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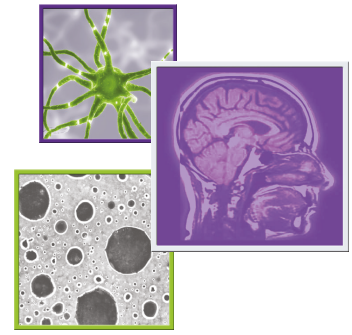

Insight about the characteristics and surgical resectability of adult pilocytic astrocytoma: tertiary center experience

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Aim: Adult pilocytic astrocytoma is a rare tumor. We aim to contribute to understanding its clinical course and prognosis. **Patients & methods:** We searched our database for patients older than 18 years with pathology-proven pilocytic astrocytoma. Patients' clinical data were analyzed. **Results:** Fifteen patients were identified. The median age at diagnosis was 25 years (range: 18–56). Tumors were supratentorial in 47%. Gross-total and near-total resections were achieved in 40%, and sub-total resection in 47%. One (7%) recurrence and no mortality were encountered during a median follow-up of 11 months (range: 1–76). **Conclusion:** Pilocytic astrocytoma behaves differently in adults compared with pediatrics. It tends to arise in surgically challenging areas where the extent of resection may be limited. Total resection should be the main therapy whenever feasible. The survival rates are good, and recurrence is low.

Plain language summary: Pilocytic astrocytoma is a benign brain tumor that most commonly arises in children. Rarely, this tumor may also arise in adults. Surgical removal of the tumor is the main treatment. In children, the tumor most commonly arises in the cerebellum, a part of the brain where surgical accessibility is good, and complete removal of the tumor significantly decreases the possibility of it recurring. In adults, the tumor is more likely to arise in critical areas of the brain or in areas of limited surgical accessibility, thus, making surgery especially challenging, and preventing complete removal. Moreover, studies found that the probability of the tumor recurring in adults is higher than in children. Studies discussing the properties of pilocytic astrocytoma in adults reported varying results. This is mainly due to the small number of patients studied. The rarity of this tumor makes it hard for large primary studies to be conducted. In this article, we report the characteristics and outcomes of 15 adult patients treated in a single center in Jordan. In our patients, the mean age was 25 years (range: 18–56), and the tumor was located above the tentorium in 47%. Complete and near-complete removal was possible in 40%. The mean duration of follow-up after surgery was 11 months (range: 1–76). The tumor recurred in only one patient. We aim to provide more data on this rare disease and contribute further to understanding its properties.

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Keywords: adult pilocytic astrocytoma • APA • grade I glioma • low-grade glioma • PCA • pilocytic astrocytoma

Pilocytic astrocytoma (PCA) is a grade I glioma according to 2016 WHO classification of brain tumors [1]. This benign brain tumor more commonly occurs in children and adolescents accounting for up to 25% of all pediatric brain tumors [2]. The incidence of PCA decreases with age; accounting for less than 2% of gliomas in adults [3]. Surgical resection of the tumor with the goal of complete removal is the main therapy in both pediatrics and adults. The prognosis in pediatrics is very good [4]. However, in adults, the tumor has different characteristics making it more aggressive [5]. Adult pilocytic astrocytoma (APA) is more likely to arise in critical locations where the extent

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of resection is limited, making complete resection more challenging [6–8]. In addition, multiple studies reported higher recurrence of the tumor in adults compared with pediatrics [9,10]. These features worsen the prognosis in adults. There have been varying reports on the tumor's features, prognosis and optimum management, mainly due to the small number of patients.

In this case series, we present the clinical characteristics of 15 patients, greater than 18 years of age, with pathology-proven PCA treated in a single institution in Jordan.

Methods

Institutional Review Board approved retrospective study done at a tertiary cancer center. We searched our database for patients older than 18 years with pathology-proven PCA. Patients with a spinal tumor, age less than 18 years old at the time of diagnosis or recurrence were excluded. Clinical data including age at diagnosis, gender, presenting symptoms, performance status score (WHO score) before and after the operation, and follow-up were analyzed. Additionally, surgical and radiological reports were analyzed to determine the degrees of resection and recurrence. Gross-total resection (GTR) was considered as no residual tumor apparent on postoperative MRI. Near-total resection (NTR) was defined as a thin amount of residual tumor less than 3 mm remaining on postoperative MRI. Sub-total resection (STR) was defined as residual tumor more than 3 mm lining the resection cavity on postoperative MRI.

Furthermore, a literature review was conducted by searching PubMed using the terms ('pilocytic astrocytoma'[Title/Abstract] AND 'adult*'[Title/Abstract]) for studies discussing PCA in adults since 2016. Five studies, excluding case reports, that reported the degrees of resection, follow-up and recurrence were chosen, and their results were summarized in Table 3.

Results

A total of fifteen adult pilocytic astrocytoma patients are included in our study. Patients were diagnosed with pilocytic astrocytoma in the period from 2006 to 2020. The patient's demographic, clinical and pathological characteristics are summarized in Tables 1 and 2. The median age at diagnosis was 25 years (range: 18–56). Males comprised 60% of the study subjects.

Tumor location differed among patients, including one left frontal (6.7%), one left temporal (6.7%), two insular (13.3%), one thalamic (6.7%), two suprasellar (13.3%), five cerebellar (33%), two brain stem (13%) and one in fourth ventricular (6.7%). Seven patients had left-sided tumors, two patients had right-sided tumors, and two patients had a midline tumor. Eight patients (53%) had infratentorial tumors, while seven patients (47%) had supratentorial tumors. One patient has neurofibromatosis.

GTR and NTR were achieved in six patients (40%), STR in seven patients (47%), and biopsy in one patient. Of the eight infratentorial tumors, GTR and NTR were achieved in three (37.5%), STR in three (37.5%), and one (12.5%) biopsy. In the seven supratentorial tumors, three (43%) had NTR, and four (57%) had STRs.

The performance status score before the operation was 0 in five patients, 1 in four patients, 2 in one patient, and 3 in two patients. After the operation, it was 0 in seven patients, 1 in one patient, 2 in one patient, and 3 in two patients.

Most patients were only observed postoperatively. One patient received adjuvant chemotherapy following STR of a suprasellar tumor. Two patients were administered adjuvant radiotherapy; one after STR of a posterior fossa tumor, and the other after STR of a suprasellar tumor. One patient received adjuvant chemo-radiotherapy after a biopsy for a cerebellar tumor. Two patients required resurgery; one after partial tumor resection in another center 5 months previously, and one for recurrence of the tumor 3 years after primary surgery (partial resection) in another center.

The follow-up period ranged between 1 and 76 months (median of 11 months). Only one patient (7%) presented with recurrence 3 years after the primary surgery (partial resection). No deaths were reported during the follow-up period.

Table 1. Data of each included subject.

No.	Age at diagnosis	Gender	Location	Laterality	Extent of resection	Preoperative performance status	Postoperative performance status	Cystic component	Resurgery	Chemotherapy	Radiotherapy	Tumor recurrence	Follow-up (months)	Neurofibromatosis	Vital status at last follow-up
1	18	Male	Cerebellar	Left	Biopsy	2	–	Yes	–	Yes	Yes	No	30	No	Alive
2	18	Male	Insular	Left	Near-total	0	0	Yes	No	No	No	No	2	No	Alive
3	20	Male	Suprasellar	Midline	Near-total	0	0	Yes	No	Yes	No	No	23	No	Alive
4	21	Male	Cerebellar	–	Sub-total	–	–	–	–	–	Yes	No	4	–	Alive
5	22	Female	4th ventricle	–	–	0	0	–	No	No	No	No	1	No	Alive
6	23	Male	Temporal	Left	Sub-total	1	1	Yes	Yes	No	No	No	76	No	Alive
7	23	Male	Insular	Left	Near-total	3	3	Yes	No	No	No	No	7	No	Alive
8	25	Female	Suprasellar	Right	Sub-total	–	–	Yes	No	No	Yes	–	–	–	–
9	28	Female	Brain stem	Left	Sub-total	1	3	Yes	No	No	No	No	11	No	Alive
10	31	Male	Frontal	Left	Sub-total	0	0	Yes	No	No	No	No	28	No	Alive
11	38	Female	Cerebellar	Left	Total	1	0	Yes	No	No	No	No	53	Yes	Alive
12	43	Female	Thalamic	Right	Sub-total	1	0	Yes	No	No	No	No	72	No	Alive
13	44	Female	Brain stem	Midline	Sub-total	3	2	Yes	No	No	No	No	11	No	Alive
14	53	Male	Cerebellar	–	Near-total	0	0	No	Yes	No	No	Yes	3	No	Alive
15	56	Male	Cerebellar	–	Total	–	–	–	–	–	–	No	13	–	Alive

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Table 2. Descriptive statistics of included patients.

Variables	Pilocytic astrocytoma patients (n = 15)
Age at diagnosis (median)	25 (range: 18–56)
Gender	
– Male	9 (60%)
– Female	6 (40%)
Location	
– Frontal	1 (6.7%)
– Temporal	1 (6.7%)
– Insular	2 (13.3%)
– Thalamic	1 (6.7%)
– Suprasellar	2 (13.3%)
– Cerebellar	5 (33%)
– Brain stem	2 (13%)
– 4th ventricle	1 (6.7%)
– Supratentorial	7 (47%)
– Infratentorial	8 (53%)
Laterality	
– Right	2 (13.3%)
– Left	7 (46.7%)
– Midline	2 (13%)
Extent of resection	
– Biopsy	1 (6.7%)
– Sub-total	7 (47%)
– Near-total	4 (27%)
– Total	2 (13.3%)
Preoperative performance status	
– 0	5 (33.3%)
– 1	4 (26.7%)
– 2	1 (6.7%)
– 3	2 (13.3%)
Postoperative performance status	
– 0	7 (46.7%)
– 1	1 (6.7%)
– 2	1 (6.7%)
– 3	2 (13.3%)
Cystic component	
– Yes	11 (73.3%)
– No	1 (6.7%)
Resurgery	
– Yes	2 (13.3%)
– No	10 (67%)
Chemotherapy	
– Yes	2 (13.3%)
– No	11 (73.3%)
Radiotherapy	
– Yes	3 (20%)
– No	11 (73%)
Tumor recurrence or progression (during follow-up)	
– Yes	1 (7%)
– No	13 (87%)

Data are presented as numbers (percentage) or mean (standard deviation).

Table 2. Descriptive statistics of included patients (cont.).

Variables	Pilocytic astrocytoma patients (n = 15)
Neurofibromatosis	
– Yes	1 (6.7%)
– No	11 (73%)
Follow-up (months)	Median: 12 (1–76)
Vital status at last follow-up	
– Alive	14 (93%)
– Dead	0

Data are presented as numbers (percentage) or mean (standard deviation).

Discussion

PCA is a WHO grade I glioma. 2016 WHO classification of tumors of the CNS described them as borderline benign/malignant entities with uncertain behavior patterns [1]. PCA comprises 5% of all gliomas [11]. They are well-circumscribed, cystic, slowly growing tumors derived from neuroepithelial tissue [12]. Histologically, they are characterized by a biphasic pattern with varying proportions of compacted bipolar cells with rosenthal fibers and loose textured multipolar cells with microcysts and granular bodies [13].

A review by Gregory *et al.* on the molecular aspects of PCA reported that *MAPK* is the most common molecular alteration in PCA. *KIAA1549-BRAF* fusion (*BK* fusions) are the most common driver mutations of *MAPK* but their prevalence decreases with age [14]. *BK* fusions have been associated with improved progression-free survival and an overall better prognosis in pediatrics [15,16]. Theeler *et al.* found *BK* fusions in 20% of APA patients. However, it was found that *BK* fusions do not influence outcomes in adults [14,17]. Other notable *MAPK*-activating mutations include *BRAF* mutations (*BRAFV600E*) found in 9.2% of APA patients and mutations in tyrosine kinase *FGFR1* found in 7–14% of APA patients [15,18,19].

PCA most commonly arises in the pediatric age group, comprising approximately 25% of pediatric brain tumors. The incidence of PCA decreases with age, comprising only 1.5% of adult brain tumors [3,4,20–22]. In a study done by Theeler *et al.*, only three (2.4%) out of 127 adult PCA cases were older than 60 years [6]. The median age in our group was 25 years (range: 18–56), including two patients older than 50 years.

PCA more frequently arises in the cerebellum and supratentorial structures. Maharaj *et al.* studied 28 pediatric patients with PCA; Tumor locations were cerebellar in 64%, hypothalamic in 18%, thalamic in 11%, corpus callosal in 4%, and the fourth ventricle in 4% [23]. Mair *et al.* studied 46 adult patients with PCA; 58.8% were supratentorial. Among the supratentorial lesions, 17.4% were in the optic nerve with hypothalamic involvement, 17.4% in the optic nerve without hypothalamic involvement, and 17.4% in the cerebral hemispheres. Infratentorial lesions were observed in 41.2% of patients; 17.6% were in the cerebellar hemispheres, 14.7% were cerebellar lesions with involvement of the brainstem, and 8.8% were lower brainstem/spinal lesions [10]. Johnson *et al.* and Theeler *et al.* reported that PCA in adults is more commonly supratentorial [6,24]. In contrast, Jungk *et al.* found equal tumor distribution among the supratentorial and infratentorial compartments (47 vs 53%) [25]. In our cohort, 47% of the tumors were supratentorial.

In both pediatrics and adults, the ideal treatment for PCA is GTR [7,26]. The degree of resection is affected by the location of the tumor. Tumors in eloquent and deeper areas of the brain such as the brainstem, diencephalon, insula, optic nerve and hypothalamus, for example, are harder to completely resect compared with tumors in the cerebellum or the cerebral convexity [18,23]. In our cohort, 53.3% of tumors were in critical areas where the extent of resection was limited, preventing complete resection. Jungk *et al.* found that GTR is more achievable in infratentorial than supratentorial tumors [25]. Johnson *et al.* reported GTR in 40% of tumors in adults and 45% of tumors in pediatrics [24]. Ryu *et al.* reported GTR in 55% of adults and 58% of pediatrics. More recent studies on adults reported GTR achievement ranging between 39 and 67% of their patients (Table 3) [7,10,25,27,28]. In our cohort, GTR and NTR were achieved in 40% of patients.

GTR was associated with greater than 95% 10-year survival in pediatrics [4,26,29]. In a study by Saunders *et al.*, the rate of recurrence after GTR in pediatrics was 10% [30]. Thus, PCA in pediatrics is regarded to have an excellent prognosis. However, in adults, the prognosis after surgery is not as good as in pediatrics [5,11,31–33]. Multiple studies on adults reported varying rates of recurrence ranging from 13 to 40%. The rate of recurrence after treatment varied depending on the type of treatment and the degree of resection (Table 3 summarizes the results of five

Table 3. A summary of the results of similar studies.

Study (year)	Number of patients	Age	Extent of resection	Adjuvant therapy	Recurrence	Follow-up	Survival	Ref.
Mair *et al.* (2020)	46 patients	Median age: 32.5 years (19–75)	GTR: 56.3%	Not administered	19.60%	Median 53.0 months (0.5–300.1)	5-year OS: 85.3%	[10]
			STR: 3.1%		4% after total resection		5-year PFS: 70.0%	
			Extended biopsy: 15.6%		38.9% after less than total or biopsy			
			Stereotactic biopsy: 25.0%					
Nelson *et al.* (2019)	50 patients	Median age: 29 years (16–76)	GTR: 44%	After GTR: none	40%	Whole group: median 3.5 years (0–21)	5-year OS: 80%	[27]
					18% after GTR			
			STR: 40%	After STR and biopsy: 21% received radiotherapy	60% after STR	GTR group: median 4 years (0–12)		
			Biopsy: 16%		50% after biopsy			
Jungk *et al.* (2019)	58 patients	Median age: 30 years (17–66)	GTR: 67%	Radiotherapy: 7%	28%	Median 72 months (3–259)	5-year PFS: 67%	[25]
			STR: 19%	Chemotherapy (TMZ): 2%	10% after complete resection			
			Biopsy: 14%	Hyperthermic treatment: 2%	63% after STR/biopsy			
Boschetti *et al.* (2020)	23 patients	Median age: 26 years (18–51)	GTR: 39%	Radiotherapy: one patient after GTR	19%	Median 88.9 months (1.9–330.4)	–	[28]
			STR: 22%	Chemotherapy: one patient after biopsy	9% after GTR			
			Biopsy: 26%		9% after STR			
Bond *et al.* (2018), institutional series	46 patients	Mean age: 33.6 ±13.3 years (range 18–76)	GTR: 52%	Radiotherapy: three patients after biopsy	13%	Median 73 months (1–204)	95% alive at last follow-up	[7]
			STR: 24%		9% after STR			
			NTR: 9%		4% after biopsy + radiotherapy			
			Biopsy: 9%					
			Biopsy + radiotherapy: 6%					
Bond *et al.* (2018), meta-analysis	254	–	GTR: 51%	–	31%	Weighted mean follow-up of 77.7 ± 49.6 months (31–250)	OS: 85% alive at last follow-up	[7]
			STR: 49%		28% after GTR			
					72% after STR			

GTR: Gross-total resection; NTR: Near-total resection; OS: Overall survival; PFS: Progression-free survival; STR: Sub-total resection; TMZ: Temozolomide.

recent studies). In a meta-analysis by Bond *et al.*, 254 adult patients who had undergone GTR were followed for an average of 77 months had a 28% rate of recurrence [7]. In a study by Jungk *et al.* on 58 patients, the rate of recurrence was 10% after complete resection, and 63% in patients who had incomplete resection or biopsy [25]. Mair *et al.* reported 4% recurrence with complete resection and 38.9% with incomplete resection [10]. In a Brazilian study including 23 patients, the rate of recurrence was the same after GTR and STR (9%). Interestingly, a study by Parsons *et al.* including 3380 adult patients found no difference in overall survival after GTR or STR [34]. In our group, two patients were reoperated on in our center after being treated elsewhere: one after partial resection 5 months prior, and the other for recurrence 3 years after partial resection.

While some studies on adult patients reported high recurrence rates and mortality, other studies described favorable prognosis and recurrence but still not as favorable as in pediatrics [32,35–38]. A recent meta-analysis of seven case series including 254 patients confirmed that GTR is a positive prognostic factor in adult PCA just like in pediatric PCA. However, the same study also reported a mean recurrence rate as high as 31% in adult PCA [7].

Further discussion arises on how patients with incompletely resected tumors should be further managed; whether by observation, radiotherapy and/or chemotherapy [34,39,40]. Here again has different studies yielded varying results [6,18,32,38,40,41]. Targeted therapy against *MAPK* pathway is a developing area of research expected to play a major role in the treatment of gliomas. A review by Gregory *et al.* discussed the advancements in targeted therapy against *MAPK* pathway as a treatment for APA [18].

Despite the variations in the characteristics of APA between different studies, the tendency of APA to arise in surgically challenging locations and its higher recurrence rates suggest that PCA in adults is more aggressive than in pediatrics. Further studies with a larger number of patients are required to better understand the nature of the tumor in adults. However, the rarity of adult PCA makes this difficult.

The limitations of our study are the retrospective nature of data collection, the small number of patients and patients being lost to follow-up.

Conclusion

In this case series, we presented 15 patients, greater than 18 years of age, with pathology-proven PCA treated in a single institution in Jordan. In the literature, APA is reported to behave more aggressively, with higher recurrence rates, when compared with PCA in pediatrics. In our group, tumor location was infratentorial in 53% of patients. Thirty-three percent of the tumors were cerebellar. 53.3% arose in eloquent or deeper locations where surgical respectability was restricted. Forty-seven percent of tumors were subtotally resected. Total resection and near-total could only be achieved in 40% of tumors. Only one patient suffered a recurrence. No patients died during follow-up. We aim to provide more data on this rare disease and contribute further to understanding its prognostic properties.

Summary points

- Pilocytic astrocytoma (PCA) is a tumor that most commonly occurs in pediatrics with an excellent prognosis after surgical resection.
- The incidence of PCA decreases with age, comprising less than 2% of adult brain tumors. The rarity of PCA in adults has made it hard for large primary studies to be conducted.
- Pediatric PCA is more commonly infratentorial than supratentorial with the majority being cerebellar.
- Adult pilocytic astrocytoma is more likely to arise in supratentorial locations and in areas that are more surgically challenging, such as suprasellar or insular, than in pediatrics. Therefore, achieving gross-total resection in adults is more challenging.
- Surgical treatment with the aim of total resection of the tumor is the main therapy. Recurrence rates are inversely related to the degree of resection.
- The need for adjuvant chemo or radiotherapy is still debatable in adult pilocytic astrocytoma.
- Multiple studies have reported increased rates of recurrence of the tumor in adults compared with pediatrics.
- The propensity to arise in sensitive locations and the higher rate of recurrence indicate that PCA is more aggressive in adults.

Author contributions

BA Muhsen contributed to the conception and design of the work, data collection, analysis and interpretation, in addition to revising and final approval of the manuscript. AI Aljariri contributed to the design of the work, drafting, writing and reviewing the manuscript. M Elayyan contributed to acquisition of the data and reviewing the manuscript. H Hirbawi contributed to writing and reviewing the manuscript. MA Masri contributed to acquisition of the data and reviewing the manuscript.

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

Written informed consent was obtained from the patients for publication of this paper.

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