

The Effects of Tumor Necrosis Factor Inhibitors in a Particular Association of Psoriatic Arthritis and Behcet Disease

ANCA EMANUELA MUSETESCU^{1#}, ALESANDRA FLORESCU^{2*}, ANA-MARIA BUMBEA^{3#}, LUCIAN MIHAI FLORESCU⁴,
PAULINA LUCIA CIUREA¹, ANDREI BONDARI⁴, DAN NICOLAE FLORESCU⁵, SIMONA BONDARI⁴

¹ University of Medicine and Pharmacy of Craiova, Department of Rheumatology, 2-4 Petru Rares Str., 200349, Craiova, Romania

² University of Medicine and Pharmacy of Craiova, 2-4 Petru Rares Str., 200349, Craiova, Romania

³ University of Medicine and Pharmacy of Craiova, Department of Medical Rehabilitation, 2-4 Petru Rares Str., 200349, Craiova, Romania

⁴ University of Medicine and Pharmacy of Craiova, Department of Radiology and Medical Imaging, 2-4 Petru Rares Str., 200349, Craiova, Romania

⁵ University of Medicine and Pharmacy of Craiova, Department of Gastroenterology, 2-4 Petru Rares Str., 200349, Craiova, Romania

The current case report presents a patient diagnosed with Behcet disease in concurrence with psoriatic arthritis, leading to a complex treatment, difficult management and challenging approach of both rheumatic disorders. After treatment with synthetic disease-modifying drugs and three different TNF inhibitors, the patient developed pulmonary tuberculosis, followed by tuberculosis spondylodiscitis, even after proper anti-tuberculosis therapy.

Keywords: Behcet disease, psoriatic arthritis, tuberculosis spondylodiscitis, TNF inhibitors

Psoriatic arthritis (PsA) is a chronic inflammatory disease characterized by the presence of both peripheral joint and axial spine involvement, in concurrence with psoriatic lesions and in the absence of rheumatoid factor. The term PsA comprises one of the five clinical forms: symmetrical polyarthritis, asymmetrical oligoarthritis, distal interphalangeal joint involvement, spondylitis and arthritis mutilans [1]. The central feature of the disease is considered to be the involvement of the enthesis in the inflammatory process. Other extra-articular manifestations include dactylitis, tenosynovitis and tendinitis, but also systemic involvement of the nails, eyes, heart and bowel [2].

Behcet disease (BD) is a multisystem disorder defined by the presence of recurrent oral and genital ulcers, eye, skin, gastrointestinal tract, neurological and vascular manifestations, but also articular involvement such as peripheral arthritis, usually involving the knees, ankles, wrists elbows and axial inflammatory processes in the form of sacroiliitis and enthesitis [3].

Clinical overlaps between BD and the spondyloarthropathies (SpA) group have been frequently described in literature mostly due to the presence of sacroiliitis in both pathologies [4].

Treatment in PsA has evolved over the past years from conventional synthetic disease-modifying drugs such as methotrexate, leflunomide and sulphasalazine to more targeted therapies - biological drugs. Of great importance are the tumor necrosis factor inhibitors (TNFi).

Approved TNFi for PsA include infliximab - a G1 immunoglobulin (IgG1) chimeric monoclonal antibody against TNF- α , etanercept - a dimeric fusion protein between two soluble domains of p75 receptor and the Fc fragment of IgG1, adalimumab - a fully human monoclonal antibody against TNF- α , golimumab - a fully humanized monoclonal antibody against TNF- α and certolizumab pegol - a fully humanized Fab fragment against TNF- α . The same TNFi have shown significant improvement of the outcome

of uveitis in patients with BD, except for etanercept with conflicting results [5].

Experimental part

Case report

We present the case of a 34-year old male admitted in the Department of Rheumatology with a 3-month history of recurrent bipolar oral and genital aphthosis, papulopustular lesions on the trunk and upper extremities and lower back pain, panuveitis of the right eye, intense biological inflammatory syndrome with C reactive protein levels (CRP) of 123.73 mg/L and erythrocyte sedimentation rate (ESR) of 98 mm/h. The radiograph of the pelvis showed left sacroiliitis, while the magnetic resonance imaging of the hips revealed bilateral coxitis. He was diagnosed with BD and started on methotrexate 7.5 mg per week, folic acid 5 mg per week, methylprednisolone 32 mg per day in tapering doses to 16 mg per day and colchicine 1 mg per day.

Upon reevaluation, three months later, the clinical symptoms had minimized and both CRP and ESR levels were within normal range.

Two years after being diagnosed with BD, the patient developed psoriatic lesions on the scalp and inflammatory pain of the small joints of the hands and knees.

Clinical examination revealed psoriatic lesions on the scalp, between the eyebrows and behind the ears, pain at palpation of the wrists, second and third bilateral metacarpophalangeal (MCP) joints and proximal interphalangeal (PIP) joints, swollen third digit of the right hand, positive Patrick's and Eriksen maneuver, painful and swollen right knee and pain at palpation of both ankles.

Laboratory tests showed an intense inflammatory syndrome with CRP levels of 32 mg/L and ESR levels of 44 mg/L, blood glucose levels of 154 mg/dL, negative rheumatoid factor, anti-citrullinated protein antibodies and human leukocyte antigen (HLA)-B27.

* email: alesandratoroianu@yahoo.com

The authors contributed equally to the manuscript and share first authorship.

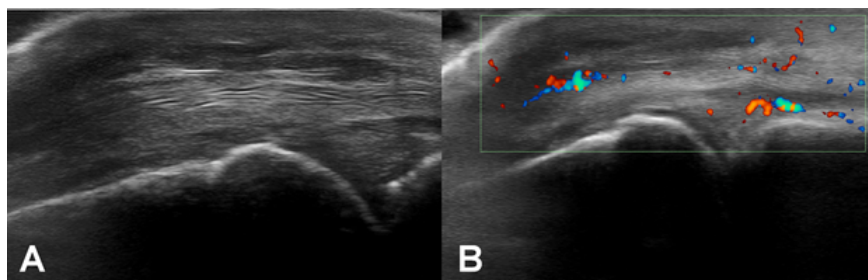


Fig. 1 (A, B). Longitudinal scans of the third dorsal MCP joint in grey-scale (A) and power Doppler (B) revealing moderate synovial proliferation of the third left dorsal MCP joint, hypoechoic extensor digitorum tendon, peritendinous edema with grade 2 power

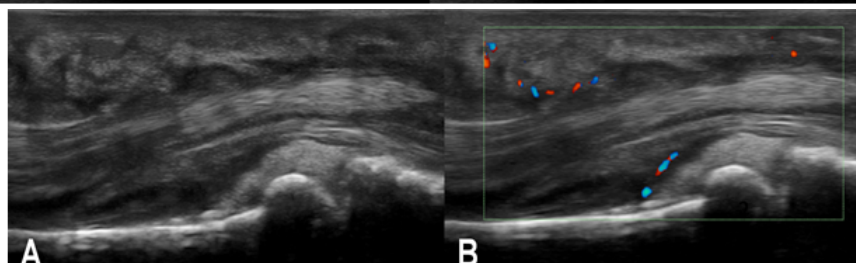


Fig. 2 (A, B). Longitudinal scans in grey-scale (A) and power Doppler (B) of the third right digit showing an aspect of dactylitis with grade 2 synovial proliferation of the MCP joint, tenosynovitis of the flexor digitorum tendon and subcutaneous edema, with grade 2 power Doppler signal

Musculoskeletal ultrasound (MUS) of the hands highlighted the presence of grade 2 synovial proliferation of the third right MCP and PIP joints, grade 2 tenosynovitis of the flexor digitorum tendon and subcutaneous edema, suggestive for dactylitis, aspect of peritendon extensor tendon inflammation (PTI) of the left third digit - moderate synovial proliferation of the third left dorsal MCP joint, hypoechoic extensor digitorum tendon, peritendinous edema with grade 2 power Doppler signal, characteristic for psoriatic arthritis and also, grade 2 synovial proliferation of the right wrist, second and third left MCP joints and bilateral third and fourth PIP joints (fig. 1, 2). MUS of the right knee revealed grade 2 synovial proliferation in the suprapatellar recess (fig. 3).

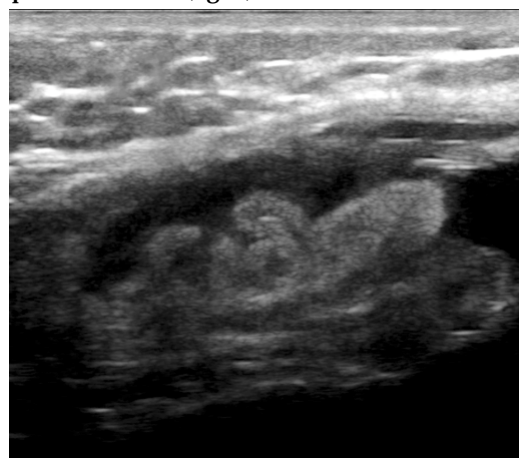


Fig. 3. Longitudinal suprapatellar scan in grey-scale - mild knee joint effusion and grade 2 synovial proliferation with villonodular aspect.

The patient had also developed complications due to the prolonged corticosteroid treatment in high doses, leading to cushingoid appearance, acneiform eruptions on the posterior thorax and upper extremities, arterial hypertension, type 2 diabetes, cataracts of both eyes and osteoporosis.

The patient was diagnosed with psoriatic arthritis according to CASPAR criteria in concurrence with BD and was started on azathioprine 100 mg per day, the dose of methotrexate was increased to 20 mg per week, folic acid 5 mg per week and methylprednisolone was lowered to a dose of 4 mg per day.

The patient was non-responsive to treatment, the inflammatory markers remaining increased, so he was started on biological therapy with adalimumab. Prior to treatment the patient had a positive Quantiferon TB Gold

Test and was administered prophylactic therapy with isoniazid for 6 months. After 5 years of treatment, the patient lost response to adalimumab and was switched to etanercept.

Three years after, the patient lost response to etanercept, with laboratory test showing an inflammatory biological syndrome with CRP levels of 18.52 mg/dL and VSH levels of 52 mm/h, so the patient was switched to golimumab.

Three months after starting treatment the patient developed night sweats, high fever, mucous cough and weight loss. He was diagnosed with pulmonary tuberculosis (TB) and followed protocol treatment for 12 months. During the treatment for tuberculosis the patient stopped all the medication for the rheumatic diseases.

One year later, the patient was admitted in the Department of Rheumatology with permanent lower back pain, with no response to anti-inflammatory drugs and painkillers.

Clinical examination revealed pain at mobilization of the spine and paravertebral muscle contraction, especially in the lumbar segment. Laboratory tests highlighted an intense inflammatory syndrome with CRP levels of 62.47 mg/L and ESR levels of 96 mm/h, but also leukocytosis $11970/\text{mm}^3$.

An MRI exam of the lumbar spine was performed, showing massive bone marrow edema (Modic I type changes) affecting both L2 and L3 vertebral bodies that extends to the L2 and L3 pedicles bilaterally. The inflammatory changes also extend to the L2-L3 intervertebral disc which is difficult to delineate and appeared to be completely reduced in size. Furthermore, the posterior borders of the vertebral bodies L2 and L3 protrudes inside the spinal canal and generate a massive compressive effect on the dural sac. The aspect depicted on this MRI examination is highly suggestive for spondylodiscitis. The MRI examination also revealed multiple round or oval lesions with fluid signal intensity located on both sides of the L2 and L3 vertebral bodies, developed inside the psoas muscles. Due to the allergic terrain of the patient, the radiologists decided not to administer an intravenous contrast agent. Therefore, in the absence of contrast administration, these lesions can be considered fluid collections, but given their location inside the psoas muscles bilaterally and the clinical context, the aspect is highly suspicious for bilateral paravertebral abscesses developed inside the psoas muscles (fig. 4, 5).

The patient was transferred to the Neurosurgical Department for surgical treatment of the lesion. Decompression at L2-L3 level, arthrodesis and posterior fixation at L1-L4 level were performed with tissue sampling

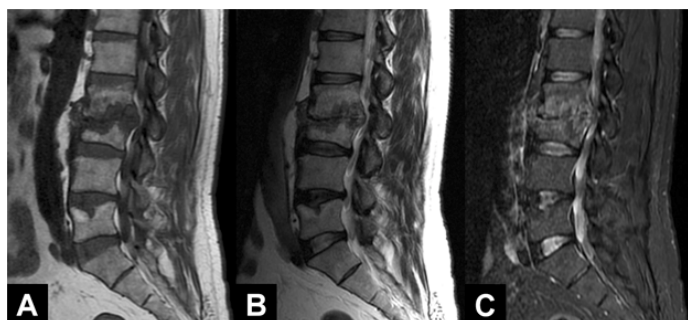


Fig. 4 (A-C). The MRI examination of the patient performed on a 1.5T MRI machine. The endplates adjacent to the L2-L3 intervertebral disc have a diffuse, irregular outline. There is massive bone marrow edema (Modic I type changes) affecting both L2 and L3 vertebral bodies (hypointense on T1-weighted image (A); hyperintense on T2-weighted image (B); hyperintense on STIR image (C)) that extends to the L2 and L3 pedicles bilaterally. The inflammatory changes also extend to the L2-L3 intervertebral disc which is difficult to delineate and appears to be completely reduced in size. Furthermore, the posterior borders of the vertebral bodies L2 and L3 protrude inside the spinal canal and generate a massive compressive effect on the dural sac. The aspect depicted on this MRI examination was highly suggestive for spondylodiscitis

for microbiological diagnosis. Studies of the samples were conducted – cultures and Gram stain were negative, Ziehl-Neelsen stain revealed scarce acid-fast bacilli compatible with *Mycobacterium tuberculosis*. The diagnosis was tuberculosis spondylodiscitis and the patient had a favorable evolution after surgery and medical treatment.

Results and discussions

Our patient was diagnosed with Behçet disease in concurrence with psoriatic arthritis, leading to a complex treatment, difficult management and challenging approach of both rheumatic disorders in order to achieve low disease activity or even remission.

Numerous studies in literature have attempted to include BD in the SpA group. The hypothesis is based on the absence of rheumatoid factor and rheumatoid nodules in both groups, the presence of radiological sacroiliitis and a tendency for familial aggregation. The frequency of sacroiliac joint involvement is increased in SpA in compared to BD, thus the inclusion of BD in the SpA group is certainly controversial [6].

Also, the presence of HLA-B27 in BD and SpA has been thoroughly debated. However, a higher prevalence of HLA-B27 has been described in SpA, while BD has been associated more frequently with HLA-B51 [7].

In terms of peripheral joint involvement, BD differs from PsA due to its typical non-erosive, non-deforming, mono or oligoarticular distribution, usually affecting the knees or the ankles. Nonetheless, the recommendation in patients with BD and psoriasis with arthritis/arthralgias is to evaluate and carefully differentiate BD joint involvement from PsA [8].

Nevertheless, cases that concurrently meet the criteria for BD and SpA, mainly ankylosing spondylitis, but also PsA have been encountered in literature, emphasizing on the possible coexistence of both pathologies, as in the case of our patient [9].

Corticosteroid treatment for BD lead to several complications in the case of our patient including the development of arterial hypertension, cataracts, type 2 diabetes mellitus and osteoporosis. Treatment with corticosteroids should include a loading dose, followed by low maintenance doses, with further dose tapering, in order

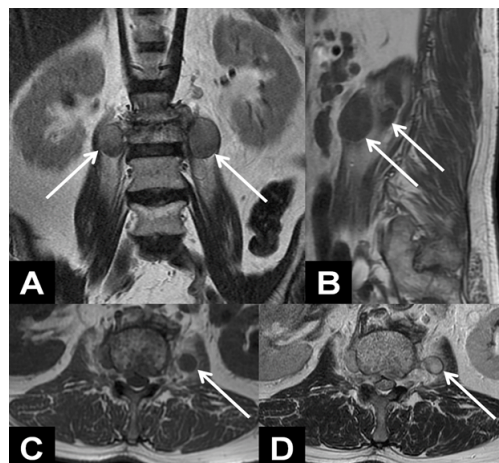


Fig. 5. (A-D). The MRI examination of the patient performed on a 1.5T MRI machine. Coronal T2-weighted images (A) and sagittal T1-weighted images (B) revealed multiple round or oval lesions with fluid signal intensity located on both sides of the L2 and L3 vertebral bodies, developed inside the psoas muscles. Non-contrast axial T1-weighted (C) and axial T2-weighted (D) images highlight the hypointense T1 and hyperintense T2 signal intensity of these lesions. The aspect is highly suspicious for bilateral paravertebral abscesses developed inside the psoas muscles

to prevent the risk of fractures and other complications [10]. Other known risk factors for the development of osteoporosis are smoking, low calcium intake, low vitamin D levels, certain inflammatory diseases such as rheumatoid arthritis, early menopause in women, medication used in the treatment of cancer and chronic kidney or liver disease [11,12].

TNF inhibitors have been widely used in many rheumatic diseases including PsA due to their substantial therapeutic effects with great results in inducing and maintaining remission. However, a high risk of developing pulmonary tuberculosis and opportunistic infections has been observed in patients treated with TNF inhibitors. Prophylaxis with anti-TB standard medication is indicated in patients with latent TB infections before or during anti-TNF- α treatment, decreasing the risk of TB reactivation [13].

TNF- α plays an important role in the protection of the organism against infections, particularly TB. The key defense mechanism is considered the capacity of TNF- α to maintain the formation and function of the TB granuloma which prevents the *Mycobacterium* bacilli from disseminating into the bloodstream. This mechanism may justify the increased risk of TB in patients undergoing treatment with TNF inhibitors. Also, several studies have proved a higher risk of TB in patients treated with monoclonal antibodies anti-TNF- α than in those treated with soluble receptors of the same class [14].

In the case of our patient, three TNF inhibitors used over a long period of time, diabetes and long-term treatment with glucocorticoids lead to the development of pulmonary tuberculosis, even if the patient had followed proper prophylactic protocol.

Tuberculosis spondylodiscitis (TS) is a rare, severe type of extra-pulmonary TB which accounts for 50% of all cases diagnosed with skeletal TB, usually involving the lower thoracic or the upper lumbar vertebrae. Among the risk factors for TS, diabetes mellitus, chronic renal failure, prolonged corticosteroid treatment, anti-TNF- α medication and HIV disease have been cited in literature. Current

recommendations state that a patient presenting with chronic back pain and a history of pulmonary tuberculosis should raise the suspicion of TS, as in the case of our patient [15].

Aseptic discitis and spondylodiscitis, described as the Andersson lesion is found in both psoriatic arthritis and Behcet disease. Associated to ankylosing spondylitis and psoriatic arthritis, the presence of squared vertebral bodies, disco-vertebral erosions with marked endplate sclerosis and ossifications of the annulus fibrosus and paramarginal ossifications are suggestive for aseptic spondylodiscitis due to fracture and secondary pseudoarthrosis. In Behcet disease, although peripheral joints are most often involved, spinal disease with few case reports of aseptic spondylodiscitis of the cervical spine are described. Nevertheless, in our particular case of Behcet disease - psoriatic arthritis association, the MRI aspect pleads for TS because of the protrusion of the posterior wall with compressive effect on the dural sac and the presence of bilateral paravertebral fluid collections developed inside the psoas muscles at L2-L3 level [16].

Conclusions

The current report presents a rare case of tuberculosis spondylodiscitis in a patient with Behcet disease and psoriatic arthritis, following corticosteroid treatment, synthetic disease modifying drugs and three biological drugs, adding value to the current literature data which provides little information regarding TS in patients with rheumatic pathologies.

References

- 1.SANKOWSKI, A.J., LEBKOWSKA, U.M., ŒWIKŒA, J., WALECKA, I., WALECKI, J., *Pol J Radiol*, **78**, no.1, 2013, p. 7-17.
- 2.WEGER, W., *G Ital Dermatol Venereol*, **146**, no.1, 2011, p. 1-8.
- 3.GUL, A., *Current Drug Targets*, **4**, no.1, 2005, p. 81-83.

- 4.YAZICI, H., TUZLACI, M., YURDAKUL, S., *Annals of the Rheumatic Diseases*, **40**, no.6, 1981, p. 558-559.
- 5.MONACO, C., NANCHAHAL, J., TAYLOR, P., FELDMANN, M., *Int Immunol*, **27**, no.1, 2015, p. 55-62.
- 6.CHANG, H.K., LEE, D.H., JUNG, S.M., CHOI, S.J., KIM, J.U., CHOI, Y.J., BAEK, S.K., CHEON, K.S., CHO, E.H., WON, K.S., *J Korean Med Sci*, **17**, no.4, 2002, p. 524-529.
- 7.SAKLY, N., BOUMIZA, R., ZROUR-HASSEN, S., HAMZAOU, A., BEN YAHIA, S., AMARA, H., KHAIRALLAH, M., MAHJOUR, S., BERGAOU, N., GHEDIRA, I., *Ann N Y Acad Sci*, **1173**, 2009, p. 564-569.
- 8.CHO, S., CHO, S. B., CHOI, M. J., ZHENG, Z., BANG, D., *Journal of the European Academy of Dermatology and Venereology*, **27**, no.1, 2012, p. 113-118.
- 9.PADULA, A., CIANCIO, G., CANTINI, F., BAROZZI, L., SCARANO, E., NICCOLI, L., OLIVIERI, I., *Clin Rheumatol*, **18**, no.6, 1999, p. 499-500.
- 10.MUSETESCU, A.E., CIOROIANU, A., CIUREA, P.L., FLORESCU, D.N., GEORGESCU, C.V., FLORESCU, L.M., BUMBEA, A.M., *Rev. Chim. (Bucharest)*, **69**, no.4, 2018, p. 971-974.
- 11.MUSETESCU, A.E., CIUREA, P.L., CIOROIANU, A., FLORESCU, L.M., BUMBEA, A.M., PIRSCOVEANU, D.F.V., BRAILA, A.D., *Rev. Chim. (Bucharest)*, **69**, no.5, 2018, p. 1122-1124.
- 12.FLORESCU, L.M., GHEONEA, I.A., ENE, D., FLORESCU, D.N., BRAIA, N., PIRICI, D., ANDRU, V., FORPOFOIU, M.C., CIUREA, T., *Rom J Morphol Embryol*, **59**, no.1, 2018, p. 297-302.
- 13.CAO, B.L., QASEM, A., SHARP, R.C., ABDELLI, L.S., NASER, S.A., *World J Gastroenterol*, **24**, no.25, 2018, p. 2764-2775.
- 14.TUBACH, F., SALMON, D., RAVAUD, P., ALLANORE, Y., GOUPILLE, P., BRÉBAN, M., PALLOT-PRADES, B., POUPLIN, S., SACCHI, A., CHICHEMANIAN, R.M., BRETAGNE, S., EMILIE, D., LEMANN, M., LORTHOLOLARY, O., MARIETTE, X., *Arthritis Reum*, **60**, no.7, 2009, p. 1884-1894.
- 15.RAJASEKARAN, S., SOUNDARARAJAN, D.C.R., SHETTY, A.P., KANNA, R.M., *Global Spine J*, **8**, no.S3, 2018, p. 96S-108S.
- GUMA, M., OLIVÉ, A., PEREZ, R., HOLGADO, S., ORTIZ-SANTAMARIA, V., TENA, X., *Clin Exp Rheumatol*, **19**, no.6, 2001, p. 740-747

Manuscript received: 23.07.2018