



Guillain-Barre Syndrome Developing During Infliximab Treatment for Psoriatic Arthritis: A Case Report

Psöriatik Artritli Bir Hastada İnflksimab Tedavisi Sırasında Gelişen Guillain-Barre Sendromu: Olgu Sunumu

Guillain-Barre Syndrome Induced by Infliximab

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Özet

Tümör nekroz faktörü (TNF)- α , immun sisteminin gelişimi, immün yanıtın düzenlenmesi ve T- hücre aracılı dokusal olaylarda birçok açıdan önemli rol oynar. Oto-reaktif T-hücreleri ve makrofajlar tarafından salınan TNF- α ' nın immün demiyelinizan nöropatilerin patogenezinde rol oynayabileceğine dair kanıtlar gözlenmiştir. Demiyelinizan nöropatiler anti TNF- α tedavisinin nadir yan etkilerindendir. Demiyelinizan nöropatilerin konvansiyonel tedavisiyle ve kullanılan ilaçların kesilmesi ile sıklıkla tablo geriler. Bu yazıda anti TNF- α (infilksimab) tedavisi sonrasında demiyelinizan nöropati kliniği gelişen bir hastanın sunulması amaçlanmıştır. Bu olguda Guillan Barre Sendromu Anti TNF tedavisine sekonder olarak gelişmektedir. Anti TNF- α tedavisinin devamının, nöropatinin uzun vadedeki seyrine etkisi net değildir. Tedavinin kesilmesi her zaman nöropati kontrolü için gerekli olmayabilir. Ancak bizim olgumuzda olduğu gibi Anti TNF- α tedavisiyle ilişkili gelişen bir Guillan Barre sendromu tablosunda tedavi sonlandırılabilir.

Anahtar Kelimeler

Psöriatik Artrit; TNF-Alfa Tedavisi; Guillain-Barre Sendromu

Abstract

Tumor necrosis factor (TNF)- α plays an important role in many aspects of immune system development, immune-response regulation, and T-cell-mediated tissue injury. The evidence that TNF- α , released by auto reactive T cells and macrophages, may contribute to the pathogenesis of immune-mediated demyelinating neuropathies is reviewed. Demyelinating neuropathies are rare adverse events of anti-TNF- α therapy. Improvement usually occurs after drug interruption and/or in association with conventional treatments for demyelinating neuropathies. We aimed to report a patient with demyelinating neuropathy occurring after TNF blocker (infiximab) treatment. The development of Guillain-Barre syndrome in this report may have been secondary to anti-TNF- α treatment. The influence of anti-TNF- α treatment continuation on the long-term course of neuropathy is variable, suggesting that anti-TNF- α treatment withdrawal is not always necessary for neuropathy control. But such as the report, anti-TNF- α treatment may be stopped.

Keywords

Psoriatic Arthritis; TNF-Alpha Therapy; Guillain-Barre Syndrome

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Introduction

Tumor necrosis factor- α (TNF- α) is an important immunomodulator, and plays a role in immune system development, immune response regulation and T-cell-mediated tissue injury [1]. Anti-TNF- α therapy has transformed the treatment of inflammatory diseases, including rheumatoid arthritis (RA), psoriatic arthritis, Crohn's disease, and idiopathic juvenile RA [1,2]. Several anti-TNF- α drugs are available: a soluble receptor able to neutralize TNF- α (etanercept) and monoclonal antibodies, which can be either chimeric antibodies of murine origin (infliximab) or humanized antibodies (adalimumab), both of which target circulating and membranous TNF- α . Since the widespread use of these drugs, various side effects have been reported [2,3]. They have been associated with different adverse effects, including local reactions, infections, congestive heart failure, malignancies, and autoimmune and neurological events [2,3]. In contrast to central nervous system (CNS) demyelinating disorders, involvement of the peripheral nervous system (PNS) appears to be rare. Peripheral neuropathies associated with anti-TNF- α treatment include acute or chronic demyelinating neuropathies and vasculitic neuropathies [2,3]. In this article, a case with psoriatic arthritis that developed Guillain-Barre syndrome (GBS) after infliximab treatment is presented.

Case Report

A 31-year-old man with an 18-year history of psoriasis was treated previously with topical steroids, etanercept, methotrexate, and psoralen-UVA. He had had psoriatic arthritis for 5 years and had been suffering from a severe symmetric polyarthritis since 2008. Despite different regimens of sulfasalazine, cyclosporin, methotrexate, and non-steroidal anti-inflammatory drugs (NSAIDs), the joint pain and swelling persisted. There was no family history of psoriasis and no personal or family history of multiple sclerosis (MS). At that time, laboratory data showed erythrocyte sedimentation rate of 55 mm/h (range: 1–20 mm/h), and rheumatoid factor and antinuclear antibodies (ANA) were negative. Other standard laboratory tests were normal. Infliximab monotherapy (5 mg/kg) was started at a standard loading dose (0, 2, 6, 14 weeks). After the second infusion, clinical remission was obtained, but 5 days following the second dose of infliximab, he developed progressive weakness involving both hands and feet and dysphasia. The pareses rapidly progressed, leading to difficulty in walking without assistance. Neurological examination (Medical Research Council score) revealed: bilateral elbow flexion (C5) 3/5, wrist extension (C6) 3/5, elbow extension (C7) 4/5, finger flexion (C8) 3+/5, and finger abduction (T1) 3+/5 at these levels, without sensory loss, and diminished reflexes. In the lower extremities, scores were: left plantar flexor (S1) 2/5, ankle dorsiflexion (L4) 4/5, toe dorsiflexions (L5) 4/5, and knee extension (L4) 3/5, and right plantar flexor (S1) 3/5, ankle dorsiflexor (L4) 4/5, toe dorsiflexor (L5) 4/5, and knee extension (L4) 4/5 at these levels, without sensory loss, and diminished reflexes. There was mild impairment in vibration sensation. Cranial nerve examination was normal, and there was no abnormality in cerebellar tests. The patient denied any bladder or bowel incontinence. After neurology consultation, neurophysiology studies demonstrated an acquired segmental demyelinating polyneuropathy consistent with GBS. In the cerebrospinal fluid

(CSF) examination, there were few cells and protein concentration was high. Brain, cervical and lumbar magnetic resonance imaging (MRI)'s were normal. Standard laboratory tests, including complete blood, erythrocyte sedimentation rate, serum glucose, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea, thyroid hormones, vitamin B12 and folate levels, viral markers (human immunodeficiency virus [HIV], hepatitis B and C), and lyme serology, were normal. ANA, anti-extractable nuclear antigen (ENA) profile, cytoplasmic anti-neutrophil cytoplasmic antibody (cANCA), perinuclear (p)ANCA, anti-double-stranded (ds)DNA, and anti-Gm1 antibodies were negative. Extension was defined in upper and lower extremities in sensory evoked potential (SEP) and visual evoked potential (VEP) latency. Brainstem auditory evoked potential (BAEP) was normal. In view of relative loss of symmetric muscle strength in the upper and lower extremities, tendon reflexes loss, absence of sensory loss, and the typical findings, the patient was diagnosed as GBS developing after infliximab infusion. The patient fulfilled the current international diagnostic criteria for the diagnosis of definite multifocal motor neuropathy with persistent conduction blocks (MMNCB). Daily 35 mg immunoglobulin (Ig) treatment was started intravenously (IVIg). Infliximab was definitively discontinued. After 5 doses of IVIg treatment, the loss in muscle power was halted, yet no clear increase was defined in muscle strength. In addition, no improvement was seen in the patient's cerebellar tests, speech or ambulation. Thus, the patient was prescribed a rehabilitation program for 6 weeks and was ambulated with crutch. A follow-up electromyographic study 3 months later showed normal findings. At the end of the 6-month follow up, the patient remained slightly symptomatic and his arthritis was active.

Discussion

We report herein a patient with GBS developed in association with TNF- α antagonist therapy. Demyelinating neuropathies are rare adverse events of anti-TNF- α therapy. TNF- α antagonist therapy has been associated with the development of both CNS and PNS disorders, mainly of demyelinating type [2-4]. With respect to the PNS, GBS, chronic inflammatory demyelinating polyneuropathy, MMNCB, distal symmetric polyneuropathy, small fibers neuropathy, and vasculitic mononeuropathy multiplex cases have been reported [3,4]. Neurologic events presumably caused by demyelination have been reported to occur with the anti-TNF biologic response modifier infliximab. Subacute autonomic neuropathy, chronic polyneuropathy clinically similar to chronic inflammatory demyelinating polyneuropathy, perineuritis and GBS, optic neuritis, motor weakness, and cognitive dysfunction have been documented [3,4].

The mechanisms by which anti-TNF- α induces demyelinating events remain to be clearly established. Systemic administration of anti-TNF- α may enhance antigen-presenting cell function, increase T-cell receptor signaling, decrease apoptosis of potentially autoreactive T-cells, and induce the production of proinflammatory cytokines including interferon-gamma (IFN- γ) [3,5]. The United States Food and Drug Administration's Adverse Events Reporting System suggests that 15 patients were diagnosed with GBS in temporal association with TNF- α antagonist therapy [4]. GBS comprises a heterogeneous group of conditions

defined by varying clinical, electrophysiological and pathological features [3]. TNF- α probably has a pro-inflammatory function in the pathogenesis of GBS (serum levels correlate with disease activity and severity) [3,5]. TNF- α also has immunoregulatory functions. TNF- α deficiency leads to failed regression of myelin-specific T-cell reactivity and prolonged survival of activated T-cells [3]. When endogenous TNF- α is blocked by repeated injections of a TNF- α antagonist, T-cell-proliferative responses and cytokine production are enhanced. The prolonged administration of TNF- α antagonists is thought to enhance autoimmune responses by altering antigen-presenting cell function, potentiating T-cell receptor signaling and decreasing apoptosis of autoreactive T-cells [3,4]. TNF- α antagonist therapy could promote the development of GBS by augmenting the number of activated peripheral T-cells or by disturbing the intrinsic balance of TNF- α and its receptors in the local PNS compartment [3,5]. These factors, alone or in combination, could induce the clinical expression of GBS in patients who are immunogenetically susceptible [4]. The British Society of Rheumatology guidelines for prescribing TNF- α blockers recommend avoidance of these agents in patients with preexisting demyelinating disease [6]. There was no family history of demyelinating disease in our patient or his relatives. In patients without previous problems, they suggest withdrawal of therapy if demyelination occurs, but do not make a comment on whether it is appropriate to try an alternative anti-TNF- α agent [6].

A number of cases of demyelinating events of the CNS or aggravation of known MS have been reported in patients treated with anti-TNF- α [4-8]. Based on a retrospective study of a database, only 44 patients affected by demyelinating neuropathies have been reported thus far, including 20 cases of GBS, 11 patient with multifocal motor neuropathy and 6 with chronic inflammatory polyradiculopathy [7].

Neuropathy started to worsen 8 hours after the first infusion (sensory mononeuropathy evolved to a sensory mononeuropathy multiplex), although the onset of neuropathy started as late as 2 years from the start of drug infusion and onset of GBS [7,8]. The infusion schedule in patients who developed neuropathy varied from the standard induction regimen (weeks 0, 2, 6 and 14) to an interval of many months (e.g. 4 infusions in 2 years) [3-8]. The total number of infusions before the onset of neuropathy varied from 1 to 12 [7,8]. The total dose administered before the neuropathy developed was not always reported, but varied from 540 to 1400 mg [3-8]. In our case, treatment was started as 5 mg/kg/day as the standard dose, and symptoms were seen at the end of the second dose (on the 20th day of the treatment); the total dose had reached 800 mg.

As a result, medication withdrawal is a prudent first step in the management of patients with suspected drug-induced neuropathy [1]. Intravenous methylprednisolone alone seemed insufficient as a therapy for GBS associated with a TNF- α antagonist. Subsequent or concurrent treatment with intravenous cyclophosphamide or IVIg led to an improvement in the neuropathy over follow-up periods of up to 9 months [1,4]. The clinical outcome of patients varied from complete resolution of neurological deficits (within 3 weeks) to treatment unresponsiveness (follow-up period of up to 9 months) [3,5,7]. In our patient given IVIg treatment, there was no neurological improvement after

5 courses of treatment (total 175 mg Ig); however, the patient was stable clinically. With such limited reporting, no definitive conclusion can be drawn about the safety of TNF- α -blocker re-challenge once patients develop a neuropathy. Conceivably, lower drug doses could treat the underlying inflammatory disease effectively without the risk of affecting the immune system to such an extent as to elicit a neuropathy [3,5,7].

The development of GBS in our patient was secondary to his anti-TNF- α treatment. Although a causal relationship between GBS and TNF- α antagonist therapy cannot be proven, clinicians should monitor patients who are receiving TNF- α antagonist therapy for neurologic signs and symptoms suggestive of demyelinating disease in either the CNS or PNS [3,8]. Patients with a history of MS or MS-like illnesses are not good candidates for TNF- α inhibition [3,8].

Competing interests

The authors declare that they have no competing interests.

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