

Case report



## ISCHEMIC STROKE VERSUS GLIOBLASTOMA OCCURRENCE – A CASE REPORT AND REVIEW OF THE LITERATURE

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### ABSTRACT

**Background:** Ischemic stroke and gliomas are pathologies with poor prognosis. Aside from different characteristics and incidences, 10% of ischemic stroke patients will develop glioblastoma in the post-ischemic period. The aim of this study is to present the interplay between cerebral ischemic stroke and glioblastoma in one patient and to review literature data.

**Case Description:** A 61-year-old patient got sick and became confused and inadequate, incorrectly replacing words and syllables. He complained of a severe headache the whole day. The patient was transported to the Emergency Department of UMHAT “Dr Georgi Stranski”, and after a neurological examination and a native CT examination of the brain, the patient was admitted to the Neurology clinic with a diagnosis of MCA ischemic stroke. The neurological examination showed a central lesion of the right VIIth and XIIth cranial nerves, Babinski sign (+) on the right side, sensory loss of the right arm and sensory aphasia. Glasgow-Liege Scale (GLS) =18. National Institutes of Health Stroke Scale (NIHSS) = 6. After 4 days of active medical treatment, the patient was discharged from the clinic with improvement. In 2 months and 10 days, the patient was admitted to the ED again with worsening of the clinical signs. An MRI (with contrast) of the head diagnosed the patient with a brain tumor (glioma), and he was admitted to the Neurosurgery clinic for operative treatment.

**Conclusion:** Ischemic stroke as an early manifestation of brain cancer is rare. Approximately 10% of patients with ischemic stroke may develop glioblastoma. Exact diagnosis and specific treatment of stroke or glioma is always challenging and requires appropriate MRI or CT protocols to make timely and accurate differentiation.

**Keywords:** glioblastoma, ischemic stroke, mimics, differential diagnosis,

### BACKGROUND:

Glioblastoma, also known as glioblastomamultiforme (GBM), is the most aggressive brain tumor. Usually, the initial signs and symptoms of glioblastoma are non-specific. They may include headache, personality changes, nausea, and neurological deficit specific to stroke. Symptoms often worsen rapidly and may progress to unconsciousness. Ischemic stroke is a medical condition characterized by impaired blood flow that causes brain cells death. Gliomas and ischemic strokes are pathologies with poor prognosis [1]. Aside from different clinical characteristics and incidences, 10% of ischemic stroke patients will develop glioblastoma in the post-ischemic period. Besides the well-known pathogenesis of post-radiation ischemic stroke in glioblastoma patients, the proper mechanism of developing glioblastomain ischemic stroke patients is still unknown [2, 3]. This study aims to present one patient’s interplay between cerebral ischemic stroke and glioblastoma and to review literature data.

### CASE DESCRIPTION:

A 61-year-old patient got sick and became confused and inadequate, incorrectly replacing words and syllables. He complained of a severe headache the whole day. The patient was admitted to the Emergency Department (ED) of UMHAT “Dr Georgi Stranski” Pleven. After a neurological examination and a native CT examination of the brain, the patient was admitted to the Neurology clinic with a diagnosis of MCA ischemic stroke. The patient had a history of arterial hypertension (treated) and lumbar degenerative disease. The following risk factors were identified: alcohol abuse, physical inactivity and obesity. No heredi-

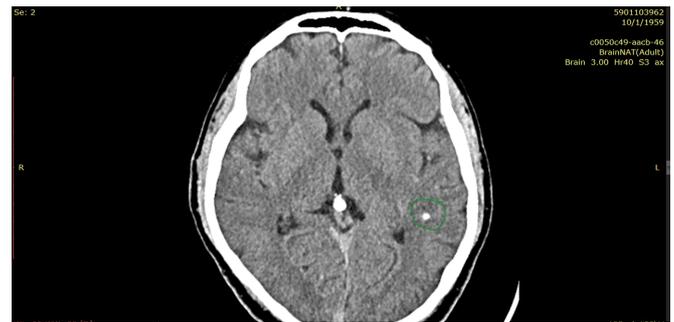
tary predilection of stroke was found. Neurological examination showed: a central lesion of the right VIIth and the XIIth cranial nerves, Babinski sign (+) on the right side, hypoesthesia of the right arm, Sensory aphasia. GLS- 18. NIHSS – 6.

CT on admission showed bilateral hypodensiscirculatory lacunar foci with dimensions 4-6 mm, ventricular system - mid-located and moderately dilated. No compression and dislocation syndrome. Calcification in the left parietal-temporal with dimensions 6/4 mm. Conclusion: Cerebrovascular disease. Cortical atrophy.

**Image 1.** CT showing lacunar ischemia in the left temporal lobe.



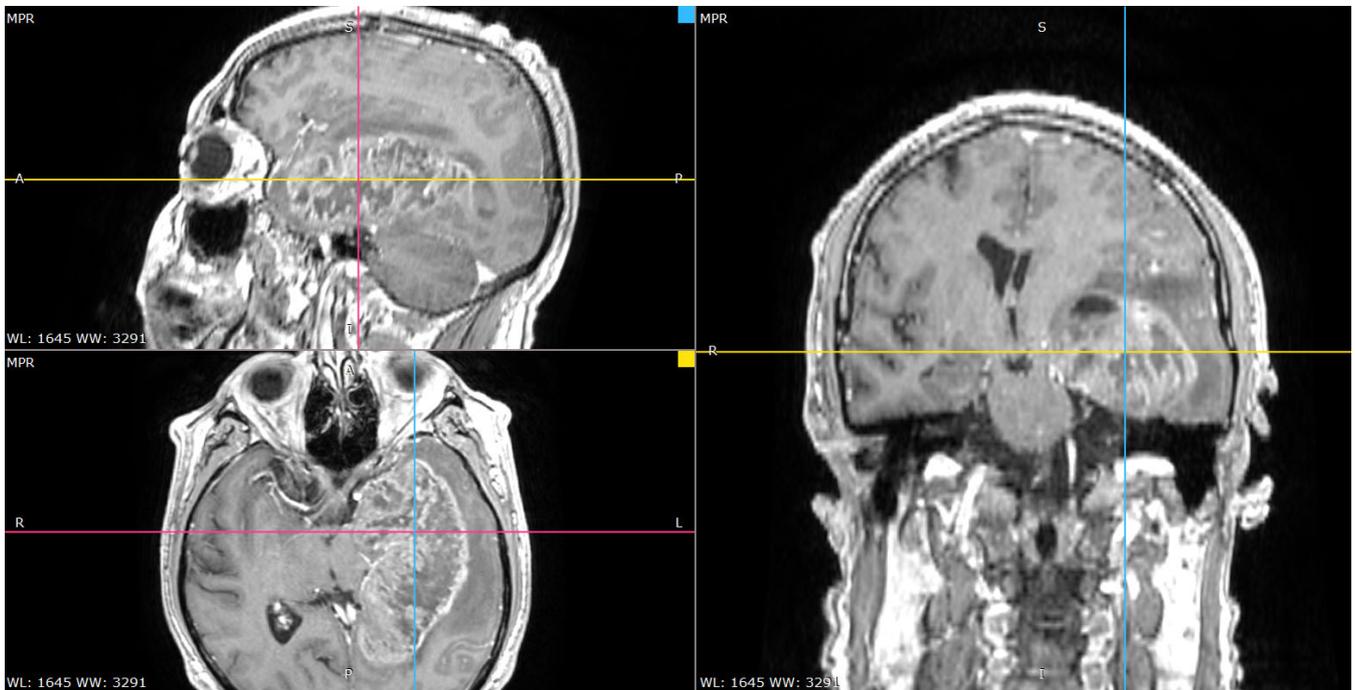
**Image 2.** CT showing calcification in the left parietal-temporal region (lateral ventricle level).



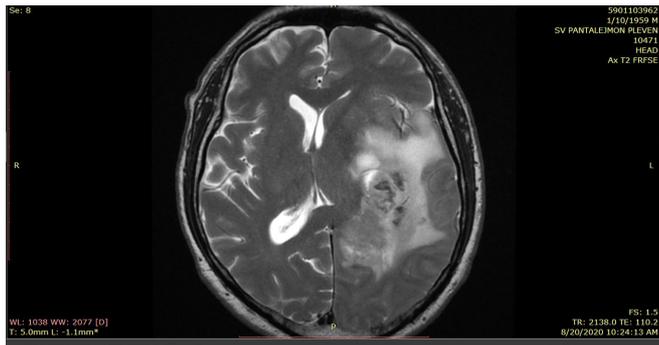
The patient was treated as follows: intravenous infusions of Sodium Chloride 9% x 500ml, Ringer solution x 500 ml. and Citicoline 2x1000 mg; subcutaneous Low Molecular Heparin 2 x 0.4, Famotidine x1 fl. i.v. and Lisinopril 5mg/daily. After 4 days of active treatment, the patient was discharged from the clinic without headache and speech disorders but with sensory loss for the right arm and a mild central lesion of the right XIIth cranial nerve. GLS- 20. NIHSS – 1.

After 2 months and 10 days, the patient was admitted again to the Emergency Department with a worsening of the clinical condition. Only after an MRI of the head the patient was diagnosed with a brain tumor and admitted to the Neurosurgery clinic for operative treatment.

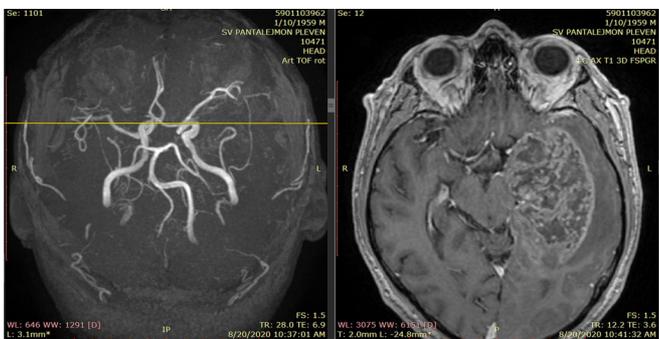
**Image 3.** MRI with contrast - 3MP RadiAnt DICOM viewer reconstruction of a sagittal, axial and coronal view of the brain tumor (glioblastoma IV grade – histologically verified).



**Image 4.** MRI T2 FRFSE axial view. Note the displacement of the lateral ventricles.



**Image 5.** MRI-arteriography (left) and MRI T1 contrasted axial view (right). Note the large tumor mass in the left temporal region - small areas of necrotizing tissue surrounded by anaplastic cells. Cerebral ischemia for MCA branches on the left side.



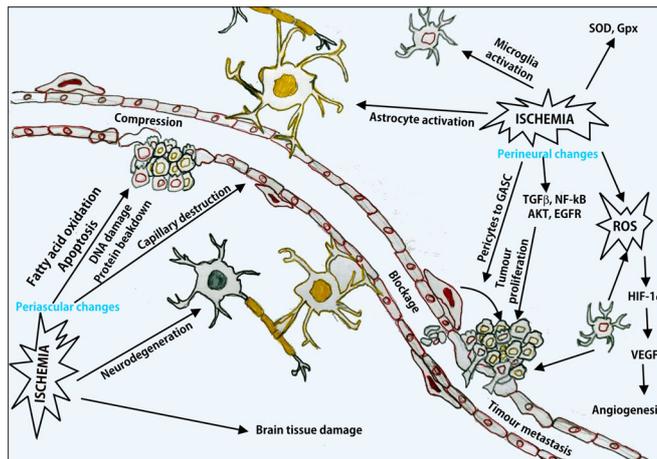
**Operative treatment:** Aftertemporal craniotomy, a sub-total tumor resection using intraoperative real-time ultrasonography had been performed.

**Histological examination** showed glial cells with nuclear atypia, cellular pleomorphism, mitotic activity, and microvascular proliferation and necrosis. GFAP (+), Ki67 >20%.

The patient was referred to Oncology Department for radio and chemotherapy (Stupp protocol).

The interrelation between cerebral ischemia and glioma is not clarified yet. A common hypoxic condition is probably the model of interrelation. The true mechanisms of pathogenesis are still in debate. Possible mechanisms include astrocyte activation, reactive gliosis, angiogenesis, peri-vascular and peri-necrotic changes [4].

**Fig. 1.** Bi-phasic role of hypoxia in tumor promoting (glioma development).



A hypothesis exists that ischemic stroke in the currently presented patient was incidental and independent of the GBM development 2 months later.

## DISCUSSION:

Primary stroke transferring into glioblastoma is uncommon and rare. It is estimated to be approximately 10% [1].

Kondziolka D, et al. [5] reported for brain tumor manifesting as intracranial infarction. Such a phenomenon is not clear and could involve two processes: neoplasm cell occlusion and tumor-induced blood coagulation changes.

Yaldizli O, et al. [6] noted a patient with ischemic stroke diagnosed primarily with a brain tumor, based on the neurological examination and CT investigation, which presented with a hyperdense lesion in the basal ganglia (with mass effect and ring-enhancement). The suspected brain tumor turned out to be a massive ischemic lesion (histologically verified). In some cases, cerebral ischemia could be a complication in the early post-brain-tumor surgery period [7].

GBMs prior to ischemic stroke have already been reported in the literature. Rojas-Marcos I, et al. [8] reported for 2 patients with ischemic strokes, 3 and 5 months respectively, after GBM resection, chemo and radiotherapy. Obeid M, et al. [9] presented a patient who experienced ischemic stroke secondary to GBM.

According to Bitzer and Topka [10], irradiation may cause cerebral ischemia due to damage to the large and small vessels, but it will appear in several months to years after the treatment. Because of the similar appearance or absent changes in native CT studies in early glioblastoma and ischemic stroke, additional diagnostic confirmation, including MRI with contrast and angiography, is needed for the precise diagnosis [11].

In 10%- 30% of the cases, the clinical diagnosis of acute stroke is mimicking other conditions such as mass lesions, seizures, hypoglycemia, demyelinating disease, encephalitis, transient global amnesia, drug toxicity, and metabolic disturbances. Neuroimaging triage is important for the exclusion of mimics and guidance of treatment strategies. Most centers in highly developed countries perform a MRI stroke protocol that often delays specific therapy [12].

**Table 1.** CT/MRI differential diagnosis ( / - is meaning “not necessary”).

	<b>Ischemic stroke</b>	<b>Intracerebral hemorrhage</b>	<b>Stroke mimics (eg. glioblastoma)</b>
<b>Focal neurological symptoms</b>	+	+	+
<b>CT native</b>	<p><b>No specific signs</b>The earliest CT signs visible are:</p> <ul style="list-style-type: none"> <li>• visualization of clot (“MCA dot sign”, “hyperdense artery”)</li> <li>• early parenchymal changes -loss of grey-white matter differentiation, and hypoattenuation of deep nuclei; cortical hypodensity with associated parenchymal swelling with resultant gyral effacement</li> </ul>	Hyper dense lesion (very sensitive)	<ul style="list-style-type: none"> <li>• irregular thick margins: iso- to slightly hyperattenuating (high cellularity)</li> <li>• irregular hypodense center representing necrosis</li> <li>• marked mass effect</li> <li>• surrounding vasogenic edema</li> <li>• hemorrhage is occasionally seen</li> <li>• calcification is uncommon</li> <li>• intense irregular, heterogeneous enhancement of the margins is almost always present</li> </ul>
<b>CT angiography</b>	Hypo enhancement or filling defect	Spot sign	/
<b>CT perfusion</b>	Low perfusion	Low perfusion	/
<b>MRI</b>		/	<p><b>Method of choice</b> – hypo/hyper to isointense mass within a white matter with central heterogeneous signal (necrosis, hemorrhage intratumorally). Enhancement is variable but is almost always present (T1+gd).                      DWI-diffusion restriction is typically intermediate, similar to normal white matter, but significantly elevated compared to surrounding vasogenic edema.                      ADC - values correlate with grade</p>
• <b>DWI</b>	Hyper intense lesions		
• <b>ADC</b>	Hypo intense lesions		

MR spectroscopy (MRS) is useful in differentiating cerebrovascular accident versus tumor. However, it currently could not replace a definitive biopsy. Increased Choline/ Creatinine (Chl/Cr) ratio and reduced N-Acetyl Aspartat (NAA) favors tumor (Glioma), while increased lactate favors radionecrosis/stroke.

**Table 2.** MR spectroscopy characteristics

	<b>Normal Brain</b>	<b>Tumor</b>	<b>Cerebrovascular Accident</b>	<b>Abscess</b>	<b>Multiple Sclerosis</b>
<b>Lipid</b>		<b>Elevated</b>			Elevated
<b>Lactate</b>	Absent	<b>Absent/Elevated</b>	<b>Elevated</b>	Elevated	Elevated
<b>NAA</b>		<b>Reduced</b>	<b>Reduced</b>	Reduced	Reduced
<b>Cr</b>				Reduced	
<b>Cho</b>		<b>Elevated</b>	<b>Reduced</b>	Reduced	Elevated or Normal

MRI is the neuroimaging method of choice in the precise diagnosis of cerebral ischemia and brain tumors (glioblastoma). CT may mask and give misdiagnosis. Diffusion restriction is more often observed in glioblastomas than in cerebral ischemia due to increased cellularity [12, 13, 14].

The brain tumor is considered to be a contraindication for intravenous thrombolysis [15]. There are few reports on glioblastoma patients who received intravenous thrombolysis [16, 17, 18]. Etgen T, et al. described two cases when the diagnosis of glioblastoma was not known and the thrombolysis was complicated by a hemorrhage in one of the patients [16, 17]. This is not surprising because of the glioblastomas characteristics for increased risk of spontaneous bleeding.

The overlapping of clinical and neuroimaging signs of these two conditions is well known and sometimes may delay the diagnosis beyond the thrombolysis therapeutic

window. Although ischemic infarction could be comparatively easy and fast diagnosed, the ratio between sufficient benefit and increased risk should always be considered [12].

#### CONCLUSION:

Ischemic stroke as an early manifestation of brain cancer is rare. About 10% of patients with ischemic stroke may develop glioblastoma. Treating stroke or glioma is always challenging and requires specific treatment strategies. Appropriate MRI or CT protocols are necessary to make precise differentiation. The exact pathogenetic mechanisms need to be clarified.

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