ABSTRACT

Background: The clinical features of multiple sclerosis during a relapse may raise the suspicion of a brain tumor as a possible differential diagnosis. Regardless of the high informative value of neuroimaging, some clinical cases remain challenging for neurologists, neurosurgeons and radiologists. Associations of brain tumors and relapsing-remitting multiple sclerosis have been described in the literature. Epilepsy, being common in brain tumors, is not among the most frequent and typical manifestations of multiple sclerosis, but both disorders appear together more commonly than by chance.

Objective: To present and discuss the diagnostic challenges in a case of coexisting epilepsy, multiple sclerosis, and glioblastoma multiforme.

Method: Case report.

Results: We present a 38-year-old patient with relapsing-remitting multiple sclerosis manifesting clinically a long period after a successfully treated epilepsy in childhood and adolescence. After reappearance of generalized tonic-clonic seizures and imaging evidence of a tumefactive lesion, the differential diagnosis between a new relapse and an initial manifestation of a brain tumor was discussed. Glioblastoma multiforme was found intraoperatively.

Conclusion: Our case study demonstrates that the likelihood of parallel development of different pathological processes, such as demyelinating and neoplastic, in the same patient, should not be underestimated. We emphasize the critical importance of biopsy for the resolution of similar diagnostic dilemmas. Yet, obtaining consent for biopsy is not always a leading point in the communication with patients and their relatives. All efforts made for an accurate diagnosis are important, as properly chosen therapeutic options influence the prognosis.

Keywords: 18F-FDG PET, Biopsy, Epilepsy, Glioblastoma, Multiple sclerosis

BACKGROUND

Clinical manifestations of multiple sclerosis (MS) during a relapse have often provoked discussions about the differential diagnosis of brain malignancy. Nowadays, in spite of the availability of multiple neuroimaging techniques, there are still clinical cases which challenge neurologists qualified in the domain of demyelinating diseases, neurosurgeons, and radiologists.

Publications in the literature describing solitary, well demarcated space occupying demyelinating lesions, requiring a broad differential diagnosis, have increased in recent years. The term of “tumefactive multiple sclerosis” has been introduced. It describes the constellation of atypical neuroimaging characteristics of MS lesions, such as: single space occupying lesion, size larger than 2 cm, mass effect, edema and/or ring enhancement, etc [1, 2]. Other definitions, including “tumefactive demyelinating lesions”, “demyelinating pseudotumor”, “tumor-like demyelinating lesions”, “giant plaques” are related to clinical cases where large, aggressive demyelinating lesions can be seen in patients with, but also without confirmed MS.

Among the frequently encountered neurological manifestations in a number of cases of MS with lateralized symptoms and MRI picture of giant plaques reminding a brain tumor with perifocal edema, are global/nominate aphasia, spastic hemiparesis, epileptic seizures, syndrome of intracranial hypertension. Such manifestations are rarely seen during a relapse in usual MS patients [1-3].

In clinical practice, the dilemma of brain tumor or demyelinating lesion emerges when focal neurological deficit appears abruptly and does not suggest more than a single location of the pathologic process, and also when some characteristic symptoms of brain tumors are imitated. It is therefore recommended to consider a pseudo tumor manifestation of MS in young patients with rapidly occurring unilateral hemiparesis and raised intracranial pressure [4].

Tavee et al. [2] have presented an unusual case of a 25-year-old woman with sudden spastic hemiparesis and
an episode with a fall and loss of consciousness. On MRI they found a lesion in the left posterior frontal region, 5.0 × 3.5 × 3.5 cm in size, causing mass effect, showing a heterogeneous increase of signal intensity on T2 and FLAIR, and hypointensity on T1. The findings were interpreted as cystic astrocytoma, but focal fields of demyelination were found on biopsy. Differential diagnostic challenges in similar cases are also related to the fact that contrast enhancement and brain edema may fade away after application of corticosteroids, the standard treatment of MS relapses [5].

Biopsy of giant pseudo tumor demyelinating lesions does not yet have an alternative. In a retrospective analysis of biopsy confirmed inflammatory demyelinating disease of the central nervous system in 168 patients, 61% having a first clinical event, 29% with relapsing-remitting, and 4% with progressive clinical course, Lucchini et al. [6] underline the diagnostic challenges in cases with atypical clinical and radiological characteristics. Actually, in nearly 10% of patients with MS, no multiple lesions are found on MRI. Demyelinating diseases affecting the corpus callosum may even present on neuroimaging as a butterfly glioma [2]. According to Navarro et al. [3], the spectroscopic picture of inflammation with cell destruction and replacement does not contribute to the differentiation between demyelinating disease and high grade glioma.

On the other hand, the possibility that two processes, demyelinating and neoplastic, can develop together at the same time, should not be underestimated.

Association of brain tumors with multiple sclerosis

The association of brain tumors such as meningiomas, oligodendrogliomas, astrocytomas, glioblastomas, diffuse gliomas, primary CNS lymphomas, and ependymomas of the spinal cord, with relapsing-remitting MS, has been known from a series of case descriptions. Usually, an initial clinical and neuroimaging based suspicion of a neoplastic process emerges, which can later be proven by means of biopsy. Patients are most likely to have a consecutive relapse with worsening or initial symptoms with evidence of a single lesion [7-9].

The development of two parallel processes, demyelinating and neoplastic, in patients with MS, can also be suspected in patients with secondary progressive MS whose condition worsens, and who do not respond to corticosteroid treatment. A careful evaluation of symptoms and MRI findings is recommended even when the clinical picture and the diagnosis are well documented, as well as in cases with long history of the disease [10-12].

If large, contrast enhancing brain lesions are found in older patients with relapsing-remitting course of MS and steroid resistant visual disturbances, primary CNS lymphoma should be considered [13, 14].

Concerning the parallel development of multiple sclerosis and later of a primary CNS lymphoma in the same patient, lymphoma can be discussed as a possible complication of chronic immunosuppression with corticosteroids, immunosuppressants and beta-interferon, leading to an immunocompromised state. The demyelinating disease, preceding the lymphoma, may on the other hand be subject to a neoplastic transformation [15, 16].

Epilepsy in brain tumors and multiple sclerosis

Epileptic seizures are a well-known manifestation of brain tumors [17, 18]. Though they are not among the most frequent and typical symptoms of MS, results of population-based studies show that MS and epilepsy occur together more commonly than by chance [19]. Occurrence of seizures during the clinical course of MS may be associated with early-onset and increased disease severity [20]. It is believed that subcortical plaques and their strategic location underlie seizure activity in patients with MS and epilepsy [21]. According to Nicholas et al., grey matter lesions in the temporal lobe in MS underlie a loss of inhibitory interneuron’s in the cortex and these changes could together with concurrent infection enhance susceptibility to seizures [22].

CASE REPORT

We present a case of development of a brain tumor in a patient with relapsing-remitting MS, clinically manifested and confirmed years after successfully treated epilepsy in her childhood and adolescence.

The patient is a 38-year-old woman whose multiple sclerosis presented for the first time in 2010 with weakness and pain in her right leg, dizziness and walking instability. The second and third relapses, in November 2010 and May 2011 respectively, presented with worsening of the symptoms, together with appearance of double vision. The patient was treated with corticosteroids and her condition improved. MRI findings in October 2011 were in line with diagnosis of MS (Fig.1.).

In December 2011 the patient was hospitalized again due to weakness and numbness of the right extremities and unstable gait. Physical exam was unremarkable. Neurologic exam showed right internuclear opthalmoparesis, paresis of the right lower extremity, hyperreflexia more pronounced on the right, bilateral Babinski and Chaddock signs, and cerebellar Romberg test. EDSS was 2.5. Laboratory tests were normal. Another steroid course led to improvement and the patient was discharged.

A year later, in 2012, another hospitalization was performed because of leg weakness, numbness of the left side of the body and the left extremities. EDSS was 4.0 because of more pronounced pyramidal and coordination symptoms. Again, steroids were applied and the patient was discharged with relative improvement.

In March 2013 she had a generalized tonic-clonic seizure. She was hospitalized and computed tomography was performed in emergency. Suspcion of a space occupying lesion in the right temporal region was raised. New findings from the neurologic exam were impaired spatial orientation, slower thinking and speech. MRI was performed (Fig.2.).

The right temporal lesion seen on CT was confirmed, 27 x 23.5 mm in size, with mild surrounding edema and mass effect, showing insignificant, non-homogeneous
contrast enhancement. The lesion had restricted diffusion and increased perfusion. It was interpreted as a possible tumor-like MS lesion or, less likely, a low-grade glioma. MRI follow-up in 3 months was recommended.

PET of the brain was performed, showing an area of increased activity, 15 mm in size, in the right temporal lobe (Fig.3.).

After fusion of PET and MRI images, the area was found to project in the ventral medial third of the MRI lesion and towards the temporal horn of the lateral ventricle (Fig.4.).

The lesion was interpreted as strongly suspicious for malignancy, most likely a high-grade glioma or lymphoma. Biopsy was recommended but the patient and her relatives refused the procedure. The patient was discharged after antiepileptic treatment was prescribed.

Two months later she presented again, this time with weakness and numbness of the extremities, more pronounced on the left, impaired speech and swallowing. Follow-up MRI was performed which showed evidence of increased size of the tumor-like lesion compared to the previous assessment. New lesions were visualized in the right parietal region and around the ventricles, with vast edema and uneven but significant contrast enhancement. Again, the interpretation was difficult, with tumefactive MS and glioma being the most feasible options. In the meantime, the general and neurologic condition of the patient had worsened. EDSS was 6.0.

Another MRI was done in June 2013. A large, diffuse, multi-centric tumor formation was visualized in the right temporal and parietal region, with pronounced mass effect and edema. Two confluent lesions were seen in the interior part of the temporal lobe, 13.5 and 27 mm in size, respectively. A third lesion, 33 mm in size, was situated in the right parasagittal region. Compression and midline shift were noted. The structure of the formation was described as heterogeneous, with hemorrhagic and necrotic areas, significantly increasing its signal intensity after application of gadolinium contrast. This time the lesion was interpreted as most probably anaplastic high-grade glioma. The patient was transferred to a neurosurgery clinic where she was operated on. The histological diagnosis of glioblastoma was finally established.

**DISCUSSION**

The present case requires discussion in several aspects. Above all, it demonstrates the development of a new lesion in a patient with relapsing-remitting MS, which needs to be determined as either demyelinating or neoplastic in character. Usually the first possible hypothesis in such cases is that a giant demyelinating lesion has developed in the course of a consecutive relapse. Though this is the more likely situation, we should not underestimate the recommendation that the association of MS with gliomas must be considered in all cases of mass lesions appearing in patients with MS. Neuroimaging is not always capable of determining the type of pathologic process, even if complementary, non-conventional techniques are applied. Similarly to tumors, MS lesions may enhance their signal after contrast imaging with gadolinium, and because of the acute edema, mass effect can be seen in large demyelinating plaques [1, 2, 12].

In order not to underestimate the possible development of two processes, demyelinating and neoplastic, it is important to carefully examine the patient if new and unusual symptoms appear in the course of development of MS. It should be noted that in numerous cases presented in the literature only a follow-up MRI and the appearance of seizures have led to a suspicion of a different process. Our case also raises the question about the diagnostic contribution of the appearance or reappearance of epileptic seizures (in case of history of epilepsy in the past) to the differential diagnosis between a consecutive relapse of MS and an initial manifestation of a brain tumor. In studies of prevalence, including a meta-analysis of 29 published series of patients with epileptic seizures and MS, it has been found that seizures affect 2.3% to 4.25% of MS patients, 3 to 6 times more than the general population. In most studies epileptic seizures are not among the initial symptoms [21, 23, 24].

The glial tumor found intraoperatively and proven on biopsy allows our case to be added to the rarely described association of MS with brain tumors. The association of MS with gliomas, though rare, requires special attention because the appearance of new complaints and symptoms is usually attributed to a relapse and consecutively no neuroimaging is performed. At the same time, when a new focal mass lesion is visualized, it is most commonly interpreted as a pseudotumor plaque. In a clinical case of a 37-year-old man diagnosed with MS, described by de la Lama et al. [12], the patient had a large lesion in the right frontal lobe, interpreted initially as a pseudotumor plaque. Two years later simple partial seizures appeared which were treated with valproate, but later became resistant to treatment. Then, on follow-up imaging, the lesion was found to be enlarged and heterogeneous in structure. It was later determined histologically as oligodendroglioma. Biopsy obtained by means of neuronavigation can be extremely useful in such cases [25] as it would help solving diagnostic dilemmas. It has to be noted though that before biopsy is performed, the patient and/or his relatives must provide informed consent. Unfortunately, like in our case, they are often reluctant.

**CONCLUSION**

Our case study demonstrates that the likelihood of parallel development of different pathological processes, such as demyelinating and neoplastic, in the same patient, should not be underestimated. We emphasize the critical importance of biopsy for the resolution of similar diagnostic dilemmas. Yet, obtaining consent for biopsy is not always a leading point in the communication with patients and their relatives. All efforts made for an accurate diagnosis are important, as properly chosen therapeutic options influence the short- and long-term prognosis.
**Fig. 1.** AxT2 MRI showing demyelinating lesions

**Fig. 2.** AxT2 MRI showing a right temporal and parietal tumor formation

**Fig. 3.** 18F-FDG PET (CT fusion images): hypermetabolism in the lesion
REFERENCES:


Please cite this article as: Dimitrov IN, Kaprelyan AG, Georgiev R, Ivanov BD, Enchev Y, Avramov T, Grudkova MV, Deleva NS. Rare Clinical Case of Glioblastoma Multiforme, Multiple Sclerosis and Epilepsy: Clinical, MRI and 18F-FDG PET Study. J of IMAB. 2015 Oct-Dec;21(4):908-913.

Received: 01/09/2015; Published online: 13/11/2015

Address for correspondence:
Ivan Dimitrov, MD, PhD
First Clinic of Neurology, Sveta Marina University Hospital
1, Hristo Smirnenski str., 9010 Varna, Bulgaria
E-mail: indimitrov@mail.bg,

http://www.journal-imab-bg.org 913