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Clinical Correlation of the Histological Properties of Glioblastoma

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Abstract

In this study we examine the correlation between histological characteristics of high-grade glioma and clinical presentation on physical exam. We retrospectively studied the files of 46 patients who presented to our institution between 2014-2016 and looked for correlations between histological findings and symptomatic presentation. We found that the tumors of patients who presented with pathological findings on neurological exam had increased staining for p53. Interestingly, the proliferation index does not seem to be strongly correlated with pathological findings on physical exam. Although more investigation is needed, these results could be helpful in further understanding of the pathogenesis of GBM.

Key Words: *Glioblastoma Multiforme, p53, Ki67, histopathological correlation*

Introduction

Gliomas are tumors arising from the glial cells or structural cells of the central nervous system. Glioblastoma (GBM) is the most common primary brain tumor in adults with a rapidly progressive and fatal course despite current therapies **[**1**]**. It is a neoplasm which has a dismal prognosis, with an estimated one-year mortality rate as high as 65% **[**2**]**. Complete resection of GBM with clear margins is nearly impossible due to its aggressive nature and diffuse structure of the tumor **[**2,3**]**. It has high recurrence rate post resection even in conjunction with chemotherapy or radiotherapy **[**2,4**]**.

These tumors are generally diagnosed based on histological characteristics and prognosis **[**5**]**. However, with the current amount of new molecular information that is available for GBM, certain mutations are also being included in the diagnosis. The new World Health Organization classification schemes utilizes both molecular and histological grading for classifying high grade glioma with more of an emphasis towards molecular diagnosis **[**6**]**.

Clinical presentation of these tumors is rather nonspecific and generally dependent on the anatomical location of the lesion. The most common presenting symptoms are headaches, seizures, focal neurological deficits, and mental status changes. Although both the molecular and clinical features of this tumor are well known, there has been little work done to correlate clinical presentation with histological properties. In this work we will examine a correlation between histological characteristics of tumor sample obtained at surgery or biopsy and clinical presentation of the patient. To our knowledge this is the first work to attempt this correlation in Glioblastoma Multiforme.

Methods

This is a retrospective study which was carried out under the protocols of the local institutional review board. Patient files were reviewed from the institutional neuro-oncological database. Patients with incomplete or inconclusive data regarding clinical presentation or pathology were excluded from the study. The files of 46 patients diagnosed with GBM and operated upon (surgical resection or biopsy) in the years 2014-2016 were reviewed. Histological information for surgical specimens sent for analysis were collected from the pathology reports of these patients. These results were correlated with clinical presentation on physical exam obtained from clinic or admission notes. All results were cross referenced with anatomical location of the lesion to rule out this factor as the sole reason for given presenting symptom or sign.

Kruskal-Wallis test was used to determine the association between the clinical presentation and P53 or Ki67 staining percentage respectively. Thereafter clinical presentation data was reorganized comparing symptomatic to asymptomatic patients, and Mann-Whitney test was used to evaluate the association between the presence of symptoms and the amount of histo-pathologic staining of Ki67 and P53 respectively. While P value of 0.05 was determined as significant, due to our small sample, P value less than 0.1 was determined as a value of borderline significance. All statistical analysis was made using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA).

Results

From December 2014 to June 2016 a total of 46 patients were diagnosed with GBM. The average age at diagnoses was 65, and there was a slight male predominance (55%). The most common presentation on physical exam was focal weakness (28.2%), followed by normal physical examination (i.e. no pathologic signs on presentation). Less frequently found on physical exam were positive Babinski sign, confusion and hypoesthesia (table 1).

Data analysis comparing the clinical presentation with the Ki67 index showed no statistical significance (p=0.262). Comparison of signs at presentation to the amount of P53 staining revealed borderline statistical significance (p=0.099). Focal weakness as a presenting symptom had the highest mean P53 staining percentage (17.92%), while dysarthria and asymptomatic appearance had the lowest amount of P53 staining (table 2). Due to the relatively small sample size, we have decided to deepen our analysis in order to determine whether there is a relationship between binary presentation (symptomatic VS asymptomatic) and the amount of P53 staining and Ki67 index. There was no relation between symptomatic presentation and levels of Ki67 in the resected or biopsied tissue as there was no difference in levels of Ki67 between symptomatic and the asymptomatic groups (19.68% VS 19.54% p=0.99). In contrast, P53 average percentage of staining was higher in the symptomatic group in comparison to the asymptomatic group (10.06% VS 3.27% p=0.055), this difference is approaching the significance

threshold (table 3). It should be noted that specific anatomic location of the tumor had no influence on symptomatic versus asymptomatic clinical presentation of the patient.

Clinical presentation	N (%)	Male (%)	Average age at diagnosis
normal	11 (23.9)	7 (63.6)	65.9
weakness	13 (28.2)	4 (30.7)	65.8
seizures	5 (10.8)	4 (80)	63.8
visual field deficit	5 (10.8)	1 (20)	62.2
CN palsy	5 (10.8)	2 (40)	65.3
Babinski	1 (2.1)	1 (100)	68.0
aphasia	2 (4.3)	2 (100)	79.0
dysarthria	2 (4.3)	2 (100)	57.5
confusion	1 (2.1)	1 (100)	44.0
hypoesthesia	1 (2.1)	1 (100)	72.0
Total	46 (100)	25 (55.5)	65.1

Table 1- Summary of presenting symptoms in our patient population

Clinical presentation		P53	KI67INDEX
normal	N	11	11
	Mean	3.0	20.0
	Std. Deviation	4.3	6.1
weakness	N	13	13
	Mean	17.9	19.8
	Std. Deviation	29.3	13.1
seizures	N	5	5
	Mean	4.0	25.0
	Std. Deviation	4.2	6.1
visual field deficit	N	5	5
	Mean	5.8	16.0
	Std. Deviation	1.1	7.4
CN palsy	N	5	5
	Mean	4.0	14.0
	Std. Deviation	6.4	4.7
Babinski	N	1	1
	Mean	7.0	15.0
	Std. Deviation		
aphasia	N	2	2
	Mean	11.5	25.0
	Std. Deviation	12.0	7.1
dysarthria	N	2.0000	2.0000
	Mean	3.0	18.0
	Std. Deviation	3.5	3.
confusion	N	1	1
	Mean	7.0	20.0
	Std. Deviation		
hypoesthesia	N	1	1

	Mean	10.0	35.0
	Std. Deviation		
Total	N	46	46
	Mean	8	20
	Std. Deviation	16.8	9.0
	P value	0.099	0.262

Table 2- Comparison of percent staining of P53 and Ki67 index within each clinical presenting symptom.

	Clinical presentation									
	asymptomatic			symptomatic			total			
	N	Mean	Std. Deviation	N	Mean	Std. Deviation	N	Mean	Std. Deviation	P value
P53	11	3.27	4.26	35	10.057	11.86	46	8.43	16.78	0.055
Ki67 index	11	19.54	6.1	35	19.68	9.8	46	19.65	8.7	0.99

Table 3- Comparison between binary presentation (i.e., symptomatic VS asymptomatic) and the Ki67 index & P53 staining.

Discussion

In this study we have looked at clinical-pathologic correlation in adult patients with GBM. To our knowledge this is the first study of its kind. Although based on a relatively small sample of patients, our study cohort represents a good demographic cross section of adult patients diagnosed with GBM **[**7,8**]**. In our study we see that there is a nearly significant correlation between symptomatic presentation and P53 staining while there is no correlation between symptomatic presentation and Ki 67 expression. In order to get a better insight into these results, we must first revisit the role of Ki 67 and P53 in tumor proliferation and progression, particularly in high grade glioma.

P53 is a critical tumor suppressor gene. This gene is activated in response to DNA damage and activation of oncogenes, and is found mutated in 50% of human cancer cells **[**9–13**]**. Mutations of P53 are found in a large variety of tumors including colorectal, head and neck, ovarian and lung cancer, thus making it a well-studied marker for grading and prognosis **[**14–17**]**. In CNS tumors, especially in gliomas, P53 mutations are known to be associated with tumorogenesis and progression. Its overexpression has been implicated in prognosis of low-grade gliomas (grade 2) **[**18–23**]**. However, the prognostic value of P53 in astrocytoma is controversial **[**24**]**.

Most studies show a mixed correlation between P53 expression and patient survival [25–29]. In more recent studies in GBM a correlation is observed between over expression of mutant P53 and poor outcome in GBM [30–32]. This data correlates with our results. In our cohort, patients with a higher expression of P53 were more likely to be symptomatic. It can be inferred that P53 expression is a measure of tumor invasiveness and the more invasive or aggressive the tumor in the central nervous system, the more likely it is for the patient to have a symptomatic presentation.

Ki 67 is a protein associated with cell proliferation and transcription of ribosomal RNA, thus it is expressed along all cell proliferation stages, but it is absent during the resting phase (G0). The ability to recognize Ki 67 using immunohistochemistry has made it a good marker for proliferation in human cancer [33–35]. It has been found that Ki 67 expression levels are valuable in the determination of prognosis in specific tumors such as prostate, breast cancer, and neuroendocrine tumors (NET) [36–39]. In CNS tumors, and GBM in particular, the significance of Ki 67 expression is controversial. A meta-analysis performed by Wen-Jie Chen et al demonstrated poor outcome (i.e. overall survival and progression free survival) in tumors expressing Ki 67 compared with absence of expression [40]. Few studies demonstrated better outcomes with higher Ki 67 expression and staining, and poorer outcomes with lower expression in GBM. Wong et al even suggested a cut-off lower than 22% for poor outcome [41,42]. Other studies that intended to demonstrate correlation between the degree of Ki 67 staining and patient's prognosis did not succeed showing any prognostic value [43–45]. This data is in line with our results, that there is no correlation between Ki 67 staining and symptomatic presentation. This data suggests that Ki 67 has a limited role in determining aggressiveness and prognosis in GBM.

Our study was performed with a small cohort of patients, which limits our ability in interpreting the results, therefore we used an extended threshold for significance. We conclude that Ki 67 had no role or influence on patient's clinical presentation. In contrast P53 staining might have some role on patient's presenting symptoms since it is likely correlated with tumor aggressiveness. More work is needed with larger sample sizes. It will also be interesting in future work to study the molecular signatures of GBM in reference to clinical presentation.

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