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Progressive multifocal leukoencephalopathy in rheumatoid arthritis and biological therapies: a case report and review of the literature

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Abstract

Background Progressive multifocal leukoencephalopathy is a rare but potentially fatal disease caused by infection of the central nervous system with John Cunningham polyomavirus. Progressive multifocal leukoencephalopathy mainly occurs in immunocompromised patients, including patients on biological and targeted synthetic therapies, such as multiple sclerosis and rheumatoid arthritis patients. Early diagnosis of progressive multifocal leukoencephalopathy is crucial for patient survival. We describe a case of progressive multifocal leukoencephalopathy with significant diagnostic delay in a rheumatoid arthritis patient using rituximab. Additionally, we give an overview of available literature on progressive multifocal leukoencephalopathy in rheumatoid arthritis patients using biologicals, focusing on the diagnostic difficulties and delays, to raise awareness of this adverse event among physicians treating rheumatoid arthritis patients with immunosuppressants.

Case presentation A 69-year-old white man of Dutch descent with rheumatoid arthritis treated with rituximab presented to a neurology outpatient clinic, complaining of difficulties in word-finding and reading without problems in visual acuity, several weeks after a mild traumatic head injury (patient's delay). Brain computed tomography-scan showed two hypodense white-matter lesions, initially considered to be of vascular origin (doctor's delay). However, magnetic resonance imaging, performed more than a week later, showed lesions consistent with progressive multifocal leukoencephalopathy. Immunosuppressants were then immediately discontinued. The patient agreed to repeat magnetic resonance imaging and lumbar puncture. Initial John Cunningham polyomavirus polymerase chain reaction on cerebrospinal fluid was negative. However, a subsequent lumbar puncture confirmed the diagnosis. The patient rejected experimental treatment with pembrolizumab and passed away a month after the initial presentation.

Conclusions This case report emphasizes the need for increased awareness and importance of timely recognition of potential progressive multifocal leukoencephalopathy in rheumatoid arthritis patients using immunosuppressive therapies. A total of 26 other cases of rheumatoid arthritis patients using biologicals who developed progressive multifocal leukoencephalopathy were identified from the literature, and we reviewed their cases. Most (24; 92%) cases occurred during rituximab or TNF-alpha inhibitor use. There was a mean delay of 2.5 months between symptom onset and diagnosis. Information on predisposing risk factors such as lymphopenia was often not reported. Physicians and patients should be aware of the symptoms of progressive multifocal leukoencephalopathy, as early diagnosis and immediate withdrawal of immunosuppressants is crucial to improve the chance of survival. This case

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report highlights the importance of awareness in recognizing progressive multifocal leukoencephalopathy symptoms in nontraditional populations.

Keywords Biological, Case report, Diagnostic delay, Progressive multifocal leukoencephalopathy, Rheumatoid arthritis

Background

Progressive multifocal leukoencephalopathy (PML) is a rare, often fatal, demyelinating disease, caused by infection of the central nervous system with John Cunningham polyomavirus (JCV). JCV leads to lysis of oligodendrocytes, causing multifocal demyelinating lesions in the brain [1].

PML almost exclusively occurs in a state of immune deficiency. Historically, it has mainly affected patients with specific underlying conditions that cause profound immunocompromise. Human immunodeficiency virus (HIV) infection continues to be the most common predisposing condition among patients with PML [2]. After the introduction of highly active anti-retroviral therapy (HAART), the incidence in this population has significantly decreased from 0.7 to 0.07 per 100 cases per year, with an associated increase in survival rate (72% at 3 years after diagnosis) [3, 4]. The second most common underlying condition is lymphoproliferative disease, with an estimated frequency of 0.07% and a 1-year mortality rate of 39.2% [2, 5]. Though PML is primarily linked to immunologic treatment or hematopoietic stem cell transplants in this population, it may also occur in untreated patients. Nowadays, it is recognized that PML can occur in a wide variety of patients with milder immunosuppression. PML cases have been described in various classes of immunotherapies [6]. Among those, natalizumab, an alpha 4-integrin antagonist used in the treatment of multiple sclerosis, is the most significant risk factor for the development of PML, with an overall frequency of 4.14/1,000 patients [7] and an associated mortality rate of 25–30% [8]. Because of the high incidence of PML in natalizumab-treated patients, a risk stratification algorithm based on prior immunosuppressant use, natalizumab treatment duration and anti-JCV antibodies has been developed to better manage this population [9, 10]. The anti-CD20 monoclonal rituximab has also been associated with PML, albeit with a much lower estimated frequency of 1 in 32,000 cases in all autoinflammatory conditions and 1 in 25,000 cases in rheumatoid arthritis (RA) patients, specifically [11–13]. For many biologicals, however, it remains uncertain whether they increase the risk for PML, because of the frequent concomitant use of multiple immunosuppressants.

With a yearly incidence of 4 in 10,000 patients, PML has also been associated with systemic lupus erythematosus (SLE) [14]. It is noteworthy that PML occurs both in untreated SLE patients and patients on immunosuppressive medication, suggesting SLE itself may predispose patients to JCV reactivation [15]. Though rare, PML without overt immunosuppression has been documented in several case reports. Due to the small number of cases, there is still insufficient data on incidence and prognosis in this population [16]. Despite research on the use of mirtazapine, mefloquine, and pembrolizumab, no treatment aside from discontinuation of immunosuppressive medication (or administration of HAART in the case of HIV infection) has proven effective in treating PML.

Rheumatoid arthritis is an autoinflammatory disease affecting mainly the small joints of the hands and feet. It is characterized by hyperinflammation in the synovial space, leading to permanent disability when untreated. Treatment of RA usually requires the simultaneous use of multiple immunosuppressants. Nowadays, a plethora of biologicals with different targets are available, such as TNF-alpha inhibitors, interleukin antagonists, and rituximab. Targeted synthetic therapies in the form of Janus-kinase (JAK) inhibitors have recently been added as RA treatment options. This combination of immunosuppressants and the need for long-lasting treatment make RA patients especially susceptible to opportunistic infections. Numerous PML cases have been reported in RA patients using biological treatments, predominantly rituximab.

As cessation of immunosuppression is the only non-experimental intervention that is currently available for PML, timely diagnosis is of pivotal value for patient survival. Diagnosis of PML, however, begins with awareness of its symptoms and existence. The aims of this report are to illustrate and provide an overview of RA patients using biologicals who developed PML with an emphasis on the diagnostic difficulties and delays, and to create awareness of this adverse event among physicians treating RA patients.

Case presentation

A 69-year-old white man of Dutch descent presented to a neurology outpatient clinic complaining of difficulties

in word-finding and reading without problems in visual acuity. The patient first noticed symptoms shortly after a mild traumatic brain injury following a fall from his bike. He then assumed the symptoms were secondary to a mild concussion. When the symptoms progressed, he decided to consult his family doctor 6 weeks later (patient's delay). He was referred for a neurological consultation and was admitted to the neurological outpatient clinic the next day with suspected posttraumatic brain injury. His medical history included rheumatoid arthritis (RA) of 23 years' duration, for which he had received oral methotrexate (MTX) 22.5 mg weekly and intravenous rituximab 1000 mg every 6 months for the preceding 3 years, of which the last dose had been administered 3 months before the onset of symptoms. Neurological examination revealed difficulties answering complex questions and sometimes difficulties following the conversation. There were signs of ideomotor and kinetic apraxia. His gait was unsteady, without evident cerebellar dysfunction. Computed tomography (CT) of the brain showed two hypodense lesions in the white matter of the left parieto-occipital lobe. Initially, this was considered to be of vascular origin, and the patient was referred for magnetic resonance imaging (MRI) to further differentiate the findings. More than a week later (doctor's delay), the MRI showed the lesions to be T2 hyper-intense lesions with a nodular aspect, strongly suggestive of PML. Rituximab and MTX were immediately discontinued, and a lumbar puncture was performed, which showed no pleocytosis (2×10^6/L leukocytes) and a negative JCV polymerase chain reaction (PCR). CD4 counts were normal (517×10^6/L). After being informed of the diagnosis, the patient agreed to repeat MRI and lumbar puncture. The second MRI, performed 2 weeks after the first, was unchanged; however, the JCV PCR of the cerebrospinal fluid (CSF) was positive, with a viral load of 116 IU/mL. The patient chose not to undergo experimental treatment with pembrolizumab. His condition worsened rapidly with progressive cognitive and motor symptoms, and he passed away a month after his initial admission to the neurology outpatient clinic. No autopsy was performed.

Discussion and conclusions

We describe a case of PML with significant diagnostic delay in a patient with RA who was treated with rituximab. The patient continued to use MTX until several weeks after symptom onset, as his symptoms were initially mistaken for posttraumatic issues by both the patient and the physician. Only after observing the characteristic lesions on MRI was immunosuppression discontinued. Timely diagnosis of PML is of pivotal value for patient survival, as cessation of immunosuppression is currently the only available nonexperimental intervention. This case report highlights the importance of awareness in recognizing PML symptoms in nontraditional populations.

Previously, only patients with hematological malignancies or HIV or patients with MS using natalizumab were considered at high risk of developing PML. Nowadays, with the surging use of biological therapies and a wide range of indications for these drugs, PML may be observed in patients that fall outside of this traditional risk profile. Since the introduction of biological therapies, the incidence of PML has increased; according to a Swedish study, the incidence went from 0.026/100,000 patient-years in 1988–2010 to 0.11/100,000 patient-years in 2011–2013 [17]. The increasing use of biological drugs makes it more likely clinicians will encounter a patient with PML.

Further complicating a timely diagnosis is the often insidious start of PML symptoms. Mild confusion and loss of coordination are common, and patients may trivialize their symptoms for a while or attribute them to an unrelated event (as in our patient) before contacting their healthcare provider. Furthermore, diagnosis may be challenging, with the gold standard for diagnosing PML being a brain biopsy or a positive JCV PCR of the CSF. As a brain biopsy is quite invasive, clinicians often rely on CSF PCR when it comes to providing a definitive diagnosis. However, its sensitivity is only moderate, at approximately 58% [18], as is illustrated by the patient from our case report, in whom JCV PCR tested positive only the second time. It is crucial that all healthcare providers are aware of the occurrence of PML outside of classical risk populations, and of the diagnostic difficulties and its signs and symptoms, as a longer diagnostic delay is associated with poorer outcomes and a higher mortality rate [19].

To further investigate diagnostic delay in the RA population using biologicals or targeted synthetic therapies, we systematically searched for additional cases of PML in RA patients using biological or targeted synthetic therapies in PubMed, Cochrane, Web of Science, and Embase. Additionally, we searched the database of the Laboratory of Medical Microbiology and Immunology for all JCV polymerase chain reaction (PCR)-confirmed PML cases. The literature search yielded 26 other cases from 17 articles in which PML had been established in RA patients using biologicals (details in Table 1). Most cases were from the USA (12; 44.4%) and Japan (4; 14.8%). Patients were mostly female (22; 81.5%) with a mean age of 65.1 years (SD 13.3). In most cases (17; 67.0%) the patients used rituximab, 7 (25.9%) patients used TNF-alpha inhibitors, and 2 (7.41%) patients used tocilizumab. One patient did not actively use biologicals, but had been exposed to etanercept, tocilizumab, and rituximab for up

Table 1 Summary of the published PML cases in RA patients using biologicals

Country	Sex	Age (years)	Comorbidities	Lymphopenia	Corticosteroids	csDMARD	Biological	Biological duration (years)	Pretreatment with biological	Symptom duration (months)	Symptoms	Differential	Diagnostic delay (months)	Mode of diagnosis	Outcome	References
USA	Male	72	Hypertension, benign prostatic hypertrophy, chronic bronchitis		Yes	MTX	Infliximab	5	No	2.5	Memory loss, confusion, falls, right-sided weakness			Histology brain biopsy	Survived with disability	Kumar *et al.* [21]
USA	Female	66			No	No	Adalimumab	2	No	3	Coordination problems, impaired writing, gait disturbance, dysarthria			PCR CSF	Unknown	Ray *et al.* [22]
Spain	Female	92					Rituximab	5		2	Sensory–motor syndrome of the right limbs, cognitive impairment			Histology brain biopsy	Death	Sala *et al.* [23]
USA	Female		Diabetes, hypertension				Rituximab	2.5			Altered consciousness, lack of coordination, abnormal gait, peripheral neuropathy			MRI	Death	Bharat *et al.* [24]
USA	Female		Colonic polyps, stroke		Yes	No	Rituximab	0.67		1	Speech disorder, aphasia, idiopathic peripheral neuropathy, abnormal gait, lack of coordination, hemiplegia			Unknown	Death	Bharat *et al.* [24]
USA	Female	75				MTX	Adalimumab				Progressive left hemiplegia, "global decline"	Age-related		Histology brain biopsy	Death	Babi *et al.* [25]
Japan	Female	74		Yes			Etanercept	0.58		2.5	General malaise, loss of appetite, disorientation, incontinence, deterioration of verbal communication	Encephalomeningitis	3	MRI	Survived with disability	Yamamoto *et al.* [26]

Table 1 (continued)

Country	Sex	Age (years)	Comorbidities	Lymphopenia	Corticosteroids	csDMARD	Biological	Biological duration (years)	Pretreatment with biological	Symptom duration (months)	Symptoms	Differential	Diagnostic delay (months)	Mode of diagnosis	Outcome	References
Japan	Female	72		No			Tocilizumab	3.33			Dementia, abnormal behavior	Infection		MRI	Survived with disability	Kobayashi *et al.* [27]
Ireland	Male	60		No			Rituximab	10		1	Ataxia, dysarthria, dysphagia			PCR CSF	Survived with disability	Darcy *et al.* [28]
USA	Female	79	Hypertension, ischemic stroke	No	Yes	No	Rituximab				Falls, gait disturbance, slurred speech, confusion			MRI	Death	Guduru *et al.* [29]
UK	Female	69				MTX	Infliximab	5		2	Progressive cognitive decline, word-finding difficulties, retrograde and anterograde amnesia, behavioral change, somnolence, apathy			PCR brain biopsy	Survived with disability	Sammut *et al.* [30]
Japan	Female	61	Anxiety disorder, Sjögren syndrome			MTX	Tocilizumab	1.33	Adalimumab, abatacept	5	Speech disorder and could no longer prepare meals	Worsening anxiety disorder, subacute cerebral infarction, malignant lymphoma	5	Histology brain biopsy	Survived with disability	Anada *et al.* [31]
USA	Female	51	Sjögren syndrome	Yes		MTX	Rituximab	5				Malignant neoplasm		Histology brain biopsy	Death	Fleischmann *et al.* [32]
Taiwan	Female	27	SLE		Yes	MTX, HCQ	None*		Etanercept, tocilizumab, and rituximab sequentially	3	Dizziness, unsteady gait, headache, nausea, vomiting, dizziness, left-hand clumsiness, left hemiparesis	Subacute infarction, vasculitis, refractory neuropsychiatric SLE, rhombencephalitis	2	PCR CSF	Survived with disability	Cheng *et al.* [20]
USA	Female	73	Hypothyroid, Sjögren syndrome	Yes	Yes	Leflunomide	Rituximab				Focal right-hand dysesthesia, ataxia, dysphasia		1	PCR CSF	Death	Clifford *et al.* [13]

Table 1 (continued)

Country	Sex	Age (years)	Comorbidities	Lymphopenia	Corticosteroids	csDMARD	Biological	Biological duration (years)	Pretreatment with biological	Symptom duration (months)	Symptoms	Differential	Diagnostic delay (months)	Mode of diagnosis	Outcome	References
Sweden	Female	72	Sjögren syndrome	Yes		MTX	Rituximab		Etanercept, adalimumab		Right hemiataxia in arm, leg, and trunk, falls		4	PCR CSF	Death	Clifford *et al.* [13]
Australia	Female	67	Sjögren syndrome	Yes	Yes	MTX	Rituximab				Cognitive decline, dysphasia		2	PCR CSF	Survived with disability	Clifford *et al.* [13]
USA	Female	62		Yes		MTX	Rituximab		Etanercept, adalimumab, anakinra		Cortical right hand dystonic tremor, later myoclonus			Histology brain biopsy	Survived with disability	Clifford *et al.* [13]
Japan	Female	65		Yes	No	MTX	Infliximab	4			Right upper limb weakness, gait disturbance, headache, nausea, dizziness, weight loss, double vision	TIA, cryptococcal meningitis	3	PCR CSF	Survived with disability	Nosaki *et al.* [33]
Unknown	Female	56			Yes	Leflunomide, MTX	Rituximab	1.92	Adalimumab, etanercept		Unknown	Unknown		Unknown	Unknown	Berger *et al.* [34]
Unknown	Male	58	SLE, opportunistic infections		Yes	MTX	Rituximab	2.33	Etanercept, infliximab		Unknown	Unknown		Unknown	Death	Berger *et al.* [34]
nknown	Female	60	SLE		Yes	MMF	Rituximab	4.67	No		Unknown	Unknown		Unknown	Death	Berger *et al.* [34]
Unknown	Female	83			Yes	MTX	Rituximab	4.75	Denosumab		Unknown	Unknown		Unknown	Death	Berger *et al.* [34]
USA	Female	55					Rituximab	2	TNF-alpha inhibitor		Unknown	Unknown		Unknown	Survived with disability	Molloy *et al.* [35]
USA	Female	41			Yes	MTX	Rituximab	1.33	Infliximab		Unknown	Unknown		Unknown	Unknown	Molloy *et al.* [35]
USA	Male	69			Yes	HCQ, CYC	Infliximab				Unknown	Unknown		Unknown	Death	Molloy *et al.* [35]
The Netherlands	Male	69	Cataract, COPD		No	MTX	Rituximab	3		1.5	Word-finding difficulties, trouble reading, uncertain gait	Hematoma, vascular	0.25	PCR CSF	Death	Case described in current article, 2022

Blank cells indicate this information was not reported

COPD chronic obstructive pulmonary disease, *csDMARD* conventional synthetic disease-modifying antirheumatic drug, *CSF* cerebrospinal fluid, *CYC cyclosporine, HCQ* hydroxychloroquine, *MMF* mycophenolate mofetil, *MRI* magnetic resonance imaging, *MTX* methotrexate, *PCR* polymerase chain reaction, *SLE* systemic lupus erythematosus, *TIA* transient ischemic attack

[*] One patient had no current biological use but had been exposed to etanercept, tocilizumab, and rituximab for up to 2 years before presentation

to 2 years before presentation [20]. Patients presented with a mean symptom duration of 2.4 months with a standard deviation (SD) of 1.2 months, and the mean diagnostic delay (defined as the time span between initial presentation and PML diagnosis) was 2.5 months (SD 1.6). Diagnosis was most often confirmed by a positive JCV PCR of the CSF (eight cases; 29.6%). Mortality was high at 48.2% with permanent disability being common among survivors.

The Laboratory of Medical Microbiology and Immunology provides JCV PCR diagnostics for the south of the Netherlands since 2007. A search in the laboratory database yielded 317 patients in whom JCV PCR was performed on CSF or brain biopsies. Out of these 317, 29 patients (9%) were confirmed to have PML by a positive JCV PCR result. Patients were mostly male (19; 68%) and had a median age of 63 years (interquartile range [IQR] 47–67 years). Information on underlying immunodeficiencies was available in 20 cases: 10 HIV infections (34%), 3 chronic lymphocytic leukemia (10%), 2 multiple sclerosis (7%), 2 RA (7%, including the patient described in this report), 1 vasculitis (3%), 1 kidney transplant (3%), and 1 without any known immunodeficiency (3%). There was an all-cause mortality of 59%, with a median of 51 (IQR 25–101) days between PCR positivity and death. In addition to the RA patient described in this case report, the other RA patient in whom PML was confirmed used MTX, prednisone, and hydroxychloroquine.

Our case report as well as the cases described in the literature all underline the importance of prompt diagnosis and immediate discontinuation of immunosuppression in RA patients with PML. We found a mean diagnostic delay of 2.5 months between initial presentation and definitive diagnosis in RA patients, which is in line with prior literature demonstrating high diagnostic delays in PML patients irrespective of the underlying condition [19].

Aside from the high prevalence of rituximab use in all retrieved cases, seven patients from the literature were treated with TNF-alpha inhibitors. Though no formal link has been established between TNF-alpha inhibitors and PML to date, these findings suggest patients using these drugs and their physicians should also be vigilant. Data from the laboratory database show a significant proportion of patients with a positive JCV PCR of the CSF fall outside of the traditional high-risk category (hematological malignancies, HIV, and natalizumab use). In natalizumab, unlike any other biological drug to date, a risk stratification algorithm is available to guide clinical decision-making regarding prevention of PML [9, 10, 36]. Established risk factors for PML development in natalizumab use are the presence of anti-JCV antibodies, treatment duration, and prior immunosuppressant use. Prolonged lymphocytopenia of CD4+T cells but also CD8+T cells are known risk factors as well. In the cases from the literature, as well as in our own case, lymphocyte abnormalities were unknown or poorly described. Prior biological use was described in only nine cases. There was limited information available on differential diagnoses. These factors contribute to the difficulties of creating a risk stratification algorithm in patients using biologicals other than natalizumab.

Limitations of the case report described in this article include limited information on lymphocyte subsets and follow-up of blood counts pre-diagnosis. However, the case and data from the literature and laboratory underscore a significant gap in awareness and data on PML in nontraditional populations, stressing the importance of further research and data collection in these at-risk groups.

In conclusion, the risk of developing PML in RA patients using biological and/or targeted synthetic therapies, particularly rituximab and TNF-alpha inhibitors, highlights the need for increased awareness, monitoring, and timely diagnosis of suspected cases. Delayed diagnosis can lead to poor outcomes and higher mortality rates. However, the rarity of the condition in this population and the subsequent insufficient data collection has made it difficult to identify strategies to minimize risks. Further research with development of risk stratification algorithms is necessary to guide clinical decision-making and to inform patients about potential risks before starting biological therapy.

Abbreviations

AIDS	Acquired immune deficiency syndrome
COPD	Chronic obstructive pulmonary disease
csDMARD	Conventional synthetic disease-modifying antirheumatic drug
CSF	Cerebrospinal fluid
CT	Computed tomography
CYC	Cyclosporine
HAART	Highly active anti-retroviral therapy
HCQ	Hydroxychloroquine
HIV	Human immunodeficiency virus
JCV	John Cunningham virus
MMF	Mycophenolate mofetil
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MTX	Methotrexate
PCR	Polymerase chain reaction
PML	Progressive multifocal leukoencephalopathy
RA	Rheumatoid arthritis
SLE	Systemic lupus erythematosus
TIA	Transient ischemic attack
TNF	Tumor necrosis factor

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Author contributions
BB—conception and design, case report, data acquisition, data analysis, and writing of manuscript. GR—case report, writing of manuscript, and critical revision of manuscript. EvP—conception and design and critical revision of

manuscript. EdV—conception and design and critical revision of manuscript. JLM—conception and design and critical revision of manuscript.

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Availability of data and materials
All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Declarations

Ethics approval and consent to participate
As this case report was a retrospective study, ethics approval or consent to participate were not applicable.

Consent for publication
Written informed consent was obtained from the patient's next-of-kin for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare that they have no competing interests.

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