Giant cell glioblastoma versus pleomorphic xanthoastrocytoma: a challenging case

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Abstract

Here we present a challenging case originally diagnosed as giant cell glioblastoma WHO grade 4 in a 48-year-old lady with a background of Li-Fraumeni syndrome. After an initial excision and neoadjuvant chemoradiotherapy the patient had a 5 year disease-free period before having a recurrence. The recurrent tumour alongside the original tumour were reviewed. By reviewing the clinical history and disease progression and combining this with improved genetic testing methodologies a reviewed diagnosis of anaplastic pleomorphic xanthoastrocytoma (PXA) WHO Grade 3 was made. This case highlights how many factors can affect a diagnosis and how the clinical course may require for diagnoses to be reviewed and refined.

Keywords glioblastoma; glioma; Li-Fraumeni; methylation; pleomorphic xanthoastrocytoma

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Case report

In 2014, a 48-year-old woman presented with a 4-week history of headaches, nausea and vomiting and one episode of seizure. She underwent imaging (Figure 1A) which revealed 2 right temporal lobe lesions. Her past medical history included a diagnosis of Li-Fraumeni syndrome and breast carcinoma 14 years prior for which she had undergone a mastectomy.

An excision biopsy was performed. On frozen section, there were sheets and bundles of markedly pleomorphic cells with multiple mitoses which focally had an epithelioid appearance and necrosis. The initial diagnosis was potential metastatic carcinoma. When the remaining specimen was received and immunohistochemistry (IHC) performed, GFAP was focally positive, reticulin highlighted the fibres around blood vessels only, EMA was negative and P53 was negative indicating an aberrant staining pattern. The diagnosis was changed to a high-grade glioma with unusual cellular morphology.

Several genetic tests were performed; chromosome 17 karyotyping, IDH mutation testing and MGMT methylation analysis. The results are summarized in Table 1. The methodology used for methylation analysis was methylation specific multiplex ligation-dependent probe amplification (MLPA). No further genetic testing was performed as was appropriate for routine clinical testing at the time. The final diagnosis was made as a Glioblastoma WHO grade 4 which was consistent with the presence of mitoses and necrosis.

The patient was treated with adjuvant chemoradiotherapy and recovered well. She had routine follow-up MRI scans and remained disease-free for 5 years. Unfortunately, in 2019 a scan revealed a small volume recurrence (Figure 1B). A second excision was performed, and histology revealed a very similar appearing tumour consisting of multinucleate and large pleomorphic cells with mitoses, vascular proliferation, and necrosis (Figure 2). Considering the patient's excellent outcome and the recurrence, the original 2014 tumour was reviewed. On morphology alone, the differential diagnoses were Giant Cell Glioblastoma WHO Grade 4 or Anaplastic Pleomorphic xanthoastrocytoma (PXA) WHO Grade 3.

Special stains and IHC were performed (Figure 3) revealing focal positivity of reticulin around blood vessels only and strong positivity of GFAP in most tumour cells. Ki-67 index was moderate at around 7% positivity and P53 showed am aberrant staining pattern. ATRX IHC was performed on both the 2014 and 2019 and showed positive staining indicating a WT result.

The 2019 tumour underwent genetic testing (Table 1) and the original 2014 tumour was retested. due to differences in testing methodologies that had been implemented. This revealed that the 2014 tumour had Loss of 1p36 and the methylation result by pyrosequencing was equivocal.

The case was reviewed at a second centre for methylation profiling. This was performed on a sample of the 2014 tumour, however there was an inconclusive result. There was no evidence of CDKN2A/B deletion and IHC for BRAF V600E was negative.

On follow up imaging a very small focus of residual tumour was detected in June 2021. A repeat scan in December 2021 revealed it had increased in size significantly and the patient underwent a third excision in January 2022. This tumour had a similar morphology to the previous two tumours, but it was also noted there were more multinucleated giant cells with abundant foamy cytoplasm myxoid changes and had a more typical appearance of PXA (Figure 4). The genetic analysis revealed an atypical NTRK2 rearrangement and heterozygous CDKN2A loss. There was no evidence of TERT promoter mutation and no evidence of NTRK1 or NTRK3 rearrangement.

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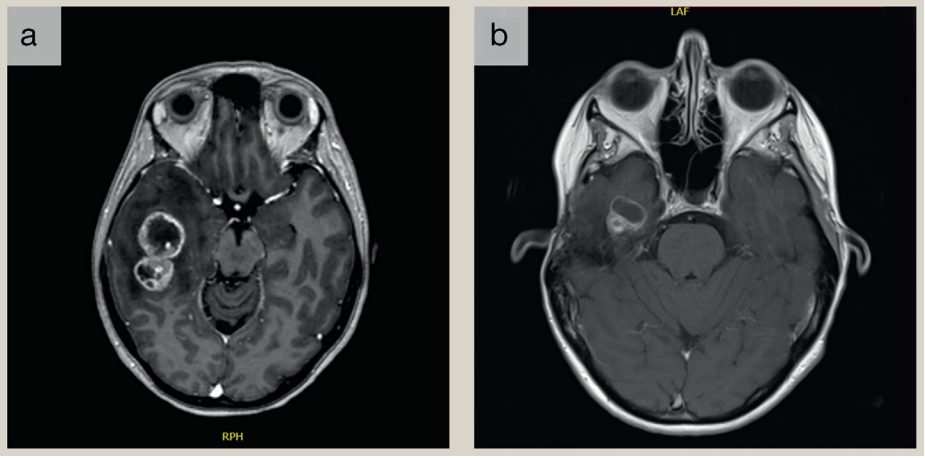

Figure 1 T1 weighted MRI head. (**a**) 2014 cystic tumour in the left temporal lobe. (**b**) Recurrence in 2019.

This tumour was again reviewed at an independent centre and underwent methylation profiling. The result was suggestive of n IDH-wildtype glioblastoma however it was noted that the classifier score used was low and therefore the result should be interpreted with great caution. Overall, it was noted that given the clinical history, histology, immunohistochemistry and other genetic results a final diagnosis of anaplastic PXA was favourable over giant cell glioblastoma.

Table 1 summarises all the diagnostic testing results for the three resected tumours in 2014, 2019 and 2022.

Discussion and conclusion

This challenging case highlights the importance of combining clinical history, morphology, and molecular features to make a diagnosis. It also highlights how technologies for molecular testing in the clinical setting have been developed over recent years and this may have implications for changes in diagnoses. When the original 2014 tumour was tested for methylation and provided a negative result, this was done by MLPA. The methodology for methylation testing of the 2019 tumour was pyrosequencing. The most likely reason for this discrepancy would be that MLPA assessed methylation of 2 CpG sites whereas pyrosequencing assessed 8 CpG sites and is therefore a more sensitive technique. Other explanations include a genuine change in methylation status of the tumour or tumour heterogeneity. The discrepancy in the FISH result of 1p/19q whereby loss was seen in the 2014 tumour and not in 2019 may indicate either tumour progression or heterogeneity as the testing methodology was unchanged.

Diagnostic testing results for the three resected tumours

	2014 Tumour	2019 Tumour	2022 Tumour
GFAP IHC	Focally positive	Strongly positive	Strongly positive
ATRX IHC	Positive (indicating wild-type)	Positive (indicating wild-type)	Positive (indicating wild-type)
P53 IHC	Negative (aberrant)	Negative (aberrant)	Negative (aberrant)
BRAF V600E IHC	Wild-type	Wild-type	Wild-type
Ki67 IHC	Moderate (7%)	Moderate (7%)	High (20%)
Ip19q FISH	No 1p/19q co-deletion *Loss of 1p36*[a]	No 1p/19q co-deletion	
EGFR FISH	No amplification	No amplification	
BRAF RT-PCR		No KIAA1549-BRAF fusion	
MGMT methylation	*Not methylated*[b]	Methylated (equivocal)	Methylated
BRAF V600E sequencing	Wild-type	Wild-type	Wild-type
TERT promoter sequencing	Wild-type	Wild-type	Wild-type
Other			Atypical NTRK2 rearrangement Monosomy 9 No NTRK1 or NTRK3 rearrangement

[a] Loss of 1p36 was detected 5 years later with repeat testing.
[b] The non-methylated result was on original testing in 2014.

Table 1

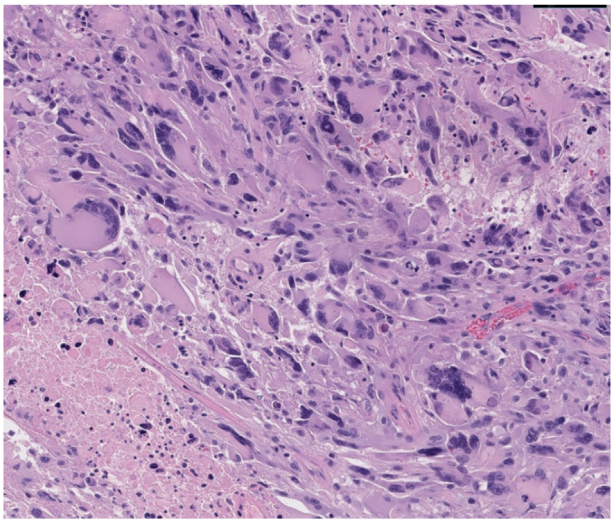

Figure 2 H&E of 2019 resected tumour with multinucleate giant cells, necrosis, vascular proliferation and mitoses.

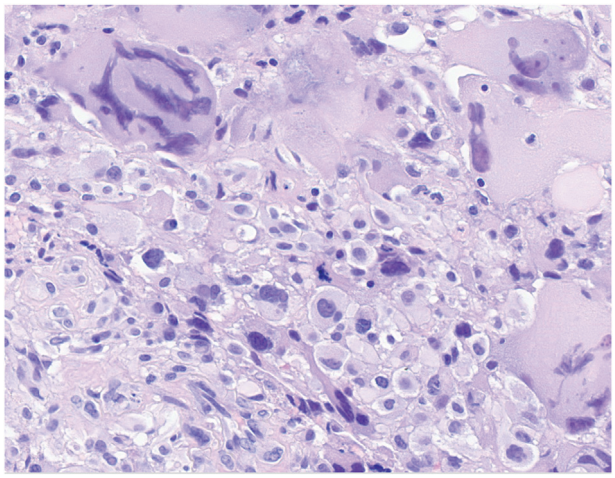

Figure 4 H&E of 2022 tumour with multinucleate giant cells, mitoses and cells with a foamy cytoplasm.

In this case, the patient had a diagnosis of Li-Fraumeni Syndrome. This is an inherited cancer predisposition syndrome whereby there is a pathogenic germline mutation in one copy of the TP53 gene. Once the patient acquires a sporadic mutation or loss of the remaining wild-type copy this will lead to tumour development and therefore this syndrome is inherited in an autosomal dominant pattern. Patients have a 90% chance of developing cancer by age 60.[4] There are several malignancies which are considered as "classic" in Li-Fraumeni sarcoma, breast, brain, adrenal gland and leukaemia.[1]

Giant cell glioblastoma was described a distinct entity until the updated fifth edition of the WHO classification of Tumour of the central nervous system.[2] It was previously described as a rare histological variant of IDH-wildtype glioblastoma characterized by bizarre multinucleated giant cells and abundant reticulin network.[3] However, in the updated classification it was removed as a distinct entity and described as a histological subtype of IDH wild-type glioblastoma with an aim to focus the categories and recognise the value of molecular genetics of.[2,3] This diagnosis was originally favoured due to the presence of necrosis and mitoses which are less commonly seen in PXA.

PXA often occur in the temporal lobe with a cystic appearance on imaging. Histologically they commonly have large pleomorphic and multinucleated cells and typically mitoses are rare but are seen in the anaplastic PXA as with this case. They are WHO Grade III and have a better prognosis than IDH wild-type glioblastoma. BRAF V600E mutations are found in 60% and TERT promoter mutations are very common in anaplastic PXA[1] however neither of these were present in this case. Also in this tumour there was evidence of heterozygous CDKN2A loss but not homozygous which is more typical for PXA. However, in the absence of a BRAF mutation the presence of a NTRK2 rearrangement is seen much more commonly in PXA compared to IDH wildtype glioblastoma where it is found in only 1–2% of cases.[1] The 5 year overall survival for grade 3 PXA is 57.1% which is considerably better than the 5 year survival for glioblastoma at 6.8%.[2]

This is a particularly challenging diagnostic case due to the morphology originally being more consistent with giant cell glioblastoma (mitoses and necrosis) and the molecular profile not fitting a typical anaplastic PXA with lack of TERT promoter mutation and BRAF wildtype. However, combining the histological features and genetic features (NTRK rearrangement) allowed for a more refined diagnosis to be made. Alongside this,

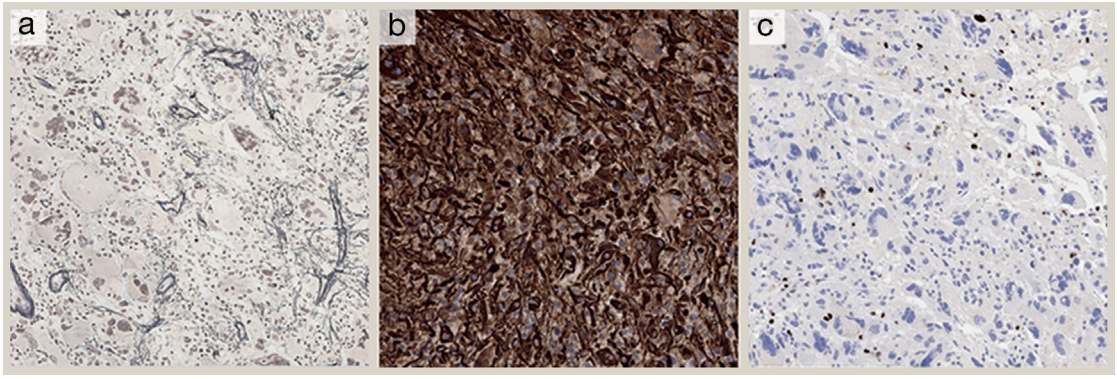

Figure 3 Special stains and IHC. (**a**) Reticulin highlighting blood vessels only. (**b**) GFAP strongly positive. (**c**) P53 showing negative tumour cells with occasional strongly positive cells indicating an aberrant staining pattern (mutated).

the patient's excellent prognosis greatly favoured the reviewed diagnosis of anaplastic PXA. ◆

REFERENCES

1 Li-Fraumeni syndrome - NORD (National Organization for Rare Disorders) [Internet]. 2022. NORD (National Organization for Rare Disorders) [cited 25 May 2022]. Available from: https://rarediseases.org/rare-diseases/li-fraumeni-syndrome/.

2 World Health Organization. Central nervous system tumours. 5th ed. [S.l.]: World Health Organization, 2022.

3 Louis D. WHO classification of tumours of the central nervous system. 4th ed. Lyon: International Agency for Research on Cancer, 2016.

4 Louis D, Perry A, Wesseling P, et al. The 2021 WHO classification of tumors of the central nervous System: a summary. *Neuro Oncol* 2021; **23:** 1231–51.

Practice points

- The fifth edition of the WHO Classification System of Tumours of the Central Nervous System (2021) does not classify giant cell glioblastoma as a distinct entity but as a subtype of glioblastoma due to a greater emphasis on categorizing tumours by their molecular genetics
- Molecular testing methodologies may change and develop over time which could potentially result in result discrepancies when retesting
- Anaplastic PXA has a far better prognosis that glioblastoma and therefore clinical history is very important when considering this as a differential along with giant cell glioblastoma

Self assessment questions

1. Which of the following features would classify a PXA as anaplastic

A. BRAF V600E expression
B. CDKN2A and or CDKN2B mutation
C. Brisk mitotic activity
D. TERT promoter mutation
E. Vascular proliferation

Answer C.

2. What grade of tumour are anaplastic PXAs in the 5th edition (2021) WHO classification

A. 2
B. 3
C. 4
D. III
E. IV

Answer B.

3. Which of the following would be unlikely to be positive in giant cell glioblastoma with immunohistochemistry?

A. IDH1
B. ATRX
C. S100
D. GFAP
E. P53

Answer A.