Case Report
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Polyneuropathy developing after infliximab therapy in a patient with recalcitrant pyoderma gangrenosum

İnfliksimab tedavisi sonrası polinöropati gelişen tedaviye dirençli bir pyoderma gangrenosum olgusu

Ralfi Singer, Cihat Örken*, Şule Güngör, Mehmet Çopur, Utkan Kızıltaç, Kübra Kızıltaç, Emek Kocatürk Göncü, Selma Şengiz Erhan**

İstanbul Okmeydanı Training and Research Hospital, Clinic of Dermatology and Venereology; *Clinic of Neurology; **Department of Pathology, İstanbul, Turkey

Abstract

The use of tumor necrosis factor-alpha (TNF-α) inhibitors has increased tremendously during the recent years. Neurological side effects associated with TNF-α inhibitors are rarely encountered, but these side effects may result in serious clinical problems. Treatment with TNF-α inhibitors is associated with demyelinating syndromes which can affect both the central and peripheral nervous systems. Short-term follow-up indicates relatively good outcomes, sometimes after just treatment discontinuation, although corticosteroids or intravenous immunoglobulin may be necessary to reverse the conditions in some cases. Here, we present a case of motor neuropathy developing after treatment with infliximab in a patient with recalcitrant pyoderma gangrenosum.
Keywords: TNF-α inhibitors, infliximab, polyneuropathy, pyoderma gangrenosum

Öz

Tümör nekroz faktörü-alfa (TNF-α) inhibitörlerinin birçok romatizmal ve otoimmün hastalığın tedavisinde kullanımları son yıllarda artmıştır. TNF-α inhibitörlerine bağlı nörolojik yan etkiler nadir görülmelerine karşın oldukça ciddi komplikasyonlar oluşturabilirler. TNF-α inhibitörleri hem santral hem de periferik sinir sistemine ilişkin demiyelinizan tablolara yol açabilir. Klinik tablo, biyolojik ajan tedavisinin kesilmesi ile düzelebildiği gibi, bazı olgularda sistemik steroid veya intravenöz immünoglobülin tedavisine gereksinim duyulabilir. Burada, standart tedaviye dirençli piyoderma gangrenosum nedeniyle infliksimab tedavisi başlanmasından sonra motor nöropati gelişen bir olgu sunulmaktadır.
Anahtar Kelimeler: TNF-α inhibitörleri, infliksimab, polinöropati, piyoderma gangrenosum

Introduction

Tumor necrosis factor-alpha (TNF-α) inhibitors have been extensively used for the treatment of many rheumatic and inflammatory diseases in the last two decades. Major side effects of these agents are infusion reactions, flu-like symptoms and infections[1,2]. These agents have less frequent side effects on the central nervous system (CNS) and peripheral nervous system (PNS)[3-5].

Pyoderma gangrenosum (PG) is a neutrophilic dermatosis characterized by chronic, destructive, and necrotizing ulcerations, more frequently seen in women between 20 and 50 years of age. The laboratory and histopathologic findings can vary and therefore the diagnosis requires

Address for Correspondence/Yazışma Adresi: Ralfi Singer MD, İstanbul Okmeydanı Training and Research Hospital, Clinic of Dermatology and Venereology, İstanbul, Turkey Phone: +90 212 314 55 55 E-mail: ralfisinger@yahoo.com
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clinicopathologic correlation[6,7]. This neutrophilic dermatosis is associated with systemic diseases such as inflammatory bowel disease, connective tissue diseases, chronic active hepatitis, primary biliary cirrhosis, human immunodeficiency virus (HIV) infection and hematologic and solid organ malignancies in 50-70% of cases[6,8]. There is currently no uniform therapeutic standard worldwide in the form of guidelines; systemic corticosteroids, cyclosporine, azathioprine, mycophenolate mofetil, and dapsone are the mainstay of treatment and intravenous immunoglobulin (IVIG) or anti-TNF agents are used in resistant cases[6,7]. Here, we present a case of polyneuropathy developing after treatment with infliximab in a patient with recalcitrant PG.

Case Report

A 38-year-old female patient presented with a painful ulcer on the right leg in 2013. On physical examination, an ulcer measuring 2x3 cm on the medial side of the right leg was noted. The borders were well-defined, violaceous and the floor was covered with fibrin and some bloody discharge (Figure 1). C-reactive protein level was 15.8 mg/L (range: 0-5 mg/L) and erythrocyte sedimentation rate was 48 mm/hour. Complete blood count, serum biochemistry, peripheral smear, serum protein electrophoresis and immunofixation electrophoresis of 24-hour urine were all normal. Hepatitis serologies and anti-HIV were negative. Anti-nuclear antibody (+); rheumatoid factor and anti dsDNA, anti SSa, anti SSb, perinuclear and cytoplasmic anti-neutrophil cytoplasmic antibodies (pANCA, cANCA), anti Jo-1, cryoglobulin, cryofibrinogen and fecal occult blood were negative. Chest X-ray, abdominal ultrasonography and arterial and venous Doppler ultrasonography were normal. Skin biopsy from the edge of the ulcer showed intense dermal neutrophilic infiltration. The patient refused colonoscopy. We performed two intralesional triamcinolone acetonide injections and tacrolimus 0.1% oinment was started. Since no improvement was noted, we started methyl prednisolone 64 mg/day. The patient received this regimen for one month and we had to add cyclosporine (4 mg/kg) to the treatment regimen due to lack of response to corticosteroids. Methyl prednisolone dosage was gradually tapered and the patient received the steroid and cyclosporine combination for six months without any improvement. Hyperbaric oxygen treatment was administered in another clinic for two months without any response. When the patient applied to our clinic once again, we noted an ulcer measuring 4x6 cm on the right medial malleolus and another ulcer measuring 2x2 cm on the left gluteal region in addition to the first lesion on the right leg. The ulcer on the gluteal region had developed after an intramuscular injection. At this time, treatment with infliximab was planned. The patient was administered infliximab (5 mg/kg) at weeks 0, 2 and 6 in combination with methotrexate 7.5 mg/week. There was partial improvement of the ulcers on the lower extremities and the ulcer on the left gluteal region showed complete healing in a month. Two weeks after receiving the third dose of infliximab, she developed weakness of arms and legs. Neurological examination revealed mild to moderate loss of strength and areflexia in the left arm and lower extremities; there was no sensory loss. Electromyography was compatible with mixed type polyneuropathy which demonstrated predominantly axonal involvement. Infliximab treatment was discontinued, but since no improvement was seen, IVIG was started (400 mg/kg, for 5 days) in our neurology clinic. The neurological symptoms regressed gradually after receiving two cycles of IVIG in the neurology department. Although the ulcer on the left leg healed, a new ulcer appeared on the same site (Figure 2) and two other ulcers developed on the right leg. After this time, she received a total of 12 cycles of IVIG, 2000 mg/day mycophenolate mofetil and local treatment with polymeric membrane wound dressings without any improvement. Currently, the patient is not receiving any therapy and the lesions continue to persist. We have informed consent of the patient.

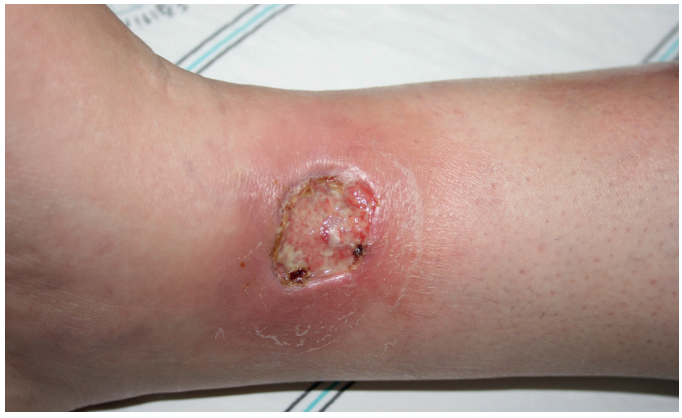

Figure 1. The ulcer with an erythematous border and fibrinous base on the right leg upon presentation

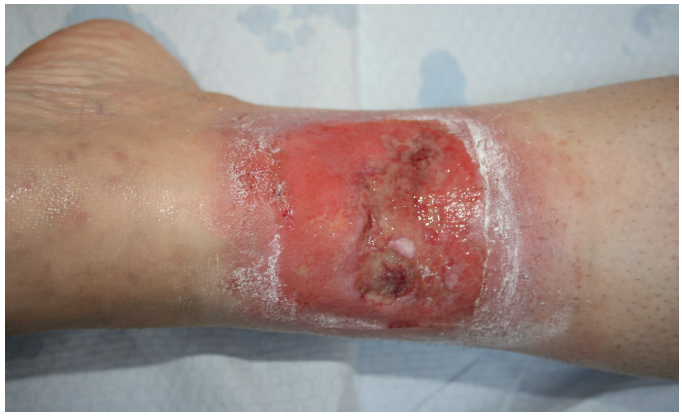

Figure 2. Clinical appearance of the large ulcer developing after regression of neuropathy

Discussion

PG is not only a disease strictly confined to the skin, but rather represents a cutaneous manifestation of a generalized inflammatory reaction[7]. The exact cause of PG is poorly understood, but abnormal neutrophil functioning, genetic variation, and innate immune system dysregulation are all considered to have a part in the pathogenesis[9]. Recent investigations have also reported abnormal cellular immunity with anergy to recall antigens or an imbalance between helper T cells and suppressor T cells[10].

During the last two decades, TNF-α inhibitors have been used in the management of rheumatoid arthritis, ankylosing spondylitis, psoriasis, psoriatic arthritis and inflammatory bowel disease[1]. The extensive use of these agents has resulted in increased frequency of adverse effects. The likelihood of a causal connection between a drug and

an adverse event is evaluated by the Naranjo Adverse Drug Reaction Probability scale[11]. The Naranjo score was 7 in our case. We think that neuropathy which developed in our case was most probably due to infliximab treatment since the clinical picture developed in a short time after treatment, there were not any other alternatives to explain the condition and polyneuropathy showed regression after discontinuation of infliximab and starting IVIG treatment. Additionally, similar adverse effects caused by anti-TNF agents were previously observed.

TNF-α inhibitors may cause adverse neurological effects on both CNS and PNS. CNS autoimmune demyelinating disorders (DD) include development of multiple sclerosis (MS), MS-like disorders, retrobulbar optic neuritis, and transverse myelitis. Peripheral nerve disorders induced by anti-TNF agents include Guillain-Barré and Miller-Fisher syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, multifocal motor neuropathy, distal symmetric polyneuropathy, mononeuritis simplex/multiplex, and axonal sensorimotor polyneuropathies[4,5,12-15].

The prevalence of adverse neurological events induced by TNF-α inhibitors is thought to be between 0.05% and 0.20%[16]. On the other hand, Kaltsonoudis et al.[17] performed a prospective study including 75 patients who were administered anti-TNF agents and they found that 3 patients (4%) developed neurological complications. Neurologic complications related to the CNS are more frequent than those related to PNS[5,8,16,18]. In a literature review carried out by Solomon et al.[18], etanercept therapy was held responsible from the majority (62%) of cases of CNS syndromes and infliximab therapy from the majority (67%) of peripheral nerve syndromes. The smaller number of cases involving therapy with adalimumab may be due to its more recent approval. Neurologic adverse events are not associated with a single anti-TNF blocker; therefore, the administration of another anti-TNF agent after discontinuation is contraindicated[5]. On the other hand, ustekinumab, which binds to p40 subunit of interleukin-12 (IL-12) and IL-23 and secukinumab, an anti-IL-17A antibody, do not induce demyelinating syndromes[19,20]. There have been two reported cases of patients who developed reversible posterior leukoencephalopathy syndrome (RPLS) while receiving ustekinumab[21,22]. RPLS is not a demyelinating disease and is characterized by confusion, headache, visual disturbances, and seizures[21].

The mechanisms by which anti-TNF agents induce DD is not fully understood[13]. It has been demonstrated that TNF Receptor 1 (TNFR1) plays a role in CNS inflammation, apoptosis and demyelination, while TNF Receptor 2 (TNFR 2) acts to limit tissue pathology by suppressing autoreactive CD4+ T cells and plays a role in remyelination[23]. Immune dysregulation caused by TNF-α inhibitors may decrease the apoptosis of autoreactive T cells and induce the production of proinflammatory cytokines by these cells. Anti-TNF agents may interfere with regulatory T cell function, trigger autoantibody production towards myelin, increase the function of antigen presenting cells or cause ischemia of nerve tissue secondary to vasculitis. Inhibition of TNF-α may also prevent the repair of axonal injuries and myelin damage[4,12,13,15,18,24]. Additionally, it has been proposed that TNF-α provides signaling support to peripheral neurons and its sequestration with TNF-α inhibitors interrupts such support[25]. The development of DD in patients receiving anti-TNF treatment can be either attributed to the unmasking of a latent preexisting DD or to the emergence of a new demyelination episode[23].

Most neuropathies improve spontaneously over a period of months by withdrawal of the TNF-α antagonists[12]; but DD may persist in some cases even if the responsible agent is withdrawn. For example, in their study, Seror et al.[3] reported that 22% of patients with CNS involvement developed MS although the anti-TNF agents were discontinued; this suggests that DD might persist despite treatment discontinuation, indicating that TNF-α inhibitors could trigger the demyelinating process which further evolves independently. Systemic corticosteroids, IVIG, cyclophosphamide and plasmapheresis are treatment options in the management of neurologic syndromes associated with TNF-α blockers[14,18].

The possibility of developing central or peripheral adverse events with anti-TNF therapy should be kept in mind and the patients should be followed with regard to neurological symptoms. TNF-α antagonists should be avoided in patients with a history of DD and should be used with caution in those with a first-degree relative with such disease; treatment should be discontinued immediately if neurological symptoms develop[19,23]. DD induced by TNF-α antagonists may rarely persist despite withdrawal of the responsible agent.

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Ethics

Informed Consent: We have informed consent of the patient.
Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: R.S., C.Ö., Ş.G., M.Ç., U.K., K.K., Concept: R.S., C.Ö., Design: R.S., C.Ö., E.K.G., Data Collection or Processing: M.Ç., U.K., K.K., Analysis or Interpretation: R.S., C.Ö., E.K.G., S.Ş.E., Literature Search: M.Ç., U.K., K.K., Writing: R.S., C.Ö.

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