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Examination of Periodontal Condition in Gliosarcoma Patients: A Case – Control Study in Greek Adults

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Abstract

Introduction: Gliosarcoma (GSM) is a very rare brain neoplasm, is considered a glioblastoma multiforme (GBM) histologic variant (GBM, IDH-wild type phenotype), and like GBM is characterized by a poor prognosis compared to other Grade IV gliomas, as is the most aggressive and brain cancer with severe symptoms and clinical signs that affects the patients' quality of life and exhibits a great genetical and morphological heterogeneity. The purpose of the current survey was to assess the possible differences regarding the periodontal status between individuals suffering from GSM diagnosed by histological examinations after performing the surgical removal of the tumor and healthy individuals.

Methods: 45 individuals suffering from GSM and 135 matching healthy ones were interviewed and oral clinically examined. The indices used to define the periodontal status for cases and controls comprised Probing Pocket Depth (PPD), Gingival Index (GI), Clinical Attachment Loss (CAL), and Bleeding on Probing (BOP). Chi-square test and logistic regression models were applied to analyze the data.

Results: GSM patients did not present a significantly high percentage of periodontal indices compared with healthy individuals, except for BOP, as it was worse in GSM (p=0.022) patients compared to healthy individuals, after adjustment for smoking and socio-economic status.

Conclusions: BOP was statistically significantly different between patients who were suffered from GSM and non-GSM individuals.

Keywords: Gliosarcoma; Periodontal disease; Adults; Risk factors

Introduction

Gliosarcoma (GSM) consists a rare but distinct clinicopathological entity in the central nervous system tumors classification and represents approximately 2% of all the malignant glial neoplasms [1]. It is considered as a grade IV neoplasm and classified as a variant of glioblastoma multiforme (GBM) in the 2016 WHO classification [2]. Clinically, GSMs are divided into "primary" and "secondary" forms, based on whether they present as GSM de novo or the sarcomatous component only arises after the recurrence of a classic GBM [2]. GSM is considered as one of the most aggressive primary brain cancer characterized by severe symptoms and clinical signs that affects the patients' life quality, is characterized by extremely poor prognosis and shows a great genetical and morphological heterogeneity [3]. The tumor represents between 1.8% and 8% of GBM cases [4]. It mainly affects supratentorial regions and is localized in the temporal and parietal lobes, followed by the frontal and occipital lobes [3,5,6]. It is observed more commonly in females, and its incidence increases significantly between ages 40 and 70, whereas it is rare in adolescents and

pediatric individuals [6,7]. Its prognosis is similar to GBM, with a higher incidence of extraxial metastases being recorded [8]. GSM is considered to be a GBM IDH-wildtype subtype [9], however it has been suggested that it may be a different entity [10,11]. The tumor progresses clinically rapidly, it exhibits a 3% higher risk of mortality as compared to GBM [12], and the primary GSM median overall survival (OS) is 17.5 months [13], whereas in a multicenter study was found a median OS of GSM as only 13 months [14]. GSM poor prognosis could be attributed to its extremely invasive and proliferative nature with highly abnormal vascularization, resistance to the conventional chemotherapy and radiotherapy and the difficulty to be completely removed surgically [15]. GSM is characterized by a mixture of gliomatous and sarcomatous elements [16]. The gliomatous component shows GBM features as it is anaplastic, frequently spatially separated, characterized by the dura, and leptomeninges invasion, and hypertrophied or hyperplastic blood vessels. The sarcomatous component shows malignant transformation signs with nuclear atypia, mitotic activity and bundles of spindle cells. Mesenchymal differentiation with collagen deposition is present in some GSM cases [17]. Brain tumors, comprising GSMs, are mainly sporadic, and only a small rate of them are associated with hereditary cancer susceptibility syndromes, such as Lynch Syndrome (LS) [18,19]. LS is an autosomal dominant tumour syndrome with a prevalence of approximately 3-5% of all bowel cancers. It can increase the risk of developing tumors in the colorectum and other body locations, such as the gastrointestinal tract, liver, ovaries, endometrium, gallbladder, brain, skin, etc. [20,21]. The risk of primary brain tumors, especially high-grade gliomas, increases by approximately four times in individuals with LS [18]. However, few clinical cases of LS patients with GSM have been reported [18]. Periodontal disease (PD), gingivitis and mainly periodontitis is the most common destructive and progressive disease of one or more periodontal tissue structures. PD may have systemic effects in diverse organs such as heart, lungs, etc, as several researches have detected significant associations between PD and systemic diseases and disorders [22]. To be more precise significant associations have been revealed between PD and cardiovascular disease, diabetes mellitus, respiratory diseases such as COPD, diverse types of cancer etc. [23]. The possible causative role of PD in cancer development has been explored by several researches in different organs such as oral cavity, oesophagus, stomach, lungs, pancreas, etc., with conflicting results, even after controlling for potential confounders such as age, smoking status, socio-economic level, etc. In contrast to the mentioned investigations, few studies have examined the oral status or periodontal condition in individuals who suffered from GSM or other cancer types, such as GBM, lung and, gastric cancer [24-33]. The current case-control study was carried out to investigate the possible differences in periodontal condition between individuals who suffered from GSM diagnosed by histopathological examination and healthy ones.

Material and Methods

Study sample

The study sample comprised 180 individuals, 101 males and 79 females aged 51-85 years which were recruited from a Neurosurgery Clinic and two private practices, a medical and a dental one between February 2022 and June 2024. The sample size definition was calculated based on the GSM prevalence and the EPITOOLS guidelines [34] considering with 95% Confidence Interval (CI) and desired power 0.8. The World Health Organization (WHO) recommendations for assessing periodontal status incidence were used for estimating age group [35]. Participants comprised in the study answered a medical and a dental health questionnaire and were examined clinically regarding their periodontal status.

Patient's eligibility criteria

45 GSM patients referred by the mentioned clinics accepted the invitation to participate in the study. GBM diagnosis was confirmed by the histopathological examination after the surgical removal of the tumour. 135 healthy individuals who were referred by a dental practice determined the control group. Cases and controls, were selected from the same region in order to avoid or eliminate possible selection biases which can result in biased associations. To avoid such outcomes a statistical approach for confounding control is the selection of healthy individuals to be based on GSM patients' environment, such as friends, colleagues, etc., and not the familial one. Cases and controls were matched regarding their age, gender and smoking status (current/ previous smokers and never smokers). Age, gender, and smoking history have been found to be as common risk factors for periodontitis development as covariates, thus both groups were matched for the mentioned variables. For each GSM patient, three healthy individuals with the same gender and of the same age (± 4 years) were selected [36-39]. Cases and controls should not have less than 15 teeth and should suffer from periodontitis, stage I to IV [40]. They ought also not to have been treated by any type of periodontal treatment, conservative or surgical, during the previous six months or prescription of anti-inflammatory or anti-biotics or other systemic drugs such as glucocorticoids during the previous six weeks [41,42]. In the study were not included individuals with diabetes mellitus, cardiovascular diseases, rheumatoid arthritis, immuno-suppressed patients or those who received treatment for the mentioned diseases, in an effort to avoid as much as possible, potential confounding influences on the indices examined. Individuals with brain metastases due to a different primary

location, were also excluded from the study protocol. The mentioned conditions could have potential effects on the oral tissues. Patients' group did not receive oral hygiene instructions for a period of two weeks after the GSM final diagnosis and before the application of any medical treatment, i.e. surgery, radio-therapy or chemotherapy, to prevent possible biases regarding the intra-examiner variance.

Study Research Questionnaire

Cases and Controls completed a modified standardized Medical and Dental questionnaire [42] which comprised epidemiological variables such as gender, age, smoking status, socioeconomic and educational level and information regarding the participants' medical history with reference to the mentioned systemic conditions/disorders, and medication. Participants' age was categorized as 51-59, 60-69, 70-79, 80+, educational status as lower (elementary) and higher (graduated from University/College) level, SES as equal or less than 1,000 and more than 1,000 €/ month, and cigarette smoking habits was categorized as never smokers (those who smoked less than100 cigarettes during their life-time), and former smokers(those who smoked at least100 cigarettes in their lifetime and stated that they now smoke "not at all")/current smokers (those who smoked at least 100 cigarettes in their life-time and stated they now smoke "every day" or "some days"). A randomly selected sample that was comprises 36 (20%) individuals was reexamined clinically by the same dentist after 2 weeks in order to assess the intra-examiner variance. No differences were observed between both clinical examinations (Cohen's Kappa= 0.96). The current case-control study was not an experimental one and was not reviewed and approved by authorized committees (Greek Dental Associations, Ministry of Health, etc). However, it was carried out in full accordance with the World Medical Association Declaration of Helsinki. Individuals who agreed to be included to the study protocol signed an informed consent form.

Periodontal clinical examination

The PD records concerned Probing Pocket Depth (PPD), Gingival Index (GI), Clinical Attachment Loss (CAL), and Bleeding on Probing (BOP), and included all permanent teeth, except the remaining roots and 3rd molars using a Williams 12 PCP probe (PCP10-SE, Hu-Friedy Mfg. Co. Inc., Chicago, IL, USA) at six sites per tooth (mesio-facial, disto-facial, facial, disto-lingual, lingual and mesio-lingual) in all quadrants.

Gingival Index (GI)

Gingival inflammation presence or absence was defined by the examination of six sites per tooth. Gingivitis severity was classified as follows: -score 0: gingival tissue normal situation and/or mild gingivitis that corresponds to Löe and Silness classification as score 0 and 1, respectively, and score 1: moderate/severe gingivitis that corresponds to Löe and Silness classification as score 2 and 3, respectively [43].

Periodontal Tissue Examination

PPD and CAL evaluation based also on the examination of six sites per tooth. In cases the Cement-Enamel Junction (CEJ) was covered by a restoration or the tooth cervix was destructed by abrasion, decay or another lesion the CEJ location was recorded by extrapolating the CEJ location from the adjacent teeth. In case the CEJ location was not visible, no record was asses-sed. PPD was coded as 0-3.00 mm (absence or mild disease) and ≥ 4.0 mm (moderate or severe disease) for mean PPD [44], attachment loss (CAL) severity was coded as mild, 1-2.0 mm and moderate/severe attachment loss, ≥3.0 mm [45]. BOP presence/absence was classified as- score 0: BOP absence, and-score 1: BOP presence and regarded positive if it observed within 15 seconds of probing.

Statistical Analysis

For estimating the relationship between the independent variables investigated and the GSM, a univariate model was carried out. Categorical data were presented as frequencies and percentages. The worst values of the indices examined were recorded and coded as dichotomous variables after the oral clinical examinations of cases and controls. Females, never smokers, individuals with a low socio-economic and low educational level were coded as 0. Initially, chi-square test was applied to estimate the associations between the independent parameters examined and GSM patients and healthy individuals, separately. A logistic regression analysis model was carried out to assess the associations between GSM as a dependent variable and the independent ones that were determined by the enter method. Adjusted Odds Ratios (OR's) and 95% Confidence Interval (CI) were assessed as well. Finally, the independent variables were included to stepwise method in order to assess gradually the variables that showed significant associations with the dependent one. The statistical package of SPSS ver.21.0 was carried out for statistical analysis. A p value less than 5% ($P< 0.05$) was considered to be statistically significant.

Results

Cases and controls showed a mean age of 65.7 years (± 3.15). Univariate analysis is presented in Table 1. No one parameter was found to be statistically significantly different between cases and controls, except BOP (p=0.037). Table 1 also shows unadjusted OR's and 95% CI. According to the step 1a of the regression model, the main finding was that BOP (p=0.054) was significantly different between cases and controls. Table 2 also presents adjusted

OR's with 95% CI and the final step (9a) in which the same index (p=0.022) was significantly different between cases and controls (Tables 1,2).

Table 1: *Univariate analysis of cases and controls regarding each independent variable examined.*

Variables	Cases (n/%)	Controls (n/%)	p-value	Odds Ratio and 95% Confidence Interval
Gender				
Males	27 (60.0)	74 (54.8)	0.544	1.236 (0.623-2.455)
Females	16 (40.0)	61 (45.2)		
Age (years)				
51-59	11 (24.4)	27 (20.0)		
60-69	14 (31.1)	36 (26.7)	0.751	_____
70-79	11 (24.4)	43 (31.9)		
80+	9 (20.0)	33 (14.2)		
Socio-economic status				
Low	26 (57.8)	81 (60.0)	0.793	0.912 (0.460-1.809)
High	19 (42.2)	54 (40.0)		
Education level				
Low	24 (53.3)	92 (68.1)	0.072	0.534 (0.268-1.063)
High	21 (46.7)	43 (31.9)		
Smoking status				
Never	13 (28.9)	46 (34.1)	0.521	0.786 (0.376-1.641)
Previous/Current	32 (71.1)	89 (65.9)		
Probing pocket depth (PPD)				
≤ 4.00 mm	15 (33.3)	52 (38.5)	0.533	0.798 (0.392-1.624)
> 4.00 mm	30 (66.7)	83 (61.5)		
Clinical Attachment Loss(CAL)				
Absence/Mild: 1.00-2.00 mm	19 (42.2)	65 (48.1)	0.490	0.787 (0.398-1.555)
Moderate/Severe: ≥ 3.0 mm	26 (57.8)	70 (51.9)		
Gingival Index (GI)				
Absence/Mild Inflammation	14 (31.1)	58 (43.0)	0.160	0.600 (0.293-1.228)
Moderate/Severe Inflammation	31 (68.9)	77 (57.0)		
Bleeding on probing (BOP)				
Absence	13 (28.9)	63 (46.7)	**0.037***	0.464 (0.224-0.961)
Presence	32 (71.1)	72 (53.3)		
* p-value : statistically significant				

Table 2: *Presentation of association between independent variables and GSM according to Enter (first step) and Wald (final step) method of logistic regression analysis model.*

Variables in the Equation									
		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	gender	,268	,367	,531	1	,466	1,307	,636	2,384
	age	,212	,176	1,465	1	,226	,809	,573	1,141
	socioecon.stat	,108	,370	,086	1	,770	1,114	,539	2,103
	educat.stat	,649	,367	2,119	1	,077	1,913	,931	2,929

	smok.stat	,354	,556	,406	1	,524	,702	,236	1,987
	PPD	,546	,552	,978	1	,323	1,326	,585	2,395
	GI	,466	,464	1,011	1	,315	1,394	,642	2,557
	CAL	,010	,421	,001	1	,982	1,010	,442	2,306
	BOP	,388	,420	2,331	1	,054*	1,928	,864	3,186
	Constant	1,517	,590	6,604	1	,010	,219		
Step 9[a]	educat.stat	,627	,351	2,186	1	,044*	1,872	,940	3,127
	BOP	,372	,403	2,655	1	,022*	2,177	,887	3,692
	Constant	1,344	229	34,369	1	,000	,261		
a. Variable(s) entered on step 1: gender, age, socioecon.stat, educat.stat, smok.stat, PPD, GI, CAL, BOP.									

Discussion

The results showed no statistically significant difference between cases and controls regarding epidemiological indices of age, gender, socioeconomic level, smoking status, PPD, GI, and CAL however, educational level and BOP were differed statistically significant between GSM patients and healthy individuals. Smoking consists a main causative factor for PD and various types of cancer initiation and progress and often acts as a confounder in studies that examine the possible association between PD and several types of cancer in which smoking is associated with cancer development. The results showed that smoking was not statistically significant different between cases and controls. PPD is a critical index for assessing PD severity, however in the present study that index was not statistically significant different between GSM patients and healthy individuals. In the literature a small amount of studies have explored the oral conditions or periodontal health status in individuals who suffered from diverse types of cancer. In a similar cross-sectional research, oral or oropharyngeal cancer patients, showed PPD 6.00 mm or greater of 76.0 % of the patients examined, whereas only 10.0 % in the control group showed the same disease severity. The authors also observed an association between cancer and more severe PD regardless of oral hygiene and dental health status [46]. In similar articles in patients with Oral Squamous Cell Carcinoma [47] and Squamous Cell Esophageal Cancer [48] no significant differences were detected, between patients and healthy individuals. Recent case-control studies in lung cancer patients recorded that PPD was statistically significant different between cases and controls [31,49]. The results also revealed that cases did not show significantly higher values in gingival inflammation severity, according to GI, compared to controls, finding that cannot be confirmed by previous reports as similar studies have not been carried out regarding GSM patients, except few recent studies which confirmed that finding in gastric [p=0.049] [32], lung cancer [p<0.001] [49], and GBM patients [p=0.04] [33]. On the other hand, the use of GI is limited in epidemiological studies, although that index measures the inflammatory load of gingival tissue. Moreover, Hujoel et al. [26] found that gingival inflammation could be a risk factor for several types of cancer development. CAL is another crucial index for assessing cumulative periodontal tissue destruction, including previous PD attacks, whereas PPD is a current disease inflammation status indicator [50]. The mentioned indices concern the chronic inflammation long-term stages including the chronic inflammatory response destructive signs [51]. The results of the present study recorded no statistically significant difference between cancer and healthy individuals regarding CAL, whereas the same finding was confirmed in Squamous Cell Esophageal Cancer [48] patients. On the other hand, previous reports have revealed statistically significant differences in GBM [p=0.001] [33], lung [p=0.028] [31], [p<0.001] [49], and gastric cancer patients [p=0.000] [32]. BOP is another essential PD index and the most valid indicator of PD activity [52]. It estimates the host vascular response as regards to hyperemia, the capillaries expansion and the increased blood flow in the inflammation region, and it is an extensively used criterion for diagnosing gingival tissues inflammation. A statistically significantly difference was recorded concerning BOP between GSM patients and healthy individuals in the current research, whereas that finding has been confirmed in lung cancer patients [p=0.01] [31]. Another important observation was that GSM patients showed more periodontal problems, i.e. gingival inflammation and more PD activity in comparison with controls, according to ORs, finding that should be regarded as clinically significant. The results indicated that PD appears to be increased in GSM patients and more severe and generalized than in healthy individuals, a clinical sign that concerns all the PD indices examined and would suggest clinical implications for the management of PD in GSM patients. The higher risk of PD in cancer patients has been suggested to be a psychological burden result rather than possible disturbances in patients' nutrition or alterations in the oral cavity regarding the quantity/quality of saliva, or disturbances in the microbiological balance and immunological parameters in the oral cavity that could be affected because of the radiotherapy or chemotherapy [53,54].

It is also possible that GSM patients are more susceptible to the periodontal tissue progression and destruction than the healthy individuals, observation that could be attributed to the extremely poor prognosis of GSM. It has been proposed that PD and cancer initiation and development is associated with chronic inflammatory response and possible abnormalities in the cellular signaling pathways. Therefore, any type of PD treatment, conservative or surgery could reduce the biomarkers and mediators levels that are involved and promote disturbed chronic inflammatory response, giving importance to the application of a strict oral care program and preventive dentistry of GSM patients [55]. The aim of the present survey was to examine a comparison between GSM patients and matched healthy individuals regarding several PD indices and not to assess a possible association between PD indices, as etiological or risk factors, and GSM appearance. Consequently, the present study has certain limitations that should be taken into account during the procedure of results interpreting. Case-control studies, are not reliable enough as the prospective ones, whereas selection, recall, random biases and the effect of known and un-known confounders are possibly higher and could result in biased secondary associations regarding the variables examined. Moreover, such studies are based on questionnaires, and the participants either could not respond or could give no reliable responses, or could over or underestimate their potential medical diseases or disorders.

Conclusion

In conclusion, periodontal disease as expressed by bleeding on probing was found statistically different in GSM patients compared with healthy individuals.

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