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Cocktail Diagnostic Of Immunohistochemical Panel (Atrx, Olig2, Gfap) In The Classification Of Adult-Type Diffuse Gliomas: Comparison With Chromogenic In Situ Hybridization

Dwi Sri Rejeki[1], Gondo Mastutik[2*], I Ketut Sudiana[2], Rita Cempaka[3], Desak Gede Agung Suprabawati[4], Indri Safitri[5]

[1]Doctoral Program of Medical Science, Faculty of Medicine, Airlangga University, Indonesia
[2]Department of Anatomical Pathology, Airlangga University, Indonesia
[3]Department of Anatomical Pathology, Faculty of Medicine, Public Health and Nursing, Gadjah Mada University, Indonesia
[4]Oncology Division, Departemen of Surgery Airlangga University , Dr. Soetomo General Hospital
[5]Department of Physiology and Medical Biochemistry, Airlangga University, Indonesia
*Corresponding author: gondomastutik@fk.unair. ac.id

ABSTRACT

Background: Molecular testing for 1p/19q codeletion using CISH is the gold standard, but it is hampered by high costs, limited facilities, infrastructure, and human resources. A simple and more economical diagnostic method is needed to differentiate adult-type diffuse gliomas. This study aimed to determine the diagnostic value of the IHC cocktail (ATRX, OLIG2, GFAP) in differentiating astrocytomas from oligodendrogliomas based on 1p/19q codeletion status.

Methods: This observational analytical study of diagnostic development used a cross-sectional design. The subjects were paraffin blocks from patients with adult-type diffuse gliomas. Protein expression was analyzed using IHC (ATRX, OLIG2, GFAP) and compared with CISH for 1p/19q codeletion.

Results: Negative ATRX expression had the best diagnostic value with moderate accuracy (55.8%), sensitivity of 56.5%, and specificity of 55.2% in differentiating astrocytoma from oligodendroglioma based on 1p/19q codeletion. The IHC cocktail diagnostic of ATRX (-), OLIG2 <7.5, and GFAP <10.5 had low sensitivity (13.0%) but excellent specificity (96.6%), and moderate accuracy (59.6%) in predicting 1p/19q codeletion.

Conclusion: Cocktail diagnostic (ATRX, OLIG2, and GFAP) showed very high specificity but low sensitivity.

KEYWORDS: Adult-Type Diffuse Gliomas, ATRX, GFAP, OLIG2, CISH..

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INTRODUCTION

Gliomas are the most common primary intrinsic tumors of the central nervous system (CNS) and encompass a wide range of tumors exhibiting diverse clinical and biological behaviors.1 Adult-type diffuse gliomas are classified based on their morphological features and categorized as IDH-mutant tumors or IDH-wild-type tumors. Adult-type diffuse gliomas are genetically determined and include three tumor types: astrocytoma (isocitrate dehydrogenase (IDH)-mutant), oligodendroglioma (IDH-mutant and 1p/19q codeletion), and glioblastoma (IDH-wild-type).1,2

Diffuse glioma affects approximately 16,600 people in the United States each year, representing 19.3% of all CNS tumors, with an annual incidence of 4.52 per 100,000 individuals.3 The incidence of diffuse glioma varies from 1.9 to 9.6 per 100,000 individuals, depending on age, sex, ethnicity, and geographic location.4,5

The evolution of molecular genetic techniques has significantly improved the ability to predict tumor diagnosis and evaluate tumor progression tendencies. In this domain, one of the in situ hybridization methods, chromogenic in situ hybridization (CISH), plays an important role in tumor identification.6 The latest advances in diagnostics based on molecular profiles are expected to improve the classification of adult type diffuse glioma tumors, which, although morphologically similar, have different molecular profiles..7

The importance of adult type diffuse glioma classification, especially in differentiating astrocytoma and oligodendroglioma based on molecular changes, aims to improve the selection and administration of appropriate therapy, and increase the number of available therapies, as well as predict prognosis.8 It is necessary to develop research on simple molecular examinations aimed at differentiating astrocytoma from oligodendroglioma using immunohistochemistry/IHC techniques using immunohistochemistry panels (ATRX, OLIG2, GFAP) which are easier, more economical and more feasible to be carried out in anatomical pathology laboratories throughout Indonesia.

METHODS

This observational, and analytical study with cross-sectional design of diagnostic development used paraffin blocks from adult diffuse gliomas diagnosed histopathologically with HE staining in the Anatomic Pathology Laboratory at Prof. Dr. Mahar Mardjono General Hospital, Jakarta. Paraffin blocks from patients aged >19 years, male, with cerebral tumors and IDH1/2 mutations were included in the study sample. Non-representative paraffin blocks were excluded from the study.

The independent variables in this study were ATRX, GFAP, and OLIG2 using the IHC method, and the dependent variable was the 1p/19q codeletion (astrocytoma and oligodendroglioma), assessed using CISH. ATRX expression was classified as positive if expressed in at least 1% of tumor cell nuclei. Deletion was assessed by observing and counting the orange and green staining in tumor cells using a fluorescence microscope at 1000x magnification.

GFAP and OLIG2 protein expression was calculated using the immunoreactive score (IRS) formula, obtained by multiplying the percentage of positive cells (PP) by the staining intensity (SI). The IRS score ranged from 0 to 12, and a cutoff value was determined using ROC curve analysis. Furthermore, GFAP and OLIG2 protein expression was categorized as weak (0-3), moderate (4-6), and strong (8-12).

The primary antibodies used were rabbit polyclonal antibody, clone N/A (Biocare, ACR3251A) at a dilution of 1:100 (ATRX); mouse monoclonal antibody, clone GA-5 (Biocare, CM 065 A, C) at a dilution of 1:100 (GFAP); and rabbit monoclonal antibody, clone EP112 (Cell Marque, CMC 38731020) at a dilution of 1:50–1:200 (OLIG2). with the secondary antibody Starr Trek Universal Link (Biocare Medical).

All data were analyzed using SPSS version 26 with a 95% confidence interval ($p < 0.05$).

RESULTS

Characteristics of the Research Sample.

All adult diffuse glioma patients were male with a mean age of 41.12 years (range, 20 to 71 years). There was no difference in age between patients with and without 1p/19q codeletions ($p = 0.474$).

Biomarker Characteristics of Adult-Type Diffuse Gliomas

ATRX positive and negative cases were found in equal numbers (50%). The majority of patients had strong OLIG2 expression (65.4%), with a mean OLIG2 of 8.15 ± 2.21 (range, 3 to 13); and the majority of patients had strong GFAP expression (96.2%), with a mean GFAP of 11.4 ± 1.58 (range, 6 to 12). There was no difference in mean OLIG2 ($p = 1.000$) and GFAP ($p = 0.901$), or ATRX ($p = 0.000$). 0.577), OLIG2 ($p = 1.000$) and GFAP classification ($p = 0.497$) between 1p/19q codeletion and non-codeletion patients (Table 1).

OLIG2 and GFAP Cutoff Points Based on CISH Examination

The OLIG2 and GFAP cutoff points were 7.5 (OLIG2 AUC 0.500 (IK95 0.342-0.658); = 1.000) and 10.5 (GFAP AUC 0.506 (IK95 0.347-0.665); = 0.941), respectively, in differentiating the diagnosis of astrocytoma and oligodendroglioma.

Association between ATRX, OLIG2, and GFAP with 1p/19q Codeletion

This study found that ATRX-negative patients were 1.6 times more likely to have a 1p/19q codeletion than ATRX-positive patients (PR = 1.600 (95% CI 0.531 – 4.818); $p = 0.577$). Patients with OLIG2 <7.5 were 1.4 times more likely to have a 1p/19q codeletion than patients with OLIG2 ≥ 7.5 (PR = 1.429 (95% CI 0.453 – 4.507); $p = 0.752$). In addition, patients with GFAP < 10.5 were 1.128 times more likely to have the 1p/19q codeletion compared to patients with GFAP ≥ 10.5 (PR = 1.128 (95% CI 0.376 – 3.382); $p = 1.000$). However, all these associations were not statistically significant ($p > 0.05$) (Table 3).

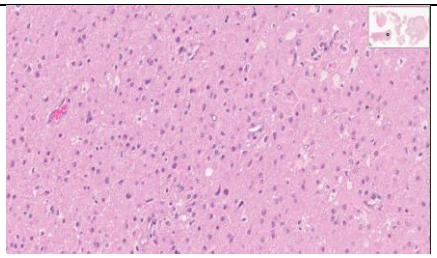
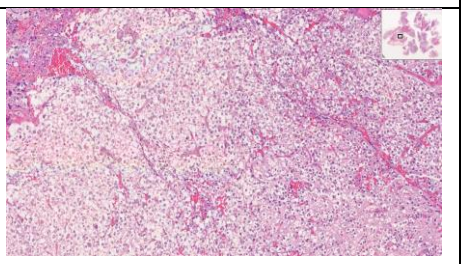
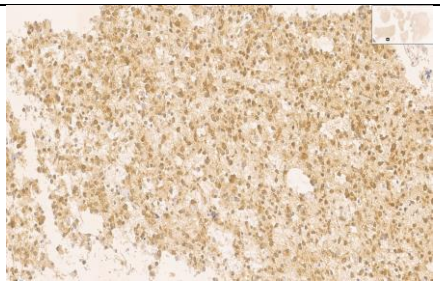
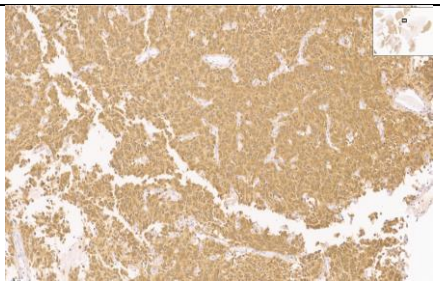
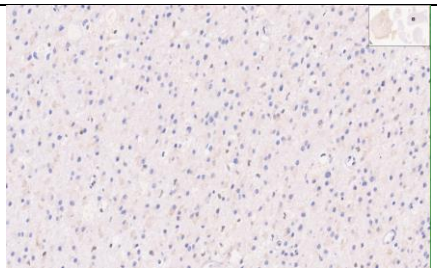
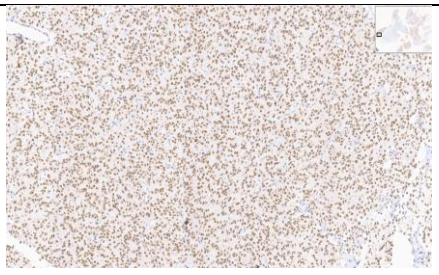
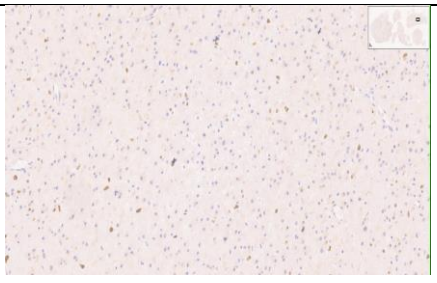
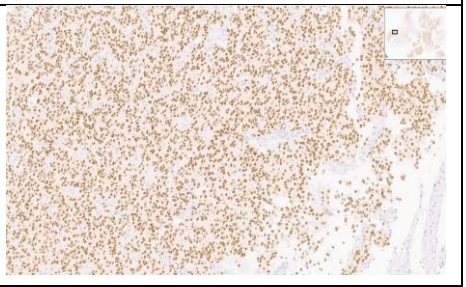
Table 1 Characteristics of the Research Sample

Characteristics	Group		Total	P value
	Codeletion 1p/19q (n = 23)	Non- Codeletion 1p/19q (n = 29)		
Gender				
- Male	23 (100)	29 (100)	52 (100)	-
- Female	0 (0)	0 (0)	0 (0)	
Age (years)				
- Mean ± SD	41.51±12.22	40.13±9.45	41.12±11.41	0.697[a]
- Median	41	40	40	
- Min- Max	17 – 71	24 – 53	17 – 71	
ATRX				
- Negative	13 (56.5)	13 (44.8)	26 (50)	0.577[b]
- Positive	10 (43.5)	16 (55.2)	26 (50)	
OLIG2				
- Mean ± SD	8.22 ± 1.86	8.10 ± 2.48	8.15 ± 2.21	1.000[c]
- Median	9	9	9	

-	Min- Max	6 - 12	3 - 12	3 - 12	
OLIG2					
-	Strong	15 (65.2)	19 (65.5)	34 (65.4)	0.406[d]
-	Moderate	8 (34.8)	8 (27.6)	16 (30.8)	
-	Weak	0 (0)	2 (6.9)	2 (3.8)	
GFAP					
-	Mean ± SD	11.48 ± 1.38	11.34 ± 1.74	11.4 ± 1.58	0.901[c]
-	Median	12	12	12	
-	Min- Max	8 - 12	6- 12	6 - 12	
GFAP					
-	Strong	23 (100)	27 (93.1)	50 (96.2)	0.497[b]
-	Moderate	0 (0)	2 (6.9)	2 (3.8)	

Table 2. OLIG2 and GFAP Cutoff Points

Biomarkers	**Codeletion 1p/19q vs Non-Codeletion 1p/19q**					
	Cut Off	AUC	CI95%	P value	Sensitivity	Specificity
OLIG2	7.5	0.500	0.342 – 0.658	1.000	65.2%	34.5%
GFAP	10.5	0.506	0.347 – 0.665	0.941	87.0%	13.8%

MICROSCOPIC	**ASTROCYTOMA**	**OLIGODENDROGLIOMA**
HE		
IDH1R132H		
ATRX		
OLIG2		

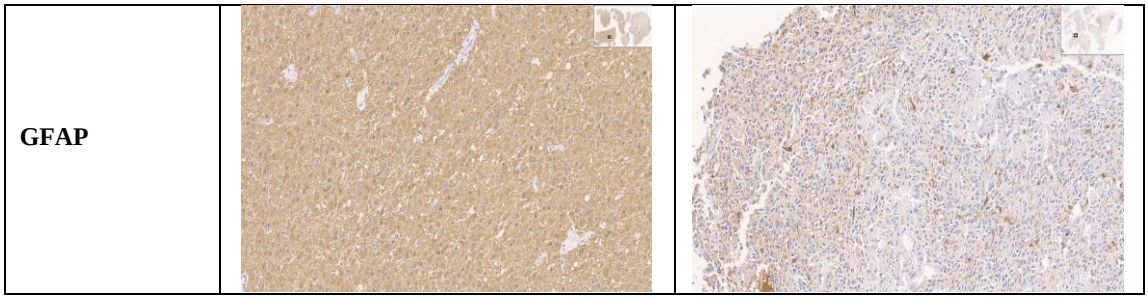
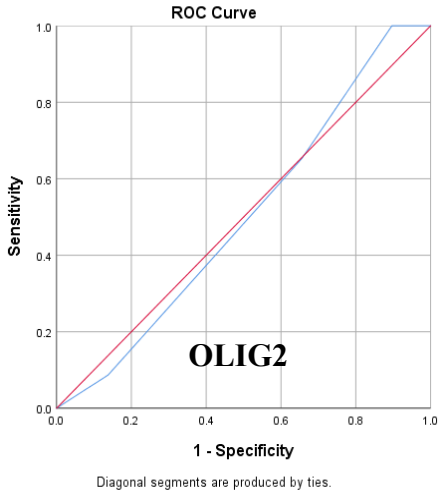
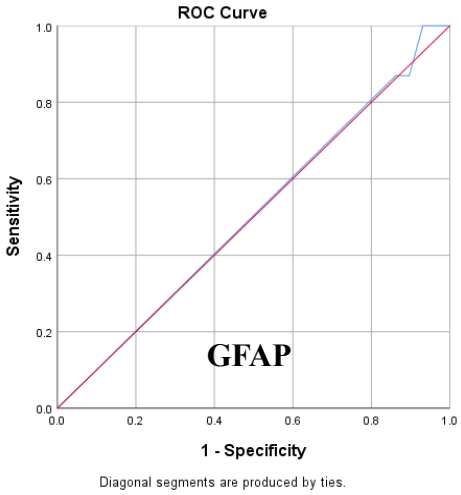


Figure 1. Comparison of Morphology and Immunohistochemical Expression between Astrocytoma and Oligodendroglioma



Cut off: 7,5
AUC 0.500
(CI95% 0.342 – 0.658; p = 1.000)



Cut off: 10.5
AUC 0.506
(CI95% 0.347 – 0.665; p = 0.941)

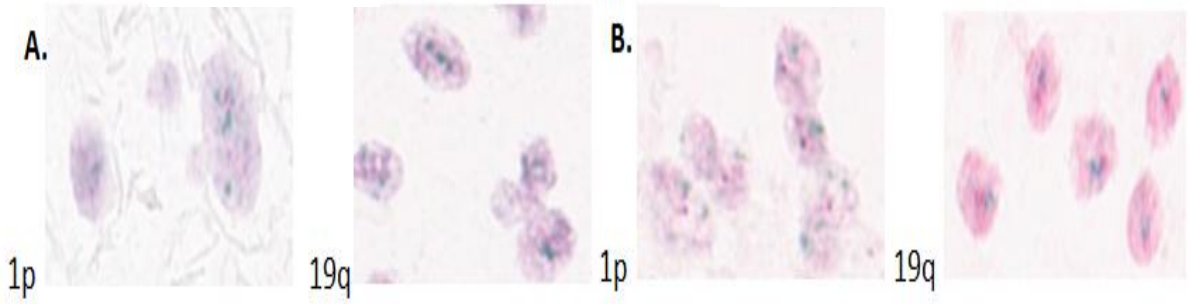


Figure 2. ROC Curve of OLIG2 and GFAP Cutoff Point

Figure 3. Chromogenic In Situ Hybridization (CISH) results for detecting 1p/19q codeletion status in gliomas. A. Case with 1p/19q codeletion, characterized by the loss of one signal (usually a single visible dot) in both chromosome arms 1p and 19q, indicating simultaneous loss of heterozygosity. B. Case with non-codeleted 1p/19q, showing two paired signals (two red/green dots) representing the presence of both alleles on each chromosome.

Table 3 Association between ATRX, OLIG2, and GFAP with 1p/19q Codeletion

Characteristics		Group		CI95%	P value
		Codeletion 1p/19q (n = 23)	Non-Codeletion 1p/19q (n = 29)		
ATRX					
-	Negative	13 (56.5)	13 (44.8)	1.600	0.577
-	Positive	10 (43.5)	16 (55.2)	(0.531-4.818)	
OLIG2					
-	< 7.5	9 (39.1)	9 (31.0)	1.429	0.752
-	≥ 7.5	14 (60.9)	20 (69.0)	(0.453-4.507)	

GFAP					
-	< 10.5	11 (47.8)	13 (44.8)	1.128	1.000
-	≥ 10.5	12 (52.2)	16 (55.2)	(0.376-3.382)	

Cocktail Diagnostic of ATRX, OLIG2, and GFAP

ATRX (-) protein expression had a sensitivity of 56.5%, specificity of 55.2%, and moderate accuracy (55.8%); OLIG2 protein expression had a sensitivity of 39.1%, specificity of 69%, and moderate accuracy (55.8%); and GFAP protein expression had a sensitivity of 47.8%, specificity of 55.2%, and moderate accuracy (52%) in differentiating astrocytoma from oligodendroglioma based on 1p/19q codeletion using CISH (Table 4). The Youden index values for each biomarker were 0.117, 0.081, and 0.030, respectively.

The diagnostic cocktail of ATRX, OLIG2, and GFAP had a low sensitivity of 13%, but excellent specificity of 96.6%, and moderate accuracy (59.6%) in differentiating astrocytoma from oligodendroglioma based on 1p/19q codeletion by CISH (Table 4).

Table 4. Cocktail Diagnostic of ATRX, OLIG2, and GFAP

Biomarkers	**Astrocytoma vs Oligodendroglioma**					
	Cut off	Sensitivity	Specificity	PPV	NPV	Accuration
ATRX (-)	-	56,5%	55,2%	0.500	0,615	55.8%
OLIG2 < 7,5	7.5	39,1%	69%	0.500	0,588	55.8%
GFAP < 8,5	10.5	47,8%	55,2%	0,458	0.571	52%
Koktail Diagnostik	-	13,0%	96,6%	0.750	0,583	59,6%

DISCUSSION

This study included 52 paraffin blocks from patients with adult-type diffuse gliomas diagnosed by CISH examination. Twenty-three patients (44.2%) had IDH-mutant and 1p/19q codeletion (oligodendroglioma) and 29 patients (55.8%) had IDH-mutant and non-1p/19q codeletion (astrocytoma). This proportion indicates a slightly higher prevalence of astrocytoma in this study. A 2017 study by Zhang et al. reported that the prevalence of astrocytoma in adults (4.23 per 100,000 patients) was slightly higher than that of oligodendroglioma (2.35 per 100,000 patients).10 Research by Natukka et al., in 2019 also reported similar results that the prevalence of astrocytoma (12.1%) was greater than oligodendroglioma (4.5%).11

Astrocytomas histologically exhibit varying morphological features depending on the tumor grade, generally consisting of astrocyte cells with scant cytoplasm and elongated or irregularly shaped hyperchromatic nuclei with indistinct nucleoli. Oligodendrogliomas histologically consist of solid cells with round nuclei and clear perinuclear spaces, a so-called "fried egg appearance," which is a technical artifact not seen in frozen sections or cytological smears.12

All patients in the sample were male with a mean age of 41.12 years. There was no significant age difference between the 1p/19q codeletion and non-codeletion groups (p = 0.697). These results indicate that age is not a risk factor for any of the adult-type diffuse gliomas in this study. At low malignancy (Grade II), the age of diagnosis of astrocytoma and oligodendroglioma was almost the same, with the mean age of diagnosis of astrocytoma being 35 years, while the median age of diagnosis of oligodendroglioma was 34.8 years. At high malignancy (Grade III), the median age of diagnosis of oligodendroglioma (39.1 years) was slightly younger than the mean age of diagnosis of astrocytoma (43 years), but not significantly. Both types of adult-type diffuse gliomas were more common in the younger group (15-47 years).13

OLIG2 is an oligodendrocytic marker and is widely expressed in almost all diffuse gliomas, while GFAP is an astrocytic marker, strongly expressed in astrocytomas but can be expressed in oligodendrogliomas, although usually weaker. The majority of samples expressed strong OLIG2 (65.4%) and strong GFAP (96.2%), and ATRX was evenly distributed (50:50) across all samples (regardless of 1p/19q codeletion status). It can be concluded that these biomarkers have low predictive value for patient prognosis or treatment response specifically related to 1p/19q codeletion.

OLIG2 and GFAP were then analyzed using ROC curves to determine cutoff points. The cutoff points with the best sensitivity and specificity were 7.5 for OLIG2 and 10.5 for GFAP. The AUC values for these two biomarkers ranged from 0.500 to 0.600 (OLIG2: 0.500; GFAP: 0.506), indicating very poor discrimination, meaning these cutoffs were not useful in distinguishing expression between the two types of adult-type diffuse gliomas. In clinical settings, an AUC value of at least 0.700 is considered appropriate for diagnostic models. A biomarker cutoff with an AUC of 0.5 should not be used for diagnostic decisions or risk stratification in patients. This cutoff can result in a very high rate of misclassification, both false-negative and false-positive.

The 1p/19q codeletion, along with mutations in the IDH (isocitrate dehydrogenase) gene, is a diagnostic marker for oligodendroglioma. The presence of the 1p/19q codeletion is generally associated with a better prognosis and a better response to certain chemotherapy and radiotherapy in glioma patients..14,15 Loss of ATRX expression and 1p/19q codeletion tend to be mutually exclusive features in IDH-mutated gliomas. IDH-mutant gliomas that harbor 1p/19q codeletion are diagnosed as

oligodendrogliomas and generally retain ATRX expression (ATRX positive) whereas IDH-mutant gliomas that harbor 1p/19q codeletion are diagnosed as astrocytomas and often show loss of ATRX expression (ATRX negative).).16 Therefore, the finding of ATRX negativity with a 1.6-fold risk of having a 1p/19q codeletion contradicts the common understanding in the WHO classification, where ATRX negativity is a hallmark of non-codeletion astrocytomas. It is necessary to re-examine whether the control group (ATRX positive) used was appropriate or whether there were other clinical/molecular considerations in the study, such as subtype or disease severity.

This study also concluded that patients with an OLIG2 score <7.5 had a 1.4-fold increased risk of having the 1p/19q codeletion. OLIG2 is a critical transcription factor essential for the specification and differentiation of oligodendrocytes, astrocytes, and neurons during development. OLIG2 is widely expressed in most gliomas, both oligodendrogliomas and astrocytomas, and plays a role in glial cell development.17 Oligodendrogliomas (which have a 1p/19q codeletion) and astrocytomas (which do not have a 1p/19q codeletion) both show OLIG2 expression. However, it is possible that lower OLIG2 expression levels (below the threshold of 7.5) are specifically associated with a subpopulation of oligodendrogliomas (1p/19q codeletion) within the studied patient cohort. Furthermore, patients with a GFAP value <10.5 had a 1.1-fold increased risk of having a 1p/19q codeletion.

GFAP is an intermediate filament protein that is a key marker for astrocytes (and their tumors, astrocytomas). Oligodendrogliomas, which are tumors with 1p/19q codeletions, tend to exhibit low or negative GFAP expression. Therefore, low GFAP levels (below the threshold of 10.5) logically slightly increase the likelihood (1.1-fold risk) of oligodendroglioma (which has 1p/19q codeletions), compared to tumors with high GFAP expression (such as astrocytomas).

Diagnostic assessment highlights the ability of each biomarker to differentiate between astrocytomas (non-codeletion) and oligodendrogliomas (codeletions). Both single biomarkers and diagnostic cocktails have shown poor ability to differentiate between oligodendrogliomas (1p/19q codeletions) and astrocytomas (1p/19q non-codeletions).

The Cocktail Diagnostic (ATRX(-), OLIG2 < 7.5, and GFAP < 10.5) yields excellent specificity (96.6%) in diagnosing 1p/19q codeletion meaning if a patient does not have these three combinations (ATRX(-), OLIG2 < 7.5, and GFAP < 10.5) the likelihood of the patient not having 1p/19q codeletion is very high so this diagnostic cocktail is very good in excluding the diagnosis of oligodendroglioma (1p/19q codeletion). However, its sensitivity is very low (13.0%), indicating that of all patients who actually have oligodendroglioma, this diagnostic cocktail can only detect 13% of them so many cases of oligodendroglioma are missed by this cocktail. This low detection rate results in a high false negative rate meaning 87% of oligodendroglioma cases are missed by this cocktail.

The results showed no significant differences in ATRX, OLIG2, and GFAP between the 1p/19q codeletion and non-codeletion groups, indicating that these three proteins are not sufficient to predict or differentiate 1p/19q codeletion status clinically. This reinforces the need to rely on direct genetic testing (CISH or FISH) to definitively determine codeletion status, rather than immunohistochemical (IHC) protein markers. 1p/19q codeletion status itself is a strong prognostic and predictive marker, and these data suggest that the IHC markers studied cannot replace such molecular information.

OLIG2 is an oligodendrocytic marker and GFAP is an astrocytic marker; their strong simultaneous expression in nearly all samples suggests that the tumors in this study may be bipotential or have undergone dedifferentiation, expressing markers from more than one glial cell lineage. Therefore, tumor classification based on purely cellular morphology (astrocytoma vs. oligodendroglioma) is increasingly ambiguous and needs to be replaced by an accurate molecular classification.

CONCLUSION

The IHC biomarkers ATRX, OLIG2, and GFAP did not individually have statistically significant power to differentiate between adult-type diffuse gliomas based on 1p/19q codeletion status. However, when the biomarkers were combined into a cocktail (ATRX(-), OLIG2 <7.5, GFAP <10.5), the diagnostic accuracy of astrocytoma (non-1p/19q codeletion) increased, due to the very high specificity (96.6%) in ruling out oligodendroglioma.

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