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Progressive multifocal leukoencephalopathy associated with infliximab

[1]L Sammut, [2]D Wallis, [2]C Holroyd
[1]Rheumatology Registrar, [2]Rheumatology Consultant, Rheumatology Department, University Hospital Southampton NHS Foundation Trust, Southampton, UK

ABSTRACT A 69-year-old female with seropositive rheumatoid arthritis presented with progressive cognitive decline following treatment with infliximab and methotrexate. Cranial MRI showed non-enhancing white matter signal abnormality consistent with demyelination was seen in the antero-inferior left frontal lobe extending into the frontal opercular white matter and into the left temporal lobe white matter. Similar appearances were seen in the inferomedial right frontal lobe. Brain biopsy showed histological changes consistent with progressive multifocal leukoencephalopathy. The cerebrospinal fluid polymerase chain reaction was negative but brain tissue polymerase chain reaction was positive for JC virus. This case highlights the association of infliximab with progressive multifocal leukoencephalopathy in a patient with known seropositive rheumatoid arthritis.

***Correspondence to** L Sammut*
Rheumatology Department
University Hospital Southampton
NHS Foundation Trust
Tremona Road
Southampton SO16 6YD
UK

***e-mail** lukesammut@doctors.org.uk*

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INTRODUCTION

Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disorder of the central nervous system caused by the reactivation of the latent human papovavirus JC. The kidneys, bone marrow and B lymphocytes may serve as sites for latency of the archetype variant of the virus, but the mechanism by which the pathogenic variant of the virus arises is unclear. Immunosuppression may play a role in leading to changes in the JC virus regulatory region, producing the tandem repeat variant of the virus that leads to PML.[1]

Infliximab is an anti-tumour necrosis factor (TNF) licensed for the treatment of active rheumatoid arthritis where the response to disease-modifying anti-rheumatic drugs, including methotrexate, has been inadequate, and for patients with severe, active and progressive disease not previously treated with disease-modifying anti-rheumatic drugs. The drug is a chimeric monoclonal IgG_1 antibody that binds both soluble and cell bound forms of TNF-α, which is a critical mediator of joint inflammation.[2] We describe a patient with rheumatoid arthritis treated with infliximab and methotrexate who was diagnosed with biopsy proven PML.

CASE REPORT

A 69-year-old female with long-standing seropositive rheumatoid arthritis was admitted to University Hospital Southampton with a two-month history of progressive cognitive decline. She had word-finding difficulties, autobiographical retrograde memory loss and behavioural change. Subsequently she developed anterograde episodic amnesia. She became somnolent, apathetic and had lack of insight. There was no motor weakness on examination.

At the time of onset of symptoms she had been prescribed infliximab (3 mg/kg) every two months, for five years. She had been taking methotrexate 20 mg weekly since the onset of rheumatoid arthritis eight years earlier. Prior to commencing infliximab she received courses of leflunomide, etanercept and adalimumab over a two-year period. HIV, toxoplasma and *Lyme borreliosis* serology were negative. CT brain showed low density involving the white matter and, to a lesser extent, cortex of the inferior left frontal lobe. There was also a similar low density in the inferior left temporal lobe and right temporal lobe. A subsequent MRI confirmed signal abnormality in the same regions (Figure 1). Electroencephalography showed abnormal slowing of the left frontotemporal region.

A lumbar puncture was performed which showed 38 polymorphs, a protein level of 0.7 g/l and glucose of 3.6 mmol/L. Cerebrospinal fluid (CSF) was negative for acid fast bacilli and cultures for *Mycobacterium tuberculosis* and fungi were negative. Cytology was normal and viral polymerase chain reaction (PCR) including JC virus PCR was negative. Due to the inability to reach a firm diagnosis, she had a brain biopsy which confirmed features consistent with PML; brain tissue JC virus PCR was positive.

Following hospitalisation, the patient was discharged to a nursing home due to persistent cognitive deficits and the inability to independently self-care. MRI of the brain performed a year after this admission showed progression of PML with a marked increase in extent of white matter signal abnormality, which involved the white matter of both cerebral hemispheres.

DISCUSSION

PML is a demyelinating disease of the central nervous system that occurs as a consequence of the destructive infection of JC virus of oligodendrocytes. The viral infection in oligodendrocytes is lytic, leading to myelin sheath breakdown in the cerebral subcortex.[1]

The clinical presentation is typically an insidious onset of focal or multifocal symptoms. These are largely related to white matter involvement that can include behavioural changes, speech deficits, motor deficits, gait disturbance, seizures, and visual disturbance. Although the presentation may be unifocal, MRI may demonstrate multifocal pathology.[3] A diagnosis of PML is classically made based on the results of CSF PCR, radiologic features and brain biopsy.[4] The specificity and sensitivity for detection of JC virus DNA by PCR in the CSF is 92–99% and 74–93%, respectively, but false negatives do occur. Possible explanations for false-negative CSF results include variations in the target sequence of the JC virus genome, low viral DNA loads in the CSF in the early stages of the disease, or utilisation of different detection thresholds. Other potential explanations for the false-negative result include loss of DNA during preparation of a low volume specimen.[5]

Prior to treatment with infliximab and methotrexate, the patient's treatment included etanercept, adalimumab and leflunomide, all of which were discontinued at least five years prior to her admission. Although she had received multiple immunosuppressive agents, infliximab had been administered for a significantly longer duration than the other immunosuppressants and she experienced symptoms while on infliximab and methotrexate. Methotrexate-associated leukoencephalopathy has also been described previously, mostly in children receiving intrathecal and intravenous methotrexate.[6] The MRI findings in this case were distinct from the majority of cases of oral methotrexate-associated leukoencephalopathy.

The precise explanation for JC virus reactivation and progression to PML in patients on infliximab is not clear. Since TNF-α plays a critical role in recruiting and activating macrophages, NK cells, T cells, and antigen presenting cells, depletion of TNF by treatment with TNF-α blockade may facilitate reactivation of JC virus infection and progression to PML.[7] This remains an area of active investigation.

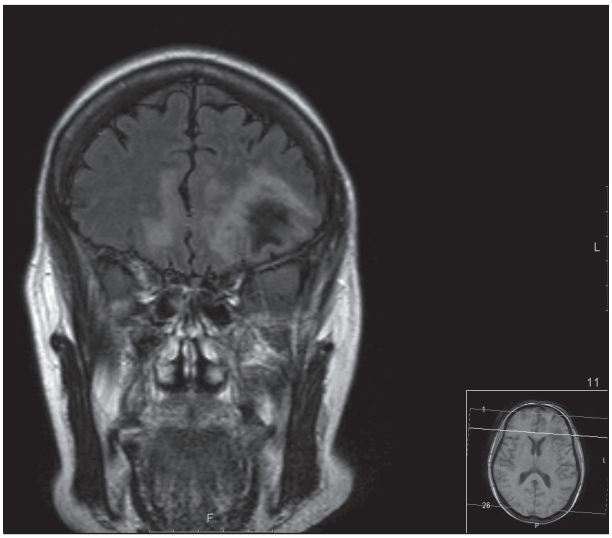

FIGURE 1 T2 FLAIR coronal MRI, showing typical appearances for PML

Data on the true incidence of viral infections after infliximab therapy are poor. Koherty et al. reported four cases of PML associated with infliximab; however this was confounded by the use of other immunosuppressive therapies and these cases were not necessarily confirmed PML.[8] Post marketing data of infliximab showed 27 clinical reports of patients with neurological symptoms associated with demyelinating lesions on MRI.[9] Of more concern is that cases of demyelination are occurring more frequently compared to the same population not using TNF inhibitors, leading to speculation that these 'demyelinating events' were in fact undiagnosed PML.

A case of PML associated with infliximab was reported by Kumar.[10] The patient initially presented with a two-week history of vertigo when leaning forward. This patient was receiving a regimen of methotrexate, infliximab and 7.5 mg prednisolone. Two years following the presentation, this case showed similar symptoms of confusion, memory loss and coordination difficulties. MRI appearances were similar to this case report with high signal change in the frontal lobes. Ray et al. described a patient who developed PML following two years of adalimumab, with MRI lesions predominantly in the cerebellum.[11] Our case and the two cases above,[10,11] had treatment with TNF inhibitors for two years or more, suggesting that a cumulative exposure to these drugs might be an important risk factor for PML.

Although attribution of blame to a single agent is challenging, we believe it is likely that infliximab was the main attributing factor for reactivation of the JC virus. This stems from the evolution of symptoms following treatment with infliximab (rather than the previous discontinued immunosuppressants) and MRI findings similar to a previous report of PML associated with infliximab.[9]

LEARNING POINTS

- This case report highlights the need for physicians to consider PML in patients who have been treated with infliximab and subsequently develop neurological symptoms.
- Although JC virus infection is very rare and may not be associated only with TNF-α blockers, physicians should maintain a very high level of suspicion for any immunosuppressed patient with new neurological symptoms, such as disorientation, ataxia, speech disturbance or visual loss.
- If the CSF PCR result for JC virus is repeatedly negative, then a brain biopsy should be considered in the context of progressive neurological symptoms in patients receiving immunosuppressants.

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