Carta al editor
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Tailored treatments: Utilizing anti-TNFs for ankylosing spondylitis and essential thrombocytosis.

Tratamientos personalizados: administración de anti-TNF para tratar la espondilitis anquilosante y la trombocitosis esencial

Dear editor:

Thrombocytosis is a condition that is often detected incidentally and can be seen both in the course of myeloproliferative diseases 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 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 ankylosing spondylitis.[2] Essential thrombocytosis is a myeloproliferative disease characterized by a prominent Janus kinase 2 (JAK2) mutation. Essential thrombocytosis should be suspected if the platelet count is consistently ≥ 450 x 10^9/L in asymptomatic individuals.[3]

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

In this case, we will discuss our experience of using anti-TNF therapy in a patient diagnosed with JAK2-positive essential thrombocytosis in the course of ankylosing spondylitis.

A 35-year-old male patient has had intermittent platelet values of ≥ 800 x 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. 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 ankylosing spondylitis based on the European Spondyloarthropathy Study Group criteria.[5] At his presentation in 2013, the patient's C-reactive protein value was 32 mg/L and the erythrocyte sedimentation rate 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 x 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 essential thrombocytosis. 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 ankylosing spondylitis 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 ankylosing spondylitis and essential thrombocytosis, with platelet values around 400 x 10^9/L.

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 > 1000 x 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 essential thrombocytosis due to the JAK2 mutation, it was not possible to exclude partial reactive thrombocytosis, which can accompany essential thrombocytosis and be seen in the course of ankylosing spondylitis.

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 ankylosing spondylitis 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.

Ankylosing spondylitis treatment is tailored to the patient's manifestations, taking into account the existing symptoms, general clinical condition, and prognostic markers. Initially, non-steroidal anti-inflammatory drugs, which aim to alter the course of the disease, are used. This is followed by disease-modifying anti-rheumatic drugs. 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 ankylosing spondylitis treatment process.[9] In our patient, we observed a significant

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improvement in the disease course, laboratory parameters, and functional indices with TNF treatments after unresponsiveness to conventional disease-modifying anti-rheumatic drugs.

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 malignancies, 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 essential thrombocytosis 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.

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