A case of essential thrombocythemia and ankylosing spondylitis treated with a combination of anagrelide, disease-modifying antirheumatic drugs, and etanercept

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SUMMARY

Introduction A high platelet count, or thrombocytosis, is either a reactive process or a result of a myeloproliferative disorder. Ankylosing spondylitis is a chronic inflammatory rheumatic disease affecting the spine and sometimes peripheral joints in which reactive mild to moderate thrombocytosis is a common finding. There have been no previously reported cases of essential thrombocythemia associated with ankylosing spondylitis.

Case Outline We report a case of a 32-year-old man with human leukocyte antigen B27-positive ankylosing spondylitis and Janus kinase 2-positive essential thrombocythemia who was treated first with a combination of anagrelide and disease-modifying antirheumatic drugs and, after liver toxicity, with a combination of anagrelide and etanercept (TNF-α antagonist). Both diseases were gradually brought under control.

Conclusion Our case of ankylosing spondylitis and essential thrombocythemia suggests that concomitant etanercept and anagrelide therapy is safe, as well as effective.

Keywords: essential thrombocythemia; ankylosing spondylitis; antirheumatic agents

INTRODUCTION

A high platelet (Plt) count, or thrombocytosis, can occur either as a reactive process or as a result of a myeloproliferative disorder [1]. Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease affecting the spine and sometimes peripheral joints, and reactive mild to moderate thrombocytosis is a common finding in AS [2]. Severe thrombocytosis (Plt >1000×10^9/l) in an asymptomatic patient should raise the suspicion of essential thrombocythemia (ET), which is diagnosed by the criteria proposed by the World Health Organization [3]. The therapeutic approach includes antiaggregation therapy and/or platelet cytoreduction [4]. With regard to the treatment of AS, no drugs have been proven to modify the course of the disease, though TNF-α antagonists have potential as disease-modifying agents [5, 6, 7].

There is a recent report of a case of concomitant myeloproliferative disorder and rheumatoid arthritis [8]. However, to our knowledge, there are no previously reported cases of ET associated with ankylosing spondylitis.

We report a case of a 32-year-man with human leukocyte antigen (HLA) B27-positive AS and Janus kinase (JAK) 2-positive ET who was treated with anagrelide, disease-modifying antirheumatic drugs (DMARDs), and etanercept (a TNF-α antagonist).

CASE REPORT

In August 2002, a 32-year-old male presenting with erythromelalgia and pain in the submental region was referred to our center for further evaluation and thrombocytosis management (Plt 500×10^9/l). The diagnosis of sialadenitis was made, and ET was suspected because of bone marrow hypercellularity, with an increased number of megakaryocytes in the bone marrow aspirate. Due to concomitant sialadenitis and incomplete diagnostic evaluation, the etiology of the thrombocytosis was not clear at that point. The patient was started on ticlopidine one half twice per day, but he did not show for further diagnostic evaluation.

The patient had a history of chronic pain in the lumbosacral region that dated from 1993, but it was not until 2005 that he was diagnosed with ankylosing spondylitis, as based on the European Spondyloarthropathy Study Group criteria [9]. Standard radiography showed irregular erosions, narrowing and subchondral scle-

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rosis of the sacroiliac joints, and signs of AS on the lumbar and cervical spine (degrees III and II, respectively, according to Calin's modified anatomical criteria) [10]. He was HLA-B27 positive. His functional inability was high: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) amounted to 6.1 and Bath Ankylosing Spondylitis Functional Index (BASFI) to 5.63 [11, 12]. Inflammatory markers were significantly raised (erythrocyte sedimentation rate [ESR] 69 mm/h, C-reactive protein [CRP] 58 mg/l). He was initially treated with sulfasalazine 2 g/day, but due to a lack of adequate response, after three months of sulfasalazine monotherapy, methotrexate was introduced at a dose of 10 mg a week, escalating to 17.5 mg per week.

As his erythromelalgia and thrombocytosis persisted, he was admitted to a hematology clinic to re-evaluate the preliminary diagnosis of ET. The findings were as follows: Plt $1{,}309\times10^9$/l, white blood cell count (WBC) 12.5×10^9/l (neutrophils 9.7×10^9/l), hemoglobin (Hb) 136 g/l, leukocyte alkaline phosphatase 120, ESR 80/121 mm, CRP 100.5 mg/l. JAKV61F7 mutation was present, and breakpoint cluster region – Abelson (BCR/ABL) rearrangement was negative; cytogenetic analyses were normal. The spleen was slightly enlarged on ultrasound examination (137×65 mm). Bone marrow aspiration and repeated bone marrow biopsies showed increased cellularity with dominant megakaryocytic hyperplasia, but also moderate granulocyte hyperplasia. Cell culture showed the spontaneous growth of erythroid burst forming unit (BFU-E) and colony-forming unit-megakaryocyte (CFU-MK). The patient was diagnosed with ET and treated with aspirin alone. Despite the treatment, his symptoms persisted, and Plts remained above $1{,}000\times10^9$/l. Therefore, anagrelide 1 mg BID was administered beginning January 2007.

Subsequently, both diseases were gradually brought under control. The patient was asymptomatic, Plt was less than 500×10^9/l, and the AS disease activity index showed an improvement (BASFI 3.98, BASDAI 4.13).

However, in July 2008, laboratory findings showed a liver lesion, which led to a reduction in methotrexate dosage to 12.5 mg weekly and sulfasalazine exclusion. As a consequence, his AS progressed, as demonstrated by radiography and laboratory findings. In August 2009, etanercept was initiated at 50 mg a week with a continuation of anagrelide 1 mg BID and the exclusion of methotrexate after dose tapering. No side effects were reported, and Plts were up to 500×10^9/l; BASDAI was 3.23 and BASFI 3.91. However, at the end of 2009 anagrelide was temporary not available, which resulted in termination of anagrelide therapy and reintroduction of aspirin. The patient was on continuous etanercept therapy. The blood count from the end of 2012 was WBC 11.89×10^9/l, erythrocyte count 6.47×10^{12}/l, Hb 149 g/l, Plt 949×10^9/l, CRP 6.8 mg/l, fibrinogen 3.3 g/l, BASFI 2.7, BASDAI 2.4.

DISCUSSION

Platelets are acute-phase reactants; therefore, secondary mild–moderate thrombocytosis is frequent in systemic inflammatory disease. Previously published studies implicate interleukin-6 might as a possible cause of thrombocytosis [13]. ET can be diagnosed by JAK2 V617F evaluation in peripheral blood, especially when the Plt count is more than $1{,}000\times10^9$/l [8]. Although ET was diagnosed in our patient, partial reactive thrombocytosis, as well as neutrophilia, due to concomitant ankylosing spondylitis, could not be excluded.

The first-line therapy for ET in low-risk patients, as in our patient, is aspirin alone [14, 15]. However, erythromelalgia did not respond to aspirin treatment in our case. The reason for this is not known. According to guidelines of the Italian Society of Hematology, platelet-lowering treatment could be introduced in the cases with severe microcirculatory symptoms, despite anti-platelet therapy [16]. Due to persisting erythromelalgia, as well as Plts over $1{,}000\times10^9$/l, JAK2 V617F-positive mutation which increases the risk of arterial and venous thrombosis [13], and presence of chronic inflammatory condition AS which potentially increase the cardiovascular risk [17], he was started on cytoreduction therapy. The pros and cons of hydroxyurea and anagrelide were discussed; considering that this was the case of a younger patient, we decided on anagrelide therapy because it is neither cytotoxic nor mutagenic [14]. In our patient, anagrelide induced a good response, causing no side effects.

The approach for therapy in patients with AS should be based on manifestations of the disease, the level of current symptoms, clinical findings, prognostic indicators, and the general clinical status [18]. Disease-modifying antirheumatic drugs (sulfasalazine, methotrexate), which are especially effective for peripheral joint involvement [18], were used as first-line therapy in our patient. He initially responded favorably to concomitant sulfasalazine and methotrexate therapy, but liver toxicity led to their withdrawal. The effect of anagrelide on liver toxicity cannot be completely excluded, though it is less probable when considering the rare cases of liver enzyme elevation during its administration [19].

TNF-α antagonists are not only better tolerated but are also a highly effective treatment in patients with active AS [20]. In our patient, the administration of etanercept was effective, leading to significant clinical improvements, reductions in indicators of inflammation and improvement of functional status, as measured by disease activity indices. Anti-TNF-α therapy seems to have moderately reduced Plt number in our case possibly through the reduction of circulating several pro-inflammatory cytokines, such as IL-1, IL-6, and IL-8, although the other, complex hematopoietic effects could not be excluded [21]. However, TNF-α antagonists should be used with caution in patients with hematological disorders. On the one hand, possible adverse effects of TNF-α antagonists include malignancies [22]; indeed, Fischer et al. [23] have reported a case of secondary acute myeloid leukemia and ET in two patients with inflammatory bowel disease treated with TNF-α antagonists. On the other hand, thrombocytopenia, although not common, is a potential side effect of anti-TNF-α therapy [24, 25, 26]. Anti-TNF-α therapy not only

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reduces Plt counts through the reduction of circulating pro-inflammatory cytokines, but it can also cause severe thrombocytopenia of unclear etiology. In our patient, no side effects were reported, even after years of continuous therapy.

In conclusion, our case of AS and ET suggests that the combination treatment of anagrelide and DMARDs as well as anagrelide and etanercept therapy is feasible and effective. In addition to effectiveness in the treatment of AS, etanercept appears to have induced a reduction in Plt count in our patient.

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Есенцијална тромбоцитемија и анкилозирајући спондилитис лечени комбинацијом анагрелида, лекова који модификују ток болести и етанерцепта: приказ болесника

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КРАТАК САДРЖАЈ

Увод Повишен број тромбоцита може бити реактивни процес или може да се јавља у оквиру мијелопролиферативних болести. Анкилозирајући спондилитис је хронична запаљењска реуматска болест која захвата кичмени стуб и понекад периферне зглобове, а често је праћена благом до умереном реактивном тромбоцитозом. У доступној литератури не постоји описан случај есенцијалне тромбоцитемије уз присуство анкилозирајућег спондилитиса.

Приказ болесника Приказан је случај 32-годишњег болесника са *HLA B27* позитивним анкилозирајућим спондилитисом и Јанус киназа (*JAK*) 2 позитивном есенцијалном тромбоцитемијом, који је иницијално лечен комбинацијом анагрелида и лекова који модификују ток болести после појаве јетрене лезије комбинацијом анагрелида и етанерцепта (*TNF-α* антагониста). Применом ове терапије у обе болести је постигнут значајан клинички одговор.

Закључак Комбинована примена етанерцепта и анегрелида у случају анкилозирајућег спондилитиса и есенцијалне тромбоцитемије се показала сигурном и ефикасном.

Кључне речи: есенцијална тромбоцитемија; анкилозирајући спондилитис; антиреуматски лекови

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