Case Report / Olgu Sunumu

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A Rare Hypersensitivity Reaction with Golimumab: Recurrent Fever After Each Injection

Golimumab İlişkili Nadir Bir Hipersensitivite Reaksiyonu: Her Enjeksiyon Sonrası Tekrarlayan Ateş

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Abstract

Ankylosing spondylitis (AS) is a chronic inflammatory disease treated with non-steroidal anti-inflammatory drugs (NSAIDs) and, in refractory cases, biologic agents such as tumor necrosis factor inhibitors (TNF-Is). While TNF-Is are generally well tolerated, rare hypersensitivity reactions may occur. We present a 31-year-old female diagnosed with AS, previously unresponsive to NSAIDs, who achieved remission with golimumab (50 mg/month) for six years. However, during the coronavirus disease-2019 pandemic, she began experiencing recurrent fever, fatigue, and elevated C-reactive protein levels 2-3 days post-injection. Extensive investigations, including antinuclear antibody, extractable nuclear antigen, antineutrophil cytoplasmic antibodies, and infectious serologies, were unremarkable. The symptoms resolved spontaneously within a week. Given the exclusion of infectious or autoimmune etiologies, a hypersensitivity reaction to golimumab was suspected. Treatment was switched to secukinumab, resulting in symptom resolution without further complications. Hypersensitivity reactions to TNF-Is, particularly fever, are rare but important adverse events. While similar reactions have been reported with infliximab, this is the first documented case associated with golimumab. Clinicians should be aware of this potential side effect to ensure prompt diagnosis and management. This case underscores the importance of vigilant monitoring for atypical adverse events during long-term biologic therapy in AS patients. Further research is needed to elucidate the pathophysiology and risk factors for hypersensitivity to TNF-Is.

Keywords: Ankylosing spondylitis, golimumab, TNF-inhibitors, hypersensitivity, fever

Öz

Ankilozan spondilit (AS), steroid olmayan anti-enflamatuvar ilaçlar (SOAİ) ve dirençli olgularda tümör nekroz faktörü inhibitörleri (TNF-İ) gibi biyolojik ajanlarla tedavi edilen kronik enflamatuvar bir hastalıktır. TNF-İ'ler genellikle iyi tolere edilmekle birlikte, nadir olarak aşırı duyarlılık reaksiyonları görülebilir. Bu makalede, SOAİ'lere yanıt vermeyen ve altı yıl boyunca aylık 50 mg golimumab ile remisyona ulaşan 31 yaşındaki AS tanılı bir kadın hasta sunulmaktadır. Ancak, koronavirüs hastalığı-2019 pandemisi sırasında, enjeksiyondan 2-3 gün sonra tekrarlayan ateş, yorgunluk ve yükselmiş C-reaktif protein düzeyleri yaşamaya başlamıştır. Antinükleer antikor, ekstrakte edilebilir nükleer antijen, antinötrofil sitoplazmik antikor ve enfeksiyöz serolojiler dahil kapsamlı incelemelerde herhangi bir anormallik saptanmamıştır. Belirtiler genellikle bir hafta içinde kendiliğinden düzelmiştir. Enfeksiyöz veya otoimmün nedenlerin dışlanmasıyla, golimumaba karşı gelişen bir aşırı duyarlılık reaksiyonundan şüphelenilmiştir. Tedavi secukinumaba geçilmiş ve hasta, semptomlarda tam düzelme sağlamıştır. TNF-İ'lere bağlı aşırı duyarlılık reaksiyonları, özellikle ateş, nadir ancak önemli olumsuz olaylardır. İnfliksimaba benzer reaksiyonlar bildirilmiş olsa da, golimumab ile ilişkili ilk olgu bu çalışmada sunulmaktadır. Klinik hekimlerin bu olası yan etkiyi tanıyabilmesi için farkındalık geliştirmesi gereklidir. Bu olgu, AS hastalarında uzun süreli biyolojik tedavi sırasında atipik advers olayların dikkatle izlenmesinin önemini vurgulamaktadır. TNF-İ'lere karşı aşırı duyarlılığın patofizyolojisini ve risk faktörlerini aydınlatmak için daha fazla araştırmaya ihtiyaç vardır.

Anahtar kelimeler: Ankilozan spondilit, golimumab, TNF inhibitörleri, hipersensitivite, ateş

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Introduction

Ankylosing spondylitis (AS) is the prototypical condition within the spondyloarthritis spectrum, characterized by inflammatory low back pain and sacroiliac joint involvement, with or without peripheral arthritis, enthesitis, and extra-articular manifestations (1). Early initiation of treatment is critical to prevent skeletal deformities and physical disability (2). First-line pharmacological management typically involves the regular use of non-steroidal anti-inflammatory drugs (NSAIDs). When NSAIDs fail to provide adequate symptom control, biologic agents, such as tumor necrosis factor inhibitors (TNF-Is) or interleukin-17 inhibitors, are recommended (3,4). Patients undergoing treatment require close monitoring for drug efficacy, disease activity, and potential adverse effects. Here, we present a case of a patient who developed recurrent fever and elevated acute-phase reactants following the administration of golimumab.

Case Report

A thirty one-year-old female patient, who was diagnosed with AS at an external center 5 years ago, presented to our clinic due to increased pain. Upon admission, the patient reported that she had discontinued her medications two years prior. She had previously used various NSAIDs but noted that her symptoms had not resolved completely. On the initial examination, the cervical and lumbar range of motion was restricted and painful, and bilateral Mennel's test was positive on the sacroiliac joint assessment. Tenderness was noted over the left spina iliaca anterior superior, left iliac crest, and left achilles tendon insertion. Disease activity and functional status were evaluated using the Bath ankylosing spondylitis disease activity index (BASDAI; score: 9) and the Bath ankylosing spondylitis functional index (score: 8).

The patient had no comorbidities. Blood tests showed normal liver and kidney function but elevated inflammatory markers, with a C-reactive protein (CRP) level of 1.77 mg/dL and an erythrocyte sedimentation rate of 36 mm/hour. The human leukocyte antigen (HLA) typing was positive for HLA B27 and previous sacroiliac magnetic resonance imaging findings confirmed sacroiliitis. Initial treatment included regular NSAID therapy combined with a proton pump inhibitor, which was maintained for two years. However, her pain persisted, with a BASDAI score of 6.8. Consequently, TNF-I therapy was initiated, and golimumab 50 mg/month was prescribed, leading to the discontinuation of NSAIDs.

The patient demonstrated significant improvement, achieving sustained remission and becoming pain-free on golimumab therapy for six years until 2021. However, during the coronavirus disease-2019 pandemic, she missed follow-up visits for one year but continued golimumab as prescribed. Over the past five months, she experienced intermittent fever, fatigue, flu-like symptoms, and elevated CRP levels (up to 12 mg/dL) two to three days following each golimumab administration. During her clinic visit, four days after her most recent golimumab dose, her temperature was 38 °C, and CRP was elevated at 4 mg/dL. No dermatological findings or other systemic symptoms were observed.

Extensive laboratory investigations, including antinuclear antibody, anti-double stranded DNA, extractable nuclear antigen, antineutrophil cytoplasmic antibodies, complement levels, rheumatoid factor, anti-cyclic citrullinated peptide, and *Brucella* tube agglutination tests, revealed no abnormalities. Internal medicine and infectious diseases consultations excluded systemic causes of fever, elevated CRP, and flu-like symptoms. Based on the clinical presentation and the exclusion of alternative diagnoses, the reaction was attributed to hypersensitivity to golimumab. Treatment was then transitioned to secukinumab, which the patient has been receiving for eight months without adverse effects. A written informed consent was obtained from the patient.

Discussion and Conclusion

Golimumab is effective in inducing and maintaining remission in patients with AS and has a long-term safety profile comparable to other TNF-Is (5). Common side effects include headache, injection site reactions (for subcutaneous administration), infusion reactions (for intravenous administration), rash, anemia, upper respiratory tract infections, cough, pharyngitis, diarrhea, nausea, and abdominal pain, occurring in over 10% of patients treated with golimumab. Other common side effects, observed in approximately 2-5% of patients, include sinusitis, bronchitis, viral infections, mild transaminase elevations, hypertension, dizziness, paresthesia, and pyrexia (6). Severe adverse events, such as life-threatening fungal or bacterial infections, heart failure, worsening or new-onset demyelinating disorders, hepatitis or tuberculosis reactivation, and lupus-like syndrome, occur less frequently. Acute infusion or injection reactions typically arise during drug administration and can vary in severity, ranging from a simple rash to anaphylaxis (7).

Drug fever, a type III hypersensitivity reaction, can be induced by various medications (8). It is a similar entity to serum sickness. Drug fever is identified as a febrile response that starts after drug administration, and resolves within 72 hours after drug possession, no other cause is identified and no recurrence of fever within 72 hours after the fever subsides. CRP elevation can accompany drug fever reactions, as observed in our case.

This case highlights a hypersensitivity reaction, manifesting as fever and elevated acute-phase reactants, which resolved spontaneously within one week after each golimumab injection. This reaction occurred despite the patient tolerating golimumab without issues for six years. The absence of abnormalities in anti-nuclear antibodies, complement levels, and other relevant investigations excluded drug-induced lupus, vasculitis, and serum sickness-like reactions. Consultations from internal medicine and infectious diseases identified no alternative diagnoses, further confirming the hypersensitivity-related nature of the response.

A literature review identified two similar hypersensitivity cases associated with TNF-Is, both involving infliximab. The first case

described a sixty one-year-old woman with ulcerative colitis who developed a fever of 38.3 °C nine days after her second infliximab dose. Anti-dsDNA and anti-histone antibody tests were negative, and no infectious etiology was identified. Her fever resolved spontaneously after 25 days (9). The second case involved a sixty five-year-old woman with rheumatoid arthritis, who experienced a high fever with rigors lasting 13 days after her second infliximab infusion. This episode was attributed to delayed hypersensitivity (10).

To our knowledge, this is the first reported case of a hypersensitivity reaction to golimumab presenting as a recurrent fever. This report aims to raise awareness among clinicians about this adverse effect.

Ethics

Informed Consent: A written informed consent was obtained from the patient.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.G., N.M., D.G.K., M.Ö., Concept: B.G., N.M., D.G.K., M.Ö., Design: B.G., N.M., D.G.K., M.Ö., Data Collection or Processing: B.G., N.M., D.G.K., M.Ö., Analysis or Interpretation: B.G., N.M., D.G.K., M.Ö., Literature Search: B.G., N.M., D.G.K., M.Ö., Writing: B.G., N.M., D.G.K., M.Ö.

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