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Tailored Treatments: Utilizing Anti-TNFs for Ankylosing Spondylitis and Essential Thrombocytosis

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Case Report

History

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ABSTRACT

Thrombocytosis is a condition that is often detected incidentally and can be seen both in the course of myeloproliferative diseases (MPD) and as a reactive condition. Ankylosing spondylitis (AS) is a chronic multisystemic inflammatory disease that mainly affects the spine. Mild to moderate thrombocytosis may occur secondary to the course of AS. In the treatment of AS, tumor necrosis factor inhibitor (anti-TNF) treatments are actively used as first-line therapy. The number of cases of MPDs occurring in the course of AS reported in the literature is limited. Although the exact effect of anti-TNF treatment on the MPD process is not fully known, there are publications stating that caution should be exercised in cases of MPD. By this case, we wanted to share our experience of using anti-TNF therapy in a patient diagnosed with ET in the course of AS. The 35-year-old male patient had been diagnosed with AS for 11 years and had been followed up by hematology with the diagnosis of essential thrombocytosis (ET) since 2010. When there was no response to indomethacin and sulfasalazine treatments, the patient was first given etanercept, and after secondary unresponsiveness, infliximab and adalimumab treatments were given. Despite the use of multiple anti-TNFs, no hematological deterioration was detected in terms of ET. Clinical and laboratory responses were also obtained in terms of AS. The patient has been stable and in remission in terms of both AS and ET since 2016.

Keywords: anti TNF, ankylosing spondylitis, essential thrombocytosis, tumor necrosis factor

Kişiye Özel Tedaviler: Ankilozan Spondilit Ve Esansiyel Trombositozda Anti-TNF'lerin Kullanımı

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ÖZET

Trombositoz sıklıkla tesadüfen tespit edilen ve hem miyeloproliferatif hastalıkların (MPH) seyrinde hem de reaktif bir durum olarak görülebilen bir durumdur. Ankilozan spondilit (AS), esas olarak omurgayı etkileyen kronik, multisistemik inflamatuar bir hastalıktır. AS'nin seyrine sekonder olarak hafif ila orta şiddette trombositoz meydana gelebilir. AS tedavisinde tümör nekroz faktör inhibitörü (anti-TNF) tedavileri birinci basamak tedavide aktif olarak kullanılmaktadır. Literatürde AS seyrinde ortaya çıkan MPH vakalarının sayısı sınırlıdır. Anti-TNF tedavisinin MPH sürecine etkisi tam olarak bilinmemekle birlikte bu vakalarda dikkatli olunması gerektiğini belirten yayınlar bulunmaktadır. Bu olguyla AS seyrinde ET tanısı alan bir hastada anti-TNF tedavisi kullanma deneyimimizi paylaşmak istedik. 35 yaşındaki erkek hastada 11 yıldır AS tanısı mevcuttu, 2010'dan beridir ise esansiyel trombositoz (ET) tanısı ile hematoloji tarafından takipliydi. Indometazin ve sulfasalazin tedavilerine yanıt alınamayınca hastaya önce etanercept, sekonder yanıtsızlık üzerine de infliksimab ve adalimumab tedavileri verildi. Çoklu anti-TNF kullanımına rağmen ET açısından herhangi bir hematolojik bozulma saptanmadı. AS açısından da klinik ve laboratuvar yanıtı alındı. Hasta 2016 yılından bu yana hem AS hem de ET açısından stabil ve remisyonda izlenmektedir.

Anahtar Kelimeler: anti TNF, ankilozan spondilit, esansiyel trombositoz, tümör nekroz faktörü

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Introduction

Thrombocytosis is a condition that is often detected incidentally and can be seen both in the course of myeloproliferative diseases (MPDs) and as a reactive condition. When seen as reactive, it is present in a secondary disease course and regresses with the treatment of the underlying condition. However, in clonal cases, it is associated with thrombotic events and bleeding. In such instances, cytoreductive treatments may be required(1).

Ankylosing spondylitis (AS) is a chronic multisystemic inflammatory disease that mainly affects the spine but may also involve peripheral joints. Mild to moderate thrombocytosis may occur secondary to the course of AS(2). Essential thrombocytosis (ET) is a MPD characterized by a prominent Janus kinase 2 (JAK2) mutation. ET should be suspected if the platelet count is consistently ≥450.10^9/L in asymptomatic individuals(3).

In the treatment of AS, tumor necrosis factor inhibitor (anti-TNF) treatments are actively used as first-line therapy after non-steroidal anti-inflammatory drugs (NSAIDs). The number of cases of MPDs occurring in the course of AS reported in the literature is limited. Although the exact effect of anti-TNF treatment on the MPD process is not fully known, there are publications stating that caution should be exercised in cases of MPD(4).

By this case, we wanted to share our experience of using anti-TNF therapy in a patient diagnosed with JAK2-positive ET in the course of AS.

Case

A 35-year-old male patient has had intermittent platelet values of ≥ 800.10^9/L since 2010. He was monitored with aspirin for thrombocytosis in the hematology outpatient clinic and presented to our rheumatology outpatient clinic in 2013 with low back and hip pain that had been ongoing for seven years. Sacroiliac MRI was planned for the patient, and the MRI result was found to be compatible with bilateral sacroiliitis (see figure 1). The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) at the time of presentation was 6.5. The patient, who was also HLA-B27 positive, was diagnosed with AS based on the European Spondyloarthropathy Study Group criteria(5). At his presentation in 2013, the patient's C-reactive protein (CRP) value was 32 mg/L and the erythrocyte sedimentation rate (ESR) was 46 mm/h. Previously, the patient had been treated with indomethacin and sulfasalazine. In 2014, etanercept treatment was initiated for the patient, who had no laboratory or clinical response during follow-up. Initially, a significant response was obtained with etanercept.

During follow-up, the patient's platelet levels remained persistently high, around 700.10^9/L, and he was referred back to the hematology outpatient clinic. Bone marrow aspiration and biopsy were planned for the patient by hematology. As a result of aspiration and biopsy performed in 2015, an increase in the myeloid series and megakaryocytes, a decrease in the erythroid series, and dysplasia findings were detected. The pathology was reported as compatible with ET. The JAK2V617F mutation was detected as positive in the patient, while the breakpoint cluster region–Abelson (BCR/ABL) rearrangement was negative, and cytogenetic analyses were reported as normal. Since he was also using anti-TNF therapy, he was frequently and jointly monitored by hematology and rheumatology. Hematology evaluated him as having a high risk of thrombosis and bleeding, and hydroxyurea was added to his aspirin treatment.

During AS follow-up, the patient developed uveitis twice while on etanercept, so he was switched to infliximab in 2015. After developing arthritis following nine months of infliximab treatment, he was considered secondarily unresponsive to treatment and was switched to adalimumab in 2016. Since 2016, the patient has been monitored as stable and in remission in terms of both AS and ET, with platelet values around 400.10^9/L.

Discussion

Since platelets are acute phase reactants, we expect a moderate increase in all systemic inflammatory events. However, even in systemic inflammatory diseases, when platelet counts are persistently high, especially at values >1,000.10^9/L, further investigation is required. The JAK2V617F mutation is actively used for diagnosis in these cases(6). Although our patient was diagnosed with ET due to the JAK2 mutation, it was not possible to exclude partial reactive thrombocytosis, which can accompany ET and be seen in the course of AS.

Aspirin is the first-line agent used in the treatment of thrombocytosis in the clinic. In cases where platelet counts remain high despite anti-platelet therapy and the estimated risk of thrombosis is high, agents such as hydroxyurea are added in clinical practice(7, 8). In our patient, the presence of an accompanying mutation and the chronic inflammatory condition seen in AS would increase the risk of arterial and venous thrombosis. Therefore, hydroxyurea was initiated by the hematologist in addition to aspirin. There were no side effects from hydroxyurea, and we observed a positive response to the treatment.

AS treatment is tailored to the patient's manifestations, taking into account the existing symptoms, general clinical condition, and prognostic markers. Initially, NSAIDs, which aim to alter the course of the disease, are used. This is followed by disease-modifying anti-rheumatic drugs (DMARDs). In cases of unresponsiveness, anti-TNF treatments are administered. TNF antagonists are well tolerated by patients and have proven to be highly effective in the AS treatment process(9). In our patient, we observed a significant improvement in the disease course, laboratory parameters, and functional indices with TNF treatments after unresponsiveness to conventional DMARDs.

There are also publications in the literature indicating that anti-TNF treatment reduces the number of platelets.

It is thought that these treatments may cause thrombocytopenia due to their reduction of cytokines such as IL-1, IL-6, and IL-8, as well as their unexplained complex hematopoietic effects(10). Another theory on this subject is that TNF antagonists increase the formation of immune complexes, which then bind to the platelet wall and cause platelet destruction(11). In our case, TNF antagonists used in accordance with these theories may have had positive effects on the patient's thrombocytosis. However, caution should be exercised in the use of anti-TNFs in hematological diseases, as one of the possible effects associated with these drugs is the development of malignancies(12). On this subject, it has been reported in the literature that secondary ET and acute myeloid leukemia can develop in individuals using anti-TNF therapy for inflammatory bowel disease(4). However, in our experience with this patient, we did not encounter any negative situations despite using TNF antagonists for many years.

Conclusion

In conclusion, when clonal stem cell diseases such as ET are accompanied by rheumatological conditions like AS, caution is needed when considering anti-TNF treatments. In this case, remission of AS was achieved, along with positive progress in managing thrombocytosis.

Patient consent: Informed consent was obtained and signed from the patient regarding the use of patient health information.

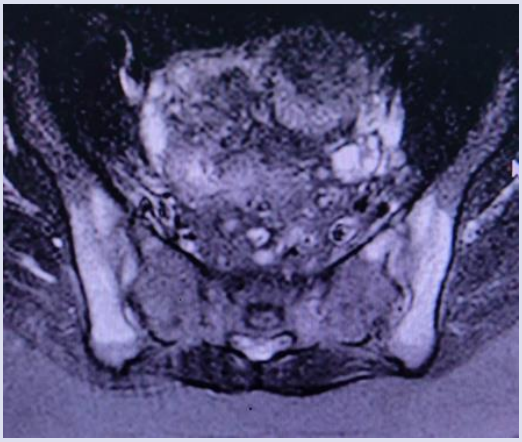

Figure 1: Magnetic resonance imaging showing bilateral sacroiliitis

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