Coexistence of systemic lupus erythematosus after TNF inhibitor therapy in patient with ankylosing spondylitis

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Summary

A 33-year-old single Thai male was diagnosed with ankylosing spondylitis that not responded to treatment with conventional disease-modifying antirheumatic drugs (csDMARDs) then he received tumor necrosis factor (TNF) inhibitor and developed anemia and thrombocytopenia and positive test for antinuclear antibody (ANA) positive 1:320 homogeneous pattern, it is considered secondary to systemic lupus erythematosus (SLE) induced by the use of TNF inhibitors.

Case presentation

A 33-year-old single Thai male, diagnosed with ankylosing spondylitis three years ago, presented with chronic peripheral joint pain, uveitis, and plantar fasciitis. He was found to be Human leukocyte antigen-B27 (HLA-B27) positive, and pelvic X-rays revealed bilateral stage 3 sacroiliitis. The patient had not responded to treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and csDMARDs (sulfasalazine and methotrexate) and was initiated on infliximab two months prior to presentation. However, due to adverse effects, Infliximab was discontinued and switched to adalimumab.

The patient reported a two-month history of anorexia and a weight loss of 7 kilograms (10% of body weight). Three days before hospital admission, he developed low-grade fever, dry cough, and fatigue. Upon evaluation at a private hospital, anemia and pneumonia were noted, and he received a red blood cell transfusion and was referred to Rajavithi Hospital. Physical examination at our hospital revealed fever, pallor, and right cervical lymphadenopathy. Laboratory investigations showed hemoglobin 7.7 gm/dL, hematocrit 20.4%, white blood cell count 10,960 cells/mm^3, and platelet count 234,000 cells/mm^3. Chest X-ray revealed reticulonodular infiltrates in the right upper lung. Sputum examination confirmed the presence of drug-sensitive mycobacterium tuberculosis. A biopsy of the right cervical lymph node also demonstrated mycobacterium tuberculosis. Further tests revealed Human Immunodeficiency virus (HIV) infection (Cluster of Differentiation 4 (CD4) count 15) and latent syphilis, for which the patient was treated with Penicillin G and an anti-tuberculosis regimen (isoniazid/ Rifampicin/ Pyrazinamide/ Ethambutol), along with antibiotics.

Two weeks after initiating tuberculosis treatment, the patient continued to have persistent fever. Repeated laboratory tests showed hemoglobin 6.4 g/dL, hematocrit 17.6%, white blood cell count 2,660 cells/mm^3, and platelet count 32,000 cells/mm^3. Bone marrow examination showed normal cellular trilineage marrow with a 70:30 cell-to-fat ratio, and no bacteria, fungi, or mycobacterium tuberculosis were identified. A computerized tomography scan (CT scan) of the chest and abdomen revealed multifocal centrilobular nodules with a "tree-in-bud" appearance in both lungs, consolidation and atelectasis in the superior segment of the left lower lobe, and multiple enlarged lymph nodes in the lower cervical, axillary, intraabdominal, pelvic, and groin regions, measuring up to 3.4 cm. Further serological tests were positive for ANA (1:320, homogeneous pattern), while Anti-double stranded DNA (anti-dsDNA) and anti-Smith (anti-Sm) were negative. Complement levels were low (complement 3: 0.81 g/L [0.82-1.85], complement 4: 0.1 g/L [0.15-0.53]), and the direct Coombs test was weakly positive, while the indirect Coombs test was negative.

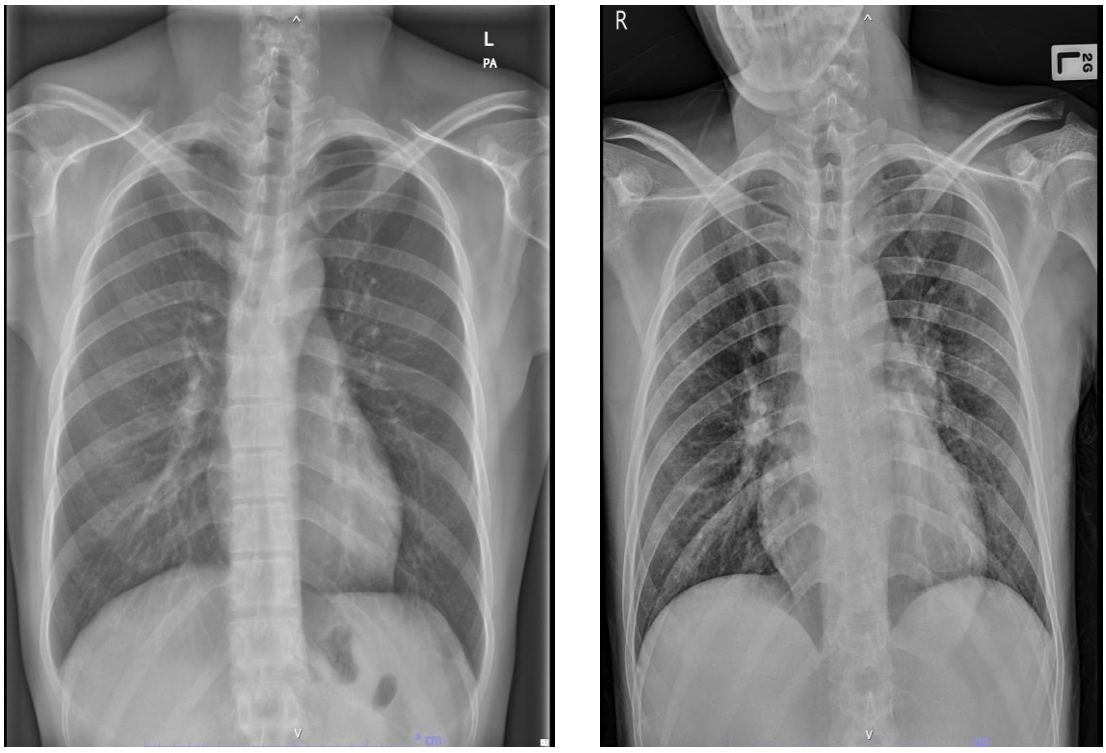
The patient was initially treated with prednisolone 20 mg/day for one week, followed by 50 mg/day for another week, and then intravenous methylprednisolone 500 mg daily for three days, in

combination with dapsone and intravenous immunoglobulin (IVIG) (1g/kg for two days). Despite treatment with medium- to high-dose oral glucocorticoids, intravenous methylprednisolone, dapsone, and IVIG, despite the white blood cell count and hematocrit returning to normal levels but the platelet count remained low. Therefore, the treatment was escalated with high-dose oral glucocorticoids, danazol, azathioprine, and eltrombopag.

Table 1: The initial investigations

Parameters	Results
Hemoglobin (g/dL)	7.7
Hemotocrit (%)	20.4
Mean corpuscular volume (fL)	79.2
RBC distribution width (mm.)	23
White blood cell count (cells/mm^3)	10,960
Polymorphonuclear cell (%)	74.3
Lymphocyte (%)	17.3
Monocyte (%)	8.2
Eosinophil (%)	0.0
Basophil (%)	0.2
Platelet count (cells/mm^3)	234,000
Lactate dehydrogenase (U/L)	808
Serum ferritin (µg/L)	3,207
Serum iron (µg/dL)	19
Total iron binding capacity (µg/dL)	100
SI/ TIBC	0.19
Reticulocyte count (cells/mm^3)	0.9
Direct antiglobulin test	Weakly positive
Indirect antiglobulin test	Negative
ESR (mm./ hour)	107
High sensitivity-C reactive protein (<0.5 mg/L)	21.09
Urine analysis	RBC 5-10, WBC 1-2, protein 1+, glucose negative
Total protein (g/dL) (6.6-8.7)	8.4
Albumin(g/dL) (3.5-5.2)	2.5
Globulin(g/dL)	5.9
Total bilirubin(mg/dL) (0.1-1.2)	0.47
Direct bilirubin(mg/dL) (< 0.3)	0.29
Aspartate transferase (U/L) (0-50)	60
Alanine transaminase (U/L) (0-50)	23
Alkaline phosphatate (U/L) (35-104)	226
Antinuclear antibody (ANA)	positive 1:320, homogeneous pattern
Complement 3 (0.81-1.85)	0.81
Complement 4 (0.15-0.53)	0.1
Anti-dsDNA	Negative
Anti-Sm	Negative
Anti-HIV	Reactive
%CD4	15
CD4	177 cell/cum
HbsAg, anti-HBc, anti-HBs, anti-HCV	Negative
RPR (Rapid Plasma Reagin)	1:2
Syphilis	Reactive
Cryptococcal antigen	Negative

Sputum for AFB Sputum gene x pert	Positive 2+ Mycobacterium tuberculosis detect, no rifampicin resistance
Right cervical lymph node tissue biopsy	- Acute necrotizing granulomatous lymphadenitis - - No microorganism is detected by AFB and GMS staining - Negative for malignancy - **Positive PCR for mycobacterium tuberculosis complex**
CT scan of chest with whole abdomen with contrast	Multifocal areas of centrilobular nodules/ tree in bud appearance in both lungs, consolidation and atelectasis at superior segment of the left lower lung zone, multiple enlarged lower cervical/ axillary/intraabdominal/pelvis and both groins lymph nodes up to 3.4 cm.
Bone marrow biopsy	• Normocellular trilineage marrow with 70:30 of cell: fat ratio • **Wright strain, AFB, mAFB** not found • **PCR for TB:** MTB not detected • **Bacterial culture:** no growth in 3 days • **Fungus culture:** no growth in 30 days



(A) (B)

Figure1.

(A) Chest X-ray previous visit

(B) Chest X-ray at the diagnosis. Presence of reticular infiltration at left upper lung field.

Diagnosis

In this patient, the diagnosis was HIV infection accompanied by disseminated tuberculosis. Regarding the anemia and thrombocytopenia, it is considered TNF inhibitors induced systemic lupus erythematosus as the patient has a history of receiving TNF inhibitors for 2 months prior to the onset of thrombocytopenia, anemia, and fever. Additionally, ANA positivity and low complement levels were detected. The second most likely cause is secondary to HIV infection.

Treatment and Outcomes

For the disseminated tuberculosis and syphilis infections, the patient was treated with the standard regimen of isoniazid, rifampicin, ethambutol and pyrazinamide for 2 months followed by isoniazid and rifampicin for 4 months (2IRZE/4IR and intramuscular penicillin G 2.4 million units weekly, for 3 weeks. Antiretroviral therapy (ART) with the tenofovir/ lamivudine/ dolutegravir (TLD) regimen was initiated 4 weeks after starting the tuberculosis treatment.

The thrombocytopenia and anemia were suspected to be secondary to drug-induced autoimmune disease related to TNF inhibitors. Consequently, Infliximab was discontinued, and the patient was treated with prednisolone 20 mg/day for 1 week, followed by 50 mg/day for another week, then intravenous methylprednisolone 500 mg daily for 3 days, in combination with dapsone 100 mg/day and IVIG 1 g/kg for 2 days. Despite the white blood cell count and hematocrit returning to normal levels, the platelet count remained low. Treatment was continued with prednisolone 50 mg/day for 4 weeks, alongside azathioprine 50-100 mg/day, dapsone 100 mg/day, and danazol 200 mg/day. The prednisolone dose was successfully tapered after initiating eltrombopag 25 mg/day for 2 weeks, during which the platelet count was stabilized between 30,000-50,000 cells/mm^3.

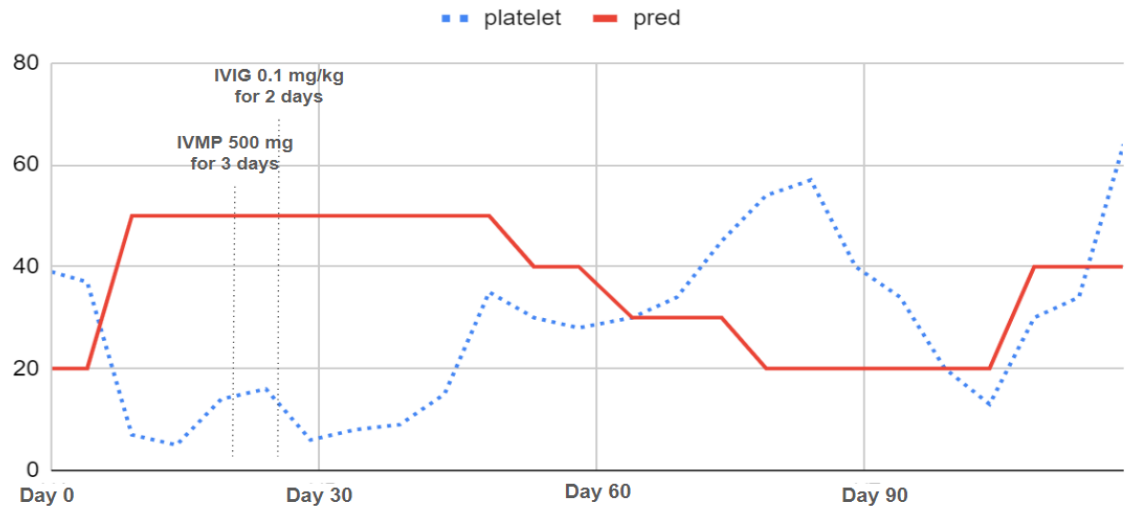


Figure 2 Platelet count and prednisolone dosage during treatment and follow up.

Table 2 Improvement of platelet count and medications during treatment and follow up

Duration (days)	0	15	30	30	60	90	105	120
Platelet (cells/mm^3)	39,000	5,000	6,000	6,000	6,000	40,000	13,000	64,000
Prednisolone (mg/day)	20	50	50	50	50	20	20	40
Azathioprine (mg/day)						100	100	100
Eltrombopag (mg/day)						25	25	25

Literature review and Discussion

From Figen Tarhan et al. “Coexistence of systemic lupus erythematosus and ankylosing spondylitis: another case report and review of the literature” found that the coexistence of systemic lupus erythematosus (SLE) and ankylosing spondylitis (AS) is very rare. Although it has been suggested that the very rare combination of the susceptibility genes of each disease may explain the rarity of coexistence, epidemiological data concerning the genetic risks for the coexistence of SLE and AS are not available.

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease of unknown etiology that may affect the skin, joints, kidneys, lungs, nervous system, serous membranes, and/or other organs of the body. Ankylosing spondylitis (AS) is a chronic inflammatory disease of the axial skeleton which manifests as inflammatory back pain and progressive stiffness of the spine.[1-2] These are two autoimmune rheumatologic diseases, which have a different etiopathogenesis as well as diverse clinical and genetic characteristics, are rarely seen together. To the best of our knowledge, there are only 9 reported cases of the coexistence of SLE and AS in the English literature.[3-11] Most of the cases are female and SLE generally precedes the occurrence of AS.

In our patient, Thai male AS who had been treated with TNF inhibitors then developed the onset of thrombocytopenia, anemia, and fever. Additionally, ANA positivity and low complement levels were detected. One of the explanations of these was coexistence of systemic lupus erythematosus and ankylosing spondylitis but as the previous report; the coexistence of these two diseases was very rare.

Another explanation of this patient was secondary to autoimmune disease induced by the use of TNF inhibitors. Induction of autoantibodies is frequently observed in patients treated with TNF inhibitors and the possible development of drug-induced lupus erythematosus (DILE) remains a matter of concern. The prevalence of DILE secondary to TNF inhibitors is estimated around 0.5-1% and clinical features include arthritis/arthralgia, rash, serositis, fever, myalgias, cytopenias, among others. According to the literature, DILE secondary to TNF inhibitors differs in several ways from the clinical and laboratory findings typically associated with classic DILE.

The study in Portugal; Ana Martins et al. had been estimated the incidence of induction of antinuclear antibodies (ANA) and DILE in a monocentric cohort of patients with spondyloarthritis and psoriatic arthritis treated with TNF inhibitors. [12]

In this study, the spondyloarthritis group, and the psoriatic arthritis group were included. This study observed high serology conversion rates (positive ANA in 67.9% and 58.6% of patients with spondyloarthritis and psoriatic arthritis, respectively), with similar conversion rates between different TNF inhibitors. Three patients with spondyloarthritis (1.0%) and 1 patient with psoriatic arthritis (0.9%) developed DILE. Etanercept was the causative agent in 2 cases, infliximab and adalimumab in 1 case, each. Peripheral arthritis (new onset or abrupt worsening) occurred in 2 cases, serositis in 1 case, constitutional symptoms in 2 cases, subnephrotic proteinuria in 1 case, lymphopenia in 2 cases and hypocomplementemia in 1 case. Specific treatment was prescribed to the 4 patients (oral corticosteroids) and they achieved complete recovery. After TNF inhibitors treatment interruption, no patient had recurrent disease. Patients with DILE had a significantly longer disease duration (> 8.4 years; p=0.04) and a significantly longer duration of therapy with TNF inhibitors (> 4.0 years; p=0.04) when compared to patients without DILE.

After discontinuance of TNF inhibitors, our patient improved in thrombocytopenia and anemia by treatment with prednisolone, immunosuppressive drug and TPO-receptor agonist by rheumatologist and hematologist.

Conclusion

The coexistence of SLE and AS is very rare. Including the present case, there are only nine reported cases. Moreover, the development of DILE secondary to TNF inhibitors is rare too. Although it is rare, drug-induced lupus can occur. Therefore, in patients receiving TNF inhibitors, it is essential to monitor for many side effects such as drug-induced lupus

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