Published in final edited form as:

J Neurooncol. 2013 January ; 111(1): 59–69. doi:10.1007/s11060-012-0991-4.

Anaplastic PXA in adults: case series with clinicopathologic and molecular features

Yao Schmidt¹, B.K. Kleinschmidt-DeMasters^{1,2,3}, Dara L. Aisner¹, Kevin O. Lillehei², and Denise Damek^{2,3}

¹Department of Pathology, The University of Colorado Health Sciences Center, Aurora, Colorado, USA

²Department of Neurosurgery, The University of Colorado Health Sciences Center, Aurora, Colorado, USA

³Department of Neurology, The University of Colorado Health Sciences Center, Aurora, Colorado, USA

Abstract

Background—Pleomorphic xanthoastrocytomas with anaplastic features (PXA-As) are rare tumors about which little is known regarding clinicopathological and molecular features. Several studies have identified *BRAF V600E* mutations in PXA-As, but the percentage with mutation may differ between adult and pediatric examples, and limited information exists about immunohistochemistry for IDH1 (isocitrate dehydrogenase 1). Design: 10 cases of adult PXA-As seen at our institution since 2000 were assessed for *BRAF V600E* mutation by polymerase chain reaction testing (PCR) and IDH1 by immunohistochemistry.

Results—Patients ranged in age from 18–68 years; 4 PXA-As affected temporal lobe and 2 were cystic. Four patients underwent gross total resection; and 9/10 received cranial irradiation and/or adjuvant chemotherapy. Five survived less than 5 years, although 2/5 died from non-tumor causes. Four long-term survivors are alive at 7.5, 9.8, 11.4, and 11.9 years post-diagnosis. 2 of 4 long term survivors had *BRAF V600E* mutation: patients were ages 18 and 28 years. A 48-year old male without *BRAF* mutation survives at 9.8 years, even with thalamic location; conversely a 68-year-old female with temporal lobe tumor and *BRAF* mutation survived 1.9 years after diagnosis. All tumors were IDH1 immunonegative.

Conclusion—This case series details clinicopathological features of a subset of rare PXA-As in adults. *BRAF V600E* mutation was identified in 50% of these cases.

Keywords

pleomorphic xanthoastrocytoma; PXA; anaplastic; *BRAF*; IDH1; clinical outcome

Corresponding author: B.K. Kleinschmidt-DeMasters, M.D. 12605 E. 16th Avenue, Room 3026, MS F768, Aurora, CO 80045, Phone: 720-848-4387, Fax: 720-848-4454, bk.demasters@ucdenver.edu.

Presented in abstract format at the 101st annual United States and Canadian Pathology meeting, Vancouver, B.C., March, 2012

Disclosure/Conflict of Interest: No conflicts of interest to report.

Introduction

Pleomorphic xanthoastrocytomas (PXAs) are rare WHO grade II tumors, first fully characterized by Kepes *et al.* [1], which demonstrate a relatively favorable clinical course [1-3]. PXA with anaplastic features (PXA-A) designates a subset with more aggressive histopathologic features and more adverse prognosis, and has yet to be assigned a formal WHO grade [2]. PXAs and PXA-As collectively constitute no more than 1% of astrocytic tumors and are usually seen in children and young adults [1-3], with a mean age of 26 years [3]. Nearly 2/3 of examples occur in patients less than age 25 years [3].

Adult examples are thus uncommon, although well-documented cases have been seen in patients 40 years or older [4-9]. Some authors have suggested a worse prognosis is associated with older patient age [9]. PXA-As may arise *de novo* [10, 11], or may develop anaplastic features, including necrosis and/or increased mitotic index [3] at recurrence of a previous WHO grade II PXA [3, 5, 7, 10-16]. Recent reviews, by Tekkok *et al.* [14], Okazaki *et al.* [15] and Vu *et al.* [16], emphasize the fact that for either *de novo* PXA-As or for those that acquire anaplastic features at recurrence, the prognosis is often, but not invariably, poor.

Which histological feature(s) correlates best with prognosis in individual patients remains somewhat unclear. A seminal study of 71 cases and review of an additional 121 published cases of PXA by Giannini *et al.* in 1999 [3], lead the World Health Organization (WHO) in 2007 to adopt her findings that mitotic activity of greater than or equal to 5 mitoses per 10 high power fields (HPFs) is the sole independent predictor of overall survival by multivariate analysis [2]. A “significant association of necrosis with survival” was also acknowledged, although this did not reach statistical significance on multivariate analysis [2]. On univariate analysis, three categories of patients with differing recurrence-free survival and overall survival rates could be identified: those with 0 mitoses, those with 1-4 and those with ≥ 5 mitoses [3]. Korshunov *et al.* in their 2001 series of 34 patients [17] were more clearly able to identify three subsets of PXAs: *typical*: tumors without mitoses per 20 HPFs; *proliferating*: tumors with mitoses but without necrosis; and *malignant*: tumors with elevated mitotic index and necrotic foci. There were no recurrences or death amongst *typical* tumors. In contrast, 36% of *proliferating* tumors recurred and 1 patient died, and 5/5 *malignant* tumors rapidly recurred and 4/5 succumbed. Other authors have placed emphasis on necrosis [18, 19] and MIB-1/Ki-67 cell cycling rate [10-12].

Recently, mutation in *BRAF* V600E at position 600, specifically V600E (NM_004333.4 c. 1799T>A, hereafter referred to as *BRAF* V600E), has been identified as a common finding in certain central nervous system (CNS) tumors, most commonly in PXAs, (WHO grade II) and PXA-As. The same mutation has also been found in ganglioglioma and extra-cerebellar pilocytic astrocytoma [20-22]. Amongst CNS tumors, the presence of *BRAF* V600E may be helpful in distinguishing PXAs from diffuse astrocytic tumors WHO grades II, III, and IV [22], since the latter almost always lack this finding [20].

In contrast, a common mutation in isocitrate dehydrogenase 1 (*IDH1*) is typical of the majority of diffuse astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas of

WHO grades II and III [23]. Immunohistochemical (IHC) staining for IDH1 correlates strongly with the *IDH1* mutational status as assessed by polymerase chain reaction testing [24] and thus can serve as a cost- and time-effective substitute.

Relatively few examples of adult PXA-As have been studied for *BRAF* mutational status. Studies by Schindler *et al.* hint that there may be age-related differences in *BRAF* V600E mutational status, based on the fact that, in their study, 38% of adult PXA-As showed this mutation (5/13 adult cases), compared to 100% of pediatric PXA-As (10/10 pediatric cases) [20].

Finally, although IDH1 immunoreactivity appears to be a signature of diffuse astrocytomas and not PXAs, large numbers of adult PXA-A cases have also not been assessed [23]. We undertook this study of PXA-As to address these issues. We confined our work to a series of adult patients well-known within our system for which treatment data and long term clinical followup could be obtained.

Materials and Methods

Case accrual

Institutional research review board approval was obtained for this study. Cases were identified by diagnosis from our pathology department databank and/or personal files of the authors for the years 2000-2011, inclusive. Medical records were reviewed by the neuro-oncologist (DMD) to obtain neuroimaging features, treatment regimens, and survival data. Followup data was sought for all patients, and patients recorded as alive or dead. Those who died were recorded as succumbing either to disease (ie., their PXA-A) or from other causes. For those patients still living, survival data was calculated from time of PXA-A diagnosis to 3/2012, the closure of study.

All slides were re-reviewed for diagnosis confirmation (BKD). For diagnosis of PXA-A, criteria identified by Giannini *et al.* [2, 3] were utilized. All cases in this study contained the major histological findings previously identified as essential to diagnosis, including multinucleated pleomorphic large cells (seen in 92% of PXA cases in her study [3]), GFAP immunoreactivity (98% of cases), granular bodies (93%: eosinophilic 81%/pale 71%), lymphocytic collections (83% of cases), foci of increased reticulin (81%), and xanthic cells (66% of cases). Most cases were quite stereotypic and similar in features. All cases had pleomorphic cells and GFAP immunoreactivity. Granular bodies, especially eosinophilic, refractile, droplet-like, eosinophilic, PAS-positive (Periodic acid Schiff-positive) granular bodies were specifically sought and tabulated (see Table). As noted by Giannini *et al.*, “although it was not stressed in the original description of PXA or in the WHO monograph, granular bodies of varying size, texture, and eosinophilia are a regular feature of this tumor” [3]. In our own experience, the presence of granular bodies has been the single most distinctive and helpful clue since they are usually not identified in glioblastomas (lipidized, giant cell or ordinary), the main tumor type in the differential diagnosis for PXA-A.

Methods for histology

For light microscopy, tumor sections were cut at 4 microns and stained with hematoxylin and eosin (H&E), reticulin (Gordon Sweet reticulum II), and periodic acid Schiff in selected cases where eosinophilic granular bodies were rare on H&E. Immunohistochemistry for glial fibrillary acidic protein (GFAP, Dako #M761, Carpinteria, CA, monoclonal, 1:100 dilution) and synaptophysin (Ventana 790-4286, Tucson, AZ, rabbit monoclonal, Pre Dilute) was additionally utilized for diagnosis.

Immunohistochemistry for IDH1 (Dianova HistoBio, Miami Beach, Florida, clone H09, monoclonal, 1:40 dilution) and MIB-1 cell cycle labeling (Ventana 790-4286, Tucson, AZ, rabbit monoclonal, Pre Dilute) was conducted on all cases. All assessments for IHC were performed on the first resection at which PXA-A diagnosis was made.

Mitotic figures were counted at high power objective (40×), with ten consecutive fields counted after identifying a mitosis. Considerable variation in mitotic rates from one region to the next was encountered in all cases, a feature previously well described by others in the literature [3, 27]. The presence or absence of eosinophilic granular bodies was assessed and recorded as present, rare, single, or absent on H&E; in select cases, on PAS, was performed. Necrosis and microvascular proliferation were also assessed and recorded, detailed in the Table. MIB-1 was assessed as percentage of immuno-positive tumor nuclei on 1000 cell counts, avoiding non-tumoral cells such as lymphocytes in the counts.

Methods for V600E *BRAF* mutational analyses

Blocks (or in one case unstained slides with scrape of tissue) with PXA morphology were specifically targeted for assessment. In the case of the scraped slides, paraffin sections were thoroughly deparaffinized in xylene, hydrated through graded alcohols to water and stained with Gill's hematoxylin. Slides were covered with glycerol to prevent cell dispersion and isolated under dissecting microscope using a scalpel point or hollow borosilicate glass pipette. The scraped material was washed in PBS and digested in proteinase K overnight at 37°C in ATL Buffer (Qiagen Inc.). DNA was then isolated using QIAamp DNA FFPE extraction kit (cat # 56404) according to manufacturer instruction.

In the case of paraffin tissue blocks (remaining cases), paraffin scrolls were deparaffinized in xylene as above, followed by reconstitution in graded alcohols and PBS and treated in parallel fashion. DNA yields were then quantified using a Nanodrop spectrophotometer ND-1000 (Thermo Fisher Scientific Inc., Waltham, MA).

For direct sequencing, approximately 10 ng of template DNA was PCR amplified using 5 pmol each of forward (5'TGCTTGCTCTGATAGGAAAAT3') and reverse (5'TCAGGGCCAAAATTAAATCA3') *BRAF* exon 15 primers KAPA2G™ Robust HotStart Enzyme and PCR master mix with KAPA™ dNTP mix (KAPA Biosystems cat# KK5525 and KK1017) in a 25µl reaction. PCR was performed on an ABI 9700 thermocycler with an initial denaturing step at 95°C, followed by 20 cycles of touchdown PCR (starting annealing temperature of 65°C, decremented 0.5°C per cycle) and 25 cycles at 94°C denaturation, 55°C annealing and 72°C extension finished by a 10 minute 72°C final extension. The resultant PCR products were purified with the QIAquick 96 well PCR

cleanup kit (Qiagen cat# 28106). The purified PCR products were sequenced in forward and reverse directions using an ABI 3730 automated sequencer that utilizes BigDye Terminator Version 1.1 (Applied Biosystems). Each chromatogram was visually inspected for any abnormalities, using NM_004333.4 as a reference sequence, with particular attention directed to codon 600. Sequences were also evaluated using Mutation Surveyor software (Soft Genetics, State College, PA). Mutations were determined to be present when peaks reached a threshold value above baseline calculated from background level, combined with visual inspection of the chromatogram.

Results

Demographic, clinical, treatment, and survival data is listed in Table 1, with histological and genetic features detailed in Table 2. Ten patients were identified (5 females, 5 males). Patients ranged in age from 18-68 years; 4 PXA-As affected temporal lobe and 2 tumors were cystic. Patients had been treated as high grade gliomas with surgery, external beam irradiation, and chemotherapy, except for one patient who refused treatment beyond subtotal resection (patient #7, see Table 1), and another who could not tolerate a full course of radiotherapy (patient #9). Data was not available for 2 cases (see Table 1). Most patients receiving chemotherapy had been treated with standard temozolomide and 4 had undergone a second surgical resection after the PXA-A diagnosis (see Table). One patient had a past medical history of neurofibromatosis type I (patient #1), one had colon cancer (patient #2), and one had a previous diagnosis of a high grade glioma antecedent to their PXA-A diagnosis at our institution (patient #8). Patient #8 had been diagnosed with anaplastic astrocytoma 3 years before. Slides from this surgical procedure performed at an outside facility were not available for review. The remaining 9 patients with PXA-As occurred *de novo*.

Tumors predominantly affected frontal or temporal lobes (see Table 1), with a single case involving subcortical gray matter (patient # 6). The range of neuroimaging features is illustrated in Figure 1. Since a significant number of our cases had first been diagnosed with PXA-As in the early 2000's, 4/5 of the survivors have been followed for >7 years (range: 7 years, 5 months to 11 years, 9 months). The final patient was diagnosed more recently and, as of the study closure time point of 3/2012, had a clinical followup time of 7 months (see Table 1). Of the 5 survivors known to be alive at study closure, mean clinical followup time has been 8 years, 5 months, with a median of 9 years, 8 months. Nine of the 10 patients in this cohort were able to followed to demise or to study closure date; the 10th patient (patient #8) was lost to followup two years after diagnosis.

Microscopically, the majority of cases showed classic PXA areas adjacent to higher-grade glioma showing variable mitotic activity, necroses, some microvascular proliferation (see Table 2). In 7 cases the two areas were relative distinct. In 3 examples (patients #2, 4, 7), however, there was a more intimate blend between the neoplastic pleomorphic cells with xanthic or granular cell changes and smaller cells manifesting ordinary high grade glial tumor features. In some cases the higher-grade glioma manifested small cell glioblastoma features (examples: patients #1, #3, #10), a feature described years ago [25, 26]. In these instances the areas of high-grade glioma were completely indistinguishable from ordinary

high-grade gliomas. This raised the obvious issue of whether sampling errors might have contributed to the diagnosis of a diffuse high grade glioma in patient #8. The areas of PXA-A contained large pleomorphic giant cells with nuclear pseudoinclusions, GFAP immunoreactivity, glassy eosinophilic pale bodies, and variable numbers of EGBs (eosinophilic granular bodies, highly refractile eosinophilic droplet-like structures) (see pictures). Several cases had rare or single EGBs (patients #2, #5, #6) and one of these (patient #5) did manifest positive *BRAF V600E* mutational status. Conversely, some cases (example, patient #1) had profuse numbers of EGBs, yet lacked the *BRAF V600E* mutation. Thus, morphological features of the PXA-As were indistinguishable based on *BRAF* mutational status, at least in our small case series. The histological features seen in these rare adult PXA-As are illustrated in Figures 2 and 3. The PXA features of two representative patients, one with, and one without, *BRAF* mutation, are shown in Figure 2. Histological features for high grade glioma areas of these tumors are shown in Figure 3.

Four patients were known to have recurrences of their tumors within the study time period (see Table 1, patients #1, 4, 5, and 6). MIB-1 indices of the PXA-As at the time of the initial resections, for these patients with known recurrences were not obviously higher than for those without known recurrences. These four patients had MIB-1 rates, respectively, of 9%, 8.5%, 9% and 8.5% (Table 2). In contrast, patient #7 had an initial MIB-1 rate of 5.5% and died of his disease within 1.7 years of initial diagnosis. Small cohort size precluded any definitive conclusions about MIB-1 rate and tendency for recurrence or overall survival.

Five patients who succumbed survived less than 5 years, although 2 of these 5 died from non-tumor causes (see Table 1). Long term survivors are alive at 7-11+ years post-diagnosis. Of these long term survivors, 2 of 4 had *BRAF V600E* mutation in the tumor: these two patients were ages 18 and 28 years. Another young patient, 22 years old, did possess the *BRAF V600E* mutation, and succumbed to his disease 1.7 years after diagnosis; he received only subtotal resection and was the single patient who had refused postoperative chemo- or radiotherapy.

In our series, 3 of 4 patients over age 45 years were *BRAF* negative: a 68-year-old did show *BRAF* mutation; her survival after diagnosis was 1.9 years. A 48-year-old male without *BRAF* mutation survives at 9.8 years, even with thalamic location. The small sample size limits any meaningful correlation between *BRAF* mutational status and survival.

Discussion

We have been interested in PXA-As since 2001 when we encountered a particularly tragic case where his treatment, not tumor, led to his demise [27]. This 34-year-old man developed a radiation-induced CNS sarcoma 11 years after receiving cranial irradiation (but no chemotherapy) for a “glioblastoma” diagnosed at an outside facility [29]. On obtaining his original 1990 slides, the tumor, in retrospect, proved to be a PXA-A with copious numbers of eosinophilic granular bodies, focal lymphocytic collections, xanthic cells, Rosenthal fibers, and elongate spindle tumor cells, all features of PXA, but with superimposed necrosis, microvascular proliferation, and mitoses, features of PXA-A. He succumbed less than one year later to his radiation-induced sarcoma, despite several therapies. Clearly in this

example, the risks of overly aggressive treatment were obvious. Giannini *et al.* also mention a patient with a high mitotic index but no necrosis at first surgery who died 5.7 years after primary surgery from a contralateral postirradiation anaplastic oligodendroglioma [3]. On the other hand, the single patient in our current study in who only a subtotal resection could be achieved and who declined any adjuvant treatment, succumbed after 1.7 years, suggesting that adjuvant radio/chemotherapy may have therapeutic benefit. At our institution, additional therapy has always been recommended, and almost always received.

Our study was confined to PXA-As in adults, which make up a smaller subset of an already-rare glioma tumor type [3], explaining the limited case numbers in our study. Most of our cases were *de novo* PXA-As. PXA-A may occur *de novo* with anaplastic features at first resection or may evolve from PXA grade II to PXA-A, but both have variable, but often poor, outcomes [3, 14-16]. One of our cases had been biopsied elsewhere and diagnosed as anaplastic astrocytoma; sampling error cannot be excluded since the high grade glioma portion of PXA-As is usually indistinguishable from ordinary diffuse high grade glioma, a point made many years ago by Kepes *et al.* [25] and Macaulay *et al.* [26].

All of our cases met criteria for PXA-A based on either mitotic rate >5/10 HPFs or presence of necrosis, and most examples had both (see Table). In addition, we conducted MIB-1 immunostaining on all cases. The likely importance of MIB-1 cell cycle labeling was anticipated by others in smaller series [10-12] and indeed, rates above 5.5% were found in all adult PXA-A cases in this series. MIB-1 may assist in distinguishing PXA-A versus PXA, WHO grade II, given the wide variation in distribution of mitotic figures in these cases, as noted previously [3, 28]. In addition, it should be noted that some patients have manifested adverse clinical outcome [10] even when fewer than the 5 mitoses/10 HPFs (recommended as a criteria for PXA-A diagnosis [2, 3]) have been identified; these did, however, have modestly elevated MIB-1 rates of 4.9% and 5.4% [10].

While our oldest patient, a 68-year-old woman, succumbed within 2 years of diagnosis, our next-oldest patient has survived for more than 9 years. Thus, we cannot reach the same conclusion as Ng *et al.*, that advanced patient age is automatically a negative prognostic factor in adult PXA-As [9].

Similar to previous research [20-22], *BRAF* V600E mutation was not seen in 100% of our adult PXA-As. In our study, 50% (5/10) PXA-As demonstrated the mutation. Schindler *et al.* investigated a large number of PXAs (64: 38 adult/26 pediatric) and PXA-As (23: 13 adult/10 pediatric) and found the mutation in 66% of PXAs overall (63% adult, 69% pediatric) and 65% of PXA-As (38% adult, 100% pediatric) [20]. In contrast, Dias-Santagata *et al.* found the mutation in 60% of WHO grade II PXAs, but only in 1 of 6 PXA-As [22]. Differences may relate to the fact that only 6 PXA-As were available for analyses in the latter study [22]. Alternatively, the fact that all 6 were adults, as opposed to pediatric patients, and 5/6 were 40 years of age or older, including a 62.1-year-old female and an 86.8-year-old male, may also have influenced results [22]. Thus, there may be some differences for *BRAF* V600E mutation status in adult versus pediatric PXA-As. Although limited by the small number of cases, the current study contributes additional data to the issue of percentage of adult PXA-As with this mutation.

Thus, up to one-third of PXAs and PXA-As appear to be negative for *BRAF* V600E mutation and it is currently unclear if one, or more, as-yet-undiscovered genomic alterations might be present in this subpopulation without *BRAF* V600E mutation. Dougherty *et al.* noted that negative PXAs and PXA-As did not show *KIAA1549-BRAF* fusions [21]. At least in our study, we do not feel that regional heterogeneity accounts for the presence or absence of *BRAF* V600E mutation in our patients, since, in each case, the tissue block with the best morphological features of PXA was selected for mutational analysis and each block was confirmed to have the minimum tumor cellularity to have confidence in the sequencing assay. Whether there is heterogeneity at the single cell level cannot be discerned with this sequencing technique.

Finally, our study of PXA-As contributes to the literature on IDH1 status in these rare tumors. All of our cases were IDH1 negative by immunohistochemistry. Balss *et al.* assessed a total of 685 brain tumors, 7 of which were PXAs WHO grade II and all seven are negative for IDH1 mutation [23]. We now add to the literature 10 PXA-As, all in adults that are also negative for IDH1.

Acknowledgments

The authors thank Mrs. Diane Hutchinson and Ms. Diana Doyle for excellent manuscript preparation and Ms. Lisa Litzenberger for expert photographic assistance

References

1. Kepes JJ, Rubinstein LJ, Eng LF. Pleomorphic xanthoastrocytoma: a distinctive meningocerebral glioma of young subjects with relatively favorable prognosis. A study of 12 cases. *Cancer*. 1979; 44:1839–1852. [PubMed: 498051]
2. Giannini, C.; Paulus, W.; Louis, DN.; Liberski, P. Pleomorphic xanthoastrocytoma. In: Louis, DN.; Ohgaki, H.; Wiestler, OD.; Cavenee, WK., editors. *WHO Classification of Tumours of the Central Nervous System*. 3rd. IARC; Lyon: 2007. p. 22–24.
3. Giannini C, Scheithauer BW, Burger PC, Brat DJ, Wollan PC, Lach B, O'Neill BP. Pleomorphic Xanthoastrocytoma. *Cancer*. 1999; 85:2033–2045. [PubMed: 10223246]
4. MacKenzie JM. Pleomorphic xanthoastrocytoma in a 62-year-old male. *Neuropathol Appl Neurobiol*. 1987; 13:481–487. [PubMed: 3447073]
5. Marton E, Feletti A, Orvieto E, Longatti P. Malignant progression in pleomorphic xanthoastrocytoma: personal experience and review of the literature. *J Neurol Sci*. 2007; 252:144–153. [PubMed: 17189643]
6. Kros JM, Vecht CJ, Stefanko SZ. The pleomorphic xanthoastrocytoma and its differential diagnosis: A study of five cases. *Hum Pathol*. 1991; 22:1128–1135. [PubMed: 1743696]
7. Chakrabarty A, Mitchell P, Bridges LR, Franks AJ. Malignant transformation in pleomorphic xanthoastrocytoma--a report of two cases. *Br J Neurosurg*. 1999; 13:516–519. [PubMed: 10627788]
8. Fu YJ, Miyahara H, Uzuka T, et al. Intraventricular pleomorphic xanthoastrocytoma with anaplastic features. *Neuropathol*. 2010; 30:443–448.
9. Ng WH, Lim T, Yeo TT. Pleomorphic xanthoastrocytoma in elderly patients may portend a poor prognosis. *J Clin Neurosci*. 2008; 15:476–478. [PubMed: 18255294]
10. Prayson RA, Morris HH 3rd. Anaplastic pleomorphic xanthoastrocytoma. *Arch Pathol Lab Med*. 1998; 122:1082–1086. [PubMed: 9870856]
11. Hirose T, Ishizawa K, Sugiyama K, Kageji T, Ueki K, Kannuki S. Pleomorphic xanthoastrocytoma: a comparative pathological study between conventional and anaplastic types. *Histopathology*. 2008; 52:183–193. [PubMed: 18184267]

12. Sugita Y, Shigemori M, Okamoto K, Morimatsu M, Arakawa M, Nakayama K. Clinicopathological study of pleomorphic xanthoastrocytoma: correlation between histological features and prognosis. *Pathol Int.* 2000; 50:703–708. [PubMed: 11012983]
13. Tan TC, Ho LC, Yu CP, Cheung FC. Pleomorphic xanthoastrocytoma: report of two cases and review of the prognostic factors. *J Clin Neurosci.* 2004; 11:203–207. [PubMed: 14732386]
14. Tekkök IH, Sav A. Anaplastic pleomorphic xanthoastrocytomas. Review of the literature with reference to malignancy potential. *Pediatr Neurosurg.* 2004; 40:171–181. [PubMed: 15608490]
15. Okazaki T, Kageji T, Matsuzaki K, et al. Primary anaplastic pleomorphic xanthoastrocytoma with widespread neuroaxis dissemination at diagnosis--a pediatric case report and review of the literature. *J Neurooncol.* 2009; 94:431–437. [PubMed: 19326050]
16. Vu TM, Liubinas SV, Gonzales M, Drummond KJ. Malignant potential of pleomorphic xanthoastrocytoma. *J Clin Neurosci.* 2012; 19:12–20. [PubMed: 22137880]
17. Korshunov A, Golanov A. Pleomorphic xanthoastrocytomas: immunohistochemistry, grading and clinico-pathologic correlations. An analysis of 34 cases from a single Institute. *J Neurooncol.* 2001; 52:63–72. [PubMed: 11451204]
18. Pahapill PA, Ramsay DA, Del Maestro R. Pleomorphic xanthoastrocytoma: case report and analysis of the literature concerning the efficacy of resection and the significance of necrosis. *Neurosurgery.* 1996; 38:822–829. [PubMed: 8692406]
19. Bayindir C, Balak N, Karasu A, Kasaroglu D. Anaplastic pleomorphic xanthoastrocytoma. *Child's Nerv Syst.* 1997; 13:50–56. [PubMed: 9083703]
20. Schindler G, Capper D, Meyer J, et al. Analysis of BRAF V600E mutation in 1,320 nervous system tumors reveals high mutation frequencies in pleomorphic xanthoastrocytoma, ganglioglioma and extra-cerebellar pilocytic astrocytoma. *Acta Neuropathol.* 2011; 121:397–405. [PubMed: 21274720]
21. Dougherty MJ, Santi M, Brose MS, et al. Activating mutations in BRAF characterize a spectrum of pediatric low-grade gliomas. *Neuro-Oncology.* 2010; 12(7):621–630. [PubMed: 20156809]
22. Dias-Santagata D, Lam Q, Vernovsky K, et al. BRAF V600E mutations are common in pleomorphic xanthoastrocytoma: diagnostic and therapeutic implications. *PLoS One.* 2011; 6:e17948. [PubMed: 21479234]
23. Balss J, Meyer J, Mueller W, et al. Analysis of the *IDH1* codon 132 mutation in brain tumors. *Acta Neuropathol.* 2008; 116:597–602. [PubMed: 18985363]
24. Capper D, Weissert S, Balss J, et al. Characterization of R132H mutation-specific IDH1 antibody binding in brain tumors. *Brain Pathol.* 2010; 20:245–254. [PubMed: 19903171]
25. Kepes JJ, Rubinstein LJ, Ansbacher L, Schreiber DJ. Histopathological features of recurrent pleomorphic xanthoastrocytomas: further corroboration of the glial nature of this neoplasm. A study of 3 cases. *Acta Neuropathol.* 1989; 78:585–593. [PubMed: 2816300]
26. Macaulay RJ, Jay V, Hoffman HJ, Becker LE. Increased mitotic activity as a negative prognostic indicator in pleomorphic xanthoastrocytoma. Case report. *J Neurosurg.* 1993; 79:761–768. [PubMed: 8410257]
27. Kleinschmidt-DeMasters BK, Kang JS, Lillehei KO. The burden of radiation-induced central nervous system tumors: a single institution's experience. *J Neuropathol Exp Neurol.* 2006; 65(3): 204–216. [PubMed: 16651882]

Figure 1.

A: Axial T1 post-contrast MRI shows a heterogeneously enhancing cystic mass in the right thalamus with mass effect but minimal surrounding vasogenic edema. Patient #6 illustrated.

B. Axial T1 post-contrast MRI shows an enhancing mural nodule in the left lateral temporal cortex associated with a large rim-enhancing cyst. Patient #9 illustrated.

C. Axial T1 post-contrast MRI shows an inhomogeneously enhancing lesion in the mesial left temporal lobe. Patient #4 illustrated.

D. Axial T1 post-contrast MRI shows a large heterogeneously enhancing lesion with complex cystic component within the right temporal lobe. Note the paucity of mass effect and the relative absence of vasogenic edema. Patient #2 illustrated.

Figure 2.

Direct comparison between PXA areas in Patient #1 (a, c, e, g) (a 27-year old female with relatively separate classic PXA and high grade glioma areas of tumor in whom no BRAF mutation was detected yet is a 10+ year survivor) versus Patient #3 (b, d, f, h) (a 68 year-old female also with relatively separate classic PXA and high grade glioma areas in whom BRAF mutation was detected yet survived less than 2 years). Note typical features of PXA including brisk non neoplastic lymphocytic collections (a, b), large pleomorphic cells (b inset, c), focally increased reticulin fibers (d), eosinophilic granular bodies (arrows, e, f) and negative immunostaining for IDH1 (g, h). Hematoxylin and eosin (a 100×, b 400×, b inset 600×, c 600×, e 600×, f 600×), reticulin stain (d 200×), and immunostaining for IDH1 with light hematoxylin counterstain (g, h, both 400×).

Figure 3.

Direct comparison between high grade glioma areas in Patient #1 (a, c, e, g) (a 27-year old female with relatively separate classic PXA and high grade glioma areas of tumor in whom no BRAF mutation was detected yet is a 10+ year survivor) versus Patient #3 (b, d, f, h) (a 68 year-old female also with relatively separate classic PXA and high grade glioma areas in whom BRAF mutation was detected yet survived less than 2 years). Note hypercellularity (a, b, c, d), necrosis (arrows, a, b), microvascular proliferation (arrows, c, d), vascular thrombosis (arrows e, f), and elevated MIB-1 cell cycling rate (g, h). Hematoxylin and eosin (a 100×, b 200×, c 400×, d 200×, e 400×, f 100×,) and immunostaining for MIB-1 with light hematoxylin counterstain (g, h both 400×).

Table 1

PXA-As: Clinical, pathologic, and survival data

#	Age	Sex	Significant Clinical History	Location	Cystic lesion	Extent of surgical resection	Initial therapy	Additional Treatment	Alive vs dead	Survival (years) calculated as of study closure
1	27	F	Neurofibromatosis, type I; mother with NF1	L frontal	N	GTR	RT TMZ	Re-resection 5 years later	Alive	11 years, 4 months
2	52	F	Colon cancer 5 years prior	L frontal	N	Unknown	Unknown	None known	Died of other causes	1 year, 1 month
3	68	F	Initially biopsied: diagnosed as PXA-A (Mayo); resection soon thereafter	R temporal	N	GTR	RT TMZ	None known	Died of disease	1 year, 9 months
4	51	M	No known relevant history	L temporal	N	Subtotal resection	RT TMZ	Re-resection at outside hospital 2 years after first surgery; pathology “identical to first resection material”	Died of other causes	1 year, 6 months
5	28	M	No known relevant history	L fronto-parietal	N	Subtotal resection	RT BCNU	SRS Re-resection 5 years after first surgery: extensive radionecrosis + some tumor	Alive	11 years, 9 months
6	48	M	No known relevant history	R thalamus	Y	Subtotal resection	RT TMZ	TMZ Re-resection 9 years after first surgery: residual tumor histologically similar to original tumor	Alive	9 years, 8 months
7	22	M	No known relevant history	R temporal	N	Subtotal resection	None	None known	Died of disease	1 year, 7 months
8	26	F	Diagnosed as anaplastic astrocytoma 3 years prior elsewhere (2003); treated with RT, re-presented after delivery of child	R frontal	N	Unknown	Unknown	None known	Lost to follow-up after 2 years	2+ years
9	18	F	No known relevant history	L temporal	Y	GTR	Gladel wafer placement Partial RT (ceased due to intolerance) TMZ	Additional TMZ	Alive	7 years, 5 months
10	38	M	History of many years migraines, recently worsened	R frontal	N	GTR	RT Avastin TMZ	None	Alive but <2 years from surgery	7 months

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Patient survival assessed as of study closure date of 3/2012

Key: GTR=gross total resection; RT=radiation therapy; SRS=stereotactic radiosurgery; TMZ=temozolomide; BCNU=carmustine, bis-chloroethylnitrosourea

Table 2

PXA-As: Histological and genetic features

#	Age	Sex	Histologic features	Mitotic count	MIB-1 rate	IDH1 by IHC	<i>BRAF</i> V600E mutation status
1	27	Female	EGBs Necrosis MVP	5/10 HPFs	1.9%	Negative	No mutation detected
2	52	Female	Rare EGBs Necrosis MVP	7/10 HPFs	23%	Negative	No mutation detected
3	68	Female	EGBs Necrosis MVP	15/10 HPFs	22%	Negative	V600E mutation present
4	51	Male	Single EGB No necrosis No MVP	6/10 HPFs	8.5%	Negative	No mutation detected
5	28	Male	Rare EGB Necrosis No MVP	9/10 HPFs	9%	Negative	V600E mutation present
6	48	Male	EGBs No necrosis Focal MVP	7/10 HPFs	8.5%	Negative	No mutation detected
7	22	Male	EGBs Focal remote Hemorrhagic necrosis No MVP	8/10 HPFs	5.5%	Negative	V600E mutation present
8	26	Female	EGBs Necrosis MVP	15/10 HPFs	16%	Negative	V600E mutation present
9	18	Female	EGBs Necrosis MVP	5/10 HPFs	5.5%	Negative	V600E mutation present
10	38	Male	EGBs Necrosis MVP	34/10 HPFs	49.5%	Negative	No mutation detected

Key: EGBs=eosinophilic granular bodies; MVP=microvascular proliferation; HPFs=high power microscopic fields; IDH-1=isocitrate dehydrogenase-1; IHC= immunohistochemistry