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Case Report

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Exceptional Long-term Survival in BRAF V600E-mutant Anaplastic Pleomorphic Xanthoastrocytoma: A Case Report with 12-year Disease-free Follow-up

Bilgehan Solmaz[1], Özlem Mermut[2], İbrahim Taşkın Rakıcı[3], Cem Leblebici[4]

[1]*University of Health Sciences Türkiye, İstanbul Training and Research Hospital, Clinic of Neurosurgery, İstanbul, Türkiye*
[2]*University of Health Sciences Türkiye, İstanbul Training and Research Hospital, Clinic of Radiation Oncology, İstanbul, Türkiye*
[3]*University of Health Sciences Türkiye, İstanbul Training and Research Hospital, Clinic of Radiology, İstanbul, Türkiye*
[4]*University of Health Sciences Türkiye, İstanbul Training and Research Hospital, Clinic of Pathology, İstanbul, Türkiye*

ABSTRACT

Anaplastic pleomorphic xanthoastrocytoma (APXA) is a rare World Health Organization (WHO) grade 3 glial neoplasm with limited long-term survival data. While grade 2 pleomorphic xanthoastrocytoma (PXA) demonstrates favorable 5-year overall survival rates of 80-90%, anaplastic variants carry a significantly worse prognosis with 5-year survival of approximately 55-57%. BRAF V600E mutations are detected in 50-78% of PXAs and have been associated with improved clinical outcomes; however, cases with follow-up exceeding 10 years are exceptionally rare in the literature, making long-term prognostic assessment challenging. We report an exceptional case of BRAF V600E-mutant APXA with 12-year disease-free survival following gross total resection and comprehensive multimodal adjuvant therapy. A 30-year-old woman presented in October 2014 with a generalized tonic-clonic seizure. Magnetic resonance imaging (MRI) revealed a 32×27 mm contrast-enhancing mass in the left temporal lobe. The patient underwent left temporal craniotomy with gross total resection. Histopathological examination demonstrated pleomorphic tumor cells with bizarre hyperchromatic nuclei, multinucleated giant cells, rhabdoid and spindle-shaped morphology, and lipid-laden xanthomatous cells with eosinophilic cytoplasm. Immunohistochemistry showed glial fibrillary acidic protein and S-100 positivity, Ki-67 proliferation index of 15%, and 13 mitoses per 10 high-power fields. BRAF V600E mutation was confirmed by molecular analysis, and the tumor was diagnosed as PXA, WHO grade III. The patient was lost to follow-up after the first surgery. Eight months postoperatively, the patient presented with tumor recurrence following another seizure, and second surgery achieved gross total resection. Upon histopathological re-evaluation, findings were consistent with APXA recurrence rather than malignant transformation. Ten days after the second surgery, adjuvant treatment was initiated with dynamic arc radiotherapy delivering a total dose of 6000 centigray, concurrent temozolomide 75 mg/m^2, followed by six cycles of adjuvant temozolomide 150 mg/m^2. Follow-up cranial MRI scans performed at regular intervals over the subsequent 12 years consistently demonstrated stable post-surgical changes without any evidence of tumor recurrence. At 12-year follow-up, the patient remains clinically stable and disease-free. This case demonstrates that exceptional long-term survival exceeding 12 years is achievable in BRAF V600E-mutant APXA with gross total resection and comprehensive multimodal adjuvant therapy. The BRAF V600E mutation may serve as a favorable prognostic biomarker and represents a potential therapeutic target. This case underscores the importance of molecular profiling for accurate prognostication and identification of targeted therapeutic options in this rare tumor entity.

Keywords: Neuro-oncology, pleomorphic xanthoastrocytoma, anaplastic, BRAF V600E, long-term survival

Introduction

Pleomorphic xanthoastrocytoma (PXA) is a rare astrocytic neoplasm first described by Kepes et al. [1] in 1979, accounting for less than 1% of all astrocytomas and predominantly affecting children and young adults [2]. The tumor typically arises in the superficial cerebral cortex, most commonly in the temporal lobe, and frequently involves the overlying leptomeninges. The 2021 World Health Organization (WHO)

Address for Correspondence: PhD., Bilgehan Solmaz MD, University of Health Sciences Türkiye, İstanbul Training and Research Hospital Hospital, Clinic of Neurosurgery, İstanbul, Türkiye

E-mail: bilgehansolmaz@yahoo.com.tr **ORCID ID:** orcid.org/0000-0003-2015-9484

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Classification of Central Nervous System Tumors categorizes PXA as either grade 2 or grade 3 (anaplastic) based on mitotic activity, with ≥5 mitoses per 10 high-power fields defining anaplastic histology [3]. While grade 2 PXA demonstrates favorable 5-year overall survival rates of 80-90%, anaplastic PXA (APXA) carries a significantly worse prognosis with 5-year survival of approximately 55-57% [2,4].

BRAF V600E mutations are detected in 50-78% of PXAs and have been associated with improved clinical outcomes compared to BRAF wild-type tumors [5,6]. The presence of this mutation also offers potential targeted therapeutic options with BRAF and mitogen-activated protein kinase kinase inhibitors, which have shown promising results in recurrent or refractory cases [7,8]. We present an exceptional case of BRAF V600E-mutant APXA with a 12-year disease-free survival following gross total resection and comprehensive, multimodal adjuvant therapy.

Case Report

A thirty-year-old woman with no significant past medical history presented in October 2014 with a generalized tonic-clonic seizure. Written informed consent was obtained from the patient for publication of this case report and accompanying images. The neurological examination was unremarkable. Magnetic resonance imaging (MRI) revealed a 32×27 mm space-occupying lesion in the left temporal lobe, demonstrating a hyperintense signal on T2-weighted and fluid-attenuated inversion recovery sequences, a hypointense signal on T1-weighted imaging, and an intense homogeneous contrast enhancement (Figure 1). The patient underwent a left temporal craniotomy with careful attention to language preservation, maintaining a posterior resection margin of less than 4.5 cm from the temporal pole to protect Wernicke's area.

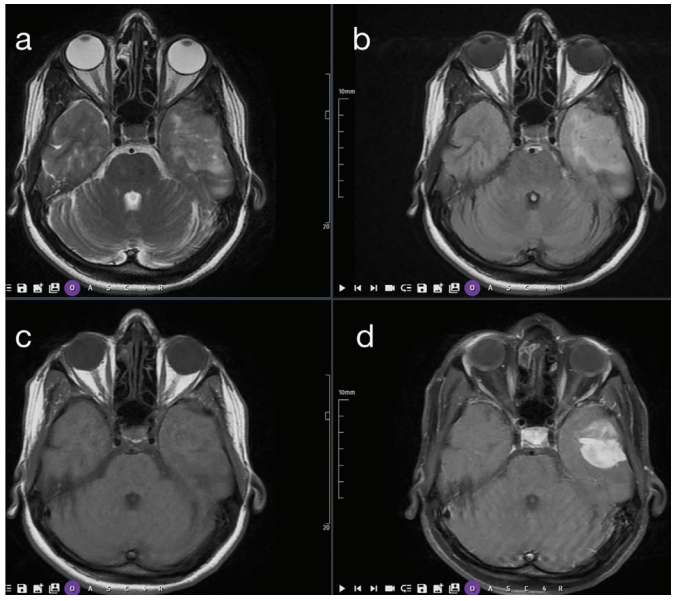

Figure 1. Preoperative magnetic resonance imaging of the left temporal lobe mass. A 32×27 mm space-occupying lesion demonstrates hyperintense signal on T2-weighted (a) and fluid-attenuated inversion recovery (b) sequences, hypointense signal on T1-weighted imaging (c), and homogeneous contrast enhancement on post-contrast fat-suppressed T1-weighted sequences (d) in axial planes. The lesion is located in the left temporal lobe with associated mass effect

Histopathological examination revealed pleomorphic tumor cells characterized by bizarre hyperchromatic nuclei, multinucleated giant cells, rhabdoid and spindle-shaped morphologies, and lipid-laden xanthomatous cells with eosinophilic cytoplasm (Figure 2a). Immunohistochemistry demonstrated glial fibrillary acidic protein and S-100 protein positivity; a Ki-67 proliferation index of 15%; p53 expression in 5% of tumor cells; and 13 mitoses per 10 high-power fields. BRAF V600E mutation was confirmed by molecular analysis. Based on these findings, the tumor was diagnosed as a PXA (WHO grade III). The patient was lost to follow-up after the first surgery.

Eight months postoperatively (June 2015), the patient presented with another generalized seizure. MRI demonstrated tumor recurrence at the previous resection site. A second surgery was performed, achieving gross total resection. Histopathological examination of the recurrent specimen showed lipid-laden xanthomatous cells with eosinophilic cytoplasm, and epithelioid/rhabdoid tumor cells (Figure 2b). The specimen was initially diagnosed as glioblastoma, WHO grade IV. However, upon re-evaluation, considering the same anatomical location, histological similarity, and clinical course, this diagnosis is now considered incorrect; the findings are more consistent with recurrence of the same APXA rather than a true malignant transformation to glioblastoma.

Ten days after the second surgery, adjuvant treatment was initiated according to the glioblastoma protocol, based on the initial pathological interpretation. Between June 11 and July 23, 2015, the patient received dynamic arc radiotherapy using 6 MV photons. Phase 1 delivered 4600 centigray (cGy) in 23 fractions (200 cGy/day) to the tumor bed with an edema margin, followed by Phase 2, which delivered 1400 cGy in 7 fractions (200 cGy/day) to the tumor bed with a reduced margin, for a total dose of 6000 cGy. Concurrent temozolomide 75 mg/m^2 was administered throughout radiotherapy, followed by six cycles of adjuvant temozolomide 150 mg/m^2. The patient tolerated the treatment well, with

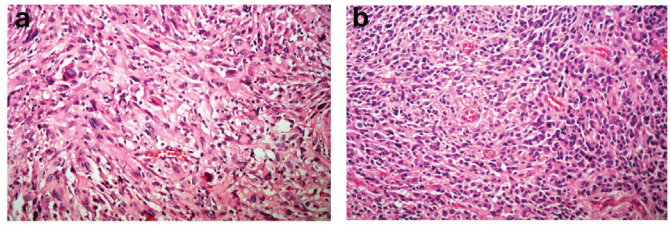

Figure 2. Histopathological findings from the surgical specimens. (a) Hematoxylin and eosin (H&E)- stained section from the first surgical specimen showing pleomorphic tumor cells with bizarre, hyperchromatic nuclei, including multinucleated giant cells, as well as pleomorphic, rhabdoid, and spindle-shaped cells (original magnification ×400). (b) H&E-stained section from the second surgical specimen demonstrating characteristic lipid-laden xanthomatous cells with eosinophilic cytoplasm and epithelioid/rhabdoid tumor cells (original magnification ×400)

no significant acute or late toxicities. Follow-up cranial MRI scans, performed at regular intervals over the subsequent 12 years, consistently demonstrated stable post-surgical changes without any evidence of tumor recurrence (Figure 3). At the 12-year follow-up, the patient remains clinically stable and disease-free while on levetiracetam 500 mg daily for seizure prophylaxis.

Discussion

This case demonstrates exceptional 12-year disease-free survival in APXA, substantially exceeding the expected 55-57% 5-year survival reported in the literature [2,4]. The patient's age of 30 years is consistent with typical PXA demographics, as this tumor predominantly affects children and young adults with median ages ranging from 20 to 26 years [2,9]. Histopathological examination confirmed grade 3 PXA with characteristic features including xanthomatous cells with lipid accumulation, marked cellular pleomorphism, high mitotic activity (13 mitoses/10 high-power field), and Ki-67 proliferation index of 15%, fulfilling the WHO criteria for anaplastic designation [3,10].

The BRAF V600E mutation identified in this case is a well-established favorable prognostic factor in PXA. Multiple studies have demonstrated that BRAF-mutant tumors are associated with significantly improved survival compared to wild-type counterparts [2,5]. The underlying biological mechanisms may include distinct tumor behavior and enhanced sensitivity to conventional therapies including radiation and alkylating chemotherapy [11,12]. Although our patient was treated according to a glioblastoma protocol, the multimodal approach combining gross total resection, high-dose radiotherapy (6000 cGy), and temozolomide chemotherapy likely contributed to this exceptional outcome.

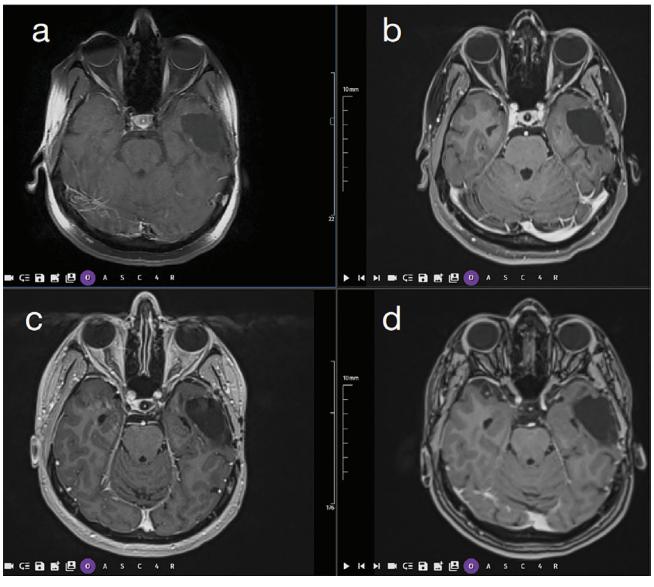

Figure 3. Follow-up magnetic resonance imaging (MRI). Post-contrast fat-suppressed T1-weighted MRI axial images obtained during follow-up show no evidence of residual or recurrent disease in the top row (a, 2018; b, 2020) or the bot tom row (c, 2022; d, 2026)

Treatment strategies for residual or recurrent grade III PXA remain a subject of ongoing debate. Radiotherapy with doses ranging from 45 to 60 Gy is frequently administered for patients with incomplete resection or anaplastic histology, with or without concurrent temozolomide. Gross total resection consistently emerges as the most important independent prognostic factor across multiple studies [2,4,9]. For BRAF V600E-mutant tumors, targeted therapy with vemurafenib has demonstrated response rates of approximately 50%, while dabrafenib and trametinib combination has shown significant benefit in recurrent cases [7,8].

Study Limitations

This case has certain limitations. Comprehensive molecular profiling including CDKN2A/B homozygous deletion and TERT promoter mutation status was not performed, which could provide additional prognostic information [11,13]. The differential diagnosis included epithelioid glioblastoma; however, the classic PXA features, BRAF V600E mutation, and favorable clinical course support the APXA diagnosis [1].

Conclusions

This case demonstrates that exceptional long-term survival exceeding 12 years can be achieved in a patient with BRAF V600E-mutant anaplastic PXA after gross total resection and comprehensive multimodal adjuvant therapy. The findings underscore the importance of molecular profiling for accurate prognostication and identification of potential therapeutic targets in this rare tumor entity.

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.S., Concept: B.S., Design: B.S., Data Collection or Processing: B.S., Ö.M., İ.T.R., C.L., Analysis or Interpretation: B.S., Ö.M., İ.T.R., C.L., Literature Search: B.S., Writing: B.S., Ö.M., İ.T.R., C.L.

Conflict of Interest: No conflict of interest was declared by the authors.

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