

*Letter to the Editor*

**Diffuse malignant transformation of pleomorphic xanthoastrocytoma 21 years later: a matter of time?**

**R. D. Dickerman<sup>1</sup>, A. Anderson<sup>2</sup>, J. Morgan<sup>2</sup>, and A. J. Cohen<sup>3</sup>**

<sup>1</sup> Department of Neurosurgery, North Texas Neurosurgical Associates and HCA Medical Center of Plano, Plano, Texas, USA

<sup>2</sup> Departments of Pathology and Neurosurgery, North Shore University-Long Island Jewish Medical Center, New Hyde Park, NY

<sup>3</sup> Department of Neurosurgery, Weil Medical College of Cornell University, New York, NY

**Dear Editor**

Gil-Gouveia *R et al.* presented an interesting report on “Pleomorphic xanthoastrocytoma of the cerebellum: illustrated review”. The case exemplifies the ongoing complexities in the pathological definition of pleomorphic xanthoastrocytoma (PXA) [4]. There are several cases of primary infratentorial PXAs as well as glioblastoma multiforme (GBM) [6]. The obvious dilemma is properly characterizing the PXA as low grade or mixed and then following an appropriate treatment algorithm. There are reports of PXA recurrence up to 20 years after initial resection [1, 5, 11]. The medical community often questions the initial pathology in these cases, however, the survival time extending beyond five years would agree with PXA versus GBM. Example is the case of a 16 year old female who underwent gross total resection of a right frontal GBM. Twenty years later she presents with a right cerebellar mass pathology revealing a PXA with atypical features [5]. Retrospective analysis of the initial histopathology 20 years earlier and clinical behavior led to a corrective diagnosis of PXA with atypical features [5]. The cascade for malignant transformation remains unclear. There are cases of radiation-induced genetic alterations leading to malignant transformation in several tumors [1]. PXAs have been reported with initial malignant craniospinal and meningeal dissemination [11]. In addition the time-frame for recurrence is highly variable without clear histopathological criteria for aggressive behavior. An 11 year-old female presented with a left temporoparietal PXA with necrosis and proliferating cell nuclear antigen (PCNA)

on pathology but without mitoses. She developed tumor recurrence eight months later, underwent resection and pathology was unchanged. Three months later she developed diffuse meningeal gliomatosis and subsequent death [9]. Recurrence for primary brain tumors, including PXAs, is usually within the initial operative site, not distant, however there are reports of recurrence of PXA 15 years after radiation therapy at a distant site [1]. Long-term survival in a patient with an initial diagnosis of GBM leads one to reexamine the pathology. There’s a report of a patient with a diagnosis of PXA 18 years prior without postoperative radiation therapy and is still alive [12]. Pathological analysis of five patients with PXA revealed that survival was dependent on mitotic activity and MIB-1 labeling index correlate best with biological behavior and that histological appearance is of little benefit in prognosis [13]. In brief, PXA’s have pleomorphic cells with astrocytic differentiation, a morphological appearance that can be fibrillary astrocytes or giant cells, often multinucleated with lipid accumulation within the cytoplasm [14]. Differentiating PXA from a lipidized GBM is an important clinical tool. Low mitotic rate, reticulin staining, absence of vascular proliferation and necrosis distinguish PXA from GBM. PXA is classified by WHO as a grade II glioma, however, the PXA with anaplastic features, may share some of the features of GBM and thus a poorer prognosis [14].

The obvious difficulty in the treatment algorithm of any patient with a PXA is determining the likelihood for recurrence. The incidence of recurrence was reviewed in 13 children with diagnosis of PXA whom underwent

gross total resection without adjuvant therapy, revealing a recurrence rate of 15% at approximately 3.5 year follow-up [2]. A more recent retrospective review of eight cases with histologically proven PXA whom underwent gross total resection without adjuvant therapy revealed survival of all patients ranging from 7–14 years follow-up [7]. Im *et al.* when onto state that immunohistochemical studies undertaken as a part of this study support astrocytic and neuronal differentiation of PXA, and indicate that PXA is probably a developmental neuroglial tumor with prominent glioproliferative changes associated with focal cortical dysplasia [7]. Studies analyzing the genetic alterations in PXA in comparison to invasive gliomas has demonstrated that the normal P53 alterations that occur within invasive gliomas are present in less than 2% of PXAs, in addition, the typical chromosomal and genetic aberrations associated with diffuse infiltrating astrocytic and oligodendroglial gliomas are different from PXAs [3, 8]. These genetic differences likely contribute to the favorable behavior of PXAs. We offer a case of PXA resection in a 18 year-old male that occurred in his right parietal lobe who underwent primary gross total resection without complications and no adjuvant therapy. The patient was managed initially on antiepileptics and followed with CT scans for two years postoperatively and was tapered off and has enjoyed 21 years of asymptomatic life (initial pathology slides and CT scans unavailable due to storage capabilities when over 20 years). The patient returns 21 years later with rapidly declining mental status changes. The patient had an MRI which revealed diffuse infiltration of

the supratentorial and infratentorial compartments along with meningeal dissemination (Fig. 1). The patient underwent stereotactic biopsy with neuropathological microscopic description of a highly cellular neoplasm, necrosis, rare mitosis and cells with marked pleomorphism and glioblastomatous vessels. The patient and family decided on an attempt for chemotherapy in an attempt to slow the process and the patient eventually succumb to death two months after therapy. This case demonstrates that PXA, despite gross total resection and 21 years of symptom-free survival may recur as a high grade glioma. Is the patient with a PXA genetically predisposed for an eventual high grade recurrence? Ongoing molecular studies will hopefully elucidate the malignant transformation cascade in PXAs and eventually allow for genetic testing of these tumors after initial resection to provide insight on prognosis and need for adjuvant therapy.

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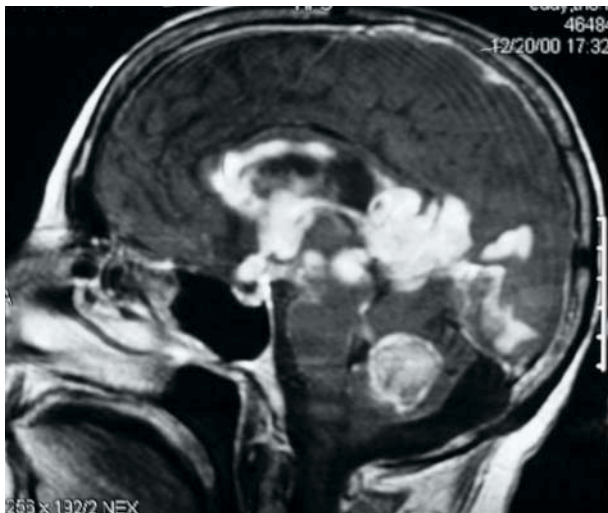


Fig. 1. Sagittal T1-weighted MRI with contrast revealing diffuse infiltrating glioma of the supratentorial, infratentorial compartments and meningeal dissemination

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### Author's Reply

Dickerman RD *et al.* pointed out, based in cases of their own experience, some of the important issues linked to the pleomorphic xanthoas-

trocytomas (PXA), namely their precise nature, the histopathological criteria allowing the differential diagnostic between PXAs (with or without atypical features) with other malignant astrocytomas, the unpredictable postoperative behaviour of at least some of the cases, and, related to this last point, the most useful diagnostic tools (e.g., tumour cell proliferative capacity by measuring mitotic activity and/or MIB-1 labelling index, and cytogenetic alterations) for predicting their future behaviour. Yet, these are also topics of discussion concerning the neuroepithelial tumours in general, many of them still unsolved. We believe, based in our neuropathological experience, that cytogenetics, in association with histopathology, should be considered more and more as an important tool for the choice of the right postoperative therapy and prediction of the biological behaviour of many of the intracranial tumours.

*Raquel Gil-Gouveia*

Correspondence: Rob D. Dickerman, Department of Neurosurgery, 3001 Communications Blvd. Suite 1027, Plano, TX, 75093, USA.  
e-mail: drrdd@yahoo.com