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Case Report

Significance of Molecular Markers and Deletion of 1p/19q In Oligodendroglioma Patients by Fluorescence in Situ Hybridization Technique: An Institutional Study

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Abstract

Background: 1p/19q loss is caused by a non-balanced translocation t (1;19) (q10; p10), which causes one of the derived chromosomes to be lost. Since 1p/19q deletion is almost exclusively found in glial tumors with Oligodendroglial morphology up to 90% of oligodendrogliomas and up to 50% of oligoastrocytomas, with the exception of pediatric cases, where this mutation is uncommon. It is thus a particularly useful genetic marker. IDH status has major prognostic implications for patients with diffuse gliomas and was suggested to be a better predictive factor for benefit to chemotherapy in the Radiation therapy oncology group trial on adjuvant Procarbazine, Lomustine, and Vincristine (PCV) chemotherapy in anaplastic Oligodendroglial tumors.

Materials and Method: In present study, formalin-fixed, paraffin-embedded (FFPE) blocks of 25 Glioma patients enrolled for study of 1p/19q codeletion. Signal pattern for FISH results is OOGG for normal & OOG for deletion. Orange signal was tagged for target and green signal tagged for control. Statistical analysis was performed by SPSS software and p valve ≤ 0.05 was considered as significant.

Results: In present study, 19(76%) patients had 1p/19q co-deletion, 2(8%) normal, 4(16%) had partial deletion of 1p or 19q. Results were correlated with variables and found that 1p deletion status shows significant with IDH, 19q deletion status shows significant with tumor type & tumor grade and co-deletion of 1p/19q shows significant with tumor type, tumor grade, P53 status.

Conclusion: As compare to 19q deletion, 1p is frequently shows deletion and ratio of 1p deletion is more compared to 19q deletion. These findings suggest that genetic alterations involving 1p and 19q may be important in glioma development and progression and may be associated with other molecular markers such as IDH and p53. The significance of 1p deletion with IDH status and 19q deletion with glioma type grade status may indicate potential interactions or pathways involved in glioma tumorigenesis. The significant association of 1p/19q co-deletion with type of glioma, grade of glioma, Ki67 expression, and p53 status may suggest that 1p/19q co-deletion could be a useful biomarker in predicting the behavior and prognosis of gliomas. FISH is powerful tool to analyses cytogenetic abnormality in patients with 1p/19q co-deletion

Keywords: electric shock; hemoptysis; pulmoner injury

Introduction

Gliomas are the most common type of brain tumor. The category of gliomas includes three main types: Astrocytomas, Ependymomas and Oligodendrogliomas (Mónica L. Mendonça et al; 2023). Of all reported cases, 1.25% were women and 1.81% were men with gliomas worldwide (Hyuna Sung et al; 2021). In India, the frequency of different types of gliomas in descending order were diffuse astrocytomas (22.8%), pilocytic astrocytomas (6.3%), and oligodendrogliomas (4.5%). Anaplastic astrocytomas accounted for 7.0% and oligoastrocytomas accounted for 4.8% of all gliomas in 2021 (Suyash Singh et al; in 2021). Our hospital reported a total of 279 glioma cases in 2021, including 174 males and 105 females. Over the past two decades, there has been a significant increase in the number of glioma cases detected, largely due to improved diagnostic techniques (Szymon Grochans et al;2022). The order of occurrence of gliomas is as follows: Frontal, Temporal, Parietal, Occipital lobes and other structures. (Farina Hanif et al; 2017, Andrew Bohn; 2018). Tumors with lower grades and slower growth rates usually have a longer median survival time than their more aggressive and faster-growing counterparts (https://www.aaroncohen-gadol.com). The following molecular markers such as IDH, MGMT promoter methylation, CIC, FUBP 1, EGRF, ATRX,

and 1p/19q co-deletion status are commonly involved in tumorigenesis of gliomas. (M B Pinkham et al; 2015, Elie Massaad et al; 2022)

1p19q co-deletion is thought to be an early oncogenic event as it is present throughout the tumor at initial resection and remains unchanged between initial diagnosis and recurrence (Sebastian Brandner et al; 2022). 1p/19q loss is caused by an unbalanced translocation t(1;19)(q13;25), which causes one of the derived chromosomes to be lost. This genetic alteration is commonly found in oligodendrogliomas, a type of brain tumor that arises from the oligodendrocytes, the cells responsible for producing the protective myelin sheath around nerve fibers (Pinkham et al; 2015). The reasons why 1p19q co-deletion is associated with improved outcomes remain unclear, but may be related to a process of oncogenesis that allows functioning apoptotic pathways to persist or to the loss of gene products that drive treatment resistance or confer tumor suppression (Sebastian Brandner et al; 2022). It is known that co-deletion of chromosome arms 1p and 19q defines a subset of patients with better prognosis, probably due to higher sensitivity to genotoxic stress. Patients with 1p/19q co-deleted oligodendrogliomas have demonstrated better response rates to chemotherapy regimens, such as the combination of procarbazine, lomustine, and vincristine (PCV) (Martin J van den Bent et al; 2013). Because of the strong association between loss of 1p/19q alleles and favorable patient outcome, 1p/19q status is routinely investigated in pure and mixed Oligodendroglial tumors. The most common method for determining 1p/19q status is Fluorescence in Situ Hybridization (FISH), which allows detection of 1p/19q allele loss on paraffin-embedded tissue samples and matching of cell shape with genetic alterations (Senetta Rebecca, et al; 2013). FISH was selected for the present studies because of its considerably higher resolution compared with CGH analysis and its higher sensitivity compared with Loss of Heterozygosity analysis. Our aim was to investigate 1p/19q co-deletion in glioma patients using the FISH technique & correlation of markers with disease subtypes.

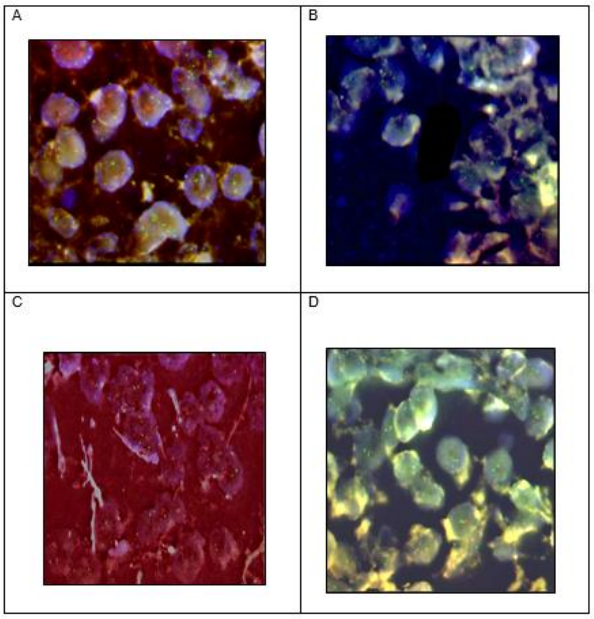

Figure 1: Represents the signal patterns of 1p and 19q. 2(A) 2 Green 2 Orange signals shows 1p normal 2(B) 2 Green 1 Orange signals shows 1p deletion 2(C) 2 Green 2 Orange signals shows 19q normal 2(D) 2 Green 1 Orange signals shows 19q deletion

Material and method

Patients and tissue samples

A total of 25 formalin-fixed, paraffin-embedded tumor tissue samples from gliomas were included in the current retrospective study conducted at the Gujarat Cancer & Research Institute. Age, sex, tumor type, tumor grade, microscopic examination, MRI examination, and Immuno Histo Chemistry reports were taken from the patient records maintained in the medical department of the institute. These 25 cases were initially diagnosed as: 15 Oligo dendroglioma, 6 Anapestic oligo dendroglioma, 3 Astro cytoma, and 1 Glioblastoma. Study was approved by Institutional Review committee.

FISH technique

FISH was performed to detect 1p/19q codeletion using Zytovision 1p/19q fluorescent probe kit. The FISH technique was performed using the ZytoLight SPEC 1p36/1q25 dual color probe where orange fluorochrome specific for 1p36 and green fluorochrome specific for 1q25.3 region. In ZytoLight SPEC 19q13/19p13 dual color Probe mixture orange fluorochrome specific for the region 19q13.32-q13.33 and green fluorochrome specific for 19p13.3 region.

For FISH formalin-fixed paraffin-embedded tumor tissue was sectioned to produce 3–4 μm thick slices. Then, pretreatment was performed according to the manufacturer's instructions by ZytoVision FISH kit. After pretreatment Dual-color FISH was performed on all samples using commercially available dual color probes and following standard methods suggested by the manufacturer's protocol. Then slides were captured under the OLYMPUS BX 61 fluorescent microscope (OLYMPUS BX61, Japan), & image analysis in ISIS software.

FISH interpretation

The assessment and interpretation of the FISH results were conducted according to the College of American Pathologists (CAP) criteriaJ (**Rebecca Senetta et al 2013**). For each case, 100 neoplastic nuclei are counted, and the ratios of 1p36/1q25 and 19q13/19p13 was recorded. Results are reported as the ratio of total number of red to green signals for each probe set (1p36:1q25 and 19q13.3: 19p13 signals) which was shown in table 1.

Signal ratios	Interpretation
<0.8	Deletion
0.8–0.89	Rescore sample
0.9–1.29	Normal
>1.3	Gain

Table :1 FISH signal ratio and interpretation of 1p/19q co deletion results

Statistical analyses

The statistical package for the social sciences (SPSS) was used for data management and calculation of mean and median to describe quantitative data. Multiple comparisons between 1p/19q co-deletion and various categorical data were analyzed by Chi square test. Differences were considered statically significant when the 'p' value was less than 0.05.

Results

Clinical data

In the present study total 25 patients included. There were only 14(56%) males and 11(44%) females with a mean age of 43 years. Patients were divided into younger age groups (≤43 years) and older age groups (>43 years) based on the median age. Accordingly, 11 patients (44%) were in the older age group and 14 patients (54%) were in the younger age group. The tumor's location in the brain was chosen for statistical analysis as being in a lobe. In term of tumor location 2(8%) patients had tumor at the Temporal ,5(20%) Parietal, 11(44%) Frontal, 5(20%) Fronto Parietal,1(2%) Fronto Temporal,1(2%) Temporol Parietal. Out of those 25 patients 9 (36%) patients had left sided tumor & 12(48%) patients had right sided tumor whereas the data of 4 patient about tumor site was not obtained.

Histological data

According to the 2016 WHO criteria for glioma, the patients' grade was determined. 3 (12%) patients had Astrocytoma, 21 (84%) had Oligodendroglioma, 1 (4%), Glioblastoma found were studied under a microscope. In the case of tumor Grade 13(52%) patients had Grade II, 9(36%) had Grade III, 3(12%) Grade IV.

Immunohistochemistry (IHC)

In case of IHC examination for all 25 patients IDH, ATRX, P53 and Ki67 which is molecular markers of Glioma tumors were reported by Department of Immunohematology laboratory at GCRI. Immuno Histochemistry data were correlated with 1p/19q deletion status. Form all 25 patients 23(92%) IDH positive, 1(4%) wildtype & 1(4%) equivocal patients were found. For ATRX 23(92%) retained, 1(4%) Focal & in 1 patient data is not obtained. 7(28%) patients were p53 positive and 18 (68%) patients were wild type enrolled in the study. For Ki67 the Median was 10 and the range was 1- 75% for all 25 patients. Out of that 14(56%) had High proliferation 8(32%) were had Low proliferation and in 3 patients' data was not obtained.

Out of 19 patients, 1p deletion found in 3 patients & only 19q deletion found in 1 patient and 2 patients do not have deletion.

As shown in Table 2, 1p deletion was significantly associated with wildtype IDH (100%) as compared to IDH positive (91%) and IDH equivocal cases (0%, $\chi 2$ =7.70, r = -0.43, p =0.03). The association of 1p deletion was not significant with other clinicopathological parameters. Further, 19q deletion was significantly higher in patients with oligodendroglioma (90%) as compared to those with astrocytoma (33%) and glioblastoma (0%, $\chi 2$= 9.79, r = -0.58, p=0.002). Additionally, 19q deletion was significantly present in grade II tumors (92%) followed by grade III tumors (77%) and grade IV tumors (33%, $\chi 2$ = 5.34, r = -0.43, p=0.03). Moreover, a trend towards significant association of 19q deletion was observed IDH positive (95%) and p53 wildtype gene (89%) as compared to their respective counterparts ($\chi 2$= 4.34, r= -0.35, p=0.08). No other significant associations of 19q deletion were observed with rest of the clinicopathological parameters.

Variables	Total patients (%) (n=25)	1p status			19q status		
		1p Deletion (n=22) (88%)	1p not deleted (n=3)	Statistical Values	19q Deletion (n=20) (80%)	19q not deleted (n=5)	Statistical Values
Age (Range: 17-60) (year)							
≤43	14	12 (86)	2(14)	$\chi 2$= 0.15 r= 0.07 p = 0.70	12 (86)	2(14)	$\chi 2$ = 0.64 r = -0.16 p=0.44
≥43	11	10 (90)	1 (10)		8 (73)	3 (27)	
Gender							
Male	14	11(79)	3 (21)	$\chi 2$=2.67 r=0.32 p=0.11	11 (79)	3 (21)	$\chi 2$ = 0.04 r = 0.04 p =0.84
Female	11	11(100)	0		9 (81)	2 (19)	
Type of Glioma							
Astrocytoma	3	1 (33)	2 (67)	$\chi 2$ =9.87 r = -0.31 p =0.12	1 (33)	2 (67)	$\chi 2$= 9.79 r = -0.58 **p =0.002**
Oligodendroglioma	21	20 (95)	1 (5)		19 (90)	2 (10)	
Glioblastoma	1	1 (100)	0		0	1(100)	
Tumor Grade							
Grade II	13	12 (92)	1 (8)	$\chi 2$ =1.52 r =-0.21 p =0.30	12 (92)	1 (08)	$\chi 2$ = 5.34 r = -0.43 **p =0.03**
Grade III	9	8 (89)	1 (11)		7 (77)	2 (23)	
Grade IV	3	2 (66)	1 (34)		1 (33)	2 (67)	
Laterality							
Left	9	9 (100)	0	$\chi 2$ =2.94 r =0.37 p =0.09	9 (100)	0	$\chi 2$ = 0.13 r = -0.07 p =0.73
Right	12	12 (100)	0		11 (91)	1 (09)	
Not Obtained	4	0	0		0	0	
Tumor Location							
Temporal	2	2 (100)	0	$\chi 2$ =1.92 r =0.12 p =0.55	2 (100)	0	$\chi 2$ = 1.36 r = 0.01 p =0.93
Parietal	5	4 (80)	1 (20)		4 (80)	1 (20)	
Frontal	11	9 (82)	2 (18)		8 (73)	3 (27)	
Fronto Parietal	5	5 (100)	0		4 (80)	1 (20)	
Fronto Temporal	1	1 (100)	0		1 (100)	0	
Temporol Parietal	1	1 (100)	0		1 (100)	0	
IDH							
Positive	23	21 (91)	2 (8)	$\chi 2$ =7.70 r = -0.43 **p =0.03**	20 (95)	1 (05)	$\chi 2$= 4.34 r= -0.35 p=0.08
Wildtype	1	1 (100)	0		0	1 (100)	
Equivocal	1	0	1(100)		0	1 (100)	
ATRX							

Retained	23	20 (86)	2 (14)	$\chi2$ =0.14 r =0.07 p =0.71	18 (78)	5 (22)	$\chi2$= 0.27 r= 0.10 p=0.61
Focal	1	1 (100)	0		1 (100)	0	
P53							
Wildtype	18	17 (94)	1 (16)	$\chi2$=2.52 r = -0.31 p = 0.12	16 (89)	2 (11)	$\chi2$=3.17 r = 0.35 p =0.08
Positive	7	5 (71)	2 (29)		4 (57)	3 (43)	

Table 2: Correlation of Clinical, Histological and Molecular data with 1p deletion status and 19q deletion status.

Additionally, correlation of 1p/19q co-deletion with the clinicopathological parameters revealed that 1p/19q co-deletion was significantly higher in oligodendroglioma patients (90%) than the other subtypes ($\chi2$ = 15.3, r = -0.70, p = 0.0003). Also, co-deletion was significantly higher in grade II (92%) tumors as compared to grade III (78%0) and grade IV tumors (0%, $\chi2$ = 11.4, r = -0.59, p = 0.002). Further, 1p/19q co-deletion was significantly associated with wildtype p53 (89%) as compared to positive p53 (43%, $\chi2$ = 5.86, r = -0.48, p = 0.014). No other significant association was observed with rest of the clinicopathological parameters (Table 3).

Variables	**Total patients (n=25) (%)**	**1p/19q Co-deletion (n=19) (76%)**	**1p/19q Not Co-deleted (n=6)**	
Age (Range: 17-60) (year)				
≤43	14	11 (71)	3 (29)	$\chi2$ = 0.11 r = 0.06 p = 0.74
≥43	11	8 (72)	3 (28)	
Gender				
Male	14	10 (71)	4 (29)	$\chi2$ = 0.36 r = 0.12 p = 0.56
Female	11	9 (81)	2 (19)	
Type of Glioma				
Astrocytoma	3	0	3 (100)	$\chi2$ = 15.3 r = -0.70 **p = 0.0003**
Oligodendroglioma	21	19 (90)	2 (10)	
Glioblastoma	1	0	1 (100)	
Tumor Grade				
Grade II	13	12 (92)	1 (08)	$\chi2$ = 11.4 r = -0.59 **p = 0.002**
Grade III	9	7 (78)	2 (22)	
Grade IV	3	0	3(100)	
Laterality				
Left	9	9 (100)	0	$\chi2$ = 0.10 r = 2.23 p = 0.76
Right	12	10 (83)	2 (17)	
Not Obtained	4	0	0	
Tumor Location				
Temporal	2	2 (100)	0	$\chi2$ = 2.23 r = 0.02 p = 0.92
Parietal	5	4 (80)	1 (20)	
Frontal	11	7 (64)	4 (36)	
Fronto Parietal	5	4 (80)	1 (20)	
Fronto Temporal	1	1 (100)	0	
Temporol Parietal	1	1 (100)	0	
IDH				
Positive	23	18 (78)	5 (22)	$\chi2$ = 0.354 r = -0.33 p = 0.106
Wildtype	1	1 (100)	0	
Equivocal	1	0	0	
ATRX				
Retained	23	17 (74)	6 (26)	$\chi2$ = 0.34 r = 0.120 p = 0.57
Focal	1	1 (100)	0	
P53				
Wildtype	18	16 (89)	2 (11)	$\chi2$ = 5.86 r = -0.48 **p = 0.014**
Positive		3 (43)	4 (57)	

Table 3: Correlation of Clinical, Histological and Molecular data with 1p/19q co-deletion status.

Discussion

The majority of primary CNS tumours fall under the category of gliomas, which includes several clinically and genetically different subtypes. The most frequent kind, diffuse gliomas, which comprise oligodendrogliomas (WHO grades II and III) and astrocytomas (WHO grades II–IV), are distinguished by their extensive infiltrative features. The identification of 1p/19q codeletion can help refine the classification and grading of oligodendrogliomas. The World Health Organization (WHO) classification system incorporates 1p/19q codeletion status as a key criterion in distinguishing different grades of oligodendrogliomas. Accurate classification is essential for appropriate patient management, including surgical strategies and adjuvant therapies[Sebastian Brandne et al 2022]. In present study 14(56%) males and 11(44%) females with a mean age of 43 years. Patients were divided into younger age groups (≤43 years) and older age groups (>43 years) based on the mean age. Glioma

slight male predominance, reported from 1.1 -2, as low as 0.92 male to female ratio in one study. The results were comparable with Jun-Jie Qin et al in 2015 mean age (45 years), Kavita S Reddy et al in 2008 (51.5 years) & Senetta Rebecca et al in 2013 (50 years). In the current study, the presence of 1p/19q codeletion was found to be significant in patients diagnosed with Oligodendroglioma and Anaplastic Oligodendroglioma, with a frequency of 76%. This observation is consistent with previous studies conducted by Vandita Y Singh et al (2014) with a frequency of 61%, Elie Massaad (2022) with a frequency of 100%, Reifenberger J et al (1994) with frequencies ranging from 67% to 81%, and J S Smith et al (1999) with a frequency of 64%. Consequently, these findings support the categorization of Oligodendroglioma tumors as a distinct entity. Out of total 25 cases 19 case have codeletion, 2 case have no-deletion & 4 cases have partial deletion, which accounts for 16% of the cases with partial deletion, with some showing only 1p deletion (16%) and others only 19q deletion (4%). Similar findings were reported by Senetta Rebecca et al (2013), who observed 18.18% and 13.6% of cases with 1p and 19q deletions, respectively and by Zixi Yang et al (2021), who found 4.9% of cases with 1p deletion and 3.9% with 19q deletion. In our current study we observed a significant correlation between the grade of glioma and the presence of 1p/19q codeletion (P<0.028). Notably, the frequency of codeletion was higher in low-grade gliomas compared to high-grade gliomas. These findings contradict the results reported by Kavitha et al (2016) and Kenneth et al (2004), where codeletion was more frequently observed in high-grade gliomas than in low-grade gliomas. However, our findings align with the results of Reddy et al (2018), which reported similar observations. In terms of laterality, a higher number of patients were found to have right-sided tumors and exhibited codeletion, accounting for 83% of the cases. This observation is consistent with the findings of Zixi Yang et al (2021). The frontal region of the brain had the highest percentage of patients with codeletion, followed by the temporal region, while the other tumours affected the diencephalon and parietal lobe among other sites. These results are consistent with the research by Kavitha et al. (2016), in which frontal tumours predominated and temporal tumours were also common.The 1p/19q codeletion and IDH status were not significantly correlated in the current investigation. With a p-value of 0.03, however we found a significant relationship between the status of 1p deletion. It was discovered that more patients with IDH positive status had 1p/19q codeletion in a later study by Zixi Yang et al. (2021). Interestingly, there were also cases where IDH wild-type patients exhibited codeletion or partial deletion More of the cases in the analysis that still had ATRX expression had co-deletion. However, no statistically significant correlation between 1p/19q co-deletion and ATRX gene involvement was found, which is in line with the findings of Wan-Ming Hu et al. (2020) and David E. Reuss et al. (2015). A significant association was observed between tumors with 1p/19q codeletion and wildtype p53, accounting for 88% of cases (p=0.01). This finding aligns with the study conducted by Andrew L. Lin et al. (2014), which reported that p53 positive tumors are more commonly found in gliomas with intact 1p/19q status, while p53 wildtype tumors are more frequently associated with codeletion. Additionally, the analysis of p53 expression revealed higher levels of the p53 protein in astrocytomas and glioblastomas, with 65.7% and 58.5% of cells labeled, respectively, compared to oligoastrocytomas (46.1%) and oligodendrogliomas (12%) (p=0.01). Furthermore, in comparison to other tumors (54.5%, P = 0.001), tumors with 1p/19q codeletion showed poorer p53 labeling (11.4%) by Karine S Durand, et al 2010.

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