

Pleomorphic xanthoastrocytoma – a clinico-pathological review

Pleomorficzny żółtakogwiaździak – przegląd kliniczno-patologiczny

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Abstract

Pleomorphic xanthoastrocytoma (PXA) is a rare primary brain tumour which occurs in children and young adults. PXA is designated as low-grade astrocytoma (WHO II), although an anaplastic variant and malignant potential have been described. Pathologically, cellular pleomorphism is the rule and includes spindle cells, mononucleated and multinucleated giant cells, and granular bodies in a reticulin-rich background with few mitoses; necrosis is usually absent. The tumour cells stain positive for glial fibrillary acidic protein (GFAP).

Surgery is the mainstay of treatment with gross surgical resection being accomplished due to its well-circumscribed nature and peripheral location. The role of adjuvant treatment remains yet to be clearly defined. To date, the majority of PXAs have been reported as single or small case series; consequently data of this rare brain tumour are fragmentary. The present paper reviews the pathogenesis, neuroradiological features, prognostic factors and treatment options for PXA.

Key words: brain tumour, pleomorphic xanthoastrocytoma, review.

Streszczenie

Pleomorficzny żółtakogwiaździak (*pleomorphic xanthoastrocytoma* – PXA) to rzadki pierwotny guz mózgu, który występuje u dzieci i dorosłych. Jest klasyfikowany jako gwiaździak o małym stopniu złośliwości (WHO II), chociaż opisywano również odmianę anaplastyczną i możliwość progresji złośliwości. W badaniu histopatologicznym regułą jest pleomorfizm komórkowy, w tym komórki wrzecionowate, jednojądrowe i wielojądrowe komórki olbrzymie oraz ciała ziarniste w sieci włókien retikuliny; figury podziału są nieliczne; zwykle nie występuje martwica. Komórki guza wykazują ekspresję kwaśnego gładkiego białka włóknienkowego (GFAP). Główną metodę leczenia stanowi chirurgiczne wycięcie guza, które może być doszczętne ze względu na wyraźne granice guza i jego obwodowe umiejscowienie. Rola leczenia uzupełniającego wymaga dopiero określenia. Dotąd przedstawiano jedynie opisy przypadków lub małych serii przypadków PXA, dlatego informacje na temat tego rzadkiego guza mózgu są fragmentaryczne. W niniejszym artykule zebrano informacje dotyczące patogenezy, cech stwierdzanych w badaniach obrazowych, czynników rokowniczych i możliwości leczenia PXA.

Słowa kluczowe: guz mózgu, pleomorficzny żółtakogwiaździak, przegląd.

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Introduction

Pleomorphic xanthoastrocytoma (PXA) is a rare tumour of childhood, described for the first time by Kepes *et al.* in 1979. [1-3]. They described a distinct clinical meningocerebral entity *sui generis* that despite its highly pleomorphic and bizarre-looking cytology, which suggested malignant behaviour, appeared to have a favourable prognosis and a relatively benign course. The histopathological features led them to the conclusion that these tumours represented a form of astrocytomas that are localized superficially and involve the leptomeninges. Previously, such tumours were classified as giant cell glioblastomas.

PXA is an uncommon tumour comprising less than 1% of all astrocytic tumour and the majority of the data published on these rare tumours are in the form of case reports [4-18]. PXA occurs in children and young adults below 30 years and is most frequently discovered in the second decade of life. The aetiology of PXA is unknown. Rarely, PXAs have been reported in patients with neurofibromatosis type 1 [19] but the majority arise sporadically without any evidence of genetic predisposition [20]. There is no gender predilection [21]. Typical clinical presentation includes seizures and symptoms of a mass lesion whilst increased intracranial pressure appears to be a less frequent finding [22]. PXAs are located superficially, predominantly in the supratentorial region, with a predilection for the cerebral hemispheres, particularly the temporal lobes, followed by the

parietal, frontal and occipital lobes, respectively [21]. PXAs may arise in the cerebellum, spinal cord, sella, retina and pineal region.

Pathogenesis

Given their superficial location, frequent involvement of leptomeninges, abutment of dura, and composition of pleomorphic cells along with spindle and xanthic cells in a reticulin-rich background, PXAs were considered mesenchymal tumours [2]. However, once the expression of glial fibrillary protein (GFAP) was demonstrated, these tumours were labelled as astrocytomas [1]. There are reports of existence of a composite PXA with a ganglioglioma [23-27] and recent studies [28-30] using immunohistopathological examination have suggested a neuronal phenotype favouring ganglioneural rather than an astrocytic differentiation. Although a controversial discussion revolves around its glial versus mesenchymal origin, the consensus shared by most neuropathologist has led to the inclusion of PXA as a variant of astrocytoma in the recent WHO classification. The tumour is postulated to arise from subpial astrocytes as it demonstrates presence of prominent basal lamina, which is a characteristic property of subpial astrocytes and is usually absent in typical astrocytomas [1-3].

Pathological features

The characteristic pathological features that enable the diagnosis of these rare brain tumours are listed in Table 1. Kepes *et al.* [1] first described the histopathological picture of PXA which is characterized by marked cellular pleomorphism including spindle cells, mononuclear or multinucleated giant tumour cells with bizarre nuclei, prominent lipid droplets in cytoplasm, frequent perivascular lymphocytic infiltration, and eosinophilic granular bodies with a dense reticulin network. Gianini *et al.* [21] described PXA as a moderately cellular astrocytoma often located superficially that partly occupied the leptomeninges. The tumour is associated with invasion of the adjacent brain parenchyma and has a tendency of perivascular space involvement. The presence of granular bodies and eosinophilia is also reported as a consistent feature. Necrosis is usually not present. In fact, Kepes *et al.* [1] had excluded the tumour from classification within PXA once the presence of necrosis was seen but Pahapill *et al.* [15] pointed out that PXAs can

Table 1. Pathological features of pleomorphic xanthoastrocytomas

Macroscopic
Superficially located.
Frequent involvement of leptomeninges
Abutment of dura
Microscopic
Pleomorphic cells
Spindle cells
Bizarre giant cells
Eosinophilic bodies
Lipidized astrocytes
Abundant reticulin-rich background
Few mitoses
Necrosis usually not present
Focal perivascular lymphocytes

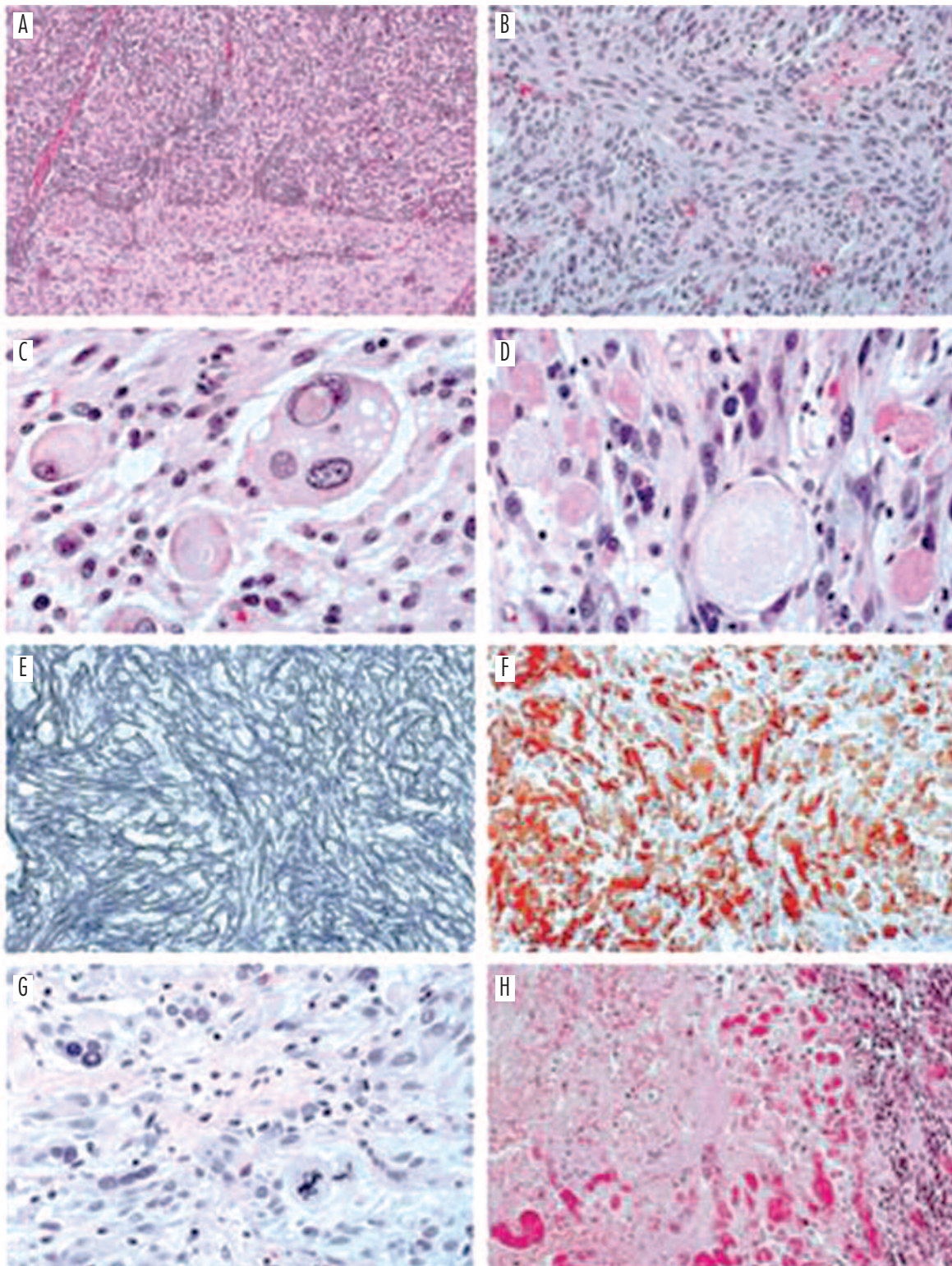


Fig. 1. Histological features of pleomorphic xanthoastrocytoma (PXA). (A) Typically superficial in location, it variably involves leptomeninges, infiltrates underlying parenchyma, and extends into perivascular spaces. (B) Cellular pleomorphism is the rule and includes spindle cells as well as mononucleated and multinucleated giant cells, occasionally with (C) vacuolated cytoplasm. (D) Granular bodies, intensely eosinophilic or pale, are an almost constant finding. (E) Reticulin staining surrounds individual or clustered tumour cells. (F) Glial fibrillary acidic protein staining varies in extent but is often intense (from [21] with permission). (G) and (H): In some cases mitotic figures and/or necrosis are present

demonstrate necrosis. Necrotic PXAs differ from glioblastoma with regard to lack of high incidence of endothelial proliferation, superficial location and less aggressive clinical behaviour.

Electron microscopic findings and immunohistochemistry

Electron microscopy [31] reveals presence of abundant intermediate filaments admixed with abundant cytoplasmic organelles, lipid droplets, lysosomes and presence of surface basement membranes which are characteristic of astrocytic differentiation. However, a few may show evidence of microtubules, dense core granules and/or clear vesicles suggestive of neuronal differentiation. GFAP expression is mandatory for definitive diagnosis of PXA and effectively segregates it from mesenchymal tumours. Immunoreactivity to synaptophysin and neurofilament proteins in various studies [21,27,32-36] have ranged from 38% to 100% and from 8% to 71%, respectively. S-100 protein immunoreactivity is usually diffusely and strongly present in all tu-

mours. The immunohistochemistry and electron microscopic findings are summarized in Table 2.

Molecular genetic basis

The molecular pathogenesis of PXA is unclear. Few molecular and cytogenetic studies have been reported, of which the majority have failed to link a specific genetic aberration to these rare tumours. Weber *et al.* [37] studied chromosomal imbalances in 50 PXAs and reported the loss of chromosome 9 as the most common chromosomal alteration in PXAs, which occurred in as many as half of the patients.

Differential diagnosis

As mentioned in Table 3, PXA mimics a variety of central nervous tumours from which it needs to be differentiated. The immunohistochemical and ultrastructural evidence favouring an astrocytoma segregates it from brain sarcomas and meningiomas. PXA has an astrocytic origin, but it is set apart from juvenile pilo-

Table 2. Immuno-histochemistry and electron microscopic findings in pleomorphic xanthoastrocytomas

Immunohistochemical studies
GFAP positive
Histiocyte marker positive
Electron microscopy
Cytoplasm contains intermediate filaments
Cytoplasm contains lipid
Basal lamina surrounds tumour cells

GFAP – glial fibrillary acidic protein

Table 3. Differential diagnosis of pleomorphic xanthoastrocytomas

Glioblastoma multiforme
Anaplastic astrocytoma
Gangliocytoma
Ganglioglioma
Pilocytic astrocytoma
Meningioma
Fibroanthoma
Fibrosarcoma
Metastatic central nervous system tumours



Fig. 2. Post-contrast T1-weighted MRI image showing solid-cystic pattern of pleomorphic xanthoastrocytoma; the solid component shows vivid contrast enhancement whereas the cyst wall shows partial contrast enhancement (from Faulodi M., et al. Pleomorphic xanthoastrocytoma: favourable outcome after complete surgical resection. *Neuro Oncol* 2001; 3: 184-192, with permission)

cytic astrocytomas and subependymal giant cell astrocytomas as it demonstrates an aggressive course with a higher frequency of recurrence, anaplastic transformation and death. Although cellular pleomorphism is a characteristic feature, the absence of significant mitotic activity and necrosis differentiates it from malignant gliomas, glioblastoma multiforme and lipidized malignant gliomas [3,38]. PXAs are histologically designated as grade II in the WHO classification [39], with lesions that demonstrate significant mitotic activity and/or areas of necrosis being designated as 'PXA with anaplastic features' [40].

Neuroradiological features

The classical appearance of PXA is of a cystic superficially located supratentorial mass containing a mural nodule that is adjacent to the leptomeninges [14,17,22,40], although as many as half of the PXAs may not show a cystic change. Crespo-Rodriguez *et al.* [41] on the basis of radiological features divided these tumours into PXAs with a classic pattern that demonstrated a cystic supratentorial mass containing a mural nodule and the other atypical PXAs comprising a solid mass devoid of a cystic change. The radiological differential diagnosis of PXA includes astrocytomas, gangliogliomas, fibroxanthomas, meningiomas, haemangiopericytomas, meningiosarcomas, metastasis, lymphoproliferative masses, inflammatory lesions and granulomatous disease.

On CT scan, PXAs are usually seen as superficially located, well-defined partially cystic lesions. The solid component tends to be heterogeneous and is isodense to grey matter. The incidence of surrounding oedema is low and, when present, is minimal. However, PXA may rarely present with marked peritumoural oedema. The incidence of intratumoural calcification is low but in some series has been reported to be as high as 40% [41]. The solid component of PXAs shows intense and a vivid contrast enhancement, whereas the cyst wall may or may not enhance at all.

MRI findings [42] reveal a superficial, supratentorial location along with partial cystic lesions which are hypo- to isointense to the grey matter on plain T1-weighted images and hyperintense on T2-weighted images. On gadolinium-enhanced T1-weighted sections these tumours show intense enhancement of the solid part. The inner table of the skull bone may sometimes be eroded by the underlying tumour. Perifocal oedema is usually minimal.

Prognostic factors

PXAs demonstrate a wide range of biological behaviour with regard to histological appearance and clinical course. The role of histological features and tumour grade in predicting biological behaviour of PXA is still unclear. The treatment outcome of PXA depends on several factors that are listed in Table 4. Macaulay *et al.* [43] were the first to link increased mitotic activity as a negative prognostic indicator in a surgically resected PXA that eventually evolved into glioblastoma. Giannini *et al.* [21] in a review of 71 cases reported that survival was significantly better in patients who underwent gross total resection rather than a subtotal resection. On multivariate analysis, the only other factor that could independently predict tumour recurrence and survival was high mitotic index defined as presence of 5 or more mitoses per 10 high-fields. Although the presence of necrosis is associated with a less favourable outcome [15,16], the prognosis of PXAs is often more favourable and less precipitous than other astrocytomas that demonstrate the same histopathological features. Other histopathological factors that could possibly indicate an unfavourable prognosis include endothelial proliferation, high ki-67 labelling index, anaplasia comprising diffuse proliferation of monomorphic tumour cells rather than pleomorphic tumour cells, and a decreased number of reticulin fibres.

Treatment

The mainstay of treatment is surgery [15,21,43]. As these lesions are well circumscribed, superficially located and demonstrate a cyst/mural nodule architecture, complete excision is relatively easily achieved. In 1993, Giannini *et al.* [21], in one of the largest series ever published on these rare tumours, reported that the extent of surgical resection was the single most important predictor of recurrence-free and overall survival for patients

Table 4. Prognostic factors for pleomorphic xanthoastrocytomas

Extent of surgical resection
Increased mitotic activity
High ki-67 labelling index
Endothelial proliferation
Foci of necrosis
Diffuse proliferation of monomorphic cells

with PXA. In contrast, Macaulay *et al.* [43] in 1993 reviewed 48 cases in whom the intra-operative extent of surgical resection (complete gross excision vs. incomplete resection) was available and found that there was no difference in overall survival amongst patients undergoing gross total excision versus those undergoing incomplete resection. Papahill *et al.* [15] reported improved survival outcomes in non-necrotic PXA patients who underwent gross total excision.

Data to support the role of adjuvant treatment are scanty and sparse. Macaulay *et al.* [43] addressed the role of adjuvant radiation therapy in these tumours and reported a trend towards better recurrence-free survival with use of adjuvant radiation. However, the difference in overall survival was not statistically significant despite a long follow-up period of fifteen years. Similarly, Papahill *et al.* [15] reported that the survival curve of patients receiving adjuvant irradiation was not significantly different from those not subjected to it. It is not acceptable to directly compare the survival, as the extent of surgical resection, which is an independent prognostic factor for survival, was not available in either of the studies. Furthermore, none of the above-mentioned studies was sufficiently powered to detect a small but statistically significant survival advantage. With the retrospective nature of these studies, there could be an element of selection bias with the less favourable prognostic subset of PXAs (comprising either subtotal excised or those having adverse histopathological features such as high mitotic index, necrosis, endothelial proliferation) being subjected to adjuvant radiotherapy while those with gross total excision and favourable histopathological features were kept on observation. Despite this bias, the use of adjuvant radiation therapy was associated with similar overall survival even after long periods of follow-up. Hence, adjuvant radiation therapy should be offered to all unfavourable PXAs. The role of radiation in the favourable prognostic group is less clear as it is difficult at present to identify the subset which will relapse; molecular and cytogenetic studies may hold promise in future.

Data to support the role of adjuvant chemotherapy are sparse. Adjuvant therapy may not be offered to patients who achieve gross total excision and have no adverse histopathological features, whereas PXAs that are subtotal excised or have adverse histopathological features may often be subjected to adjuvant treatment that includes radiotherapy and/or chemotherapy.

Clinical outcome and malignant progression

The tumour has a favourable outcome [1-18]; overall survival ranges between 70% and 85% after gross total resection [21]. Despite its relatively benign behaviour, few patients will experience recurrence even after gross total resection with time [16,17,21]. Kepes *et al.* [44] reported post-surgical recurrences of PXA in a more malignant type, either an anaplastic astrocytoma or a glioblastoma. Similarly, Weldon-Linne *et al.* [45] reported a less favourable outcome in patients who underwent malignant transformation. The most common sign of malignant transformation is increased mitotic activity and foci of necrosis; the time required for such transformations varies from 7 months to 15 years. Hence, a few PXAs will undergo malignant transformation after a long latent period of dormancy. As many as 15-35% will recur and up to 20% of PXAs will undergo anaplastic transformation [21]. Although the pattern of relapse is usually local, leptomeningeal involvement, either isolated or in combination with a local relapse, is not rare. Management of recurrence includes surgical excision whenever possible, radiation therapy and or chemotherapy. The majority of these recurrent PXAs will eventually succumb to progressive disease, although patients with isolated local recurrence that do not show evolution and transformation into a higher grade can be salvaged and may experience freedom from recurrence.

Disclosure

Authors report no conflict of interest.

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