Anaplastic astrocytoma mimicking progressive multifocal leucoencephalopathy: a case report and review of the overlapping syndromes

Ema Kantorová, Michal Bittšanský, Štefan Sivák, Eva Baranovičová, Petra Hnilcová, Vladimír Nosál, Daniel Čierny, Kamil Zeleňák, Wolfgang Brück, and Egon Kurča

Abstract

Background: Co-occurrence of multiple sclerosis (MS) and glial tumours (GT) is uncommon although occasionally reported in medical literature. Interpreting the overlapping radiologic and clinical characteristics of glial tumours, MS lesions, and progressive multifocal leucoencephalopathy (PML) can be a significant diagnostic challenge.

Case presentation: We report a case of anaplastic astrocytoma mimicking PML in a 27-year-old patient with a 15-year history of MS. She was treated with interferon, natalizumab and finally fingolimod due to active MS. Follow-up MRI, blood and cerebrospinal fluid examinations, and biopsy were conducted, but only the latter was able to reveal the cause of progressive worsening of patient’s disease.

Conclusions: Anaplastic astrocytoma misdiagnosed as PML has not yet been described. We suppose that the astrocytoma could have evolved from a low grade glioma to anaplastic astrocytoma over time, as the tumour developed adjacent to typical MS plaques. The role of the immunomodulatory treatment as well as other immunological factors in the malignant transformation can only be hypothesised. We discuss clinical, laboratory and diagnostic aspects of a malignant GT, MS lesions and PML. The diagnosis of malignant GT must be kept in mind when an atypical lesion develops in a patient with MS.

Keywords: Anaplastic astrocytoma, Multiple sclerosis, Tumefactive lesion, Progressive multifocal leucoencephalopathy, Immune reconstitution syndrome

Background

Multiple sclerosis (MS) is a disabling inflammatory demyelinating disease of the central nervous system (CNS). Early initiation of immunotherapy and its adjustment in view of ongoing inflammatory disease activity is desirable [1]. The main treatment goals aim at terminating inflammation and at reducing axonal damage [1]. Establishing MS diagnosis and decisions about the initial and ongoing treatments should not be made until other disorders that could better explain neurological symptoms and signs are excluded [1]. Although glial brain tumors (GT) have occasionally been reported in patients with MS, with only about 80 cases described in medical literature so far [2–5], this co-occurrence is uncommon since MS is caused by putative CNS autoimmune mechanisms whereas brain neoplasms may depended on a subclinical immunosuppressive state [6]. However, the last 15 years have seen increased use of immunomodulatory therapies (IMT) for relapsing MS, and considerable progress in the development of new, much stronger IMT for MS [7]. That rises questions about long-term safety of IMT as well as their risks and benefits [7]. Currently we know that several IMT make patients more susceptible to developing dangerous brain infection caused by John Cunningham virus (JCV) called progressive multifocal leucoencephalopathy (PML) [8–12]. However, MRI findings of tumefactive demyelinating lesions (TDL), PML...
and GT can overlap [12–19]. The first appearance of atypical brain lesion in an MS patient should lead to more extensive investigation in order to exclude another disease [15–19]. However, in some cases only biopsy is capable to reveal the cause of atypical MRI lesion [20, 21].

Here we describe the case of a malignant GT in a patient with early onset of MS. To the best of our knowledge, anaplastic astrocytoma misdiagnosed as PML has not yet been described. We discuss diagnostic tools that can help in differential diagnosis.

Case presentation
Here we report on a 27-year-old woman with the first neurological symptoms suggesting MS in 1999 at the age of 12. Her medical and psychosocial history was negative, but her family history was positive. Patient’s father is also treated for MS. The patient’s clinical timeline follows (Figs. 1, 2, 3, 4, 5, 6 and 7):

1999
A 12-year-old girl with negative medical history presents with vestibular syndrome lasting three weeks.

1999–2006
After having experienced several relapses with various symptoms (paresthesias of her left and right upper limbs, paresthesias of her distal limbs, weakness of upper limbs), she fulfilled McDonald criteria for definite relapsing-remitting MS due to demyelinating lesions in MRI (Fig. 1a, b, c), positive oligoclonal bands type 2 in cerebrospinal fluid (CSF) and positive visual evoked potentials (VEP).

2006
Several rounds of intravenous boluses of methylprednisolone were effective and the patient improved. When she started treatment by interferon beta la (Rebif® Merck-Serono), her Expanded Disability Status Scale (EDSS) was 2.0.

2008–2009
The treatment was interrupted due to her pregnancy in February 2008. In January 2009 she gave birth. During the early postpartum period the patient’s neurological status was unstable.

2009 January to April
The patient suffered three relapses (sensitive symptoms, left-sided hemiparesis, paraparesis of distal limbs) and her EDSS increased to 4.0 although she obtained several rounds of intravenous methylprednisolone.

2009 May
She resumed interferon beta la (Rebif® Merck-Serono) and reached remission.

2011 March to May
Her disease progressed again, her EDSS increased to 4.5 and follow-up MRI reflected clinical activity (Fig. 2a, b). Central quadriparesis was more pronounced in her left limbs and spinal ataxia varied over time between a need of assistance when walking longer distances and mild deficit. She responded well to intravenous methylprednisolone rounds.

2012 August
To stop the disease progression she was indicated to natalizumab (Tysabri® Biogen Idec), receiving 12 infusions (august 2012 - september 2013).

2013 September
The follow-up brain 3.0 Tesla MRI showed enlargement of the lesion in the right frontal lobe, evaluated by radiologists as PML (Fig. 3a, b, c, d). We also noticed seroconversion of JCV antibodies, but JCV index was low (0.38) and CSF PCR of DNA revealed no copies of JCV (Focal diagnostics, CYPRESS, California, USA).

2013 December
Not meeting Slovak indication criteria, the patient ceased taking natalizumab. The patient started treatment with fingolimod (Gilenya® Novartis Pharmaceuticals UK). At that time she was quadraparetic, more prominent on the left side. She needed assistance due to wide-based gait and she had intermittent headaches (mild to moderate congestive-dull or pulsating headache located in bi-temporal areas, partially alleviated by analgesics) EDSS was 5.0.

2014 February
A follow-up 3.0 Tesla MRI of the brain showed enlargement of the prior frontal lobe lesion (Fig. 4a, b, c), misinterpreted as PML again. A new CSF examination showed normal proteinorhachia (0.22g/l) and cellularity (1ymphocyte), not increased lactate (1.91 mmol/l), positive oligoclonal bands type 2 (14 bands), and increased IgG index 1.44. The PCR test of DNA JCV was negative again (0 copies UNILABS, Denmark). We decided to continue with fingolimod.

2014 December
Over the following several months she developed new clinical symptoms: headache, sporadic epileptic seizures, disorientation.

2015 May
1H-magnetic resonance spectroscopy (1H-MRS) detected decreased creatin to cholin ratio in several small areas of the frontal lobe, possibly suggesting tumorous mass (Fig. 5) Brain biopsy of the tumefactive lesion from the right frontal lobe.

Histopathological findings revealed presence of anaplastic astrocytoma (Fig. 6a, b, c, d, e)

2015 June
The patient needed anti-oedematous (dexamethason or methylprednisolon, boluses of manitol) and anti-epileptic therapy (valproic acid and levetiracetam) due to repeated secondary generalized epileptic seizures and intracranial hypertension syndrome.

2015 August
Before starting oncological treatment, 11methyl-methionine positron emission tomography (11C MET PET) showed cortical localization of the brain tumor (Fig. 7). Patient’s condition remained unstable due to frequent epileptic seizures. Three weeks later she suddenly died during status epilepticus (23/Aug/2015).

Discussion and conclusions
Our case shows that MS can have variable presentation therefore concurrence of MS with brain tumours may remain undetected for some time. One possible explanation is that an association of MS with overall risk of cancer has not been proved [22, 23]. One meta-analysis even identified a small but significant reductions of total cancer risk in patients with MS (odds ratio [OR] 0.92; 95% CI 0.87–0.97, p = 0.004) [24]. Another meta-analysis suggested lower overall co-occurrence of cancer in patients with MS [24]. On the other hand, a recent large systematic study evaluating risk and survival of brain tumours among patients with autoimmune disorders found higher standardised incidence of brain tumours in OS (OR 2.14; 95% CI 1.65–2.73) than in other autoimmunity disorders of the CNS [25]. The most frequent brain tumours were gliomas with OR 1.49; 95% CI 0.91–2.31. In this study, the risk of glioma-associated deaths in MS patients was relatively high (OR 2.3; 95% CI...
1.47–3.61). In addition, the data on survival showed the same decrease for both benign and malignant types of tumours co-occurring with MS [25]. Curiously, MS was the only autoimmune disease for which the overall brain cancer and especially glioma-specific survival appeared to decrease in recent years [25]. One explanation could be that comorbidity weakens patient’s physical condition. Moreover in MS, glial tumours interfere with mortality burden due to reduced treatment options and lower capacity of the affected brain to resist tumour growth. Another explanation could be that brain tumours remain hidden in demyelinated brain tissue and therefore they are diagnosed later, in advanced stages, which was also our case.

At the beginning of our patient’s disease the pathological lesion was connected to the frontal pole of lateral ventricle stretching to the periphery dispersing into the white matter. It was T2- and FLAIR- hyperintense and its localisation near the ventricle favoured TDL over GT (Fig. 1b,c). MRI of the atypical lesion fulfilled the reported characteristics of TDL [15–18]. However, MRI signs of TDL and GT can overlap easily [15, 17, 18]. Brain CT examination may be helpful in differentiation between the TDL and malignant GT [26] but we did not perform it in the early stage. Later, growth activity of the atypical lesion in the frontal lobe, good response to steroids, and absence of clinical signs suggesting tumour [15–18] led to treatment escalation. The effect of natalizumab and fingolimod to the lesion growth was evident and its MRI characteristics evoked suspicion of PML [11–13]. Double Inversion Recovery (DIR) (Fig. 4c) confirmed cortical involvement but did not add new information. Cortical lesions are typical for advanced forms of MS but they can be found in PML as well as GT [11–13, 17–20]. Diffusion Weighted Imaging (DWI) hyperintensities (Fig. 3d) favoured PML [11–13]. ¹H–MRS revealed decreased creatine to choline ratio in several areas of the lesion. We did not find changes of glutamate and glutamine peaks, as was reported by Yamashita [14]. ¹H–MRS is able to identify brain tumours or demyelination [11, 28–31] although several authors recommend caution when interpreting ¹H–MRS measured concentrations of metabolites in isolation [11, 31]. As our lesion was not well defined its precise place was estimated. Its localisation and size was finally revealed by ¹¹C MET PET. Increased uptake of ¹¹C–MET, i.e. high proliferation index of ¹¹C–MET indicating malignancy [32], was found in the right cortical frontal area. Slightly increased uptake of ¹¹C–MET was also found in left frontal and occipital cortex.

Cortical clinical symptoms, including disorientation, confusion, epileptic seizures, behavioural changes and headaches appeared in our patient in terminal stages of GT progression. They can also be found in patients with PML [8–11]. Moreover, symptomatic seizures correlate with cortical demyelination in advanced forms of MS [33], and could be associated with TDL [15, 16].

Basic CSF examination in our patient showed normal proteinorhachia and cell count, but increased number of oligoclonal bands type 2 (14 bands) and IgG index 1.44. These findings suggest active demyelinating processes associated with MS [15, 34] or PML-IRIS [10, 11]. This reaction is unusual in GT, where increased lactate in CSF and hyperproteinorhachia would be expected [6]. However, we did not prove it.

Retrospective analysis of the blood cellular immunity over the years showed chronic increase of CD4+ (50–
66%) and mild deficit of CD8 (11–12% with higher CD4/8 index (4.5–5.0) at the beginning of her disease (2007–2009). During interferon beta I treatment, CD4+ (55%) and CD8 (10%) remained unchanged, while CD16 + CD56 Natural Killers (NK) (4%, 66 abs) fell, and CD19 rose (31%, 513 abs). Natalizumab chronically decreased CD8 subpopulations of T lymphocytes. Fingolimod reduced CD4+ but significantly increased % of NK (49%). Humoral immunity remained normal and unchanged during all that time. Deficit of NK cells in our patient could decreased resistance against brain tumour growth, as NK cells can play an important role in anti-tumour immunity [35]. Moreover, it is known that in MS, autoimmune conditions are mediated mostly by CD4+ T-cells with a proinflammatory Th1 and Th17 phenotype, causing inflammation and demyelinating lesions in the CNS [36]. The dominancy of glial tumours in MS leads to a hypothesis that chronic hyperactivation of glial cells via Th1/Th17 pathways could cause their neoplastic transformation in demyelinated lesions [34]. On the other hand, if MS-associated proinflammatory Type17 T-cells mediate potent antitumour immunity [34], suppression and sequestration of those cells could potentially cause its breakdown. We did not test our patient’s Th17 lymphocytes, the mechanism could only be hypothesised. During natalizumab and fingolimod treatment we found lymphocytes decreased in periphery but we are not able to describe changes in the brain of our patient. This selective deficiency could have been involved in inefficient antitumour immune surveillance and tumour progression [37, 38].

Treatment by IMT could potentially trigger a variety of immunologic abnormalities that are typical for patients with malignant brain tumours [38, 39]. IMT may targeted many factors such as impaired responsiveness of peripheral blood lymphocytes to mitogens [39], failure of the T cells mediating adaptive immune responses within the local tumour micro-environment [40], and induction of regulatory T cells [41]. Development of GT can potentially be influenced by immunosuppressive cytokines (such as IL-10, TGF-β, and prostaglandin E2), and by down modulation of co-stimulatory molecules by antigen presenting cells (APCs) resulting in loss of T cell effector function [41]. Long-term monitoring of these markers in patients treated by highly effective IMT could be beneficial.

In tumour vessels, aggressive endothelial proliferation [42, 43], increases CD34+, a marker of endothelial progenitor cells [42]. Although natalizumab treatment results in an increase in CD34+ progenitor cells in both the bone marrow and the blood [44], it is not clear whether it can enhance tumour angiogenesis in a brain tumour. Moreover, increased angiogenesis was also described in PML lesions [11].

Indeed, the CNS biopsy remains the most useful method for defining the histological type of an atypical brain lesion suggestive of tumour. In our patient, Vimentin’s over-expression in cancer correlates well with increased tumour growth, invasion and poor prognosis [45]. OLIG2 is highly expressed in all diffuse gliomas [46] and was found expressed in our patient’s anaplastic astrocytoma samples. Tumourous cells were Nogo positive, Nogo-A exerts a growth inhibitory function leading to restricted axonal regeneration [47]. In our case Ki-67 was ≤5% but >2%. Worsened survival has been associated with Ki-67 > 2% [48]. Mutation of IFH1 and positive p53 in our patient suggests secondary nature of the astrocytoma [49].
Fig. 3  a FLAIR, Fluid-Attenuated Inversion Recovery, transverse (2013): Progression of the non-homogeneously hyper-intensive demyelinated lesion of the right frontal lobe, involving U-fibers. The lesion is well-defined to cortex, confluent with white matter, and irregular in shape. b T1w, T1-weighted MRI, transverse (2013): Hypointense irregular lesion at the rim of the right corner of the lateral ventricle in the right frontal lobe and several slightly hypointensive areas subcortically with no post-Gad enhancement. c T2w, T2-weighted MRI, transverse (2013): Irregular signal intensity within the lesion in the right frontal lobe. d DWI, Diffusion Weighted Imaging (2013): High signal intensity in the right frontal cortico-subcortical region and slightly increased signal in periventricular regions of both hemispheres

Fig. 4  a FLAIR, Fluid-Attenuated Inversion Recovery, sagittal (2014): Large non-homogenous hyperintense lesion of the right frontal lobe involving demyelination and oedema with mild mass-effect. It is relatively sharply defined to grey matter and confluent with white matter. Glial tumour is undetectable. b FLAIR, Fluid-Attenuated Inversion Recovery, transverse (2014): Diffuse hyperintense lesion of the right frontal lobe - demyelination. It has mild mass-effect. It is well-defined to cortex and to white matter and irregular in shape. c 3D DIR, 3D Double Inversion Recovery, sagittal (2014): Multifocal cortical involvement in the right frontal cortex adjacent to demyelinated lesions, diffuse confluent hyperintensive lesion in cortico-subcortical fronto-polar region
Fig. 6 Histopathology findings. (HE, LFB-PAS, Bielschowsky, CD3, SV40, Olig2, GFAP, Vimentin, Nogo-A, IDH1, p53): a The hematoxylin–eosin (HE) staining revealed grey and white matter with a markedly increased cellularity. Cells appeared pleomorphic and demonstrated a diffuse invasion into the CNS tissue. The tumour cells were embedded into a glial matrix. The nuclei showed a pronounced variation with respect to size and shape and depicted an increased nucleolar prominence. Mitosis was detectable. Signs of necrosis or microvascular proliferation were absent. b The immunohistochemical staining for Glial Fibrillary Acidic Protein (GFAP). Vimentin marked the majority of the tumour cells. c Some of the tumour cells were positive for Olig2. The tumour cells were not positive for NogoA. The proliferation ranged between 2 and 3% as determined by Ki67 immunohistochemistry. d The tumour cells were positive for isocitrate dehydrogenase1 (IDH1) and p53. e, f T-lymphocytes were not increased in the CD3 immunohistochemistry. No SV40 positive cells were detected.
In our patient we did not prove the histopathological triad of PML (multifocal demyelination, hyperchromatic, enlarged oligodendrogial nuclei, and enlarged bizarre astrocytes with lobulated hyperchromatic nuclei) [11, 27], which would have been a rather convincing evidence of the disorder. In Table 1, we summarise the differential diagnoses of tumefactive demyelinated lesions, malignant glial tumours, PML and PML associated with IRIS. We hypothesise that IMT may have transformed the glial cells into malignant GT. However, in a descriptive study among 22,563 French MS patients, including patients receiving IMT, brain tumours were not detected in total of 253 patients (1.2%) with a history of cancer [45]. In the SENTINEL trial of natalizumab in combination with interferon beta-1a, the incidence rate of cancer in the combination group (n = 589) was 1% compared to 2% in the interferon beta-1a alone group (n = 582) [50]. In interim analysis of TOP study, including 4821 patients from 16 countries, the incidence of malignancies was 0.5%. There were 24 patients with 12 types of malignancies. Glioblastoma was detected in 1 patient, while breast cancer was the most common, affecting seven patients (all female) [51].

Our patient was the carrier of human leukocyte antigens (HLA)-DRB 1*15 and DRB 1*11 alleles, and heterozygote of single nucleotide polymorphism rs3135388, which is typical for multiple sclerosis [52]. Although expression of HLA antigens is important for the immune response against infectious agents and malignant cells, there is an information gap about the link between HLA antigens and brain glial tumours. However, one prospective study, focused on HLA typing of German Caucasian patients, found that HLA-DRB1*15 in combination with HLA-DRB1*11 was associated with higher (a 13.4-fold increased) risk of glioma than was found for other HLA alone or in other combination [53]. It might explain the occurrence of astrocytoma Grade III in our patient.

We suppose that the anaplastic astrocytoma in our patient, developed after the diagnosis of MS, could have arisen in demyelinating plaques with reactive gliosis and could have evolved from a low grade glioma to anaplastic astrocytoma over time. The role of the immunomodulatory treatment as well as other immunological factors in malignant transformation of the tumour can only be hypothesised. The association between gliomas and MS is uncommon but it must be kept in mind when an atypical tumefactive lesion develops in a patient with MS. In our case, it is the first time when malignant glioma was misdiagnosed as PML.
| TDL | malignant GT | PML | PML-IRIS | References |
|-----|--------------|-----|----------|------------|
| **Clinical sy** | motor, cognitive (aphasia, apraxia, agnosia, Gerstman, coma) sensitive, cerebellar, brain stem. Visual field defects, Epileptic seizures | altered mental status (aphasia), motor, limb and gait ataxia, visual symptoms: homonymous hemianopia, cortical blindness, diplopia. Epileptic seizures. No optic nerve and spinal cord involvement. | altered mental status (aphasia), motor, limb and gait ataxia, visual symptoms: hemianopia, cortical blindness, diplopia. Epileptic seizures. No optic nerve and spinal cord involvement. | [8-14], [52] |
| MRI T2w/ FLAIR | Unilateral or bilateral. Frontal, parietal. Periventricular, juxta cortical. 2 cm, large lesion with little mass effect and edema. Variable rate of hyper-intensity. Central dilated vessel. Irregular border. Supra-tentorial WM, partially GM involvement. | Unilateral. Supra-tentorial. Hyper or hypo intense. Irregular border. Central necrosis. Intensive vascular edema and mass effect. | Bilateral. Supra-Intra-tentorial. Cortex, deep gray matter. (Frontal, parietal, occipital. Subcortical location, U-fibers, cortex, basal ganglia). 3 cm. Early new lesions. Hyper-intense. Ill-defined to WM, sharp to GM. No mass effect. Punctuate perilesional lesions. | [11-18], [16, 26, 54] |
| MRI T1w | Hypo-intense. CT- hypo-intensity | Hypo-intense. CT-hypo-intensity | Hypo-intense. CT-hypo intensity | [11-18], [26, 54] |
| MRI Gd + | incomplete rim enhancement | complete rim enhancement | negative or variable, punctuate and rim like | positive or variable, punctuate and rim like | [11-18], [26, 54] |
| MRI - PWI, DWI | decreased PWI in lesions, increased DWI in active demyelination | increased PWI, increased DWI in central necrosis | DWI always hyper-intense, with peripheral rim. | +/- restricted DWI | [9-18, 26] |
| 1H- MRS | increased Cho, lipids, lactate, mildly decreased NAA and NAA/Cr (differ from malignant GT) | increased Cho and Cho/Cr, lipids, lactate, decreased NAA, lack of βγ-Glx elevation | A decrease of NAA/Cr ratio, NAA and Cr. An increase of Lac/Cr, Cho/Cr, Cho, lipids/G, mins, Lac, Lip. Increased Cho, decreased NAA, the presence of Lac/lipids at 1.3 ppm, and the presence of mIns, Higher Cho/Cr, mins/Cr, Lip1/Cr, and Lip2/Cr in PML-IRIS than PML. Lower NAA/Cr than PML. | [11], [13, 14], [28-31] |
| CSF native | normal or mild increased proteinorhachia and white blood count. Positive oligoclonal bands, elevated IgG index | GFAP+ cells | mildly increased cellularity, normal proteinorhachia | mild to moderate increase of lymphocytes and protein levels | [10, 11], [14, 15] |
| CSF JCV DNA | negative, infrequently low positivity (less than 25) | negative? unknown | JCV-specific IgG, DNA copies, infrequently negative | JCV-specific IgG, DNA copies. Sometimes negative | [12-18], [31] |
| Response to corticoids | very good | only partial | none | good | [2, 9-11], [15, 27] |
| Histology | Hyper-cellularity, myelin protein-laden macrophages, variable lymphocytic inflammation, reactive gliosis and relative axonal preservation. | moderate cellularity, bizarre cells with hyperchromatic nuclei, moderate pleomorphic, gemistocytes, perivascular lymphocytes, rare areas of necrosis, neo-vascularization. GFAP + cells: immature, | swelling of oligodendrocyte and multi-lobular astrocytes, basophilic nuclei, eosinophilic inclusion bodies, 2/3 of number of T cells in PML-IRIS. Positive DNA JCV staining in all types of cells. Active gene copies in high | Hyper-cellularity, CD8+ positive T cells dominate - their number the same as in active MS lesions, fewer CD4+ and CD20+ T cells in perivascular cuffs. High plasma and B cells in PML-IRIS-lesions. | [2, 10], [15, 17-20, 49], [41-43, 46-48], [54, 55] |
Table 1 Differential diagnoses of tumefactive demyelinated lesions, malignant glial tumours, progressive multifocal leukoencephalopathy and progressive multifocal leukoencephalopathy associated with immune reconstitution syndrome (Continued)

| Outcome | as typical MS | reactive, and neoplastic astrocytes and ependymal cells | numbers of vitally infected cells, as well as a low inflammatory infiltrate. | No or low number JCV-infected cells. |
|---------|--------------|--------------------------------------------------------|-------------------------------------------------------------------------|------------------------------------|
| Immunological markers in peripheral blood | upregulation of transcription factors of Th1 (pSTAT1 and T-bet) and Th17 (pSTAT3) in circulating CD4+, CD8+ T-cells and monocytes. CD4+ T-cells with a proinflammatory Th1 and Th17 phenotype. | lower T-bet, pSTAT1, and pSTAT3 in CD4+, CD8+ T-cells, and monocytes. Lower CD4+ Th1 and Th17. Increased IL-10, TGF-β, PGE2, down modulation of co-stimulation molecules by APCs. Tumor angiogenesis, expression of CD34+ progenitor cells. Deficit of NK cells | variable data: stable CD4+ and CD8+, non-significant decrease or increased T cells but unchanged CD4/CD8 ratio. Decrease expression of CD49d, CD29 (VLA-4), CD11a, CD62L, CXCR3 on T cells. Decreased expression of VLA4 on myeloid dendritic cells, decreased count of dendritic cells. Production of CD34+ cells, increase of memory B cells. Increased IL-10. | Increased IFN-γ, IL-12p70, IL-4, IL-10, IL-5, IL-13, CD4+, Th1 + PSTAT3+, CD8+, PSTAT1+, T-bet +, Decreased CD4+, CD25+ FoxP3+ |

TDL: tumefactive demyelinating lesion, GT: glial tumour, PML: progressive multifocal leukoencephalopathy, PML-IRIS: PML-immune reconstitution inflammatory syndrome, MRI T2w: T2 weighted images of magnetic resonance imaging, DWI: diffusion weighted images, PMI: perfusion weighted images, GAD: gadolinium enhancement, WM: white matter, GM: gray matter, CT: computer tomography, 1H-MRS: proton magnetic resonance spectroscopy, Cho: cholin, NAA: N-acetyl aspartate, Cr: creatine, Lac: lactate, mIns: myoinositol, βγGlx: βγ-glutamate + glutamin, Lip: lipids, NK: natural killers, α4 integrin 4, IL-10, 12,13, CD4 T helper lymphocytes, CD8 T suppressor lymphocytes, CD71 a component of various integrins, CD80 B-lymphocyte antigen, CD28 proteins expressed on T cells that provide co-stimulatory signals required for T cell activation and survival, CD34+ hematopoietic progenitor cell antigen, CD49 an integrin alpha subunit, CD62 a cell adhesion molecule found on lymphocytes, CD25+ FoxP3+ regulatory T cells, IgG: immunoglobulin G, CXCR3 a chemokine receptor that is highly expressed in effector T cells and plays an important role in T cell trafficking and function, JCV: John Cunningham virus, TGF-β: transforming growth factor β, PGE2: prostaglandin E2, GFAP: glial fibrillary acidic protein, STAT 1,3: Signal transducer and activator of transcription 1,3, Th1 T1 lymphocytes, Th17 T17 lymphocytes, T-bet transcription factor, APC antigen presenting cells, CSF: cerebrospinal fluid, DNA: deoxyribonucleic acid.
Abbreviations
11C-MET PET; 1H methyl-methionine positron emission tomography; 1H MRS: 1H-proton MR spectroscopy; APC: Antigen Presenting Cell; CNS: Central Nervous System; CSF: Cerebrospinal Fluid; CT: Computer Tomography; DNA: Deoxyribonucleic Acid; EDSS: Expanded Disability Status Scale; GFAP: Glial Filibrillary Acidic Protein; GTL: Glial Tumour; HE: Hematoxylin and Eosin; HLA: Human Leukocyte Antigens; IDH: Isocitrate Dehydrogenase-1; IL-10: Interleukin-10; IMT: Immuno-modulatory Treatment; IRS: Immune Reconstitution Inflammatory Syndrome; JCV: John Cunningham virus; Ki-67: a nuclear protein that is associated with cellular proliferation; MRI: Magnetic Resonance Imaging; MS: Multiple Sclerosis; Nogo-A: a high molecular weight transmembrane protein expressed by oligodendrocytes in white matter of the CNS; Olig2: Oligodendrocyte transcription factor; p53: cellular tumour antigen; PCR: Polymerase Chain Reaction; PML: Progressive Multifocal Leukoencephalopathy; SV40: Simian Virus 40; TDL: Tumefactive Demyelinating Lesion; TGF-β: Transforming Growth Factor-β; VEP: Visual Evoked Potentials

Acknowledgements
The authors wish to thank Ms. Hana Jesenska who assisted in the proofreading of the manuscript.

Funding
The work has been supported in the data analysis and writing of the study by the Project VEGA 1/0287/16 and Grant APVV 15/0107.

Availability of data and materials
The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions
EkA: manuscript writing, analysis and interpretation of data; JM: patient follow-up examination; WB: histopathological analysis; MB, PH, EB, SS, EkU: literature search, analysis and interpretation of data; KZ: analysis and interpretation of radiological tests; DC: genetic analysis; All authors read and approved the final manuscript.

Competing interests
On behalf of all authors, the corresponding author states that there is no conflict of interest. The authors alone are responsible for the content and writing of the paper.

Consent for publication
Written informed consent was obtained from the next of kin of the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editor of this journal.

Ethics approval and consent to participate
Ethics committee of Jessenius Faculty of Medicine at Comenius University (Slovakia) approved the study under number EK 1678/2015.

Author details
1Clinic of Neurology, Jessenius Faculty of Medicine, Comenius University in Bratislava, Kollárová 2, 03659 Martin, Slovak Republic. 2Department of Medical Biochemistry, Jessenius Faculty of Medicine, Comenius University in Bratislava, Kollárová 2, 03659 Martin, Slovak Republic. 3Department of Radiodiagnostyics, Jessenius Faculty of Medicine, Comenius University in Bratislava, Kollárová 2, 03659 Martin, Slovak Republic. 4Institut für Neuropathologie Universitätsmedizin Göttingen, Robert-Koch-Str, A 37075 Göttingen, Germany.

Received: 7 July 2016 Accepted: 9 June 2016
Published online: 19 June 2017

References
1. Wiend H, Toyka KV, Reckmann P, Gold R, Hartung HP, Hofffield R. Basic and escalating immunomodulatory treatments in multiple sclerosis: current therapeutic recommendations. J Neurol. 2008;255:1449–63.
2. Currie S, Urlich H. Concurrence of multiple sclerosis and glioma. J Neurol Neurosurg Psychiatry. 1974;37:598–605.
3. Kalimo H, Frey H, Raine CS, Törmä T, Rytäät M. Late-onset malignant astrocytoma in a case of multiple sclerosis. Clinical, neuropathological, virological, and tissue culture studies. Acta Neuropathol. 1979;46:231–4.
4. Hofer S, Linnebank M, Weiler M, et al. Cancer risk among patients with multiple sclerosis and their parents. Neurology. 2010;74:614–5.
5. Wenneck LC, Scola RH, Arruda WD, Torres LF. Glioma and multiple sclerosis: case report. Arg Neuropsiquiatr. 2002 Jun;60:469–74.
6. Planzond D, Renina R, Sbardella E, Koudriavtseva T. Concurrence of multiple sclerosis and brain tumors. Front Neurol. 2015;6:40.
7. Hutchinson M. Safety first, efficacy second in disease modifying therapies. Mult Scler. 2011;17:380–1.
8. Sorensen PS, Bertolotto A, Edan G, et al. Risk stratification for progressive multifocal leukoencephalopathy in patients treated with natalizumab. Mult Scler. 2012;18:143–52.
9. Bloomgren G, Richman S, Hotermans C, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. N Engl J Med. 2012;366:1870–80.
10. Tan CS, Koralnik U. Progressive multifocal leukoencephalopathy and other disorders caused by JC virus: clinical features and pathogenesis. Lancet Neurol. 2010;9:425–37.
11. Berger JR, Akram A, Clifford DB, et al. PML diagnostic criteria: consensus statement from the AAN Neuroinfectious disease section. Neurology. 2013;80:1430–8.
12. Wattjes MP, Richert ND, Killestein J, et al. The chameleon of neuroinflammation: magnetic resonance imaging characteristics of natalizumab-associated progressive multifocal leukoencephalopathy. Mult Scler. 2013;19:1862–40.
13. Shah R, Bag AK, Chapman PR, Cure JK. Imaging manifestations of progressive multifocal leukoencephalopathy. Clin Radiol. 2010;65:431–9.
14. Yamashita S, Kimura E, Hirato T, Uchino M. Tumefactive multiple sclerosis. Inter Med. 2009;48:1113–4.
15. Lucchetti CF, Gavrilova RH, Metz I, et al. Clinical and radiographic spectrum of pathologically confirmed tumefactive multiple sclerosis. Brain. 2008;131:1759–75.
16. Given CA, Stevens BS, Lee C. The MRI appearance of tumefactive demyelinating lesions. AJR Am J Roentgenol. 2004;182:195–9.
17. Cunliffe CH, Fischer I, Monoky D, et al. Intracranial lesions mimicking neoplasms. Arch Pathol Lab Med. 2009;133:101–23.
18. Huismann TAGW. Tumor-like lesions of the brain. Cancer Imaging. 2009;9:510–3.
19. Lee M, Walsh K, Rey-Dios R, Anderson M. Progressive multifocal leukoencephalopathy mimicking high grade glioma in an immunocompetent patient: a case report. Neuro Oncology. 2014;16:149–50.
20. Burger PC, Vogel FS, Green SB, Strike TA. Glioblastoma multiforme and anaplastic astrocytoma. Pathologic criteria and prognostic implications. Cancer. 1985;56(5):1106–11.
21. Kingwell E, Bajdik C, Phillips N, et al. Cancer risk in multiple sclerosis: findings from British Columbia. Canada Brain. 2012;135:2973–9.
22. Fois AF, Wotton CJ, Yeates D, et al. Cancer in patients with motor neuron disease, multiple sclerosis and Parkinson's disease: record linkage studies. J Neurol Neurosurg Psychiatry. 2010;81:215–21.
23. Handel AE, Ramagopalan SV. Multiple sclerosis and risk of cancer: a meta-analysis. J Neurol Neurosurg Psychiatry. 2010;81:1413–4.
24. Catala-Lopez F, Suarez-Pinilla M, Suarez-Pinilla P, et al. Inverse and direct cancer comorbidity in people with central nervous system disorders: a meta-analysis of cancer incidence in 573,013 participants of 50 observational studies. Psychother Psychosom. 2014;83:89–105.
25. Hemminki K, Liu X, Först A, Ji J, Sundquist J, Sundquist K. Subsequent brain tumors in patients with autoimmune disease. Neuro Oncology. 2013;15:1142–50.
26. Kim DS, Na DG, Kim KH, Kim J, Kim E, Yun BL, et al. Distinguishing tumefactive demyelinating lesions from glioma or central nervous system lymphoma: added value of unenhanced CT compared with conventional contrast-enhanced MR imaging. Radiology. 2009;251:467–75.
27. Kühle J, Gosert R, Büller R, et al. Management and outcome of CSF-JCV virus PCR-negative PML in a natalizumab-treated patient with MS. Neurology. 2011;77:2010–6.
28. Cuvinciuc V, Martin-Blondel G, Marchou B, Bonneville F. Proton MR spectroscopy of progressive multifocal leukoencephalopathy—immune reconstitution inflammatory syndrome. Arq Neuoradiol. 2010;75:699–704.
29. Cianfoni AS, Niku SG, Imbesi SG. Metabolite findings in tumefactive demyelinating lesions utilizing short echo time proton magnetic resonance spectroscopy. Am J Neuroradiol. 2007;28:272–277.
30. Hawe FA, Opstad KS. 1H MR spectroscopy of brain tumours and masses. NMR Biomed. 2003;16:123–31.
31. De Stefano N, Caramanos Z, Preul MC, Francis G, Antel JP, Arnold DL. In vivo differentiation of astrocytic brain tumors and isolated demyelinating lesions of the type seen in multiple sclerosis using 1H magnetic resonance spectroscopic imaging. Ann Neurol. 1998;44:273–8.

32. Chung J-K, Kim Y, Kern S, et al. Usefulness of 11C-methionine PET in the evaluation of brain lesions that are hypo or isometabolic on 18F-FDG PET. Eur J Nucl Med Mol Imagine. 2002;29:176–82.

33. Horakova D, Kalincik T, Blahova-Dusankova et al. Clinical correlates of grey matter pathology in multiple sclerosis BMC Neurology. 2012;12:10.

34. Wiener HL. The challenge of multiple sclerosis: how do we cure a chronic heterogeneous disease? Ann Neurol. 2009;65:239–48.

35. Kmiecik J, Zimmer J, Chekenya M. Natural killer cells in intracranial neoplasms: presence and therapeutic efficacy against brain tumours J Neuro-Oncol. 2013;11:161–9.

36. Okada H, Khoury SJ. Type17 T-cells in central nervous system autoimmunity and tumors. J Clin Immunol. 2012;32:280–2.

37. Kmiecik J, Poli A, Brons NH, Waha A, Eide GE, Enger PØ, et al. Elevated CD3+ and CD8+ tumor-infiltrating immune cells correlate with prolonged survival in glioblastoma patients despite integrated immunosuppressive mechanisms in the tumor microenvironment and at the systemic level. J Neuroimmun. 2013;264:71–83.

38. Perrin G, Schnuriger V, Quiriquerre AI, Saas P, Pannetier C, de Tribolet N, et al. Astrocytoma infiltrating lymphocytes include major T cell clonal expansions confined to the CD8 subset. Int Immunol. 1999;11:1337–50.

39. Elliott LH, Brooks WH, Rosman TL. Cytokine basis for the impaired activation of lymphocytes from patients with primary intracranial tumors. J Immunol. 1984;132:1208–15.

40. Fontana A, Hengartner H, de Tribolet N, Weber E. Glioblastoma cells release interleukin 1 and factors inhibiting 2-mediated effects. J Immunol. 1984;132:1837–44.

41. Wei J, Barr J, Kong LY, Wang Y, Wu A, Sharma AK, et al. Glioblastoma cancer-initiating cells inhibit T-cell proliferation and effector responses by the signal transducers and activators of transcription 3 pathway. Mol Cancer Ther. 2010;9:67–78.

42. Soda Y, Marumoto T, Friedmann-Morvinski D, Soda M, Liu F, Michiue H, et al. Transdifferentiation of glioblastoma cells into vascular endothelial cells. Proc Natl Acad Sci U S A. 2011;108:4274–80.

43. Jain RK, di Tomaso E, Duda DG, et al. Angiogenesis in brain tumours. Nat Rev Cancer. 2001;1:31–40.

44. Jin H, Aiyer A, Su J, Borgstrom P, Stupack D, Friedlander M, et al. A homing mechanism for bone marrow-derived progenitor cell recruitment to the neovasculature. J Clin Invest. 2006;116:6552–62.

45. Satell A, Li S. Vimentin as a potential molecular target in cancer therapy or Vimentin, an overview and its potential as a molecular target for cancer therapy. Cell Mol Life Sci. 2011;68:3033–46.

46. Ligon KL, Albert BA, Witten JS, Weiss J, Kwaan MR, Nutt CL, et al. The oligodendroglial lineage marker OLIG2 is universally expressed in diffuse gliomas. J Neuropathol Exp Neurol. 2004;63:499–509.

47. Schwab EM. Functions of Nogo proteins and their receptors in the nervous system. Nat Rev Neurosci. 2010;11:799–811.

48. Fisher B, Naumova E, Leighton CC, Naumov GN, Kerkhoven N, Fortin D, et al. Ki-67: a prognostic factor for low-grade glioma? Int J Radiat Oncol Biol Phys. 2002;52:996–1001.

49. Khalil A, Serracino H, Damek DM, Nye D, Lillehei KO, Kleinschmidt-DeMasters BK. Genetic characterization of gliomas arising in patients with multiple sclerosis. J Neuro-Oncol. 2012;109:261–72.

50. Rudick RA, Stuart WH, Calabrese PA, et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. N Engl J Med. 2006;354:911–23.

51. Butzkueven H, Kappos L, Pellegrini F, Trojano L, Wiendl H, Patel RN, et al. Belachew S; TYSABRI observational program (TOP) investigators. Efficacy and safety of natalizumab in multiple sclerosis: interim observational programme results. J Neurol Neurosurg Psychiatry. 2014;85:1190–6.

52. International Multiple Sclerosis Genetics Consortium, Hafler DA, Compston A, Sawcer S, Landers ES, Daly MJ, De Jager PL, de Bakker PI, Gabriel SB, Mirel DB, Iwinsen AJ, Percik-Vance MA, Gregory SG, Rioux JD, McCauley JL, Haines JL, Barcellos LF, Cree B, Okenberg JR, Hauser SL. Risk alleles for multiple sclerosis identified by a genomewide study. N Engl J Med. 2007 Aug 30;357:851–62.

53. Machulla HK, Steinbom F, Schaaf A, Heidecke V, Rainov NG. Brain glioma and human leukocyte antigens (HLA)-I: is there an association? J Neuro-Oncol. 2001;52:253–61.

54. Frisullo G, Paterella AK, Nociti V, Gianfoni A, Iorio R, Bianco A, et al. Glioblastoma in multiple sclerosis: a case report. J Neurol. 2009;259:141–4.

55. Metz I, Radue E-W, Oterino A, et al. Pathology of immune reconstitution inflammatory syndrome in multiple sclerosis with natalizumab-associated progressive multifocal leukoencephalopathy. Acta Neuropathol. 2012;123:235–45.

56. Lebrun C, Vennersch P, Braissant D, et al. Cancer and multiple sclerosis in the era of disease-modifying treatments: J Neurol. 2011;258:1304–11.