

Neurooncological Observation

Malignant transformation of pleomorphic xanthoastrocytoma

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Summary

A 31-year-old woman presented with a pleomorphic xantho-astrocytoma (PXA) manifesting as epilepsy. The tumour was partially resected. Histological examination revealed cellular pleomorphism and cytoplasmic vacuolation consistent with PXA, but no mitoses, necrosis, or endothelial proliferation. Follow-up neuro-imaging showed the residual tumour had grown rapidly with dissemination in the spinal cord. The recurrent lesion was totally resected and was shown to be glioblastoma. The patient has survived without signs of recurrence for 36 months after adjuvant radiochemotherapy. The biological behaviour of PXA cannot be predicted based on the histological features and careful follow up is essential.

Keywords: Glioblastoma; malignant transformation; pleomorphic xanthoastrocytoma.

Introduction

Pleomorphic xantho-astrocytoma (PXA) is a rare cerebral neoplasm first described in 1979 and added to the World Health Organization classification of central nervous system neoplasms in 1993 [8, 9]. PXA predominantly occurs in young patients and manifests itself first as seizures followed by focal neurological deficits. The histological features include spindle-shaped cells, pleomorphic cell population with hyperchromasia and multinucleated giant cells, lipid droplets in tumour cells, granular bodies, and a dense reticulin network [7, 18]. The interesting characteristic of this neoplasm is the relatively benign clinical behaviour despite the histological pleomorphism [1, 5, 16]. Survival rates were 81% at 5 years and 70% at 10 years in a series of 71 patients [4].

Another clinical peculiarity is the development of malignant transformation in 10–15% of cases leading to poor outcomes [19]. Such malignant transformation may be associated with the degree of mitotic activity and presence of necrosis [4, 15].

Here we describe a case of PXA without malignant findings such as mitoses or necrosis at initial presentation, which subsequently transformed to glioblastoma 16 months after partial resection. This case illustrates the difficulty of prediction of malignant transformation in PXA based only on the histological findings.

Case report

History and examination

A 31-year-old female had a history of complex partial seizures persisting for 16 years. She had undergone surgical resection of a cystic lesion in the left temporal lobe at another hospital at the age of 16 years. Although the histological specimen obtained at this resection is regrettably unavailable and re-examination is impossible, the clinical record of this patient has noted that the histological diagnosis was an arachnoid cyst. Subsequently she was free from seizures until epileptic attacks gradually appeared again 6 years after the resection. Her symptoms were refractory to anticonvulsants, so she was admitted to our hospital for surgical treatment.

She suffered complex partial seizures mainly consisting of automatism and motion arrest that rarely progressed to secondary generalised convulsions. Electroencephalography recorded with scalp electrodes during the ictal/interictal period proved her symptoms were caused by mesial temporal lobe epilepsy. Magnetic resonance (MR) imaging showed a mass lesion in the inferior temporal gyrus which was homogeneously enhanced by gadolinium and a remarkable atrophic change of the left temporal lobe (Fig. 1a).

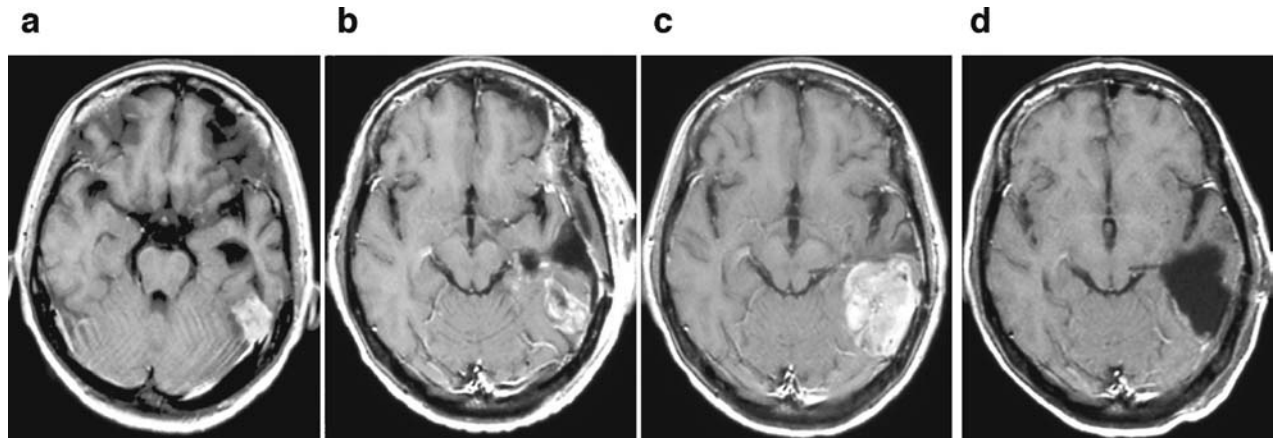


Fig. 1. T1-weighted magnetic resonance images with gadolinium-diethylenetriaminepenta-acetic acid. Before the operation, a solid enhanced lesion was located in the posterior portion of the inferior temporal gyrus (a). Anterior temporal lobectomy and partial resection of the enhanced lesion was performed (b). Sixteen months after the partial resection, the enhanced mass had enlarged (c). Gross total removal of the tumour was confirmed after the second operation (d)

Operation and postoperative course

Anterior temporal lobectomy was performed to treat her seizures on October 18, 2000. The cortex related to the verbal function was accurately confirmed during the operation using intraoperative cortical stimulation in the awake condition as previously reported [11]. Resection of the gadolinium-enhanced mass lesion was simultaneously performed,

but inevitably resulted in partial removal to avoid surgical damage to Wernicke's center (Fig. 1b). The patient was completely free from epilepsy without neurological deficits after the operation. The histological diagnosis was PXA without anaplastic features, so no adjuvant radiotherapy or chemotherapy was given. She was discharged from our hospital and subsequent follow-up MR imaging showed no changes for 10 months. However, the tumour suddenly began to grow 13 months



Fig. 2. T1-weighted magnetic resonance images with gadolinium-diethylenetriaminepenta-acetic acid. Scattered enhancement along the spinal cord suggests meningeal dissemination of the tumour (a). The dissemination disappeared after radiochemotherapy and recurrence was not detected for 36 months (b)

after the operation and rapidly caused a mass effect on the surrounding brain tissue (Fig. 1c).

The recurrent tumour had the characteristic appearance of a malignant glioma and was totally resected on February 21, 2002 (Fig. 1d). Histological examination showed the tumour had transformed to glioblastoma. MR imaging also disclosed disseminated lesions in the spinal cord (Fig. 2a). She received 30 Gy adjuvant irradiation to the whole brain and spinal cord followed by additional 30 Gy to the local field covering the resected cavity and its margin. Chemotherapy was then given using 1-(4-amino-2-methyl-5-pyrimidinyl)methyl-3-(2-chloroethyl)-3-nitrosourea (ACNU). The tumours in the spinal cord disappeared and consecutive careful observation for 36 months has not detected any recurrences in either the brain or spinal cord (Fig. 2b).

Histological findings

The specimen obtained at the first resection was a pleomorphic neoplasm consisting of enlarged bizarre cells with foamy or vacuolated cytoplasm and multinucleated giant cells. No endothelial proliferation or other indicators of malignancy such as mitoses or necrosis were found (Fig. 3a). Immunostaining for glial fibrillary acidic protein was positive for almost all tumour cells. The Ki67 labelling index, expressed as the positive cell percentage in 1000 tumour cells, was low at about 3% in the maximum positive area (Fig. 3b). These histological characteristics supported the diagnosis of PXA without anaplastic features [7, 18].

The specimen from the second resection consisted of anaplastic glial cells with marked pleomorphism and high cellular density.

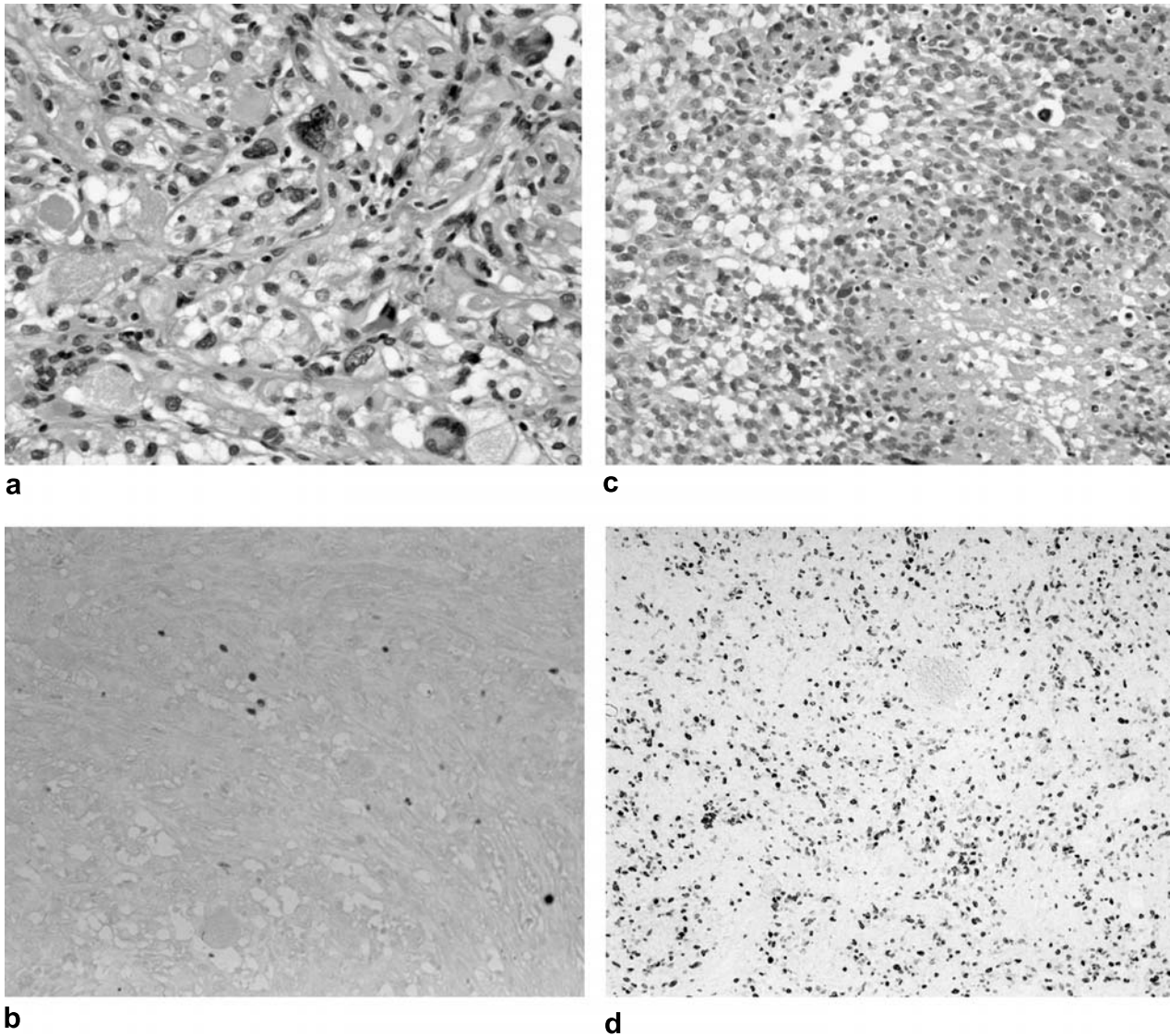


Fig. 3. (a, b) Photomicrographs of the first resected tissue showing the features of pleomorphic xantho-astrocytoma. Endothelial proliferation, mitoses, and necrosis are absent. Enlarged bizarre cells with vacuolated cytoplasm and multinucleated giant cell are seen (a: H&E, original magnification $\times 200$). Approximately 3% of tumour cells are positive for Ki67 labelling (b: Ki67, original magnification $\times 100$). (c, d) Photomicrographs of the second resected tissue demonstrating the histological transformation to glioblastoma. The recurrent tumour shows hypercellularity, nuclear hyperchromatism, numerous mitotic activity, and pseudopalisading (c: H&E, original magnification $\times 200$). About 40% of tumour cells are positive for Ki67 labelling (d: Ki67, original magnification $\times 100$).

Numerous mitotic figures, up to 10 to 15 mitoses per 10 high-power fields, were observed. There were many blood vessels showing endothelial proliferation and necrosis with pseudopalisading arrangement of the tumour cells (Fig. 3c). The Ki67 labelling index had increased to 40% (Fig. 3d). The histological diagnosis was glioblastoma. The admixture of tumour cells with xanthomatous cytoplasm suggested vestiges of PXA. Consequently, these findings supported the diagnosis of glioblastoma transformation from the initial PXA without anaplastic features.

Discussion

Distinguishing between patients with PXA who have a good prognosis and those at risk for early progression is very important for the clinical management of PXA. Several authors have tried to identify the important factors for the prediction of biological behaviour [4, 14, 15]. Increased mitotic activity was proposed as a negative prognostic indicator [14]. A recent clinical study analysed the significance of the mitotic index, the presence of necrosis, and the extent of resection, and found that the mitotic index and the extent of resection were the main predictors for recurrence-free survival and overall survival rates [4]. A grading scheme was proposed consisting of tumours without mitoses per 20 high-power fields (Grade 1), tumours with mitoses but without necrosis (Grade 2), and tumours with elevated mitotic index and necrotic foci (Grade 3). No cases of recurrence or death were found in the Grade 1 group, whereas 36% of cases in Grade 2 and 100% of cases in Grade 3 showed recurrence [10].

Our patient developed drastic malignant transformation despite the absence of histological features such as mitosis and necrosis. Our experience questions whether specific histological factors are reliable predictors of future biological behaviour.

Another clinical feature in the current case is spinal dissemination demonstrated in MR image. This phenomenon is substantially rare and not elucidated concerning its clinical influence. Leonard *et al.* has reviewed 14 fatal PXA cases including 2 cases with leptomeningeal dissemination [12]. Lubansu *et al.* reported a case of fatal PXA presenting mitotic activity and spinal dissemination at initial presentation followed by aggressive progression only 4 weeks after the treatment [13]. In contrast to these fatal cases, Ettl *et al.* reported a patient with recurrent PXA with spinal metastasis who had been successfully treated for four years by a near-total resection of the recurrent intracranial lesion and neuraxis radiation [2]. Mitotic activity of these cases was not consistent and had no relevance to leptomeningeal dissemination. It is remarkable that

recurrence was not detected for 36 months in our case and 4 years in the reported case after surgical resection followed by neuraxis radiation therapy, while other cases had shown fatal progression after surgery and chemotherapy in one case, surgery and local radiation therapy in the other case [2, 12, 13]. Although a large number study is certainly essential for definitive significance, this inconsistent result suggests that the potential of neuraxis radiation therapy for leptomeningeal dissemination in PXA seems to be worth clarifying in a prospective study.

Various molecular genetic changes are associated with PXA [3, 4, 6, 17]. The TP53 tumour suppressor genes, CDKN2A (p16^{INK4a}), CDK4, MDM2, and EGFR genes, are well known to occur in diffuse infiltrating astrocytic glioma including anaplastic astrocytoma and glioblastoma, but are not involved in the pathogenesis of PXA [6]. These genetic differences seem to be responsible for the distinct biological behaviour of PXA. Our patient has survived without any signs of recurrence for 36 months, even after the diagnosis of malignant transformation to glioblastoma and spinal dissemination. We suggest that the pleomorphism of PXA and the histological malignant transformation are not related to the biological behaviour induced by the genetic aberrations related to diffuse malignant astrocytic tumour.

Close follow up is mandatory for the clinical management of PXA, because PXA probably originates in genetic changes which lead to its unpredictable biological behaviour.

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Comments

Nakajima *et al.* describe the case of a young female patient with a supratentorial pleomorphic xantho-astrocytoma manifesting as epilepsy. After first subtotal removal, the tumour grew rapidly metastasising to the spinal cord. At second surgery, the lesion turned out to have become a glioblastoma. This well-written report concisely reviews the currently available literature on these rare tumours.

The authors bring to light that close clinico-radiological follow-up is indispensable for correct management of these tumours, because of the unpredictable biological behaviour of pleomorphic xantho-astrocytomas probably due to intrinsic genetic features of the neoplasm.

I believe that the most important message from this paper consists in the recognition of the need for both retrospective and prospective investigations on PXA to determine features with prognostic significance, and evaluate on larger number of patients, indications to and results of post-operative, radio-chemotherapy.

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Nakajima report on a female patient with epilepsy, who was operated on for a cystic lesion of the temporal lobe at the age of 16. At the age of 31 a pleomorphic xanthoastrocytoma (PXA) was resected at this location, and 16 months later a large glioblastoma recurrence showing spinal dissemination was resected. In general, this is a well written Case Report, but a few open questions remain.

Since unfavorable clinical behavior might be related to genetic features, it is unfortunate that the PXA and its malignant recurrence were not genetically analyzed, given that the techniques can be retrospectively performed using paraffin materials. The karyotype as well as the mutational status of “glioma genes” such as *TP53*, *EGFR*, *PTEN*, *CDKN2A* would have been of major interest.

Furthermore, re-examination of the histological specimens obtained from the very first surgical resection at the age of 16 years would have been very interesting. The authors state that the patient’s clinical record noted that the histological diagnosis at that time was an arachnoid cyst. Because both the putative cyst and the PXA arose at a left temporal location and PXA is commonly cystic, some reservations about the diagnosis of arachnoid cyst appear justified.

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