Multicentric pleomorphic xanthoastrocytoma in a patient with neurofibromatosis Type 1

Case report and review of the literature

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The authors report an unusual case of multicentric pleomorphic xanthoastrocytoma (PXA) in a 36-year-old woman with neurofibromatosis Type 1 (NF1). Both lesions were diagnosed as PXA but demonstrated different neuroimaging features and very different outcomes. Although the occipital lesion was cured surgically, the cerebral tumor recurred three times and underwent malignant transformation into an anaplastic oligodendroglioma.

The authors discuss the causes of PXA and suggest that it could originate from common bipotential precursor cells with two phenotypes.

KEY WORDS • intracranial lesion • pleomorphic xanthoastrocytoma • multicentric lesion • neurofibromatosis Type 1 • anaplastic transformation • oligodendroglioma

NEUROFIBROMATOSIS are genetic disorders inherited as autosomal-dominant traits. They consist of two distinct syndromes: NF1 and NF2.

Neurofibromatosis Type 1 represents 90% of all reported cases of NF and is associated with an increased risk for the development of benign and malignant tumors involving neural and nonneural tissues. In addition to multiple peripheral neurofibromas, NF1 predisposes to tumors of the central nervous system; most of which are pilocytic astrocytomas located in the optic pathways and the brainstem.

The appearance of a PXA during the course of NF1, PXA–NF1, is rare. To the best of our knowledge, only four such cases have been reported. The authors describe the first case of multicentric PXA–NF1.

Case Report

History. This 30-year-old woman was admitted to our hospital in December 2000, with the complaint of headaches and gait disturbance throughout the previous month. Two years earlier, while pregnant with her second child, the patient was examined and found to have NF1. The diagnosis was based on the presence of more than 15 café-au-lait spots larger than 10 mm, 10 Lisch nodules on her trunk, peripheral neurofibromas, NF1 predisposes to tumors of the central nervous system, most of which are pilocytic astrocytomas.

Examination. At admission the neurological examination revealed a gait instability, a decrease in fine motor coordination in the right upper extremity, and a lateral gaze nystagmus with no other deficit. Visual acuity was normal and there was no visual field defect. The fundi were normal.

Magnetic resonance imaging revealed a cystic right occipital lesion and a diffuse, poorly delimited right cerebellar tumor (Fig. 1).

First Operation and Postoperative Course. The patient underwent surgery in January 2001. Both tumors were removed through a right parietooccipital craniotomy. Neither lesion adhered to the dura mater. The occipital lesion was well circumscribed and was totally removed; the wall of the cyst contained a yellowish fluid. The cerebellar lesion was infiltrative and, notably in its inner part, was not easily distinguishable from the cerebellar parenchyma; whether we had achieved total resection therefore could not be ascertained. The postoperative course was uneventful, although a neurological examination demonstrated a left hemianopsia and a moderate right cerebellar syndrome.

First Recurrence and Treatment. In July 2001, a control MR image revealed regrowth of the cerebellar tumor (Fig. 2A). Given the small volume of the recurrent lesion and the absence of any complaints, no surgery was attempted at that time. An MR image obtained in November 2001 revealed a second, fleshy cerebellar recurrent tumor adherent to the dura mater (Fig. 2B).

A second operation was performed in November 2001. The tumor was adherent to the leptomeninges and was well circumscribed when compared with its appearance during the previous surgery. A total removal was performed, and

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Despite the inner limits of the surgical bed, a histological examination was uneventful. Therapy (60 Gy).

Second Recurrence and Treatment. The patient was diagnosed as having two cycles of chemotherapy, but not without a second operation (Fig. 2A). Given the small volume of the recurrent lesion and the absence of any complaints, no surgery was attempted at that time. An MR image obtained in November 2001 revealed a second, fleshy cerebellar recurrent tumor adherent to the dura mater (Fig. 2B).

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the inner limits of the residual cavity were excised separately for histological examination. The postoperative course was uneventful. The patient underwent a course of radiotherapy (60 Gy).

Second Recurrence and Treatment. A cerebellar recurrence was diagnosed in November 2002 (Fig. 2C). Four cycles of chemotherapy with Temodal were given to the patient but proved to be ineffective (Fig. 2D). A third operation was performed in May 2003. A firm tumor, closely adherent to the dura mater, was totally removed. The dura mater around the tumor mass and surrounding gliosis were also resected. Although macroscopically the resection appeared total, a histological examination of the excised dura and the surrounding gliosis showed diffuse tumor infiltration.

Third Recurrence, Treatment, and Outcome. The cerebellar tumor recurred once again in September 2003, and MR imaging demonstrated diffuse infiltration on the right side of the tentorium (Fig. 2E and F). In view of the poor clinical status of the patient—who had a disabling right cerebellar syndrome—the early recurrence, and the diffuse meningeal infiltration, additional surgery was ruled out and the patient received chemotherapy with procarbazine, lomustine, and vincristine. She died at home in December 2003. No autopsy was performed.

Pathological Findings. A light microscopy examination of the cerebellar specimen obtained at the first operation (Fig. 3A) showed cerebellar tissue containing a densely packed cellular tumor, which was quite pleomorphic, being composed of spindle-shaped cells with elongated nuclei and eosinophilic cytoplasm, large cells with polymorphic nuclei and droplet material, and some multinucleated giant cells. The astrocytic component with a dense intercellular reticulin network (highlighted using silver impregnation) was predominant. Few neuronal elements were seen throughout the specimen, but there were many eosinophilic granular bodies. Clusters of lymphocytes infiltrate with a perivascular distribution were seen, and some of these vessels displayed features of endothelial hyperplasia. There was no necrosis and mitoses were rare; the Ki-67 proliferative index was 3%. Focally, the tumor invaded the adjacent cerebellar parenchyma.

A light microscopy examination of the occipital specimen (Fig. 3B) showed tissue that was greatly similar to the cerebellar specimen, albeit with fewer multinucleated cells. The lymphocytic infiltrates were more dominant, but the specimen lacked endothelial hyperplasia and mitotic activity. The Ki-67 proliferative index was 3%. Neither the adjacent brain parenchyma nor the leptomeninges had been invaded.

An examination of the cerebellar specimen obtained at the second operation (Fig. 3C) showed that the tumor limits were clearly differentiated from the cerebellar parenchyma, although brain invasion was observed focally. In this specimen, in addition to the multinucleated giant cells, an important oligodendroglial element was present and predominant in comparison with the astrocytic pattern. There were more mitoses, with a Ki-67 labeling index of 10%. Vascular proliferation was seen throughout the specimen with no necrosis. Specimens labeled "limits of excision" did not show any tumor infiltration.

The third cerebellar specimen obtained at the third operation (Fig. 3D) clearly demonstrated numerous anaplastic features. The multinucleated giant cells had huge nuclei. An oligodendroglial pattern with a high cellular density was the most predominant feature of this specimen. Mitoses were significant with a Ki-67 labeling index of approximately 35% (Fig. 4A). A glomerulus-like endothelial hyperplasia was observed, but necrosis was not seen. The tumor invaded the adjacent cerebellar parenchyma through the Virchow–Robin spaces. The dura mater was also diffusely infiltrated (Table 1 lists the histological features of the different specimens).

An immunohistochemical analysis of the four specimens was performed, and the majority of the multinucleated and foamy cells proved to be positive for glial fibrillary acidic protein. Scattered tumor cells expressed neurofilament, synaptophysin markers (Fig. 4B), and CD117 (Fig. 4C). The cells exhibited immunostaining for vimentin, but did not stain for CD-34.

A pathologist confirmed the diagnosis of PXA.
A comparative genomic hybridization assay was performed. Because of the poor quality of the specimens, no meaningful conclusions could be drawn.

Since the first time it was described by Kepes and colleagues\(^1\) in 1979, PXA has become a recognized clinicopathological entity that occurs mainly in children and young adults, in whom it causes seizures. It is usually characterized by a benign clinical course and a superficial hemispheric location with attachment to the dura mater. Pleomorphic xanthoastrocytoma has been reported to occur almost exclusively in supratentorial compartments—notably in the temporal lobe—although a few lesions have been found in other areas such as the cerebellum, sellar region,\(^3\) thalamus,\(^\text{21}\) and cortical dysplasia,\(^\text{31}\) which have been described in patients with NF1 (Tuberous Sclerosis Complex) and other genetic disorders.

The histogenesis of PXA is poorly understood, although Kepes and colleagues\(^1\) have suggested that these tumors originate from subpial astrocytes. In recent studies, investigators have posited that it might originate from bipotential precursor cells\(^\text{27}\) or mesenchymal cells\(^\text{31}\) of the neural germinal matrix. The histogenesis of PXA remains a matter of debate, with some authors proposing that it arises from astrocytes and oligodendroglia, while others propose that it originates from bipotential precursor cells.

There are two phenotypes of the same lesion, one type that follows a benign course and another that displays malignant behavior. This occurred in our patient, although the mechanism of malignant transformation is still unknown.

**Neuroimaging Features of PXA**

The typical neuroimaging features of PXA include a well-demarcated, often cystic, mass with intense contrast enhancement of the solid portion of the tumor on computed tomography scans and MR images, though the cyst walls may or may not enhance after the infusion of the contrast agent. Other neuroimaging features include edema, mass effect, and enhancement of the cyst walls. Neuroimaging data on PXA–NF1 cases have included descriptions of similar patterns.

Two different sets of neuroimaging features have been described in patients with PXA–NF1. One type displays the classic features of PXA, while the other type displays features atypical for PXA, such as multiple lesions, diffuse enhancement, and mass effect.

**Fig. 2.** A: Axial Gd-enhanced T\(_1\)-weighted MR image obtained 6 months postoperatively, revealing a recurrence of the cerebellar lesion. B: At 11 months, a second local recurrence was seen in the cerebellar hemisphere together with enhancement of the residual cavity walls. C: An MR image obtained 1 year after the second surgery, demonstrating a local recurrence. D: Despite chemotherapy, the tumor continued to grow. Five months after the third operation the tumor recurred, displaying a diffuse meningeal infiltration (arrow in E) and a tentorial infiltration (arrow in F) on axial and coronal Gd-enhanced T\(_1\)-weighted images, respectively.

**Fig. 3.** Photomicrographs of histological features obtained during the course of the disease. A: Tissues obtained from the first resection of the cerebellar tumor, showing pleomorphism of the component tumor cells including large multinucleated cells against an elongated fibrillary astrocytic cell background. B: The occipital lesion displaying a predominantly pilocytic astrocytoma-like pattern with fewer multinucleated cells. The inset shows the area in the square at a higher magnification, focusing on the multinucleated cell. C: The first cerebellar recurrence showing an oligodendrogial component; there is a greater incidence of mitosis (arrow). D: The tumor in the second recurrence displaying anaplastic features with a densely packed oligodendroglial component. H & E, original magnification \(\times 400\) (A–D) and \(\times 1000\) (inset in B).
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A comparative genomic hybridization assay was performed. Because of the poor quality of the specimens, no meaningful conclusions could be drawn.

**Discussion**

Since the first time it was described by Kepes and colleagues in 1979, PXA has become a recognized clinicopathological entity that occurs mainly in children and young adults, in whom it causes seizures. It is usually characterized by a benign clinical course and a superficial hemispheric location with attachment to the dura mater. Pleomorphic xanthoastrocytoma has been reported to occur almost exclusively in supratentorial compartments—notably in the temporal lobe—although a few lesions have been found in other areas such as the cerebellum, the sellar region, the thalamus, and the spinal cord. Its association with other lesions, such as vascular malformation and cortical dysplasia, is uncommon, and only four cases have been described in patients with NF1 (Table 2).

The histogenesis of PXA is poorly understood, although Kepes and colleagues postulated that this disease could originate from subpial astrocytes. In recent studies, investigators have posited that it might originate from bipotential precursor cells or mesenchymal cells or arise from a residual germinal matrix. Our case showed progression from a typical PXA into an oligodendroglioma, possibly indicating that PXA arises from bipotential precursor cells common to astrocytes and oligodendrocytes. We believe that there are two phenotypes of the same lesion, one type that follows a benign course and another that displays malignant behavior. This occurred in our patient, although the mechanism of malignant transformation is still unknown.

**Neuroimaging Features of PXA**

The typical neuroimaging features of PXA include a well-demarcated cortical, often cystic, mass with intense contrast enhancement of the solid portion of the tumor on computerized tomography scans and MR images, although the cyst wall may or may not enhance after the infusion of the contrast agent. The few previous reports that have included neuroimaging data on PXA–NF1 cases offered descriptions of similar patterns. Our case had two different sets of neuroimaging features. The occipital lesion demonstrated the classic features of a PXA, but the cerebellar lesion initially displayed features atypical for PXA. Cerebellar imaging could be indicative of foci of increased signal intensity in the white matter, also known as UBOs, which are common in cases of NF1 and are characterized by a benign course. These UBOs are located primarily in the basal ganglia, brainstem, or cerebellum and are rarely found in patients older than 20 years of age because UBOs disappear as the patient ages. Most importantly, UBOs can be easily distinguished from tumors because they do not enhance after infusion of a contrast agent and they do not exhibit any mass effect. On recurrence, the cerebellar lesion demonstrated more characteristic neuroimaging features of PXA, thus indicating that a PXA may evolve over time.

**Diagnosis of PXA**

Our case satisfied the features of PXA. Its histological features can be summarized as a striking pleomorphic cellular component with spindle-shaped and multinucleated, giant, foamy, lipid-laden xanthomatous cells. There was no mitosis or necrosis, and there was a rich reticulin network. Immunohistochemically, the tissue became stained with glial fibrillary acidic protein. The existence of complex PXA-containing components with neuronal differentiation, composite PXA–ganglioglioma, and combined oligodendroglioma–PXA has been reported, but no such findings have been described for PXA–NF1. This is the first case

**Histological features of the different PXA tumors and recurrences**  

<table>
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<tr>
<th>Histological Feature</th>
<th>Occipital Lesion</th>
<th>Primary</th>
<th>1st Recurrence</th>
<th>2nd Recurrence</th>
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* 1/10 HF = one mitosis per 10 high-field magnifications (×1000); +/− = extremely rare; + = rare; ++ = moderate component; +++ = important component.
in which differentiation toward an oligodendroglioma occurred in a patient with NF1. Although most often characterized as a relatively benign glial tumor, increasingly frequent reports of recurrence\(^{1,13}\) and malignant progression to a high-grade PXA\(^{6,15,21,29}\) malignant astrocytoma,\(^{12,30}\) or glioblastoma multiforme\(^{29}\) have rendered this characterization doubtful. The time required for such a transformation varies from 7 months to 13 years, and almost 10 to 20% of PXAs have undergone malignant transformation.\(^{2,15}\)

The PXA–NF1 association is rare; previously reported cases have occurred as a single lesion in the supratentorial compartment.\(^{11,12,17,23}\) Isolated PXAs have been described as multiple lesions arising at different times in diverse locations;\(^{12}\) and as simultaneous multicentric PXAs,\(^{6}\) but we are not aware of a concomitant double location for isolated PXAs or PXAs–NF1 with different biological behaviors. An atypical pleomorphic astrocytoma\(^{22}\) has recently been described that resembles a PXA very closely and causes difficult problems in differential diagnoses. Additional cases are needed to clarify the exact nature of this tumor as well as any connection it may have with PXA.

### Prognostic Features

Thus far no one has identified a reliable predictive factor to determine which benign PXA can recur or transform before the malignant features appear.\(^{6,13,15,21,25,26,30}\) This lack of predictive factors of malignant transformation exemplifies the discrepancy between the tumor’s histological findings and clinical behavior.

### Treatment of PXA

Complete resection is considered the best therapeutic option for both primary and recurrent tumors,\(^{6,13,15,21}\) but there is still no consensus about the roles of radiotherapy and chemotherapy. The place of radiotherapy is unclear because it does not appear to have a major impact on the clinical course of the disease.\(^{9,30}\) Therefore, postoperative radiotherapy is reserved mainly for patients whose lesions have anaplastic characteristics or are recurrent tumors with malignant changes.\(^{6,15}\) because there is no alternative therapy with proven efficacy. Chemotherapy also has not proved useful for such lesions, as our case and others like it have shown.\(^{25}\)

### Conclusions

Pleomorphic xanthoastrocytoma most often is a benign glial neoplasm with a favorable outcome, although recurrence and malignant transformation may occur rapidly. In some cases of recurrent PXA, the ultimate outcome may be worse than originally thought, even when adjuvant radiotherapy or chemotherapy are used. It is not known how NF1 affects the prognosis of PXA, but according to previous reports it seems that PXA–NF1 follows the same behavior as PXA not associated with NF1. Nevertheless, the number of cases of PXA–NF1 that have been observed is too small to draw any conclusions.

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### References


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