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A Recurrent Pleomorphic Xanthoastrocytoma in the Cerebellum in a Young Adult: A Case Report and Review of the Literature

Ruba Aljendi[a] Mohammed Amr Knifaty[b] Mohammed Amin[b] Souliman Diab[b] Muhammad Saleh Ali[c] Zuheir Alshehabi[d]

[a]Faculty of Medicine, Cancer Research Center, Tishreen University, Lattakia, Syria; [b]Tishreen University Hospital, Cancer Research Center, Tishreen University, Lattakia, Syria; [c]Department of Neurosurgery, Tishreen University, Lattakia, Syria; [d]Department of Pathology, Cancer Research Center, Tishreen University, Lattakia, Syria

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Pleomorphic xanthastrocytoma · Cerebellum · Infratentorium · Astrocytoma · Gliomas

Abstract
Pleomorphic xanthoastrocytoma (PXA) is a rare glioma. It accounts for less than 1% of all astrocytomas. About 98% of PXAs originate supratentorially with the temporal lobe being the most common location. Cases of infratentorial PXAs are rarely reported in the medical literature. The tumor presents with a wide variation of symptoms based on the neuroanatomy involved with the location and size of the tumor, with seizures being the most reported symptom. The diagnosis depends on histological and clinical features along with radiologic features. We searched the keywords "Pleomorphic xanthastrocytoma, PXA, cerebellum, infratentorium, astrocytoma, gliomas" in the PubMed database; from 1979 to the current date, 28 cases were found in the medical literature featuring PXA in the infratentorium. We present the 29th case in the literature and the first in Syria. Our patient had a lesion in the right cerebellum and presented with a history of intermittent headache for 5 months followed by progressive gait disturbances and blurry vision and was misdiagnosed at the time of presentation with a high-grade glioma which is a common confusion because of the histological and clinical similarities. The patient underwent a suboccipital craniotomy, and adjuvant therapy with a combination of radiotherapy and chemotherapy with temozolomide was initiated at first. Then, the patient presented with a relapse of symptoms and went through another surgery where frozen sections suggested the diagnosis of PXA; further histopathological and immunohistochemical studies confirmed the

Correspondence to:
Souliman Diab, soulimandiab@gmail.com

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diagnosis. Alongside highlighting the diagnostic challenge of this rare tumor, we did a brief review of the literature.

Introduction

Pleomorphic xanthoastrocytoma (PXA) is a glioma that mainly affects young adults. It was first classified in the 1993 World Health Organization (WHO) classification of tumors of the central nervous system [1]. It was first described by Kepes et al. [2] in 1979 as a low-grade glial tumor. It presents as solid, cystic, or mixed lesions, and arises supratentorially most commonly in the temporal lobe. PXAs are extremely rare; they represent less than 1% of all astrocytomas [3]. Symptoms depend on the neuroanatomy involved with the tumor location. Notably, seizures are the most frequent symptom [4]. We present a very rare case of PXA in the cerebellum as we reviewed the literature of PXAs and found that this is the 29th case of infratentorial PXA. Our 32-year-old patient was misdiagnosed at the time of presentation with a high-grade glioma which is a common confusion because of the histological and clinical similarities. In this paper, we aim to emphasize the possibility of encountering this rare tumor in such an uncommon location. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000529741).

Case Presentation

A 32-year-old male presented with a history of intermittent headache for 5 months followed by progressive gait disturbances and blurry vision. His medical and family history was insignificant. His physical examination showed ataxia and cerebellar signs including dysmetria and dysdiadochokinesia in the right upper and lower limbs. Decreased visual acuity was noted in both eyes with bilateral papilledema on ophthalmologic exam. The rest of the examination was otherwise normal. Brain MRI revealed a lesion in the right cerebellar hemisphere. The patient underwent a suboccipital craniotomy. During the procedure, frozen sections were misinterpreted as high-grade malignant glioma. The neurosurgeon decided to proceed with subtotal resection because the risks of gross total resection (GTR) outweighed the benefits considering the aggressive nature of the suspected tumor. Adjuvant therapy with a combination of radiotherapy and chemotherapy with temozolomide was initiated. Two years after surgery, the patient complained of reemergence of symptoms including gait disturbance and morning headaches suggestive of increased intracranial pressure. Brain MRI showed a 4.4 × 4.0 cm ill-defined lesion in the right cerebellum with a mixed cystic-solid pattern (shown in Fig. 1). Cystic components of the tumor were hypointense on T1- and hyperintense on T2-weighted images, whereas the solid components of the tumor were hypointense or isointense on T1- and slightly hyperintense on T2-weighted images. Gadolinium-enhanced T1-weighted images showed marked enhancement of the cystic walls. The unusual clinical course and radiologic features raised suspicion for a more benign tumor than high-grade glioma. The patient underwent another surgery to alleviate the symptoms and reassess the residual lesion. During this surgery, the frozen sections suggested the diagnosis of PXA; therefore, the neurosurgeon conducted GTR. The histopathological and the immunohistochemical studies confirmed the diagnosis of PXA and eliminated the initial

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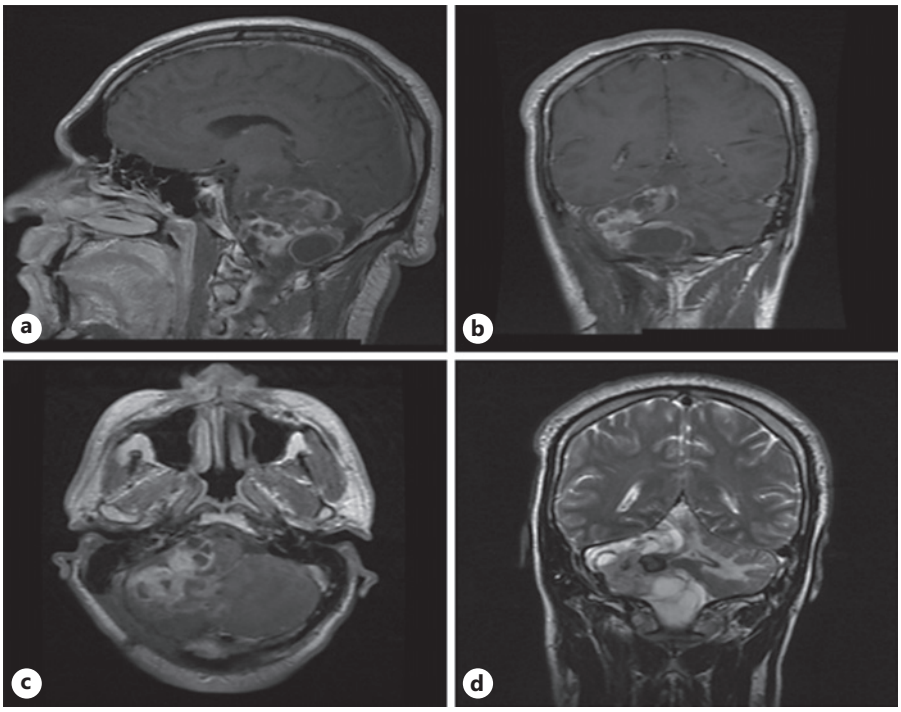

Fig. 1. Mixed cystic-solid pattern of PXA. MR images show multiple cystic lesions and solid masses located in the right cerebellar hemisphere. **a** Sagittal view T1-weighted with contrast. **b** Coronal view T1-weighted with contrast. **c** Axial view T2-weighted with contrast. **d** Coronal view FSE T2-weighted.

diagnosis as high-grade glioma is not consistent with the histopathological studies' findings. The postoperative follow-up was without complications. The patient was closely monitored thereafter.

Pathological Findings

The patient underwent surgical resection of the tumor. Microscopical studies were obtained and confirmed that the tumor was consistent with a glial neoplasm with variable morphology. Sections revealed diffuse proliferation of variable sized glial cells, mainly astrocytes and occasional giant and bizarre forms such as multinucleation and showing round or elongated hyperchromatic nuclei, scanty or clear cytoplasm, and occasional mitotic figures and scattered foci xanthomatous cells (shown in Fig. 2). Further immunohistochemical workup demonstrated that the tumor cells showed positive reaction for glial fibrillary acidic protein whereas cytokeratin was negative. The Ki-67 index was 5%, and the final pathological diagnosis was identified as PXA (shown in Fig. 3).

Discussion

Astrocytomas are graded according to the presence of anaplastic features in low-grade (or WHO grade II) and high-grade tumors (either WHO grade III or anaplastic and WHO grade IV or glioblastoma). Grade I gliomas are well-demarcated gliomas and if completely resectable can be cured. The grade II–IV gliomas are among the so-called diffuse gliomas for which a

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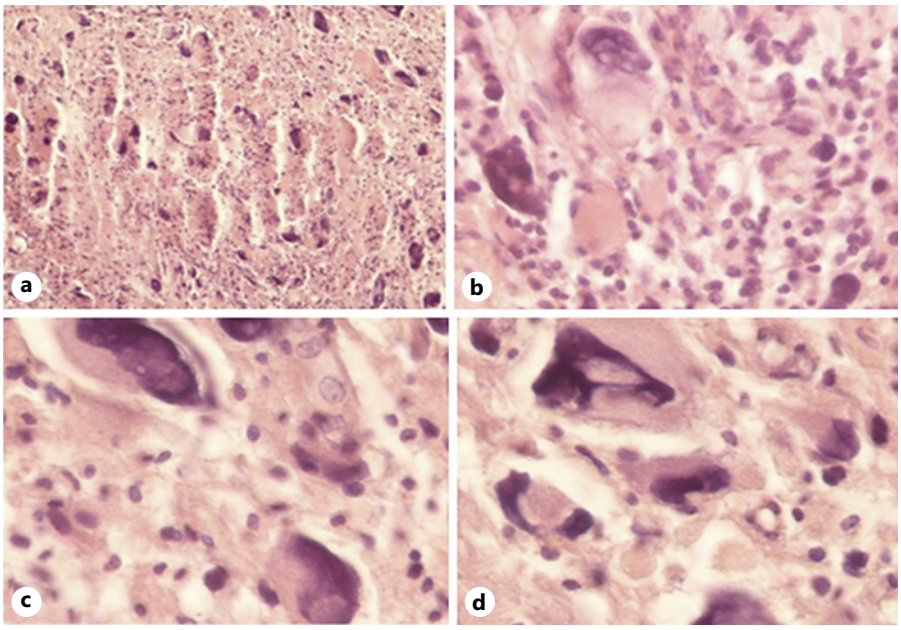

Fig. 2. Histopathological findings of resected neoplastic tissue. **a** Pleomorphic tumor cells with sheet-like growth, as well as multinucleated giant cells (H&E ×100). **b** Pleomorphic cells with atypical nuclei and eosinophilic bodies (H&E ×400). **c, d** Giant bizarre cells and visible mitoses (H&E ×600).

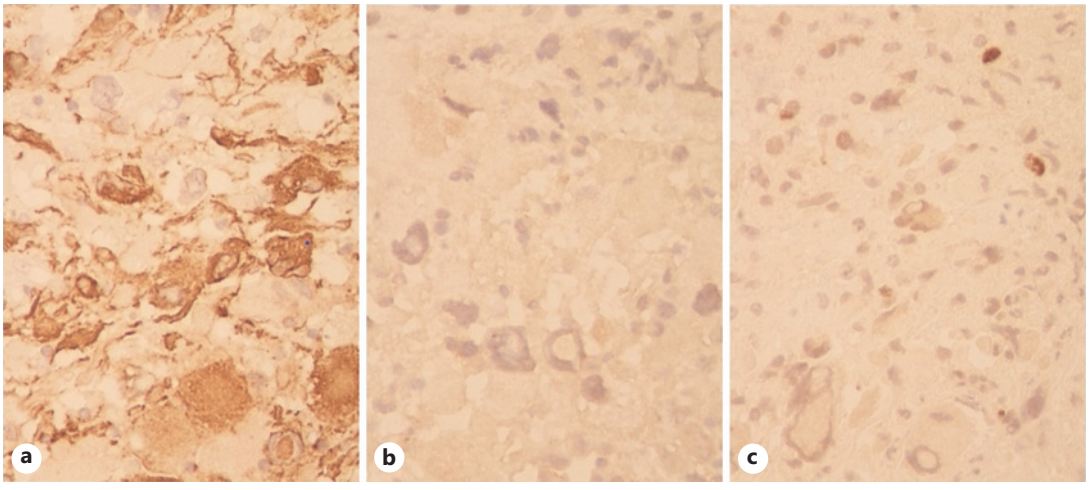

Fig. 3. Immunohistochemical studies. **a** Positive immunoexpression for glial fibrillary acidic protein (GFAP+). **b** Absence of immunoexpression in neoplastic cells for cytokeratin. **c** Low proliferative index Ki-67 of 5%.

curative treatment is not available [5]. Histologically, astrocytomas can be classified into two main groups: diffuse astrocytomas and localized astrocytomas. Diffuse astrocytomas include grade II (diffuse astrocytoma): nuclear atypia alone, grade III (anaplastic astrocytoma): nuclear atypia + focal/dispersed anaplasia, and grade IV (glioblastoma): nuclear atypia, mitoses, microvascular proliferation, or necrosis, whereas localized astrocytomas include pilocytic astrocytoma: corresponding to WHO grade I, subependymal giant cell astrocytoma:

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Table 1. Cases reported in the literature of pure PXA in the infratentorium

Author (year)	Age/sex	Imaging	Location	EOR	Recurrence
Washdal et al. (1994) [10]	48 years/F	Solid	Posterior cerebellum	Non-GTR	Yes
Glasser et al. (1995) [11]	36 years/F	Solid	Right cerebellar hemisphere	GTR	Yes
Lim et al. (1999) [12]	3 months/F	Solid	Cerebellum	Non-GTR	No
Rosemberg et al. (2000) [13]	68 years/M	Solid	Cerebellum	Non-GTR	No
Kumar et al. (2003) [14]	15 years/M	Solid and cystic	Right cerebellar hemisphere	Non-GTR	NA
Gill-Gouveia et al. (2004) [15]	51 years/M	Solid	Right cerebellopontine angle	GTR	Yes
Naidich et al. (2004) [16]	51 years/F	Solid	Vermis and both cerebellar hemispheres	GTR	No
Saikali et al. (2005) [17]	30 years/F	Solid	Right cerebellar hemisphere	GTR	Yes
Kurschel et al. (2006) [18]	6 years/F	Solid and cystic	Left cerebellopontine angle	GTR	No
Han et al. (2006) [19]	49 years/F	Solid and cystic	Midline of cerebellum	GTR	No
Chang et al. (2006) [20]	4 years/F	Cystic	Vermis	GTR	No
Hirose et al. (2008) [21]	24 years/F	Solid	Cerebellum	GTR	No
Hamlat et al. (2007) [22]	58 years/F	Cystic	Left cerebellar hemisphere	Non-GTR	No
Chapmann et al. (2009) [23]	15 years/M	Solid and cystic	Fourth ventricle and tectal region	GTR	No
Yeaney (2009) [24]	16 years/M	Solid and cystic	Cerebellum	GTR	NA
Schindler et al. (2011) [25]	NA	NA	Cerebellum	NA	NA
Gardiman (2012) [26]	14 years/F	Solid and cyst	Fourth ventricle	NA	NA
Lim (2013) [27]	35 years/F	Solid	Right cerebellar hemisphere	GTR	Yes
Moore et al. (2014) [28]	NA	NA	Brainstem, mainly pons	NA	NA
Ida et al. (2015) [29]	>18 years/NA 2 cases	NA	Infratentorial	NA	NA
Takei et al. (2015) [30]	33 years/F	Solid	Left cerebellar hemisphere	GTR	Yes
Dodgshun et al. (2016) [31]	12 years/NA	NA	Cerebellum	Non-GTR	Yes
Garces et al. (2016) [32]	30 years/M	Solid	Vermis	NA	Yes

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Table 1 (continued)

Author (year)	Age/sex	Imaging	Location	EOR	Recurrence
Huang et al. (2016) [33]	56 years/M	Solid	Fourth ventricle	Non-GTR	Yes
Gupta et al. (2018) [34]	16 years/M	Solid and cystic	Middle cerebellar peduncle	GTR	No
Kim et al. (2020) [35]	18 years/F	Solid and cystic	Left cerebellar hemisphere	GTR	No
Luna et al. (2020) [4]	28 years/F	Solid and cystic	Left cerebellar hemisphere	GTR	No
Mathkour et al. (2021) [36]	30 years/M	Solid and cystic	Vermis	GTR	Yes
Present case (2021)	32 years/M	Solid and cystic	Right cerebellar hemisphere	Non-GTR	Yes

F, female; M, male; NA, not available; PXA, pleomorphic xanthoastrocytoma; EOR, extent of resection; GTR, gross total resection.

grade I, PXA: grade II, and anaplastic pleomorphic: grade III [6]. PXA is a rare, often benign tumor (mostly WHO grade II and rarely WHO grade III). It is generally prevalent in children and young adults. The most reported location is the supratentorium specifically the temporal lobe, and therefore, the most common presentation is seizures [7]. However, other locations were reported as well. These include cerebellum, spinal cord, and the retina [8]. The symptoms and presentation depend on the exact location. Although the cerebellum is the most prevalent location of presentation of central nervous system tumors in children, it is extremely rare in adults. The classification of cerebellar tumors can comprise variety of benign and malignant neoplasms. Common clinical classification of malignant tumors of the cerebellum is, respectively, medulloblastoma, epyndymoma, teratoid tumors along with many other embryonal tumors. On the benign aspect, pediatric low-grade glioma is the most common, dysplastic gangliocytoma and hemangioblastoma (commonly seen in von Hippel-Lindau disease patients). Along the other rare miscellaneous tumors, we can see dysembryoplastic neuroepithelial tumor, ganglioglioma, gangliocytoma, desmoplastic infantile astrocytoma/ganglioglioma, and cerebellar liponeurocytoma. This highlights the prominence of cerebellar tumor location variations [9]. Our patient tumor was located in the infratentorium, where only about 28 case reports were reported up to the current date. Hence, it is reported very rarely especially in this location (Table 1). The symptoms and signs of PXA are similar to any posterior fossa tumor with no unique features in terms of symptoms. The duration from onset of symptoms to the diagnosis was around 5.3 months [10]. PXA involves the infratentorium in a rare fashion; unlike the predominant cystic appearance that accounts for the majority of the supratentorial PXA cases, infratentorial PXAs have a slight tendency to form solid lesions [10]. We reviewed the 28 cases of the infratentorial PXA that appear in the literature plus our case (Table 1). There were 25 cases with identified patterns on MR imaging, 12 cases (48%) appeared as solid lesions, 10 cases (44%) appeared as solid-cystic lesions (including our case), and 2 cases appeared as cystic lesions (8%) (Table 1). Currently, there is no definite guide to treat PXAs. However, in general for all PXAs, a GTR is one of the most important factors for recurrence-free survival [7]. Upon the 29 cases of PXA in the cerebellum listed in (Table 1), 16 reported full resection of the tumor, 6 of these cases reported recurrences and 1 case did not report any

information regarding recurrences. Seven cases underwent non-GTR, 5 of them reported recurrences, and one case did not mention any information regarding the recurrences. Five cases did not include the extent of resection in their case reports. Worth noting, the role of adjuvant treatment for this tumor is not well established in the literature [11]. Khalafallah et al. [12] in their retrospective cohort showed that radiotherapy was associated with significantly increased mortality rates in post-surgical adult patients. Therefore, the use of adjuvant radiotherapy routinely is not recommended in this patent group. Regarding chemotherapy, Mallick et al. [12] in their meta-analysis study conducted on 167 patients with grade II PXA reported that the relationship between adjuvant chemotherapy and overall survival in univariate analysis was not statistically significant. This result was confirmed by Khalafallah et al. [13] in multivariate analysis. Nevertheless, many studies recently conducted have demonstrated that PXA with BRAF V600 mutations has responded to targeted chemotherapy using the BRAF inhibitors like vemurafinib or dabrafenib. However, further studies are required before the relationship between targeted chemotherapy and overall survival can be established.

Conclusion

PXA is a challenging tumor to identify largely because of its rarity and varied symptoms that often mimic those of other more common tumors, especially tumors that show marked cellular pleomorphism. The aims of this case report were to heighten disease awareness and to promote proper investigation before establishing a final diagnosis. Our case and other cases reviewed in the medical literature highlight the fact that cerebellar PXAs differ clinicopathologically from PXAs located in the cerebral hemisphere. Recognizing the possibility of encountering such a rare tumor in an uncommon location has a notable impact on the accuracy of the diagnosis.

Study Limitations

Unavailability of the patient's initial histopathological studies, the scarcity of data on this specific glioma in the literature and the unavailability of further genetic studies in our country.

Statement of Ethics

This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors declare no conflict of interest.

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Author Contributions

Ruba Aljendi, Mohammed Amr Knifaty, and Mohammed Amin contributed to the design and conception of the work, drafted the work, and approved the final version to be published. Souliman Diab contributed to the design of the work, revised it critically, and approved the final version to be published. Muhammad Saleh Ali contributed to the analysis and interpretation of data and approved the final version to be published. Zuheir Alshehabi contributed to the analysis and interpretation of data, revised the work critically, and approved the final version to be published.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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