CASE REPORT

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Development of Crohn´s disease in a patient with ankylosing spondylitis and essential thrombocythemia following etanercept therapy - A case report and the review of the literature

Pojava Kronove bolesti kod bolesnika sa ankilozirajućim spondilitisom i esencijalnom trombocitemijom tokom terapije etanerceptom

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Abstract

Introduction. The development of inflammatory bowel disease during the treatment with tumor necrosis factor-α inhibitors is seen in patients with ankylosing spondylitis. Crohn´s disease is the mainly developing form, and etanercept is the most frequently associated agent. Although thrombocytosis in patients with ankylosing spondylitis and inflammatory bowel diseases is often seen due to chronic inflammation, iron deficiency anemia or drug administration, presence of essential thrombocythemia is not common. To our knowledge, there is no published data of coexistence of these three diseases in one patient. **Case report.** We reported a 35-year-patient with simultaneous presentation of ankylosing spondylitis and essential thrombocythemia. Due to hepatotoxicity of initial treatment with sulfasalazine and metotrexate, tumor necrosis factor-α inhibitor (etanercept) was introduced. Both diseases were well controlled until Crohn´s disease emerged. Two years after switching from etanercept to adalimumab all three coexisting diseases were in remission. **Conclusion.** Treatment with tumor necrosis factor-α inhibitors significantly improved clinical outcome of patients with chronic inflammatory diseases. However, the appearance of adverse effects may cause a discontinuation or change of a drug. The existence of comorbidities additionally complicates the treatment of such patients.

Key words:
biological therapy; comorbidity; crohn`s disease; drug utilization; spondylitis, ankylosing; thrombocythemia, essential.

Apstrakt

Uvod. Tokom terapije inhibitorima faktora nekroze tumora alfa kod bolesnika sa ankilozirajućim spondilitisom može doći do nastanaka inflamatorne bolesti creva. Kronova bolest je najčešća forma, a etanercept je lek koji se najviše povezuje sa pojavom bolesti. Iako se trombocitoza često javlja kod bolesnika sa ankilozirajućim spondilitisom kao rezultat hronične inflamacije, sideropenijske anemije ili primene lekova, pojava esencijalne trombocitemije nije česta. Nema objavljenih radova o koegzistenciji ove tri bolesti kod jednog bolesnika. **Prikaz bolesnika.** Prikazali smo složen slučaj bolesnika starog 35 godina sa istovremenom pojavom ankilozirajućeg spondilitisa i esencijalne trombocitemije. S obzirom na hepatotoksičnost izazazvanu inicijalno uvedenim lekovima, sulfasalazinom i metotreksatom, započeto je lečenj etanerceptom, inhibotorom faktora nekroze tumora alfa. Obe bolesti su bile zadovoljavajuće kontrolisane sve dok nije dijagnostikovana Kronova bolest. Dve godine nakon zamene etanercepta adalimumabom, sve tri bolesti su bile u remisiji. **Zaključak.** Terapija inhibitorom faktora nekroze tumora alfa je značajno poboljšala klinički ishod lečenja bolesnika sa hroničnim inflamatornim bolestima. Ipak, pojava neželjenih efekata može usloviti prekid ili promenu leka. Prisustvo komorbiditeta dodatno komplikuje terapijski pristup tim bolesnicima.

Ključne reči:
biološka terapija; komorbiditet; kronova bolest; lekovi, korišćenje; spondilitis, ankilozirajući; trombocitemija, esencijalna.

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Introduction

Ankylosing spondylitis (AS), which is the most frequently occurring form of spondyloarthritis (SpA), is a chronic immunomediated inflammatory disease characterized by inflammation that predominantly affects the axial skeleton [1]. Inflammatory bowel diseases (IBD) [Crohn´s disease (CD) and ulcerative colitis (UC)] are the most frequent extra-articular manifestations of AS. Although the most significant genetic association for SpA is with the genes related to the MHC (HLA-B27), several polymorphisms outside the MHC were identified, including IL-23R, PSMG1, ERAP1/2 and TNFSF15 which are also established IBD loci [2]. The discovery of several inflammatory pathways in both AS and IBD led to the era of the biologic therapies, which meant a revolution in their treatment and prognosis. All tumor necrosis factor α inhibitors (TNF-α inhibitors) are efficacious in treating AS, but there are differences regarding IBD. Monoclonal antibodies [infliximab (INF), adalimumab (ADA), certolizumab-pegol (CPG), golimumab (GOL)] are efficacious in the treatment of IBD whereas etanercept (ETA) is not [3]. Paradoxal adverse events (PAEs) refer to the occurrence of pathological condition opposite to the effect which would normally be expected. The development of IBD during the treatment with TNF-α inhibitors is seen in patients with AS. CD is the mainly developing form of IBD, and ETA is the most frequently associated agent. Paradoxal IBD is generally well controlled by the interruption of the damaging by TNF-α inhibitor and switching to the monoclonal antibodies.

Essential trombocythemia (ET) is a Philadelphia chromosome (Ph)-negative myeloproliferative neoplasm (MPN) characterized by thrombocytosis and megakaryocytic hyperplasia of the bone marrow, with the presence of Janus kinase 2 valin 617 phenylalanine (JAK2V617F) mutation in 50%–60% of patients. ET can transform into myelofibrosis and acute myeloide leukemia in the minority of cases and, in general, life expectancy is considered not far from that of healthy population [4]. HLA-B27 has been suggested to be important in the pathogenesis of AS, furthermore; HLA-B27 seems to also raise the risk of hematological malignancies, notably myelodysplastic syndrome (MDS), acute leukemia and lymphoid malignancies but not Ph-negative MPN [5].

Case report

We reported a 35-year-old man presented with a 10-year history of morning pain and stiffness in the low back, buttocks and hips. He was positive for human leukocyte antigen (HLA-B27) and plain radiography showed bilateral sacroilitis. The patient was diagnosed with AS in 2005 according to the modified New York criteria [6]. He started with nonsteroidal anti-inflammatory drugs (NSAIDs), but after several months sulfasalazine (SSZ) 2 g/day was introduced due to right knee arthritis. Only after methotrexate (MTX) 17.5 mg/week was administered, the patient started to feel better.

Even before the patients was diagnosed with AS, in 2002, he was examined due to the symptoms of erythomelalgia and thrombocytosis. After bone marrow biopsy preliminary diagnosis of ET was made. The patient was advised to take antiplatelet drug and to undergo further evaluation. However, he decided to visit hematologist four years later, when erythomelalgia symptoms got worse. Further analysis proved JAK2V61F7 mutation, breakpoint cluster region – Abelson (BCR/ABL) rearrangement was negative and cytogenetic analyses were normal. Bone marrow aspiration and repeated bone marrow biopsies showed hypercellularity with dominant megakaryocytic hyperplasia. After the definite diagnosis of ET was made (November 2006), he started taking aspirin, but when anagrelide was introduced his platelet (PLT) count was below 1,000 cells/mm³ (normal range is 140,000–440,000 cells/min^3). At that time, the patient was taking SSZ and MTX for AS and the disease activity was mild [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score was 3.7].

In July 2008, laboratory findings indicated hepatotoxicity, and the Roussel Uclaf Causality Assessment Method (RUCAM) [7] for estimation of drug-induced liver injury was performed for all medications that the patient was taking. MTX was assigned the highest RUCAM score at 6 (the probable cause of liver injury), SSA was 3 (possible cause) and anagrelide was 1 (unlikely cause). According to RUCAM scoring results, SSZ and MTX were suspended. Soon, his back pain worsened, BASDAI was 6.7 and MRI pointed at active sacroiliitis. His ET was satisfactory controlled (PLT below 500 cells/mm³). Regarding all of the above, we decided to induce TNF-α inhibitor in the therapy of AS and in August 2009 ETA was initiated sc with the dose of 50 mg/weekly. After four months of ETA therapy, the patient was much better, his BASDAI score dropped to 2.4, C-reactive protein (CRP) was 4.9 and his liver enzymes were in normal range. Anagrelide was terminated in November 2009 and aspirin was reintroduced. For the next six years the patient was stable, taking only ETA and aspirin.

In May 2016, the patient reported cramping abdominal and anal pain associated with diarrhea (4–5 movements/day) and fever. The patient's laboratory findings were as follows: CRP 41 mg/L (normal range < 3 mg/L), white blood cells count (WBC) 16.97 cells/mm³ (normal range 4,500–10,000 cells/mm^3 hemoglobin (Hb) 142 g/L (normal range 138–142 g/L), PLT 982 cells/mm³. ETA was discontinued. The patient was referred to a gastroenterologist and colonoscopy was performed. Colonoscopy and histological finding showed changes consistent with CD with perianal fistula. Pelvic magnetic resonance imaging (MRI) showed complex intersphincteric perianal fistulas with abscess. Abscess drainage and seton placement were performed with the use of antibiotics (ciprofloxacin, metronidazole) followed by prednisolone 40 mg/day. After three months, antibiotics were discontinued and the patient was on steroid tapering regimen. He was in clinical remission without fistula draining. But, in September 2016, his back pain returned, BASDAI was 6.2 and Ankylosing Spondylitis Disease Activity Score (ASDAS) 3.8, inflammatory markers were elevated, and colonoscopy revealed no flare of CD. In November 2016, second TNF-α inhibitor, ADA 40 mg every two weeks was

started. After only two months of ADA treatment, the patient started to feel better and the inflammation declined. The patient is currently taking only ADA and aspirin. He has no gastroenterological or musculoskeletal signs that implicate active disease. Laboratory findings from May 2019 were as follows: PLT 992 cells/mm³, hemoglobin 139 g/L, leukocytes 7.6 cells/mm³, CRP 2.3 mg/L.

Discussion

The association of AS with IBD has already been described and subclinical gut lesions resembling CD seen in up to 50% of patients, up to 10% which developed clinically overt IBD with time [8]. Data from the IBSEN study reported the prevalence of AS in IBD to be 3.7% (2.6% in UC; 6% in CD), compared to about 1% in the general population [9].

All available TNF-α inhibitors are similarly efficacious in the treatment of AS, whereas monoclonal antibodies are efficacious in the treatment of IBD and ETA is not [3]. Furthermore, ETA is the main TNF-α inhibitor associated with paradoxal IBD, predominantly CD. In order to analyze the incidence of flares and new onset of IBD in patients with AS treated with anti-TNF agents, Braun et al. [10] analyzed data from 9 separate trials. A history of IBD was reported in 76 (6.7%) out of 1,130 patients. The relative risk for flare of IBD or development of a new-onset IBD during ETN treatment was determined as 18 times higher compared to INF therapy, but with no significant difference for the placebo group [10]. O'Toole et al. [11] searched for cases of IBD provoked by ETA from an IBD Referral Center and Food and Drug Administration (FDA) in period between 1998 and 2014. A total of 443 cases (297 CD, 146 UC) were identified and data of 49 patients (44 CD, 5 UC) were complete. Number of AS patients who developed IBD following ETA treatment was 14 (11CD, 3UC). French series described 14 patients with AS and new-onset IBD under TNF-α inhibitor treatment (10 cases with ETA, 2 with INF). Most of the patients had CD and Crohn's-like disease (1 case with unclassified colitis), and all patients were successfully treated by switching the TNF-α inhibitor to INF or ADA [12]. A recent publication analyzing all adverse events regarding TNF-α inhibitors reported to the FDA described 158 cases of new-onset IBD, most of them involved ETA (105 cases) [13]. Paradoxal IBD is generally well controlled by the interruption of the damaging TNF-α inhibitor and switching to a monoclonal antibody. The mechanism underlying paradoxical events developed during ETA treatment remain unknown. A potential pathophysiological hypothesis might be that, in predisposed patients having certain genetic factors, the introduction of TNF-α inhibitor and notably ETA, modify the cytokine balance and lead to the circumstances for development of IBD. Apoptosis is an important cellular process involved in CD remission. Anti TNF-α monoclonal antibodies can induce apoptosis of peripheral blood cells and *lamina propria* T cells but not ETA [14]. In addition, ETA only partially respects the production of TNF-α and may induce the production of interferon-γ (IFN-γ), favoring the inflammation in the bowel mucosa and granuloma formation, while anti–TNF-α monoclonal antibodies inhibit IFN-γ release [12].

It stays unclear if development of the CD in our patient was paradoxal effect of ETA or mere occurrence of rather common extra-articular manifestation of AS, regarding the fact that ETA is not efficient in IBD. However, after ETA was discontinued from the therapy and ADA was introduced, successful control of both diseases was accomplished.

Although thrombocytosis in AS and IBD patients is often seen due to chronic inflammation, iron deficiency anemia or drug administration, developing of ET or other Ph-negative MPN is not a common condition. We have found only four reports on the association between AS and Ph-negative MPN, three of them emerge after TNF-α inhibitor was introduced. Caramaschi et al. [15] report a case of a 62-year-old Italian with AS and bone involvement due to polycytemia rubra vera (JAK2V617 positive). The case of a 69-year-old men with AS and ET who was treated with ETA and hydroxyurea and developed mantle cell lymphoma has been described [16]. Finally, the cases of a 34-year-old Korean man who developed ET following adalimumab therapy and a 31-year-old Italian who was treated with infliximab and developed PRV, both of whom shared similar genetic background (HLA-B27-positive, JAK2V617-negative), have been described [17, 18]. Our patient was diagnosed with ET years before ETA was introduced, so there was no association between the occurrence of the disease and TNF-α inhibitor therapy.

Today, 17 years after TNF-α inhibitors were approved for the use in AS, data from the real-world national registries demonstrated no increased risk of overall malignancies compared to both general population and patients with AS without TNF-α inhibitor treatment [19]. The risk we accepted introducing TNF-α inhibitors in the treatment of ET was significant, regarding the fact that there were little data about adverse effects back in 2010. Our patient was carefully observed by a hematologist, and there was no sign of ET transformation. On the contrary, ET was in remission.

To our knowledge, there is no literature reporting association between AS, ET and CD. Although the coexistence of these diseases in our patient is probably a pure coincidence, there is a possible bond. Janus kinase (JAK)/signal transducers and activators of transcription (STAT) pathway appear to have a pivotal role in the pathogenesis of many immune-mediated diseases by facilitating the signal transduction of many different cytokines and other molecules [20]. Evidence suggests that the inhibition of JAK-mediated pathways may be a promising approach for the treatment of patients with both CD and AS. The currently marketed drugs, tofacitinib (JAK1/3 inhibitor) and baricitinib (JAK1/2 inhibitor), show efficacy and acceptable safety in rheumatoid arthritis, UC and psoriatic arthritis, and there are encouraging results in the clinical trial of tofacitinib in AS and SpA [21]. The new selective JAK1 inhibitors that are close for FDA approval for both AS and CD are upadacitinib and filgotinib [22]. On the other hand, JAK2 is crucial for signal transduction downstream of the erythropoietin, thrombopoetin, and related receptors that control erythrocyte and megakar-

yocyte expansion. Following the discovery of JAK2V617F in 2005 as the driver mutation of the majority of Ph-negative MPNs, quest for JAK2 inhibitor began. So far, only one JAK2/JAK1 inhibitor (ruxolitinib) has been approved by the FDA in the treatment of intermediate to high-risk MP and hydroxyurea-resistant or intolerant PV. As for ET, the MAJIC trial showed the lack of superiority of ruxolitinib compared to current second-line therapies for these patients [23].

Conclusion

The recent investigations and studies have improved the understanding of the pathogenesis of chronic inflammatory diseases like AS and CD, and also facilitated the development of new treatment strategies. The existence of comorbidities additionally complicates the treatment of such patients. Therefore, an individual approach is essential for every physician.

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