Pleomorphic xanthoastrocytoma and oligodendroglioma: collision of 2 morphologically and genetically distinct anaplastic components

Case report

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With the exception of oligoastrocytoma, mixed gliomas are rarely encountered, and the astrocytic component of mixed oligoastrocytoma is almost always fibrillary and diffusely infiltrative. Pleomorphic xanthoastrocytoma (PXA) has occasionally been described in conjunction with ganglioglioma, as well as in 1 case of oligodendroglioma. In this latter case, described by Perry et al., 1p/19q codeletions were not detected.

The authors report on a 25-year-old woman with a combined PXA/oligodendroglioma in which concurrent 1p/19q codeletions were detected in the oligodendrogliom al component only. The patient presented with a 1-month history of headaches. Neuroimaging revealed a heterogeneous left temporal mass with focal enhancement, cystic changes, hemorrhage, and left-to-right midline shift. The patient underwent a craniotomy and gross-total resection. Pathological examination revealed a glial tumor composed of 2 apparently distinct components. The largest component exhibited a prominent fascicular, reticulin-rich, spindle cell arrangement admixed with areas of highly pleomorphic cells, with bizarre cytological features reminiscent of PXA. A smaller component was composed of cellular sheets and lobules of oligodendroglial cells. Both components were characterized by anaplastic features. Dual-color fluorescence in situ hybridization for 1p/19q codeletions was performed. Only the oligodendrogliomal component showed the combined 1p/19q deletions.

This case represents the first instance in which PXA has been reported in conjunction with an oligodendroglioma exhibiting the “molecular signature” characteristic of oligodendroglial neoplasms. The different genetic alterations seen in the 2 components of this neoplasm argue in favor of a “collision tumor” rather than a mixed glioma of the same genotype. (DOI: 10.3171/2010.11.JNS10739)

Key Words • collision tumor • fluorescence in situ hybridization • mixed glioma • oligodendroglioma • pleomorphic xanthoastrocytoma

The past 2 decades have witnessed a revolutionary shift toward recognizing the heterogeneity of individual glial tumors, and the concept of mixed gliomas is not only acceptable, but has become mainstream. In fact, mixed gliomas may account for more than one-third of gliomas in some medical centers.20 However, this topic has been anything but free of controversy. The concept of mixed gliomas has largely been based on the morphological observations of more than 1 tumor cell type within the same glioma. Most mixed gliomas are termed “diffuse,” containing a mixture of 2 cell types, but occasionally they are called “biphasic,” showing 2 morphologically distinct but juxtaposed areas of cell differentiation.14 Little in the form of molecular evidence exists to substantiate claims of the existence of mixed gliomas. The most common form of mixed glioma by far is mixed oligoastrocytoma. Although the concept of mixed glioma is not exclusive to oligoastrocytoma, only rarely is the diagnosis of other forms of mixed gliomas made. For example, PXA has occasionally been described in conjunction with ganglioglioma and dysembryoplastic neuroepithelial tumor.3,8,9,10,17,22 In addition, Perry et al.18 reported a case of combined oligodendroglioma/PXA in which 1p/19q codeletions were not detected. We report a case of a combined PXA/oligodendroglioma in which 1p/19q codeletions were identified exclusively in the oligodendrogliomal component.

Abbreviations used in this paper: CEP = centromeric enumeration probe; EGFR = epidermal growth factor receptor; FISH = fluorescence in situ hybridization; GFAP = glial fibrillary acidic protein; PXA = pleomorphic xanthoastrocytoma.

This article contains some figures that are displayed in color online but in black and white in the print edition.
Composite pleomorphic xanthoastrocytoma/oligodendroglioma

Case Report

History and Examination. This 25-year-old right-handed woman, who was 4 months postpartum, presented with a 1-month history of progressively worsening headaches. She described the headaches as sharp, pulsatile, and worse at night. They were accompanied by nausea and vomiting, prompting an emergency room visit. Results of a neurological examination were unremarkable.

Neuroimaging Studies. A CT scan of the head revealed a hyperdensity in the left temporal lobe. An MR imaging study showed a heterogeneous mass measuring approximately 4.5 × 3.8 × 3.2 cm in anteroposterior, craniocaudal, and transverse dimensions, centered within the left inferior temporal lobe, and with surrounding vasogenic edema that extended to the left frontal lobe and the left basal ganglia and internal capsule. This resulted in a left-to-right midline shift of 6 mm. The lesion demonstrated an anterior, homogeneous, lobulated, strongly enhancing component with an adjacent lateral area of cystic changes (Fig. 1).

First Operation and Adjuvant Therapy. In November 2005, the patient underwent left frontotemporal craniotomy with gross-total resection of the mass. Frozen section interpretation was consistent with a high-grade glialoma, which resulted in the neurosurgeon opting for Gliadel wafer (Eisai, Inc.) placement. Permanent histological sections showed a tumor with both anaplastic oligodendroglioma and PXA, as described below in the Pathological Findings section. A postoperative MR imaging study demonstrated small foci of low signal enhancement, consistent with blood products. Definite residual tumor could not be identified. One month later, the patient underwent radiation therapy (6000 cGy) in conjunction with daily temozolomide (75 mg/m²) for 42 days. This was followed by a 5-month course of temozolomide (200 mg/m² for 5 days per 28-day cycle). She developed left trigeminal neuropathy, but otherwise tolerated the adjuvant therapy regimen.

Tumor Recurrence, Repeat Operations, and Postoperative Course. The patient later experienced a complicated series of events starting with tumor recurrence 7 months postoperatively, for which she underwent a redo craniotomy with tumor resection. The recurrence consisted exclusively of anaplastic PXA. Six months after a procarbazine-lomustine-vincristine systemic chemotherapy regimen was completed, an MR imaging study revealed increased nodular enhancement around the left temporal lobe resection cavity, for which she underwent her third craniotomy, and pathological examination revealed changes consistent with radiation necrosis, but no residual tumor was identified. Eight months later, surveillance MR imaging showed a dural-based lesion in the left parietal lobe, which was consistent with fibroblastic meningioma. After that, the patient experienced multiple recurrent dural-based lesions showing striking rhabdoid morphological features (rhabdoid meningioma), and over the last few months of her life she developed distant metastases to the spine, ribs, scalp, and soft tissues of the neck. She eventually died of metastatic rhabdoid meningioma in March 2009. Details regarding this unusual occurrence of rhabdoid meningioma are beyond the scope of this paper, but may be the topic of a future publication.

Pathological Findings. The specimen was received in fragments, with an aggregate measurement of 5 × 5 × 2.1 cm. Microscopic examination disclosed a glial tumor that was composed of 2 apparently distinct components. The largest component (approximately 80% of the tumor) exhibited a prominent fascicular spindle cell arrangement admixed with areas of highly pleomorphic astrocytic cells, with bizarre cytological features and xanthomatous changes reminiscent of PXA (Fig. 2A and B). This component was relatively discrete and showed prominent subarachnoid and perivascular involvement (Fig. 2C). Other features of PXA, including lipidized, epithelioid, and gemistocytic cells, and perivascular lymphocyte infiltrates, were identified. Eosinophilic granular bodies were numerous (Fig. 2D). The astrocytic cells were mitotically active (up to 10/10 hpf) and the tumor demonstrated rare foci of vascular proliferation and palisading necrosis (Fig. 2E and F), prompting the diagnosis of PXA with anaplastic features. The fascicular areas demonstrated remarkably intense intercellular reticulin deposition (Fig. 2G) and GFAP (predilute IR524) immunoreactivity (Fig. 2H). The MIB-1 (Ki 67, predilute IR626) labeling index was estimated at approximately 5%–8% in the most proliferative areas (Fig. 2I). Alpha-1 antitrypsin antibody (predilute IR505) showed focal weak positivity, and neuron-specific enolase (predilute IR612) was immunoreactive in scattered cells (all antibodies were obtained from Dako Corp.).
A smaller but morphologically distinct component (approximately 20% of the tumor) was composed of cellular sheets and lobules of oligodendrogial cells. This component was characterized by numerous microcysts and decorated by the characteristic chicken-wire vessels of oligodendroglioma (Fig. 3A and B). The oligodendrogial cells were particularly mitotic (10–15/10 hpf; Fig. 3C), and occasional foci of microvascular proliferation were noted. Interestingly, the oligodendrogial component was peppered by large, atypical, lipidized astrocytic cells identical to those present within the PXA component (Fig. 3D). Unlike the PXA component, no pericellular reticulin (Fig. 3E) or GFAP expression was identified. Immunostaining for alpha-1 antitrypsin and neuron-specific enolase yielded negative results. Immunostaining with MIB-1 antibody demonstrated an elevated proliferative rate of up to 10% (Fig. 3F). These morphological features are consistent with anaplastic oligodendroglioma.

To address the issue of whether the oligodendrogial component showed the “molecular signature” of oligodendroglioma, we performed dual-color FISH for 1p36/19q13 chromosomal codeletions. Four 5-μm-thick sections mounted on positively charged slides were cut from a formalin-fixed, paraffin-embedded block containing both PXA and oligodendroglioma components. The DNA probes obtained from Vysis, Inc. (Vysis LSI; 1p36/1q25 and 19q13/19p13 [catalog no. 32–231004]) were used as previously described.4 Each tumor component was subjected to signal enumeration. Samples with >90% of the nuclei showing bright signals were considered acceptable, and 100 nonoverlapping nuclei were scored for signals from the CEP 1p36 (red)/1q25 (green) and 19q13 (red)/19p13 (green) under the fluorescence microscope with a magnification of 1000. We used the established criteria for 1p/19q codeletions.3,16 The cells bearing more than 3 copies of signals were scored separately, and the scores were compared against the pooled normal control. If the cell population contained more than 3 copies...
of signals beyond the cutoff value (mean ± 3 SDs of normal control), the tumor was recognized as polysomic.3,16 In this case, only the oligodendroglial component showed the combined 1p36/19q13 deletions (Fig. 4A and B). The PXA tumor component showed extensive polysomic change (Fig. 4C).

A p53 mutation analysis was performed on formalin-fixed, paraffin-embedded sections on both histological components as previously described.13 In addition, FISH analysis for EGFR was performed on formalin-fixed, paraffin-embedded tissue sections from both components by using EGFR/CEP 7 Dual Color Probe containing centromere chromosome 7 (CEP 7, Spectrum Green; Vysis, Inc.) and EGFR gene located at 7p12 (EGFR, Spectrum Orange; Vysis, Inc.), as previously described.15 Both p53 mutation and EGFR amplification were absent in the PXA and oligodendroglioma components. Interestingly, the PXA component showed polysomic change, whereas the oligodendroglioma showed disomy. On immunohistochemical analysis, approximately 10% and 2% of the tumor cells were highlighted by p53 (predilute DO-7; Dako Corp.) in PXA and oligodendroglioma, respectively. Both components were negative for EGFR (1:200 H11; Dako Corp.).

**Discussion**

Pleomorphic xanthoastrocytoma was first described by Kepes et al.12 in 1979, and there have been well over 200 cases reported in the literature since.14 These lesions are frequently superficial in location and associated with a long history of seizures.7 Characteristic features of PXA include marked cellular pleomorphism and nuclear atypia, bizarre multinucleated giant cells, xanthomatous change, eosinophilic granular bodies, and a rich reticulin network.9,12 The differential diagnosis of a PXA should always include glioblastoma, because the 2 may show many similar features. However, the lipidized cells embedded in an intense reticulin network and the numerous eosinophilic granular bodies seen in our patient’s tumor favor a diagnosis of PXA. In addition, the absence of p53 mutation and EGFR amplification further argues in support of the diagnosis of PXA and against glioblastoma.11 Pleomorphic xanthoastrocytomas generally have a favorable prognosis, but as many as 15%–20% may show anaplastic features.8 Increased mitotic activity and necrosis, as seen in our case, have been shown to be predictors of a worse prognosis; however, other histological features associated with highly aggressive behavior in other as-
tropic tumors, such as nuclear atypia and vascular proliferation, do not correlate with prognosis in PXAs.\(^6\),\(^9\)

The recurrence of the tumor described herein, over such a very short period of time (7 months), despite gross-total resection, radiation, and chemotherapy, demonstrates the potentially aggressive behavior of a PXA with anaplastic features. Recently, neuronal differentiation has been described in PXAs, including multiple reports of composite PXA/ganglioglioma,\(^2\),\(^5\),\(^7\),\(^17\),\(^22\) and a single case with combined histological features of PXA and dysembryoplastic neuroepithelial tumor.\(^10\)

In addition, there has been 1 previously reported case of a combined PXA/oligodendroglioma, described by Perry et al.\(^18\) in 2001. In this case, the combined 1p/19q deletions characteristic of the majority of oligodendroglialomas\(^1\),\(^8\),\(^21\) were not detected in either component. In contrast, the tumor described herein unequivocally demonstrated the combined 1p/19q chromosomal deletions in the oligodendroglial component, but not in the PXA component. The clearly different molecular alterations seen in the 2 elements of this neoplasm suggest that these components arose from 2 different clones, and are therefore genetically and morphologically distinct; that is, representing a "collision tumor" as opposed to a most unusual form of mixed oligoastrocytoma in which PXA represents the astrocytic component. Alternatively, the 2 components may have shared a common precursor clone and developed distinct molecular variations later.

The biological behavior of collision tumors is very difficult to predict, but may be a function of the most predominant component of the two. In our case, the PXA constituted the majority (80%) of the tumor. The short recurrence interval of 7 months is consistent with the aggressive but unpredictable behavior seen in PXAs with anaplastic features. In contrast, the case described by Perry et al.\(^18\) was predominantly oligodendroglioma (90%), and this patient was alive without recurrence almost 3 years after surgery, consistent with the less aggressive nature of WHO Grade II oligodendrogliomas, which are generally slowly growing; patients with these lesions have relatively long survival periods.

Our patient was young and exceptionally prone to malignancy. She developed multiple different histological tumors with multiple recurrences over a span of less than 4 years. Given the circumstances, this raises the possibility of a cancer susceptibility syndrome. A \(p53\) gene analysis was performed, and the results were negative. Unfortunately, the patient died before we were able to obtain consent from her for further genetic testing for a possible cancer susceptibility syndrome.

**Conclusions**

This case illustrates the first example of a combined PXA/oligodendroglioma, in which the latter component showed the characteristic combined 1p36/19q13 chromosomal deletions, establishing it as morphologically and genetically distinct from the juxtaposed astrocytic component. With increasing numbers of morphologically complex glial tumors being recognized, molecular studies are of paramount importance in enhancing our understanding of these tumors, and should be routinely performed.

**Disclosure**

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Acquisition of data: all authors. Analysis and interpretation of data: Hattab, Martin, Cheng. Drafting the article: Hattab, Martin, Cheng. Critically revising the article: Hattab, Martin. Reviewed final version of the manuscript and approved it for submission: all authors. Administrative/technical/material support: Hattab. Study supervision: Hattab.

**References**

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