Progressive Multifocal Leukoencephalopathy in a Patient with Polymyositis: Case Report and Literature Review

To the Editor:

We describe a fatal case of progressive multifocal leukoencephalopathy (PML) in a patient with polymyositis (PM) and antisynthetase syndrome treated with conventional immunosuppressive drugs.

PML is a rare and fatal demyelinating disease caused by the ubiquitous John Cunningham virus (JCV)\(^1\). JCV infection is usually an asymptomatic event in childhood and about 60%-80% of the normal adult population are seropositive for antibodies against JCV\(^1,2\). After primary infection, the virus remains in a latent form in the bone marrow, lymphoid organs, and kidney and some studies have demonstrated that it also can establish latency in healthy brain tissue although this is a matter of debate\(^3,4\). The virus may later reactivate, undergoing genomic rearrangement in the non-coding regulatory region, and migrate to the brain, where it infects glial cells and causes a lytic infection known as PML\(^5,6\). Reactivation usually occurs during conditions of immunosuppression but there are also reports of PML development in immunocompetent individuals\(^6\). The mechanisms behind the pathway leading to viral reactivation remain insufficiently defined. The risk of PML in autoimmune diseases has recently been highlighted because of an increasing number of PML cases occurring during treatment with new biological immunosuppressive agents including natalizumab (for multiple sclerosis, MS), rituximab (RTX; for rheumatic diseases), and efalizumab (for psoriasis) and also with the newer immunosuppressant agent mycophenolate mofetil (MMF)\(^7\). In the more rare autoimmune diseases polymyositis/dermatomyositis (PM/DM) there are a few reports of PML developing in patients treated with conventional disease-modifying antirheumatic drugs\(^7\), but also in patients during off-label treatment with RTX\(^8\). The increased risk for PML associated with the new biologics has raised the question of whether these treatments involve a biological explanation for the increased risk. The background risk for PML in autoimmune diseases is, however, not known, since epidemiological studies are lacking on the incidence of PML in autoimmune diseases and data to date are dependent on case reports or case series.

A 65-year-old woman negative for human immunodeficiency virus (HIV) and having bronchial asthma, type 2 diabetes mellitus, and substituted hypothyroidism presented in our clinic because of fever, fatigue, symmetrical polyarthritis, myalgia in her proximal muscles, paresthesia, and dyspnea. She had a history of connective tissue disease-modifying antirheumatic drugs, mycogeneryx (for multiple sclerosis, MS), rituximab (RTX; for rheumatic diseases), and efalizumab (for psoriasis) and also with the newer immunosuppressant agent mycophenolate mofetil (MMF)\(^7\). In the more rare autoimmune diseases polymyositis/dermatomyositis (PM/DM) there are a few reports of PML developing in patients treated with conventional disease-modifying antirheumatic drugs\(^7\), but also in patients during off-label treatment with RTX\(^8\). The increased risk for PML associated with the new biologics has raised the question of whether these treatments involve a biological explanation for the increased risk. The background risk for PML in autoimmune diseases is, however, not known, since epidemiological studies are lacking on the incidence of PML in autoimmune diseases and data to date are dependent on case reports or case series.

The patient was switched to oral azathioprine 150 mg/day; however, this was stopped after 6 weeks due to nausea and increased liver enzymes. Oral prednisone 17.5 mg/day was continued.

Four months later, roughly 2 years after she was diagnosed with PM and antisynthetase syndrome, she developed fatigue, vertigo, and balance problems. Neurological examination demonstrated horizontal nystagmus, dysarthria, ataxia of the left extremities, and a mild left-side hemiparesis. Laboratory tests showed CRP and ESR within normal ranges and slightly elevated WBC count (11.8 × 10^9/l, with normal lymphocyte count 1.3 × 10^9/l). Brain magnetic resonance imaging (MRI) revealed 2 hyperintense white-matter lesions in the left cerebellar hemisphere and 1 hyperintense white-matter lesion in the brain stem, and supratentorial diffuse hyperintense lesions of the white matter. The lesions had no expansive effect or contrast enhancement (Figure 1). The patient was incorrectly suspected to have central nervous system vasculitis. Intravenous (IV) pulse methylprednisone 1000 mg daily on 2 consecutive days was started, but vertigo and balance disturbances worsened. A new MRI scan of the brain showed progression of the cerebellar lesions and appearance of a new pontine lesion without mass effect or contrast enhancement. Despite treatment with IV prednisone 60 mg/day and subcutaneous low molecular weight heparin, the patient’s condition worsened and developed progressive tetraparesis and dysphagia. A lumbar puncture showed a normal cell count, slightly elevated albumin, and a positive JCV polymerase chain reaction (PCR) analysis with detection of > 200 copies/ml (SMI, Stockholm, Sweden; exact number of JCV copies not analyzed), which confirmed the diagnosis of PML. Prednisone was tapered from 40 to 12.5 mg/day. Antiviral therapy was discussed but the patient declined any further medication. Her condition deteriorated and she died 4.5 months after the first neurological symptoms had presented. Brain autopsy revealed PML lesions in the brain stem and cerebellum and positive in situ staining for JCV DNA. No supratentorial PML lesions were observed; the diffuse lesions seen on MRI were of degenerative origin. A general autopsy revealed only mild atherosclerosis of the coronary arteries and moderate aortic atherosclerosis.

We performed an updated literature search of PML cases in PM/DM patients with no other autoimmune disease. We identified 8 cases that were treatment-naive for the newer biologics, summarized in Table 1. All patients were HIV-negative and 8 had no other underlying disease; 1 patient also had chronic renal insufficiency. The patients developed PML after a range of 7 months to 5 years of disease duration of PM/DM. Seven patients were diagnosed with DM and 2 with PM. Six were women and the age span at disease onset was 29–72 years. One patient, with a favorable outcome, had no treatment when presenting with symptoms suggestive of PML, and had earlier been treated only with hydroxychloroquine. Three patients were treated only with oral prednisone at time of PML diagnosis (including the present case). One patient had ongoing treatment with MMF at the time of development of PML. 2 patients had ongoing treatment with azathioprine, another 2 had ongoing treatment with cyclosporine, and 1 patient was treated with cyclophosphamide and IV immunoglobulins upon developing PML. Five patients had supratentorial white-matter lesions on MRI, which is the most typical localization of PML. 3 patients had only infratentorial white-matter lesions, including our case, and gadolinium enhancement was seen in 2 patients. One female patient had a negative PCR analysis for JCV DNA in 2 repeated cerebrospinal fluid (CSF) analyses despite multiple supratentorial white-matter PML lesions, and the PML diagnosis was instead confirmed by brain biopsy\(^13\). That case demonstrates the importance of repeating the PCR analysis for JCV in CSF with ultrasensitive techniques or proceeding to a brain biopsy if suspicion of PML persists.

Six patients died and 3 survived and improved clinically; 2 of the survivors had been treated only with mild immunosuppressants (prednisone, hydroxychloroquine), but the third had been treated with MMF and cyclosporine in addition to prednisone. After PML diagnosis, 4 patients received treatment with cytokine-aminoside, which might have been suc-
successful in the 2 that survived. The time to death after onset of PML symptoms ranged between 1 and 5 months.

We also found 1 recent report on a patient with PM who experienced fatal PML during treatment with the biological agent RTX (Table 1, Patient 1017. This patient developed clinical signs of PML after 5 infusions of RTX and 6.5 years’ duration of PM. The patient was treated with RTX because her treatment had been refractory to conventional immunosuppressive therapy.

We describe a patient with PM and antisynthetase syndrome who developed clinical symptoms of PML after 22 months of conventional immunosuppressive treatment including prednisone, oral cyclophosphamide for 13 months, MTX for 6 months, and azathioprine for 6 weeks. The diagnosis of PML was based on detection of JCV DNA in her CSF. The current diagnostic test for PML is detection of JCV DNA in CSF, using PCR methods, or in brain tissue obtained by biopsy or autopsy. There are, however, reports of negative JCV PCR tests in CSF collected early in the course of PML disease18, as well as reports of false-negative results for JCV in CSF despite high levels of virus load, due to genomic variability and use of incorrect sets of primers and probes19. Interestingly, the majority of PML cases occurring in patients with MS treated with the new biological agent natalizumab have had much lower JCV load in their CSF (≤ 500 copies/ml)20 at time of diagnosis, compared to reports of PML not associated with new biological treatments21,22.

Through the literature search we found another 8 cases of PML after conventional immunosuppressive treatment. The previously reported cases with PML in patients with PM and DM were similar to our case in their PML features, but 3 of the previously reported 8 cases survived, whereas our patient did not. The surviving patients seemed to have received fewer immunosuppressive agents before developing PML, compared to our case, and 2 of the survivors received antiviral treatment, which may have affected the outcome.

PML has been recognized as a potential risk in patients treated with biological agents. No biological agent has to date been approved for treatment of PM or DM. One phase II randomized double-blind placebo-controlled study using RTX for DM and PM was recently performed, with no reports of cases of PML23. However, 1 patient with PM developing PML was reported during off-label use of RTX treatment17. We have also received information on 3 other reported cases of PML in patients with DM or PM treated with RTX (Roche Pharmaceuticals, personal communication). These data may indicate a high number of PML cases in a rare inflammatory disease where the number of patients treated with RTX to date is limited. The prevalence of inflammatory myopathies is about 1/15–50 compared to systemic lupus erythematosus and 1/800 compared to rheumatoid arthritis24. Therefore the number of reported cases with PML in patients with PM/DM might be higher compared to other autoimmune diseases, but to clarify this issue, the background risk of PML in PM and DM must be known.

There is at present no treatment for PML. The most important action is...
withdrawal of immunosuppressive drugs and, if possible, rapid elimination of the specific biological agent. Administration of the serotonin receptor antagonist mirtazapine has been tried with varying results (serotonin receptors are used by JCV for entry into the cell), but because clinical studies are lacking, this procedure is discouraged. The antimalarial drug mefloquine was shown to inhibit JCV replications in vitro, but a subsequent clinical study was discontinued due to lack of significant efficacy (www.clinicaltrials.gov). There are case reports and series that have reported favorable outcomes of PML after treatment with cytosine-arabinoside, including a few patients with rheumatic diseases; however, a large placebo-controlled trial on the effect of cytosine-arabinoside for HIV-associated PML failed to demonstrate any effect of the drug. A recent study on the first 35 postmarketing cases of PML in patients with MS treated with natalizumab identified several factors associated with improved survival, including shorter time from symptom onset to diagnosis of PML, younger age at diagnosis, less disability before PML, and more localized disease on MRI.

One suggested strategy to assess risk for PML is to screen for seropositivity of JCV antibodies to determine whether the patient has been infected with JCV. This is recommended as a potential tool for stratifying PML risk in persons with MS, prior to initiation of natalizumab treatment. Patients who are found to be JCV-seronegative should be followed for seroconversion repeatedly during immunosuppressive treatment. By contrast, several studies have demonstrated that screening for JCV DNA in blood, CSF, or urine does not enhance the ability to predict development of PML.

The mechanisms behind JCV reactivation are not understood; immunosuppression is a major causative factor, but host and viral factors are also important. The table below summarizes data on patients with polymyositis/dermatomyositis developing progressive multifocal leukoencephalopathy (PML).

Table 1. Data on patients with polymyositis/dermatomyositis developing progressive multifocal leukoencephalopathy (PML).

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex, Age, yrs</th>
<th>Underlying Disease and Duration</th>
<th>IST Before PML</th>
<th>IST at PML</th>
<th>PML Symptoms</th>
<th>MRI Findings</th>
<th>CSF JCV DNA PCR</th>
<th>PML Diagnosis</th>
<th>PML-specific Treatment</th>
<th>PML Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>113</td>
<td>F 52</td>
<td>DM, 5 yrs</td>
<td>Prednisone</td>
<td>Prednisone</td>
<td>↓ Psychomotor performance, memory loss, aphasia, N VII palsy</td>
<td>Supratentorial and infratentorial T2 WM lesions, Gd+ cranial nerve roots VII and VIII</td>
<td>Negative × 2</td>
<td>Brain biopsy: pos JCV DNA PCR</td>
<td>CYT-ARA</td>
<td>Improved</td>
</tr>
<tr>
<td>123</td>
<td>M 44</td>
<td>DM, 2.5 yrs</td>
<td>Prednisone MMEF, IVIG, CYC AZA</td>
<td>Prednisone MMEF, IVIG, CYC AZA</td>
<td>↓ Visual acuity hemianopsia</td>
<td>Supratentorial T2 WM lesions</td>
<td>Positive</td>
<td>JCV copies/ml</td>
<td>Pos CSF JCV DNA PCR</td>
<td>CYT-ARA, mirtazapine</td>
</tr>
<tr>
<td>134</td>
<td>F 72</td>
<td>DM, unknown</td>
<td>Prednisone, IVIG</td>
<td>Prednisone, IVIG</td>
<td>Cognitive deficits, personality changes</td>
<td>Supratentorial G4+ T2 WM lesions</td>
<td>JCV DNA PCR</td>
<td>Brain biopsy and autopsy: pos JCV DNA ISH</td>
<td>CYT-ARA</td>
<td>Death in 1 mo</td>
</tr>
<tr>
<td>414</td>
<td>F 45</td>
<td>DM, 7 mo, chronic renal insufficiency</td>
<td>Prednisone MMEF, IVIG, CYC</td>
<td>Prednisone MMEF, IVIG, CYC</td>
<td>Altered consciousness, progressive tetraparesis</td>
<td>Supratentorial T2 WM lesions</td>
<td>?</td>
<td>Autopsy: intranuclear viral bodies and inflammation</td>
<td>None</td>
<td>Death in 1 mo</td>
</tr>
<tr>
<td>514</td>
<td>F 43</td>
<td>DM, 5 yrs</td>
<td>Prednisone, AZA</td>
<td>Prednisone</td>
<td>Gait ataxia, dysarthria, corticospinal tract involvement</td>
<td>T2 WM lesions cerebellum and brainstem</td>
<td>Negative</td>
<td>Brain biopsy: pos JCV ab</td>
<td>Cidofovir, cytarabine</td>
<td>Death in 3 mo</td>
</tr>
<tr>
<td>614</td>
<td>F 29</td>
<td>DM, unknown</td>
<td>HCQ</td>
<td>None</td>
<td>Left hemiparesis, diplopia, nystagmus, N III, N VI palsy, altered behavior, impaired memory, ataxia</td>
<td>Supratentorial WM lesions, 1 thalamic lesion</td>
<td>?</td>
<td>“Pos brain biopsy”</td>
<td>IV steroids, mirtazapine</td>
<td>Improved</td>
</tr>
<tr>
<td>716</td>
<td>M 54</td>
<td>PM, unknown</td>
<td>Prednisone, chlorambucil</td>
<td>?</td>
<td>Altered behavior, impaired memory, ataxia</td>
<td>?</td>
<td>Not done?</td>
<td>Brain biopsy: pos JCV ab</td>
<td>None</td>
<td>Death in 5 mo</td>
</tr>
<tr>
<td>815</td>
<td>M 67</td>
<td>DM, 4 yrs</td>
<td>Dexamethasone, Dexamethasone, sirolimus, IVIG</td>
<td>Dexamethasone, Dexamethasone</td>
<td>Dysthria, trunk ataxia, confusion, balance distribution</td>
<td>Supratentorial T2 WM lesions</td>
<td>Positive</td>
<td>Not performed</td>
<td>Cidofovir</td>
<td>Death within weeks</td>
</tr>
<tr>
<td>9</td>
<td>F 67, present case</td>
<td>PM, 2 yrs</td>
<td>Prednisone, CPP, IVIG, MTX, AZA</td>
<td>Prednisone</td>
<td>Limb ataxia, nystagmus, L hemiparesis, dysarthria</td>
<td>T2 WM lesions cerebellum and brainstem</td>
<td>Positive</td>
<td>Pos CSF JCV DNA PCR; brain biopsy: pos JCV DNA ISH</td>
<td>None</td>
<td>Death in 4.5 mo</td>
</tr>
<tr>
<td>1017</td>
<td>F 43</td>
<td>PM 6.5 yrs</td>
<td>Prednisone, MTX, AZA, MMF, CYC, IVIG, rituximab</td>
<td>Prednisone, rituximab</td>
<td>Bilat hemianopsia, ↓ visual acuity</td>
<td>Supratentorial subcortical and cortical T2 and FLAIR WM lesions</td>
<td>Positive</td>
<td>Pos CSF JCV DNA PCR</td>
<td>None</td>
<td>Death in 8 mo</td>
</tr>
</tbody>
</table>

IST: immunosuppressive treatment; DM: dermatomyositis; PM: polymyositis; MMEF: mycophenolate mofetil; AZA: azathioprine; CPP: cyclophosphamide; CYC: cyclosporine; HCQ: hydroxychloroquine; MTX: methotrexate; IVIG: intravenous immunoglobulins; Gd+: gadolinium enhancement; CYT-ARA: cytosine-arabinoside; ISH: in situ hybridization; ab: antibody; WM: white matter; CSF: cerebrospinal fluid; JCV: John Cunningham virus; MRI: magnetic resonance imaging; PCR: polymerase chain reaction.

Note: Withdrawal of immunosuppressive drugs and, if possible, rapid elimination of the specific biological agent.
tainly important as well. As the use of biological agents in autoimmune disease increases, it is important to improve our knowledge about the mechanisms behind JCV reactivation leading to PML, regardless of treatment, to develop effective strategies to reduce risk of PML. While in theory any immunosuppressive regimen can increase the risk of PML, it had not been seen with MS, Crohn’s disease, or psoriasis until the introduction of natalizumab and efalizumab, despite the relatively aggressive immunosuppressive regimens used in these conditions. This may suggest that there is some contribution to the development of PML from the underlying condition being treated.

Patients with autoimmune diseases also carry a risk for reactivation of JCV and PML with milder immunosuppressive treatment, and more rarely, without such treatment. The frequency of PML in autoimmune diseases remains unknown because confirming epidemiological data are sparse. In this context the background prevalence of PML in patients with PM or DM will be important and there is great value in reporting cases such as ours.

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Supported by the Regional Agreement on Medical Training and Clinical Research (ALF) between Stockholm County Council and Karolinska Institutet.

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