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Review Article

1p/19q co-deleted fibrillary astrocytomas: Not everything that is co-deleted is an oligodendroglioma

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ABSTRACT

The presence of chromosome 1p/19q co-deletion is one of the hallmark required criteria for the diagnosis of oligodendroglioma, using the 2016 World Health Organization (WHO) Classification of Tumours of the Central Nervous System. Descriptions in the literature of astrocytomas, primarily glioblastomas, demonstrating partial losses on one or the other chromosome have been described. The significance of these small deletions is uncertain. Only rarely have cases of fibrillary astrocytoma been described as having co-deletion, which may potentially cause diagnostic confusion with oligodendroglioma. The goal of this study is to examine a large number of fibrillary astrocytomas to document how often 1p/19q co-deletions are present by Fluorescent In Situ Hybridization (FISH) testing (the testing method of choice in many institutions) and to evaluate what other markers may be helpful in avoiding misdiagnosis.

This study is a retrospective evaluation of 359 fibrillary astrocytomas (55 grade II, 62 grade III and 242 grade IV) encountered between June 2016 and June 2019, we identified 11 tumors (3.1%) that had 1p/19q co-deletion by FISH testing. The clinical and pathologic features of these cases were reviewed. The 11 cases with co-deletion included 5 females who ranged in age from 37 to 86 years (median 63 years). Tumors arose in the temporal lobe in 5 patients, frontal lobe in 2, parietal lobe in 2, occipital lobe in 1, and cerebellum in 1. Final diagnoses included glioblastoma in 8 patients, anaplastic astrocytoma in 2, and diffuse astrocytoma in 1. Only 1 case (anaplastic astrocytoma) demonstrated evidence of IDH-1 immunoreactivity; none of the other 10 tumors showed evidence of an IDH1/2 mutation by PCR testing. Four tumors demonstrated p53 immunostaining of 30% or more. ATRX mutation as evidenced by loss of staining was observed in only 2 cases. Evidence of EGFR amplification by FISH testing was noted in 5 cases. Of particular note in the one case that demonstrated both 1p/19q co-deletion and an IDH-1 mutation, LOH testing was done and showed only partial losses on both chromosomes. Additionally, this tumor also demonstrated evidence of ATRX and p53 mutations by immunohistochemistry. In conclusion, co-deletions were noted in a minority of astrocytomas (3.1% of cases in the current study). Only 1 of 11 of these cases also demonstrated evidence of an IDH mutation, potentially raising differential diagnostic confusion with oligodendroglioma. Use of LOH 1p/19q testing, if available, or other markers such as ATRX, p53 and EGFR may be helpful in avoiding misclassification of such tumors as oligodendroglioma.

1. Introduction

In 2016, the World Health Organization (WHO) revised the grading and classification of brain tumors [1]. Prior to this, tumors were graded and typed purely on histologic morphology. The most common of the glial tumors are fibrillary astrocytomas and oligodendrogliomas; distinction between the two tumor types is important from a prognostic standpoint and from a treatment perspective [1]. Grade for grade, oligodendrogliomas do better and respond better to treatment. According to the 2016 WHO, oligodendrogliomas demonstrate morphology marked by generally rounded cells with scant cytoplasm, an isocitrate dehydrogenase (IDH)-1 or 2 mutation, and co-deletion on chromosomes 1p/19q [1]. It is well established, that a subset of astrocytomas also demonstrate evidence of IDH mutations [2-7]. Fewer cases also have been shown to demonstrate evidence of deletions on chromosomes 1p and/or 19q [8-12]. Only rare cases of co-deleted astrocytomas have been documented. Given the differences in prognosis and treatment approaches, distinction of such cases from oligodendroglioma is important.

This study will retrospectively examine a large group of fibrillary

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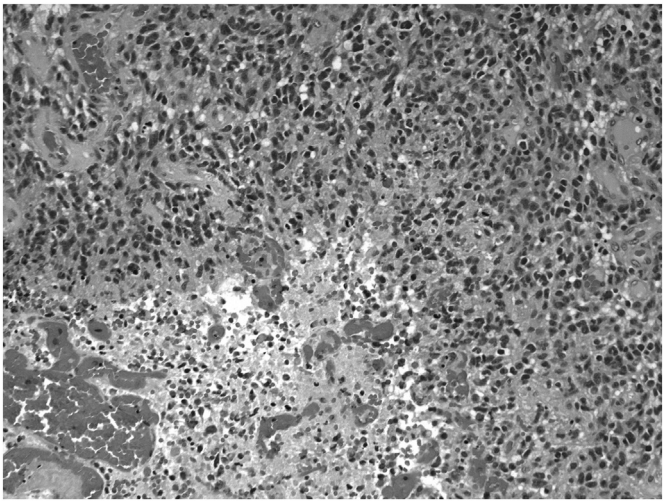

Fig. 1. Case 2. Glioblastoma WHO grade IV marked by prominent cellularity, an occasional mitotic figure and geographic necrosis (hematoxylin and eosin, original magnification 200×).

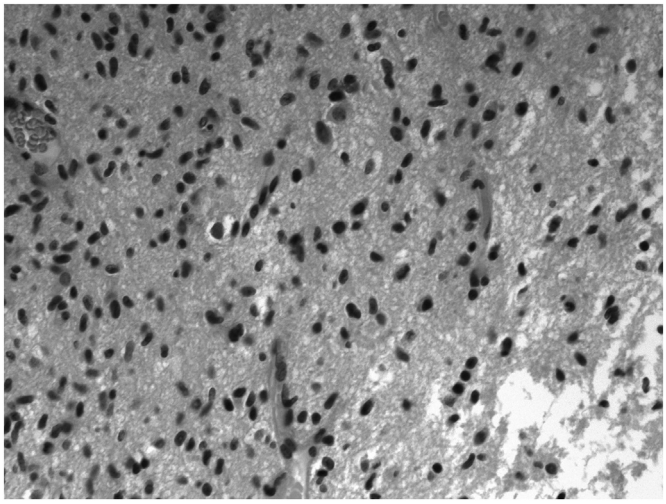

Fig. 3. Case 9. Diffuse astrocytoma WHO grade II characterized by mild increased cellularity and atypical appearing astrocytic cells (hematoxylin and eosin, original magnification 400×).

astrocytomas to determine how often chromosome 1p/19q co-deletions are observed and to evaluate what other markers may be useful to help avoid misdiagnosis as oligodendroglioma.

2. Materials and methods

Institutional Review Board Approval was obtained prior to commencement of the study. The surgical pathology files were searched for astrocytic tumors that had interphase fluorescence in situ hybridization (FISH) testing performed from June 2016–June 2019, looking for evidence of deletions on chromosomes 1p and 19q. Of the 381 fibrillary astrocytomas examined during that time frame, 359 cases (94.2%) had 1p/19q FISH testing performed. Cases which demonstrate evidence of deletion on one or both chromosomes were identified and form the study group. The WHO grading schema was used to grade the tumors (Figs. 1–3) [1]. Clinical information on these patients was obtained by review of the medical record.

For each of these cases, a panel of antibody stains were evaluated including IDH-1 (R132H) (1:40 dilution. Histo BioTec. Miami Beach, FL) (Fig. 4), ATRX (1:200 dilution. Sigma Aldrich. St. Louis, MO)

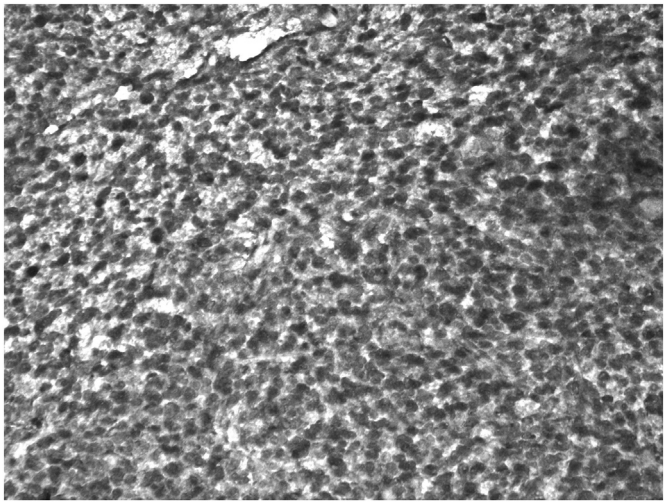

Fig. 4. Case 10. Diffuse positive immunostaining with antibody to IDH-1 (R132H) is seen here, consistent with a mutant status (original magnification 200×).

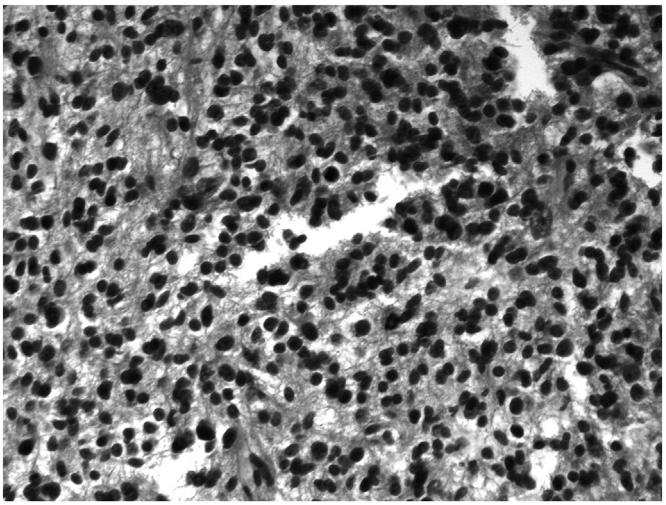

Fig. 2. Case 10. Anaplastic astrocytoma WHO grade III marked by moderate hypercellularity and an occasional mitotic figure (hematoxylin and eosin, original magnification 400×).

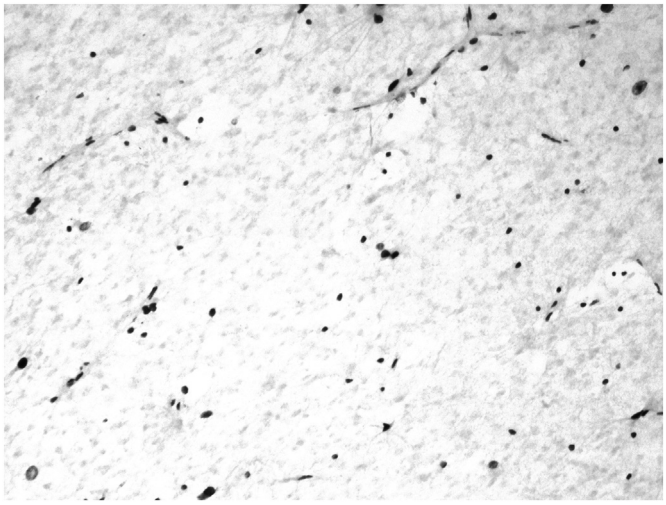

Fig. 5. Case 10: Loss of ATRX staining was observed, consistent with a mutant status (original magnification 200×).

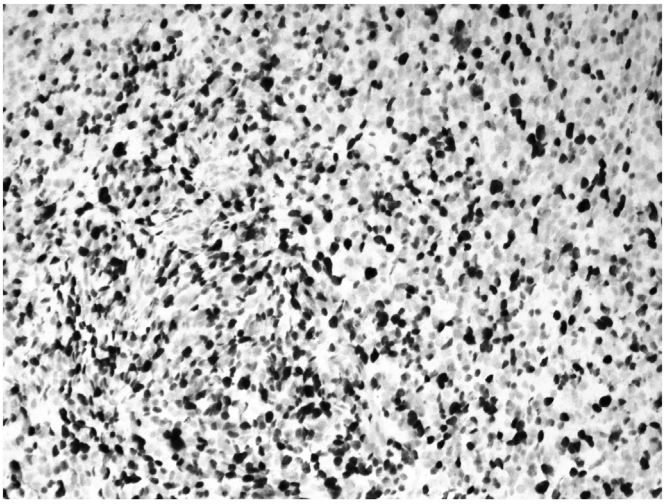

Fig. 6. Case 10: Increased p53 immunoreactivity was present, consistent with a likely TP53 mutation (original magnification 200×).

(Fig. 5) (Haase et al. 2018), and p53 (1:20 dilution. Agilent DAKO, Santa Clara, CA) (Fig. 6). Immunostains were performed on 10% formalin-fixed, paraffin embedded tissues sectioned at 4 μm.

1p/19q FISH testing will be performed on 4-μm thick sections generated from 10% formalin –fixed, paraffin embedded tissue. Locus specific probes (1p36 and 19q13) along with reference probes (1q25 and 19p13) (Abbott Molecular/ Vysis, Des Plaines, IL) were used. Analysis was performed on tumor cells and only atypical nuclei with two or more reference probe signals were counted (Figs. 7, 8). Reported results represent an average count of 40 tumor cell nuclei. Loss is defined as a ratio of less than or equal to 0.7 of probe target to reference probe.

Epidermal growth factor receptor (EGFR) FISH testing was similarly performed on 4-μm thick sections generated from 10% formalin-fixed, paraffin embedded tissue. EGFR (7p12) and chromosome 7 pericentromeric (7p11.1-q11.1) (CEP7) probes (Abbott Molecular/Vysis, Des Plaines, IL) were used. Analysis was performed on 40 tumor cell nuclei. Amplification for EGFR was defined as a ratio of the EGFR signals to the CEP7 signals of > 2.0.

IDH1/2 PCR testing was performed using DNA which was extracted from tissue sections cut from the 10% formalin-fixed, paraffin embedded tissue block. Library construction was done, utilizing the custom Cancer Hotspot Panel v.1 (Life Technologies, Grand Island, NY). DNA sequencing of gene mutation hotspot regions was performed on the MiSeq instrument (Illumina, San Diego, CA). NextGENe software (Softgenetics, State College, PA) was used to analyze FASTQ files to identify hotspot mutations if present. Sequence changes outside the analyzed mutation hotspots, including intronic, non-coding, and splicing site variants were not identified. Any insertions larger than 20 base pairs or deletions larger than 40 base pairs cannot be reliably identified. The lower limit of detection of the assay used is approximately 5% allele proportion.

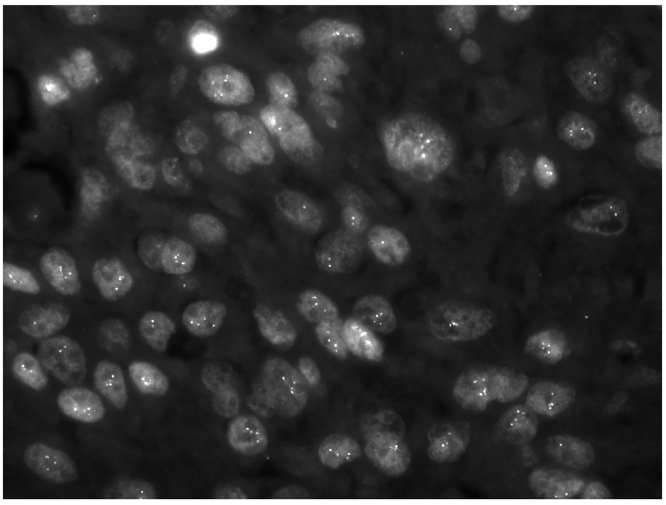

Fig. 7. FISH testing in a normal astrocytoma showing 4 bright spots- two correspond to the 1q25 probe marker indicating that there are two copies of chromosome 1 present and two corresponding to the 1p36 probe marker.

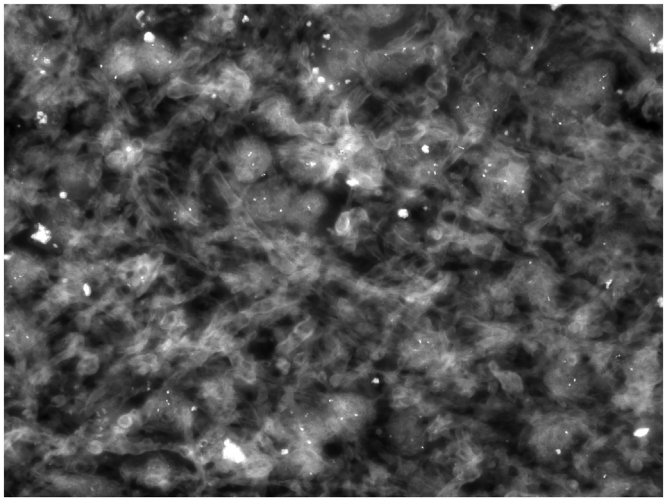

Fig. 8. Case 10. Only 3 bright spots are noted due to the presence of 1p36 locus in only of the copies of chromosome 1, indicating a deletion.

3. Results

Of the 381 fibrillary astrocytomas evaluated during the time period of the study, 1p/19q FISH testing results were available in 359 cases (94.2%) and this group comprised the cohort that was examined in this study. Of the 359 cases, 55 were diagnosed as diffuse astrocytoma (WHO grade II), 62 were diagnosed as anaplastic astrocytoma (WHO grade III), and 242 were diagnosed as glioblastoma (WHO grade IV). The mean age at the time of diagnosis for the entire cohort was 57 years (range 4 to 90 years) and the cohort included 207 males (57.7%) and 152 females (42.3%). Of the 341 tumors for which a location was known, the most common locations of the tumors in the overall cohort were frontal lobe (N = 131, 38.4%), temporal lobe (N = 110, 32.3%), parietal lobe (N = 68, 19.9%), occipital lobe (N = 11, 3.2%), and thalamus (N = 9, 2.6%). Table 1 summarizes the clinical and pathologic features of the cohorts examined in this study.

Of the 359 cases of astrocytoma, 19 patients (5.3% demonstrated a loss on chromosome 1p only). This group included 14 males and 5 females whose initial surgery was performed at a mean age of 59.9 years (range 26 to 77 years). The most common locations of tumors in this group include frontal lobe (N = 8), temporal lobe (N = 4), and parietal lobe (N = 2). Diagnoses included 1 grade III tumor and 18 grade IV tumors.

Of the 359 cases of astrocytoma, 35 patients (9.7% demonstrated a loss on chromosome 19q only). This group included 27 males and 8 females whose initial surgery was performed at a mean age of 56.5 years (range 26 to 82 years). The most common locations of tumors in this group include frontal lobe (N = 11), temporal lobe (N = 11), and parietal lobe (N = 7). Diagnoses included 3 grade II tumors, 4 grade III tumors, and 28 grade IV tumors.

Of the 359 cases of astrocytoma, 11 patients (3.1%) demonstrated evidence of co-deletion on both chromosomes 1p and 19q on FISH

Table 1
Summary of clinical and pathologic features of study groups.

Parameters	Total cohort	1p Loss only	19q Loss only	1p/19q co-deleted
Number of patients	359	19	35	11
Age (years)	Mean: 57 Range: 4–90	Mean: 59.9 Range 26–77	Mean: 56.8 Range: 26–82	Median: 64 Range: 37–86
Gender				
Male	207 (57.7%)	14 (73.7%)	27 (77.1%)	6 (54.5%)
Female	152 (42.3%)	5 (26.3%)	8 (22.9%)	5 (45.5%)
Most common location				
Frontal	131 (38.4%)	8 (42.1%)	11 (31.4%)	2 (18.2%)
Temporal	110 (32.3%)	4 (21.1%)	11 (31.4%)	5 (45.5%)
Parietal	68 (19.9%)	2 (10.5%)	7 (20%)	2 (18.2%)
Occipital	11 (3.2%)	0	3 (8.6%)	1 (9.1%)
Diagnosis				
Grade II	55 (15.3%)	0	3 (8.6%)	1 (9.1%)
Grade III	62 (17.3%)	1 (5.3%)	4 (11.4%)	2 (18.2%)
Grade IV	242 (67.4%)	18 (94.7%)	28 (80%)	8 (72.7%)
IDH Mutated				
(N)	101/358 (28.2%)	4 (21.1%)	13/34 (38.2%)	1 (9.1%)
p53 ≥ 30% Positive				
(N)	111/346 (32.1%)	5/18 (27.8%)	9/34 (26.5%)	4 (36.4%)
ATRX Loss				
(N)	78/350 (22.3%)	2 (10.5%)	10 (28.6%)	2 (18.2%)
EGFR Amplification				
(N)	114/323 (35.3%)	5/18 (27.8%)	9/32 (28.1%)	5 (45.5%)

testing. The median 1p36/1q25 ratio observed in this group was 0.62 (range 0.39–0.70). The median 19q13/19p13 ratio observed in this group was 0.68 (range 0.60–0.74). Table 2 summarizes the salient clinical, pathologic and molecular results for this group of 11 patients. Patients ranged in age from 37 to 86 years (median 64 years). The patients included 6 males and 5 females. Tumor locations include temporal lobe (N = 5), frontal lobe (N = 2), parietal lobe (N = 2), occipital lobe (N = 1) and cerebellum (N = 1). Final diagnoses included glioblastoma WHO grade IV (N = 8), anaplastic astrocytoma WHO grade III (N = 2) (Fig. 4) and diffuse astrocytoma grade II (N = 1).

Of the 11 cases, only 1 patient (case 10) demonstrated evidence of immunostaining using antibody to IDH-1 (R132H). The remaining 10 patients showed no evidence of IDH-1 immunostaining; none of those 10 patients showed evidence of an IDH-1 or IDH-2 mutation by PCR testing. p53 immunostaining was observed in all cases to some degree and ranged from < 5% to about 70%. Four tumors (cases 3, 5, 6, and 10) demonstrated 30% or more immunostaining with p53, more suggestive of a TP53 mutation. ATRX mutation as evidence by loss of staining was observed in only 2 tumors (cases 3 and 10). Evidence of EGFR amplification by FISH testing was observed in 5 tumors (cases 1, 2, 4, 7, 8).

Of particular note in Case 10, the tumor demonstrated both molecular findings typically associated with oligodendrogliomas (1p/19q codeletion and IDH mutation). LOH testing was done on this particular case and showed only partial losses on both chromosomes, not typical of the large deletions seen in oligodendroglioma. Additionally, this tumor also demonstrated evidence of an ATRX mutation and p53 mutation by immunohistochemistry, both findings that would be very unusual for an oligodendroglioma.

4. Discussion

According to the WHO Classification of brain tumors, most recently revised in 2016 [1], a diagnosis of oligodendroglioma is predicated on three findings: 1) morphology classically ascribed to that tumor type (i.e. a proliferation of cells with generally rounded nuclei and scant cytoplasm accompanied by an arcuate capillary vascular pattern), 2) the presence of a demonstrable mutation of IDH-1 or IDH-2, and 3) the presence of co-deletion of the tumor on chromosomes 1p and 19q. Complicating this definition is the fact that a subset of fibrillary astrocytomas may contain areas that histologically resemble oligodendroglioma. The designation of tumors with overlapping morphologic features of an astrocytoma and oligodendroglioma as mixed glioma or oligoastrocytoma was a widely employed designation prior to 2016. The WHO now encourages pathologists to try and classify these tumors with overlapping morphologic features as one or the other, based on molecular findings. Additionally complicating matters is the recognition that a significant subset, up to 2/3 of cases in some series, of fibrillary astrocytomas may also demonstrate an IDH mutation [2-4,7]; therefore, IDH mutations do not equate with a diagnosis of oligodendroglioma.

Deletions on chromosomes 1p and 19q, the other signature molecular feature of oligodendrogliomas, may also be encountered in a subset of fibrillary astrocytomas. Kaneshiro et al., in reviewing FISH results in 337 glioblastomas looking for deletions on chromosomes 1p and 19q, found evidence of 1p deletions in 17 tumors (5.1%) and deletions on chromosome 19q in 18 tumors (5.3%) [10]. Nine of the tumors (3.7%) in the same study demonstrated evidence of co-deletion [10]. The deletions in oligodendrogliomas are classically near full arm deletions. One of the limitations of FISH testing, is that it can detect deletions at a particular locus but cannot assess the extent of the deletion (partial or full arm). To do so requires the use of other molecular testing such as polymerase chain reaction(PCR)-based loss of heterozygosity (LOH) testing, comparative genomic hybridization (CGH), or whole exome sequencing [8,12].

Sim and colleagues evaluated 80 glioblastomas using multiple testing modalities to assess for 1p/19q co-deletion (FISH, array-CGH

Table 2
Summary of 1p/19q co-deleted astrocytomas.

Case	Age (years)	Gender	Location	Diagnosis	WHO Grade	IDH-1 (R132H) Stain	IDH-1/2 PCR	p53	ATRX	EGFR Amplification
1	64	M	L Parietal	GB	IV	−	−	10–15%	−	+
2	86	F	L Frontal	GB	IV	−	−	15%	−	+
3	55	F	Cerebellum	GB	IV	−	−	30–40%	Loss	−
4	48	F	R Temporal	AA	III	−	−	5%	−	+
5	83	M	R Temporal	GB	IV	−	−	40%	−	−
6	57	M	L Temporal	GB	IV	−	−	70%	−	−
7	62	M	R Parietal	GB	IV	−	−	10–15%	−	+
8	85	F	L Temporal	GB	IV	−	−	20%	−	+
9	72	F	Temporal	DA	II	−	−	< 5%	−	−
10	37	M	L Frontal	AA	III	+	Not done	60%	Loss	−
11	63	M	R Occipital	GB	IV	−	−	10%	−	−

Abbreviations: M = male, F = female, L = left, R = right, DA = Diffuse astrocytoma, AA = Anaplastic astrocytoma, GB = Glioblastoma.

and whole exome sequencing) [8]. FISH testing in their study showed 1p/19q co-deletion in two tumors (2.5%), isolated 1p deletions in six tumors (7.5%) and isolated 19q deletions in two cases (2.5%). The array CGH and whole exome sequencing showed isolated deletion of 19q in four cases (5%) and 19 monosomy in only 1 case (1.3%); 1p/19q co-deletions were not observed in any of the tumors. Eleven cases were noted to show discordant 1p/19q results between FISH testing and the other two testing modalities; most of these showed that 1p and/or 19q deletions seen on FISH corresponded to only partial deletions when evaluated using the other modalities. Despite these findings, FISH testing for 1p/19q co-deletions remains a widely employed methodology in evaluating gliomas.

In the current study using FISH testing, isolated 19q deletions were noted in 9.7% of tumors and isolated 1p deletions were observed in 5.3% of tumors. These findings or of uncertain significant in astrocytomas and do not cause confusion in terms of diagnosis. Eleven tumors (3.1% in the current study) showed evidence of 1p/19q co-deletion by FISH testing. These later cases may potentially be confused with oligodendrogliomas, particularly if an IDH mutation was also present. A coexistent IDH mutation was only observed in one of these eleven cases, observed by IDH-1 (R132H) immunostaining. The other 10 cases were evaluated by PCR testing to exclude an IDH-1 or IDH-2 mutation that would not have been picked up by immunostaining. PCR-based LOH testing of the 1 co-deleted, IDH-mutated tumor showed that the deletions were only partial losses, inconsistent with those seen in oligodendrogliomas. In such rare cases, additional molecular testing to further assess the extent of deletions is recommended.

The current study also presented an opportunity to explore other immunomarkers that could be helpful in resolving the differential diagnosis in the rare 1p/19q co-deleted astrocytoma. Alpha-thalassemia/mental retardation syndrome X-linked gene (ATRX) missense and truncating mutations are common in astrocytomas and not oligodendrogliomas [13-18]. These mutations can be detected by loss of immunostaining. Liu et al. noted loss of immunostaining with ATRX in 27% of Grade II astrocytomas and 41% of grade III astrocytomas, which fairly well correlated with mutation rates [16]. Others have found similar or even higher mutation rates in astrocytomas [17,18].

Similarly, TP53 mutations have been long recognized as being present in a subset of fibrillary astrocytomas and are generally not found in oligodendrogliomas [19-21]. EGFR amplification or overexpression has also been noted in a subset of astrocytomas, particularly higher grade tumors; it is generally not observed in oligodendrogliomas [22-24]. Of the 11 tumors which were co-deleted in the current study, four tumors demonstrated significant TP53 immunostaining highly suggestive of a mutation and a diagnosis of astrocytoma and 2 cases demonstrated loss of ATRX staining also consistent with astrocytoma. EGFR amplification by FISH testing was observed in 5 cases, likewise favoring an astrocytomas diagnosis in those cases. The one case with IDH-1 mutation demonstrated both additional molecular findings, corroborating the astrocytoma diagnosis.

In conclusion, a small subset of fibrillary astrocytomas may demonstrate molecular features (IDH mutations and 1p/19 co-deletions) which are currently used to define oligodendrogliomas. Because of significant treatment and prognostic implications, making the correct diagnosis is important. In astrocytomas which may demonstrate an IDH mutation and 1p/19q co-deletion by FISH testing, additional molecular testing to determine the size of the chromosomal deletions can be useful. Other testing with ATRX and TP53 immunostains or EGFR FISH testing may also be helpful in confirming a diagnosis of astrocytoma, if abnormalities are detected.

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Declaration of competing interest

Both authors declare no potential conflicts of interest.

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