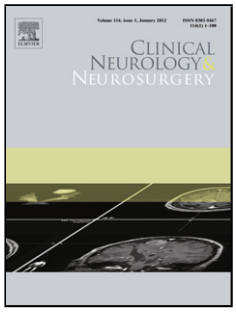

Cerebellar Pleomorphic Xanthoastrocytoma in the Setting of Neurofibromatosis Type-I:Does it Portend a Different Prognosis? A Case Report and Systematic Review

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PII: S0303-8467(20)30689-2

DOI: https://doi.org/10.1016/j.clineuro.2020.106346

Reference: CLINEU 106346

To appear in: *Clinical Neurology and Neurosurgery*

Received Date: 24 September 2020

Revised Date: 19 October 2020

Accepted Date: 27 October 2020

Please cite this article as: Mathkour M, Banerjee S, Werner C, Hanna J, Abou-Al-Shaar H, Dindial R, Scullen T, Boehm L, Tubbs RS, Ware ML, Cerebellar Pleomorphic Xanthoastrocytoma in the Setting of Neurofibromatosis Type-I:Does it Portend a Different Prognosis? A Case Report and Systematic Review, *Clinical Neurology and Neurosurgery* (2020), doi: https://doi.org/10.1016/j.clineuro.2020.106346

Cerebellar Pleomorphic Xanthoastrocytoma in the Setting of Neurofibromatosis Type-I:Does it Portend a Different Prognosis? A Case Report and Systematic Review

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Highlights

- Pleomorphic xanthoastrocytoma (PXA) is a benign tumor not typically considered a neurofibromatosis type 1 (NF-1) associated lesion.
- This case presented herein demonstrates a rare cerebellar PXA in a patient with NF-1.
- This presentation spurred a systematic review of NF-1 associated PXA, yielding 4 similar cases of cerebellar PXAs.
- The review indicated the potential of greater recurrence in cerebellar PXA as influenced by NF-1.
- Non cerebellar PXAs associated with NF-1 have been more commonly reported, demonstrating the rarity of this presentation and the recurrence potential warrants further exploration.
- Our review suggests that infratentorial PXAs have a higher recurrence and lower survival rates than non-cerebellar NF-1-associated PXAs and non-NF1 PXAs in general.
- Gross total resection remains the optimal treatment modality however the inclusion of adjuvant therapy for malignant transformations may be indicated in certain presentations.
- Interestingly, the BRAF-V600E mutation has been identified in PXAs and may assist in diagnosis; with BRAF inhibitors representing a way forward in treatment.

ABSTRACT

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

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

Method: We present a case of NF-1-associated PXA arising in the cerebellar region. We also reviewed the literature in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines to identify published cases of cerebellar vs. non-cerebellar NF-1-associated PXA and NF1 vs. non-NF1 PXAs, highlighting their management paradigm, prognosis, and outcomes.

Result: Our systematic review yielded only four previously reported cases of NF-1-associated PXAs in the cerebellar region. Our review suggests that infratentorial PXAs have a higher recurrence and lower survival rates than non-cerebellar NF-1-associated PXAs and non-NF1 PXAs in general.

Conclusion: Early and precise diagnosis is important for these lesions with the aid of imaging features, histology, immunohistochemistry, and genetic markers. Surgical resection with goal of GTR remains the mainstay management strategy for PXA, with adjuvant therapy usually reserved for anaplastic or malignant lesions. The identification of BRAF-V600E mutation and role of BRAF inhibitors hold promise as a diagnostic tool and treatment modality, respectively, for PXAs, and their relationship to NF-1 is worth further exploration.

MANUSCRIPT

Introduction

Pleomorphic xanthoastrocytoma (PXA) is a rare tumor occurring most commonly in the cerebral and cerebellar hemispheres of young adults and children.[1,2] PXA is benign tumor with a favorable prognosis, although 20% of patients experience recurrence and/or progression to high-grade gliomas, both of which are mostly correlated with incomplete surgical resection.[3]

Neurofibromatosis type 1 (NF-1) is an autosomal dominant genetic disorder with complete penetrance that involves the chromosome 17q11.2 gene locus.[4] NF-1 is associated with pilocytic astrocytoma in 2-20% of NF-1 patients.[5] PXA is not traditionally considered an NF-1-associated lesion; however, the number of reported NF-1-associated PXAs has been steadily increasing since their first description in 1993.[3,6–21] In this report, we present a rare case of NF-1-associated PXA arising in the cerebellar region. We also performed a comprehensive and systematic literature review of cerebellar vs. non-cerebellar NF-1-associated PXA, highlighting their management paradigm, prognosis, and outcomes.

Methods

We present a case of NF-1-associated PXA arising in the cerebellar region. We also reviewed the literature in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines to identify published cases of NF-1-associated PXA (Figure 1). We searched EMBASE using the terms "pleomorphic xanthoastrocytoma" and "neurofibromatosis type 1". The search yielded 33 publications. The same search on PubMed yielded 17 publications. Two additional primary sources were identified through other resources. When duplicates were removed, 39 publications remained. Abstracts were screened for case reports, specifically involving original cases of PXAs in patients with NF1. This led to the exclusion of 20 articles, and a total of 18 cases of NF-1-associated PXAs were identified and included in the final analysis (Figure 1).

Results

Case Presentation

A 30-year-old male presented to our service with a two-week history of progressive gait instability, ataxia, and lethargy. The patient's history was significant for mild developmental delay and NF-1. On physical exam, he demonstrated significant ataxia with marked disturbance of his gait and slurring of speech.

Magnetic resonance imaging (MRI) of the brain revealed a 2.5 x 1.9 x 5.6 cm expansile heterogenous cystic and solid mass centered in the region of the cerebellar vermis with local mass effect compressing on the fourth ventricle resulting in obstructive hydrocephalus of the third and lateral ventricles and mild to moderate herniation of the cerebellar tonsils (Figure 2).

A thorough discussion was conducted with the patient regarding the management options and the patient elected to proceed with surgery. The patient underwent a staged suboccipital craniotomy and C1

laminectomy utilizing the stealth navigation system (Medtronic, Inc. Minneapolis, MN) for posterior fossa decompression and tumor resection. Intraoperative visualization of the cerebellum revealed bulging cerebellar hemispheres secondary to the mass effect; these were retracted to allow access to the vermis. The vermis was then opened to expose a firm greyish-yellow tumor. Macro- and microscopic debulking and resection of the tumor was performed. The tumor margins extended to the superior border of the brainstem, grossly displacing the cerebellar hemispheres with sparing of the fourth ventricle. The tumor was debulked and mass effect was reduced. However, residual tumor was left behind at areas adherent to vital structures to avoid injury and postoperative neurological deficits.

The patient tolerated the procedure with no complications. He was discharged to inpatient rehabilitation on postoperative day 8. Follow-up MRI revealed a residual 1.9 x 1.7 x 3.5 cm heterogeneous enhancing lesion within the region of the cerebellar vermis with continued compression of the fourth ventricle (Figure 3, A-C). Despite this residual tumor, the patient was determined not to be a candidate for radiation or chemotherapy. He was followed expectantly in clinic for six months, during which the residual tumor grew to 2.4 x 2.8 x 4.5 cm (Figure 3, D-F), which resulted in recurrence of his original symptoms. At this time, the patient returned to the operating room for a second operation, during which gross total resection was achieved, as evidenced by postoperative imaging and resolution of hydrocephalus (Figure 4, A-C and Figure 5,A). The patient tolerated the second operation well; however, his postoperative course was complicated by transient dysphasia and left lower extremity weakness, which persisted despite rehabilitation. Three years later, a recurrent tumor was found on his follow-up MRI (Figure 4, D-F), and he underwent chemotherapy with no change in tumor size. The patient was given the option of ventriculoperitoneal shunting to alleviate his hydrocephalus; however, he refused the procedure. He succumbed to his illness and, unfortunately, died three months afterwards owing to the mass effect and hydrocephalus from the recurrent tumor (Figure 5, B).

Histopathological examination of the tumor demonstrated a world health organization (WHO) grade II pleomorphic xanthoastrocytoma with solid and infiltrative components. Immunohistochemical staining revealed strong diffuse immunoreactivity for glial fibrillary acidic protein (GFAP) and S100 protein most evident in the solid areas of the tumor, corresponding to leptomeningeal infiltration. A reticulin stain highlighted a local increase in reticulin, with pericellular distribution, best seen in the areas of leptomeningeal extension. Synaptophysin and neurofilament stains were positive, although the solid portion of the tumor was largely devoid of axons. Chromogranin and IDH1 were negative, and the Ki-67 labeling index was low to moderate.

Literature review

A total of 18 cases of NF-1-associated PXAs were identified and included in the final analysis. We found four previously-reported cases of NF-1-associated PXAs of the cerebellum and 14 reported cases of non-cerebellar NF-1-associated PXAs as discussed below.

Discussion

PXA Diagnosis

PXA is a subtype of astrocytoma classified by the WHO as a grade II tumor, though a WHO grade III classification has been suggested for PXAs with anaplastic features.[22] Cerebellar PXAs are indistinguishable from other cerebellar neoplasms on imaging such as pilocytic astrocytomas, gangliogliomas, and high-grade (anaplastic) astrocytomas. Since pilocytic astrocytoma is the most commonly implicated pathology for a cerebellar tumor in NF-1, proper identification and diagnosis of cerebellar PXA is of a paramount importance. Therefore, biopsy/resection and confirmatory diagnostic testing are essential.[23]

The histological characteristics of PXAs include eosinophilic granules, xanthomatous droplets, as well as nuclear and cellular pleomorphism.[24] Because they are histologically similar to other tumors, PXAs are distinguished by immunohistochemical, structural, and genetic markers. These are especially

important given the tendency for misdiagnosis as glioblastoma multiforme (GBM). Our patient's tumor was notably heterogeneous with moderate pleomorphism in different areas of the tumor, a high degree of vascularization, and multinucleated giant cells, all of which can be seen in GBM. However, the low Ki-67 proliferation index and the absence of mitoses and necrosis favored against GBM.

Another diagnostic possibility to be considered in the differential diagnosis for such tumors is pleomorphic granular cell tumors, which are just as uncommon as PXA. Both tumors share a similarly indolent course and the basic histology of lipidized pleomorphic astrocytes.[25,26] These tumors can be differentiated from PXA by the absence of reticulin fibers and the presence of numerous mitochondria.[27] The diffuse GFAP positivity also distinguishes PXA from these pleomorphic granular cell tumors, though not perfectly, as GFAP can be weakly positive in the latter. In our case, diffuse GFAP positivity and strong reticulin staining supported the diagnosis of PXA.

In addressing the problem of optimally diagnosing PXA, a new study by Koelsche et al. identified BRAF V600E gene mutation in 70% of PXAs, which could distinguish PXA reliably from morphologically and even immunohistochemically similar lesions.[28] Additionally, the BRAF mutation has been shown to have prognostic value in PXA.[22] Mutations in BRAF and other RAS genes are rarely found in GBMs.[29] The BRAF V600E mutation is however shared by pilocytic astrocytoma, however those tumors have different morphological characteristics from PXA. Zou et al. studied the molecular profiles of 13 patients with PXAs and found that in addition to the BRAF V600E mutation, FANCA/D2/I/M, PRKDC, NOTCH2/3/4, NF1 mutations occurred frequently.[30] PTEN and EGFR, which are frequently found in GBMs, were not found in PXAs, thus providing another molecular tool for differentiating between the two similarly appearing tumors.[30] Koelsche et al. work suggests a common molecular mechanism of abnormal RAF kinase activity that could underlie both NF-1-associated PXA and NF-1 lesions in general.[3,28] However, this association is complicated by three reports of NF-1-associated PXA that tested negative for BRAF.[3,8,18] Historically, most NF-1-associated PXAs have not been tested, limiting the sample size for this observation and the generalization of their findings.

NF-1 Cerebellar PXAs

We found four previously reported cases of NF-1-associated PXAs of the cerebellum (Table 1).[3,6-8] Unsurprisingly, they share a common presentation of gait instability and headache secondary to mass effect and hydrocephalus, respectively. Three of them occurred in women aged 30, 33, and 51 years, while the last occurred in an 18-year-old male. Our patient is therefore the second male to be reported.

The oldest patient, reported by Naidich et al., had a cerebellar PXA involving the cerebellar vermis and hemispheres bilaterally. [6] Initial surgery with gross total resection (GTR) was curative with no signs of residual tumor or recurrence. The left cerebellar PXA case reported by Takei et al. in a 33-year-old woman had a course similar to our case.[3] Their patient underwent surgical resection of the tumor with GTR. However, their patient suffered recurrence at three months, which required radiation and subsequent surgical resection a year later.[3]

Similarly, our patient's cerebellar PXA recurred, and he underwent a second operation with GTR six months later. Ronen et al. reported an 18-year-old male with a right cerebellar PXA. The patient underwent partial resection of the lesion followed by adjuvant chemotherapy. The tumor recurred six months later, requiring a second round of surgery and postoperative radiotherapy. He had no recurrence two years after the second operation and radiation therapy.[8] Saikali et al. reported a PXA of the occipital lobe and cerebellum in a 30-year-old woman with NF-1. Although the occipital tumor did not recur after GTR of the lesion, the cerebellar tumor recurred three times and underwent a malignant transformation into an anaplastic oligodendroglioma that ultimately led to the patient's death.[7] That case, considered together with the tendency for recurrence demonstrated by other comparatively benign NF-1-associated PXAs of the cerebellum, may elucidate to a possibly increased neoplastic potential portended (or directly influenced) by the syndromic association with NF-1.

NF-1 Cerebellar vs Non-Cerebellar PXAs

We found 14 previously reported cases of non-cerebellar NF-1-associated PXAs (Table 2).[9-21] We identified multiple clinically relevant differences between NF1-associated cerebellar and non-cerebellar cases. Patients with non-cerebellar NF-1-associated PXAs had a median age of presentation of 25.5 (range 10-42 years), while patients with cerebellar form had a median age of presentation 36 years (range 18-51 years). Forty percent of NF-1-associated cerebellar (two out of five cases) and 64% of non-cerebellar PXAs (nine out of 14) were male. In the 2014 review of 74 patients with PXAs, Ida et al., reported an average age of presentation of 21.5 years.[22] Forty percent of NF-1-associated cerebellar (two out of five cases) and 44% of non-cerebellar PXAs (four out of nine cases) were anaplastic. Furthermore, 80% (four out of five) of cerebellar NF-1 PXAs were recurrent compared to 20% (two out of 10 with follow-up) of non-cerebellar NF-1 PXAs.[22] This rate is higher than the PXA recurrence rate of 20% in the general population.[3] A larger sample size is needed to confirm the anaplastic potential and

recurrence rates of cerebellar PXA; thus, proper identification and diagnosis of patients with NF-1-associated cerebellar PXAs is of a paramount importance.

Surgical management

Surgical resection of PXA remains the mainstay management strategy for these tumors. Gross total resection is curative for most PXAs; however, the tumor can recur, especially after incomplete resection, as in our case and many in the literature.[3,6,7,13,20] According to the recent review by Ida et al., anaplastic features and mitotic index were the most important predictors of survival in PXA, while time to gross total resection was the most important predictor of recurrence.[22]

Adjuvant therapy

Temozolomide, bevacizumab, CPT 11, and sorafenib have been reported in the adjuvant management of PXA due to their potential to inhibit PXA tumor growth regardless of the presence or absence of BRAF V600E mutation.[31] Various studies have depicted that the BRAF mutation is more common in PXAs of the temporal lobe, and contemporary reviews have shown the BRAF mutation is associated with longer progression-free survival in PXAs compare to those without BRAF mutation.[22,32] For recurrent PXAs harboring BRAF mutation, salvage therapy with BRAF inhibitor vemurafenib has achieved some success in small studies.[33] In the larger VE-BASKET study for BRAF V600 mutant gliomas, half of the PXA patients on vemurafenib experienced prolonged radiographic stabilization, which indicates a potential clinical benefit of such therapy.[34] Forthcoming work by Hofer et al. showed further promise that BRAF V600E could be a good prognostic indicator in the management of BRAF-muted PXAs.[35] Our pathology did not test for the BRAF mutation; therefore, we advocate such analysis to be performed routinely on these tumors.

Additionally, anaplastic PXAs tend to require adjuvant therapy, although no specific protocol or consensus have been established to date. Bagriack et al. reported that temozolomide is most effective for reducing the viability of anaplastic PXAs in vitro, although their sample size was small.[36] Of note, the cerebellar PXA described by Saikal et al., which underwent malignant transformation, did not respond to four cycles of Temodar. However, the great potential of these advances relies on more thorough data collection and analysis of large pool of studies.

Prognosis

Whether the association of PXA with NF-1 portends a different prognosis remains uncertain. Eighty percent of cerebellar NF-1 PXAs were recurrent compared to 20% of non-cerebellar NF-1 PXAs. This aligns with work from Kim et al., which suggests that infratentorial PXAs have a higher rate of recurrence than PXAs overall.[37] Among the 18 patients with NF-1-PXAs (15 with well-documented follow-up), six tumors were anaplastic and one underwent malignant transformation (33% of cases). NF-1-associated-PXAs therefore have worse outcomes than PXAs in other locations, in which malignant or anaplastic transformation is estimated to range from 9-20%.[38,39] Additionally, NF-1-associated PXAs have an estimated survival rate of 64% compared to 75-80% for non-cerebellar PXAs.[22] This possible increase in anaplastic potential and mortality rate in NF-1-associated PXAs makes correct identification and early diagnosis and management of these patients highly important.

Conclusion

Our systematic review yielded only four previously reported cases of NF-1-associated PXAs in the cerebellar region. PXAs present similarly to other infratentorial tumors characteristically associated with NF-1. Therefore, early and precise diagnosis is important for these lesions with the aid of imaging features, histology, immunohistochemistry, and genetic markers. However, despite these measures, definitive diagnosis of PXA remains challenging. Surgical resection with goal of GTR remains the mainstay management strategy for PXA, with adjuvant therapy usually reserved for anaplastic or malignant lesions. The identification of BRAF-V600E mutation and role of BRAF inhibitors hold promise as a diagnostic tool and treatment modality, respectively, for PXAs, and their relationship to NF-1 is worth further exploration. Our review suggests that infratentorial PXAs have a higher recurrence and lower survival rates than non-cerebellar NF-1-associated PXAs and non-NF1 PXAs in general.

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Figure legends:

Figure1: Flow chart of literature review.

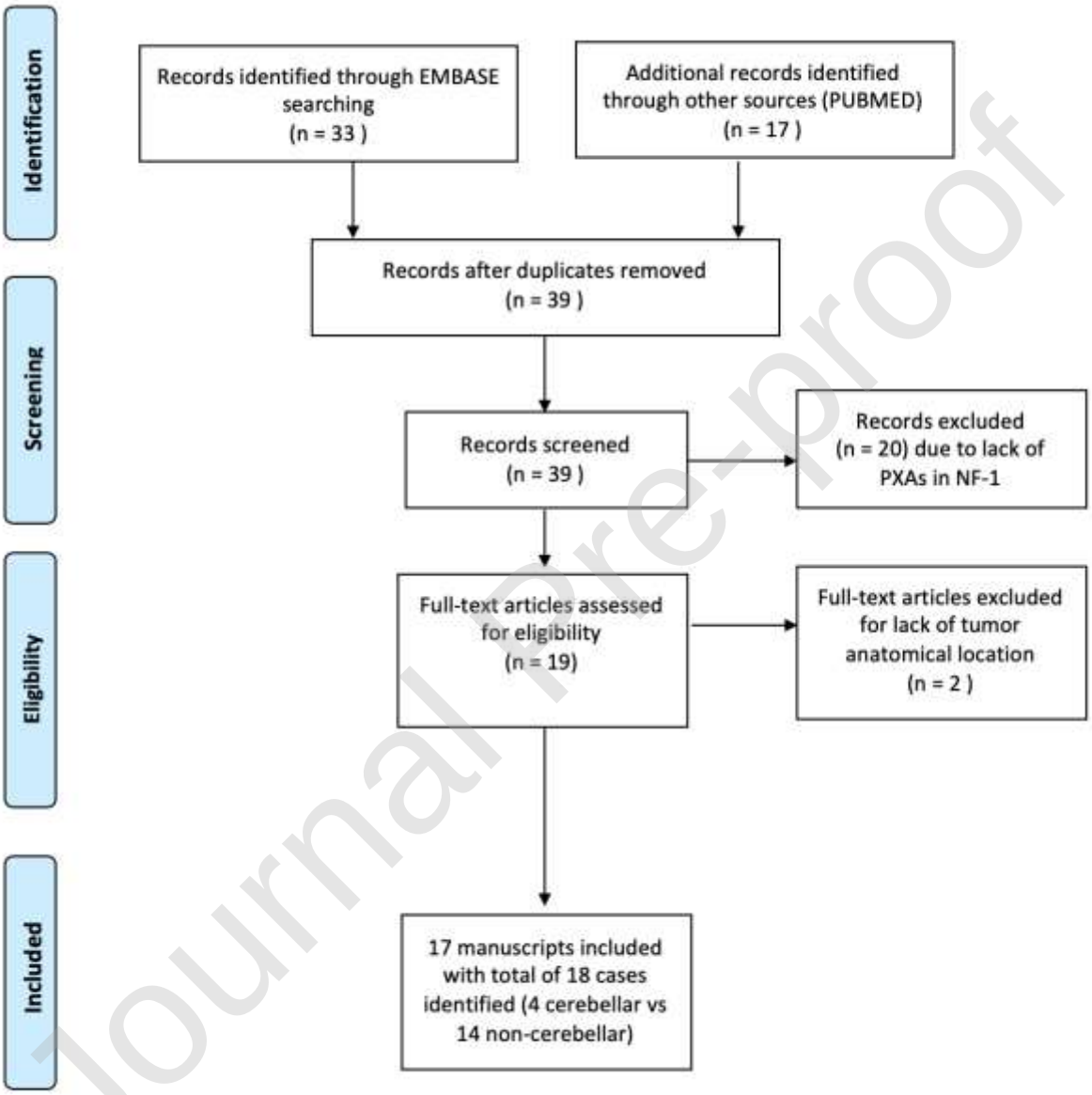

Figure 2: Preoperative magnetic resonance imaging (MRI) of the brain: axial (A) T1 weighted without contrast and axial, sagittal and coronal (B-D) T1 weighted with contrast revealed an expansile heterogeneous cystic and solid mass centered in the region of the cerebellar vermis with local mass effect resulting in obstructive hydrocephalus and mild to moderate herniation of the cerebellar tonsils

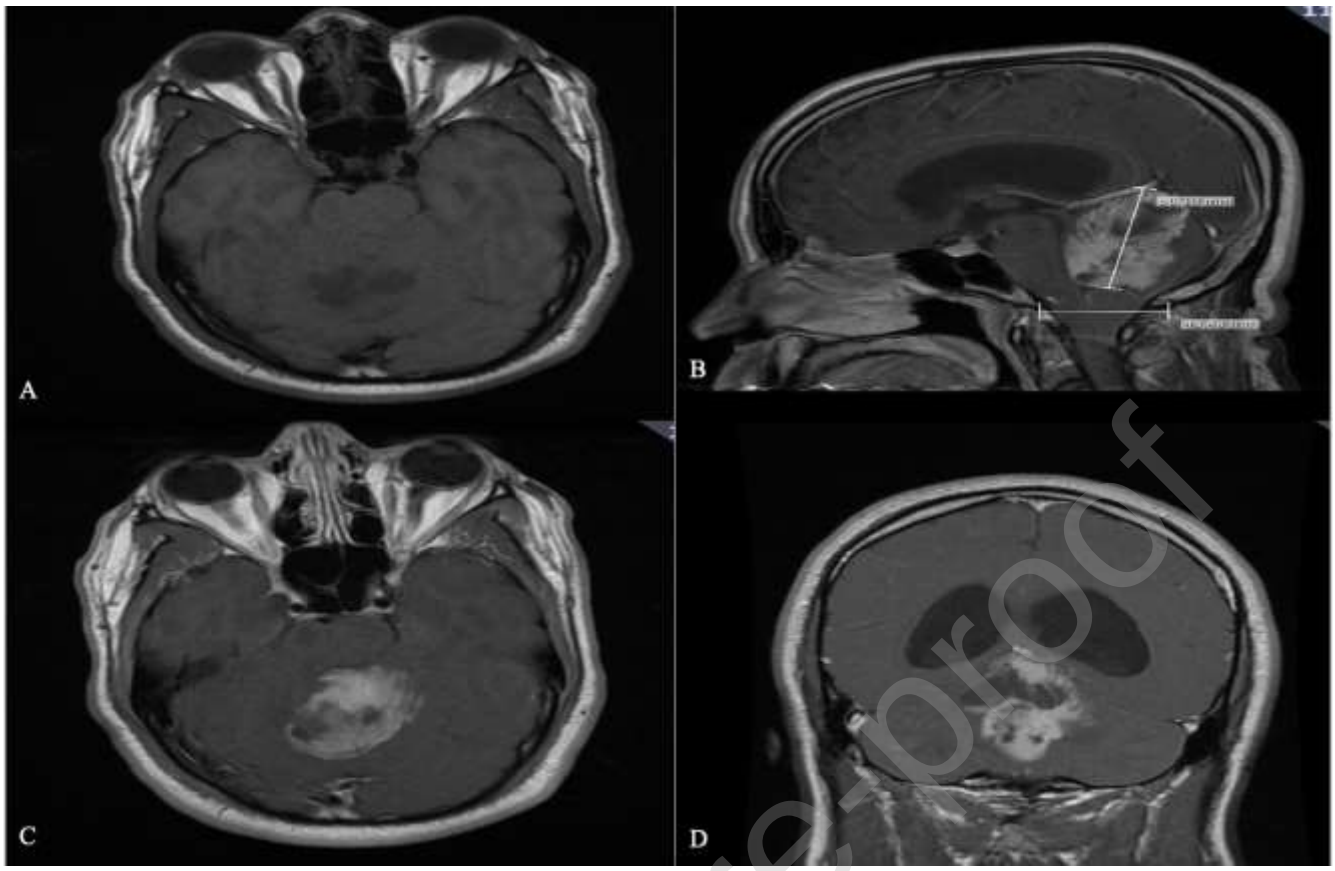

Figure 3: Postoperative follow-up MRI T1 weighted with contrast axial, sagittal and coronal views (A-C) revealed a residual heterogeneous enhancing lesion with postoperative changes. Follow up MRI T1 weighted with contrast axial, sagittal and coronal views at six months showing tumor progression (D-F).

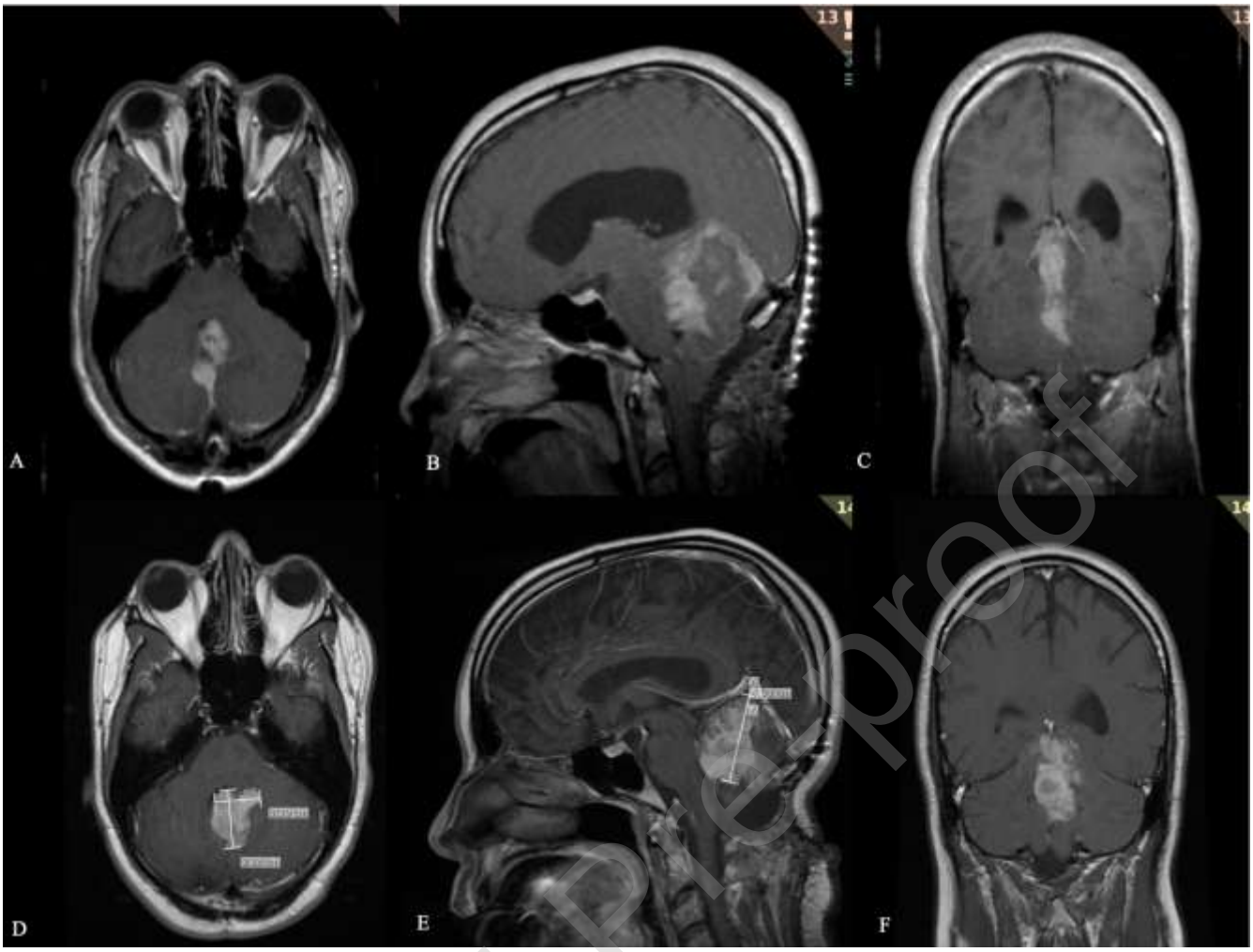

Figure 4: Postoperative MRI T1 following second operation T1 weighted with contrast axial, sagittal and coronal views (A-C) revealed complete gross total resection with resolution of hydrocephalus and postoperative changes. Repeat MRI three years later T1 weighted with contrast axial, sagittal and coronal views (D-F) showing recurrent tumor.

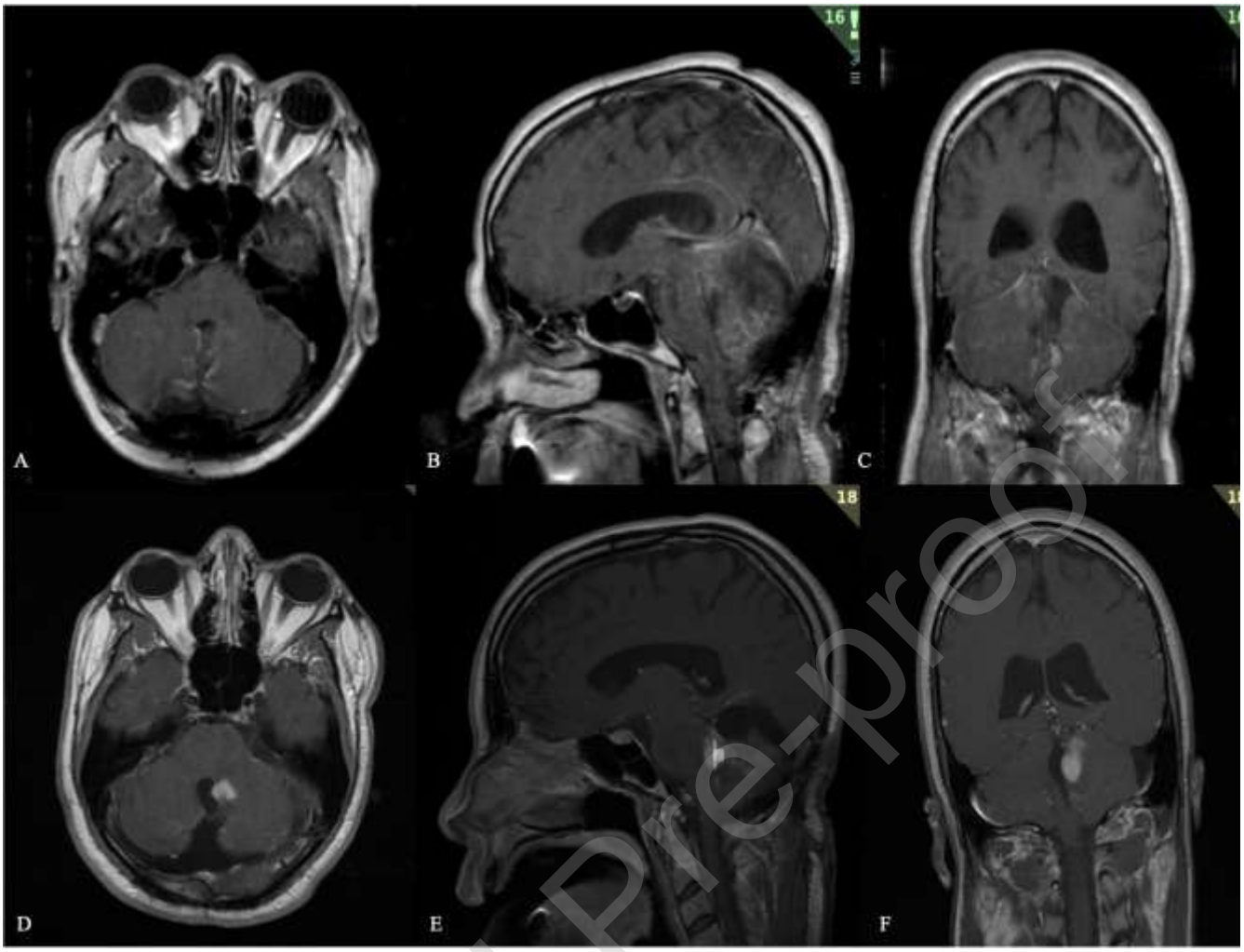

Figure 5: Postoperative computed tomography (A), following second operation with postoperative changes and resolution of hydrocephalus and (B) last follow up CT showing developing hydrocephalus.

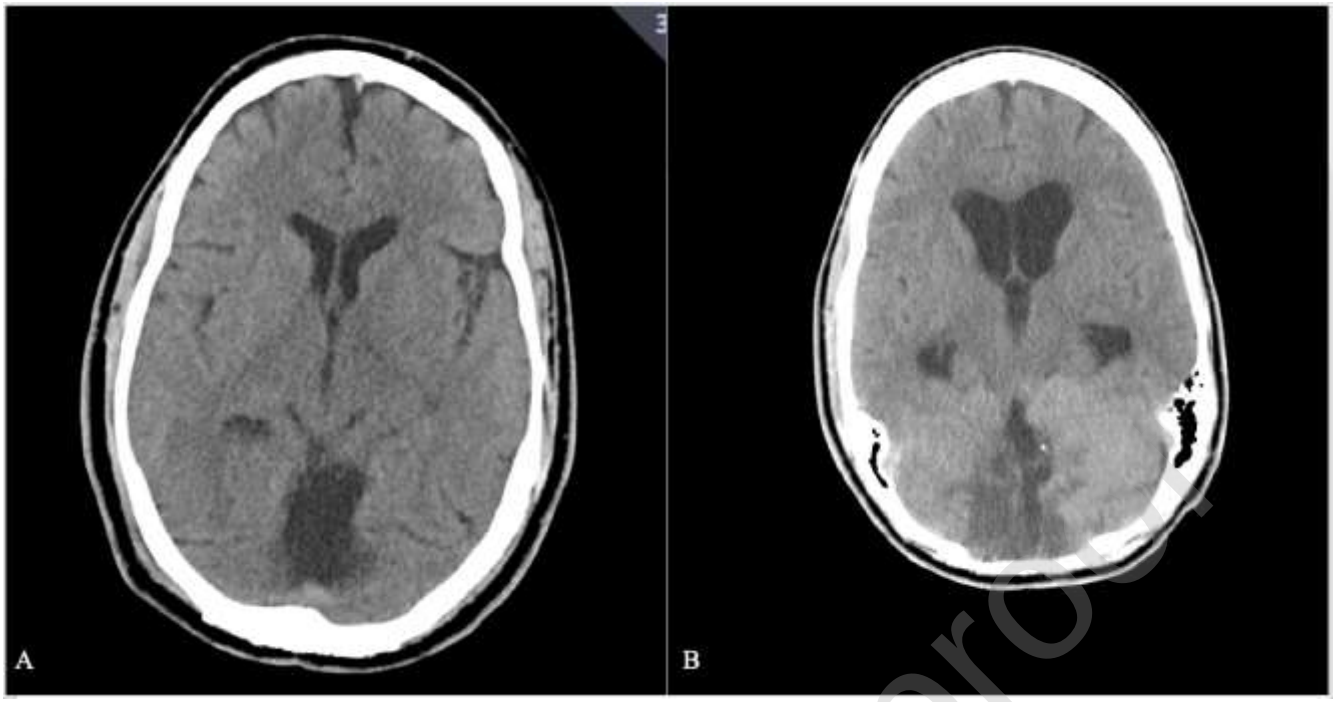

Table legends:

Table 1: A literature review of NF-1-associated cerebellar PXAs. *GTR = gross total resection.*

Author	Age, Sex	Location	Treatment	Histological features	Follow up	Molecular analysis
Naidich et al. 2004 [6]	51, F	Cerebellar, vermian	Radiotherapy, GTR. GTR for recurrence	Anaplastic	Recurrence at two months	NR
Saikali et al. 2005 [7]	36, F	Occipital deep, cerebellar cortical	Resection	Anaplastic	Died after three recurrences	NR
Takei et al. 2015[3]	33, F	Cerebellar	GTR, radiation for recurrence	Benign	Recurrent	BRAF, IDH-1, IDH-2 negative
Ronen et al. 2016 [8]	18, M	Right cerebellar	Partial resection, post-op radiotherapy	Benign	No secondary recurrence two years post-treatment	c.3198-2A>G; BRAF (V600E negative); IDH1 (R132H negative)
Present case	30, M	Cerebellar, vermian	Resection, GTR for resection	Benign	Died after two recurrences	NA

F=female, M= male, BRAF= proto-oncogene B-Raf and v-Raf murine sarcoma viral oncogene homolog B, GTR = Gross total resection, IDH= Isocitrate dehydrogenase, R123H= arginine 132, NR=not reported, NA= not available

Table 2: A literature review of NF-1-associated non-cerebellar PXAs. *GTR = gross total resection.*

Author	Age (years), Sex	Location	Treatment	Histological features	Follow up	Molecular analysis
Ozek et al. 1993[9]	14, M	Medial temporal	GTR	neoplastic	no recurrence at one month	NA
Kubo et al. 1996[10]	21, F	Parietal cortical	Surgical resection	No	NA	NA
Ohta et al. 1999[11]	40, M	Temporal-parietal cortical	GTR and radiotherapy	Anaplastic	No recurrence at 18 years	N/A
Koeller and Henry 2001[12]	13, M	Frontal, cortical		NA	NA	NA
Hariharan et al. 2006[13]	39, F	Frontal deep	Radiotherapy, Resection	Anaplastic	Died three years later due to recurrence	NA
Horiguchi et al. 2011[14]	32, M	Basal ganglia	Radiotherapy, chemotherapy	neoplastic	Died 1.5 years later	NA
Adeleye et al. 2012[15]	10, M	Ventricular, thalamic	GTR	neoplastic	No recurrence at ten months	NA
Neal et al. 2012[16]	23 M	Parietal	GTR	NA	No recurrence at three years	NA
	28, M	Occipital	GTR	NA	No recurrence at 17 months	NA
Prayson et al. 2012[17]	38, F	Temporal, occipital	Resection	neoplasm	No recurrence at six months	NA
Vizcaino et al. 2014[18]	20, F	Left frontal	Resection	Anaplastic	unknown	negative for CD34, IDH1, BRAF (V600E)
Thara et al. 2017[19]	42, M	Left temporoparietal	resection	anaplastic	unknown	N/A
Seddighi et al. 2017[20]	34, F	Cerebellopontine angle	GTR	neoplasm	Died at six months from recurrence	BRAF T1799A
Hanna et al. 2020[21]	17, M	Pineal	GTR	no	No recurrence at nine months	NA

BRAF=proto-oncogene B-Raf and v-Raf murine sarcoma viral oncogene homolog B, GTR = gross total resection, IDH= Isocitrate dehydrogenase, NA= not available