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Adult pilocytic astrocytomas: clinical features and molecular analysis

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Background. Adult pilocytic astrocytomas (PAs) are rare and have an aggressive clinical course compared with pediatric patients. Constitutive Ras/RAF/MAPK signaling appears to be an important oncogenic event in sporadic PA. We evaluated clinical data and molecular profiles of adult PAs at our institution.

Methods. We identified 127 adult PAs in our institutional database. Cases with available tissue were tested for BRAF-KIAA1549 fusion/duplication (B-K fusion) by fluorescence in situ hybridization and submitted for mutation profiling using the Sequenom mutation profiling panel. Subgroup analyses were performed based on clinical and molecular data.

Results. The majority of adult PAs are supratentorial. Twenty-two percent of cases had an initial pathologic diagnosis discordant with the diagnosis made at our institution. Recurrence was seen in 42% of cases, and 13% of patients died during follow-up. Adjuvant radiotherapy following surgical resection was associated with a statistically significant decrease in progression-free survival ($P = .004$). B-K fusion was identified in 20% (9 of 45) of patients but was not associated with outcome. No BRAF V600E mutations (0 of 40 tested) were found.

Conclusion. This was the largest single institution series of adult PA. A significant proportion of adult PAs follow an aggressive clinical course. Our results support a period of observation following biopsy or surgical resection. B-K fusion in adult PA does not influence outcome, and BRAF V600E mutation appears to be a very rare event. Further study of tumor biology and optimal treatment is needed, given a more aggressive clinical behavior.

Keywords: BRAF mutation, low-grade astrocytoma, pilocytic astrocytoma.

Pilocytic astrocytoma (PA) is a World Health Organization (WHO) grade I neoplasm with an expected benign course following surgical resection and a 10-year survival rate of more than 95%.[1,2] PA can localize throughout the neuraxis; sporadic PAs are typically located in the cerebellum, while PAs associated with neurofibromatosis type I are typically located in the optic pathways. PA is more common in pediatric patients and is the most common primary CNS neoplasm diagnosed from ages 5–14 years. The majority of PAs (69% of 4 655 PA cases) diagnosed in the United States from 2004–2008 were diagnosed at ages 19 years or younger.[3]

Constitutive activation of Ras/RAF/MAPK signaling appears to be an important oncogenic event in sporadic PAs.[4] Most frequent is the BRAF-KIAA1549 fusion/duplication (B-K fusion) due to tandem duplication of 7q34, a mutation found in more than 67% of sporadic PAs.[5–17] B-K fusion is found with even higher frequency in the brainstem, especially cerebellar PA. The BRAF V600E mutation has also been reported in a minority of sporadic, mainly extracerebellar PAs.[18]

PA is rare in adults, with the largest previous single institution series including 44 patients.[19,20] A recent population study from the SEER database found that survival in adults with PA was negatively correlated with age, extracerebellar site, and radiotherapy.[21] We hypothesized that adult PA may have a more aggressive clinical course compared with that of pediatric patients and that differences may exist in the genetic profile of adult PA that may correlate with outcome. To test this hypothesis, we performed a retrospective

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analysis of all adult PA cases with longitudinal follow-up at our institution. In cases with available tissue, we tested for B-K fusion and performed mutation profiling.

Materials and Methods

We conducted a retrospective data and tissue analysis of all adult PA patients in the MD Anderson Cancer Center institutional database from 1990–2012 under a protocol with waiver of consent approved by the institutional review board. All patients had a biopsy or surgical resection with a pathological diagnosis of PA and were diagnosed at an age of 18 years or older. Patients with a previous diagnosis of a primary brain tumor prior to age 18 years were excluded. We collected demographic, treatment, and survival data from the database. Additional clinical, neuropathologic, and neuroimaging data were obtained from the institutional electronic medical records.

Adjuvant radiotherapy (RT) was defined as RT given as part of the initial treatment following surgical resection and within 6 months of surgical resection. Extent of resection was categorized as gross total resection (GTR), subtotal resection (STR) or biopsy, as recorded in the institutional database, and was based mainly on the neurosurgeon's or neuro-oncologist's assessment and postoperative imaging when available.

Progression was determined to be the earliest date of clinical and/or radiographic worsening. Progression-free survival (PFS) was defined as the period from date of diagnosis until progression or until death (in cases where progression prior to death was not documented) and was calculated using the Kaplan–Meier method. The log-rank test was used to determine significance of differences in PFS among analyzed subgroups. Comparisons of proportions were done using the Fisher's exact test. Statistical calculations were performed using GraphPad Prism version 6.00 for Windows (GraphPad Software).

Slides from cases with available formalin-fixed, paraffin-embedded tissue were retrieved from the pathology archives and reviewed to confirm diagnosis and to choose a representative block for molecular studies. B-K fusion was tested by fluorescence in situ hybridization on 5-micron thick paraffin sections using custom-made BAC probes labeled by nick translation (Abbott Molecular) with SpectrumOrange for *BRAF* (RP11-837G3) and SpectrumGreen for *KIAA1549* (RP11-92N1). Technical validation was performed on metaphase spreads and normal tonsil specimens. A centromeric reference probe labeled with SpectrumAqua (CEP7, Abbott Molecular) was used to control for ploidy and to help determine baseline spacing of alleles. Signals were scored in at least 100 non-overlapping, intact nuclei. B-K fusion was considered present in cases with at least 10% of scored nuclei showing pairs of closely spaced signals ("doublets") for both orange and green probes (indicating duplication) as well as overlap of one signal from each "doublet," resulting in one yellow signal (indicating fusion). Tumor genomic DNA was extracted from deparaffinized tissue scrolls using magnetic beads (ChargeSwitch, Invitrogen) and submitted to mass spectrometry array mutation profiling (MassARRAY system, Sequenom) of 132 hotspot codons in 39 cancer-related genes (*AKT1, AKT2, AKT3, ALK, BCOR, BRAF, CDK4, CSMD1, CTNNB1, EGFR, EPHA3, FBXO4, FBXW7, FGFR1, FGFR2, FGFR3, FOXL2, GNA11, GNAQ, GNAS, GRM3, IDH1, IDH2, KIT, KRAS, MAP2K2, MET, MGA, NRAS, PDGFRA, PIK3CA, PPP2R1A, RAF1, RET, RPL22, SFRS9, SMO, SRC,* and *TGM2*). Sequenom testing is a recently developed technology with very high sensitivity and a specificity approaching 100%.[22] Validation of this clinical assay on 255 cancer cases at our institution yielded a 100% concordance with the Sanger sequencing approach (unpublished observation).

Table 1. Clinical characteristics of adults with pilocytic astrocytomas

Total	127
Males (%)	54 (43)
Females (%)	73 (57)
Median age (years)	29
Age 18–39, *n* (%)	95 (75)
Age 40–59, *n* (%)	29 (23)
Age 60 and over *n* (%)	3 (2)
Median follow-up	61 months
Cerebrum/lobar, *n* (%)	29 (23)
Brainstem, *n* (%)	30 (24)
Optic pathway/hypothalamus, *n* (%)	21 (17)
Ventricular, *n* (%)	17 (13)
Cerebellum, *n* (%)	17 (13)
Spinal cord, *n* (%)	13 (10)

Results

Clinical Characteristics

We identified 127 adult patients who were diagnosed with PA and had a median follow-up of 61 months (Table 1). The median age was 29 years (range, 18–72 years), and median KPS at diagnosis was 90. There were 73 females and 54 males. Race was recorded as white in 101, mixed race in 8, black in 6, Asian in 5, Hispanic in 3, and unknown in 4. Comorbidities in these patients included neurofibromatosis (NF) type 1 in 5 cases (4%), NF type 2 in 1 case, and intriguingly, a medical history of autoimmune disease in 17 cases (13%: 11 with autoimmune thyroid disease, 3 with rheumatoid arthritis, 1 each with psoriasis, idiopathic thrombocytopenic purpura, antiphospholipid antibodies, myasthenia gravis, and 2 with multiple autoimmune diseases). A history of breast cancer was seen in 2 cases and a history of skin cancer in was seen 2 cases (1 basal cell carcinoma, 1 mycosis fungoides).

There were 64 supratentorial, 50 posterior fossa, and 13 spinal cord cases (Table 1). There was a trend towards prolongation of PFS in supratentorial cases, excluding optic pathway tumors (median, 178.8 months), compared with posterior fossa and spinal cord cases (median, 79.0 and 91.0 months, respectively), although this was not statistically significant ($P = .27$, log-rank test for trend). Spinal cord PA had the highest proportion of recurrence (62%); however, this was not statistically significant compared with supratentorial (34%) and posterior fossa cases (44%) ($P = .14$, Fisher's exact test).

Neuropathologic Findings

Twenty-eight cases (22%) had outside pathology discordant with neuropathologic review at our institution. There were 12 discordant cases diagnosed initially as astrocytoma not otherwise specified or glial neoplasm without grading, 4 diagnosed as glioblastoma, 3 as anaplastic astrocytoma, 3 as diffuse grade II astrocytoma, 3 as

Table 2. Comparison of progression-free survival based on initial treatment of adult pilocytic astrocytomas

	Stable Disease	Progression	Median PFS (mo)
Overall, *n* (%)	74 (58)	53 (42)	>178.8
Biopsy, *n* (%)	16 (64)	9 (46)	>190.0
Subtotal resection, *n* (%)	32 (52)	29 (48)	>79.0*
Gross total resection, *n* (%)	26 (63)	15 (37)	>178.8
Adjuvant radiotherapy, *n* (%)	16 (39)	22 (61)	37.5
No adjuvant radiotherapy, *n* (%)	57 (70)	25 (30)	>105.5**

Note that the final 2 rows of Table 2, Adjuvant radiotherapy and No adjuvant radiotherapy, both include patients with biopsy as the initial procedure. These patients are excluded from the analysis in Table 3.
*Gross total resection versus subtotal resection; $P = .64$, Log-rank test.
**Adjuvant radiotherapy versus no adjuvant radiotherapy; $P < .02$, log-rank test.
Abbreviations: PFS, progression-free survival.

Table 3. Clinical characteristics of patients treated with surgical resection plus or minus adjuvant radiotherapy

	Resection Alone	Resection Plus Adj RT	*P* value
Total, *n*	68	28	–
Males/Females, *n*	29/39	10/18	NS
Median age (years)	29	29	–
Age 18–39, *n* (%)	52 (76)	21 (75)	–
Age 40–59, *n* (%)	16 (24)	6 (21)	–
Age 60 and over, *n* (%)	0	1 (4)	–
Median KPS	90	90	–
Discordant pathology *n* (%)	10 (15)	14 (50)	$P < .001$
B–K fusion positive, *n* (% tested in sub-group)	4 (17)	5 (42)	NS*
Cerebrum/Lobar, *n* (%)	15 (22)	6 (21)	NS
Brainstem	15 (22)	9 (32)	NS
Optic pathway/Hypothalamus	6 (9)	4 (14)	NS
Ventricular	14 (20)	1 (4)	NS**
Cerebellum	12 (18)	3 (11)	NS
Spinal cord	6 (9)	5 (18)	NS
Gross total resection	32 (47)	7 (25)	$P = .011$
Median PFS, months	>226.6	28.3	$P = .004$

There were significantly more cases with discordant initial pathology ($P < .001$, Fisher's exact test) in patients treated with adjuvant radiotherapy, and significantly more patients treated with resection alone had a gross total resection ($P = .011$, Fisher's exact test). Those cases treated with resection alone had a significantly prolonged progression-free survival compared with those treated with adjuvant radiotherapy ($P = .004$, log-rank test).
*Four of 28 tumors (17%) tested had B-K fusion in the resection-alone subgroup, and 5 of 12 tumors (42%) tested in the resection plus adjuvant radiotherapy subgroup had B-K fusion ($P = .10$, Fisher's exact test).
**Trend towards more ventricular tumors in cases treated with resection alone ($P < .06$, Fisher's exact test).

ependymoma, 2 as nondiagnostic, and 1 as ganglioglioma. There were 3 PAs with anaplasia and 1 pilomyxoid astrocytoma. Two cases were associated with malignant degeneration at recurrence (1 glioblastoma, 1 anaplastic ganglioglioma) and 1 case had both a cerebellar PA and a right parietal glioblastoma.

Treatment Characteristics and Outcome

Treatment characteristics of patients are shown in Table 2. Fifty-three (42%) patients had tumor recurrence after initial treatment at a median of 15.5 months from diagnosis. Ninety-nine (78%) patients were stable at a median 72 months of follow-up. Thirty-two of the 53 patients (60%) with tumor recurrence were stable at last follow-up. Seventeen (13%) patient deaths occurred at a median of 31 months from diagnosis (range, 2–178 months). The cause of death was the brain tumor in 13 patients, unknown in 3, and infectious complication in one.

Thirty-eight of 95 patients aged 18–39 years had progression events and had a median PFS of >178.8 months. In patients aged 40 years and over, 15 progression events occurred in 32 patients, and the median PFS was >79.0 months; the difference of PFS in these 2 subgroups was not statistically significant ($P < .22$, log-rank test). Two of 3 (67%) patients aged 60 years and over had progression events.

The PFS was prolonged in patients treated with GTR (>178.8 months) versus STR (>79.0 months), although this result was not statistically significant ($P = .68$, log-rank test, Table 3). Of the 62 patients who received RT, 38 were treated in the adjuvant setting and 17 at tumor recurrence (unknown RT setting in 2 patients, and adjuvant RT given to 5 patients >6 months after initial surgery. Adjuvant RT consisted of external beam RT in 25 cases (median dose, range 5040–7400 Gy), proton RT (5040–5400 Gy) in 4 cases, stereotactic radiosurgery or Cyberknife RT in 5 cases (of whom 2 received external beam and stereotactic RT at an unknown dose), concurrent chemoradiotherapy with temozolomide in 3 cases, and craniospinal RT in setting of disseminated disease (unknown dose) in 2 cases; the type of RT was unknown in 6 cases. Including cases with biopsy, GTR, and STR, PFS was significantly reduced in cases treated with adjuvant RT versus those who did not receive adjuvant RT ($P < .02$, 37.5 vs >105.5 months, log-rank test).

The reasons for choosing radiation therapy were mostly related to the initial histologic diagnosis: 15 of the 45 patients treated with adjuvant RT had discordant outside pathology compared with interpretation at our institution. Ten were treated based on diagnoses of a grade II to IV diffuse glioma, 3 based on a diagnosis of ependymoma, and 2 with astrocytoma without specification of grade. One patient treated with adjuvant RT had an anaplastic PA. Both patients with malignant transformation/progression received adjuvant radiotherapy.

Excluding biopsied cases, patients treated with upfront surgical resection (GTR or STR) alone had significantly longer PFS of >226.6 months compared with a PFS of 28.3 months with upfront resection plus adjuvant radiotherapy ($P = .004$, log-rank Test). Note that 19 progression events (68%) occurred in those treated with resection and radiotherapy, while only 20 progression events (29%) occurred in the patients treated with resection alone. There were no significant differences in age, sex, median KPS, and proportion

with B-K fusion (Table 3). There were also no statistically significant differences in anatomic distribution, although there was a trend towards more ventricular tumors in the group treated with resection alone ($P < .06$, Fisher' exact test). There were significantly more GTRs than STRs in those treated with resection alone versus those treated with adjuvant RT (47% vs 25%, $P = .011$, Fisher 'exact test). Fifty percent of patients' who underwent resection plus adjuvant RT, when compared with 15% of those treated with upfront resection alone, had discordant initial pathology with a diagnosis other than PA ($P < .001$, Fisher' exact test).

Twenty-seven patients received chemotherapy: 10 in the adjuvant setting and 17 at tumor recurrence. The median number of cycles was 4 (range, 3–22) with 11 patients receiving temozolomide alone or in combination with other agents. Other regimens used in 2 or fewer patients included PCV (procarbazine, CCNU, vincristine), TPCH (6-thioguanine, procarbazine, CCNU, and hydroxyurea), and carboplatin plus etoposide. Three patients received bevacizumab in the setting of tumor recurrence; one patient received 13 cycles. Eleven of the patients treated with chemotherapy died during follow-up. Seven patients who received adjuvant chemotherapy and 5 who were treated with chemotherapy at recurrence were stable at last follow-up.

Leptomeningeal dissemination (LMD) was seen in 7 patients (median follow-up of 18.6 months) during the course of their disease. Of the 4 patients who developed LMD at recurrence, 3 died at 2.8, 11.8, and 41.3 months from initial tumor diagnosis, and 1 patient was alive with progressive disease at 18.6 months from tumor diagnosis. Three patients with LMD at diagnosis were alive and progression free at 8.3, 42.4, and 48.4 months from initial tumor diagnosis; 2 of these patients received craniospinal RT, and 1 received intrathecal topotecan.

Molecular Analysis

B-K fusion status was obtained by fluorescence in situ hybridization on 45 patients; 9 were positive (20%), including 3 supratentorial, 3 posterior fossa, and 3 spinal cord cases. Five of the 9 (56%) patients with B-K fusion progressed after initial treatment compared with 16 of 36 (44%) without the fusion ($P = .71$). To determine the presence of other molecular alterations in oncogenic genes, mutation profiling (Sequenom) was obtained on 40 patients, with 4 showing Ras mutations (3 N-Ras, 1 K-Ras) and 1 showing PIK3CA mutation. The patient with a K-Ras mutation also had B-K fusion. No BRAF V600E mutations were found. The clinical characteristics of the patients with either B-K fusion or specific mutations are shown in Supplementary Appendix 1a and b.

Discussion

The median age for diagnosis of PA in adults was ~30 years, with the majority (~70%) being between ages 18 and 39 years; PAs are exceedingly rare in adults over the age of 60 years. In our series, only 3 of 127 patients (2.4%) were aged 60 years or older, which was comparable to the data from a review of the Surveillance, Epidemiology, and End Results (SEER) cancer incidence database in which only 58 of 865 (7%) adult PA patients were aged 60 years or older.[21] There was a slight female predominance (53%) in our cohort and in other published studies. These results differ from the SEER data that showed a slight male predominance (52% vs 48%), which is similar to that seen in pediatric PA.[21]

Of particular interest, we noted that 13% of our patients had a medical history of an autoimmune disease, mainly autoimmune thyroid disease. This is in contradistinction to the known inverse association between glioma risk and inflammatory conditions, especially asthma, in epidemiologic studies.[23] However, this finding may represent a referral bias, or it may be due to the relatively small number of patients in our study. Larger population-based studies would be needed to properly evaluate an association between adult PA and inflammatory conditions.

The reported median age of occurrence of anaplastic PA in one study was 35 years, and 62.5% of patients with histogically 'aggressive' PA in another cohort were also of adult age.[24,25] These findings suggest an association between aggressive phenotype and adult age group. Consistent with this, 42% of patients in our cohort progressed after initial treatment, which has also been reported in most published adult PA studies with recurrence rates of 30% or more.[19,20,24] From a mortality perspective, a declining 60-month survival rate was seen with increasing age in adult PA patients in the SEER database.[21] There was a nonsignificant increase in PFS in patients aged 18–39 years in our study. Note that 75% of the patients in our cohort were aged 18–39 years, and only 3 patients were aged 60 years and older. Progression events occurred in 2 of 3 patients aged 60 years and older, which is in concert with the findings of the worst overall survival (OS) outcomes in this age group in the SEER study.[21] In our cohort, 13% of patients died during follow-up, an unexpectedly high mortality rate for this WHO grade I neoplasm with a 5- and 10 year survival rate of over 95% in pediatric patients.[2] A similar result was seen in the largest of previous studies, in which 18% of adult patients with PA were reported dead during follow-up; this study also noted that 14% of 44 cases had anaplastic histology.[19] However, in our large cohort of adult patients, only 3 cases had anaplastic histology, and only 2 cases underwent malignant progression; in the majority of cases, this suggests that aggressive clinical behavior cannot be predicted reliably when based on histologic features alone.

The majority of adult PAs reported in several studies[19–21,24] were supratentorial in location, in contrast to pediatric PAs, which predominantly occur in the cerebellum. We did not find a statistically significant association between anatomic location and disease progression. In our cohort, supratentorial tumors, excluding optic pathway tumors, had the lowest rate of recurrence after initial treatment and a longer PFS, but these results were not statistically significant. One prospective study of 19 adult supratentorial PAs noted recurrence in only 1 patient with a thalamic PA.[26] The assertion that supratentorial adult PAs have better survival outcomes and the clinical and molecular correlates therein require further study.

GTR was associated with improved survival outcomes in some adult PA studies,[19,21] but extent of resection did not correlate with improved outcome in others.[20,26,27] In our cohort, GTR was associated with doubling of PFS, although this result was not statistically significant. Extent of resection was not determined based on postoperative volumetric imaging, and this likely impacted our results. Interestingly, and unlike with other gliomas, patients in our cohort who underwent a biopsy also had a prolonged PFS; this result has been observed in other series of adult PA.[19,27] This could be because tumors selected for biopsy are biologically different from those chosen for surgical resection. This may be particularly true of tumors located in the optic pathway and brainstem,

which are more likely to be biopsied, if surgical intervention is pursued at all.

A period of observation following a surgical procedure is warranted in most adult PA patients, given the unclear benefit of adjuvant RT. The importance of expert neuropathologic review cannot be overstated, given that 22% of cases overall and 33% of those treated with adjuvant RT had an initial pathologic diagnosis other than PA; this may have contributed to the decision to use adjuvant RT in some cases. In our study, patients treated with RT and the subgroup of patients treated with surgical resection plus adjuvant RT had significantly reduced PFS compared with patients who were not irradiated. This is in contrast to previous studies in adult PA patients, who showed no difference in survival in patients treated with or without RT.[20,26,27] However, in the SEER study,[21] RT was one of 3 factors, including age and noncerebellar tumor site, that was associated with increased mortality in adult PA. We did find that significantly more cases treated with resection alone had a GTR; this suggests that selection bias may have contributed to the patients selected for adjuvant radiotherapy. These results may be explained by the possibility that RT may adversely influence tumor biology and clinical outcome. In a study of anaplastic PA, a history of nonanaplastic PA and prior irradiation was associated with reduced PFS and OS, after adjusting for age and tumor site.[25] In a literature review by Parsa et al, malignant transformation was not noted to occur spontaneously in PA but was only reported in previously irradiated tumors.[28] In a series of 20 adult PA patients, the 3 cases treated with adjuvant radiotherapy underwent malignant transformation.[29] In our study, both patients who had tumors with malignant transformation received RT prior to malignant transformation. However, the number of patients with these outcomes was too small to arrive at definitive conclusions. Our results may also have been influenced by an inherent selection bias or effects from other unaccounted factors in this retrospective study.

Hence, understanding the effect of RT on PA biology requires further systematic study. Radiographic changes due to RT or pseudoprogression, as seen in glioblastomas following chemoradiation, could also account for some of the cases of presumed progression. Rates of pseudoprogression in PAs are unknown, which makes it difficult to account for this phenomenon.

Due to the retrospective design of our study with nonuniform RT regimens, these results are not sufficient to discount the benefit of adjuvant RT in a subset of PA patients.

Systemic chemotherapeutic agents including temozolomide and platinum-based regimens have been used to defer radiation and as salvage agents in pediatric and adolescent PA patients.[30–32] This study does not provide further insight into the effectiveness or optimal chemotherapy regimen in adults given the small number of patients treated, the various regimens used, and the varied timing of treatment (adjuvant vs recurrence). Adjuvant and salvage chemotherapy in adult PA needs to be prospectively evaluated.

The outcomes for LMD appear to be significantly better in PA compared with other primary glial neoplasms.[33] A recent report noted stable disease at 24 months in 5 of 6 pediatric PA patients with LMD treated with CSI.[34] A literature review including 58 PAs with LMD reported a median OS of 65 months, although no statistically significant difference was noted in patients with LMD at diagnosis (vs at recurrence) or in patients treated with CSI.[33] In our series, 3 patients were diagnosed with LMD at diagnosis, 2 were treated with CSI and were stable at last follow-up. 4 patients had LMD at tumor recurrence with death occurring in 3 of 4 cases.

Only 20% of 45 cases tested in our study had B-K fusion, which is present in 60% or more of sporadic pediatric PAs.[35] In a previous study of 37 adult patients (aged 21 years and older), Hasselblatt et al reported that 24% of cases were positive for B-K fusion; a declining frequency was seen with increasing age when broken down by age group.[16] Hawkins et al. showed that B-K fusion was associated with an improved prognosis in a 'clinically relevant' subgroup of pediatric PA patients with subtotally resected noncerebellar gliomas that included PAs and diffuse astrocytomas.[9] As in other series reported to date,[10,12,15,36,37] we were not able to show any difference in prognosis in patients with or without B-K fusion.

BRAF V600E mutations have been reported in adult PA patients,[18,38] but the frequency may be below that seen in pediatric patients. One study identified BRAF V600E mutation in 9% of 97 PAs overall and 20% of extracerebellar PAs.[18] However, none of the 40 patients included in our molecular analysis had BRAF V600E mutations. The low frequency of the BRAF V600E mutation in adult PA and the overall better prognosis of this tumor type make it challenging to assess the effects of targeted agents, such as vemurafenib in patients whose tumors harbor these mutations. The effects of such therapy may be best studied in such tumors in the setting of tumor recurrence or aggressive clinical growth. We found 3 Ras and 1 PIK3CA mutation, which may represent other actionable mutations important in a small subset of patients.

The B-K fusion and IDH1 or IDH2 mutations were suggested as markers to differentiate pilocytic from diffuse astrocytomas in a study comparing mainly supratentorial diffuse astrocytomas with posterior fossa PAs, where these biomarkers are enriched.[11] Diagnostic markers would be ideal in brainstem and spinal cord cases, given the limited amount of tissue available from biopsy specimens and the overlapping distribution of these tumors in these anatomic locations. Given the very low overall reported rate of B-K fusion in diffuse astrocytoma (~2%),[7–13] the presence of this marker is particularly helpful as a diagnostic tool for PA, although its absence does not rule out the diagnosis. IDH1 mutations, on the other hand, are rare in posterior fossa and spinal cord diffuse grade II and III diffuse gliomas,[39] and therefore the absence of this marker is not likely to be diagnostically useful in these locations. When considering that some PAs may have an oligodendroglial morphology, it is worth noting that a subset of oligodendrogliomas may have both IDH1 mutations and B-K fusion.[14]

This study has several weaknesses: the principal limitation is its retrospective design, which has inherent bias and lack of uniformity of the patient population. In addition, the data are derived from a single US cancer center population, and as such these results may not be generalizable. Treatment was not uniform across cases, and factors not captured in a retrospective study may have impacted treatment decisions and survival outcomes in our subgroup analyses. Due to the prolonged survival with this tumor type, OS could not be determined. Further, PFS may not be a good surrogate endpoint for OS in adult PA. The PFS outcomes in our study must be interpreted with caution as a limited number of progression events occurred overall and in the analyzed subgroups. Only a subset of patients had tissue available for testing of B-K fusion and mutation profiling, thus the proportions of patients with B-K fusion or the mutations tested may not be reflective of the larger population of adult PA patients. Since our Sequenom panel includes known

mutations in only 39 cancer-related genes, a broader, genomic approach will be necessary to better characterize the molecular drivers specific to adult PA.

Conclusions

This is the largest, single institution series of adult PA reported to date. PAs in adults are predominantly extracerebellar, with the largest proportion located supratentorially. We observed an association with autoimmune disease, an observation at odds with prior data in diffuse glioma. Similar to previous studies, adult PA patients follow a more aggressive clinical course compared with pediatric patients. Our results support a period of observation following biopsy or surgical resection. The decision to use adjuvant radiotherapy following surgical resection should be considered carefully and in a multidisciplinary setting whenever possible, given the decreased PFS observed in this study and the association with decreased OS in the SEER population. Neuropathology review is essential to ensure an accurate diagnosis and informed treatment planning. B-K fusion was present in ~20% of adult PAs, whereas BRAF V600E mutation appears to be a very rare molecular event. We also found a small number of potentially actionable mutations such as Ras and PIK3CA. Further study of the tumor biology of adult PA is needed, particularly given a more aggressive than expected clinical behavior observed across studies. Due to the rarity of this tumor, prospective, multicenter efforts will be needed to address the gaps in our understanding of both biology and the optimal treatment approach in adult PA.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology* (http://neuro-oncology.oxfordjournals.org/).

Disclaimer

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