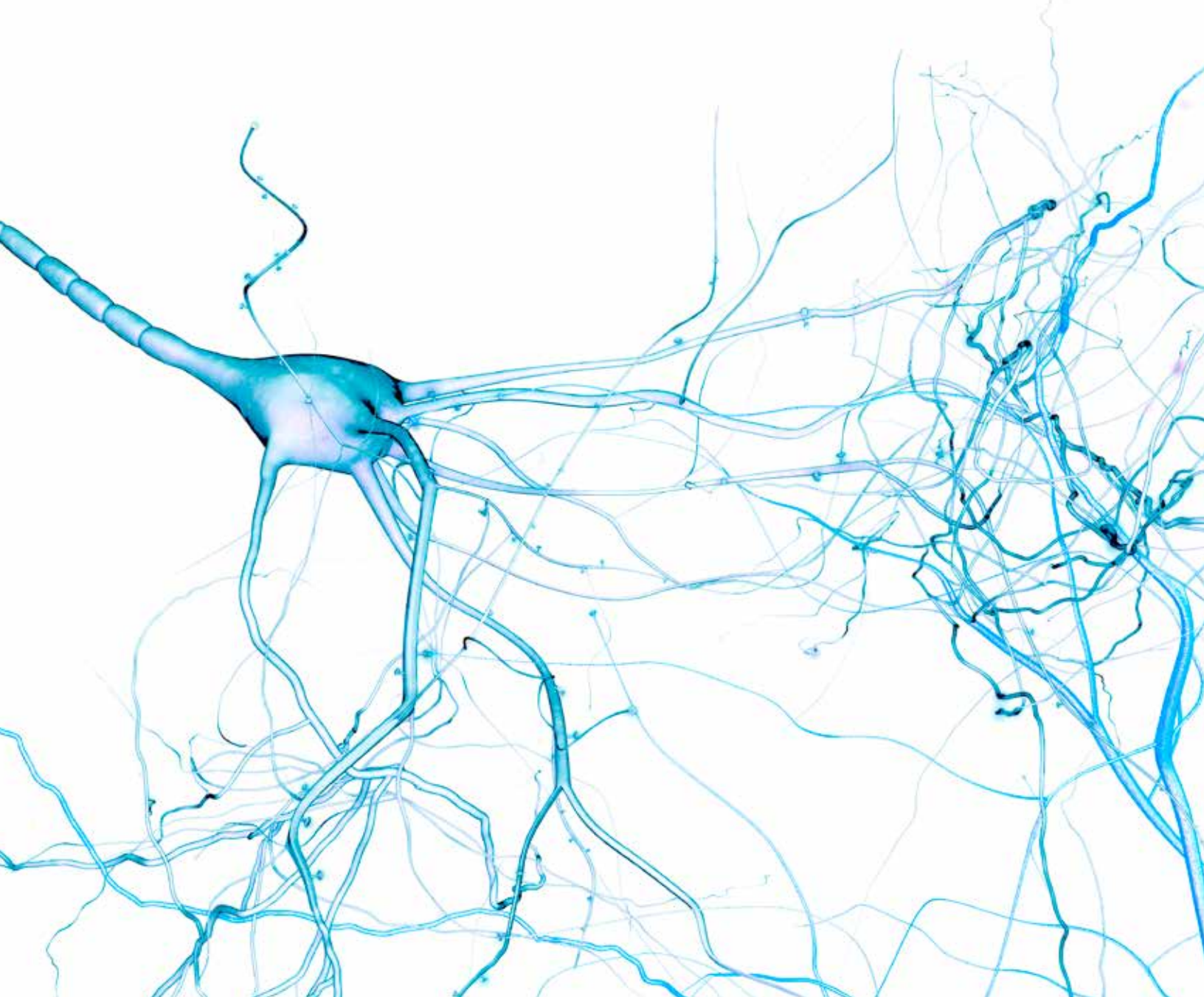
MAYO CLINIC
LABORATORIES

INFORMATIVE CASES FROM MAYO CLINIC:

NEURO-ONCOLOGY

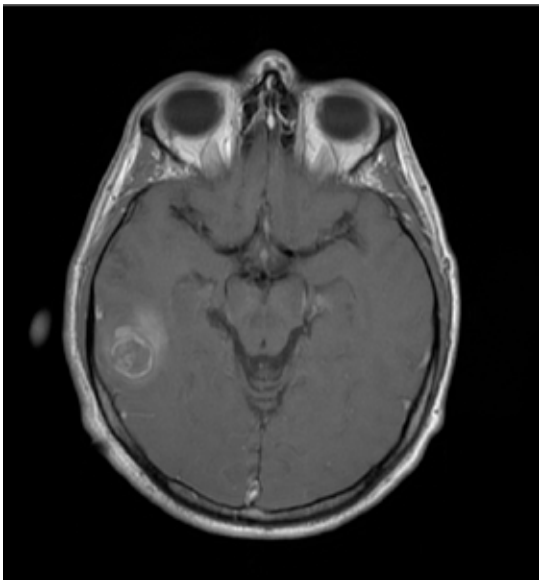


CASE 1

BACKGROUND

A 46-year-old man presented with seizures and was found to have a right temporal lobe ring-enhancing tumor. The patient underwent tumor resection at Mayo Clinic.

Figure 1. T1-weighted axial MRI: right temporal enhancing lesion



HISTOPATHOLOGICAL FINDINGS

- The resected specimen showed a high-grade infiltrating glioma composed by monomorphous tumor cells with round nuclei and high nuclear-to-cytoplasmic ratio. Mitotic activity was brisk and microcalcifications were focally present. Microvascular proliferation and necrosis were observed. Immunohistochemical studies excluded the most common *IDH1* mutation (p.R132H), while ATRX protein expression was retained.
- The diagnoses considered included: 1) IDH-wild-type small-cell glioblastoma, 2) IDH-mutant glioblastoma, or 3) IDH-mutant and 1p/19q codeleted anaplastic oligodendroglioma.

GENETIC TESTING

- Neuro-oncology next-generation sequencing (NGS) panel was consistent with the absence of an *IDH* mutation and revealed a *TERT* promoter mutation.
- Chromosomal microarray showed intact 1p/19q status, *EGFR* amplification associated with gain of chromosome 7, loss of chromosome 10, *CDKN2A/B* homozygous loss, and gain of chromosomes 19 and 20.
- The overall genetic findings, in conjunction with the morphology, led to the final integrated diagnosis of IDH-wild-type small-cell glioblastoma (WHO grade IV).

TEACHING POINTS

- Small-cell glioblastoma is a subtype of IDH-wild-type glioblastoma that morphologically overlaps with anaplastic oligodendroglioma due to the nuclear regularity, high nuclear-to-cytoplasmic ratio, microcalcifications, and lack of cellular pleomorphism.
- *TERT* promoter mutations are characteristic of both IDH-wild-type glioblastoma and IDH-mutant oligodendroglioma, which is molecularly defined by the concurrent presence of an *IDH* mutation and 1p/19q co-deletion. The finding of a *TERT* promoter mutation in the absence of an *IDH* mutation, as seen in this case, is consistent with an integrated diagnosis of IDH-wild-type glioblastoma.
- Frequent molecular features of small-cell glioblastoma include *EGFR* amplification (~70%) and losses of chromosome 10 (>95%), as observed in this case.[1]

Figure 2. Histopathological findings

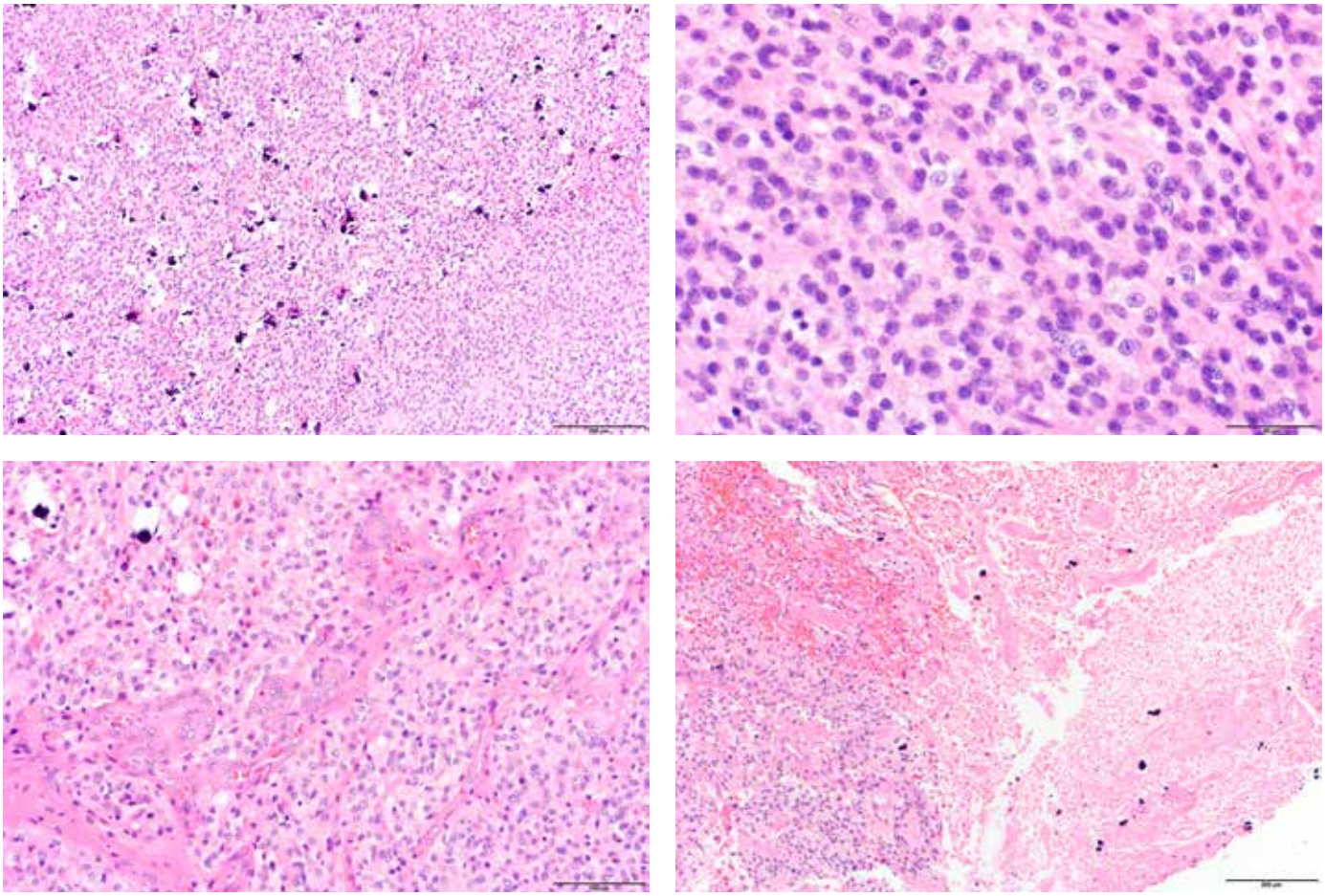
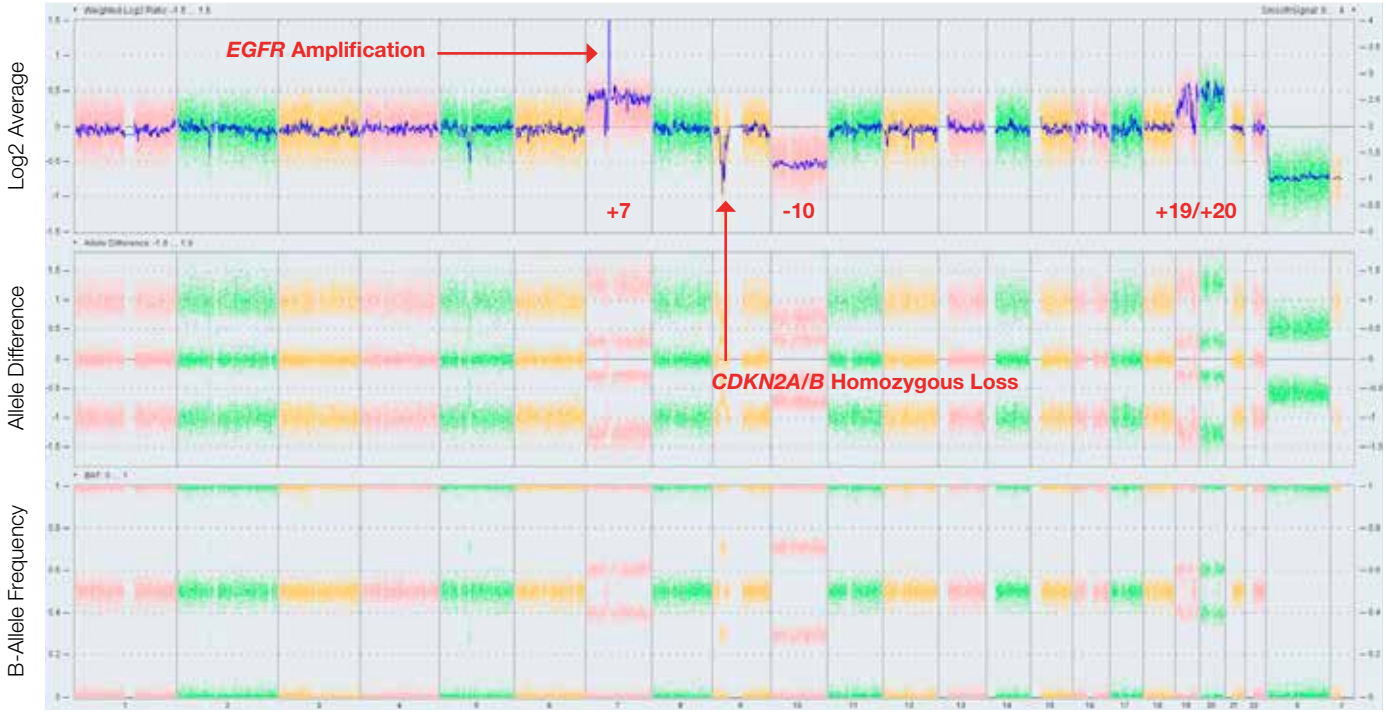


Figure 3. A typical chromosomal microarray pattern for glioblastoma, IDH-wild-type and TERT promoter-mutant

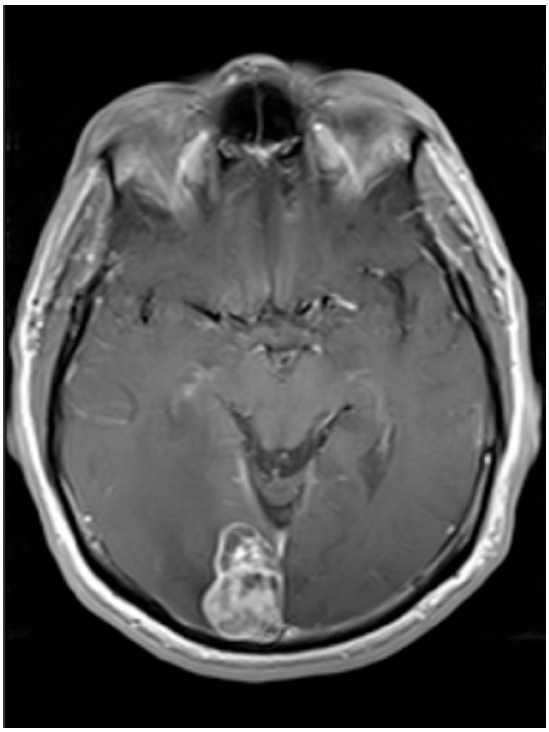


CASE 2

BACKGROUND

A 65-year-old man presented with visual changes and was found to have a large right occipital lobe heterogeneously enhancing tumor. The patient underwent tumor excision at an outside institution, and the case was sent for a neuropathology consultation at Mayo Clinic.

Figure 4. T1-weighted axial MRI: right occipital enhancing lesion



HISTOPATHOLOGICAL FINDINGS

- The resection specimen showed a well-demarcated relatively solid glioma with perivascular arrangement consistent with pseudorosettes. Mitotic activity was low (up to 4/10 HPF), and neither necrosis nor microvascular proliferation was observed. Tumor cells were immunoreactive for GFAP, which highlighted radially arranged perivascular processes, showed a “dot-like” cytoplasmic staining with EMA, and absent Olig2 expression.
- These findings were consistent with the histopathological diagnosis of ependymoma (WHO grade II).

GENETIC TESTING

- Neuro-oncology NGS panel revealed a fusion between *C11orf95* and *RELA*, supporting the integrated diagnosis of *RELA* fusion-positive ependymoma (WHO grade II).
- Chromosomal microarray showed chromothripsis of chromosome 11 (including *RELA*), which is the mechanism that mediates the *C11orf95-RELA* fusion event. Additionally, gain of 1q and whole chromosome 7 were present. These findings were also consistent with a *RELA* fusion-positive ependymoma.

TEACHING POINTS

- *RELA* fusion-positive ependymoma is a newly introduced subtype of supratentorial ependymomas (2016 WHO Classification of CNS Tumors), genetically defined by the presence of gene fusions involving *RELA*.
- *RELA* fusions, of which *C11orf95-RELA* is the most frequent, are mediated by chromothripsis of chromosome 11 and occur exclusively in supratentorial ependymomas.[2,3]
- *RELA* fusion-positive ependymomas account for approximately 85% and 60% of pediatric and adult supratentorial ependymomas, respectively, and available data suggest that they are associated with adverse outcomes.[3]

Figure 5. Histopathological findings

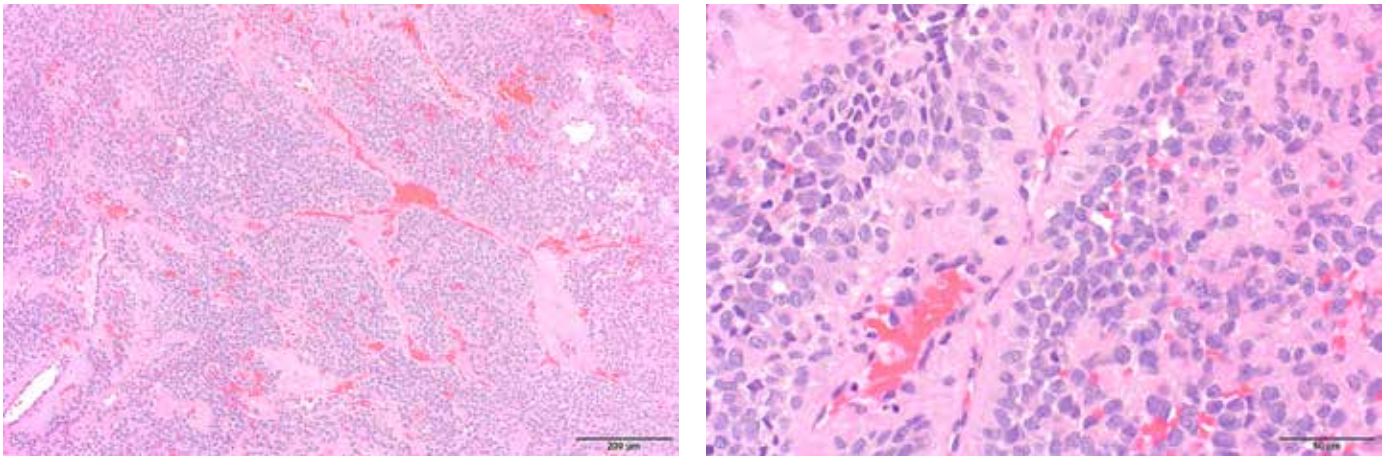


Figure 6. Chromosome 11 chromothripsis in *RELA* fusion-positive ependymoma

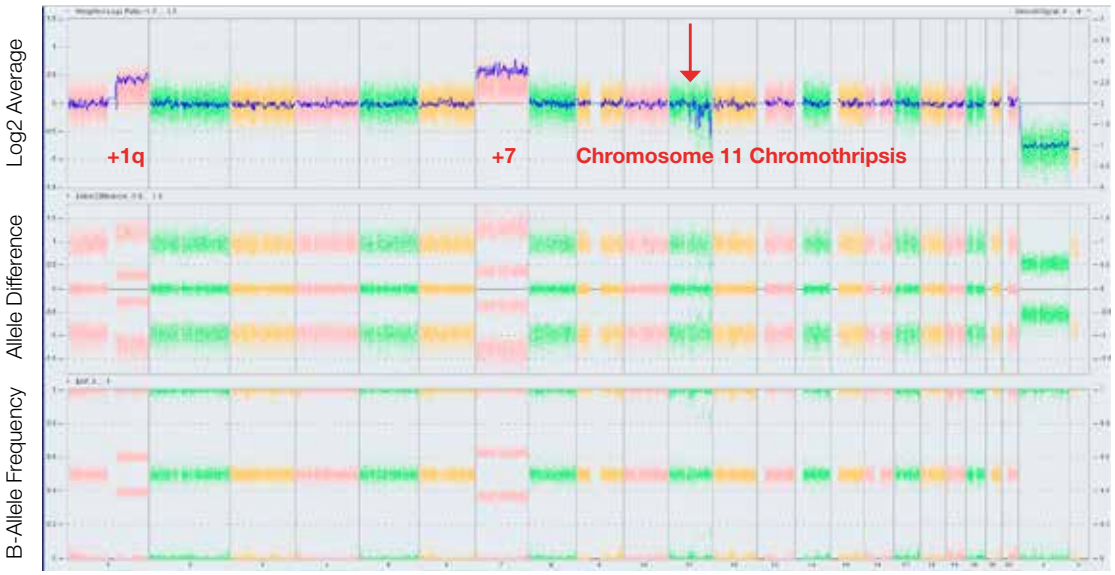
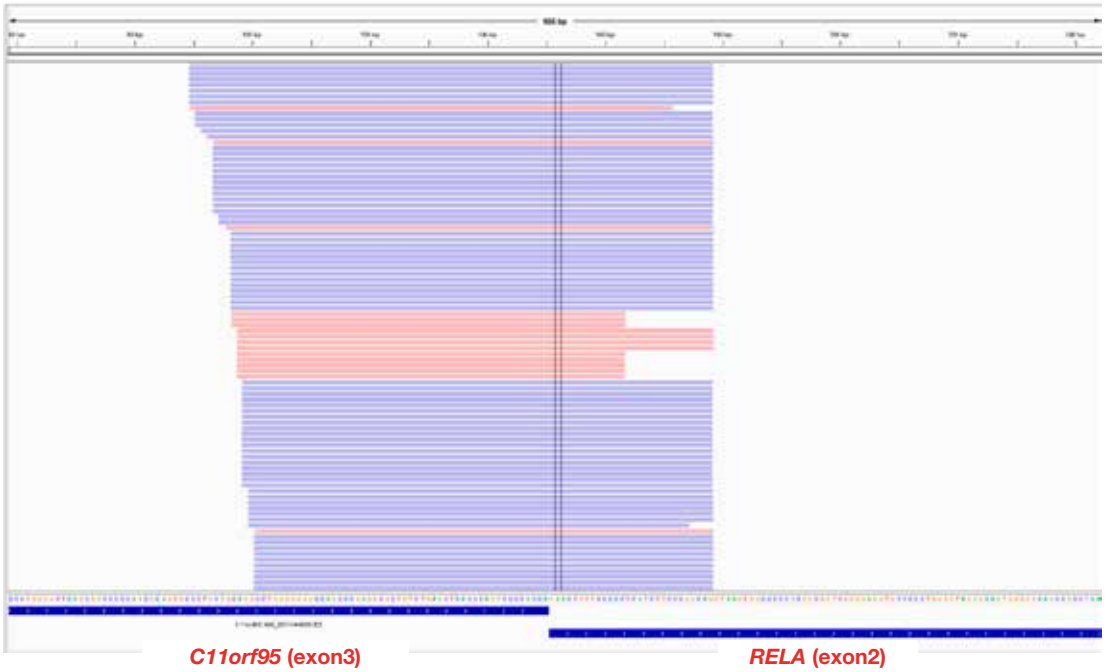


Figure 7. Integrated genomics view (IGV) of the chimeric *C11orf95* (exon 3) and *RELA* (exon 2) fusion gene

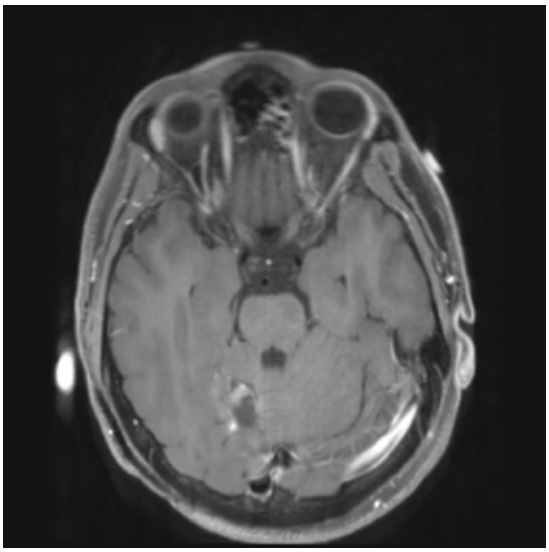


CASE 3

BACKGROUND

A 37-year-old man presented with a recurrent right cerebellar contrast-enhancing tumor. The patient has a history of a right cerebellar anaplastic astrocytoma, resected 7 years ago and treated with radiotherapy. Imaging studies revealed a recurrent right cerebellar contrast-enhancing tumor. The patient underwent surgical re-excision at Mayo Clinic.

Figure 8. T1-weighted axial MRI: right cerebellar enhancing lesion



HISTOPATHOLOGICAL FINDINGS

- The resected specimen showed a high-grade neoplasm with an infiltrative growth pattern and areas showing either an astrocytic or embryonal morphology. Slides from the prior surgery were not available for comparison. Immunohistochemical studies excluded the most common *IDH1* mutation (p.R132H), while demonstrating retained ATRX protein expression and focal synaptophysin immunoreactivity.
- The diagnoses considered included: 1) a recurrent high-grade astrocytoma with a primitive neuronal component, or 2) a second embryonal tumor.

GENETIC TESTING

- Neuro-oncology NGS panel revealed a *TERT* promoter and a *PTCH1* mutation. While this result could be seen in the context of a high-grade IDH-wild-type astrocytoma, this mutation profile has been recurrently observed in adult sonic hedgehog (SHH)-activated medulloblastoma. Indeed, clinico-pathological correlation favored this tumor to be a medulloblastoma, SHH-activated, and TP53-wild-type (WHO grade IV).
- Chromosomal microarray showed gain of 3q, loss of 7q, and copy-neutral loss of heterozygosity (cnLOH) of 20p. While unusual for a diffuse glioma, this copy-number pattern has been described in SHH-activated medulloblastoma, further supporting this diagnosis.

TEACHING POINTS

- Medulloblastoma can now be classified in four main subtypes based on molecular features, according to the 2016 WHO Classification: 1) WNT-activated, 2) SHH-activated and TP53-mutant, 3) SHH-activated and TP53-wild-type, and 4) non-WNT/non-SHH.
- *TERT* promoter mutations have been primarily observed in adult SHH- and WNT-activated tumors.[4,5]
- *PTCH1* mutations have been described almost exclusively in medulloblastoma, primarily in the medulloblastoma, SHH-activated and *TP53*-wild-type subgroup, which encompasses the majority of adult medulloblastoma.[6]
- Therapies targeting the canonical SHH pathway, such as small-molecule inhibitors of SHH-component smoothened (SMO) protein (e.g., vismodegib and sonidegib), are available. Preclinical and early clinical studies suggest potential clinical benefit in treating patients with SHH-activated medulloblastoma harboring a *PTCH1* mutation using SMO inhibitors.[5]

Figure 9. Histopathological findings

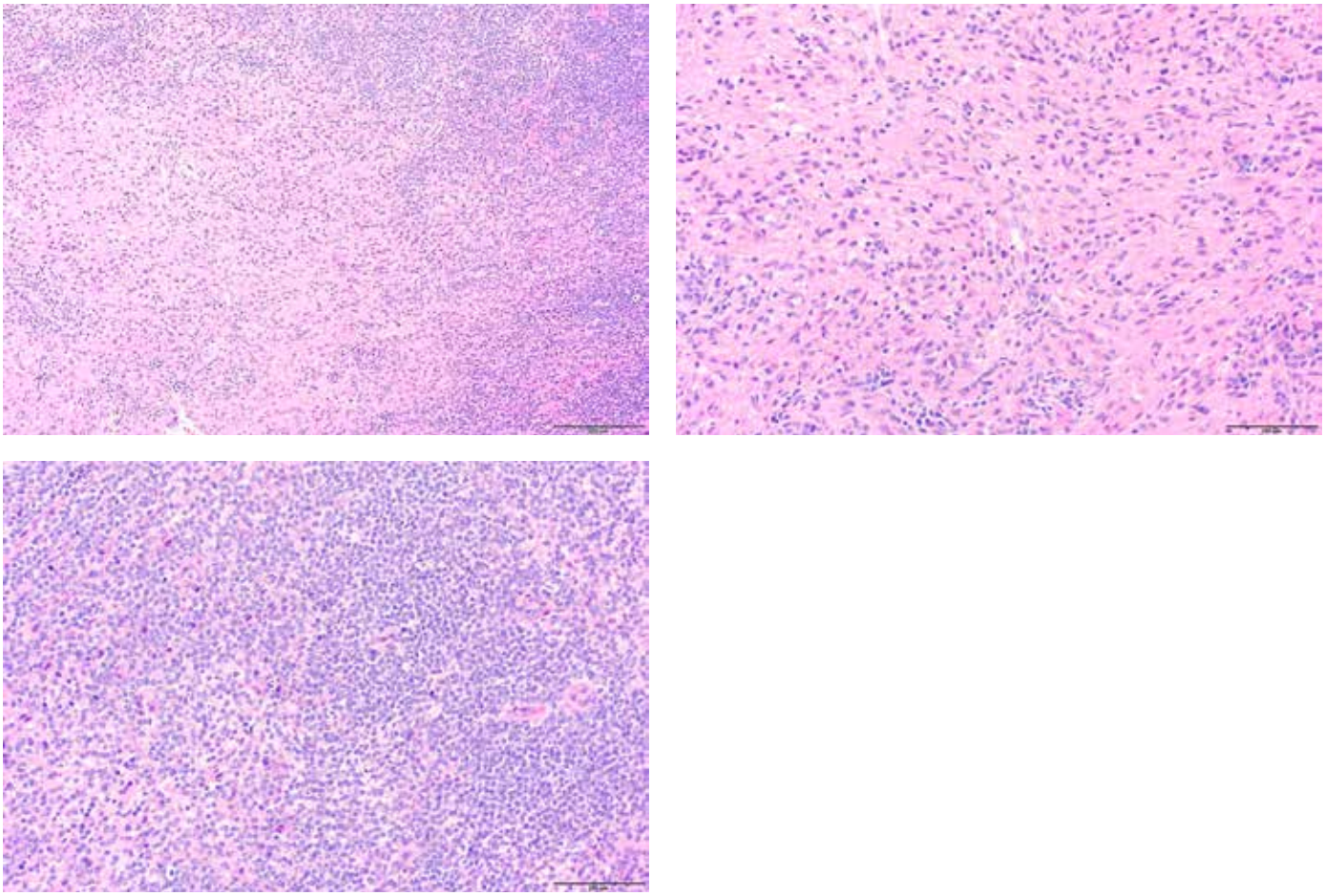
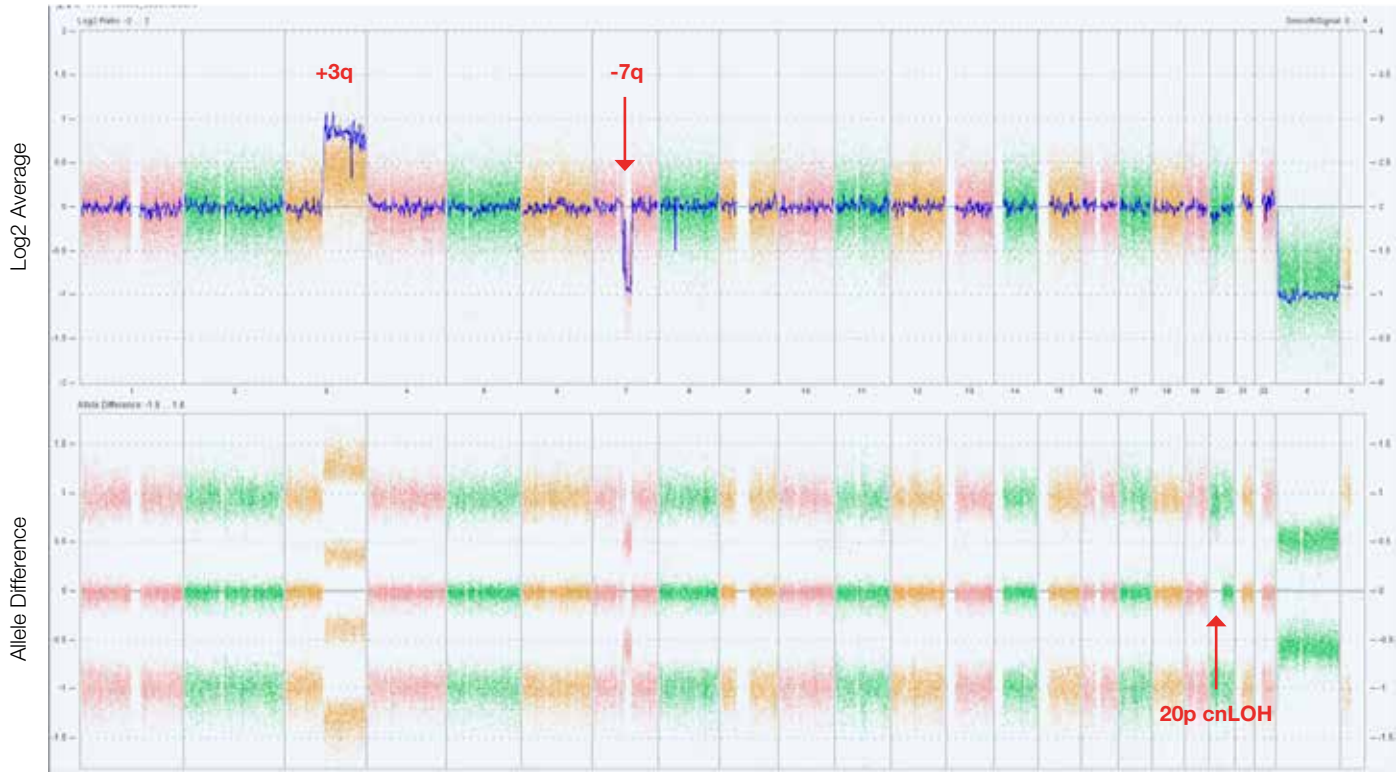


Figure 10. Copy number changes recurrently seen in SHH-activated medulloblastoma



CASE 4

BACKGROUND

A 3-month-old girl was found to have a large, heterogeneous tumor involving the left cerebral hemisphere. She underwent a tumor resection at an outside institution, and the case was sent for a neuropathology consultation at Mayo Clinic.

HISTOPATHOLOGICAL FINDINGS

- The resection specimen showed a highly cellular and mitotically active embryonal tumor. Scattered tumor cells had rhabdoid features, characterized by eccentrically located nuclei with prominent nucleoli and dense eosinophilic globular cytoplasm. Immunohistochemical studies showed that tumor cells had diffuse Olig2 expression with focal GFAP, EMA, and smooth muscle actin staining, along with loss of INI1 nuclear expression. These findings are diagnostic of an atypical teratoid/rhabdoid tumor (AT/RT) (WHO grade IV).

GENETIC TESTING

- Neuro-oncology NGS panel revealed a *SMARCB1* mutation with high allelic frequency/read counts (approximately 87%) in the context of high tumor content (80–90%), consistent with biallelic inactivation of *SMARCB1* in the tumor and suggesting a somatic (rather than germline) origin for this mutation.
- Chromosomal microarray revealed a 22q (including *SMARCB1* gene) cnLOH as the sole copy-number abnormality. The 22q cnLOH resulted in duplication of the acquired *SMARCB1* mutation and biallelic inactivation of this gene.

TEACHING POINTS

- AT/RT is a high-grade CNS embryonal tumor predominantly occuring in young children, defined by inactivation of either *SMARCB1* (a.k.a., *INI1*) or, extremely rarely, *SMARCA4* (a.k.a., *BRG1*).
- Approximately 35–40% of AT/RTs may occur in the context of the rhabdoid tumor predisposition syndrome (RTPS).[7]
- RTPS is an autosomal dominant disorder that arises in the vast majority of cases from a *de novo* germline *SMARCB1/SMARCA4* pathogenic alteration. Therefore, most individuals with RTPS report a negative family history. Additionally, families may show incomplete penetrance and gonadal mosaicism, resulting in an apparent negative family history.
- Given the high frequency of RTPS in patients with an AT/RT, genetic testing may identify the *SMARCB1/SMARCA4* pathogenic alteration and suggest a somatic (i.e., tumor-specific) or germline (i.e., constitutional) origin; if likely somatic in origin, as seen in this case, follow-up germline testing is likely not necessary.

Figure 11. Histopathological findings

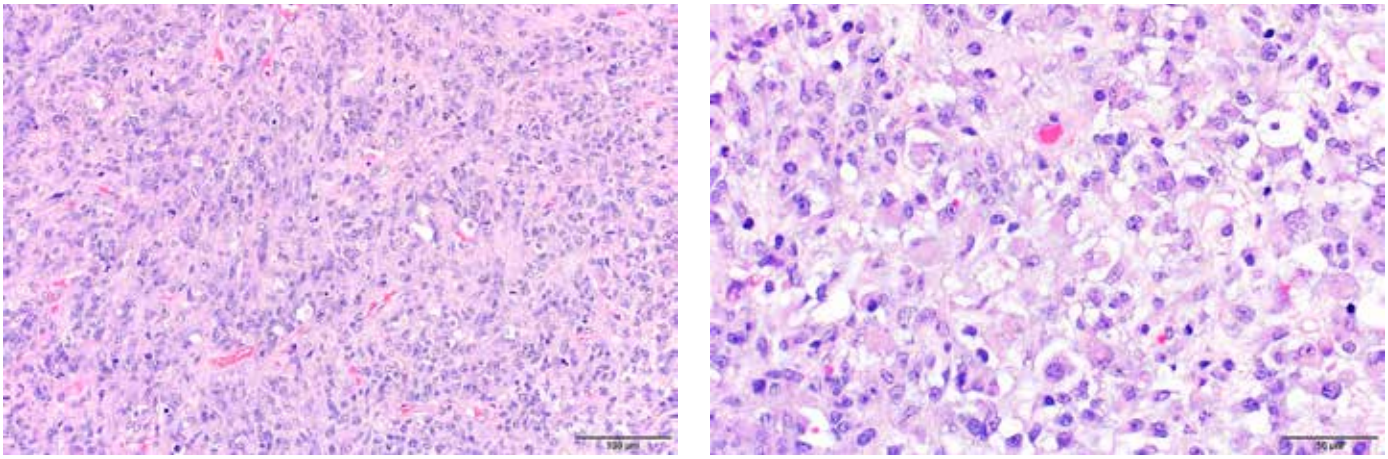
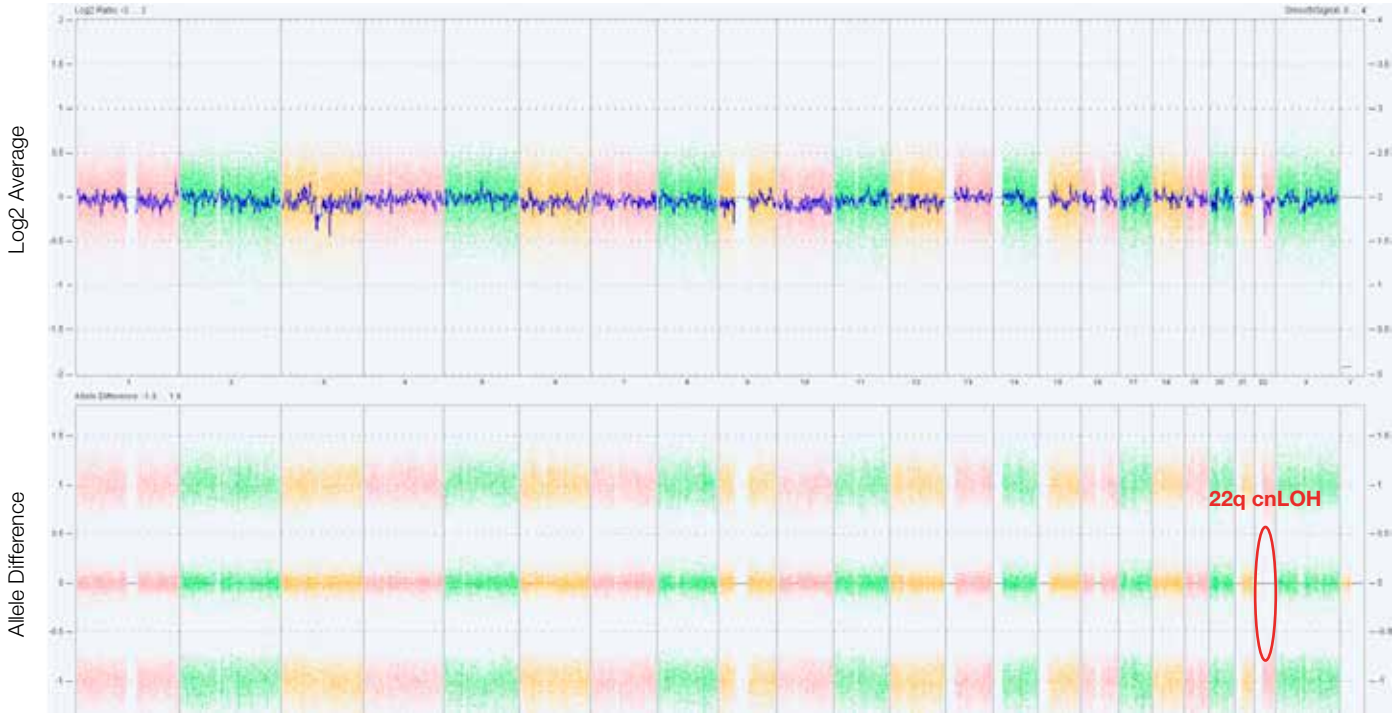


Figure 12. Copy-neutral loss of heterozygozity of chromosome 22q (including *SMARCB1*) in an AT/RT

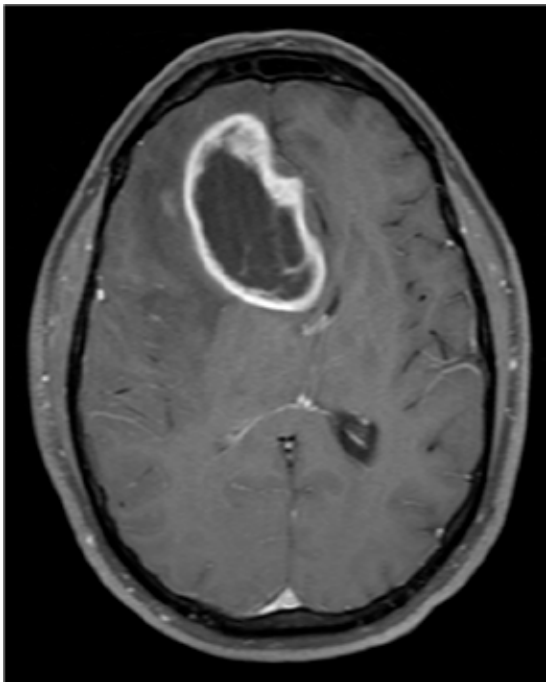


CASE 5

BACKGROUND

A 38-year-old woman was diagnosed with a right frontal glioblastoma at an outside institution. Studies performed at the outside institution showed mutant IDH1 (p.R132H) expression and 1p/19q co-deletion by FISH analysis, a profile more in keeping with oligodendroglioma. Given the discordance between the histopathological diagnosis and the genetic profile, the case was sent for a neuropathology consultation at Mayo Clinic.

Figure 13. T1-weighted axial MRI: right frontal enhancing lesion



HISTOPATHOLOGICAL FINDINGS

- The infiltrating glioma cells showed astrocytic morphology with high mitotic activity, necrosis, and microvascular proliferation. IDH1 R132H immunostain was positive while ATRX protein expression was lost.
- The possibility was considered that this might represent an IDH-mutant glioblastoma and the reported 1p/19q co-deletion result by FISH might represent a false positive.

GENETIC TESTING

- Neuro-oncology NGS panel revealed an *IDH1* R132H mutation, an *ATRX* mutation, and a *TP53* mutation (with twice the allelic frequency of the *IDH1* and *ATRX* mutations). No *TERT* promoter mutation was observed.
- Chromosomal microarray was near tetraploid and extremely complex. Abnormalities included partial loss of 1p and 19q, multiple sub-terminal deletions, chromothripis of 5q and 17, and cnLOH of 17p (including *TP53*). The cnLOH resulted in duplication of the *TP53* mutation accounting for the double allelic frequency observed by NGS.
- These genetic findings, including the overall complexity of the array, are characteristic of IDH-mutant high-grade infiltrating astrocytomas, and in conjunction with the morphology, led to the final integrated diagnosis of an IDH-mutant glioblastoma (WHO grade IV).

TEACHING POINTS

- Approximately 5% of TERT-mutant IDH-wild-type glioblastomas and 10% of IDH-mutant astrocytomas will have partial deletions of both 1p and 19q. Chromosomal microarray can differentiate between whole and partial arm deletions, while FISH analysis cannot.
- IDH-mutant astrocytomas usually acquire *TP53* and *ATRX* mutations. This combination of mutations generates defects in homologous recombination and, thus, chromosomal instability. This pattern is easily evaluated by chromosomal microarray.
- IDH-mutant astrocytomas usually have cnLOH of 17p resulting in duplication of the acquired *TP53* mutation, as seen in this case. When such tumors do not have 17p cnLOH, they often acquire two *TP53* mutations.
- The median survival of IDH-mutant glioblastomas is approximately 3 years when treated with concurrent temozolomide and radiotherapy.[8] The median survival of WHO grade III IDH-mutant astrocytomas and IDH-mutant codeleted oligodendrogliomas is approximately 5.5 and 14.7 years, respectively, when treated with PCV and radiotherapy.[9]

Figure 14. Histopathological findings.

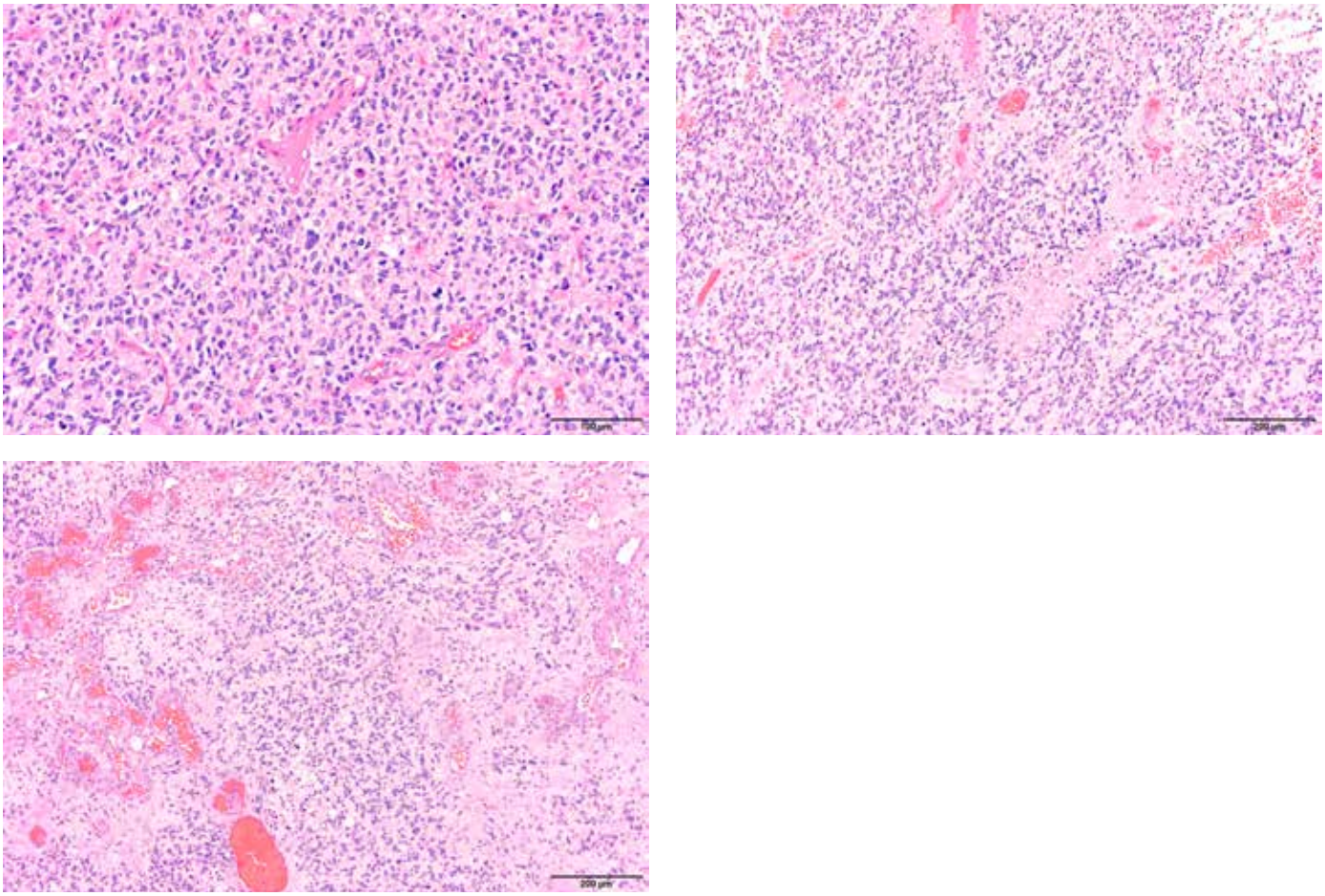
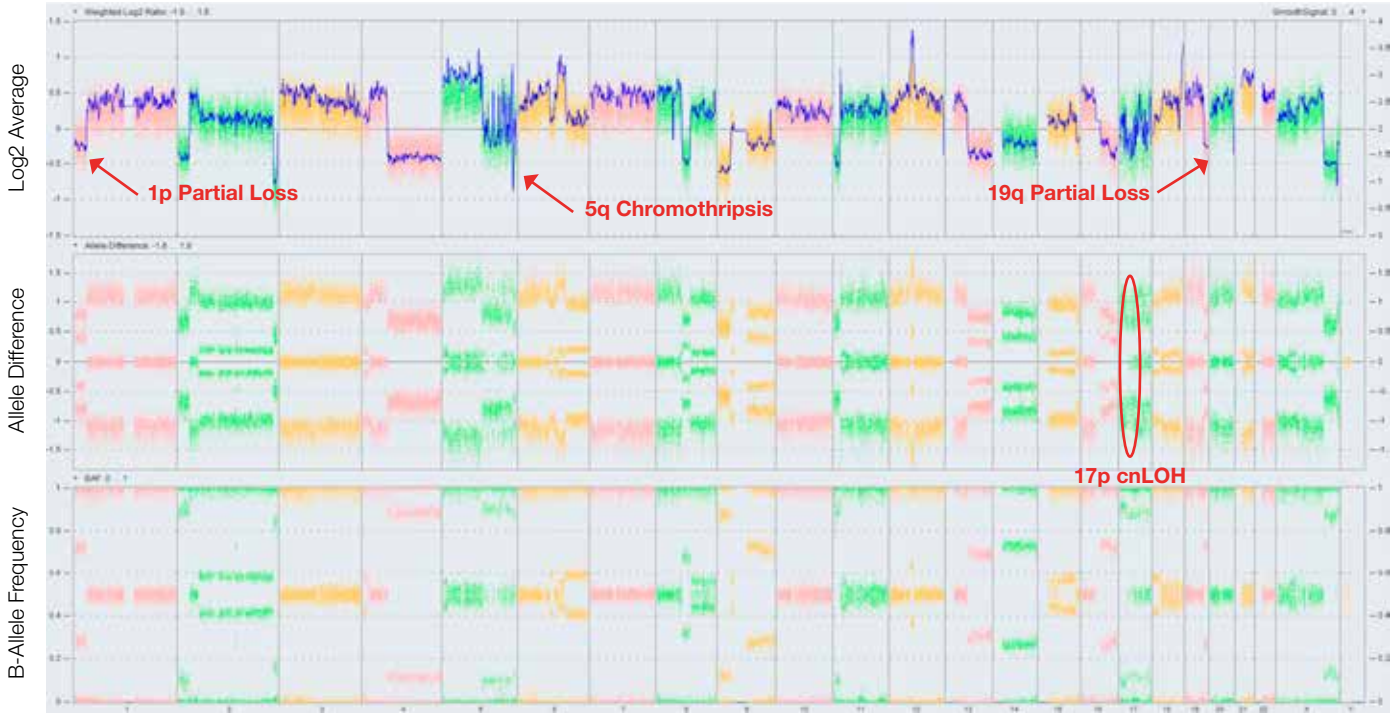


Figure 15. A very complex chromosomal microarray pattern



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