Cancer Association of South Africa (CANSA)

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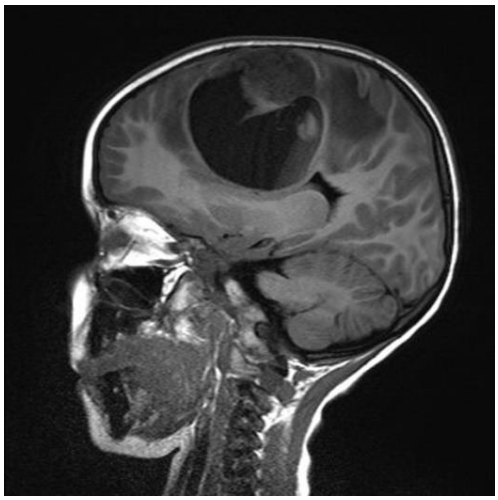
Fact Sheet on Juvenile Pleomorphic Xanthoastrocytoma

Introduction

Pleomorphic xanthoastrocytoma (PXA) is a brain tumour that occurs most frequently in children and teenagers. The average age at diagnosis is said to be 12 years.



[Picture Credit: Pleomorphic Xanthoastrocytoma]

Pleomorphic xanthoastrocytoma usually develops within the supratentorial region (the area of the brain located above the tentorium cerebelli). It is generally located superficially (in the uppermost sections) in the cerebral hemispheres, and involves the leptomeninges (the inner two meninges, the arachnoid and the pia mater, between which the cerebrospinal fluid circulates). It rarely arises from the spinal cord. In about 20% of cases, tumours exist in more than one lobe.

Pleomorphic Xanthoastrocytoma (PXA)

Pleomorphic Xanthoastrocytomas are a type of rare, low-grade astrocytoma (WHO Grade II) found in young patients who typically present with temporal lobe epilepsy. Pleomorphic Xanthoastrocytomas affect males and females equally.

Mathkour, M., Banerjee, S., Werner, C., Hanna, J., Abou-Al-Shaar, H., Dindial, R., Scullen, T., Boehm, L., Tubbs, R.S. & Ware, M.L. 2021.

Background: Pleomorphic xanthoastrocytoma (PXA) is a rare brain tumor occurring supra- and infra-tentorially in both young adults and children. PXA is a benign tumor with a favorable prognosis. It is not traditionally considered as a neurofibromatosis type 1 (NF-1)-associated lesion, and its prognosis remains largely unknown, on the contrary to non-NF-1 PXA tumors.

Objective: Herein, we present a rare case of cerebellar PXA in a patient with NF-1 and performed systematic review of NF-1-associated PXA.

Researched and Authored by Prof Michael C Herbst
[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic Counselling; Dip Audiometry and Noise Measurement; Diagnostic Radiographer; Medical Ethicist]
Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

Method: We present a case of NF-1-associated PXA arising in the cerebellar region. We also reviewed the literature in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines to identify published cases of cerebellar vs. non-cerebellar NF-1-associated PXA and NF1 vs. non-NF1 PXAs, highlighting their management paradigm, prognosis, and outcomes.
Result: Our systematic review yielded only four previously reported cases of NF-1-associated PXAs in the cerebellar region. Our review suggests that infratentorial PXAs have a higher recurrence and lower survival rates than non-cerebellar NF-1-associated PXAs and non-NF1 PXAs in general.
Conclusion: Early and precise diagnosis is important for these lesions with the aid of imaging features, histology, immunohistochemistry, and genetic markers. Surgical resection with goal of GTR remains the mainstay management strategy for PXA, with adjuvant therapy usually reserved for anaplastic or malignant lesions. The identification of BRAF-V600E mutation and role of BRAF inhibitors hold promise as a diagnostic tool and treatment modality, respectively, for PXAs, and their relationship to NF-1 is worth further exploration.

Vaubel, R., Zschernack, V., Tran, Q.T., Jenkins, S., Caron, A., Milosevic, D., Smadbeck, J., Vasmatzis, G., Kandels, D., Gnekow, A., Kramm, C., Jenkins, R., Kipp, B.R., Rodriguez, F.J., Orr, B.A., Pietsch, T. & Giannini, C. 2021.
"Pleomorphic xanthoastrocytoma (PXA) is a rare astrocytoma predominantly affecting children and young adults. We performed comprehensive genomic characterization on a cohort of 67 patients with histologically defined PXA (n = 53, 79%) or anaplastic PXA (A-PXA, n = 14, 21%), including copy number analysis (ThermoFisher Oncoscan, n = 67), methylation profiling (Illumina EPIC array, n = 43) and targeted next generation sequencing (n = 32). The most frequent alterations were CDKN2A/B deletion (n = 63; 94%) and BRAF p.V600E (n = 51, 76.1%). In 7 BRAF p.V600 wild-type cases, alternative driver alterations were identified involving BRAF, RAF1 and NF1. Downstream phosphorylation of ERK kinase was uniformly present. Additional pathogenic alterations were rare, with TERT, ATRX and TP53 mutations identified in a small number of tumors, predominantly A-PXA. Methylation-based classification of 46 cases utilizing a comprehensive reference tumor allowed assignment to the PXA methylation class in 40 cases. A minority grouped with the methylation classes of ganglioglioma or pilocytic astrocytoma (n = 2), anaplastic pilocytic astrocytoma (n = 2) or control tissues (n = 2). In 9 cases, tissue was available from matched primary and recurrent tumors, including 8 with anaplastic transformation. At recurrence, two tumors acquired TERT promoter mutations and the majority demonstrated additional non-recurrent copy number alterations. Methylation class was preserved at recurrence. For 62 patients (92.5%), clinical follow-up data were available (median follow-up, 5.4 years). Overall survival was significantly different between PXA and A-PXA (5-year OS 80.8% vs. 47.6%; P = 0.0009) but not progression-free survival (5-year PFS 59.9% vs. 39.8%; P = 0.05). WHO grade remained a strong predictor of overall survival when limited to 38 cases defined as PXA by methylation-based classification. Our data confirm the importance of WHO grading in histologically and epigenetically defined PXA. Methylation-based classification may be helpful in cases with ambiguous morphology, but is largely confirmatory in PXA with well-defined morphology."

Incidence of Pleomorphic Xanthoastrocytoma (PXA) in South Africa
The National Cancer Registry (2017) does not provide any information regarding the incidence of Pleomorphic Xanthoastrocytoma.

Differential Diagnosis of Pleomorphic Xanthoastrocytoma (PXA)

Main differential diagnosis is that of other cortical tumours, with helpful distinguishing features including:

- Ganglioglioma
- Dysembryoplastic neuroepithelial tumours (DNET)
- Oligodendroglioma
- Desmoplastic infantile ganglioglioma
- Cystic meningioma

Diagnosis of Pleomorphic Xanthoastrocytoma (PXA)

Diagnosis is usually made by utelising:

- Computerised tomography (CT scan)
- Magnetic resonance imaging (MRI)
- Digital subtraction angiography (DSA): a fluoroscopy technique used in interventional radiology to clearly visualise blood vessels in a bony or dense soft tissue environment.

She, D., Liu, J., Xing, Z., Zhang, Y., Cao, D. & Zhang, Z. 2018. MR imaging features of anaplastic pleomorphic xanthoastrocytoma mimicking high-grade astrocytoma. *AJNR Am J Neuroradiol.* 2018 Aug;39(8):1446-1452. doi: 10.3174/ajnr.A5701. Epub 2018 Jun 14.

BACKGROUND AND PURPOSE: Anaplastic pleomorphic xanthoastrocytoma, which has been recently defined as a distinct entity in the 2016 World Health Organization classification, may exhibit aggressive clinical behaviour and relatively worse prognosis than pleomorphic xanthoastrocytoma. This study aimed to investigate whether there were any differences in MR imaging characteristics between these 2 tumors.

MATERIALS AND METHODS: This retrospective study included 9 patients with anaplastic pleomorphic xanthoastrocytoma and 10 patients with pleomorphic xanthoastrocytome who underwent MR imaging before an operation. DWI was performed in 17 patients (8with anaplaxtic pleomorphic xanthoastrocytome, 9 with pleomorphic xanthoastrocytoma); and DSC-PWI, in 9 patients (5 with anaplastic pleomorphic xanthoastrocytoma, 4 with pleomorphic xanthoastrocytoma). Demograhics, conventional imaging characteristics (location, size, cystic degeneration, enhanvement, peritumoral edoema, and leptomengeal contact) minimum relative ADC ratio, and maximum relative CBV ratio were evaluated between the anaplastic pleomorphic xanthoastrocytoma and pleomorphic xanthoasrocytoma groups.

RESULTS: Anaplasatic pleomorphic xanthoastrocytoma was more likely to demonstrate high-grade features than pleomopnic xanthoastrocytoma, including greater maximum tumor diameter (4.7 ± 0.6 cm versus 3.1 ± 1.1 cm, *P* = .001), more frequent heterogeneous contrast enhancement of solid portions (88.9% versus 20.0%, *P* = .01), more obvious peritumoral edema (2.3 ± 0.9 cm versus 1.0 ± 0.9 cm, *P* = .008), lower minimum relative ADC on DWI (1.0 ± 0.2 versus 1.5 ± 0.4, *P* = .008), and higher maximum relative CBV on DSC-PWI (2.6 ± 0.8 versus 1.6 ± 0.2, *P* = .036).

CONCLUSIONS: Anaplastic pleomorphic xantoastrocytomas often have more aggressive MR imaging features mimicking high-grade astrocytomas than pleomorphic xantoastrocytomeas. DWI and DSC-PWI might be useful in the characterization and differentiation of anaplastic pleomorphic xanthoastrocytomas than pleomorphic xanthoastrocytomas.

Treatment of Pleomorphic Xanthoastrocytoma (PXA)

The following treatments may be used alone or in combination to treat Pleomorphic Xanthoastrocytoma (PXA):

- Neurosurgery to remove as much of the tumour as possible. If the tumour is completely removed, no other treatment is required other than serial MRIs to monitor for re-growth. A second surgical procedure may be performed if the tumour cannot be completely removed and increases in size, or if it comes back.
- Gross total resection usually eliminates seizures
- Radiation therapy may be considered, but does not influence long-term outcomes.
- Biologic therapy

Ronsley, R., Dunham, C., Yip, S., Brown, L., Zuccato, J.A., Karimi, S., Zadeh, G., Goddard, K., Singhal, A., Hukin, J. & Cheng, S. 2021.

Background: Anaplastic pleomorphic xanthoastrocytoma (APXA) is a rare subtype of CNS astrocytoma. They are generally treated as high-grade gliomas; however, uncertainty exists regarding the optimal therapy. Here, we report on 3 pediatric cases of APXA.

Methods: Our institutional database was queried for cases of APXA and 3 cases were identified. Surgical samples were processed for methylation profiling and chromosomal microarray analysis. Methylation data were uploaded to the online CNS tumor classifier to determine methylation-based diagnoses to determine copy number variations (CNVs).

Results: Two patients were male, 1 female, and all were aged 12 years at diagnosis. All underwent a gross total resection (GTR) and were diagnosed with an APXA. Immunohistochemical analysis demonstrated that 2 cases were BRAF V600E positive. Methylation-based tumor classification supported the APXA diagnosis in all cases. CNV analyses revealed homozygous *CKDN2A* deletions in all and chromosome 9p loss in 2 cases. All patients received radiation therapy (54 Gy in 30 fractions) with concurrent temozolomide. Two patients received maintenance chemotherapy with temozolomide and lomustine for 6 cycles as per the Children's Oncology Group ACNS0423. The third patient recurred and went on to receive a second GTR and 6 cycles of lomustine, vincristine, and procarbazine. All are alive with no evidence of disease >4 years post-treatment completion (overall survival = 100%, event free survival = 67%).

Conclusions: The natural history and optimal treatment of this rare pediatric tumor are not well understood. This case series supports the use of adjuvant chemoradiotherapy in the treatment of APXA. The genetic landscape may be informative for optimizing treatment and prognosis.

Khalafallah, A.M., Rakovec, M. & Mukherjee, D. 2020.

Background: Pleomorphic Xanthoastrocytoma (PXA) is a low-grade central nervous system (CNS) tumor with a generally favorable prognosis. However, due to its rarity, optimal adjuvant treatment guidelines have not been established by large scale studies. In this study, we investigated the effect of adjuvant radiation therapy (RT) on overall survival (OS) in adult patients with PXA to help address this unanswered question.

Methods: The National Cancer Database (NCDB) was used to identify adult patients (age ≥ 18 years old) diagnosed with histologically confirmed grade II PXA (2004-2016). Patient demographics, tumor characteristics, and treatment information were collected. Kaplan-Meier curves were generated to study OS, and factors that affected OS were identified using a multivariate Cox proportional hazards (CPH) model.

Results: A total of 546 patients were identified. The average age of patients at diagnosis was 36.6 years old, and overall median survival was 128.6 months. RT was used to treat 179 (33.3 %) patients. Those who received RT had a shorter median OS (33.3 months) compared to those who did not (>128.6 months, $p < 0.001$). Our multivariate model demonstrated receiving RT was independently

associated with a significantly higher risk of death (hazard ratio [HR] = 4.28, 95 % confidence interval [CI] = 1.77-10.38, p = .0013). Patients ≥65 years of age also demonstrated significantly higher risk of death (HR = 2.20, CI = 1.54-4.16, p = .006) and had a decreased median OS (26.0 months).
Conclusion: In adults with PXA, treatment with RT is independently associated with a significantly higher risk of mortality. The routine use of this modality in treating PXA warrants further study.

Lundar, T., Due-Tønnessen, B.J., Frič, R., Krossnes, B., Brandal, P., Stensvold, E. & Due-Tønnessen, P. 2019.
OBJECTIVE: The authors conducted a study to delineate the long-term results of the surgical treatment of pediatric pleomorphicxanthoastrocytomas (PXAs).
METHODS: All consecutive children and adolescents (0-20 years) who underwent primary tumor resection for a PXA during the years 1972-2015 were included in this retrospective study on surgical morbidity, mortality rate, academic achievement, and/or work participation. Gross motor function and activities of daily living were scored according to the Barthel Index.
RESULTS: Of the 12 patients, 8 patients were in the 1st decade of life and 4 in the 2nd. The male/female ratio was 6:6. No patient was lost to follow-up. One patient presented with severe progressive tumor disease and died within 3 months after repeated resection. Another child died 3 days following a second surgical procedure involving gross-total resection (GTR) 8 years after the initial operation. The other 10 patients were alive at the latest follow-up when they reached the median age of 34 years (range 11-60 years). The median follow-up duration was 22 years (range 2-41 years). Barthel Index score was 100 in all 10 survivors. A total 18 tumor resections were performed. Five patients underwent a second tumor resection after MRI/CT confirmed recurrent tumor disease, from 6 months up to 17 years after the initial operation. Only one of our patients received adjuvant therapy: a 19-year-old male who underwent resection (GTR) for a right-sided temporal tumor in 1976. This particular tumor was originally classified as astrocytoma WHO grade IV, and postoperative radiotherapy (54 Gy) was given. The histology was reclassified to that of a PXA. Seven of 8 children whose primary tumor resection was performed more than 20 years ago are alive as of this writing-i.e., 88% observed 20-year survival. These are long-term survivors with good clinical function and all are in full- or part-time work.
CONCLUSIONS: Pediatric patients with PXA can be treated with resection alone with rewarding results. Recurrences are not uncommon, but repeated surgery is well tolerated and should be considered in low-grade cases before adjuvant therapy is implemented. Follow-up including repeated MRI is important during the first postoperative years, since individual patients may have a more aggressive tumor course.

About Clinical Trials
Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides

information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.
For additional information, please visit: www.sanctr.gov.za/

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