Case report

Multiple sclerosis in the context of TNF blockade and inflammatory bowel disease

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The case

In August 1999, a 26-year-old Caucasian woman presented with abdominal pain, diarrhoea and weight loss. Active small bowel Crohn’s disease (CD) was diagnosed on barium follow-through and confirmed histologically following ileal resection in October 1999. Subsequent radiological and endoscopic investigations demonstrated extensive small bowel and foregut involvement with stricturing disease. Despite treatment with 6-mercaptopurine (6-MP) (1.25 mg/kg/day) and corticosteroids, control of disease activity was suboptimal and four further laparotomies were required. Or stricturoplasties and adhesiolysis. Between January and July 2004, she had received four infliximab (Remicade\textsuperscript{\textregistered}, Schering-Plough) (5 mg/kg) infusions with limited efficacy. In June 2007 the humanized anti-tumour necrosis factor (TNF) agent, adalimumab (Humira\textsuperscript{\textregistered}, Abbott Ltd.), was commenced (80 mg loading dose, then 40 mg every second week) with good clinical effect.

In October 2007, she presented with ‘pins and needles’ affecting the fingertips of her left hand and the right side of her face. These symptoms evolved over 2 weeks to include parasthesias affecting her left arm and intermittent diplopia. Her left hand became clumsy and her left leg weak. In addition to adalimumab she was also treated with mercaptopurine, ketamine, gabapentin, esomeprazole, folic acid and loperamide. Her mother suffered from rheumatoid arthritis.

Clinical examination revealed bilateral internuclear ophthalmoplegia with associated horizontal nystagmus. There was reduced sensation to light touch and pin prick in the left upper and lower limbs. There was mild pyramidal weakness on the left arm and leg with finger–nose ataxia, predominantly right-sided. Reflexes were brisk throughout and there was an upgoing left plantar response. She was afebrile and demonstrated no signs of sepsis.

Haematological and biochemical parameters including full blood count, renal and thyroid function, vitamin B12, folate and C reactive protein were normal. Rheumatoid factor, anti-nuclear and anti-neutrophil cytoplasmic antibodies were negative. MRI scanning of the central nervous system (CNS) demonstrated a number of white matter lesions with high signal seen in the pons, medulla, cerebellar peduncles, periaqueductal region, left temporal lobe and periventricular white matter (Figure 1a and b). Serial MRI scans showed the development of new lesions in the left parietal white matter (Figure 2).

Cerebrospinal fluid (CSF) analysis showed 10 white blood cells (all lymphocytes), mildly elevated protein at 0.70 g/l (normal range 0.14–0.45 g/l) and CSF glucose 3.1 mmol/l (normal range 2.3–4.5, with normal serum glucose). CSF and blood cultures were negative as was CSF viral PCR including JC polyomavirus PCR. IgG oligoclonal bands were detected in the CSF with no corresponding serum bands.
Differential diagnosis

The development of subacute brainstem symptoms in an immunosuppressed patient with inflammatory bowel disease presents a broad differential diagnosis. A priority is to exclude an infectious cause such as listeria meningitis or progressive multifocal leucoencephalopathy that can both present with brainstem manifestations associated with white matter abnormalities. However, the relatively quiescent CSF and negative JC virus PCR make this less likely. Nutrition-related neurological complications such as vitamin B12 deficiency and central pontine myelinolysis are also seen in patients with Crohn’s disease.

However, the clinical picture here is best explained by an episode of inflammatory demyelination. This is further confirmed by the subsequent clinical course with the evolution of MRI changes in a manner consistent with a diagnosis of multiple sclerosis. The presenting brainstem event was unusually severe and the patient has been left with a significant residual neurological deficit. There have been no subsequent relapses, although new MRI lesions have appeared over a 4-year period. Adalimumab was discontinued and she received pulsed methylprednisolone but minimal neurological improvement was observed within 4 weeks of therapy.

Additional treatment with plasmapheresis was undertaken after repeat MRI imaging at 6 weeks demonstrated a new lesion (Figure 2). Her neurological disability improved initially with this treatment and she continued to be followed up with yearly brain MRI that showed mild progression of her brainstem lesions, and by March 2010 showed new demyelinating plaques within periventricular regions and parietal lobes. Clinically she has

Figure 1. Index MRI scan (A) FLAIR transverse image shows three periventricular white matter hyperintensities, and one subcortical hyperintensity in the frontal lobe (arrows). Multiple additional similar lesions were seen scattered throughout the brainstem and cerebral white matter (B) Sagittal MRI view demonstrating a posterior pontine lesion.

Figure 2. Repeat MRI scan at 6 weeks. T2-weighted image shows a new lesion (arrow) in the right insular sub-cortical white matter.

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suffered mild progression of her disease but with no discrete relapses.

With respect to Crohn’s disease, maintenance therapy with 6-MP was discontinued in 2009, largely due to her concerns regarding long-term safety. Unfortunately, her disease recurred after cessation of therapy, with her the development of an inflammatory duodenal (D1/D2) stricture. At the time of last review (April 2011), she is on parenteral nutrition and is being considered for gastric bypass surgery.

Case discussion

The development of multiple sclerosis in this scenario raises a number of important questions of disease mechanism but also pragmatic questions of patient management. These questions are:

1. Does treatment with TNF-\(\alpha\) blockade cause or contribute to the development of multiple sclerosis?
2. Are the current pharmacovigilance measures in place for biologic agents in diseases such as Crohn’s disease adequate to detect secondary autoimmunity caused by drugs?
3. What treatment options are available for the treatment of both Crohn’s disease and multiple sclerosis?

Data from animal models suggest that TNF and the TNF receptor systems play a pivotal role in the pathogenesis of Multiple sclerosis (MS). The published data have been comprehensively reviewed by Magnano et al.\(^1\) and are summarized below. The development of experimental autoimmune encephalitis, an established animal model for human MS, is inhibited by both polyclonal and monoclonal anti-TNF-\(\alpha\) antibody preparations. Similarly, the severe, progressive demyelinating disease that develops in transgenic mice selectively over-expressing TNF-\(\alpha\) in the CNS, can be reversed with the administration of a monoclonal anti-TNF antibody. Conversely, TNF-\(\alpha\) homozygous knockout mice have been demonstrated to develop extensive CNS demyelination; treatment with recombinant TNF-\(\alpha\) reduces disease severity. There are two TNF-\(\alpha\) receptors; TNFR1 and TNFR2. Murine experiments have concluded that TNF-\(\alpha\) signalling mediated via the TNFR2 pathway promotes CNS progenitor cell proliferation, which are later required for remyelination. Overall, these pre-clinical studies suggest that although TNF-\(\alpha\) accelerates the process of acute demyelination, its presence in the CNS is required for remyelination and repair processes.\(^1\)

In clinical studies, a controlled trial of anti-TNF therapy (lenecercept) in 168 patients with MS demonstrated a significantly increased risk of disease exacerbation, although attack severity and duration were unaffected.\(^2\) Despite these clinical findings there was no significant increase in the number of new active lesions demonstrated on MRI scanning. In two patients with rapidly progressive MS treated with infliximab, a transient increase in the number of MRI lesions was observed but there was no significant clinical neurological deterioration.\(^3\)

Anti-TNF therapy is effective and used in a number of inflammatory diseases, most commonly Crohn’s disease and rheumatoid arthritis. An overview of TNF inhibitors in common usage is outlined in Table 1. Demyelination following anti-TNF therapy has been reported in inflammatory bowel disease (IBD) and arthropathies;\(^4\) the majority of individuals have an improvement of their neurological symptoms after discontinuation of anti-TNF treatment, often with the addition of corticosteroid therapy.\(^4\) In adalimumab treated CD patients in placebo-controlled trials and open-label extension studies worldwide, the incidence of demyelination/ optic neuritis is reported as two events per 1000 patient-years.\(^5\) Cases are reported in the index studies of infliximab in ulcerative colitis (UC) and CD.\(^6,7\) In the UK, the incidence of MS is 7.2 per 100 000 person-years [95% confidence intervals (CI) 6.5–7.8] in women and 3.1 per 100 000 person-years (95% CI 2.6–3.5) in men.\(^8\) It is recognized that there is an increased incidence of MS, demyelination and optic neuritis in patients with IBD [for CD, incidence rate ratio (IRR) 2.12, 95% CI 0.94–4.50; for UC, IRR 2.63, 95% CI 1.29–5.15].\(^9\) However, data are conflicting with regard to the incidence of autoimmune disorders in patients with MS and their families. One multi-centre case-controlled study failed to demonstrate any increased incidence of autoimmune diseases (including CD),\(^10\) yet other observational studies have shown an increased incidence in conditions

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<th>Table 1</th>
<th>TNF-(\alpha) inhibitors in common usage</th>
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<td>Inhibitor</td>
<td>Trade Name and Manufacturer</td>
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<tr>
<td>Infliximab</td>
<td>Remicade, Schering-Plough</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Humira, Abbott</td>
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<td>Enanercept</td>
<td>Enbrel, Amgen, Wyeth</td>
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such as Rheumatoid arthritis, psoriasis and goitre. 11,12

In the UK, 36 cases of CNS demyelination and 1040 other neurological events complicating anti-TNF therapy had been reported to the Medicines and Healthcare products Regulatory Agency (MHRA) by November 2010. In Edinburgh, this is the most severe of three definite neurological events among 202 IBD patients treated with anti-TNF agents (620 patient-years) and the second case of demyelination we know of in Scotland, a well-established high incidence area. 13,14 This is the first case report of a patient who received two different anti-TNF agents and subsequently developed a demyelinating illness. It is not clear if, first, she would have developed a demyelinating neurological illness irrespective of anti-TNF therapy; secondly, if its earlier onset was precipitated by anti-TNF therapy and finally, if the effect of two sequential anti-TNF agents compounded her risk. Although she received four infusions of infliximab in 2004 without complication, there is a clear temporal relationship in the development of neurological symptoms following the use of adalimumab, suggesting that adalimumab was the precipitating or causative agent.

There is an important question as to whether current pharmacovigilance measures are adequate to detect the development of drug-induced autoimmunity in the treatment of conditions that are associated with a higher than normal incidence of autoimmune disease. This question affects all specialties including neurology and gastroenterology where novel biologic agents are being used and licenced based on short-term efficacy data but limited longer-term safety data. Drug trials are probably not adequately powered to address this issue unless, for example in the case of alemtuzumab treatment of multiple sclerosis, secondary autoimmune events are common. 15 The observational study design that best detects these events is a biologics registry-based model where adverse events in the biologic-treated population is compared to a patient cohort with the same autoimmune disease receiving standard or no therapy. Neurological and gastroenterological communities in the UK are currently establishing such registers.

The development of two concomitant autoimmune disorders raises the question of immunotherapies that might be efficacious in both Crohn’s disease and multiple sclerosis. Natalizumab, azathioprine and alemtuzumab have all been used with differing degrees of success for the treatment of both multiple sclerosis and Crohn’s Disease. 7,15 However, efficacy of these treatments has only been demonstrated in relapsing forms of the disease, suggesting they may be of limited benefit to this patient.

Anti-TNF therapy is contraindicated in patients with a history of demyelination, and used with caution in at-risk populations, such as those with a strong family history. It is important to note that inflammatory CNS demyelination has been reported in the context of TNF-blockade achieved by both monoclonal antibodies and soluble fusion proteins (such as etanercept), suggesting that this effect is not specific to monoclonal antibodies, rather the biological effects of TNF blockade. 16 This case also highlights the importance of formal counselling of the risks associated with anti-TNF therapy, particularly the recognized but less common serious complications such as demyelination (together with malignancy and lymphoma) before embarking on treatment. It is unclear whether this risk is cumulative, drug- or even population-specific; therefore we advocate the need for formal registration of biological agents across specialities to assess rigorously the safety profile, with respect to these presumed rare complications.

Conflict of interest: J.S. has lectured at, and organized, MSD-sponsored symposia in 2010–11; and is a principal investigator on the PYRAMID registry of long-term safety of adalimumab, supported by Abbott.

References


