CASE REPORT

Guillain-Barré syndrome in association with antitumour necrosis factor therapy: a case of mistaken identity

Kurvi Patwala,¹ Nicholas Crump,² Peter De Cruz^{1,3}¹Department of Gastroenterology, Austin Health, Heidelberg, Australia²Department of Neurology, Austin Health, Heidelberg, Australia³Department of Medicine, The University of Melbourne, Melbourne, Australia**Correspondence to**

Dr Peter De Cruz, ppdecruz@gmail.com

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SUMMARY

Guillain-Barré syndrome (GBS) is an immune-mediated disease characterised by evolving ascending limb weakness, sensory loss and areflexia. Two-thirds of GBS cases are associated with preceding infection. However, GBS has also been described in association with antitumour necrosis factor (TNF) therapies including infliximab and adalimumab for chronic inflammatory disorders such as rheumatoid arthritis, ankylosing spondylitis and inflammatory bowel disease. We present the case of a patient who developed GBS while undergoing treatment with adalimumab in combination with azathioprine for severe fistulising Crohn's disease, and review the literature on neurological adverse events that occur in association with anti-TNF therapy. We also propose an approach to the optimal management of patients who develop debilitating neurological sequelae in the setting of anti-TNF therapy.

BACKGROUND

Tumour necrosis factor (TNF) antagonists including infliximab and adalimumab are widely used in the treatment of conditions such as rheumatoid arthritis (RA), ankylosing spondylitis and inflammatory bowel disease (IBD). They are generally well tolerated; however, common side effects include injection site reactions, intravenous infusion reactions, increased susceptibility to infection, lymphoproliferative disease and rarely worsening of demyelinating disorders.¹

Patients are often counselled about the risk of anti-TNF drugs unmasking or aggravating demyelinating disorders such as multiple sclerosis. However, Guillain-Barré syndrome (GBS) is a less well-recognised but potentially debilitating immune-mediated neurological disorder that has also been described in association with anti-TNF therapy.

Characteristic features of GBS include evolving ascending limb weakness, sensory loss and areflexia. A number of GBS variants exist, the most common being Miller Fisher syndrome; this presents with external ophthalmoparesis, ataxia and areflexia, and is associated with the anti-ganglioside Q1b (anti-GQ1b) antibodies. However, others include bifacial weakness with paraesthesias, pharyngeal-brachial-cervical weakness and paraparetic GBS. The incidence of GBS varies between 1.1 and 1.8/100 000 and is slightly more common in men. Two-thirds of

GBS cases are associated with preceding infection. Up to 30% of patients with GBS can progress to respiratory failure and approximately 5% of GBS cases lead to complications resulting in death.²

This paper discusses a case of a patient who developed GBS while undergoing treatment with adalimumab in combination with azathioprine for severe fistulising Crohn's disease. We review the literature on cases of GBS following the use of infliximab and adalimumab anti-TNF therapies and propose an approach to patient management. GBS should be considered in any patient who develops sensory changes, motor weakness, areflexia and ataxia in the setting of anti-TNF therapy. Patients should cease anti-TNF therapy and be referred promptly to a neurologist.

CASE PRESENTATION

A 37-year-old man with a 20-year history of perianal and luminal Crohn's disease presented with a 6-day history of acute-onset bifacial weakness, mild upper limb weakness and global areflexia 9 months after having started 160 mg of adalimumab subcutaneously at week 0 followed by 80 mg at week 2, 40 mg at week 6 and then 40 mg fortnightly thereafter. Adalimumab was initiated after poor disease control on azathioprine and a previous infusion reaction to infliximab. During this 9-month period, the patient did not experience any adverse effects or similar neurological symptoms. Prior to presentation, no dosage adjustments had been made to the adalimumab and the patient had been well medically.

INVESTIGATIONS

Routine bloods done on admission revealed a normal white cell count, no renal dysfunction and mild inflammation with a C-reactive protein (CRP) of 6. Coagulation studies done prior to a lumbar puncture were normal. A subsequent lumbar puncture revealed a raised protein of 1.97 g/L (<0.45 g/L), a normal glucose and no white cells or erythrocytes. Cerebrospinal fluid (CSF) cultures remained negative at 48 hours and excluded ureaplasma. CSF cytology was normal. Viral antibody testing for cytomegalovirus and Epstein-Barr virus was negative. Testing for syphilis, HIV and tuberculosis utilising QuantiFERON Gold returned as normal. An autoimmune panel was positive for anti-nuclear antibody (ANA) and extractable nuclear antigen

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(ENA) SSA (Ro); however, all other ENA forms were negative. Other blood tests including an ACE level, GM1 and GQ1b antibody were all negative.

A multiplanar multisequence MRI brain and orbits performed on admission with particular attention paid to the posterior fossa and brainstem excluded a mass lesion, focal haemorrhage and meningeal enhancement, thereby ruling out meningitis or encephalitis. There was no evidence of focal demyelination to suggest acute disseminated encephalomyelitis. An MRI spine was not performed.

Initial nerve conduction studies revealed prolonged peroneal F wave without other definitive demyelinating features. Upper limb motor studies were normal as were sensory studies in both the upper and lower limbs. Blink responses were difficult to interpret in the setting of severe facial nerve weakness.

The investigations performed above demonstrated that there was no underlying infection accounting for the patient's symptoms. An elevated CSF protein and normal white cell count represents an albuminocytologic dissociation, suggesting GBS as a cause despite negative GM1 and GQ1b antibodies. The nerve conduction studies performed during this admission were considered non-diagnostic; however, in the clinical context, the patient was deemed to have a picture suggestive of GBS.

TREATMENT

The patient initially received one 2g/kg infusion of intravenous immunoglobulin (IVIG) as an inpatient. He subsequently developed a desquamating rash affecting his palms, scalp and face. Prior to discharge, the patient received a further dose of adalimumab as per his ongoing regimen.

OUTCOME AND FOLLOW-UP

After ongoing symptoms with minimal improvement post discharge, the patient was commenced on fourweekly IVIG infusions. The severity of the patient's neurological impairment culminated in an incident during which he was sprayed with capsaicin spray by the police who mistakenly believed that he was under the influence of methamphetamines due to his ataxic gait and bifacial paresis. After ongoing fourweekly IVIG, the patient's upper limb weakness resolved, with return of strength to baseline. His reflexes returned to varying degrees; however, his bifacial weakness persisted, worse on the right. Adalimumab was considered to be the cause of the patient's GBS and was ceased as a result. As his symptoms gradually resolved, IVIG therapy was weaned to sixweekly, then eightweekly infusions. At present, the patient has ongoing bifacial weakness and therefore receives ongoing eightweekly infusions. A combination of azathioprine and oral steroids was trialled to control the patient's Crohn's disease to minimal effect. The patient was subsequently started on induction and maintenance vedolizumab, with which he achieved clinical and endoscopic remission.

DISCUSSION

GBS is the most common acute paralytic neuropathy worldwide characterised by evolving ascending limb weakness, sensory loss and areflexia. GBS is generally preceded by an infection or other immune stimulation resulting in an autoimmune response targeting the peripheral nervous system.³ *Campylobacter jejuni* is the most common bacterial agent implicated in the pathogenesis of GBS; however, a wide range of bacterial and viral infections have been associated with the disease.⁴

The English literature to date has described 19 cases of GBS (including ours) following the use of infliximab or adalimumab

(table 1). It is difficult to assess whether anti-TNF therapy causes GBS or whether it is merely associated with it. A review of neurological complications following anti-TNF therapy suggests that the incidence of demyelinating disease among patients on anti-TNF medications is comparable with those in the community, suggesting a lack of causation.⁵ However, the presence of a temporal relationship as demonstrated in table 1, ranging from weeks to 1 year and discontinuation effect resulting in improvement of symptoms on cessation of therapy in 17 of 19 cases (89.5%), may suggest causation. Of the cases described none explored a rechallenge or re-exposure. In 2 of 19 patients (15.8%), it is unclear whether anti-TNF therapy was continued. One patient had no resolution or treatment of their symptoms and one had complete resolution with a combination of IVIG and intravenous steroids.

TNF is a key cytokine involved in the inflammatory process of diseases such as RA and IBD. It results in damage to cartilage, bone and bowel mucosa, and inhibition of TNF through the use of infliximab and adalimumab has resulted in significant clinical improvements for patients suffering from RA and IBD.¹ TNF also plays a role in the demyelination process of multiple sclerosis (MS), where the cytokine levels are raised in the CSF.⁶ However, the administration of TNF inhibitors often leads to worsening or unmasking of MS.⁶ A potential mechanism for this phenomenon may be explained by systemic TNF antagonists resulting in decreased apoptosis of autoreactive T cells, which may enhance autoimmune responses. Furthermore, this increase in autoreactive T cells may not affect treatment of RA and IBD due to increased penetration of TNF inhibitors in joint and bowel tissue compared with the peripheral and central nervous system, as a result of the blood-brain and blood-nerve barriers.⁶

Another hypothesis implicating the role of TNF antagonists is the process of unmasking latent infections or increased susceptibility to infections. Although patients undergo testing for latent infections prior to commencement of therapy, the increased risk of developing a viral or bacterial illness may result in the molecular mimicry associated with GBS.^{3,7} Three out of 19 cases reported (15.8%) had a preceding infective illness, while 1 (5.2%) had been recently started on steroids, resulting in immunosuppression and increased susceptibility to infection.

The current approach to treatment of GBS can be delineated into supportive and immunological care. Given that it is a potentially life-threatening disease, monitoring of respiratory function, management of bladder and bowel dysfunction, prevention of deep vein thrombosis and involvement of allied health teams are crucial.³ Several randomised controlled trials have shown IVIG and plasma exchange to be effective if used as soon as possible prior to irreversible nerve damage.^{8,9} It is not yet known whether IVIG given over 2 days or 5 days is more beneficial. The combination of IVIG and methylprednisolone is not significantly better than IVIG alone.¹⁰ Similarly, combination of plasmapheresis and IVIG is not more effective than either therapy alone.¹¹ Of the cases reported to date, 11 out of 19 (57.9%) received IVIG of varying doses and duration. Three of the 11 cases (27.3%) receiving IVIG reported complete resolution, while the remaining 8 cases (72.7%) reported partial resolution. Only two cases (10.5%) received plasmapheresis, both resulting in partial resolution. Four out of 19 cases (21.1%) received intravenous steroids and 3 cases (15.8%) received oral steroids.

Given the temporal nature of anti-TNF therapy and reports of GBS and its variants, cessation of therapy is considered reasonable. TNF antagonists were ceased in 17 of the 19 cases (89.5%) reported in the literature. It is unclear whether anti-TNF therapy was ceased in two of the cases; however, the clinical presentation

Table 1 Cases of peripheral neuropathies associated with infliximab and adalimumab therapy

Case	Age Gender	Dose	Time to onset	Preceding disease	Formal diagnosis	Sensory changes	Motor changes	Ataxia	Other	Cessation anti-TNF	IVIg	Plasmapheresis	Steroids	Outcome	Further treatment for disease
Infliximab															
Rheumatoid arthritis															
Alshakhee <i>et al</i> ⁴²	49 Male	3 mg/kg monthly	1 year		CIDP	✓	✓	✓	✓	✓	5 days then 6-weekly pulse			Partial resolution	Prednisolone, methotrexate, hydroxychloroquine
Shin <i>et al</i> ⁴³	56 Male	Unknown	17 months		MFS			✓	✓		10 days total		Intravenous	Partial resolution	Unknown
Silburn <i>et al</i> ⁴⁴	46 Female	3 infusions	4 months	URTI	GBS	✓	✓	✓		✓				Complete resolution	Unknown
Hooper <i>et al</i> ⁴⁵	60 Female	8 weekly	3 months		Lewis-Sumner	✓	✓			✓	2 days then 3-weekly pulse			Complete resolution	Cyclophosphamide, azathioprine
	47 Male	8 weekly	7 months		Lewis-Sumner	✓	✓	✓		✓	2 days then weekly pulse			Partial resolution	Azathioprine
Psoriasis															
Foules <i>et al</i> ⁴⁶	49 Male	5 mg/kg induction (week 0/2/6) then 8 weekly	6 months		CIDP	✓	✓	✓	✓	✓	2 days then monthly pulse		Oral	Partial resolution	Dimethyl fumarate, acitretin, ciclosporin
Nause <i>et al</i> ⁴⁷	64 Male	5 mg/kg once	4 months	Rash postinfliximab	CIDP	✓	✓	✓	✓	✓	5 days			Partial resolution	Unknown
Ankylosing spondylitis															
Paulazzi <i>et al</i> ⁴⁸	54 Male	5 mg/kg 8 weekly	9 months		MMNCB		✓			✓				Partial resolution	Unknown
Bouchra <i>et al</i> ⁴⁹	47 Female	5 mg/kg for three doses	6 months		GBS	✓	✓	✓		✓	Once		Intravenous	Complete resolution	Unknown
Richet <i>et al</i> ⁵⁰	47 Male	4 infusions	4 months		CIDP	✓	✓	✓		✓				Partial resolution	Unknown
Inflammatory bowel disease															
Ratnarajan <i>et al</i> ⁵¹	43 Female	2 infusions	9 weeks		MFS				Diplopia					No resolution	Unknown
Adalimumab															
Rheumatoid arthritis															
McGinty <i>et al</i> ⁵²	52 Male	Fortnightly	1 year		DADS neuropathy	✓		✓	✓	✓				Complete resolution	Tocilizumab
Alvarez-Lario <i>et al</i> ⁵³	50 Female	40 mg fortnightly	13 months	Preceding c. jejuni infection	GBS		✓	✓	✓	✓	2 cycles			Partial resolution	Leflunomide, rituximab
Lopez-Mendez <i>et al</i> ⁵⁴	31 Male	40 mg fortnightly	2 weeks	Bacterial meningitis	GBS	✓	✓	✓	✓	✓	Unknown		Intravenous	Complete resolution	Unknown
Wong <i>et al</i> ⁵⁵	44 Female	40 mg fortnightly	2 years	New steroids	GBS	✓	✓	✓		✓	5 days then pulse as required			Partial resolution	Unknown
Kurmann <i>et al</i> ⁵⁶	77 Female	40 mg fortnightly	2 weeks		MFS	✓	✓	✓	✓	✓			Intravenous	Partial resolution	Azathioprine
Psoriasis															
Ahmed <i>et al</i> ⁵⁷	53 Female	40 mg fortnightly	10 months		CIDP	✓	✓	✓	✓	✓	5 days then pulse as required		Oral	Complete resolution	Unknown
Inflammatory bowel disease															
Cesarini <i>et al</i> ⁵⁸	71 Male	4 infusions	1 month		GBS		✓			✓	Unknown	✓		Partial resolution	Budesonide
Patwala <i>et al</i>	37 Male	40 mg fortnightly	9 months		GBS	✓	✓	✓	✓		Once then maintenance 8 weekly			Once then maintenance	Vedolizumab

C, jejuni; Campylobacter jejuni; CIDP, chronic inflammatory demyelinating polyneuropathy; DADS, distal acquired demyelinating symmetric neuropathy; GBS, Guillain-Barre syndrome; MFS, Miller Fisher syndrome; MMNCB, multifocal motor neuropathy with conduction block; TNF, antitumour necrosis factor; URTI, upper respiratory tract infection.

in both instances was mild in severity. Partial resolution of symptoms occurred in all patients among whom the anti-TNF therapy was ceased.

In the case we described, withdrawal of adalimumab to treat the GBS resulted in worsening of IBD symptoms. After failure of traditional therapies such as steroids and azathioprine, the patient was transitioned to the selective adhesion molecule, vedolizumab. To the best of our knowledge, there are currently no studies or case reports to suggest that vedolizumab is associated with adverse neurological adverse events, which may be due to its gut selectivity. However, natalizumab, another selective adhesion molecule that crosses the blood–brain barrier, has been associated with rare but fatal cases of progressive multifocal leukoencephalopathy (PML) associated with John Cunningham (JC) virus. Patients are therefore counselled about the theoretical risk of PML with vedolizumab use. In the case of a patient with refractory IBD with associated demyelination in the setting of anti-TNF use, vedolizumab has become one of the therapies of choice.

GBS has a mortality rate between 3% and 7% and many surviving patients frequently have residual deficits impacting on quality of life.³ Although there was zero mortality in the cases described, 13 cases (68.4%) had only partial resolution resulting in ongoing deficits from the disease. We describe a case of a patient who suffered significant social stigma in association with his condition, which resulted in the police force misinterpreting his demeanour as being drug-affected.

Evidence to date suggests that there is at the very least an association between the use of anti-TNF therapy and the development of GBS. Consequently, in a patient with sensory changes, motor weakness, areflexia, ataxia or other neurological symptoms on TNF antagonists, we recommend considering GBS as a differential diagnosis, consulting a neurologist and ceasing anti-TNF therapy.

Learning points

- ▶ Antitumour necrosis factor (anti-TNF) therapy and Guillain-Barré syndrome (GBS) have been associated with each other in a number of cases.
- ▶ The pathophysiology behind the association is not well understood, however may be secondary to T cell regulation or molecular mimicry.
- ▶ GBS should be considered in patients with sensory changes, motor weakness, areflexia or ataxia in the setting of anti-TNF therapy.
- ▶ Clinical suspicion needs to be particularly high with atypical clinical presentations, such as bifacial weakness.
- ▶ Prompt referral to a neurologist, initiation of intravenous immunoglobulin and cessation of anti-TNF therapy will help prevent debilitating neurological deficits.

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