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Biljana Milić*,†, Tatjana Ilić*,†, Milica Popović*,†, Aleksandar Savić‡†, Tatiana Jocić§, Lada Petrović*†

Clinical Center of Vojvodina, *Clinic for Nephrology and Clinical Immunology Novi Sad, Serbia

University of Novi Sad,† Faculty of Medicine, Novi Sad, Serbia

Clinical Center of Vojvodina, ‡ Clinic for Hematology, Novi Sad, Serbia

Clinical Center of Vojvodina, § Clinic for Gastroenterology and Hepatology, Novi Sad, Serbia

Correspondence to: Biljana Milić, Clinical Center of Vojvodina, Clinic for Nephrology and Clinical Immunology, Hajduk Veljkova 1-3, Novi Sad, Serbia. University of Novi Sad, Faculty of Medicine, Hajduk Veljkova 3, Novi Sad, Serbia

E-mail: biljana.milic@mf.uns.ac.rs, +381637197561
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 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 drugs administration, presence of essential thrombocythemia is not common. According to our knowledge, there is no literature reporting of coexistence of these three diseases in one patient. **Case report.** We report a complex case of 35-year patient with practically 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 are in remission. **Conclusion.** Treatment with tumor necrosis factor-α inhibitors significantly improved clinical outcome of patients with chronic inflammatory diseases. However, appearance of adverse effects may cause change or discontinuation of the drug. Existence of co morbidities additionally complicates treatment of such patients.

**Key words:**

ankylosing spondylitis, Crohn’s disease, essential thrombocythemia, tumor necrosis factor-α inhibitors.

**Apstrakt**

**Uvod.** Tokom terapije inhibitorima faktora nekroze tumora alfa kod bolesnika sa ankiloizirajućim 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 ankiloizirajućim spondilitisom kao rezultat hronične inflamacije, sideropenijske anemije ili administracije lekova, pojava esencijalne trombocitemije nije česta. Nema literaturnih podataka koji opisuju koegzistenciju ove tri bolesti kod jednog bolesnika. **Prikaz bolesnika.** Prikazujemo složen slučaj 35-godišnjaka sa praktično istovremenom pojavom ankiloizirajućeg spondilitisa i

**Ključne reči:** ankirozirajući spondilitis, Kronova bolest, esencijalna trombocitemija, inhibitori faktora nekroze tumora alfa

**Introduction**

Ankylosing spondylitis (AS), which is the most frequently occurring form of spondyloarthritis (SpA), is a chronic immune-mediated 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 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 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 most frequently associated agent. Paradoxal IBD is generally well controlled by the interruption of the damaging TNF-α inhibitor and switching to a monoclonal antibody.
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 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 risk for hematological malignancies, notably myelodysplastic syndrome (MDS), acute leukemia and lymphoid malignancies but not Ph-negative MPN (5).

**Case report**

We report a 35-year-old men 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. Based on modified New York criteria, patient was diagnosed with AS in 2005 (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, patient started to feel better.

Even before he was diagnosed with AS, in 2002, he was examined due to symptoms of erytromelalgia and thrombocytosis. After bone marrow biopsy preliminary diagnosis of ET was made. Patient was advised to take antiplatelet drug and to undergo further evaluation. However, he decided to visit hematologist four years later, when erytromelalgia symptoms got worsened. 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 hipercellularity with dominant megakaryocytic hyperplasia (7). After definite diagnosis of ET was made (November 2006), he started taking aspirin, but when anagrelid was introduced his PLT count was below 1000 cells/mm³. At that time, he was taking SSZ and MTX for AS and disease activity was mild (Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score 3.7)
After two years, in July 2008, his laboratory findings indicated hepatotoxicity. Roussel Uclaf Causality Assessment Method (RUCAM) score for drug-induced liver injury was performed for all medications that the patient was taking when the elevated liver enzymes were noted (8). MTX was assigned the highest RUCAM score at 6 (the probable cause of liver injury), SSA was 3 (possible cause) and anagrelid 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 satisfactorily controlled (PLT below 500 cells/mm³). Regarding all above, we decided to induce TNF-α inhibitor in therapy of AS and in August 2009 ETA was initiated subcutaneously at a dose of 50 mg/weekly. After four months of ETA therapy, 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. Anagrelid was terminated in November 2009 and aspirin was reintroduced. For the next six years patient was stable, taking only ETA and aspirin.

In May 2016 he reported cramping abdominal and anal pain associated with diarrhea (4-5 movements/day) and fever. His laboratory findings were as follows: CRP 41 mg/l, white blood cells count (WBC) 16.97 cells/mm³, hemoglobin (Hb) 142 g/l, PLT 982 cells/mm³. ETA was discontinued. He 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 an abscess. Abscess drainage and seton placement was performed with the use of antibiotics (ciprofloxacin, metronidazole) followed by prednisolone 40 mg/day. After three months, antibiotics were discontinued and patient was on steroid tapering regime. 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 patient was started to feel better and inflammation declined. Patient is currently taking only ADA and aspirin. He has no gastroenterological or musculoskeletal signs that implicate active disease. Laboratory findings from May 2019 are as follows: PLT 992 cells/mm³, Hb 139, WBC 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 (9). 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 (10).

All available TNF-α inhibitors are similarly efficacious for 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. analyzed data from 9 separate trials. A history of IBD was reported in 76 of 1,130 patients (6.7%). 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 (11). O’Toole et al. searched for cases of IBD provoked by ETA from an IBD Referral center and Food and drug association (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) (12). 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 (13). 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) (14). 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 (15). In addition, ETA only partially respects the production of TNF-α and may induce production of interferon-γ (IFN-
γ), favoring inflammation in the bowel mucosa and granuloma formation, while anti–TNF-α monoclonal antibodies inhibit IFN-γ release (13).

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 therapy and ADA 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 common condition. We have find 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. report a case of a 62-year old Italian with AS and bone involvement due to polycytemia rubra vera (JAK2V617 positive) (16). Case of 69 year old men with AS and ET who was treated with ETA and hydroxyurea and developed mantle cell lymphoma (17). Finally, a case of 34-year Korean man who developed ET following adalimumab therapy and 31-year Italian who was treated with infliximab and developed PRV, both of them shared similar genetic background (HLA-B27-positive, JAK2V617-negative) (18,19). Our patient was diagnosed with ET years before ETA was introduced, so there is no association between occurrence of disease and TNF-α inhibitor therapy.

Today, 17 years since TNF-α inhibitors were approved for use in AS, data from real-world national registries demonstrated no increased risk of overall malignancies compared to both the general population and patients with AS without TNF-α inhibitor treatment (20). The risk we accepted introducing TNF-α inhibitors in the treatment of ET was significant, regarding the fact that there was little data about adverse effects back in 2010. Our patient was carefully observed by hematologist, and there was any sign of ET transformation. On the contrary, ET was in remission.

According to our knowledge, there is no literature reporting association between AS, ET and CD. Although 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, appears 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 (21). Evidence suggests that 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 clinical trial of tofacitinib in AS and SpA (22). The new selective JAK1 inhibitors that are close for FDA approval for both AS and CD are upadacitinib and filgotinib (23). On the other hand, JAK2 is crucial for signal transduction downstream of the erythropoietin, thrombopoietin, and related receptors that control erythrocyte and megakaryocyte 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) was approved by the FDA in treatment of intermediate to high-risk MP and hydroxyurea-resistant or -intolerant PV. As for the ET, MAJIC trial showed the lack of superiority of ruxolitinib compared to current second-line therapies for these patients (24).

**Conclusion**

In 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. Existence of co morbidities additionally complicate treatment of such patients. Therefore, an individual approach is essential for every physician.

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