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Review Article

Molecular Biology of Gliosarcoma-An Essential Review

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Abstract

Gliosarcoma (GSM) is a very rare brain neoplasm, a histologic variant (IDH-wild type phenotype of Glioblastoma Multiforme (GBM), and like GBM is characterized by a poor prognosis compared to other Grade IV gliomas. The median survival of GSM is less than one year, whereas less than 5% of GSM patients survive after 5 years after performing the conventional therapy such as surgery, chemotherapy and radio treatment. Although it has similarities to GBM, GSM displays diverse distinct differences, morphologically and molecularly. It is a highly aggressive primary brain tumor with histologic components which comprise of glial (astrocytic) and sarcomatous features. Several differences have been observed in histological and molecular elements, however, detailed data regarding the genetic background of GSM is lacking. Most of GSMs are sporadic, however it is irrefutable that a minor percentage has been associated with germline mutations and various inherited cancer susceptibility syndromes, such as Lynch Syndrome. Previous reviews have demonstrated that GSM carries somatic changes in genes coding for PI3K/Akt (*PTEN*, *PI3K*) and RAS/MAPK (*NF1*, *BRAF*) signaling pathways that are critical for tumor development. It is important to notice that the *PTEN* alterations frequency in GSMs was greater than in GBMs. Various novel translocations, such those in the *RABGEF1* gene, which create probably adverse combinations have been observed.19 conventional genes have been detected in GSM, determined as those changed in more than 5% of samples, including PTEN (66%), *TERT* promoter (92%), and *TP53* (60%). *EGFR* and *CDKN2A* also exhibited alterations in GSM cases. Tumors with available molecular profiling were mainly MGMT-un-methylated (87.5%), EGFR wild-type (100%), and IDH-1-preserved (100%). The current review highlights important molecular biology features of GSM in the light of recent literature, including its histological characteristics.

Key Words: gliosarcoma; glioblastoma; molecular biology; mutation; genetics

Introduction

GSM is a primary malignant brain tumor which shows high heterogeneity, invasiveness, and resistance to modern treatments. It is considered to be a distinct clinicopathological disease [1,2] in the central nervous system (CNS) tumors classification and comprises approximately 2% of all the glial malignant neoplasms [2-4], represents less than 0.5% of all intracranial tumors and is most common in adults between 40 and 60 years old. GSM incidence has been estimated between 1% and 8% of all malignant gliomas, constituting only 0.48% of all brain tumors and from 1.8% to 2.8% of GBM cases [5-9], and with a low incidence of 0.59%-0.76% among all adult brain tumors [10]. Males are affected more frequently, than females (M:F ratio 1.8:1) [1,5, 11]. In pediatric individuals, it is infrequent, whereas it is more common in the white and non-Hispanic population [6, 9,12, 13].

GSM is regarded as grade IV neoplasm and is classified as a GBM variant in the revised 2007 WHO classification [14-16]. GSM was first mentioned by Heinrich Strobe in 1895 as a brain tumor comprising of both glial and mesenchymal ingredients [17].

GSMs are further categorized into primary *de novo* and secondary GSM, which are characterized by different median survivals between both types (25 vs. 53 weeks) [6]. Secondary GSM is believed to have appeared as a recurrence or progression of GBM, or as a consequence of radiation therapy [6,12]. Primary GSMs commonly appear *de novo* with a

preference for the temporal lobes, whereas secondary GSM occur after cranial radiation for GBM, as mentioned [3,12]. The dura invasion and extracranial metastases were more frequent in GSM than GBM with possible prognostic consequences [3,18], although some reports detected no considerable differences regarding the overall survival (OS) between both diseases [6, 19]. GSM mainly affects supratentorial locations and is localized in the temporal and parietal lobes, followed by the frontal and occipital lobes [14,20]. GSMs affecting the spinal cord are rare, constituting about 1% of all malignant spine gliomas [21] and may indicate metastasis comes from intracranial tumors or less commonly, *de novo* development [22, 23].

In clinical level, GSM progresses quickly and patients show a 3% greater risk mortality as compared with GBMs [24]. Prognosis of GSM is similar to GBM with a greater extraxial metastases incidence being detected [25]. Cachia et al. observed that the primary GSM median OS was 17.5 months [12]. Another multi-center report assessed the GSM median OS as only 13 or 15 months, and also stated that chemotherapy with temozolomide (TMZ) was not resulted in an improvement in OS compared to radiation [26]. Similar research showed that even after standardized therapy, the mean OS time was only 6.6-18.5 months [27]. GSM is also characterized by a great rate of recurrence and metastasis. Although GSM management is in general similar to GBM, several clinical perspectives such as a tendency to extra-cranial metastasis, distinct radio-logical features and worse prognosis than GBM, indicate that GSM may be a distinctive clinicopathological disease [6].

Malignant astrocytes represent the majority of the glial element in GSMs, however, oligodendroglial elements have also been reported. GSM is a CNS mixed primary neoplasm, constituted of astrocytic anaplastic and malignant mesenchymal components [6,18, 28-32]. The gliomatous component exhibits GBM elements as it is anaplastic, often spatially distinguished, characterized by the dura and leptomeninges invasion, and hyperplastic or hypertrophied blood vessels. The gliomatous component also expresses glial fibrillary acidic protein (GFAP) and is reticulin-poor, whereas sarcomatous component is reticulin-rich but does not express GFAP [12]. The sarcomatous component shows malignant transformation signs such as mitotic activity, atypia of nucleus, and bundles of spindle cells. In some GSM cases mesenchymal differentiation with collagen deposition have been revealed [33].

According to histology, the glial element accomplishes the GBM cytologic criteria, and the mesenchymal element may exhibit a large diversity of morphologies with origin from fibroblastic, osseous, cartilaginous, striated and smooth muscle, or adipose cell origin. Conventionally, sarcomatous components resemble fibrosarcoma or malignant fibrous histiocytoma. The mentioned biphasic tumor subsequently was accepted as a result of the detailed histological analyses by Feigin et al. [34].

Because of the lack of particular and consistent diagnostic criteria however, the term GSM was also concerned tumors of glial origin which have acquired mesenchymal phenotypes, such as the ability to produce collagen fiber and reticulin network [34]. As mentioned, those tumors consist distinct diseases, the first as a glial origin tumor with mesenchymal components, known as glioma with desmoplastic metaplasia or desmoplastic glioma, and the second as a tumor with distinct gliomatous and sarcomatous components, known as GSM [35]. Other types of rare GSM transformation's concern osteosarcoma, angiosarcoma, chondrosarcoma, and liposarcomatous, leiomyomatous, myosarcomatous, and neuroectodermal tumors [32,36-40].

The mesenchymal elements would be diagnosed as fibrosarcoma or undifferentiated pleomorphic sarcoma in a soft tissue microenvironment, whereas chondroosteogenic and myogenic differentiation may also be found in that microenvironment. Variants which contain liposarcomatous, angiosarcomatous, and mixed mesodermal-type characteristics have also been observed. Squamous differentiation, grandular structures, and adenoid development may also be exhibited within the glial locations of selected cases [11].

The accurate GSM etiopathology remains unknown. It has been suggested that the sarcomatous component arises from the hyperplasic blood vessels malignant transformation, frequently found in high-grade gliomas [41]. Brain neoplasms, comprising GSMs, are mainly sporadic, and only a small rate of those have been associated with hereditary cancer susceptibility syndromes, such as Lynch Syndrome (LS) [42]. LS consists an autosomal dominant tumor syndrome with a prevalence of about 3-5% of all bowel cancers. LS is also able to increase the developing tumors risk in the colorectum and other organs, such as the gastrointestinal tract, liver, gallbladder, ovaries, endometrium, brain, upper urethra, skin, etc. [43]. It has been recorded that the primary brain tumors risk, especially high-grade gliomas, increases by about four times in LS patients. However, few clinical cases have confirmed the relationship between LS patients and GSM appearance [42]. The majority of those neoplasms appear without the presence of known predisposing factors, however they have also been associated with prior irradiation, including the Thorotrast intra-cranial instillation [11]. The essential signaling pathways involved in GSM pathogenesis are presented in Figure 1.

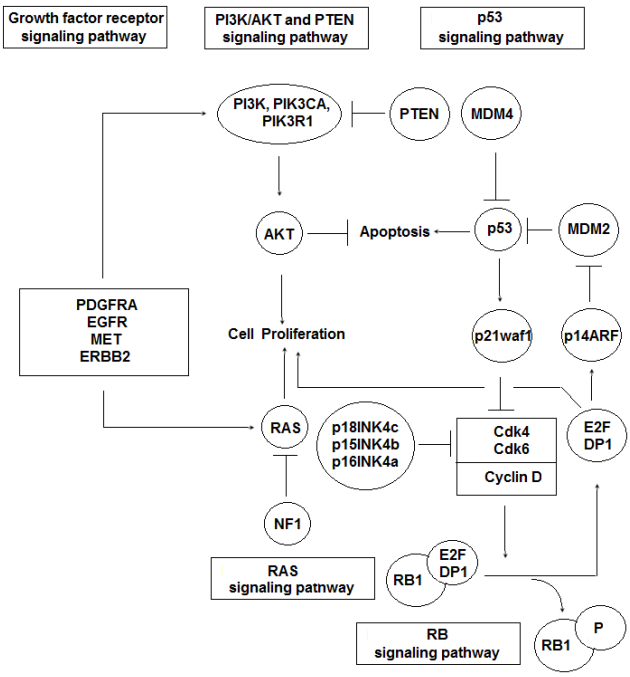

Figure 1: Essential pathways involved in GSM pathogenesis

*Displays truncating mutation caused by early stop codon

The GSM contemporary treatment is similar to the treatment used for GBM and is mainly surgical, combined with postoperative chemotherapy and radiotherapy, however, the clinical out-comes remain poor with 5-year survival rates below 10% [44], and a median survival of 9 months compared with a median 15-month survival for other GBM forms [5].

Molecular Biology

The majority of brain tumors, including GSM, is in most cases non-hereditary and is mainly influenced by somatic gene mutations and various environmental factors. Frequent mutations have been detected in *TP53*, *TERT*, *PTEN*, and *NF1*genes in GSM cases, which have been linked with known cellular functions such as cell cycle regulation, genetic stability, and cellular proliferation [45]. Similarly, in a genetic analysis by Zaki et al. [9] was detected that the most commonly genes with mutations in GSM were *TP53* (60%), *PTEN* (66%), *TERT* promoters (92%), and *NF1* (41%), indicating the complicated and various GSM pathogenesis.

GSMs and primary GBMs have similarities in their molecular profiles and show a similar ratio of *PTEN*, *RB1* and *NF1*, changes. However, *TP53* mutations are more common and the ratio of *EGFR* overexpression/amplification is lower in GSM as compared with GBM [12, 18,46]. Recent reports have examined the genetic changes in primary and secondary GSM and molecular analyses revealed a great *TP53* mutations incidence and, scarcely, *IDH* and *EGFR* mutations [4,12,18,47,48], whereas similar researches reported lower frequencies of *TP53* mutations [49,50]. GSM has been diagnostically separated into *TP53* mutated and wild type GSM variants [18]. In GSM diverse unique copy number alterations have been detected and a subsection of changes presented especially in the sarcomatous element. Genetically, GSM is unstable, with a high rate of heterozygosity loss at 10q (88%) [31]. It has also been found that the GSM monoclonal origin would be linked with the p53 mutation, recorded in 23% of GSM compared with 11% of primary GBM, and showed also the p16 deletion [9,49,51].

Recently, few studies of concise genome sequencing of GSMs, that have mentioned key somatic mutations in known oncogenes such as *TP53*, *RB1*, *PTEN*, and *NF1* and also amplifications of *EGFR*, *AKT1*, *PDGFRA*, *MDM2*, *CDK4/6*, and *MET* genes have been carried out [18,52,53]. *RB1* gene somatic alterations have been observed in 30% of GSM samples. (Table 1).

Mutations have also been observed in great frequency in GSM specific analysis concerned *TERT* promoter, *STAG2*, and *CDK2NB*. Overall, the mentioned mutations are characterized by unclear clinical and prognostic coherence, though represent an interesting pathway for further growth as prognostic or tumor-specific treatment markers. Previous reports have found that the RAS/ MAPK and PI3K/Akt pathways alterations are critical for GSM development [54].

PTEN alterations have been recorded in 26% of high-grade gliomas in the TCGA data, and identified in 45% of examined GSMs cases [52,55]. The incidence of *TERT* promoter mutations in GSM has been estimated to be 83% [31], mutation of *PTEN* varies from 28.6% to 45% and homozygous deletions of *P16 INK4alpha* was 37% [38,40]. *EGFR* amplification was observed in 4% of GSM cases [40], whereas *IDH* mutations were rare [38].

Cho et al. compared GBM with GSM using whole exome sequencing and copy number variants (CNV), and observed that the following pathways more frequently changed in GSM, such as *TP 53*, *PTEN*, *EGFR*, *RAS/MAPK*, *PI3K/Akt*, *RASGRF2*, *PAK3*, *ITGB7*, *FGFR1*, *COL5A1*. The authors also found more frequent changes in phosphatidylinositol/calcium signaling (*CACNA1F/ 1I*, *PLCB3/L1*, *ITPR1/3)* [18].

From a bio-molecular point of view, GSM carries mutations in common with sarcoma of soft tissue caused by complication in the *TP53*, *TERT* promoter, Cyclin-dependent kinase inhibitor 2A(*CDKN2A*), CDKN2B, Retinoblastoma associated Protein Type 1*(RB1)*, and Neurofibromin 1 (*NF1*) [49]. Similar to GBM, GSM inhibits mutations in *EGFR*, *PTEN*, *STAG2*, and Protein Tyrosine Phosphatase Non-Receptor Type 11 *(PTPN11)* [5,7,13]. (Table 2)

In 2000, Reis et al. carried out a GSM detailed genetic analysis, searching for mutations which were frequently found in GBM. Using polymerase chain reaction (PCR) single-strand conformation polymorphism analysis and direct sequencing, *TP53* and *PTEN* genes were analyzed, whereas the *EGFR*, *p16*, *CDK4*, and *MDM2* genes were examined via differential

PCR. With the exception of absence in amplification in *EGFR*, GSMs exhibited all of the genetic aberrations observed in primary GBM (*TP53* and *PTEN* mutations, *MDM2* and *CDK4* amplification, homozygous *p16* deletion*)*. In addition, identical mutations in *TP53, p16*, *PTEN*, and *CDK4* genes were recognized in the glial and sarcomatous elements of a GSMs subset examined [46]. (Table 1). Most GSMs carry somatic changes of RAS/MAPK (*NF1*) and PIK3/Akt (*PTEN, PI3K*) signaling pathways which are critical for tumor development [54]. *PTEN* somatic mutations/ indels were revealed in 50% of specimens and this frequency was greater than previously recorded,14% and 38%, respectively [12,46].

Tumor	Genetic Alterations*
Soft Tissue Sarcoma (STS)	TERT, DOCK8
Glioblastoma Multiforme (GBM)	PDGFRA, PIK3CA, ARID5B, IDH1, PIK3R1+13 mores
Gliosarcoma (GSM)	BRAF, SOX2, FBXW7, MSH6, SUZ12+4more
STS and GBM	CDK4, ATRX, COL7A1, GLI1, MDM2, KMT2D
GSM and GBM	PTEN, EGFR, STAG2, PTPN11
STS and GBM and GSM	TERTp, CDKN2A, CDKN2B, TP53, NF1, RB1,

Table 1: Usually altered genes in Glioblastoma (GBM), Gliosarcoma (GSM), and Soft Tissue Sarcoma

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Actually, together with focal deletions, the somatic alterations frequency in *PTEN* gene was found 70%, indicating that the alteration of *PTEN* is essential for GSM growth. *PTEN* is a mitogenic signaling mediated by class 1phosphatidylinositol 3-OH kinase (PI3K) negative regulator. *PTEN* gene mutations or deletions occur often and have been linked with therapeutic resistance in GSM [13]. *PTEN* gene is also mutated/deleted in mesenchymal GBMs in approximately 50% of cases as reported by the TCG [13], whereas *PTEN* was the most frequently altered gene in GSM cases, as 70% of specimens carried somatic mutations, indels or focal deletions in the *PTEN* gene location [56,57**]**.

Whereas the pathogenesis of GSM remains poorly understood, several reports have revealed shared mutations and cytogenetic aberrations, such as mutations of *p53* and *PTEN*, deletion of p16, amplifications of *MDM2* and *CDK4*, between gliomatous and sarcomatous components of discrete tumors, suggesting a monoclonal origin implicating improper gliomagenic cells mesenchymal differentiation [46,52,58,59]. Although it has been subsequently demonstrated that p53 protein immuno-histochemical accumulation does not definitely regard as identical to mutation of *TP53* gene, Frandsen et al. initially suggested the possibility of similar *TP53* mutations in the two components of GSM based on the p53 immuno-histochemical accumulation in their GSM cases [4]. Eventually, Biernat et al. showed identical *TP53* mutations in the glial and sarcomatous elements of two GSM cases via single-strand conformational analysis and direct DNA sequencing [59].

The GSM sarcomatous component histogenesis has been found to be controversial. Previous studies indicated that the sarcomatous elements derived from the hyperplastic blood vessels neo-plastic transformation, commonly observed in high-grade gliomas. Genetic researches detected the identical *p53* and *PTEN* mutations presence and similar chromosomal abnormalities and cytogenetic changes in GSM glial and sarcomatous elements components indicating a monoclonal origin [46]. Paulus et al. using interphase cytogenetics, i.e., *in situ* hybridisation, exhibited monosomy for chromosomes 10 and 17 in both the glial and sarcomatous components of GSM, suggesting also a monoclonal origin for both components [58].

Minor differences between GBM and GSM in *PTEN* mutations and *CDK* amplification were observed in glial and sarcomatous components [60]. Moreover, less than 12% of GSMs have O6-methylguanine-DNA methyl-transferase gene promoter (*pMGMT*) methylation, which has been linked with a good prognosis [13]. GSM biomarkers with possible therapeutic consequences concern *EGFR, CDKN2A, BRAF, PTEN,* and *NF1*[9]. *MGMT* promoter methylation is more common in GBM than in primary GSM and a tendency of increased survival in patients with hypermethylated *MGMT* promoter by improving the effectiveness of TMZ treatment was mentioned [61, 62].

The *NF1* gene was found to be changed in 30% of GSMs due to indels. In human GBM tumors somatic mutations in the *NF1* gene have been observed [56,57], amongst which splice site, non-sense, mutations, missense alterations, and frameshift indels were present. A number of the mentioned mutations have been recorded as germline changes in patients with neurofibromatosis, therefore are probably inactivating [47, 50]. It has also been recorded confirmation of the interaction between *NF1* and GSM patients. Pathological events, such as p53 increased expression, indicate that exists no overexpression of *EGFR*, as in primary GBMs, and that the proliferation indices increase could result in a poor prognosis, in general [63]. In GSM cases have been revealed *NF1* molecular changes via deleterious mutations and copy number losses. The function loss of *NF1* increases *RAS* activity, inducing *RAS/RAF/MEK/ERK* pathway activation. *MEK* inhibitors as a single agent (PD0325901 and AZD6244) have been found to be efficient against a *NF1*-deficicient GBM cells subset dependent on *RAF/MEK/ERK* signaling [63]. In GSM the frequency of *NF1* mutations was found to be 18% [56]. In a GBM mesenchymal type the *NF1* gene is frequently deleted, however the *NF1* gene deletion/mutation overall frequency was estimated to be almost 30% in mesenchymal GBM cases [57], similar to GSM specimens. It is important to notice that the *PTEN* frequency mutations or *NF1* alterations were much greater in GSMs than in GBMs, stated to be 41% for *PTEN* and only 10% for *NF1* in GBM cases [57]. (Table 2).

Gene	Type of alterations	Protein alterations [8]
TP53	Mutation	C135F, C238Y, H193R, H179Y, D281G, L111P, I255N, K132R, R175H, P80Lfs*43, R248Q, R248W, R273C, R282W, R342*, T125M, V272M, S241F, Y205H, V73Wfs*50,
PTEN	Mutation/Copy Number Alteration	Noncoding mutations appearing at hotspots C228T and C250T
TERT promoter	Mutation	C71Y, N184Efs*6, G36R, R130*, R130Q, R173C, G230*, N48K, L325P, S229*, R233*, V166Sfs*14, V175M, W274*, X55_splice, X268_splice, deep deletion
NF1	Mutation/Copy Number Alteration	E1264*, I1679, Q2589*, Y2285Tfs*5, P1847Qfs*16, Y1680del, R1534*, R2637*, Deep DELETION

RB1	Mutation/Copy Number Alteration	H733Ffs*13, S149*, R467*, M484Vfs*8, S567*S576Rfs*34, deep deletion
EGFR	Mutation/Copy Number Alteration	A289V, R222C, amplification
BRAF	Mutation	G32_A33dup, G466E, V600E
CDKN2A	Copy Number Alteration	deep deletion
CDKN2B	Copy Number Alteration	deep deletion
APC	Mutation	A735V, R876Q
STAG2	Mutation	G935Vfs*2, K906Nfs*11, M318R
MSH6	Mutation	L1244dup, T1133A
CBL	Mutation	R420L, R718*
SOX2	Copy Number Alteration	Amplification
PTPN11	Mutation	G60R, N308D, S502L
CREBBP	Copy Number Alteration	A1603T, deep deletion
ARID2	Mutation	I124T, T1180K
FBXW7	Mutation	R465H, R465C
SUZ12	Mutation	G42Afs*30, T596Nfs*6

Table 2: Targetable alterations in GSM-The top19 genes in GSM

The amplification of *EGFR* was observed in 4% of GSM compared with 35% of GBM cases [9,49,51]. GSMs have an explicit genetic profile, similar to GBMs except for the amplification of *EGFR* [46] and recent data suggested that genes amplification on proximal 12q could facilitate a sarcomatous genotype development [52]. Until now, limited information is available regarding the epithelial component's molecular genetics, observed in connection with GBM or GSM cases. Previous research showed the same standard of *TP53* mutations in astrocytic and in epithelial differentiation areas of GBMs [64]. That finding has been initially detected for glial and mesenchymal regions in GSMs [59].

GSM, does not carry *EGFR* mutations or amplifications at the same frequency, indicating that may exist extra/alternative mechanisms driving carcinogenesis and eventually mesenchymal transformation into a sarcomatous phenotype. Similar studies observed a very low *EGFR* amplification prevalence in GSM, however they also showed frequent chromosome 7 (72%) gain containing the *EGFR* locus. It is important to notice that *EGFR* mutation or amplification is not surely demanded for *EGFR* activation. It remains unclear whether the activation of *EGFR* signaling pathway is present in GSMs cases, however maybe it is present thru not direct mechanisms and not surely thru overexpression of *EGFR* caused by gene amplification [65,66]. Previous researches showed a very low or absent amplification/overexpression of *EGFR* in GSM cases [12,46], but the recent copy-number analysis utilizing CNV microarrays revealed frequent *EGFR* amplification [18]. Other GSMs genomic analyses have detected *EGFR* amplification frequencies of 4% in a survey of 22 samples, as mentioned, and 74% *EGFR* gain in another one of 18 samples with one sample expressing *EGFR* amplification [46,67]. EGFR is considered to be a key oncogenic driver in GBM, amplified in 35-45% of IDH wild type GBMs [66].

In an inclusive whole-genome copy number analysis of GSM, a report showed that amplification of *EGFR* was unusual, but also showed frequent chromosome 7 gains, which contain the *EGFR* locus, among other genes comprising *PDGF*-A, *CDK6*, and c-*Met* [67]. It is not clear whether the EGFR pathway is indirectly activated in GSM thru other mutations.

EGFR mutations- targeted treatments are not expected to be essential therapeutic options in GSM due to genetic alterations low frequency. The *EGFR* amplification rate has been estimated 35-45% in IDH-wild-type GBMs [32], whereas in general, the alterations of *EGFR* are rare in IDH-mutated GBM but more dominant in IDH-wild-type GBM [68]. Although, mutations/ indels of *EGFR* have not been recorded in GSMs, the amplification of chromosome 7 (the region where the *EGFR* gene is located) was very frequent and appeared in 40% of GSMs, however in the *EGFR* locus no focal amplification was detected [6,46].

In GSM cases the DNA copy number losses were frequent. The main part of copy number loss concern chromosomes 9 and 10, regions comprising *CDKN2A* and *CDKN2B* genes. The *CDKN2A* gene encodes for proteins p16 and p14arf, which are tumor suppressor genes and regulate the p53 and RB1 cell cycle components (https:// www. omim. Org/entry/ 600160 # mapping). The *CDKN2B* gene encodes for the p15ink4b protein, a p16ink4 (*CDKN2A*) family member, and a cell growth regulator that inhibits G1-phase progression (https:// www.omim.org/entry/ 600431?search =cdkn2b&highlight = cdkn2b). *CDNK2A* loss was frequent in 35-60% of *IDH*-wild type GBM cases [55,69,70], and *CDKN2A* homozygous loss was also frequent in GBM cases (35-50%) (International Agency for Research on Cancer, 2016), whereas in a GSMs micro-array study, *CDKN2A* homozygous loss was detected in 14 of 18 (77,7%) GSM specimens examined [67]. (Table 1).

The molecular etiology which is involved in the transformation of GBM into GSM remains unclear. The progress in GSM has been associated with alterations in signaling pathways, such as MAPK (*TP53*, *EGFR*, and *RASGRF2*), phosphatidyl-inositol/calcium (*CACAN1s*, *ITPRs*, and *PLCs*), and focal adhesion/ tight junction (*PTEN* and *PAK3*) pathways [18,49]. In GSM the mesenchymal transformation has been associated with TWIST1, SNAI2, and MMP-2/MMP-9 up-regulation [71]. According to the WHO the TWIST, SNAI2, MMP2 and MMP9 expression is a typical element of mesenchymal regions, indicating epithelial to mesenchymal transition (EMT), and may play an essential role. The molecular alterations revealed in GSM were comprised 219 cases [62], and was found lower frequency of *EGFR* copy number amplification (CNA) in GSM (8%) versus GBM (up to 50%), and also was recorded that prior case series estimating both the glial and the sarcomatous components of GSM showed that both components shared common genetic and chromosomal alterations of the conventional GBM, findings which suggest a common clonal origin for both components [62].

The increased expression of PD-1 and PD-L1, is an EMT evidenced element in a diversity of tumors [72-74]. The PD-1/PD-L1 role in the pathogenesis of GBM and the potential for targeting the mentioned pathway has been examined [75]. Elevated levels of those proteins and of tumor infiltrating lymphocytes have been detected in GSMs versus GBMs in a series comprising 233 WHO Grade IV gliomas with 9 GSM cases [76].

Other possible pathways involved in GSM concern the OX40L/OX40 pathway activation, which it is responsible for strong immunity and antitumor effects in GBM cases [77]. The loss of DNA copy number was present in regions coding for diverse OX40L/OX40 pathway protein ingredients, such as NF-kB, NF-kB2 (p52), NF-kB2 (p100), PKC-theta, Perforin, IKK-alpha, and Calcineurin A (catalytic). Inversely, various

regions that displayed chromosome loss were locations which coded for WNT pathway proteins Tcf (Lef), Dickkopf-1(DKK1), TCF 7 L2 (TCF4), beta-TrCP, Sirtuin 1, and BMI-1. Most of those WNT pathway proteins in an over-expressed or activated status, with the DKK1 exception, promote cell survival and proliferation [78]. Nevertheless, DKK1 is regarded to be a negative regulator of WNT signaling pathway, and has been implicated as a candidate gene in medulloblastoma as it is epigenetically silenced [79], whereas its loss, may result in the activation of the WNT signaling pathway with subsequent cell survival and proliferation. It has also been observed that DKK1expression resulted in glioma cell sensitivity to chemotherapy-induced apoptosis [80].

NF-kß, a protein complex which is responsible for DNA transcription controlling, is able to in-duce cell proliferation and antiapoptosis in case of improper regulated or constitutively activated. It has been recorded that NF-kß abnormal activation in GBM, led to cell invasive abilities, radio-therapy resistance, and even the promotion of mesenchymal phenotype [81].

Although the multifactorial role of NF-kß is involved in a biological processes various number, such as cell survival and proliferation, motility, DNA repair, inflammation, etc., a direct path-way which leads to GBM pathogenesis is ambiguous. In GSM cases it has been detected a copy number loss in the region encoding for NF-kß, indicating that the NF-kß pathway activation seems not to have a critical role in GSM pathogenesis. Nevertheless, it is possible that loss of NF-kß could result in DNA repair mechanisms loss, leading to neoplasia [82].

The role of *BRAFV600E* mutation in GSM cases is controversial according to previous reports [83,84]. Activating *BRAF-V600E* mutations have been frequently observed in cases of pediatric glial and glioneuronal brain neoplasms [47,48]. However, it has been reported that *BRAF V600E* mutation is present in 10% of GMS cases, compared with 3% of GBMs, whereas *SOX2* gene amplifications and mutation of *MSH6* are present about in 10% and 20% of GBM cases, respectively [85,86]. Moreover, Zaki et al., compared common gene changes, greater than 5%, in GSM, GBM, and soft tissue sarcoma, and among those, GSM shared only four genes with GBM, none with sarcomas, whereas nine common genes were found monadic to GSM amongst the 5% threshold for each respective tumor type [9]. They also reported that *BRAF* mutations (V600E protein alteration, G32A33 duo, G466E), *SOX2* amplification (11%), and *MSH6* mutations (L1244dup, T11 33A protein alteration), were special to GSM [9]. Previous studies recorded that most of those mutations overlap with GBM and other cancer types, however, GSM carries its own genetic mutations, such as, Suppressor of Zeste 12 (SUZ12), and Box and WD Repeat Domain Containing 7 (FBXW7) [5,9,13,51,86,87**]**. (Table 2).

TGF-β superfamily signaling is responsible for a broad spectrum of cellular functions both in normal and tumor growth, as is implicated in determining the mesenchymal stem cell differentiation pathway [88,89] and in the EMT regulation in lung cancer and mesothelioma cases [90,91]. TGF-β/BMP signaling plays an essential role in osteoblast-genesis and bone formation [92, 93]. TGF-β signaling pathway also activates down-stream SMADS, CTNNB1, MYC and FOS signaling pathways, which could result in the malignant induction of a pro-neural-mesenchymal transition in that tumor by increasing the following mesenchymal transcriptional factors expression, SNAI1, SNAI2, TWIST1, and ZEB1 [71,94]. Those transcription factors are responsible for re-programming and activate the mesenchymal signature transcription in the recurrent GSM tumor [18,71,91]. Consequently, TGF-β signaling seems to play a critical role in modulating mesenchymal stem cell lineage selection and imposed the mesenchymal differentiation progression into the osteo-genic lineage by controlling the main transcription factor's expression and activities [71,88].

The main noticeable difference between GSMs and GBMs concerns the collagen gene signature, indicating a more mesenchymal-like and extra-cellular matrix rich micro-environment. Collagens type I (*COL1A1*, *COL1A2*), III (*COL3A1*) and VI (*COL6A2*, *COL6A3*) were highly up-regulated in GSM cases [49]. The collagen-signature is involved in the gene's groups functional analysis which differentially expressed between GBMs and GSMs, as "focal adhesion" is one of the distinguishing groups. Especially, *COL6A3* seems to be a reliable marker of GSM tumors, as its expression was increased in the sarcomatous element, whereas it was practically absent in the gliomatous one [49].

Gene's overexpression which are associated with integrin complexes ITGA5-ITGB1-CAL4A3 and ITGB1-NRP1 in GSM cases when compared with GBMs showed that GSMs were more invasive and migratory tumors, as the mentioned integrins were implicated in the EMT processes [95,96]. A remarkable translocation between *RABGEF1* and *GTF2I RD 1P1* genes was revealed in three GSM samples. The close proximity of the mentioned genes is able to result in a possible long deletion or read-through transcript, as the distance between two fused RNA fragments is nearly three kb long. The *RABGEF1* gene last exon is fused with the *GTF2IRD1P1* gene, leading to its inactivation. As the *RABGEF1* gene was associated with some cancers development that alteration may play a significant role in GSM development, however further research is required to explain the mentioned translocation impact [97,98].

The current viewpoint concerning the GSM cellular origin maintains the monoclonal theory that both glial and mesenchymal components may be come from a common neoplastic neuro-ectodermal precursor cell [46,99,100]. From a histological point of view, gliomatous and sarcomatous components of GMSs share specific genetic alterations and possibly come from a common clonal origin [31,59]. The analysis of gliomatous and sarcomatous elements of eight GSM cases by comparative genomic hybridization after micro-dissection detected that both components shared 57% of the discovered chromosomal imbalances. Nevertheless, the chromosomal alterations number in GSMs was significantly lower than that in GBMs, suggesting a greater genomic stability in GMSs [59]. Other authors described that gliomatous and sarcomatous elements of GSM shared common genetic alterations and chromosomal imbalances of the type conventionally described in GBM [52]. Those alterations comprised gains on chromosomes 7,9q, 20q, and X, and losses on chromosomes 10, 9p, and 13q. GSMs were also recorded to have a fewer chromosomes number implicated in imbalances, indicating a genomic stability greater level in GSMs [52]. It has also been recorded those chromosomes 9 and 10 showed the highest number of losses, and the copy number of gains mainly appeared on chromosome 7 in GSM samples [67]. The loss of LOH on 10q is a common genetic alteration in primary and secondary GBM, indicating that 10q may comprise tumor suppressor genes [101]. In GSM, LOH 10q was also frequently observed (88%) [31].

Conclusions

GSM is a rare clinicopathological entity, and is difficult to differentiate from GBM on clinical information, however shows a genomic and molecular aspect distinct from GBM and soft tissue sarcoma, even though is classified by the WHO as a GBM variant. The current review demonstrated that most GSM tumors have somatic alterations of PIK3/Akt (*PTEN*, *PI3K*) and RAS/ MAPK (*NF1*, *BRAF*) signaling pathways which are essential for tumor development and therapy resistance. GSMs, regarding somatic alterations, are considerably similar to GBMs, with a greater *NF1* and *PTEN* alterations frequency, more similar to frequencies detected in mesenchymal GBMs. A better understanding of the cellular and molecular profiling of GSM and the development of targeted therapies may help individuals affected by this enigmatic tumor. In the meantime, early diagnosis and a multidisciplinary approach to treatment remain crucial against GSM and may improve further survival.

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