Atypical clinical presentation of glioblastoma mimicking autoimmune meningitis in an adult

Angelika Stapińska-Syniec[1], Marcel Rydzewski[2], Albert Acewicz[3], Iwona Kurkowska-Jastrzębska[2], Beata Błażejewska-Hyżorek[2], Michał Sobstyl[1], Teresa Wierzba-Bobrowicz[3], Wiesława Grajkowska[3,4]

[1]Department of Neurosurgery, Institute of Psychiatry and Neurology, Warsaw, Poland, [2]2nd Department of Neurology, Institute of Psychiatry and Neurology, Warsaw, Poland, [3]Department of Neuropathology, Institute of Psychiatry and Neurology, Warsaw, Poland, [4]Department of Pathomorphology, The Center of Postgraduate Medical Education, Warsaw, Poland

Abstract

Glioblastoma (GBM) is the most malignant type of glial tumor associated with a very unfavorable prognosis. Typical radiological features of GBM include the presence of a tumor with irregular contrast-enhancing margins and central necrosis surrounded by a wide area of vasogenic edema. Here, we presented an atypical clinical presentation of GBM mimicking autoimmune meningitis.

A 69-years-old previously healthy male was admitted to the emergency room due to signs of increasing cognitive impairment, weight loss, changes in behavior, difficulty in walking, and prolonged episodes of nausea over the past month. An magnetic resonance imaging (MRI) brain scan revealed hyperintense changes of the periventricular area surrounding brain ventricles in T2 and FLAIR, and post-contrast leptomeningeal enhancement and thickening of meninges involving cerebellar sulci. An additional MRI scan of the cervical spine showed an in-core contrast-enhancing lesion on the C7-Th1 level as well as leptomeningeal thickening and post-contrast-enhancement around the spinal cord. Various laboratory tests and two stereotactic biopsies were performed with no essential to diagnosis clinical findings. A couple of months after first hospital admission, the patient died. Post-mortem examination of the brain revealed numerous foci of abnormal tissue inside the subarachnoid space, lateral ventricles, and cerebral aqueduct. Histological examination showed diffuse malignant astroglial neoplasm, and diagnosis of glioblastoma NOS WHO G IV was established.

Even though the appearance of usual GBM is widely recognizable, one must bear in mind the possibility of unusual presentation. The presented case highlights the diagnostic difficulties of diffuse glioblastoma with atypical clinical presentation.

Key words: *glioblastoma, autoimmune meningitis, GBM.*

Introduction

Glial tumors are the most common primary tumors of the nervous system, constituting 40% of primary intra-cranial tumors and up to 80% of malignant central nervous system tumors [2,6,12]. Glioblastoma (GBM) is the most malignant type of glial tumor associated with a very unfavorable prognosis. GBM is diagnosed in almost half of cases of primary

Communicating author:

Angelika Stapińska-Syniec, MD, Department of Neurosurgery, Institute of Psychiatry and Neurology, 9 Sobieskiego Str., 02-957 Warsaw, Poland, e-mail: angelika.stapinska@gmail.com

malignant tumors of the central nervous system (CNS) [12].

Glioblastoma are typically diffusely infiltrating tumors arising in sub-cortical white matter and spreading through white matter tracts [6]. Typical radiological features of GBM include the presence of a tumor with irregular contrast-enhancing margins and central necrosis surrounded by a wide area of vasogenic edema, and causing marked mass effect. In 20% of cases, multifocal disease is present.

Here, we presented an atypical clinical presentation of GBM mimicking autoimmune meningitis.

Case description

A 69-years-old previously healthy male was admitted to the emergency room (ER) due to signs of increasing cognitive impairment, weight loss, changes in behavior, difficulty in walking, and prolonged episodes of nausea over the past month. Two days before first admission, the patient was consulted in the same ER, where he presented with the aforementioned symptoms and signs of the cerebellar syndrome (wide-based gait and four-limb ataxia), he remained aware, auto-psychically oriented, mildly allo-psychically disoriented, yet collaborative, and approachable. The patient also reported mild headaches, characterized as sharp, occasionally radiating from the left frontal area to the left cheek. The rest of neurological exam was clinically insignificant.

The patient refused to be admitted to the hospital and was ultimately referred to an outpatient clinic for a follow-up and additional brain imaging. An magnetic resonance imaging (MRI) brain scan was subsequently performed in T2, and FLAIR sequences it showed hyperintense changes of the periventricular area surrounding both frontal horns of lateral ventricles as well as the third ventricle, choroid plexus of both lateral ventricles, and post-contrast leptomeningeal enhancement and thickening of meninges involving cerebellar sulci (Fig. 1). Possible differential diagnoses at this point included a neoplastic process and inflammatory disease of CNS.

Two days later, the patient was brought back to the ER due to exacerbating of symptoms, and was ultimately admitted to the neurological ward. On admission, the patient developed new symptoms, including horizontal, left-beating nystagmus, upper limbs dysdiadochokinesis, and mild ataxia with intention tremor in lower limbs. Previously observed wide-based gait and four-limb ataxia were also present.

A lumbar puncture was performed, cerebrospinal fluid (CSF) examination showed a highly elevated level of protein (1,222 mg/dl), cytosis of 23/mm^3, and monocytic smear, with no laboratory signs of intrathecal synthesis of immunoglobulins, though oligoclonal bands (type 3) were detected. CSF cytometry ruled out the presence of lymphoma; however, dominating presence of macrophage-histiocytic cells was reported.

An additional MRI scan of the cervical spine showed a single, in-core, contrast-enhancing lesion of undetermined etiology on the C7-Th1 level as well as leptomeningeal thickening and post-contrast-enhancement around the spinal cord, medulla oblongata, and inferior poles of cerebellar tonsils (Fig. 2).
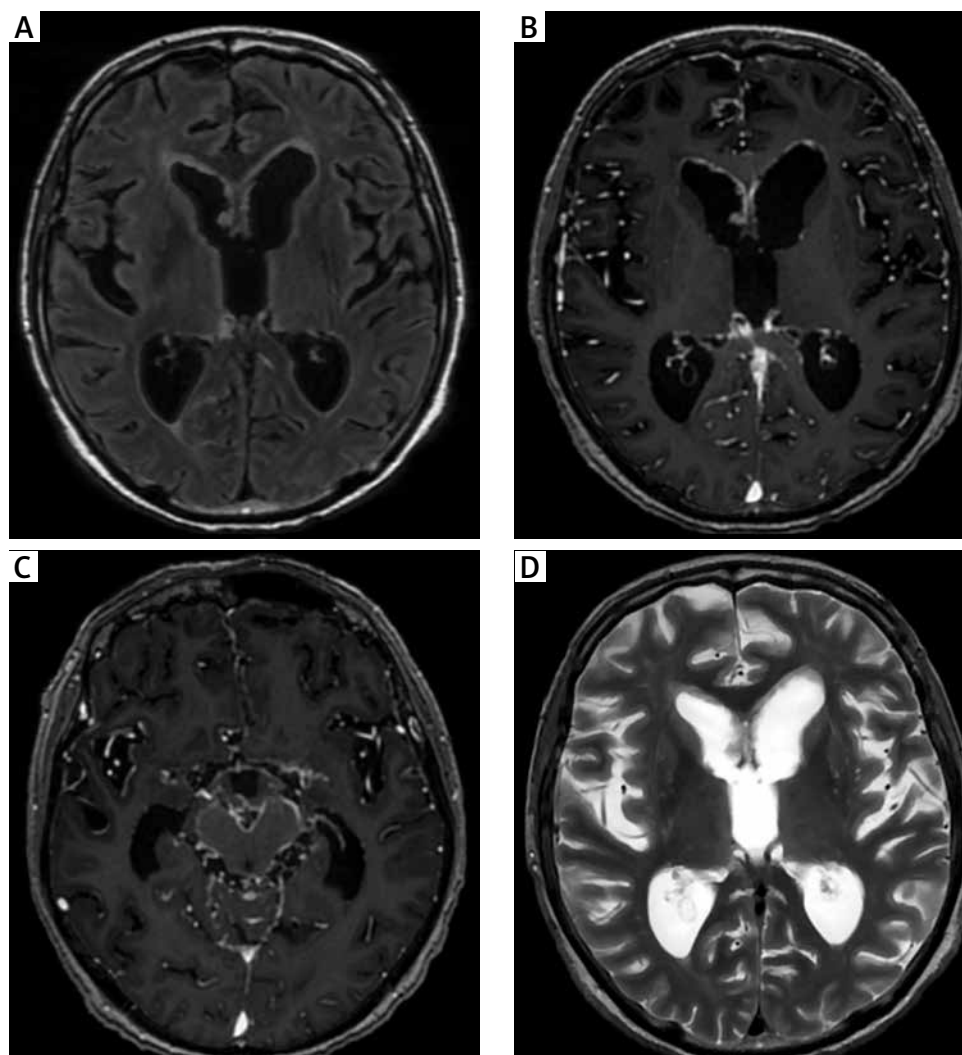
During hospitalization, the patient has developed fluctuating disturbances of consciousness. A couple of EEG tests were performed, each of them showing an increased frequency of paroxysmal changes. Anti-epileptic drugs (valproate) were prescribed with satisfactory results, and the patient quickly regained consciousness over the next days. An additional panel of infectious diseases tests of CSF was performed, and infectious background has been partially ruled out in terms of cytomegalovirus (CMV), herpes simplex virus (HSV), cryptococcus neoformans, and herpes zoster infections. Test detecting presence of onconeural antibodies in CSF was also negative.

Since autoimmunologic etiology was possible, the patient received treatment of a five-day course of methylprednisolone with little, but noticeable improvement in cognitive impairment.

A chest computed tomography (CT) scan was performed and a lesion located next to the right lung was observed, suggesting potential pleural mesothelioma. The patient was subsequently discharged from the hospital with a recommendation of an urgent thoracic surgical consultation, but due to sudden deterioration of neurological state over the next few days, he was re-admitted to the hospital.

On second admission to the neurological ward, the patient was drowsy, verbally unresponsive, occasionally agitated in bed, and without evident limb paresis.

A follow-up brain MRI scan showed no progression of previously described pathologies. A follow-up lumbar puncture revealed a noticeable decrease in cytosis and continuously elevated levels of protein in CSF. A follow-up abdomen CT scan was performed

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Fig. 1. Axial images of the brain MRI in FLAIR (**A**) and T2-weighted sequences (**D**) showing hyperintense changes of the periventricular area surrounding both frontal horns of lateral ventricles as well as the third ventricle and choroid plexus of both lateral ventricles. The post-contrast leptomeningeal enhancement and thickening of meninges involving cerebellar sulci and subependymal space, with its' thickening in the vicinity of the right frontal horn on T1-weighted axial images (**B**, **C**).

with no evident pathology detected. A thoracic surgery consultation was postponed due to deteriorating state of the patient as well as epidemiological reasons in terms of the COVID-19 pandemic at that time. Another round of immunosuppressive therapy was prescribed, including dexamethasone in decreasing doses paired with wide-spectrum antibiotics. The treatment mildly improved the patient's state of consciousness, he began selectively responding to commands, verbal contact was very superficial, the symptoms fluctuated in their intensity.

The patient was able to sit and stand with a physiotherapist's help, and was no longer dependent on nasogastric tube for feeding purposes.

Subsequently, the patient was referred to the neurosurgery ward and a stereotactic brain biopsy of periventricular lesions was performed. The obtained material contained white matter without neoplastic infiltration.

However, neurological state of the patient was continuously deteriorating, the state of consciousness was fluctuating, for a moment, the patient was
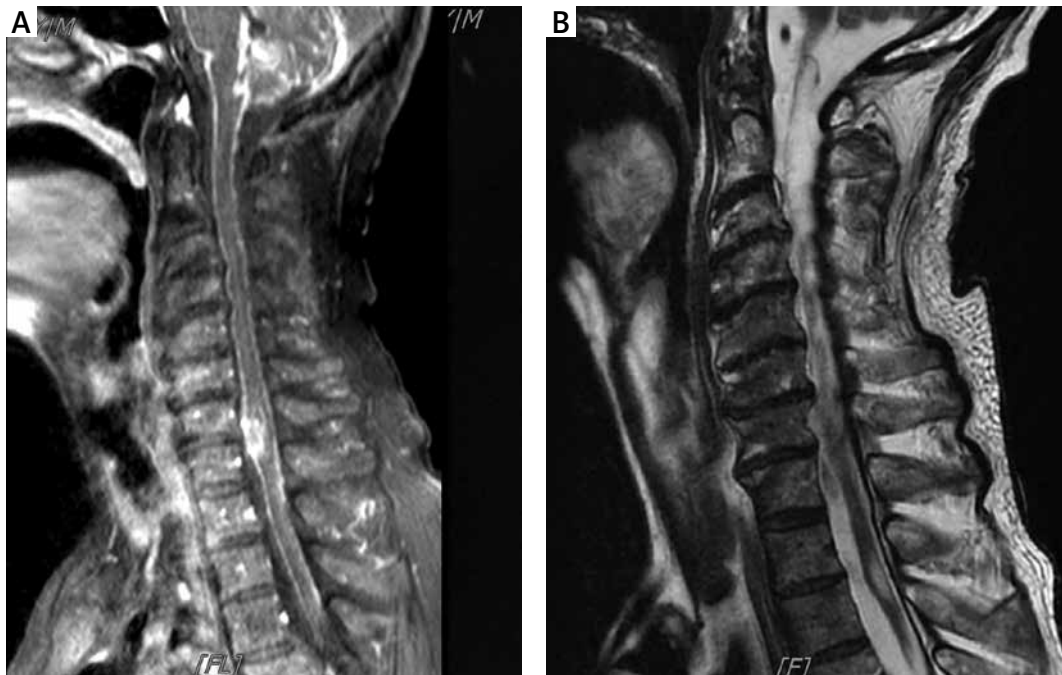
Fig. 2. The cervical spine MRI showed a single, in-core, contrast-enhancing lesion of undetermined etiology on C7-Th1 (**A**) on T1-weighted sagittal images level as well as leptomeningeal thickening and post-contrast-enhancement around the spinal cord. (**B**) T2-weighted sagittal images showing a new lesion located at Th2-Th3 levels.

not opening eyes on command or pain stimulus, the patient was completely disoriented. A follow-up cervical spine MR was performed and showed the previously described C7-Th1 lesion as well as meningeal enhancement of cervical spine, and a new, second lesion forming on the Th2-Th3 level (Fig. 2). The third sample of CSF was drawn; the level of protein was significantly lower, CSF cultures for bacterial and fungal infection came back negative, another CSF cytometry was conducted – pleocytosis was significantly lower, no cancerous or lymphoma cells detected, the morphology of studied cells in CSF was no longer suspicious – escalation of immunosuppressive treatment was suggested by the cytometry laboratory.
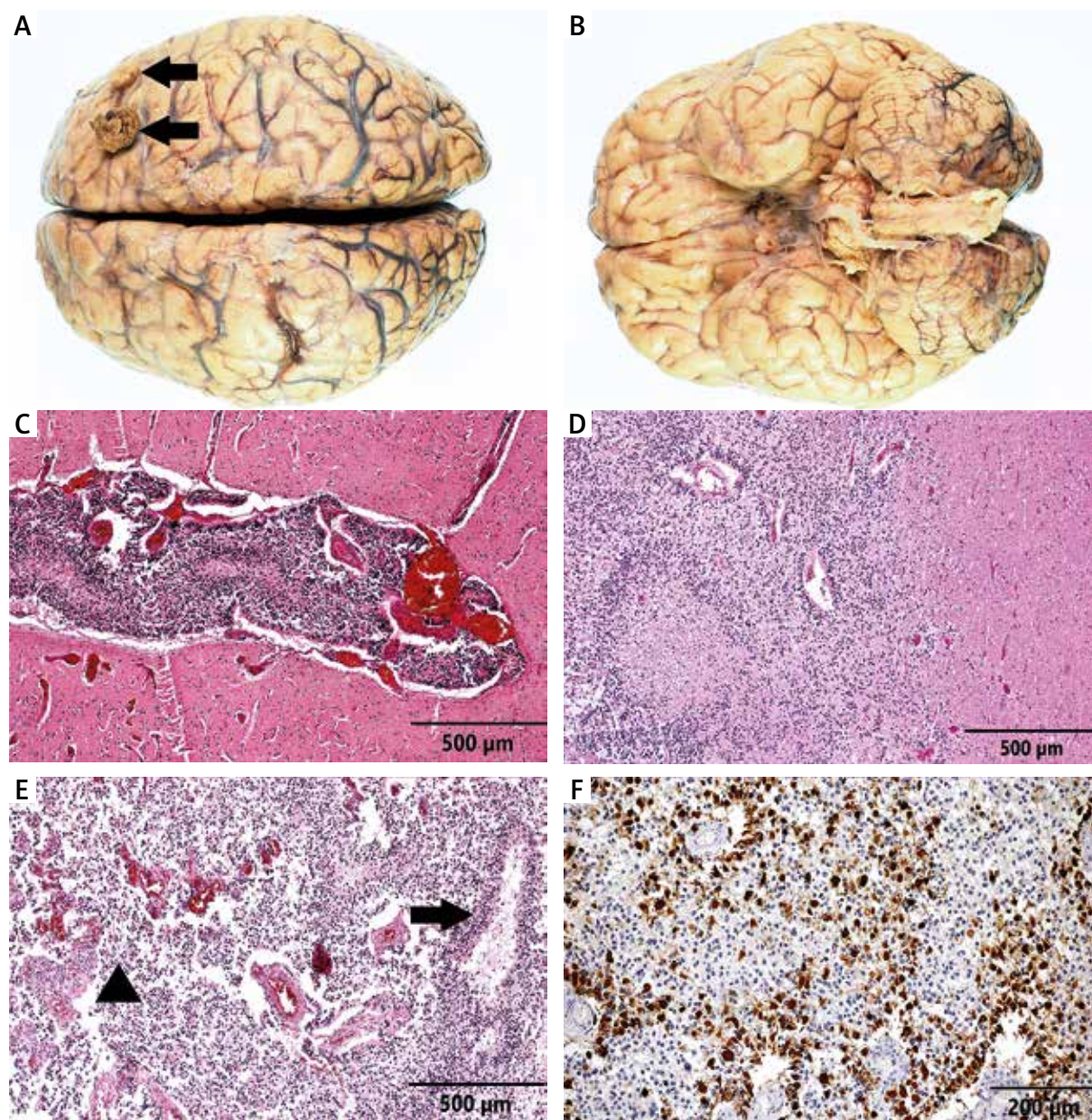
The next follow-up MRI scan of the brain and cervical spine were performed several weeks later and showed little progression in comparison with previous imaging results. Another stereotactic brain biopsy was conducted in agreement with the neurosurgery ward. Again, obtained tissue material did not contain neoplasm type of infiltration; small fragments of cortex and white matter were present.

During the stay, a possible Creutzfeldt-Jakob disease suspicion was raised, though no presence of 14-3-3 protein was found in CSF. Whipple's disease was also suspected due to unexplained periventricular and leptomeningeal enhancement; however, no Tropheryma whipplei DNA was found in stool sample, CSF DNA test was not available at the time.

Another round of empirical immunosuppressive treatment was considered again; however, the patient's condition quickly worsened. He became increasingly unresponsive over extended periods, mildly alert on pain stimulus, and decreases of saturation were observed. A control chest CT scan with an admission of a contrast agent was performed, no signs of pulmonary embolism were noted, the state of a mesothelioma-suspected lesion in the right lung was stationary with no progression over the past months. It was decided that due to the improving state and previous positive history, another round of immunomodulating treatment should be administered. The patient received five doses of intravenous immunoglobulins, with no particular positive or negative impact on the neurological state.

Over the next days, the patient's condition was further deteriorating with development of severe symptoms of pneumonia demanding administration of wide-spectrum antibiotics. The patient remained

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Fig. 3. Neuro-pathological examination. **A**) Gross photograph of the dorsal surface of the brain with post-biopsy lesions (arrows). **B**) Gross photograph of the ventral surface of the brain. **C**) Left parietal lobe with neoplastic tissue within subarachnoid space (hematoxylin-eosin [HE]). **D**) Periventricular, parenchymal neoplasm infiltration in the pons (HE). **E**) Pseudo-palisading necrosis (arrow) and microvascular proliferation (arrowhead) in glioblastoma (HE). **F**) Immuno-expression of GFAP in neoplastic cells.

in critical condition and subsequently died due to respiratory failure a couple of months after the first admission to the hospital. No unequivocal cause of neurological symptoms and findings in imaging studies were found before the patient's death.

Post-mortem examination of the brain revealed numerous foci of abnormal tissue inside the sub-arachnoid space, lateral ventricles, and cerebral aqueduct. Superficial, diffuse growth pattern infiltration of the sub-ependymal and periventricular areas in the lateral ventricles, brainstem, vermis, and cerebellar peduncles was detected. Histological examination revealed diffuse malignant astroglial neoplasm with micro-vascular proliferation, and

pseudo-palisading necrosis (Fig. 3). Neoplastic cells showed high mitotic activity and immunoexpression of glial fibrillary acidic protein (GFAP). Ki67 immuno-labeling index was about 50%. The diagnosis of glioblastoma NOS WHO G IV was established.

Discussion

Glioblastoma typically manifests with focal neurological deficits and characteristic radiological features. In most cases, head CT scan and MRI scan reveal tumors with irregular borders with enhancement after intravenous contrast agent and central necrosis [6]. The symptoms presented by the patient in the afore-mentioned case accompanied by unusual results of neuroimaging studies were suggestive of neoplastic disease or inflammatory process. The first brain MRI scan revealed in T2-weighted images and FLAIR sequences hyperintense changes of the periventricular area surrounding ventricles and choroid plexus of both lateral ventricles. The post-contrast leptomeningeal enhancement and thickening of meninges were also present. These types of findings are usually caused by meningitis, encephalitis, lymphoma, or may be present in rare cases of diffuse leptomeningeal glioneuronal tumor (DLGNT), and are not typical radiological features of GBM. DLGNT is a very rare tumor of CNS that appeared for the first time in the 2016 revised 4th edition of the World Health Organization (WHO) classification of nervous system tumors [13]. It affects mostly the pediatric population [5]. Typically DLGNT is an indolent tumor of the central nervous system characterized by diffuse leptomeningeal infiltration by glioneuronal cells, with no primary mass and the enhancement of sub-arachnoid space with cystic lesions [7]. It is rarely diagnosed in adults [5]. However, the whole clinical manifestation suggested autoimmune etiology, which was mainly suspected due to temporary noticeable neurological improvement after the first courses of intravenous immunoglobulins. The final diagnosis was made based on postmortem histological evaluation, and revealed diffuse glioblastoma, which was present in every specimen obtained from the whole brain.

A cervical spine MRI performed in the presented case showed in-core, contrast-enhancing lesions on C7-Th1 and Th2-Th3 levels, and meningeal thickening and post-contrast-enhancement. There have been reported in the literature some cases of intra-cranial dissemination from primary spinal GBM [8]. Khandwala *et al.* reported a case of a 15-year-old boy with spinal glioblastoma on the T8-L1 level, who had a brain MRI one year after treatment that showed diffuse leptomeningeal enhancement with meningeal-based deposits [8]. Typically, in the case of primary spinal GBM, radiological findings in spine MRI scans include an infiltrative and intra-medullary lesion that is hyperintense in T2-weighted images and contrast-enhancing in T1-weighted images [8]. However, these findings are not specific and may be present in other pathologies, such as different types of intra-medullary tumors or transverse myelitis [8].

Intra-ventricular GBM may be associated with cerebrospinal fluid seeding and subependymal metastases, which are typically hyperintense in FLAIR MRI sequences [8]. However, intra-ventricular GBM, whether primary or secondary, are typically characterized by a growing mass [4].

Leptomeningeal spread of neoplastic cells occurs in 4% of patients with glial tumors and is often correlated with poorer prognosis in comparison to parenchymal disease progression [3,9-11]. In a study by Andersen *et al.*, glioblastoma patients with leptomeningeal spread survive a median of 5 months [1].

To the best of our knowledge, this is the first case of diffuse glioblastoma mimicking meningitis or autoimmune process, with unusual neuro-imaging results and a very unfavorable clinical course. The described case represents a difficult clinical and diagnostic challenge in an adult affected by diffuse glioblastoma.

Conclusions

Even though the appearance of usual GBM is widely recognizable, one must bear in mind the possibility of unusual presentation. The presented case highlights the difficulties in the diagnosis of diffuse glioblastoma with atypical clinical presentation. When radiological features and clinical findings are not specific, especially with inconclusive brain biopsy results, the diagnostic process might be very difficult.

Disclosure

The authors report no conflict of interest.

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