Case Report
Clinicopathologic changes and molecular finding of epithelioid pleomorphic xanthoastrocytoma: a case report

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Abstract: We report a 49-year-old woman who presented with a 4-month-history of headache, nausea, and no epilepsy. Magnetic resonance imaging (MRI) showed a mass in the left temporal lobe region. The edges were unclear, and it was a non-cystic and obvious perifocal edema. The radiologist first considered that it was a high-grade glioma. Macroscopy found that the tumor measured 6.2 cm × 5.2 cm × 5 cm. Microscopy found that the tumor cells were pleomorphic and indicated the presence of many epithelioid/rhabdomyoid cells, multifocal necrosis, and significant bleeding. The distribution of the reticular fibers was segmented, which is difficult to diagnose when it is accompanied by partial anaplastic features. The immunohistochemical makers of the tumor cells were positive for GFAP, Oligo-2, S-100, ATRX, INI1, BRAF (V600E), and P53 but negative for IDH1 (R132H). The tumor cells exhibited a low proliferating index of Ki-67 (< 5%). Molecular pathological detection revealed that the BRAF (V600E) gene was positive, and there was no mutation in the IDH and TERT genes, no 1p/19q-codeleted, and no methylation in the MGMT promoter. The final pathological diagnosis was pleomorphic xanthoastrocytoma (PXA, WHO grade II) with partial anaplastic features. The patient had no additional adjuvant radiation and underwent temozolomide-based chemotherapy. No recurrence was found over a 30-month follow-up. Therefore, the pathological diagnosis combined with the clinicopathological features, histopathological morphology, and related molecular detection is of great significance for the accurate classification, prognostic evaluation, and precise treatment decision for glioma.

Keywords: Pleomorphic xanthoastrocytoma, BRAF (V600E), glioma

Introduction

Pleomorphic xanthoastrocytoma (PXA) is a rare low-grade astrocytic tumor (World Health Organization grade II) of the central nervous system (CNS), occurring primarily in children and young patients [1]. PXA has accounted for less than 1% of all primary brain tumors since it was first reported in 1979 [2-4]. It is characterized by pleomorphic, atypical astrocytes and can be easily misdiagnosed as malignant glioma [5]. Most cases of PXA occur in the temporal lobe. The clinical symptoms can be atypical and include dizziness, headache, vomiting, and chronic epilepsy. Imaging plays a certain role in the diagnosis of central nervous system tumors. MRI shows a clear margin of space-occupying lesions, while those accompanied by cystic changes and/or peripheral edema are not obvi-

ous. PXA may undergo a progression from low- to high-grade astrocytoma, namely anaplastic pleomorphic xanthoastrocytoma (PXA-A, WHO grade III) [6]. Histology defines it as a mitotic count of ≥ 5 mitoses per 10 HPF and/or with necrosis [7]. The significance of the necrosis is unknown. The diagnosis of PXA is difficult when it is accompanied by partial anaplastic features, such as necrosis, and significant epithelioid forms. This paper reports a case of pleomorphic xanthoastrocytoma with the characteristics of partial anaplastic features and a prominent epithelioid pattern. Here we present a case of PXA in a middle-aged woman with partial anaplastic features and a prominent epithelioid pattern and combine it with a review of the relevant literature. The aim of this study is to explore the importance of combined clinico-
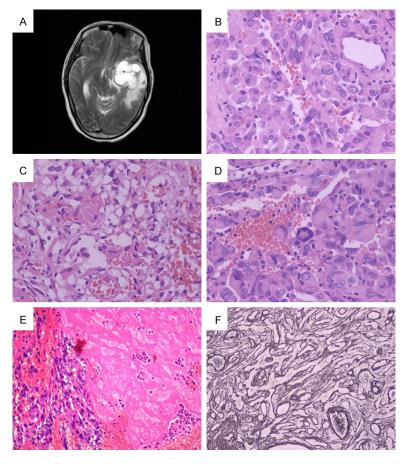
Figure 1. A. MRI (T2): A mass in the left temporal lobe region, midline shift, unclear edges, non-cystic, and with obvious perifocal oedema. B. The tumor cells were pleomorphic. Many epithelioid/rhabdomyoid cells. C. Xanthoma cells with cytoplasmic vacuoles. D. Multinucleated giant cells. E. Multiple focal necrosis and significant bleeding. F. The reticular fibers were segmented.

mor measuring 6.2 cm × 5.2 cm × 5 cm with a pale yellow and red color. Microscopy indicated that the tumor cells were pleomorphic. There were many epithelioid/rhabdomyoid cells, xanthoma cells with cytoplasmic vacuoles, and multinucleated giant cells. The cytoplasm was rich in acidophilic cells, with a small number of light-stained granular bodies. They had large nuclei and small nucleoli. The mitotic image was rare, and the tumor tissue had multiple focal necroses and significant bleeding. The distribution of the reticular fibers was segmented (**Figure 1F**). A panel of immunohistochemical staining of the tumor cells revealed that they were positive for GFAP, S-100, ATRX, INI1, and BRAF (V600E). Part of the tumor cells showed that EMA, vimentin, Oligo-2, P53, and Syn were positive, but the tumor cells were negative for IDH1 (R132H). The tumor cells exhibited a low proliferating index of Ki-67 (< 5%). Molecular pathological detection revealed that the BRAF (V600E) gene was positive (**Figure 2**), and there was no mutation in the IDH and TERT genes, no 1p/19q-codeleted, and no methylation in the MGMT promoter. The final pathological diagnosis was PXA (WHO grade II) with partial anaplastic features. The patient's symptoms improved after the operation, and no additional adjuvant radiation and temozolomide-based chemotherapy therapy was necessary. No recurrence was found over a 30-month follow-up.

pathological features and molecular detection in the integrated diagnosis of PXA.

Case report

A 49-year-old woman presented with a 4-month history of frequent headaches and dizziness. The patient had nausea, non-projectile vomiting, no epilepsy, no convulsions, and was not aware of any disorders neurological symptoms. Magnetic resonance imaging (MRI) showed a non-cystic mass in the left temporal lobe region, 4.7 cm × 4.1 cm in size, with unclear edges, and with an obvious perifocal edema (**Figure 1A**). The radiologist first considered that it was a high-grade glioma. Radical surgery was performed, and all the resected tumors were sent to our department for further pathological examination. Macroscopic pathology demonstrated a completely resected tu-

Discussion

PXA is a rare central nervous system tumor with typical clinicopathological and imaging features. However, in our case, all of the features were atypical. The case reported in this paper was a 49-year-old middle-aged woman - not a young adult. She had no history of epilepsy symptoms, and had only a slight head-
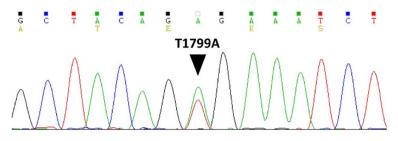
Figure 2. BRAF (V600E) mutation (arrow) was detected in T1799A site of tumor tissue.

ache. Her MRI did not show below imaging changes, such as a tumor with cystic degeneration and obscure boundaries. A space-occupying and midline shift occurred in the brain, and the tumor was surrounded by the edematous zone, which suggested that the tumor may have had an invasive growth pattern.

The final diagnosis of PAX depends on the integrated results of histology, immunohistochemistry, and molecular pathology. PXA has a series of typical features, including the variable histological appearance of the tumor cells and xanthomatous cells that have an intracellular accumulation of lipids. Moreover, granular bodies that are either eosinophilic or pale are a nearly invariable finding, and the presence of reticulin fibers is also typical [3]. In this case, we observed the pleomorphic appearance of the tumor cells, many epithelioid cells, and multifocal necrosis. Combined with the imaging findings, it was necessary to differentiate from other types of gliomas, especially high-grade gliomas.

Immunohistochemical staining revealed that the tumor cells were positive for GFAP, S-100, and Oligo-2, suggesting that the tumor cells contained glial components. The loss of INI1 expression was caused by the mutation of the INI1 gene, which is a necessary condition for diagnosing AT/RT [8]. In this case, part of the INI1 staining indicated that there was no deletion mutation. In recent years, several studies on gliomas have confirmed that approximately 75% of WHO grade II and III diffuse infiltrating gliomas and most secondary GBM have IDH1 gene mutations, which may be an early molecular change in the astrocytoma and oligodendroglioma [9, 10]. However, in this case, there was a lack of IDH1 (R132H) mutation in PXA. The proportion of ATRX mutations in low-grade gliomas with the IDH mutation is up to 70%, and

the mutation is contrary to the co-deletion of 1p/19q [11, 12]. The ATRX mutation resulted in the loss of protein expression, and the immunohistochemistry result was negative. The two gene mutations were lacking in this case.

The 2016 revised version of the WHO CNS tumor classification is included in multiple molecular detection, and partial markers are used as the main diagnostic index. The integrated diagnosis combined with morphological features and molecular detection has become the main diagnostic model of the CNS tumor classification. For example, by detecting the mutation of the IDH1/2 gene in diffuse glioma, diffuse astrocytoma, anaplastic astrocytoma, and glioblastoma are divided into IDH mutant and IDH wild types. At present, tumors with limited growth patterns and a lack of the IDH mutation and BRAF (V600E) mutation are distinguished from diffuse gliomas [13].

BRAF is a serine/threonine protein kinase and participates in the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) signaling pathway. In glioma, PXA is the most frequent tumor with the BRAF (V600E) mutation, which is found in approximately 70% of PXAs [14], while the epithelioid glioblastoma (eGBM) has a mutation rate of approximately 50%. In addition, approximately 10% of pilocytic astrocytomas and 20% of gangliogliomas can be detected in this mutation. In our study, the positive expression of the BRAF (V600E) mutation was detected.

Epithelioid glioblastoma (WHO grade IV) occurs predominantly in young people and is located in the cerebrum or diencephalon. Histological features include large epithelioid cells and rhomboid cells, eosinophilic cytoplasms, and focal xanthoma cells. Compared to other glioblastomas, more than half of the cases contain a BRAF (V600E) mutation [15]. Studies have suggested that PAX, PAX-A, and eGBM belong to the same category [16]. The epithelioid glioblastoma is an IDH wild type, with a lack of INI1 expression and a Ki-67 proliferation index often more than 10%. The atypia and high prolif-

erative index of the tumor may differentiate it from PXA.

The histological characteristics of gemistocytic astrocytoma (WHO grade II) are rich in eosinophilic cytoplasms, nuclear deviation, and small nucleoli, and the Ki-67 proliferation index is less than 4%. The WHO CNS tumor classification (2016) clearly indicates that this kind of tumor is a subtype of diffuse astrocytoma with the IDH mutation [17].

Studies have shown that the changes in three molecules associated with the IDH1/2 mutation, the TERT mutation, and the 1p/19q deletion can divide gliomas into 5 molecular subtypes, which are related to the survival rate of patients with glioma [18]. The molecular detection results in our patient included a lack of IDH1/2 and TERT mutations and no 1p/19q deletion. The patient did not have methylation of the MGMT promoter. No recurrence occurred after 30 months of follow-up.

Therefore, the integrated pathological diagnosis combined with the clinicopathological features, histopathological morphology, and related molecular detection is of great significance for the accurate classification, prognostic evaluation, and precise treatment of glioma.

Acknowledgements

Disclosure of conflict of interest

None.

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References

[1] Hsiao SJ, Karajannis MA, Diolaiti D, Mansukhani MM, Bender JG, Kung AL and Garvin JH Jr. A novel, potentially targetable TMEM106B-BRAF fusion in pleomorphic xanthoastrocytoma. Cold Spring Harb Mol Case Stud 2017; 3: a001396.

[2] Kepes JJ, Rubinstein LJ and Eng LF. Pleomorphic xanthoastrocytoma: a distinctive meningocerebral glioma of young subjects with relatively favorable prognosis. A study of 12 cases. Cancer 1979; 44: 1839-1852.

[3] Giannini C, Scheithauer BW, Burger PC, Brat DJ, Wollan PC, Lach B and O'Neill BP. Pleomorphic xanthoastrocytoma: what do we really know about it? Cancer 1999; 85: 2033-2045.

[4] Sharma A, Nand Sharma D, Kumar Julka P and Kishor Rath G. Pleomorphic xanthoastrocytoma - a clinico-pathological review. Neurol Neurochir Pol 2011; 45: 379-386.

[5] Jimenez-Heffernan JA, Freih Fraih A, Alvarez F, Barcena C and Corbacho C. Cytologic features of pleomorphic xanthoastrocytoma, WHO grade II. A comparative study with glioblastoma. Diagn Cytopathol 2017; 45: 339-344.

[6] Alexandrescu S, Korshunov A, Lai SH, Dabiri S, Patil S, Li R, Shih CS, Bonnin JM, Baker JA, Du E, Scharnhorst DW, Samuel D, Ellison DW and Perry A. Epithelioid glioblastomas and anaplastic epithelioid pleomorphic xanthoastrocytomas-same entity or first cousins? Brain Pathol 2016; 26: 215-223.

[7] Rutkowski MJ, Oh T, Niflioglu GG, Safaee M, Tihan T and Parsa AT. Pleomorphic xanthoastrocytoma with anaplastic features: retrospective case series. World Neurosurg 2016; 95: 368-374.

[8] Judkins AR, Mauger J, Ht A, Rorke LB and Biegel JA. Immunohistochemical analysis of hSNF5/INI1 in pediatric CNS neoplasms. Am J Surg Pathol 2004; 28: 644-650.

[9] Yan H, Parsons DW, Jin G, McLendon R, Rasheed BA, Yuan W, Kos I, Batinic-Haberle I, Jones S, Riggins GJ, Friedman H, Friedman A, Reardon D, Herndon J, Kinzler KW, Velculescu VE, Vogelstein B and Bigner DD. IDH1 and IDH2 mutations in gliomas. N Engl J Med 2009; 360: 765-773.

[10] Watanabe T, Vital A, Nobusawa S, Kleihues P and Ohgaki H. Selective acquisition of IDH1 R132C mutations in astrocytomas associated with Li-Fraumeni syndrome. Acta Neuropathol 2009; 117: 653-656.

[11] Kannan K, Inagaki A, Silber J, Gorovets D, Zhang J, Kastenhuber ER, Heguy A, Petrini JH, Chan TA and Huse JT. Whole-exome sequencing identifies ATRX mutation as a key molecular determinant in lower-grade glioma. Oncotarget 2012; 3: 1194-1203.

[12] Reuss DE, Sahm F, Schrimpf D, Wiestler B, Capper D, Koelsche C, Schweizer L, Korshunov A, Jones DT, Hovestadt V, Mittelbronn M, Schittenhelm J, Herold-Mende C, Unterberg A, Plat-

ten M, Weller M, Wick W, Pfister SM and von Deimling A. ATRX and IDH1-R132H immunohistochemistry with subsequent copy number analysis and IDH sequencing as a basis for an "integrated" diagnostic approach for adult astrocytoma, oligodendroglioma and glioblastoma. Acta Neuropathol 2015; 129: 133-146.

[13] Zhang J, Wu G, Miller CP, Tatevossian RG, Dalton JD, Tang B, Orisme W, Punchihewa C, Parker M, Qaddoumi I, Boop FA, Lu C, Kandoth C, Ding L, Lee R, Huether R, Chen X, Hedlund E, Nagahawatte P, Rusch M, Boggs K, Cheng J, Becksfort J, Ma J, Song G, Li Y, Wei L, Wang J, Shurtleff S, Easton J, Zhao D, Fulton RS, Fulton LL, Dooling DJ, Vadodaria B, Mulder HL, Tang C, Ochoa K, Mullighan CG, Gajjar A, Kriwacki R, Sheer D, Gilbertson RJ, Mardis ER, Wilson RK, Downing JR, Baker SJ, Ellison DW; St. Jude Children's Research Hospital-Washington University Pediatric Cancer Genome Project. Whole-genome sequencing identifies genetic alterations in pediatric low-grade gliomas. Nat Genet 2013; 45: 602-612.

[14] Dias-Santagata D, Lam Q, Vernovsky K, Vena N, Lennerz JK, Borger DR, Batchelor TT, Ligon KL, Iafrate AJ, Ligon AH, Louis DN and Santagata S. BRAF V600E mutations are common in pleomorphic xanthoastrocytoma: diagnostic and therapeutic implications. PLoS One 2011; 6: e17948.

[15] Broniscer A, Tatevossian RG, Sabin ND, Klimo P Jr, Dalton J, Lee R, Gajjar A and Ellison DW. Clinical, radiological, histological and molecular characteristics of paediatric epithelioid glioblastoma. Neuropathol Appl Neurobiol 2014; 40: 327-336.

[16] Furuta T, Miyoshi H, Komaki S, Arakawa F, Morioka M, Ohshima K, Nakada M and Sugita Y. Clinicopathological and genetic association between epithelioid glioblastoma and pleomorphic xanthoastrocytoma. Neuropathology 2018; 38: 218-227.

[17] Sahm F, Korshunov A, Schrimpf D, Stichel D, Jones DT, Capper D, Koelsche C, Reuss D, Kratz A, Huang K, Wefers AK, Schick M, Bewerunge-Hudler M, Mittelbronn M, Platten M, Hanggi D, Jeibmann A, Unterberg A, Herold-Mende C, Pfister SM, Brandner S, Wick W and von Deimling A. Gain of 12p encompassing CCND2 is associated with gemistocytic histology in IDH mutant astrocytomas. Acta Neuropathol 2017; 133: 325-327.

[18] Eckel-Passow JE, Lachance DH, Molinaro AM, Walsh KM, Decker PA, Sicotte H, Pekmezci M, Rice T, Kosel ML, Smirnov IV, Sarkar G, Caron AA, Kollmeyer TM, Praska CE, Chada AR, Halder C, Hansen HM, McCoy LS, Bracci PM, Marshall R, Zheng S, Reis GF, Pico AR, O'Neill BP, Buckner JC, Giannini C, Huse JT, Perry A, Tihan T, Berger MS, Chang SM, Prados MD, Wiemels J, Wiencke JK, Wrensch MR and Jenkins RB. Glioma groups based on 1p/19q, IDH, and TERT promoter mutations in tumors. N Engl J Med 2015; 372: 2499-2508.