glial fibrillary acidic protein, while neuronal cells with marked atypia were immunopositive for synaptophysin and neurofilament protein. This report supports a notion that PXA, like other astrocytic tumors, may have its gangliogliomatous counterpart.

Key words Pleomorphic xanthoastrocytoma
Ganglioglioma

Introduction

Cases of pleomorphic xanthoastrocytoma (PXA), were originally reported as “fibrous xanthoma of the meninges” and, thus, regarded as mesenchymal tumors [13]. However, the finding of glial fibrillary acidic protein (GFAP) expressed in such tumors subsequently necessitated modification of this opinion and in 1979 Kepes et al. [14] established PXA as originating from glial cells. Ultrastructurally, many neoplastic astrocytes were found to be covered by basal laminae, so these investigators proposed its origin to be from subpial astrocytes which are known to elaborate basal laminae in non-neoplastic condition [14]. The possibility of a histiocytic origin for these neoplasms has also been debated. Immunopositivity for such markers

as α -1-antitrypsin, α -1-antichymotrypsin, common leukocyte antigen and OKM-1 was quoted to support this opinion [24, 25]. These markers, however, are of low specificity and, therefore, their presence does not exclude a glial origin for PXA [7]. Moreover, the existence of complex tumors containing components with neuronal differentiation, may also support a hypothesis of neuroectodermal origin of PXA [3, 6, 15, 20].

Most PXA are localized superficially and supratentorially, with frequent involvement of the leptomeninges but sparing of the dura mater [11]. They often exhibit a cystic appearance and occur in young patients – with a few notable exceptions [17, 22]. Microscopically, marked cellular pleomorphism is a consistent finding. Lipidization of neoplastic cells, absence of, or low incidence of mitotic figures, abundant reticulin deposits and perivascular chronic inflammatory cells are consistent findings of PXA [9, 10, 12, 14, 16–19, 27, 28, 30]. Necrosis should cause one to refrain from diagnosing PXA since its presence points to glioblastoma [14]. In contrast to marked pleomorphism, the clinical course in most cases appears to be relatively favorable, although anaplastic changes have been described [3, 33]. Furthermore, PXA should be discriminated from the “desmoplastic” glioblastoma [2, 12].

Two cases of mixed PXA and gangliogliomas have been reported [6, 20], and in two other cases a few scattered abnormal ganglion cells in otherwise typical PXA were found. We report here an additional case of PXA with a large number of atypical ganglion cells – the gangliomatous variant of PXA.

R. Kordek · W. Biernat · J. Alwasiak
Department of Pathology, Chair of Oncology,
Medical University of Łódź, Poland

W. Sapieja
Department of Neurosurgery, Regional “Copernicus” Hospital,
Łódź, Poland

P. P. Liberski (✉)
Laboratory of Electron Microscopy and Neuropathology,
Laboratories of Tumor Biology, Chair of Oncology,
Medical University of Łódź, Paderewskiego 4,
PL-93–509 Łódź, Poland
Fax: 48-42-32-23-47

Case report

A 24-year-old woman had suffered from headaches since 1974 and epileptic seizures of the “absence” type for 3 weeks. In 1980 she complained of an exacerbation of the headache of 3-week duration, and was admitted to the Department of Neurosurgery, Regional “Copernicus” Hospital, Lodz. Left carotid angiography showed a mass lesion, displacing the anterior and medial cerebral arteries to the right. Computerized tomography (CT) was not available at that time. At surgery, a cystic cavity superficially located in the left temporal lobe was found. After aspiration of 25 ml of xan-

thochromic fluid, the cyst was opened and a mural nodule, measuring approximately 2 cm in diameter was completely resected. Subsequently the patient received radiation therapy of 40 Gy to her whole brain. She remained asymptomatic for 4 years after surgery, delivered a normal child and later was lost to follow-up.

Materials and methods

The surgical specimen was fixed in 10% buffered formalin and embedded in paraffin. Sections were stained routinely with HE and impregnated with silver for reticulin. For immunohistochemistry, slides were incubated with monoclonal antibodies against GFAP, a 200-kDa subunit of neurofilament protein (NFP), chromogranin A and synaptophysin, p53(DO7; DAKO) and proliferating cell nuclear antigen (PCNA, PC10 clone; DAKO). The streptavidin-biotin complex method was used. Fresh material was fixed in 2.5% glutaraldehyde in cacodylate buffer (pH 7.2) and used for ultrastructural examination.

Results

Histopathological features

The tumor was composed of compactly arranged partly spindle-shaped, partly pleomorphic, multinucleated and sometimes bizarre cells. Numerous large foamy cells were scattered in the tumor parenchyma. Despite a careful search, neither mitotic figures nor foci of necrosis were found. Robust lymphocytic infiltration was present at the periphery of the tumor. Furthermore, several large, round and occasionally bi- or multinucleated cells with vesicular nuclei and prominent nucleoli, reminiscent of atypical ganglion cells, were observed diffusely in all specimens. Silver reticulin staining revealed a dense reticulin network surrounding individual tumor cells. These features met the criteria of PXA, but with an admixture of a population of atypical neuron-like cells.

Immunohistochemistry

The majority of the bizarre multinucleated tumor cells and foamy tumor cells were GFAP positive (Fig. 1a). The ganglion-like cells were GFAP negative. The frequently seen binucleated cells, diffusely dispersed in all specimens, were synaptophysin and, weakly, chromogranin A positive (Fig. 1b). Using synaptophysin as a marker, we found one to four positive ganglion cells in virtually every high-power field ($\times 1000$). NFP staining revealed a network of altered axons (Fig. 1c) and numerous large spheroids, indistinguishable from those of reactive axonal swellings [8]. There was no p53 immunoreactivity but isolated astrocytic nuclei expressed PCNA (data not shown). There was no PCNA immunopositivity detected in the bizarre lipidized cells or in the ganglion cells.

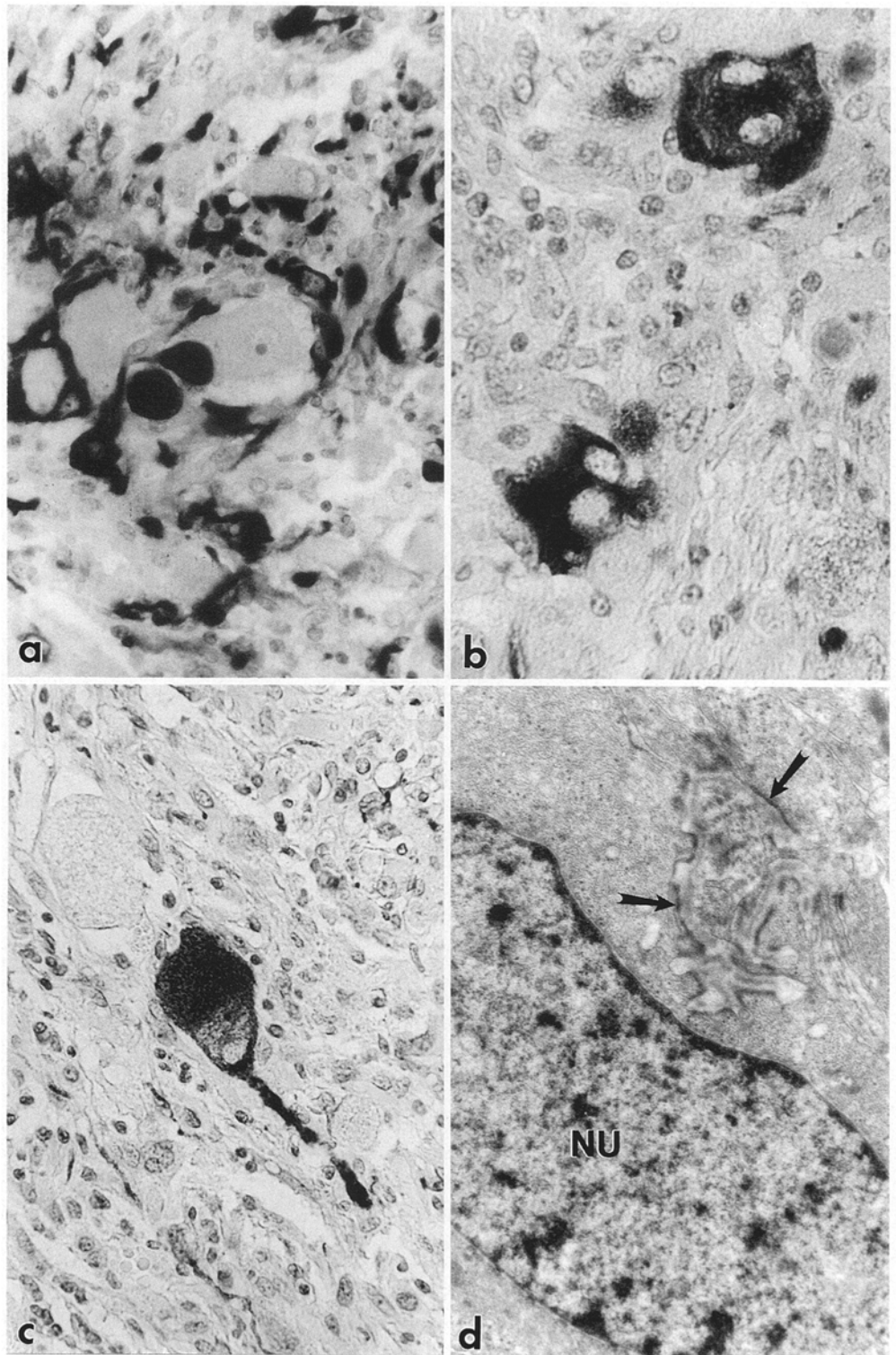
Ultrastructural examination

Electron microscopy revealed innumerable astrocytes and their processes containing large numbers of glial filaments. Astrocytic processes, connected by plaque-like long junctions were intermingled with dense bundles of collagen fibers. Numerous Rosenthal fibers of different shapes and in different stages of development were observed. Furthermore, we also noticed some astrocytic processes containing dense amorphous structures, not unlike those recently described in glioblastomas of granular appearance [5]. Many astrocytes were covered with basal laminae, which formed a complicated labyrinth invaginated into astrocytic cytoplasm (Fig. 1d). Other astrocytes contained numerous vacuoles containing myelin figures and whorls. These vacuoles probably represented the ultrastructural correlate of foamy cells seen by light microscopy. The second neoplastic component consisted of cells with pale cytoplasm, with no intermediate filaments but a few microtubules and prominent stacks of ribosomes. Infrequent dense-cored vesicles were also observed. We regarded these cells as being neuronal.

Discussion

We have documented here a case of PXA with an admixture of gangliomatous components. Ganglion cells were of unequivocal neoplastic appearance. Neuronal components in PXA have been recognized only recently. Furuta et al. [6] described a case of a tumor with two different components, ganglioglioma and PXA, in a 16-year-old boy. A similar case was reported by Lindboe et al. [20]. Reinhardt and Nahser [26] reported a tumor resembling PXA, but with a peculiar growth of neurons. They diagnosed it as a gliofibroma because of the scarcity of true ganglionic cells. Maleki et al. [23] described PXA with a few atypical ganglion cells containing membrane-bound neurosecretory granules. These cells were regarded as too sparse to warrant such a tumour being considered as gangliogliomatous. Kros et al. [17] also found neoplastic NFP- and synaptophysin-positive neuronal cells in one of their five PXA cases. These cells were often binucleated, randomly oriented and clustered. We found a large number of similar cells in our case, and this tumor should be regarded as the gangliogliomatous variant of PXA. Because of the characteristic desmoplasia, young age of the patients, and possible origination from subpial astrocytes, a similarity of these gangliomatous PXA cases with another novel neurooncologic entity, desmoplastic infantile ganglioglioma (DIG) is plausible [31, 32], although they clearly differ in several clinico-pathological features. In particular, in DIG, small, primitive cells with the prominent desmoplasia are present and this tumor occurs in younger patients than those with PXA [31]. The latter also shows a higher degree of atypia and lipidization of the tumor cells. DIG seems to be a gangliogliomatous variant of superficial cerebral astrocytoma of infancy (SCAI) [4], which has also a favorable prognosis. Furthermore, SCAI

Fig. 1 **a** Ganglion-like cell surrounded by GFAP-positive glial cells; GFAP immunohistochemistry. **b** The ganglion-like cells, often binucleated, are synaptophysin positive; Synaptophysin immunohistochemistry. **c** Axonal swellings; neurofilament protein immunohistochemistry. **d** Labyrinth-like formation of basal laminae (*arrows*) invading cytoplasm of neoplastic astrocyte (*NU* nucleus). **a, c** $\times 328$; **b** $\times 82$; **d** $\times 9840$



contains no neuronal neoplastic component, analogous to “pure” PXA [1, 4, 29]. Thus, similar to more common astrocytic tumors (pilocytic or fibrillary), “desmoplastic” astrocytic tumors such as SCAI and PXA also may have their gangliogliomatous counterpart.

It seems that there exist a spectrum of astrocytic “desmoplastic” brain tumors occurring in young patients, the

common denominator for which is the presence of basal lamina. These tumors have a relatively favorable prognosis, and the proteoglycan constituents of their basal laminae are regarded as factors which may inhibit the growth of neoplastic glial cells [21]. Neoplastic ganglion cells in these tumors may originate from bipotential neuroectodermal cells, as probably occurs in other gangliogliomas,

but the hypothesis of origin of these tumors from persistent, hamartomatous, neuro-glial lesions should also be considered [31]. This hypothesis obviously requires investigation by molecular and cell biological studies, in particular to evaluate expression of genes sequentially active during the early stages of glial and neuronal development.

Acknowledgements This work was supported in part by a grant from the State Research Committee (517-11-017). We are grateful to Prof. Herbert Budka for performing confirmatory immunohistochemical staining for NFP and Synaptophysin, and to Ms. M. Kowalewska, J. Bratosiewicz, R. Kurczewski, E. Nagańska, L. Romanska and K. Smoktunowicz for skillful technical assistance.

References

- Aydin F, Ghatak NR, Salvant J, Muizelaar P (1993) Desmoplastic cerebral astrocytoma of infancy. A case report with immunohistochemical, ultrastructural and proliferation studies. *Acta Neuropathol* 86: 666-670
- Cerda-Nicolas M, Kepes JJ (1993) Gliofibromas (including malignant forms) and gliosarcomas: a comparative study and review of the literature. *Acta Neuropathol* 85: 349-361
- Daita G, Yonemasu Y, Muraoka S, Nakai H, Maeda T (1991) A case of anaplastic astrocytoma transformed from pleomorphic xanthoastrocytoma. *Brain Tumor Pathol* 8: 63-66
- De Chadarevian JP, Pattisapu JV, Faerber EN (1990) Desmoplastic cerebral astrocytoma of infancy. Light microscopy, immunocytochemistry, and ultrastructure. *Cancer* 66: 173-179
- Del Bigio MR, Deck JHN (1993) Rosenthal fibers producing a granular appearance in a glioblastoma. *Acta Neuropathol* 86: 100-104
- Furuta A, Takahashi H, Ikuta F, Onda K, Takeda N, Tanaka R (1992) Temporal lobe tumor demonstrating ganglioglioma and pleomorphic xanthoastrocytoma components. *J Neurosurg* 77: 143-147
- Grant JW, Gallagher PJ (1983) Pleomorphic xanthoastrocytoma. Immunohistochemical methods for differentiation from fibrous histiocytomas with similar morphology. *Am J Surg Pathol* 2: 336-341
- Jellinger K, Jirasek A (1971) Neuroaxonal dystrophy in man: character and natural history. *Acta Neuropathol (Berl)* 5 [Suppl]: 3-16
- Kawano N (1991) Pleomorphic xanthoastrocytomas (PXA) in Japan: its clinico-pathologic features and diagnostic clues. *Brain Tumor Pathol* 8: 5-10
- Kawano N (1992) Pleomorphic xanthoastrocytoma: some new observations. *Clin Neuropathol* 11: 323-328
- Kepes JJ (1991) Pleomorphic xanthoastrocytomas (PXAs) and lipidized glioblastomas. *Brain Tumor Pathol* 8: 1-4
- Kepes JJ (1993) Pleomorphic xanthoastrocytoma: the birth of the diagnosis and a concept. *Brain Pathol* 3: 269-274
- Kepes JJ, Kepes M, Slowik F (1973) Fibrous xanthoma and xanthosarcomas of the meninges and the brain. *Acta Neuropathol (Berl)* 23: 187-199
- Kepes JJ, Rubinstein LJ, Eng FL (1979) Pleomorphic xanthoastrocytoma: a distinctive meningocerebral glioma of young subjects with relatively favorable prognosis. *Cancer* 44: 1839-1852
- Kepes JJ, Rubinstein LJ, Ansbacher L, Schreiber DJ (1989) Histopathological features of recurrent pleomorphic xanthoastrocytomas: further corroboration of the glial nature of this neoplasm. A study of three cases. *Acta Neuropathol* 78: 585-593
- Kleihues P, Burger PC, Scheithauer BW (1993) The new WHO classification of brain tumours. *Brain Pathol* 3: 255-268
- Kros JM, Vecht ChJ, Stefanko SZ (1991) The pleomorphic xanthoastrocytoma and its differential diagnosis: a study of five cases. *Hum Pathol* 22: 1128-1135
- Kuchelmeister K, Bergmann M, von Wild K, Hochreuther D, Busch G, Gullotta F (1993) Desmoplastic ganglioglioma: report of two non-infantile cases. *Acta Neuropathol* 85: 199-204
- Kuhajda FP, Mendelsohn G, Taxy JB, Long DM (1981) Pleomorphic xanthoastrocytoma: report of a case with light and electron microscopy. *Ultrastruct Pathol* 2: 25-32
- Lindboe ChF, Cappelen J, Kepes JJ (1992) Pleomorphic xanthoastrocytoma as a component of a cerebellar ganglioglioma: case report. *Neurosurgery* 31: 353-355
- Louis DN, von Deimling A, Dickersin GR, Dooling EC, Seizinger BR (1992) Desmoplastic cerebral astrocytoma of infancy: a histopathologic, immunohistochemical, ultrastructural, and molecular genetic study. *Hum Pathol* 23: 1402-1409
- Mackenzie JM (1987) Pleomorphic xanthoastrocytoma in a 62-year-old male. *Neuropathol Appl Neurobiol* 13: 481-487
- Maleki M, Robitaille Y, Bertrand G (1983) Atypical xanthoastrocytoma presenting as a meningioma. *Surg Neurol* 20: 235-238
- Paulus W, Peiffer J (1988) Does the pleomorphic xanthoastrocytoma exist? Problems in the application of immunological techniques to the classification of brain tumors. *Acta Neuropathol* 76: 245-252
- Paulus W, Peiffer J (1991) History, histology, histochemistry and histiocytic histogenesis of the pleomorphic xanthoastrocytoma. *Brain Tumor Pathol* 8: 67-71
- Reinhardt V, Nahser HC (1984) Gliofibroma originating from tempoparietal hamartoma-like lesions. *Clin Neuropathol* 3: 131-138
- Strom EH, Skullerud K (1983) Pleomorphic xanthoastrocytoma: report of 5 cases. *Clin Neuropathol* 2: 188-191
- Sugita Y, Shigemori M, Kuramoto S, Morimatsu M, Kepes JJ, Reifenberger G, Wechsler W (1991) Angiomatous variant of pleomorphic xanthoastrocytoma: report of two cases. *Brain Tumor Pathol* 8: 51-54
- Taratuto AL, Monges J, Lylyk P, Leiguarda R (1984) Superficial cerebral astrocytoma attached to dura. *Cancer* 54: 2505-2512
- Tsao MS, Becker L, Finlayson M (1983) Giant cell astrocytoma with histiocytic infiltrate. *Acta Neuropathol (Berl)* 59: 75-77
- VandenBerg SR (1993) Desmoplastic infantile ganglioglioma and desmoplastic cerebral astrocytoma of infancy. *Brain Pathol* 3: 275-281
- VandenBerg SR, May EE, Rubinstein LJ, Herman MM, Perentes E, Vineros SA, Collins PV, Park TS (1987) Desmoplastic supratentorial neuroepithelial tumors of infancy with divergent differentiation potential (desmoplastic infantile ganglioglioma). *J Neurosurg* 66: 58-71
- Weldon-Linne CM, Victor TA, Groothuis DR, Vick NA (1983) Pleomorphic xanthoastrocytoma: ultrastructural and immunohistochemical study of a case with the rapidly fatal outcome following surgery. *Cancer* 52: 2055-2063