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BRAF mutation and anaplasia may be predictive factors of progression-free survival in adult pleomorphic xanthoastrocytoma

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Abstract

Background: Pleomorphic xanthoastrocytoma (PXA) is a rare, low-grade glioma that frequently occurs in pediatric patients.
Objective: To analyze adult patients diagnosed with PXA and to search for pathological and molecular markers of diagnosis and prognosis.
Methods: We retrospectively included patients older than 16 years with PXA who were referred to our institution between October 2003 and September 2013. All pathological diagnoses were reviewed by a neuropathologist. Histological characteristics and immunostaining of GFAP, OLIG2, neurofilament, CD34, Ki67, p53, p16, and IDH1 R132H were analyzed. The following molecular alterations were analyzed: mutations of *IDH1/2*, *BRAF* and the histone *H3.3* and the *EGFR* amplification. Clinical data, treatment modalities, and patient outcome were recorded.
Results: We identified 16 adult patients with reviewed PXA diagnosis. No *IDH* neither histone *H3.3* mutations were found; *BRAF* V600E mutation was recorded in six patients. Ten patients presented with anaplastic features. *BRAF* mutations were associated with lower Ki67, OLIG2 expression, and lack of p16 expression. Median PFS and OS were 41.5 months (95% CI: 11.4–71.6) and 71.4 months (95% CI: 15.5–127.3), respectively. *BRAF* mutation tended to be associated with greater PFS ($p = 0.051$), whereas anaplastic features were associated with minimal PFS ($p = 0.042$).
Conclusion: PXA in adults PXA may present features distinct from pediatric PXA. Anaplastic features and *BRAF* mutation may potentially identify specific subgroups with distinct prognoses.

Keywords: Pleomorphic xantho-astrocytoma; Glioma; BRAF mutation; IDH1/2 mutation; Histone H3.3 mutation

Introduction

Pleomorphic xanthoastrocytoma (PXA) is a rare, low-grade glioma that frequently occurs in pediatric patients. Histological presentation of PXA is characterized by glial cell proliferation and the presence of pleomorphic giant tumor cells with xanthomatous cytoplasm. A dense reticulin network is frequently associated with PXA as well as eosinophilic granulations and lymphomatous infiltration. The World Health Organization classifies these tumors as Grade II astrocytic glioma.[1] Cases revealing pathological signs of anaplasia defined as ≥5 mitoses per 10 HPF and/or necrosis are classified as PXA with anaplastic features but still remain as grade II.[1] The prognostic impact of anaplasia remains a matter of debate. However, recently, a large study comprising adult and pediatric cases has clearly demonstrated the dismal prognosis of anaplasia, suggesting the requirement to reclassify these tumors as grade III.[2]

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Although clinical and neuroradiological presentations of PXA may appear heterogeneous, the prognosis remains relatively favorable.[3] However, the low frequency of these tumors has fostered heterogeneity of therapeutic approaches, particularly in adult patients. The molecular landscape of low grade glioma was recently deciphered, highlighting specific somatic genomic alterations according to glioma subsets and age. *IDH1/2* mutations characterized adult diffuse grade II and III gliomas as well as secondary glioblastoma.[4,5] Otherwise, pediatric gliomas were segregated based on genomic and epigenetic anomalies, providing new insight regarding pediatric glioma molecular drivers, such as mutations within the histone variant H3.3 occurring in diffuse glioma.[6] In contrast, MAPKinase pathway alterations occur in pilocytic astrocytoma, PXA, and glioneuronal tumors and *BRAF* mutation was described as one of the potential key pathways altered in PXA, ganglioglioma, and dysembryoplastic neuroepithelial tumors.[7,8]

Despite these findings, PXA in adults remains a difficult diagnosis and therapeutic challenge. In this study, we focused on a monocentric cohort of 16 patients diagnosed with PXA to search for pathological and molecular markers of diagnosis and prognosis.

Methods

Selection criteria

We performed a monocentric, retrospective chart review of all adult patients older than 16 years with PXA diagnosis who were referred to our institution between October 2002 and September 2013 with histological samples stored in the Assistance Publique-Hôpitaux de Marseille Tumor Bank (authorization number AC2012-1986). All pathological diagnoses were reviewed by a neuropathologist (DFB). All PXA cases were diagnosed according to the 2007 WHO classification (Louis).[1] Anaplastic features (AF) were defined based on this classification, including PXA with >5 mitoses per 10 HPF and/or necrosis. Tumor specimens were obtained after written consent in full compliance with national regulations and according to a protocol approved by the local institutional review board and ethics committee.

End-point analyses

Histological characteristics by hematein–eosin were first described. Immunostaining determination of GFAP, OLIG2, neurofilament (NF), CD34, Ki67, p53, p16, and IDH1 R132H were performed through immunohistochemistry. Furthermore, reticulin network was analyzed. *BRAF*, *IDH1/2*, and histone *H3.3 (G34 and K27)* mutations were analyzed by Sanger sequencing. In addition, *EGFR* amplification was analyzed as previously described.[9] Clinical status, neuroimaging, and treatment received were recorded.

Statistical analyses

Data were described as frequencies (percentages) and medians (range). Distinctions between patients with or without *BRAF* mutation or AF were evaluated using the chi-square test and the Mann–Whitney test. Progression-free survival was defined from PXA diagnosis to progression or death that was censored at the date of last contact. Overall survival (OS) was defined from PXA diagnosis to death by any cause that was censored at the date of last contact. Time to event endpoints was estimated using the Kaplan–Meier method and compared using the log-rank test. All analyses were performed with a bilateral alpha type 1 error of 5%.

Results

Patient characteristics (Table 1)

Sixteen adult patients with a median age of 45 years were included in this study. Majority of patients presented with neurological symptoms at diagnosis, and half of them had seizures. General status was conserved with a median KPS of 80 at diagnosis. More than 50% of tumors were located in the temporal lobe.

Ten patients underwent gross total resection at diagnosis, two received subtotal resection, and four partial resection or biopsy. After surgery, eight patients were treated with a combination of radiochemotherapy: five with radiotherapy alone; and three without adjuvant treatment.

Histological and molecular features (Table 2)

All 16 cases were reviewed by a neuropathologist (DFB) to avoid differential diagnosis. Ten patients presented with AF. All patients had inflammatory tumor infiltration and GFAP expression; the majority of them were OLIG2 negative. The median number of mitoses per 10 HPF was 5

Table 1
Patient characteristics.

Characteristics	N = 16	%
Median age (years)	45 (16–65)	
Gender (Male/Female)	9 (M)/7 (F)	
First symptom		
Epilepsy	8	*50*
Intracranial hypertension	2	*12*
Other neurological symptom	4	*26*
Asymptomatic	2	*12*
KPS		
70	3	*21*
80	7	*50*
90	4	*29*
Neuro-imaging		
Temporal	9	*56*
Other	7	*44*

The percentage values are indicated by italic.