

Transformation of IDH-wildtype glioblastoma to gliosarcoma with features of osteosarcoma

Paweł Sobczyk¹, Michał Sobstyl¹, Albert Acewicz², Joanna Rosa³, Marta Grabiec⁴, Wiesława Grajkowska⁵

¹Department of Neurosurgery, Institute of Psychiatry and Neurology, Warsaw, Poland, ²Department of Neuropathology, Institute of Psychiatry and Neurology, Warsaw, Poland, ³Department of Pathomorphology, Independent Public Clinical Hospital No. 2 PUM, Szczecin, Poland, ⁴Department of Translational Immunology and Experimental Intensive Care, Centre of Postgraduate Medical Education, Warsaw, Poland, ⁵Department of Pathomorphology, Center of Postgraduate Medical Education, Warsaw, Poland

Folia Neuropathol 2024; 62 (1): 96-101

DOI: <https://doi.org/10.5114/fn.2024.136020>

Abstract

Gliosarcoma (GS) is a rare variant of IDH-wildtype glioblastoma. It is classified as grade 4 in the latest WHO CNS classification of both glial and mesenchymal components. Gliosarcoma may arise de novo or secondary from glioblastoma. It occurs in up to 2% of patients diagnosed with glioblastoma. We present a case report of a 51-year-old patient who was initially diagnosed with glioblastoma multiforme, which transformed into secondary gliosarcoma with an osteosarcoma component 16 months after the initial diagnosis. We believe that increasing reporting of secondary gliosarcoma (sGS) will be helpful in understanding, diagnosing and providing more effective treatment for this cancer.

Key words: osteosarcoma, gliosarcoma, IDH-wildtype glioblastoma, secondary gliosarcoma, tumor transformation.

Introduction

IDH-wildtype glioblastoma is the most common primary malignancy and accounts for approximately 45% of all primary malignant brain tumors in adults. Statistically, it is more common in men than in women [16,20,21]. Studies show that in adults, glioblastoma cells can be derived from neural stem and progenitor cells that are located in the subventricular zone, subcortical white matter and the dentate gyrus of the hippocampus [10,18,23]. The tumor is most often located in the frontal (25.8%), temporal (19.7%) and parietal (12.2%) lobes, while it is relatively rarely found in the occipital lobe (3.2%), cerebellum (2.9%), brainstem (4.2%) or spinal cord (4.3%) [21]. In the clinical course, symptoms depend on the location of the tumor. Epilepsy is a symptom that occurs in up to 68% of patients with glioblastoma [6,25]. Patients present sensorimotor

deficits (20%) and, when the lesion is in the dominant hemisphere, aphasia (5%). The standard procedure in imaging diagnostics is contrast-enhanced magnetic resonance imaging (MRI). Exceptionally, computed tomography (CT) of the head may be used, but it is indicated only in acute cases. The morphological subtypes of glioblastoma cannot be clearly distinguished on MRI, despite some differences [24]. Positron emission tomography (PET) may be a helpful test before biopsy, but it is not a standard test in the diagnosis of glioblastoma [17]. The final diagnosis is always based on a histopathological examination. Macroscopically, glioblastoma takes the form of a poorly demarcated white-gray tumor with possible areas of hemorrhage and necrosis. The microscopically necessary features for the diagnosis of glioblastoma, IDH-wildtype (CNS WHO G4), is the presence of diffuse glioma infiltration with necrosis and/or microvascular proliferation. Moreover, other

Communicating author:

Prof. Michał Sobstyl, Department of Neurosurgery, Institute of Psychiatry and Neurology, Warsaw, Poland, e-mail: mrsob@op.pl

Received: 25.11.2022, Accepted: 18.01.2024, Online publication: 12.03.2024

histopathological features include cell pleomorphism, hypercellularity, nuclear atypia and high mitotic activity. In immunohistochemistry, the markers GFAP, Olig2 and S100 are used to confirm glial differentiation and Ki67 and MIB-1 indexes to assess cell proliferation. According to the latest 2021 WHO Classification of CNS tumors, assessing IDH1/IDH2 mutations is necessary to distinguish between IDH-mutant astrocytoma and IDH-wild-type glioblastoma [19].

Gliosarcoma was first described in 1895 [2,14,22]. In MRI gliosarcomas may appear as well-demarcated lesions with a higher risk of cortical involvement and abutting the dura [24]. Histologically they present a biphasic pattern with alternating areas displaying glial and mesenchymal differentiation. The glial component typically exhibits the typical features of glioblastoma. The sarcoma component may show different fields of differentiation: cartilage, bone, muscle, fat tissue, vascular or fibroblastic elements [11]. In neuropathological examination we can use histochemical staining and immunohistochemical reactions to distinguish the sarcomatous component in glioblastoma, i.e. Gomori's silver staining, reaction with vimentin antibody. Gliosarcoma occurs only in approximately 2% of patients diagnosed with glioma [2,7,8,11,14,16], more often in men than in women, with a ratio of 1.8 : 1. It usually appears in the fourth to sixth decade of life [1,2]. The most common location is the temporal lobe [9]. Gliosarcoma may arise *de novo* or secondary from glioblastoma. Such a tumor is called secondary gliosarcoma. Most secondary gliosarcomas occur after adjuvant therapy. Cases of gliosarcoma with osteosarcoma components are extremely rare. Only several cases have been documented so far [7,13]. Gliosarcomas with features of osteosarcoma manifest in an analogous way to gliosarcomas with no specific clinical manifestations. They are more common in men than women (8 : 5, respectively) and occur between the 4th and 7th decades of life, according to Chen *et al.* [7]. It is noteworthy that among the reported cases, 4 were secondary gliosarcomas and in all 4 cases radiotherapy was used in the postoperative treatment [7].

Case description

A 51-year-old patient was admitted to the Department of Neurosurgery because of a tumor in the left posterior occipital region identified on the basis of an MRI of the head. The diagnosis was based on visual disturbances, with right-sided hemispheric amblyopia. Moreover, for 2 weeks the patient suffered from headaches and periodic vomiting. MRI of the head showed a polycystic tumor of the left parieto-occipital lobe with dimensions of 48 × 31 × 43 mm, showing marginal enhancement, surrounded by a zone of edema

(Fig. 1). The patient underwent a left parieto-occipital craniotomy with subtotal removal of the brain tumor. The postoperative course was uneventful. Afterwards the patient received adjuvant treatment in the form of chemotherapy and radiotherapy. During the follow-up visit 4 months after the initial operation, imaging studies revealed features of tumor regrowth. Repeat surgery of the patient was planned and done with subsequent removal of the tumor (first reoperation). Three weeks after reoperation, there was also a collection of the cerebrospinal fluid in the left parieto-occipital area under the musculocutaneous flap. Local punctures were made to drain the fluid, but they proved to be ineffective. For this reason, the left parieto-occipital craniotomy was performed again (second reoperation). The residual recurrence of the brain tumor was removed, and the dura mater was watertight sutured and sealed with tissue glue. Lumbar drainage was placed and left for 6 days. No fluid leakage was noted upon discharge from the hospital. After 10 months following the last re-operation, the patient developed headaches, nausea, and intensified speech problems of the amnesic aphasia type. A follow-up CT scan was performed, which showed a poorly defined, an irregularly calcified mass in the left temporo-occipital region measuring 5 × 4 × 4.5 cm, indicating regrowth of a glioblastoma multiforme. The patient underwent another left parieto-occipital craniotomy and removal of the recurrent brain tumor (third reoperation). The postoperative period passed with no new deficits. The patient, diagnosed with "a malignant tumor with osteosarcoma morphology", died nearly 2 months after the third reoperation.

Neuropathological findings

Histologic examination revealed diffuse infiltration of astrocytic glioma with nuclear pleomorphism, high mitotic activity, microvascular proliferation and foci of necrosis (Fig. 2). The tumor showed positive immunostaining for GFAP, Olig2, and ATRX, negative for IDH1 (R132H) and p53, and a high Ki-67 index (Fig. 2). Due to the typical histological picture and convincing immunostaining status we abandoned further molecular testing and established the diagnosis of glioblastoma, IDH-wildtype, CNS WHO G4 according to the current guidelines. Histopathological examination after the third reoperation: histologic examination revealed a sarcomatous tumor composed of areas of ill-defined spindle cells of high cellularity and lace-like osteoid depositions intermingled with neoplastic cells with marked atypia and numerous mitotic figures (Fig. 3). Spindle cells showed reticulin fiber networks in Gomori's silver staining and strong immunoreaction of vimentin, but not GFAP and S100 (Fig. 3). On the basis

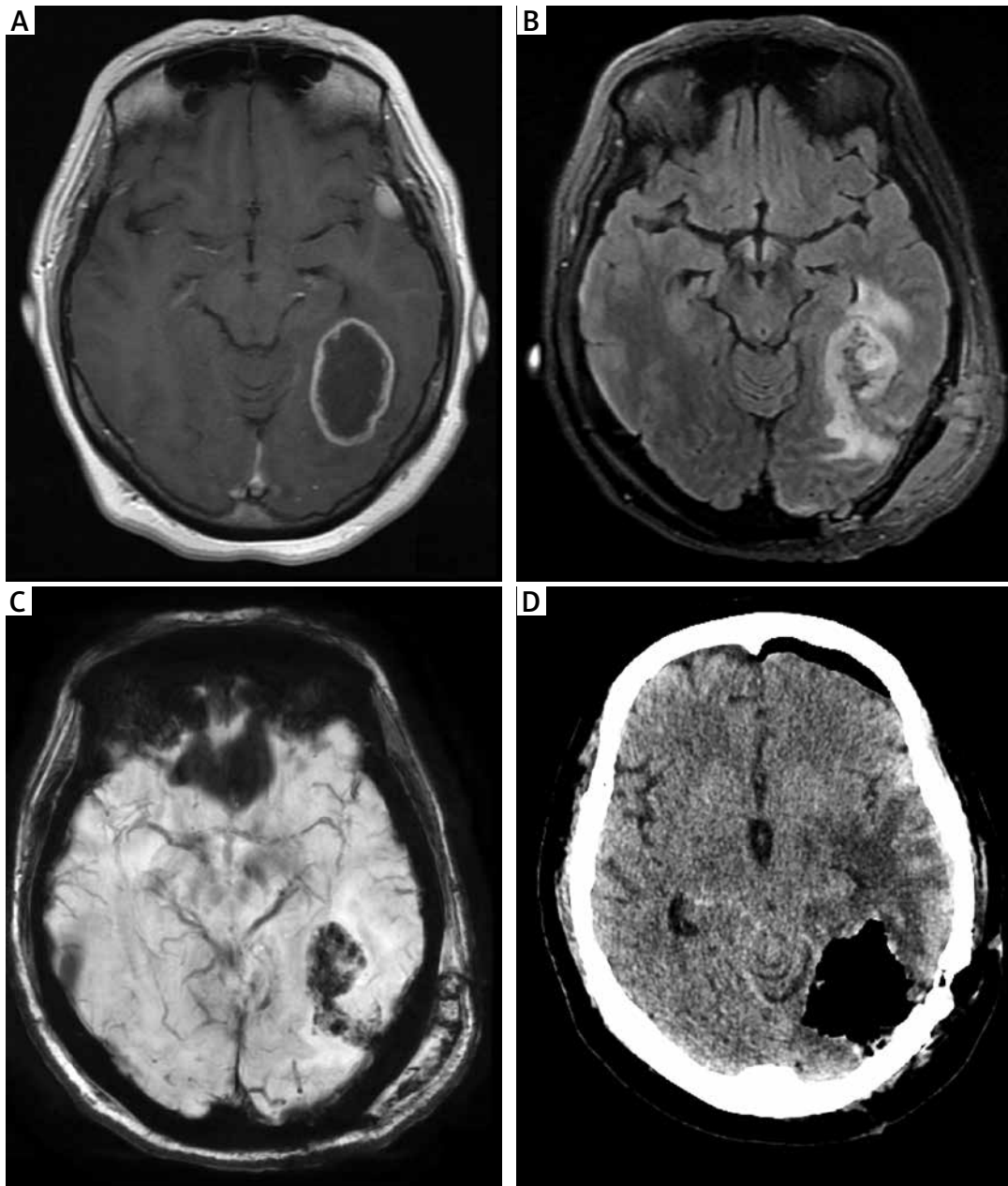


Fig. 1. Neuroimages of glioblastoma before surgery (MRI): **A)** Axial MRI image T1-weighted post contrast sequences, **B)** T1-weighted-fluid-attenuated inversion recovery (FLAIR), **C)** Susceptibility weighted imaging (SWI), **D)** Axial CT performed after the third reoperation.

of the previous histopathological findings, a diagnosis of gliosarcoma with osteosarcoma-like foci was made.

Discussion

The occurrence of gliosarcoma with osteosarcoma differentiation secondary to glioblastoma is extremely rare. These cases are related to the use of radiotherapy

previously as part of the treatment, as demonstrated by Han *et al.* [13]. In order to be able to state a causal relationship between therapeutic irradiation and activation of neoplastic processes, the following criteria must be met: 1) the tumor appears in the area of irradiation, with a latency period between irradiation and tumor appearance, 2) the tumor is absent prior to irradiation, and 3) the new tumor is of a type histologically

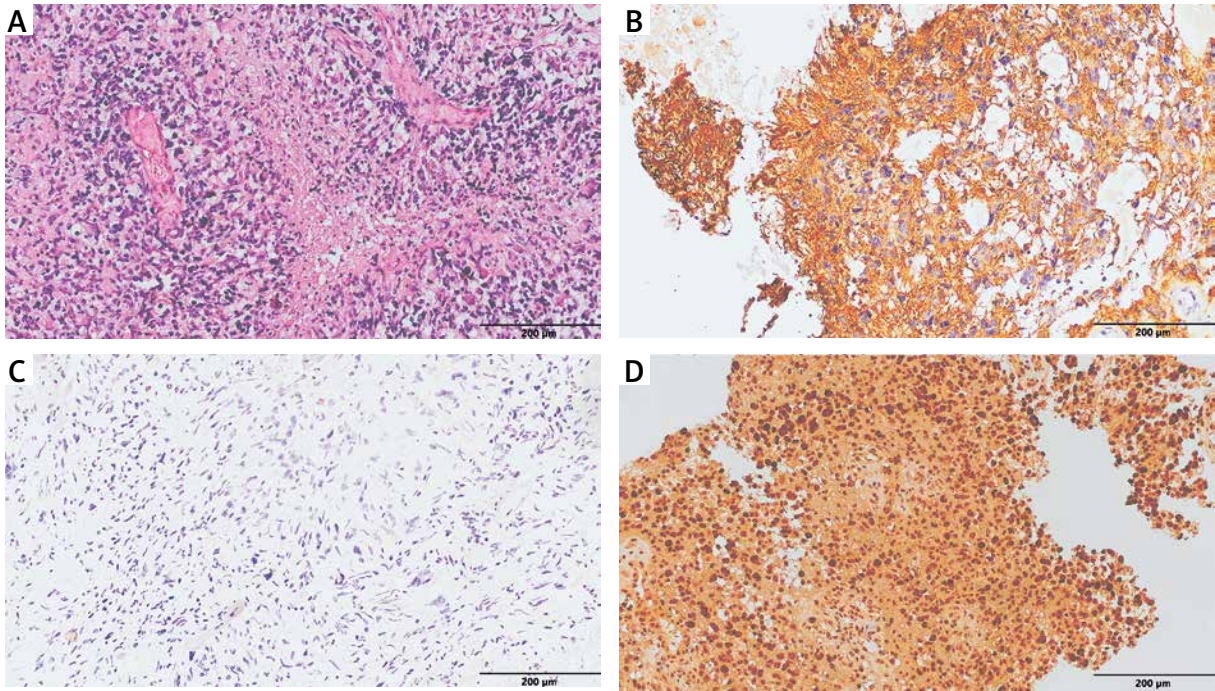


Fig. 2. Histological findings. **A)** Diffuse infiltration of high-grade glioma with microvascular proliferation and foci of necrosis (H&E). **B)** Strong immunorexpression of GFAP in neoplastic cells. **C)** Negative staining for IDH1. **D)** Retained nuclear ATRX immunoreactivity within tumor cell nuclei.

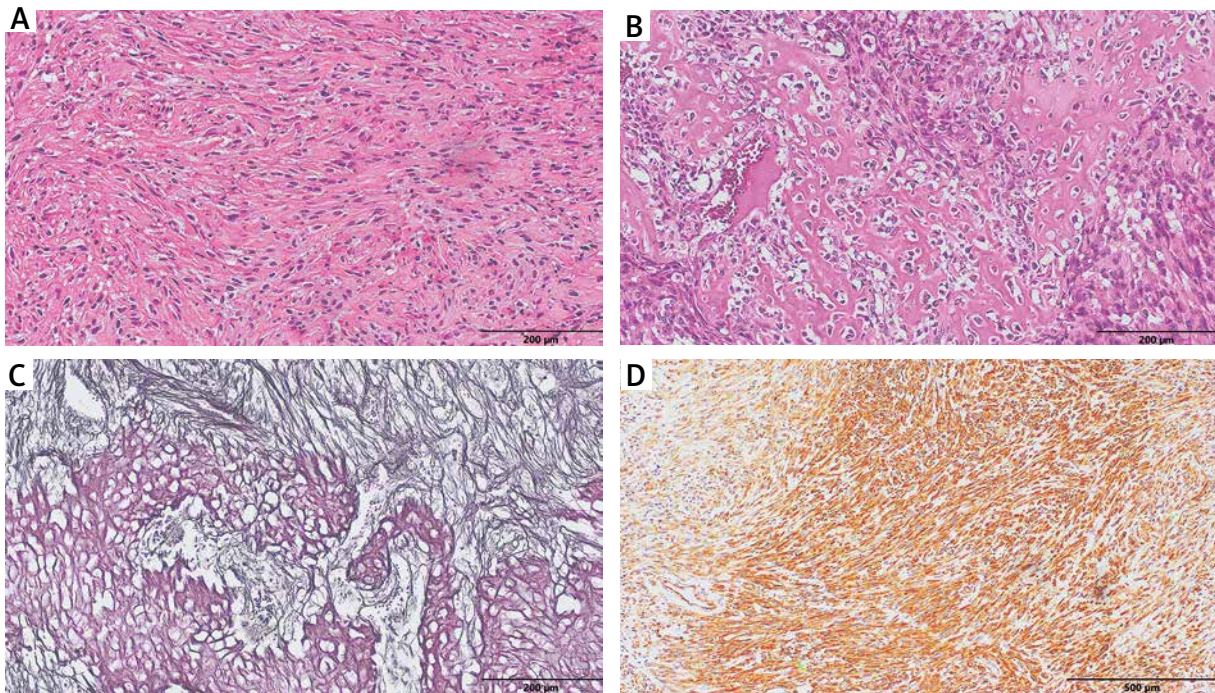


Fig. 3. Histological findings. **A)** Sarcomatous tumor showing spindle cell proliferation (H&E). **B)** Osteoid depositions intermingled with neoplastic cells with marked atypia and numerous mitotic figures resembling osteosarcoma (H&E). **C)** Silver stain shows reticulin fiber networks in the mesenchymal compartment (Gomori). **D)** Immunohistochemistry for vimentin highlighting the sarcomatous component.

distinct from the first tumor [1,2,13]. The features of glioblastoma were visualized in the samples collected during the first operation and the two reoperations – both occurred 6 months after the initial surgery. In the reported case, the transformation took place within 16 months, similarly to the case described by Andaloussi-Saghir *et al.* [2], because after this time another reoperation was performed. In the sample taken at third reoperation, histological examination revealed a sarcomatous tumor composed of areas of high cellularity of poorly demarcated spindle cells and lacy osteoid deposits. Both components of gliosarcoma arise from clonal proliferation of the same precursors and result from a phenotypic change in the glioblastoma cells, reflecting the clonal evolution of a tumor. Electron microscopy and immunohistochemical studies indicate that these precursors can include fibroblasts, mesenchymal pluripotent cells, vascular adventitia or perivascular and vascular spaces of smooth muscle cells [3]. In immunohistochemistry, the marker GFAP is useful in distinguishing between glioblastoma and gliosarcoma, because a positive reaction occurs in a very small percentage of sarcomas. Vimentin is a common positive marker for sarcomas, but not for gliomas [1,4,5,15]. The loss of s100 staining in the spindle cells of the sarcoma area is noteworthy, as it can accompany mesenchymal transition in glioblastoma [3].

The median survival following secondary gliosarcoma is estimated at 6.6 months (range 1.2-9.0 months). After diagnosis, the patient survived for another 2 months, but as Han *et al.* pointed out, it is impossible to estimate the life expectancy in secondary gliosarcoma due to the high heterogeneity of the applied treatment methods [12,16]. However, it should be remembered that the entire course of the patient's disease lasted 18 months. The cause of the transformation of glioblastoma to gliosarcoma has not been established unequivocally. The risk factor proposed by the researchers is exposure to radiation. It can affect both the *de novo* tumor formation and the mesenchymal transformation of glioblastoma. There is no doubt that radiation-induced gliosarcoma and secondary gliosarcoma should be treated as separate entities. Han *et al.* suggested that the incubation period for radiation-induced gliosarcoma is longer than for secondary gliosarcoma, but less than one year [13]. This may be an argument in favor of the transformation of glioblastoma in the present case.

It is difficult to clearly define the course of the disease and to propose effective treatment due to the small number of cases described so far, the large variety of disease development and the still unknown pathogenesis of the formation of both glioblastoma and secondary gliosarcoma.

Conclusions

The present case is an example of an extremely rare phenomenon which is the transformation of glioblastoma to gliosarcoma with an osteosarcoma component. These transformations are poorly understood, highlighting the complex pathogenesis and pathophysiology of glioblastoma. Hence, it is crucial to explain the mechanisms behind it and consequently to diagnose and treat this type of disease more efficiently.

Disclosure

The authors report no conflict of interest.

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