The Development of Primary Central Nervous System B-Cell Lymphoma in Multiple Sclerosis

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Abstract

When coupled with classical clinical signs and symptoms, magnetic resonance imaging can significantly aid in the diagnosis of multiple sclerosis (MS). However, the differential diagnosis of multiple sclerosis is large and, in the absence of pathognomonic clinical features, can be challenging to diagnose initially. Some conditions, such as primary central nervous system lymphoma (PCNSL) and progressive multifocal leukoencephalopathy (PML), can mimic clinically some of the symptoms prominent in multiple sclerosis. Early treatment with corticosteroids can dramatically improve patient symptoms in MS and PCNSL. We report a case of a man diagnosed with histologically confirmed relapsing remitting multiple sclerosis who subsequently developed histologically confirmed primary central nervous system lymphoma. Immunosuppressant therapy in the treatment of multiple sclerosis may be a potential catalyst in the development of central nervous system lymphoma. The course of his disease and treatment are presented and the current literature reviewed.

Keywords

multiple sclerosis, primary central nervous system lymphoma, brain biopsy, interferon, magnetic resonance imaging

Introduction

The association of relapsing remitting multiple sclerosis (RRMS) and the development of primary central nervous system lymphoma (PCNSL) are not clear. Both conditions can initially respond to corticosteroid administration. Patients can be misdiagnosed with a demyelinating disease while actually harboring a neoplastic process. Other patients can potentially develop a neoplastic disease several years following their diagnosis of multiple sclerosis. We report a case of a man with multiple sclerosis who, after immunosuppressive treatment over 1 year, subsequently developed histopathologically confirmed primary central nervous system B-cell lymphoma.

vertigo recurred. A follow-up MR of the brain demonstrated subcortical hyperintensity on the T2 weighted images and FLAIR images in the right and left frontal lobes. In addition, there was a new abnormal signal in the left superior cerebellar peduncle. Cervical MR showed a lesion consistent with an MS plaque in the ventral aspect of the spinal cord at C4. He did not undergo cerebrospinal fluid analysis. These symptoms persisted over the following 2 months along with dysarthria, dyscoordination, and sphincteric dysfunction. He was diagnosed with possible multiple sclerosis and treated with 3 days of methylprednisolone, resulting in improvement in his symptoms. He was referred to our institution 4 months later with the presumptive diagnosis of relapsing remitting multiple sclerosis (RRMS).

Case Description

A previously healthy 53-year-old man developed acute diplopia and vertigo which persisted for 10 weeks and then resolved. A magnetic resonance (MR) imaging study of the brain demonstrated a subtle increased T-2 weighted non-enhancing signal abnormality in the right middle cerebral peduncle. It was interpreted by neuroradiology as a normal study. No treatment was pursued. One year later, following an emergency appendectomy, the symptoms of diplopia and

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Figure 1. T-1 weighted axial brain magnetic resonance (MR) imaging demonstrating cystic encephalomalacia with heterogeneous gadolinium enhancement in the parasagittal right frontal lobe.

Figure 2. T-2 weighted axial brain magnetic resonance (MR) imaging showing a hyperintense MS plaque in the anterior right medulla (arrow).

The patient developed gradual neurological deterioration 6 months later and underwent a 5-day treatment with methylprednisolone, which resulted in some improvement in his symptoms. Subsequently however, he continued to have progressive symptoms. Magnetic resonance imaging demonstrated increased abnormal signal with new cystic changes in the right frontal lobe and a new lesion in the right anterior medulla (Figures 1 and 2). The previous subcortical lesion seen 1 year earlier was no longer present and considered consistent with MS. The patient was scheduled to be enrolled in the CombiRx (interferon beta-1a and glatiramer acetate) trial. Although the new MR findings could be considered due to potentially tumefactive form of MS, the imaging features were considered somewhat unusual for RRMS. Consequently, because of the changes in the appearance of the white matter lesions and in order to confirm that this remained a demyelinating process as opposed to a neoplastic process a stereotactic brain biopsy was performed. Biopsy confirmed demyelinating disease with CD68 stain demonstrating numerous macrophages. There was no evidence of malignancy. The patient began the CombiRx trial 2 months later. The patient tolerated the trial well over the next 12 months without progression of symptoms, until he presented with an acute episode of confusion and delusional behavior. Repeat brain MR revealed a diffusely enhancing mass involving both frontal lobes crossing the anterior corpus callosum (Figure 3). Stereotactic brain biopsy revealed a diffuse large B-cell

lymphoma expressing CD20 and CD45. The MIB-1 index, reflecting mitotic activity, was 80% in the malignant cells. The patient underwent 1 cycle of methotrexate chemotherapy and expired 1 month following the diagnosis of primary central nervous system lymphoma.

Discussion

Multiple sclerosis is chronic demyelinating disease affecting the central nervous system (CNS) and classically presents with exacerbating and relapsing neurological symptoms. Patients harboring a different disease process are misdiagnosed with MS in 5% to 10% of cases.¹ Several conditions including, Lyme disease, progressive multifocal leukoencephalopathy, mitochondrial disorders, metabolic deficiencies, and lymphoma have been initially confused with MS.^{1,2} Progressive multifocal leukoencephalopathy (PML) is also a demyelinating disorder secondary to central nervous system infection with the JC papovavirus. Infection of oligodendrocytes results in the inability to maintain myelin. Imaging characteristics can be easily confused with MS. The lesions are hyperintense on T2-weighted images and hypointense on T-1 weighted images.^{3,4} Prior to AIDS, PML was very uncommon. However, recently, reports of patients receiving natalizumab for MS have been identified with PML.⁵ Similar to the clinical presentation in our case, the sudden onset of marked cognitive impairment has been associated with the

Figure 3. T-1 weighted axial brain magnetic resonance (MR) imaging demonstrating diffuse gadolinium enhancement of the frontal lobes involving the corpus callosum with vasogenic edema and mass effect.

development of PML and rapidly progressing MS.⁵ Contrast enhancement in PML is considered unusual, however, nearly 10% of patients with PML will have some contrast enhancement.⁵ These features can make the differential between MS and PML difficult.

The report by Alderson and colleagues described sentinel lesions of primary CNS lymphoma.³ They reported 4 immunocompetent patients with contrast enhancing brain lesions who underwent brain biopsies. Of the 4, 3 had received a preoperative course of corticosteroids. Of the biopsies, 2 were consistent with demyelination, 1 showed nonspecific inflammation, and 1 was normal. All patients subsequently developed biopsy-confirmed B-cell lymphoma within 7 to 11 months.³ As the authors pointed out, preoperative corticosteroids are cytotoxic to lymphocytes and can result in a negative biopsy. The presence of diffusely enhancing intraaxial brain lesions should make the clinician aware of the possibility of PCNSL. Prior to the availability of immunosuppressive and immunomodulating (IS) treatments, reduced rates of cancer were linked to multiple sclerosis. During the past 20 years, there has been a significant increase in the number of IS medications available for the treatment of MS.⁶⁻¹² Several reports over the past 2 decades have suggested an increase in cancer risk among MS patients, potentially related to the immunosuppressive therapies.^{11,13,14} Other more recent reports have not found an increased risk of cancer in MS patients.^{6,15,16} Recently, Lebrun and colleagues reported an exhaustive multicenter review of 7418 MS patients in France

evaluating the impact of disease-modifying therapies and the incidence of cancer.¹⁶ They found no evidence of an increased risk of cancer following the diagnosis of MS. In fact, they noted that men with MS had a statistically significant decrease in the incidence of cancer. Whereas in women, there was an increased risk of breast cancer in those patients receiving more than 1 IS modality.¹⁶ However, it is important to note that the immunosuppressive treatments during the 12 months following the diagnosis of MS in our patient cannot be excluded as a potentially contributing factor to the development of his PCNSL.

Characteristically, the MR imaging in PCNSL reveals a diffusely enhancing mass, often with little vasogenic edema associated with the size of the mass. The lesions are often periventricular in location, but that is not always the case. The radiographic appearance of the MS plaque can be even less distinct. Plaque enhancement in MS can be absent, ring-enhancing, or solid. While CNS lymphoma will often show diffuse enhancement with gadolinium administration and demyelinating plaques much less likely to do so, it is not an absolute finding. Consequently, PCNSL can be confused with multiple sclerosis.^{1,2} In our case, the extensive homogeneous enhancement pattern found on the follow-up MR was dramatically different than the pattern noted on the original MR where the initial biopsy was consistent with demyelinating disease and no evidence of neoplasm. In addition, corticosteroid administration will often result in substantial clinical improvement and potentially radiographic resolution of abnormal imaging findings in PCNSL, which can be interpreted as a steroid-induced remission of MS.²

There is no reported link between the immunosuppressive therapy of interferon beta-1a and glatiramer acetate and the subsequent development of B-cell lymphoma. Interestingly, Krumbholz and coworkers reported their findings on B-cell-activating factor of the tumor necrosis factor (TNF) family (BAFF).¹⁷ Human astrocytes were discovered to secrete BAFF following stimulation with interferon and TNF. They found that in multiple sclerosis plaques in brain lesions with B-cell components, BAFF expression was strongly upregulated to levels similar in lymphatic tissue.¹⁷ In addition, BAFF receptors were strongly expressed in PCNSL. They postulated that CNS produced BAFF may support B-cell survival in inflammatory diseases, such as multiple sclerosis and primary B-cell lymphomas. Similar to our case, Yang and Wu reported a case of a 33-year-old patient with multiple sclerosis who developed central nervous system lymphoma 3 years following the initial diagnosis.¹⁸ Although their patient did receive beta interferon and subsequently developed an immunocompromised state, there is no compelling evidence of a causal relationship. They postulated that neoplastic transformation may occur in CNS inflammatory disorders such as MS.¹⁸

Currently, the majority of the evidence suggests that patients with multiple sclerosis are not at an increased risk for the development of cancer, save possibly breast cancer in

women. Awareness of the possibility that the sentinel lesion of PCNSL exists is an important consideration, particularly in immunocompetent patients without other radiographic, electrophysiologic, or serologic features that would be more consistent with MS. There is no conclusive evidence that there is an association between immunosuppressive treatment in multiple sclerosis and the development of PCNSL. Gadolinium-enhanced MR imaging and cerebrospinal fluid analysis should aid in distinguishing between RRMS and PCNSL. Continued dependence upon corticosteroid therapy is uncommon in multiple sclerosis and should alert the clinician to the possibility of primary central nervous system lymphoma.

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