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Case report

Intravascular lymphoma mimicking multiple sclerosis

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ABSTRACT

Diagnosis of relapsing–remitting multiple sclerosis requires demonstration disseminated symptoms in time and space on the basis of neurological assessment or magnetic resonance imaging findings. In addition, the diagnosis is conditioned by ruling out other conditions that may explain the clinical symptoms.

We describe the patient presenting in the initial stage of the disease neurological symptoms and magnetic resonance imaging lesions, that met criteria for relapsing–remitting multiple sclerosis diagnosis.

The patient was administered immunomodulatory treatment. However, the subsequent course of the disease tended to verify the diagnosis. Finally, the patient was diagnosed with intravascular B-cell lymphoma.

Intravascular lymphoma is a rare form of lymphoma characterized by the development of cancerous cells in the lumen of small and medium-sized blood vessels.

Due to the lack of characteristic biomarkers in laboratory tests and neuroimaging, the diagnosis is based on histopathological examination of the sample of the affected organ taken by biopsy. It should be consider in all cases of central nervous system damage of unknown, undiagnosed etiology.

1. Introduction

Diagnostic criteria for relapsing–remitting multiple sclerosis (RR–MS) require disseminated symptoms in time and space on the basis of clinical presentation or magnetic resonance imaging (MRI) findings. In addition, the diagnosis is conditioned by ruling out other causes that may explain the clinical symptoms.

The sensitivity and specificity of the current criteria for the diagnosis of multiple sclerosis (MS) is quite high and amounts to 60% and 87% respectively. However, there is always a risk of

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Abbreviations: MRI, magnetic resonance imaging; RIS, radiologically isolated syndrome; CSF, cerebrospinal fluid; MS, multiple sclerosis; RR–MS, relapsing–remitting multiple sclerosis; CT, computer tomography; IVL, intravascular lymphoma; CNS, central nervous system.

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wrong diagnosis, particularly with respect to rare diseases that mimic MS both in the clinical presentation and MRI [1,2].

We present a case of a female patient presenting neurological symptoms and MR lesions appropriate for relapsing–remitting form of MS (RR–MS). The patient was administered immunomodulatory treatment. However, the subsequent course of the disease tended to verify the diagnosis. Finally, the patient was diagnosed with intravascular B-cell lymphoma.

Only a few cases of intravascular lymphoma imitating multiple sclerosis were so far described. Generally, they had more rapid progress from the beginning. No description of a lymphoma mimicking the relapsing–remitting form of MS was available in the literature. Therefore, we presented the case because alive diagnosis is extremely difficult in this disease and poses a challenge to a neurologist.

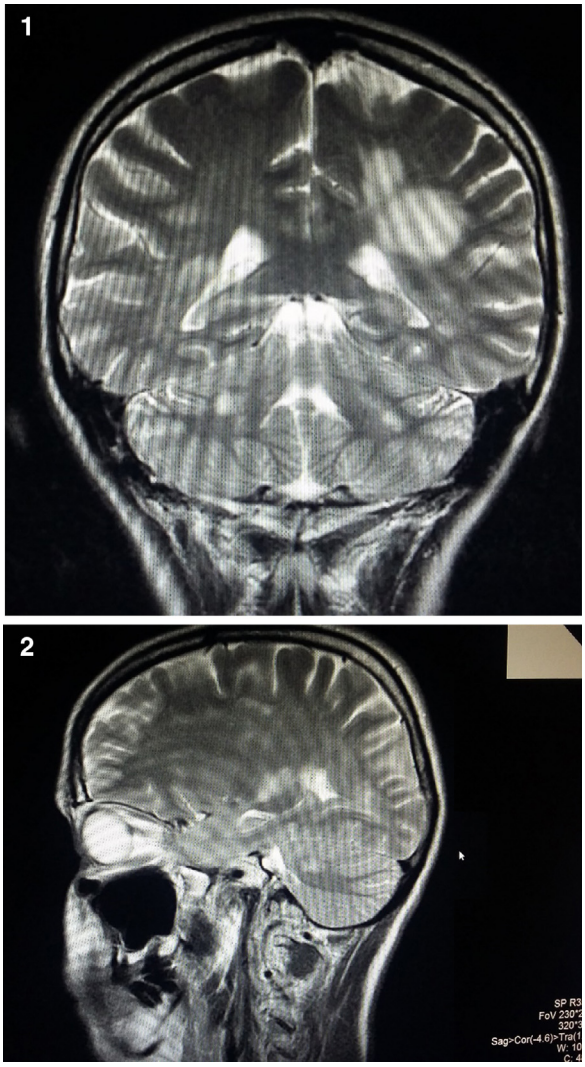
2. Case report

A 47-year-old patient complained periodically of headaches with nausea since May 2014. Neurological examination did not reveal any abnormalities. Computer tomography (CT) of the head was performed followed by histopathological examination of the sample from the left maxillary sinus and fungal sinusitis was diagnosed. The patient was treated symptomatically with temporary improvement. Due to recurring headaches, MRI of the brain was performed which revealed numerous small hyperintensive T2 lesions, located periventricular, in the corpus callosum and the cerebellum and hypointensive T1 lesions, partly with gadolinium enhancement. The findings met the MRI criteria for RR–MS. Due to the lack of other clinical symptoms than headaches, radiologically isolated syndrome (RIS) was diagnosed.

In September 2014, the patient experienced subacute dizziness and slight right-sided hemiparesis. Control MRI of the head showed an increase in the number of lesions (Figs. 1 and 2).

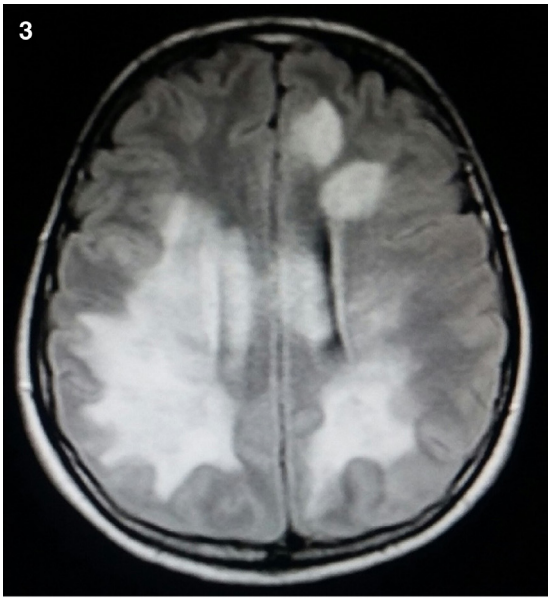
A lumbar puncture was performed. Cerebrospinal fluid (CSF) was clear and colorless, cytosis – 0 cells, protein 56 mg/dl, glucose 67 mg/dl, chloride 114 mmol/l. There was no presence of oligoclonal bands, neuroborreliosis was ruled out. The patient was administered 1 g of methylprednisolone intravenously for 5 consecutive days and neurological symptoms resolved.

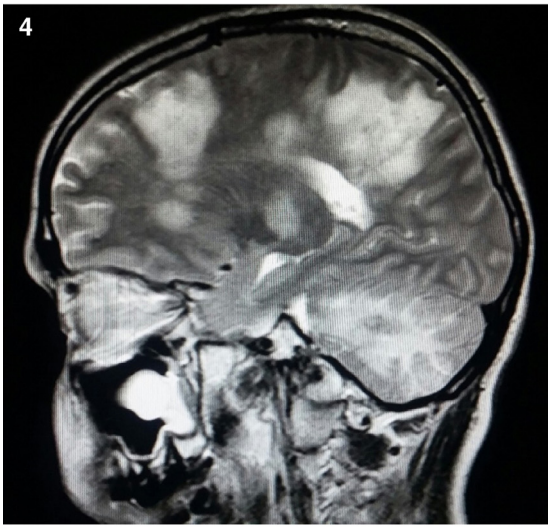
Over the next month, the disease exacerbated again in the form of double vision, right-sided hemiparesis, balance disorders and severe headaches. The patient was treated with steroids with positive outcome. Relapsing–remitting form of MS was diagnosed at that time and interferon β1b (IFN-β1b) was administered. The patient was stable and without neurological deficit during first 3 months of IFN-β treatment. Then relapse occurred – double vision, balance disorders and right-sided hemiparesis. In addition, the patient showed signs of depression. Methylprednisolone was administered and neurological symptoms resolved again. A month later – in February 2015 generalized seizures occurred. At that time, since depression and epilepsy were diagnosed, treatment with interferon was discontinued.

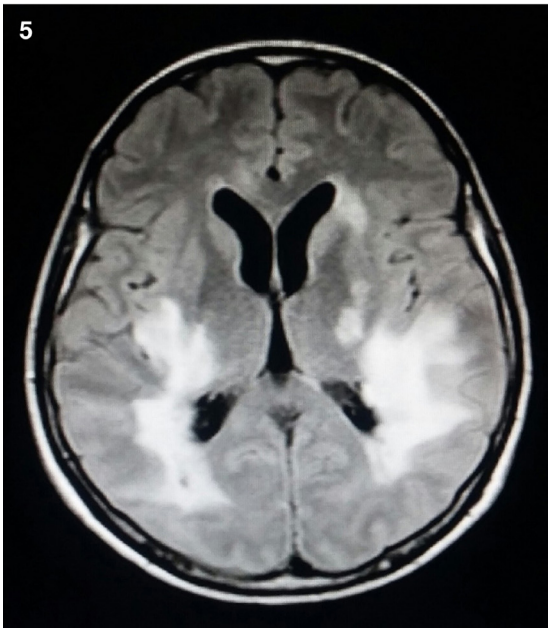


Figs. 1 and 2 – Brain MRI performed at first stage of the disease. It shows numerous hyperintensive T2-lesions located periventricular and in the cerebellum.

The patient was in stable condition until March 2015, when orientation, speech, balance disorders and right-sided hemiparesis gradually escalated. She was admitted to the hospital and head MRI revealed extensive hyperintensive T2 lesions – 20–34 mm in diameter in both hemispheres of the brain, the cerebellum, pons and thalamus. Most lesions were with gadolinium enhancement. Standard methylprednisolone therapy was administered intravenously, but with no improvement. The clinical condition even deteriorated. Disorientation and pyramidal paresis of the lower extremities and the left upper limb progressed. Damage to the 7th left cranial nerve and quadriplegic ataxia occurred. The patient fell backward in Romberg's test and could not walk independently. The results of additional tests were following Hb 12.4 g/dl, RBC 4.04×10^6/μl, PLT 145×10^3/μl. MRI of the cervical spinal cord was normal, EEG showed generalized periodic slow delta waves. The following conditions were considered in the diagnostic process: the systemic vasculitis, malignancy, acute disseminated encephalomyelitis (ADEM) and progressive multifocal







leukoencephalopathy (PML), however additional tests: ANA, ANCA, dsDNA, anticardiolipin antibodies, anti-β2glicoprotein I antibodies, complement components, immunoglobulins, protein electrophoresis, LE cells, serum tumor markers, OB, abdominal ultrasound, chest X-ray were normal. LDH was not determined. No pathologies in CNS vessels were found (MRI angiography). Anti-JC virus antibody was present.

Plasmapheresis treatment was attempted but due to lack of improvement it was discontinued after the third procedure. The patient's condition deteriorated rapidly – she was drowsy with a significant paresis of the left upper limb and lower limbs. MRI of the head was repeated, which showed a significant increase in size of previously reported lesions, some of that had hemorrhagic character accompanied by considerable swelling (Figs. 3–5). Methylprednisolone and acyclovir, antifungal agent, immunoglobulin were administered again. No improvement was observed. The patient required ventilation after 2 weeks of hospitalization and died on the 18th day of the treatment. Histopathological examination of brain tissue revealed the presence of cells of lymphoid origin (LCA+, CD20+) in the lumen of the small and medium blood vessels, small perimural thrombus in some vessels, chronic inflammatory infiltration of CD3+ around blood vessels. No significant lesions were found in other organs.

The cause of death was determined as the proliferative disease of the lymphatic system located in the CNS – intravascular B-cell lymphoma (Fig. 6).

3. Discussion

Intravascular lymphoma (IVL) is a rare form of non-Hodgkin's lymphoma characterized by the development of cancerous cells in the lumen of small and medium-sized blood vessels including capillaries. The incidence of this condition is rare – less than 1 case per million. It affects people aged 34–90 years, on average in their 60s and 70s, the incidence is equal in men and women. The most common organ locations include the central nervous system (41%) and skin (20%), but almost any organ can be affected – lungs, liver, spleen, kidneys, adrenals, rarely bone marrow, lymph nodes [3–7].

General symptoms include fever of unknown etiology (25%), less frequently fatigue, loss of appetite, night sweats [5].

In case of the nervous system, mainly the brain, less frequently the spinal cord, nerve roots and peripheral nerves are affected. Clinical presentation includes headaches, seizures, consciousness disorders, cognitive disorders and focal symptoms depending on the location of focal damage.

Neurological syndrome in patients is determined based on a complex multifocal CNS damage, recurrent stroke episodes, subacute progressive encephalopathy, dementia, myelopathy, polyradiculoneuropathy, including cauda equina syndrome, cranial neuropathies [4–6].

Figs. 3–5 – Brain MRI performed at final stage of the disease. It shows extensive hyperintesive T2- and FLAIR-lesions accompanied by considerable swelling in both hemispheres of the brain, the cerebellum and thalamus.

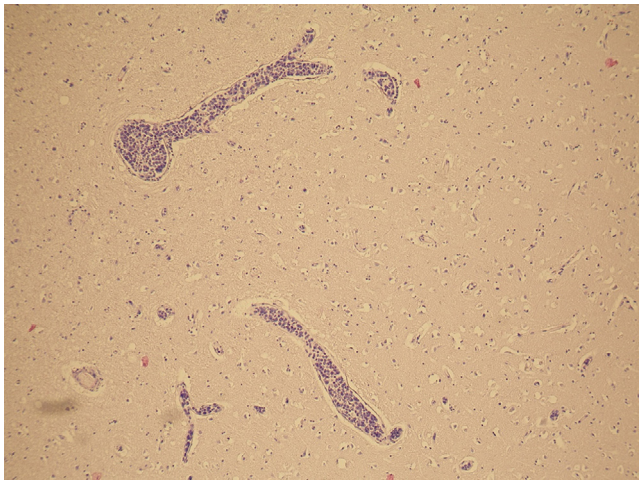


Fig. 6 – Photomicrograph of the brain (H and E stain) showing the presence of the lymphoid neoplastic cells in the lumen of the small blood vessels.

In our patient headaches were the first clinical symptoms which and as a nonspecific symptom were explained by sinusitis. Also subsequent course did not arouse suspicion of disease of the lymphatic system. The patient had recurrent scattered neurological symptoms and the results of laboratory tests were normal.

Routine laboratory examination usually detects elevated ESR and CRP, slight anemia (63%), high levels of lactate dehydrogenase (82%), beta2-microglobulin (86%), soluble Il-2 receptors and Il-6 in patients with intravascular lymphoma. Thrombocytopenia and leucopenia are less frequent (24%). In less than 5% of cases lymphoma cells are found in peripheral blood smear [4,5,7–9].

Increased pleocytosis and elevated protein levels are usually in cerebrospinal fluid (CSF). Baehring et al. described a group of seven patients with IVL of the brain, lymphocytosis was found in CFS of six of them [11]. However, pleocytosis was not found in case of our patient and protein levels were within the range observed in patients with RR–MS. These facts were in favor of maintaining the diagnosis of RR–MS. In addition, no atypical cells were found in CSF, which is consistent with most authors' observations, since the presence of lymphoma cells in smears of CSF is rarely observed even in advanced cases [4,8,9,11].

MRI of the brain in IVL patients shows multiple scattered foci hyperintensive in T2-weighted and FLAIR images suggesting lesions of vascular or demyelinating origin located mainly in the white subcortical and cortical matter. These lesions may be the subject to contrast enhancement. Major lesions with surrounding edema can mimic a tumor. Sometimes there is a focal reinforcement in dura [8,9]. MRI of our patient at the early stage of disease showed the presence of lesions with morphology and location typical for MS.

The MR image was found atypical only in the subsequent tests. Despite the treatment, the number and size lesions increased, some were the subject of secondary hemorrhagic transformation accompanied by extensive swelling. There were also lesions within the basal ganglia.

The cerebral angiography may not show any lesions, as in the present case. However, in approximately 45% of cases, a multifocal narrowing and widening of vessels or their obstruction as in vasculitis are observed [12].

Due to the lack of characteristic biomarkers in laboratory tests and neuroimaging, the diagnosis is based on histopathological examination of the sample of the affected organ (brain, lung, skin, marrow) taken by biopsy [3,5,9,11]. Skin biopsy of not only the affected sites but also from several seemingly unchanged sites is particularly helpful in the diagnosis. It should be conducted in all cases of CNS damage of unknown, undiagnosed etiology.

Lymphoma cells are in most cases derived from B-cells (CD19+, CD 20+, CD 22+, CD79+) (88% of cases), rare (2–8%) of T cells and NK cells [3–7]. Histopathology test revealed the presence of LCA+, CD20+ cells in our patient, therefore it was diagnosed as a B-cell lymphoma.

The basic treatment is chemotherapy, according to R-CHOP (rituximab, cyclophosphamide, adriamycin, vincristine, prednisolone). High doses of methotrexate, corticosteroids and plasmapheresis are used in cases of CNS involvement [5,7–10].

Steroids were administered repeatedly and also plasmapheresis during a significant exacerbation in the reported case. Initially, the condition of the patient improved, but at a later period that treatment was no longer effective. Most likely, this was due to the significant progress of the underlying disease.

The presented case shows considerable difficulties in the diagnostic process of patients with multifocal brain damage. The diagnostic criteria for RR–MS were met in our patient – the course of exacerbations and remissions, multifocal lesions changing in time in MRI of the brain. This allowed to establish the diagnosis of RR–MS and start the treatment with beta-1b interferon. The fact that the existing neurological symptoms resolved after treatment with steroids supported the diagnosis. Further rapid course of the disease tended to verify the diagnosis. Intravascular lymphoma was not taken into account in the differential diagnosis, especially that there were no typical skin lesions and deviations in the blood results. Correct determination of MS diagnosis, although it is based on specific diagnostic criteria, always requires careful differential diagnosis and considering other alternative diagnoses including very rare diseases to explain the clinical symptoms.

Conflict of interest

None declared.

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None declared.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involv-

ing humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

REFERENCES

[1] Kamm CP, Uitdehaag BM, Polman CH. Multiple sclerosis: current knowledge and future outlook. Eur Neurol 2014;72 (3–4):132–41.

[2] Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011;69 (2):292–302.

[3] Bi Y, Huo Z, Liang Z, Meng Y, Jia C, Shi X, et al. Intravascular NK-cell lymphoma: a case report and review of the literature. Diagn Pathol 2015;10:84.

[4] Abuzinadah A, Almalik Y, Shabani-Rad MT, Ho CH, George D, Alant J, et al. Cauda equina syndrome secondary to intravascular lymphoma. Neurol Clin Pract 2012;2(2):158–61.

[5] Garcia-Munoz R, Rubio-Mediavilla S, Robles-de-Castro D, Munoz A, Herrera-Perez P, Rabasa P. Intravascular large B cell lymphoma. Leuk Res Rep 2014;3(1):21–3.

[6] Kawata E, Isa R, Yamaguchi J, Tanba K, Tsutsumi Y, Nagakane Y, et al. Diffuse large B-cell lymphoma presenting with central pontine myelinolysis: a case report. J Med Case Rep 2015;9:131.

[7] Fonkem E, Lok E, Robinson D, Gautam S, Wong ET. The natural history of intravascular lymphomatosis. Cancer Med 2014;3(4):1010–24.

[8] Gan LP, Ooi WS, Lee HY, Nq WH. A case of large B-cell intravascular lymphoma in the brain. Surg Neurol Int 2013;4:99.

[9] Takamine Y, Ikumi N, Onoe H, Hayase M, Nagasawa Y. Diagnostic value of brain biopsy in intravascular large B-cell lymphoma mimicking progressive multifocal leukoencephalopathy: case report. Nihon Rinsho Meneki Gakkai Kaishi 2014;37(2):111–5.

[10] Bazhenova L, Higginbottom P, Ason J. Intravascular lymphoma: a role for single-agent rituximab. Leuk Lymphoma 2006;47(2):337–41.

[11] Baehring JM, Longtine J, Hochberg FH. A new approach to the diagnosis and treatment of intravascular lymphoma. J Neurooncol 2003;61:237–48.

[12] Jethwani DP, Yadaw R, Chickabasaviah YT. A 58-year-old lady with progressive neurological syndrome: presence of an intravascular lymphoma. Neurol India 2015;63:225–9.