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Listeriosis Complicating Infliximab Treatment in Crohn's Disease

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Abstract

Listeria monocytogenes, a gram-positive rod, infects the central nervous system in neonates, pregnant woman and those immunosuppressed by naturally occurring illnesses and by therapeutic agents, including agents such as infliximab. We report here the first published case of Listeriosis complicating Infliximab therapy in Crohn's disease in Australia.

Keywords

Listeria, Brain abscess, Infliximab, Crohn's disease

Case Report

A 45-year-old Caucasian woman presented to the emergency department with a two-day history of increasing right lower limb weakness. Her sandals would slip off her right foot due to toe weakness and at times her foot would drag. There were no associated pain, sensory changes or sphincter-related symptoms. Two days earlier she had experienced chills, rigors, myalgia and mild headache, but no respiratory or gastrointestinal symptoms.

She had a 6-year history of small bowel Crohn's disease, which had been poorly controlled despite treatment with Methotrexate (20 mg per week with folic acid supplementation), Prednisone (50 mg daily, then weaned to 10 mg daily) and Mesalazine (2 g twice daily). Azathioprine had not been tolerated. However, she had excellent clinical response to Infliximab (5 mg/kg) infused on two occasions, most recently a month prior to the current presentation.

On examination, she was comfortable and afebrile. The only consistent abnormality was marked weakness of flexion and extension of all the toes on her right foot. Power at the right hip, knee and ankle varied from near normal (with encouragement) to moderately weak in the absence of pain. Sensation was unimpaired. The plantar responses were flexor and the tendon jerks were present and symmetrical in all four limbs. Examination of the right arm, left limbs and cranial nerves was unremarkable. At no stage was there headache, meningism or altered sensorium.

Initial blood work showed normal total white cell count (4.32 $\times$ 10^9/L) but a lymphopenia (0.6 $\times$ 10^9/L). Electrolytes and liver

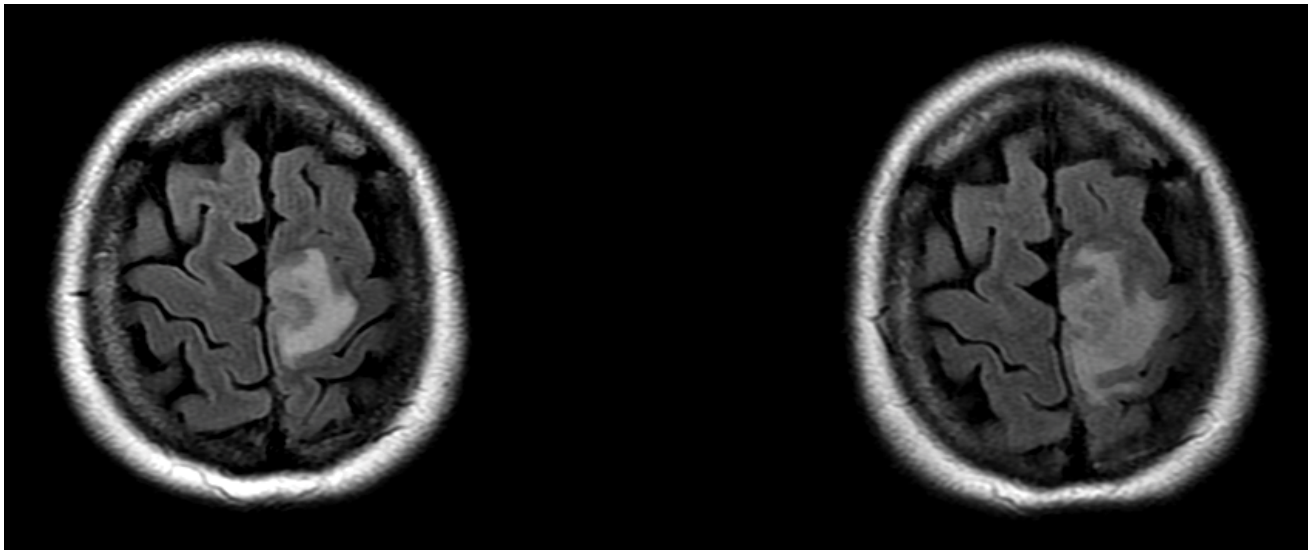

Figure 1: MRI brain at similar level on day 2 (left) and 9 (right) post admission. Early abscess/cerebritis of the left medial frontal lobe is apparent.

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function tests were normal. The admission Computed Tomography (CT) brain (without contrast) was reported to be normal.

She was admitted for investigation, including Magnetic Resonance Imaging (MRI) to exclude Infliximab-induced myelopathy and neurophysiologic studies to exclude focal neuropathy but her condition deteriorated significantly overnight. Power in all right lower limb muscles from hip to toes was reduced to Medical Research Council (MRC) grade 3 (easily overcome). Tendon jerks remained symmetrical initially but there was unsustained (initially) clonus at the right ankle, on which side the plantar response was extensor. Sensation remained normal.

MRI of the entire spine (to exclude infliximab-induced demyelination) was normal. Repeat CT brain with contrast excluded sinus thrombosis but showed subtle low attenuation in the white matter at the vertex of the left frontoparietal junction without definite enhancement; in retrospect, this was discernible on the admission CT. Expedited MRI brain (Figure 1) confirmed a left frontal cortex abnormality consistent with a cerebral abscess, in addition to further regions of early abscess formation in the left frontal and left temporal lobes. Lumbar puncture was unremarkable (cells, protein, glucose, microscopy and culture). Ceftriaxone 2 g twice daily, and Metronidazole 500 mg twice daily were commenced intravenously after blood cultures were taken from the afebrile patient. The regimen was modified to Ampicillin 8 g daily and Gentamicin 1mg/kg three times daily intravenously after *Listeria monocytogenes* was cultured from the blood. Methotrexate and Infliximab were ceased but Prednisolone 10mg daily was continued. Gentamicin was administered for 3 weeks, followed by Benzylpenicillin by Baxter pump for 2 months followed by Sulfamethoxazole/ Trimethoprim for 4 months.

Neurologic function and MRI imaging began to improve about three weeks after commencement of antibiotics. Lower limb function had recovered fully by 5 months post presentation, and the Crohn's disease remained in remission on Mesalazine 2 g twice daily and Prednisone 7.5 mg daily. The patient has been advised to avoid unpasteurised dairy products.

Discussion

Listeria monocytogenes, a Gram-positive rod, infects the central nervous system in neonates, pregnant woman and those immunosuppressed by naturally occurring illnesses (e.g. diabetes, alcoholism) and by therapeutic agents, including agents such as Infliximab. However, about a third of patients infected by *Listeria* are immune-competent [1].

Typically central nervous system Listerosis manifests as meningitis or meningo-encephalitis, which was not the case in our patient. Cerebritis and abscess formation occur in about 1% of patients, predominantly in men and carry a mortality three times higher than other brain abscesses [2].

In our patient, Infliximab, a TNF-α blocker, was very effective in remediating her inflammatory bowel disease. Such agents have revolutionised the management of Crohn's disease, exerting their effect by binding and clearing soluble TNF-α, neutralizing its pro-inflammatory actions, as well as binding to cell-bound TNF-α on macrophages and T-cells, interfering with direct cell-to-cell interactions [3-5].

However, Infliximab and similar agents impair the crucial role of TNF in host defences against intracellular pathogens including *Listeria, Histoplasma, Salmonella and Mycobacterium* [4]. The US Food and Drug Administration has documented 38 cases of serious infection due to *Listeria* in patients on Infliximab. Most were being treated for rheumatoid arthritis or Crohn's disease and most were on an additional immunosuppressant [6,7]. In two thirds of cases, *Listeria* infection was evident within 3 infusions [6], as was the case in our patient.

Other neurological complication of Infliximab include demyelination of the central or peripheral nervous systems, hence the initial MRI of the spinal cord in our patient. Optic neuritis is also described.

It is unclear whether *Listeria* infection in immuno-compromised hosts originates from contaminated foodstuffs or from chronic faecal carriage [8]. The occurrence of infection shortly after the initiation of therapy with TNF-α blocker favours reactivation of latent infection [9], but vulnerable patients should avoid unpasteurised dairy products and should reheat processed meats [8]. The extent to which other immuno-modulating drugs influence susceptibility to serious infections in patients on Infliximab is unclear; although it is likely that concomitant use of these agents may increase the risk significantly [8, 10].

To this date, this is the first reported case of *Listeria* abscess induced by Infliximab infusion in Australia. This case highlights the need for physicians to consider *Listeria* infection in patients taking TNF-α inhibitors, alone or in combination with other immunosuppressants, presenting with neurological illness even when the clinical presentation is atypical for this opportunistic pathogen. To this end, the US FDA includes *Listeria* in a boxed warning for the entire class of TNF-α blockers.

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