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Coexistence of multiple sclerosis and brain tumours: Case report and review

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ABSTRACT

In the present report, a review of the literature on the combination of multiple sclerosis and brain tumours is performed. Additionally, the frequency of such combination, possible etiopathogenetic mechanisms, current diagnostic criteria and treatment approaches are reviewed. Furthermore, the case of a 30-year-old man with multiple sclerosis and anaplastic astrocytoma of the right temporal lobe is described in detail. Specifically, the patient underwent a series of tests, including laboratory analyses of blood and cerebrospinal fluid, brain MRI in various modes, MR spectroscopy and excised tumour's pathohistological and immunohistochemical examination. Results of the tests are reported here. A staged examination and treatment of the patient allowed the researchers to perform a correct diagnosis and obtain a satisfactory functional outcome.

1. Introduction

The incidence of multiple sclerosis (MS) in a population varies widely [1,2]. Of note, according to the WHO classification, there are currently approximately 100 subtypes of 29 histological variants of primary central nervous system (CNS) tumours [3,4]. Gliomas make up to ~70% of all cerebral neoplasms, and glioblastomas are the most common and malignant histological subtype among them [5]. According to literature, including CBTRUS, 61.5% of all gliomas are glioblastomas, 18.8% are non-glioblastoma astrocytomas, 10.7% are oligodendrogliomas, 3.6% are ependymomas, and 5.4% are other gliomas [6].

The combination of MS and cerebral tumours of glial origin is such comorbidity has been rarely reported in the scientific literature [7]. It was first described in 1912 by Bosch [8]. Since 1960, numerous cases have been described.

MS is considered to be a primary pathology, with subsequent development of brain gliomas, frequently of astrocytic origin [9,10]. The association between MS and non-glioma histological subtypes of cerebral tumours has also been described [4]. Nevertheless, assessment of the true occurrence of brain tumours in MS patients is complex.

In the present article, we describe a rare case of combined MS and a glial tumour, specifically an astrocytoma.

2. Case presentation

The case presented here involves a 30-year-old man admitted to the neurology clinic with a 3-week complaint of headache, general weakness and fervescence. Over the previous few weeks, the patient had been treated by an ENT doctor for pansinusitis. Anamnesis revealed a history of meningococcal meningitis at the age of 8 months. There were no indications of a burdened family history, professional or household risk factors. Somatically, the patient had a low-grade fever (37.2 °C). His neurological status included the asthenic syndrome, horizontal end-position nystagmus to the right, and hyperanisoreflexia, primarily on the right. With the goal of identifying the headache's secondary cause, the patient underwent maxillary sinuses CT. The latter revealed focal changes in the right temporal lobe. To clarify the nature of brain dis-

Abbreviations: CNS, Central nervous system; CSF, Cerebral spinal fluid; MS, Multiple sclerosis

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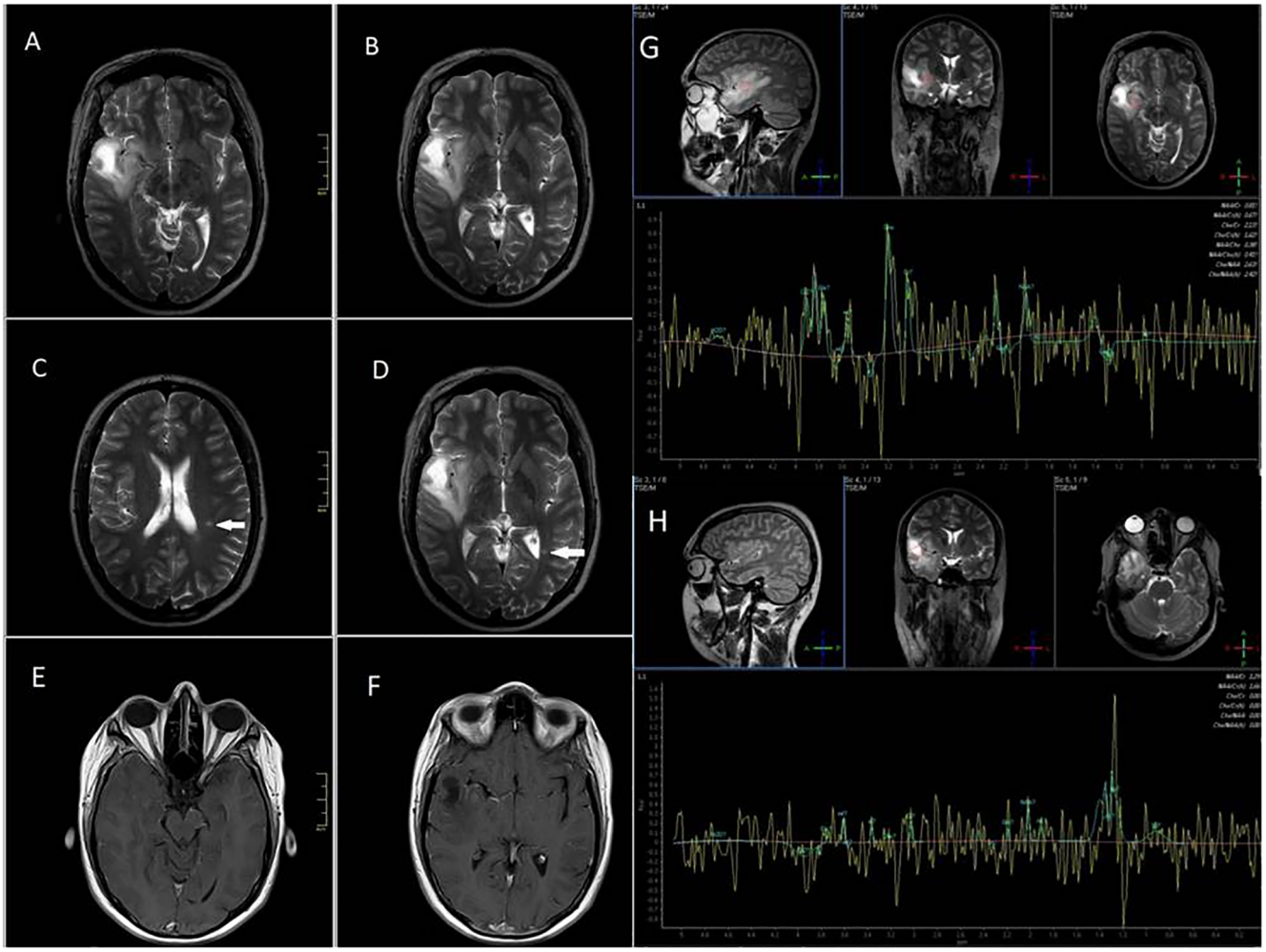

Fig. 1. Brain MRI and MR spectroscopy. A 5.6 × 4.2 × 3.8 cm T2 hyperintense lesion was visualised in the right temporal lobe and the insula. The lesion had irregular edges and blurred outlines and involved both the grey and white brain matter (A, B). In the T2 mode, two hyperintensive lesions, over 3 mm along the long axis, were visualised periventricularly in the left hemisphere (C, D). Through T1 post-contrast images, low contrast accumulation was observed along the periphery of the lesion in the right temporal lobe with cystic cavity in the centre. On the contrary, the left hemisphere lesions did not accumulate contrast (E, F). Spectroscopy in the perifocal area of the right temporal lobe (around the cystic area) revealed the following characteristics: an increase of a Cho peak, a decrease of NAA and a Cr peak, an unsharply expressed Lip peak, and an inverted Lac (G) peak. An area of cystic transformation expressed an increase of Lip peak and a decrease of all other peaks. The identified changes corresponded to inflammation (H).

ease, brain MRI, contrast MRI, and MR spectroscopy were performed (Fig. 1). Results of this imaging indicated inflammatory brain disease.

Cerebral spinal fluid (CSF) examination indicated increased protein content (1.2 g/l), and lymphocytes induced cell cytosis. CSF's examination for infections revealed antibodies to the following viruses: type I herpes simplex virus, cytomegalovirus, Epstein-Barr virus and Coxsackievirus. Based on these results, the patient's status was considered as viral encephalitis. Therefore, he was treated with IV Herpevir, followed by Acyclovir orally. He was discharged one month post-hospitalisation with a clinical response.

Two months post-discharge, the patient's condition deteriorated. Specifically, he developed painful sensations when looking to the left and blurred vision in the left eye. Ophthalmoscopy indicated signs of optic nerve oedema on the left. The patient's neurological status had a negative trend: low-amplitude horizontal nystagmus when looking to the right, high-amplitude rotatory nystagmus when looking to the left, hyper right anisoreflexia, ankle clonus, Babinski's symptom, bilateral Chaddock's symptom, and instability during the Romberg test. A brain MRI indicated a decrease in the right temporal lobe lesion. Additionally, it revealed multiple 4–6 mm lesions of both the frontal and parietal lobes (enhanced signal) in T2 and FLAIR modes. New lesions located supratentorially in the periventricular and juxtacortical areas accumulated the contrast agent (Fig. 2).

On the basis of the clinical data and the lesions' nature by MRI scans, MS was suspected. A CSF examination revealed increased protein content (464 mg/l) and blood/CSF hematoencephalic barrier disturbance. Additionally, intrathecal IgG synthesis and oligoclonal IgG antibodies were found in the CSF. Such findings suggested a chronic inflammatory CNS disease. Specifically, the patient was diagnosed with MS, cerebral form, EDSS. Based on this diagnosis, he was treated with

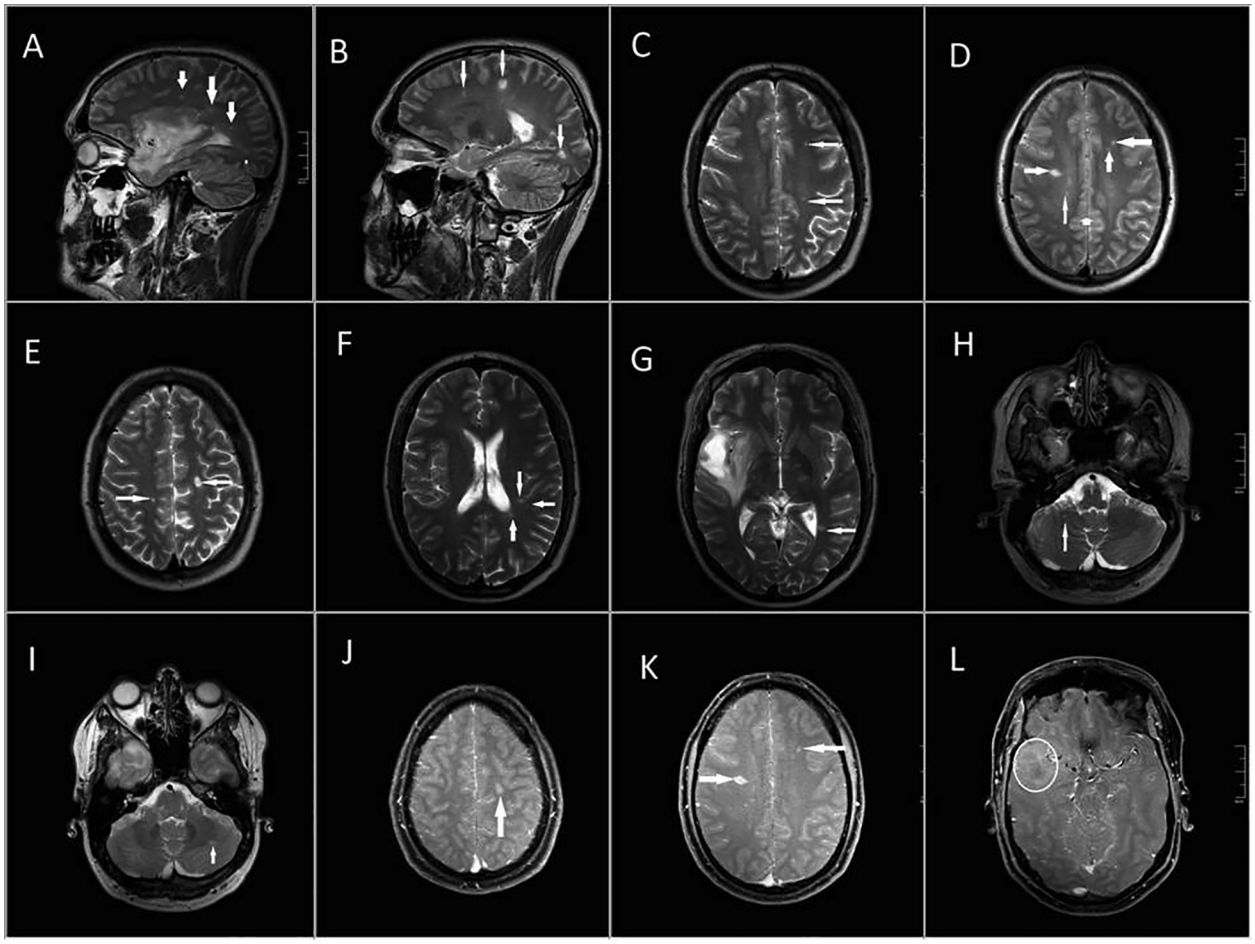

Fig. 2. Sagittal plane MRI: Lesions were identified in both the right (A) and left (B) hemispheres. Axial plane MRI: New T2 hyperintense lesions of different diameters in the large hemispheres and cerebellum (C–I). IV enhanced MRI: New lesions located juxtacortically (J, K) and a large lesion in the right temporal lobe (L) accumulated the contrast agent.

IV Solu-Medrol pulse therapy, which gave a clinical response.

However, a repeated aggravation took place after 4 months. At that time, the patient had a generalised convulsive seizure with loss of consciousness. To identify the cause of the seizure, the patient underwent a brain MRI (no negative trend). An anticonvulsant Carbamazepine therapy was prescribed, followed by Levitiracetam, 750 mg twice a day.

After 6 months, IV enhanced follow-up MRI revealed a negative trend. Specifically, focal changes in the right temporal lobe in the form of an increased lesion and an area of perifocal oedema were observed. A 27 × 23.5 mm lump in the right temporal lobe, posterior basal sections of the right frontal lobe, i.e. the insula, was identified. The lesion was hyperintense in T2 and FLAIR modes and had a cystic component with moderate perifocal oedema, a mass effect, and a non-homogeneous structure (probably of a glial nature). MR spectroscopy indicated additional data of the intracerebral tumour, a Gr III glioma (Fig. 3).

The intracerebral tumour of the right temporal lobe with median growth and expansion into ventricular system was surgically excised.

Microscopic examination revealed an anaplastic oligoastrocytoma with signs of persistent DNA virus infection and focal demyelination (Fig. 4).

Tumour cells were positive for the following immunohistochemical markers: GFAP, IDH-1, Ki-67 (Fig. 5). Based on these findings, an anaplastic oligoastrocytoma (IDH mutant, malignancy grade III) (WHO grade III, ICD-O code 9382/3) was diagnosed.

Based on the pathohistological findings on the excised tumour, the patient underwent a course of radiation therapy one month post surgery in the right temporal lobe (i.e. the excision area) using a linear accelerator (60 Gy dosage, 2 Gy per session). Glioma chemotherapy was not prescribed because of its possible negative effects on MS. Additionally, considering active MS's therapy possible negative effects on tumour development, follow-ups were performed every 3 months.

A 4-month IV enhanced MRI revealed a 60 × 45 × 26 mm cystic cavity filled with CSF in the right temporal lobe's excision area.

Numerous round and oval 3–11 mm (in the right semi-oval centre) lesions (high in T2 and FLAIR) were identified in the following locations: corpus callosum; deep and subcortical white matter of frontal, parietal, and temporal lobes; area of the pons; right middle cerebellar peduncle; and left cerebellar hemisphere. Additionally, small isolated lesions in the subcortical sections were observed (Fig. 6).

No contrasting of revealed lesions or development of new lesions was observed. This MRI image corresponds to the inactive stage of

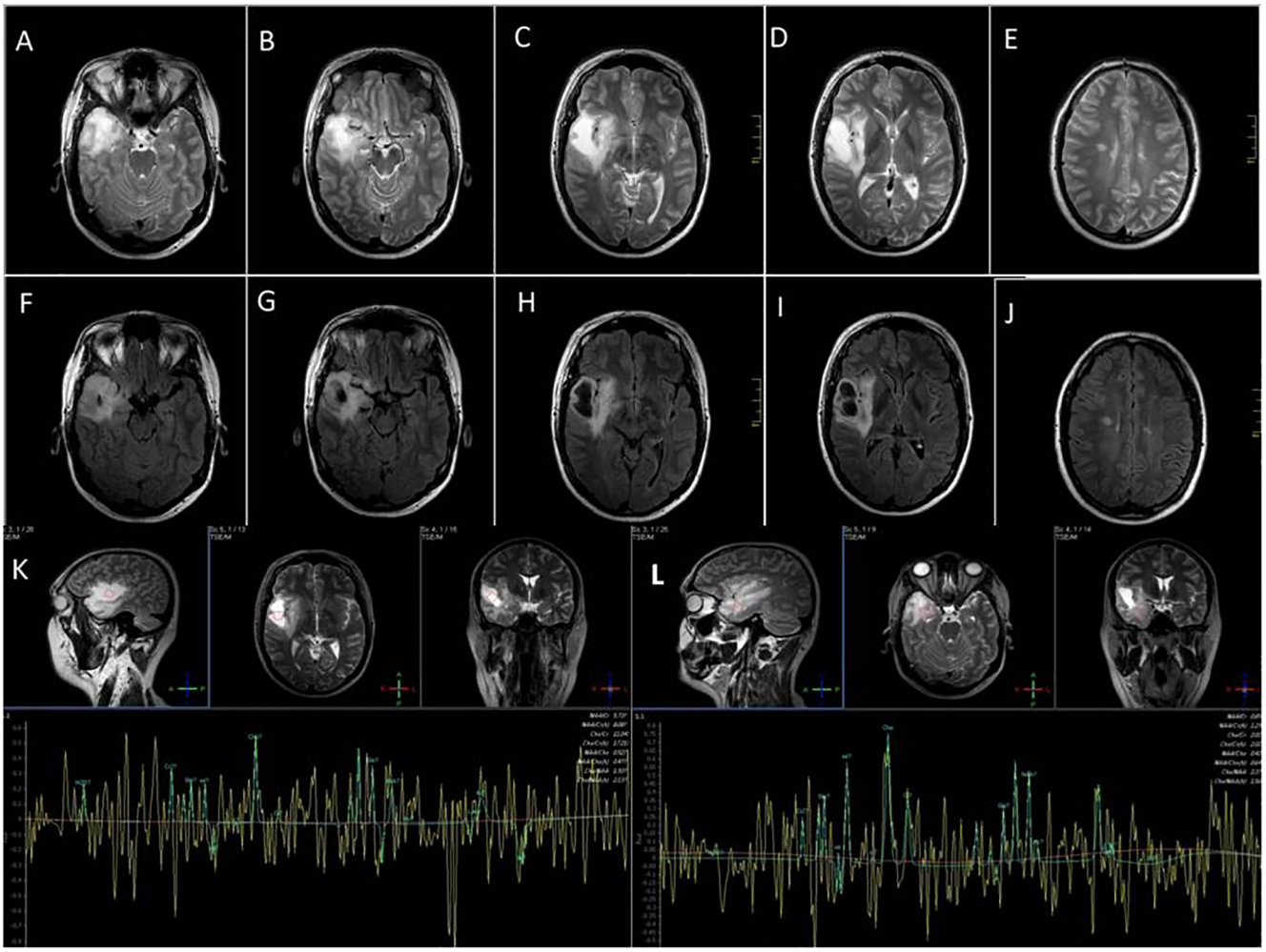

Fig. 3. Negative trend: focal changes in the right temporal lobe in the form of an increased lesion and an area of perifocal oedema. Juxtacortical lesions were unchanged. T2 mode MRI (A–E). FLAIR mode MRI (F–J). MR spectroscopy in the solid portion (K) of the mass indicated a decrease in the NAA and a relative increase in the Cho peaks. The Cr peak in the pathological mass's area did not decrease, and the bases of the Cho and Cr peaks were expanded. Expressed Lip and inverted Lac peaks. A decrease in the NAA and relative increase in the Cho peaks in the cystic portion (L) of the mass. The Cr peak slightly decreased. Expressed Lip and inverted Lac peaks.

demyelination, with infra- and supra-tentorial lesions (cortical, juxtacortical and periventricular). Of note, spinal cord MRI during the patient's examination and treatment found no pathological lesions.

As of the time of preparation of this article (18 months before surgery), according to clinical data and neuroimaging, there were no signs of continued tumour growth and MS progression. Neurological status did not include increased pathological symptoms. No convulsive seizures were reported post surgery. The patient continues to be under active supervision of a neurologist and a neurosurgeon.

3. Discussion

The global risk of malignant neoplasms' development in MS patients is important. MS patients undergo immunomodulatory therapy, which increases cancer risk in any location [11]. However, current data on the occurrence of cancer in MS patients are contradictory [12–15].

Malignant brain tumour occurrence and detectability in MS patients is typically higher than in the general population [16,17]. According to some authors, systematic analysis of the data did not show increased or decreased risk of glioma in MS patients, while an increased risk was found for meningiomas [18].

Common etiopathogenetic factors of malignant brain tumours and MS cannot be excluded. This applies to ethnic factors and race. Of note, both gliomas and MS are more common in Caucasians [1,6]. Influences of infections, viruses, and allergens increase the risk of both MS and CNS lymphoma development but not glial tumours [19]. No significant correlations with etiological factors such as age, sex and brain cancer risk factors have been observed.

Discussions are ongoing on the impact of immunomodulatory treatment in MS patients on cancerogenesis. According to a recent study, MS patients receiving immunosuppressants generally have a higher cancer risk [20].

Currently, brain tumours and MS's diagnosis are based on clinical and neuroimaging data [21]. Of all cerebral tumours, MS is frequently

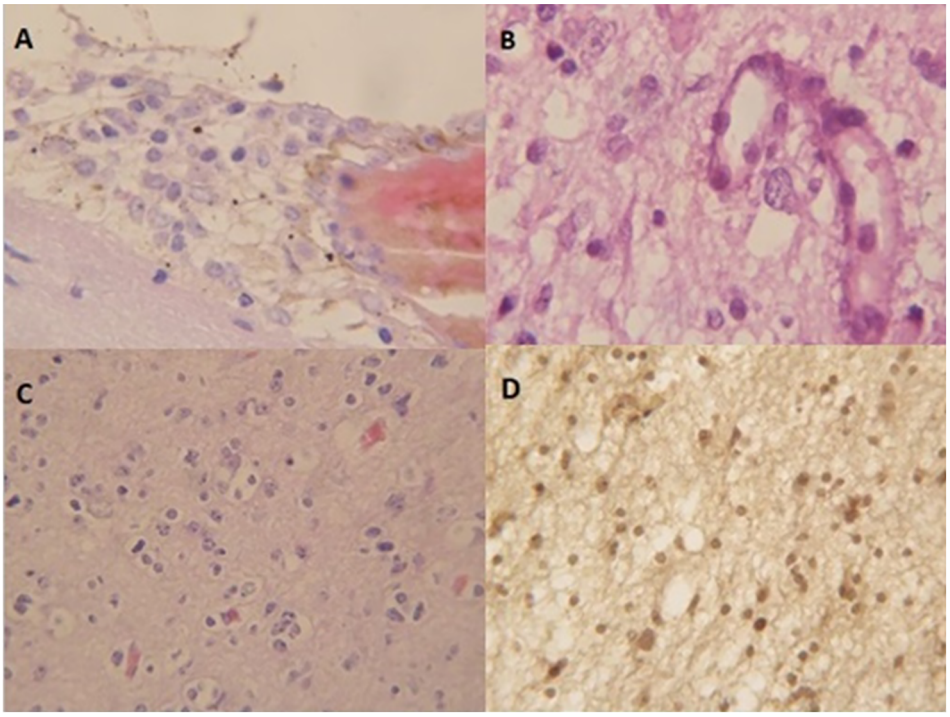

Fig. 4. Proliferative reactive changes with angiodystonic effects and increased vascular permeability, characterised by indirect signs of persistent non-bacterial infection, focal meningothelium proliferation and effects of significant proliferate cells polymorphism with karyopyknosis. Hematoxylin-eosin, 400× (A): In the area of brain matter, the following characteristics can be identified as invasion: perivasal and pericellular tissue oedema, neuronophagy, satelletosis, astrocyte body hyperplasia, paretic vasodilation, endothelial cells swelling and proliferation with changed intercellular distances. Hematoxylin-eosin, 800× (B): Changes in the nuclei of different cell types characterised by the presence of fine inclusions and nucleoli can be considered to be indirect signs of persistent viral infection. The cellular composition of anaplastic oligoastrocytomas is represented by the proliferation of both polymorphic astrocytes and cluster oligodendrocytes. Hematoxylin-eosin, 400× (C): Severe oedema with a formation of spike-like structures, representing the effects of focal periaxonal demyelination. Hematoxylin-pikrofuksin according to Van Gieson, 400X (D).

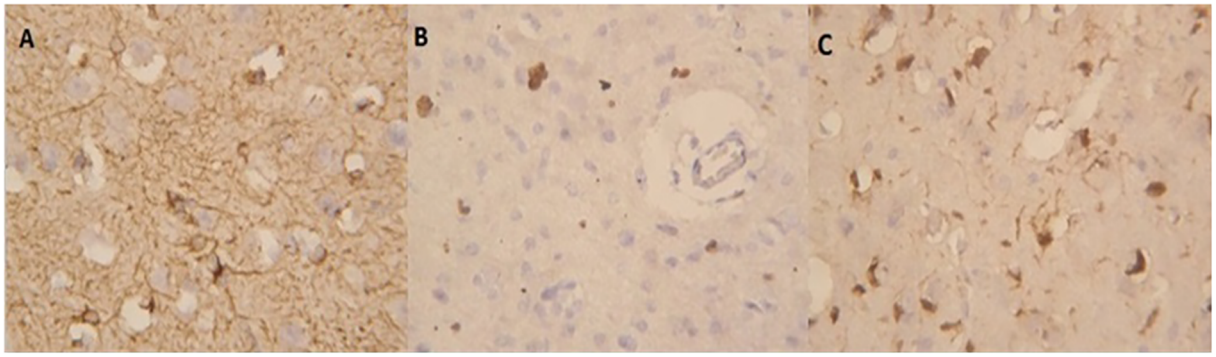

Fig. 5. Immunohistochemistry: non-uniform cell density and finely-divided degradation of astroglia processes. Immunoreactivity against antibodies to glial fibrillary acidic protein, with additional hematoxylin staining, 800× (A): proliferating cells (immunopositive nuclei) are strongly polymorphic. Immunoreactivity against Ki-67 antibody, with additional hematoxylin staining, 800× (B): immunopositive response, characterised by IDH expression in individual tumour astrocytes. Immunoreactivity against EGFR antibodies, with hematoxylin staining, 800× (C).

masked by primary CNS lymphomas that have similar neuroimaging parameters [22].

Recent data on possible common genetic determinants of MS, cancer, and neurodegenerative diseases were made public [23].

Several assumptions indicate the possible relationship between MS and cerebral neoplasms. Specifically, chronic inflammation causes destruction of nerve fibres' myelin sheaths and hyperproliferation of cells involved in remyelination [24].

This theory is supported by occasional studies focusing on morphological changes in MS's brain tissues, when cells with signs of dysplasia and intermediate characteristics between reactive glial cells and tumour cells were detected [25]. Similarly, neurotropic growth factors stimulate MS's oligodendrocytes and remyelination recovery, possibly contributing to neoplastic transformation of nerve glial cells [4].

Additionally, MS patients have a higher incidence of multifocal gliomas, which can be explained by the Willis theory. Specifically, neoplastic transformation occurs in two stages. First, changes in brain parenchyma occur because of MS. Then, external stimuli stimulate neoplastic transformation.

In line with previous theories, we histologically verified a persistent DNA virus infection in biopsy cells of the present case.

However, there are insufficient data to understand whether MS affects tumour growth intensity. Diagnosis complexity and neuroimaging errors are noteworthy. Furthermore, new symptoms may indicate MS's clinical progression rather than tumour growth, and vice versa.

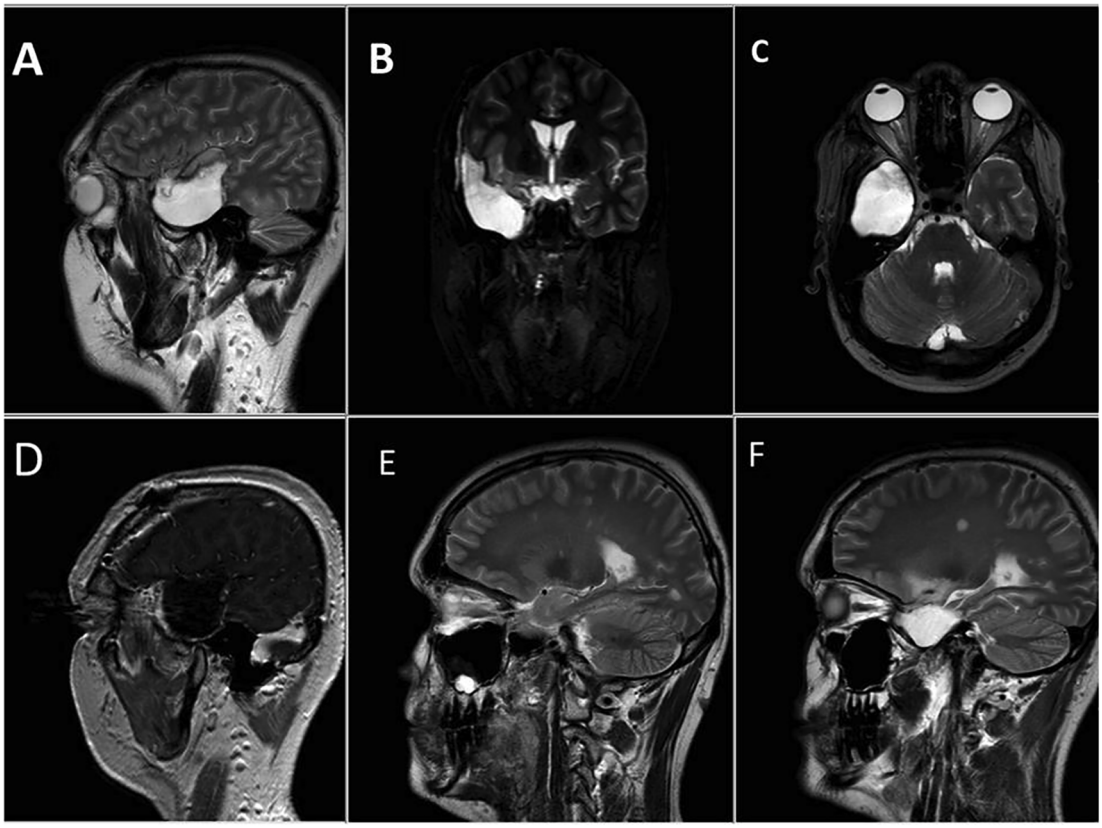

Fig. 6. Follow-up brain MRI was performed 4 months post surgery. Condition after the right temporal lobe oncotomy. Sagittal (A), frontal (B), axial plane (C), and IV enhanced (D) MRI. T2 mode MRI; sagittal sections: left (E) and right (F) hemispheres.

4. Conclusion

Although brain gliomas and MS comorbidity are rare, they have been previously described in the literature. It is not completely clear whether their occurrence is accidental or consequential to carcinogenesis-like pathophysiological mechanisms.

Atypical MS symptoms observed in our clinical case require a more detailed examination with the application of additional diagnostic techniques.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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