Atypical Progressive Multifocal Leukoencephalopathy in a Patient with Antisynthetase Syndrome

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Abstract

Antisynthetase syndrome is a disorder belonging to the dermatomyositis/polymyositis group, with high rates of morbidity and mortality. We herein present the case of a 71-year-old man who was diagnosed with antisynthetase syndrome and treated with rituximab. Almost three years later, the patient showed right-sided hemiparesis that ultimately progressed to complete hemiplegia and advancing cognitive deterioration with a poor clinical outcome. The neuropathological diagnosis was progressive multifocal leukoencephalopathy. Treatment with rituximab for antisynthetase syndrome itself plays a fundamental role in the development of infectious complications.

Key words: Anti-Jo-1, antisynthetase syndrome, rituximab, progressive multifocal leukoencephalopathy, JC virus

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Introduction

Antisynthetase syndrome is included in the group of dermatomyositis disorders. It is a systemic inflammatory disease with high rates of both morbidity and mortality of infectious origin. Rituximab is a biological agent used to treat such patients and is well tolerated (1-5). Although rituximab therapy appears to increase the incidence of infectious complications (6, 7), there is a lack of sufficient long-term data regarding this point. Among infectious complications, progressive multifocal leukoencephalopathy (PML) is extremely rare in patients with dermatomyositis associated with rituximab treatment (8). PML presents as a series of classic symptoms with three atypical variants: i) cerebellar involvement, ii) encephalopathy or iii) inflammatory involvement. We herein present the case of a patient with antisynthetase syndrome who developed atypical PML after receiving rituximab.

Case Report

The patient was a 71-year-old man with a diagnosis of antisynthetase syndrome associated with fever, weakness of the hip and shoulder girdle, Raynaud’s phenomenon, polyarthralgia and polyarthritis in both wrists, diffuse interstitial disease with cytogenic organizing pneumonia and autoimmunity presenting with extractable nuclear antigen (ENA) (Anti-Ro antibodies 233 U/mL), antinuclear antibody (ANA) (1/640, speckled and cytoplasmic pattern) and anti-Jo-1 antibodies 445 U/mL. We started treatment with methylprednisolone (1 mg/kg/day) and azathioprine (0.75 mg/kg/day), and the patient’s symptoms subsided. However, six months after the diagnosis, he developed a fever and muscle weakness in both wrists (4/5). A laboratory analysis showed an aspartate aminotransferase (AST) level of 730 U/L, alanine aminotransferase (ALT) level of 339 U/L, creatine kinase (CK) level of 6,310 U/L, myoglobin level of 4,170 μg/L, lactate dehydrogenase (LDH) level of 1,190 U/L and ferritin level of 1,090 ng/mL. A muscle biopsy revealed inflamma-
tory myopathy compatible with polymyositis. Therefore, the dose of methylprednisolone was increased (1 mg/kg/day), and azathioprine (2 mg/kg/day) was added to the treatment regimen. After six months without a response, therapy with rituximab was administered (375 mg/m²/week) for four weeks, with good symptom improvement. Nevertheless, nine months after the start of treatment with rituximab, the patient exhibited a new outbreak of myositis. The dose of methylprednisolone was again increased (1 mg/kg/day), and mycophenolate mofetil was added (720 mg/12 hours), in addition to a second cycle of rituximab, which also resulted in a good response. Ten months after the beginning of the second cycle of rituximab, the patient presented with right-sided hemiparesis with brachial predominance and hyperreflexia as well as a right-sided extensor plantar cutaneous reflex. A cerebral CT scan revealed cortico-subcortical atrophy and a left cerebellar ischemic lesion. Cerebral MRI (Fig. 1, 2) showed multiple intra-axial lesions with millimetric peripheral ring enhancement coexisting with poorly defined areas and irregular enhancement in the left pre-Rolandic area, right parieto-occipital region and left cerebellar hemisphere. Serology for herpes simplex virus, varicella zoster virus, cytomegalovirus, HIV, Toxoplasma gondii, Treponema pallidum and Borrelia burgdorferi was negative. The cerebrospinal fluid (CSF) displayed slight hyperproteinorrachia with a normal adenosine deaminase (ADA) titer. The results of flow cytometry and oligoclonal bands in the CSF were not pathologic. Cultures for bacteria, mycobacteria and fungi were negative, as was polymerase chain reaction (PCR) for Mycobacterium tuberculosis, cytomegalovirus, herpes virus and JC virus in the CSF.

During hospitalization, the patient progressed towards complete hemiplegia and with cognitive deterioration associated with episodes of psychomotor agitation and a decreased level of consciousness. He ultimately died after an episode of bronchoaspiration; a general autopsy revealed aspiration pneumonia as the cause of death. An examination of the brain did not show any relevant alterations in the cortical pattern, and the surface vessels contained minimal amounts of plaque of atheroma, without significant stenosis. Sections

Figure 1. An image showing multiple intra-axial lesions with millimetric peripheral ring enhancement coexisting with poorly defined areas and irregular enhancement in the left cerebellar hemisphere.
of both brain hemispheres exhibited wide focal lesions in the left peri-Rolandic region and white subcortical matter of the right parietal and occipital lobes, with a yellowish area of retraction (Fig. 3). The lesions were connected to wide areas occupied by foamy histiocytes associated with a limited amount of interstitial and perivascular lymphocytic infiltrates (Fig. 4A). Images showed frequent cell elements compatible with oligodendrocytes containing amphophilic nuclei with a ground glass pattern (Fig. 4B) as well as giant astrocytes with irregular or multilobulated nuclei (Fig. 4C) immunoreactive for glial fibrillary acidic proteins (Fig. 4D). The lesions primarily affected the subcortical white matter and spread focally to the suprajacent cortex, with severe gliosis, frequent ballooning neurons and occasional giant astrocytes. Images also revealed millimetric and demyelinating subcortical lesions without foamy histiocytes in the frontal, parietal, lateral temporal and parahippocampal cortices. Meanwhile, the left cerebellar hemisphere exhibited cavitated lesions with an irregular edge along the surface meas-
uring 4×2 cm and a histological pattern similar to that seen in the white matter, with intense cortical atrophy. The neuropathological diagnosis was progressive multifocal leukoencephalopathy.

Discussion

Antisynthetase syndrome is classified as a form of dermatomyositis. Predisposing factors for opportunistic infections in the dermato/polymyositis group include thoracic myopathy, lymphopenia, esophageal involvement and treatment with cytotoxic drugs (8).

Among second-line drugs for antisynthetase syndrome, rituximab is used in refractory cases (1-5), although it may induce infectious complications (6, 7), with an incidence of severe infections of up to 9% in patients with autoimmune diseases (9). In a study of 279 patients with dermatomyositis and infection, there was a single case of PML associated with previous treatment with rituximab (8). Other cases of PML associated with other immunosuppressant therapies have also been described, although they are rare (10, 11).

PML is a severe disease caused by demyelination of the central nervous system due to reactivation of the JC virus (12). The JC virus is a small ubiquitous DNA neurotropic virus in the family of polyomaviridae (which includes other viruses such as KI, WU, Merkel and BK). The pathogenesis of KI and WU infection in humans is currently under discussion (13-15). The BK virus is primarily detected in patients with AIDS and has not been described in patients with autoimmune diseases (16). Meanwhile, the JC virus is commonly found in humans and remains latent in the kidneys, bone marrow and lymphoid tissue (12). Studies of the seroprevalence of the JC virus have demonstrated a prevalence of up to 86% in healthy populations (12). The JC virus damages oligodendrocytes and astrocytes, thus resulting in neurological deficits associated with areas of demyelination (12, 17).

The virus causes symptoms in patients with severe immunodeficiency (AIDS, autoimmune diseases and hematologic neoplasms) (18, 19). An analysis of 9,675 patients with PML revealed 0.44% of the cases to involve patients with systemic lupus erythematosus, 0.25% rheumatoid arthritis and 0.06% other connective tissue diseases (20). Rituximab is a biological drug reported to induce monoclonal-associated PML; however, its role in the development of PML is unclear. Although humoral control plays a secon-
diary role in the latency of the JC virus, the loss of B cells is fundamental.

The present patient presented with a clinical form including combined elements of the inflammatory variant and cerebellar involvement, which has not previously been described in patients with autoimmune diseases.

The clinical symptoms are non-specific, including cephalalgia, apraxia, convulsions, hemianopsia, cognitive deficits, dementia, aphasia and sensorimotor deficits (12, 16). These symptoms develop over the course of weeks, as in the present case, leading to infradiagnosis.

The diagnosis is usually reached based on a combination of clinical, microbiology and radiology results. Cerebral biopsies (the gold standard procedure) are used only in complex cases, with a sensitivity ranging from 64 to 96% and specificity of 100% (21). The findings are similar for PCR of the CSF, with a sensitivity of 60-92% and specificity of 92-100%, although the results depend largely on the laboratory, degree of immunodepression and spectrum of infection (22-24). Therefore, in patients treated with immunodepressant drugs, a negative PCR finding does not rule out a diagnosis of PML, as in the current case (10).

The classic form of presentation of PML involves multifocal symmetrical or asymmetrical lesions on cerebral MRI, without a vascular distribution, contrast enhancement or mass effect, affecting the white matter (12). However, our patient exhibited features compatible with non-classic PML on MRI, such as increased enhancement (which suggested edema and rupture of the brain-blood barrier) and cerebellar involvement (very rare radiological lesions) (12, 22). On the other hand, forms of polyomavirus other than the JC virus, such as the BK virus, may involve the cerebellum, which has a tendency to increase enhancement (16) and thus prompt us to consider the possibility that our patient’s PML symptoms were caused by a polyomavirus other than the JC virus.

However, this discussion is merely academic, as there is no specific treatment, and the only possible line of action is to recover the patient’s immunodepression. Although some cases of partial success have been described among patients treated with cidofovir (25), the mortality rate of those with PML after receiving rituximab is approximately 90% (12, 26).

In conclusion, rituximab is a biological drug that may induce the development of monoclonal-associated PML. It is necessary to consider the possible role of polyomaviruses other than the JC virus in patients with antisyntethase syndrome and atypical PML. In addition, a negative result for the JC virus in the CSF in these patients does not rule out a diagnosis of PML.

The authors state that they have no Conflict of Interest (COI).

References


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