

# TNF- $\alpha$ inhibitor administration in psoriatic arthritis patient with latent tuberculosis and cardiovascular disease as an extra articular manifestation



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## ABSTRACT

**Introduction:** Psoriatic arthritis is a spondyloarthropathy subtype with a broad clinical spectrum and diverse symptoms. The use of biological disease-modifying antirheumatic medications (DMARDs), such as TNF inhibitors is recommended as pharmacological therapy for PSA in cases of axial involvement and high disease activity level. Since Indonesia has the second-highest tuberculosis (TB) cases globally, and patients receiving TNF inhibitors have an elevated risk of latent TB reactivation, evaluation of latent TB before starting TNFi is necessary and challenging.

**Case Presentation:** A 63-year-old male psoriatic arthritis patient with bilateral hip joint osteoarthritis, bilateral knee effusions and bilateral frozen shoulder. The patient also had coronary heart disease with a history of underwent coronary artery bypass graft (CABG), diabetes mellitus type 2 and confirmed latent TB. Psoriatic arthritis had high activity based on the Bath Ankylosing Spondylitis Disease Activity (BASDAI) score and Ankylosing Spondylitis Disease Activity Score (ASDAS). TNF inhibitor treatment started a month after latent TB treatment. The patient responded satisfactorily to the TNFi treatment, as demonstrated by clinical evaluation and decreased disease activity. Latent TB treatment was continued for up to six months, followed by latent TB activity monitoring during TNFi administration to prevent latent TB reactivation.

**Conclusion:** This case highlights the challenges in management of axial psoriatic arthritis patients with high disease activity, concomitant latent TB infection, and early extra-articular symptoms of cardiovascular disease.

**Keywords:** Spondyloarthritis, psoriatic arthritis, axial psoriatic arthritis, latent tuberculosis, TNF inhibitor.

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## INTRODUCTION

Spondyloarthritis is a group of interrelated chronic inflammatory rheumatic disorders with similar characteristics and a common hereditary predisposition yet manifest in different symptoms.<sup>1,2,3</sup> Psoriatic arthritis (PSA) is a subtype of spondyloarthropathy with a prevalence of 0.06% in Southeast Asia.<sup>4</sup> PSA has a broad clinical spectrum with diverse symptoms, including skin and nail changes, peripheral joint inflammation, enthesitis, dactylitis, and axial symptoms.<sup>4</sup> PSA patients with axial involvement (axial PSA or psoriatic spondylitis) exhibit inflammatory low back pain and joint stiffness, which are confirmed by radiological findings such as sacroiliitis and spine ossification. PSA patients with axial involvement have a higher disease activity and worse quality

of life.<sup>5</sup>

Uveitis, colitis, metabolic syndrome (hypertension, dyslipidemia, obesity, and insulin resistance), and cardiovascular disease are all common extra-articular symptoms and comorbidities of PSA. Cardiovascular disease increases mortality and is the leading cause of death in PSA patients. A complete assessment of PSA patients should be carried out, including the possibility of this comorbidity.<sup>4</sup>

The use of biological disease-modifying antirheumatic medications (bDMARD), such as tumor necrosis factor (TNF) inhibitors (TNFi) or interleukin 17 (IL-17) inhibitors (IL-17i), are recommended as pharmacological therapy for PSA in cases of axial involvement and high disease activity.<sup>6</sup> As Indonesia has second-highest tuberculosis (TB) cases globally, and patients receiving TNFi medication have

an increased risk of latent TB reactivation, evaluation of latent tuberculosis infection (LTBI) prior to TNFi therapy is necessary. In this case report, we highlight some important issues of a PSA patient with latent TB and cardiovascular disease receiving TNFi.

## CASE PRESENTATION

A 63-year-old male from Papua, self-employed, married, Javanese, presented to the Rheumatology Clinic at Dr Soetomo General Academic Hospital with joint swelling and pain complaints. The patient had joint pain ten months before admission and the pain was primarily in the pelvis and persistent, particularly at night, worsened with rest, and improved with activity. The patient felt stiffness roughly an hour after getting up. Pain in knee,



**Figure 1.** Clinical appearances of the patient. Red rashes on body abdomen (A), chest (B), arms (C) and knees (D and E); and nodules on the earlobe (F).

**Figure 2.** X-ray examination of patient showing the chest (A), pelvic (B), knee (C-F) and palms (G and H).

back, and neck joints and the fingers, toes, soles of the feet, and bilateral ankles were also reported. Stiffness improved when the patient started to move. No numbness or radiating pain during walking. The patient also complained of swelling in the knees and finger joints and the pain increased in last three months prior the admission. The knee and the hip joints crepitated when forced to walk. Moreover, changing position from sitting to standing caused severe back discomfort, making it difficult for the patient to stand or walk. The fingers lost grip ability and the patient's

mobility became increasingly problematic, particularly while lifting weights or loads.

He reported the fever, itching, and red rashes around the elbows, arms, thighs, knees, and abdomen a month before the admission (Figure 1A-E). There were nodules on the earlobe, nose bridge, fingers, soles with no soreness; redness at the site of the papules and nodules (Figure 1F). The patient denied any numbness in specific skin sites or nail alterations and skin peeling. The patient also observed no cough, night sweats, or weight loss. No complaints about urination or defecation.

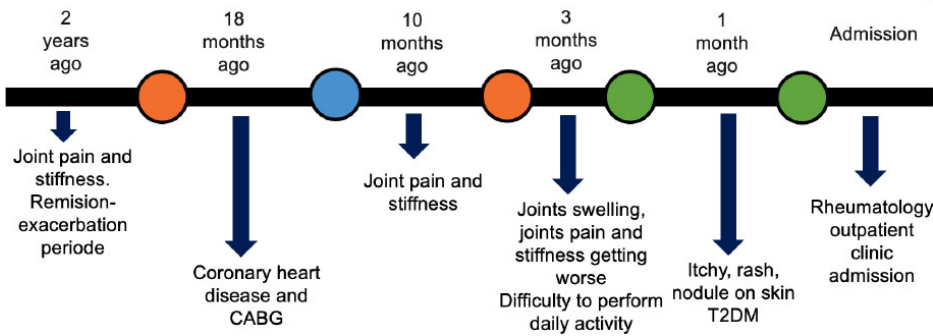
The patient previously went to the local doctor and received medications such as diclofenac sodium and methylprednisolone (MP) and the pain diminished transiently after using diclofenac sodium. The patient received cetirizine and hydrocortisone ointment to reduce the itching. The patient was diagnosed with type 2 diabetes mellitus (DMT2) and received glimepiride 2 mg and metformin 500 mg. The patient also had coronary heart disease since 18 months ago and underwent coronary artery bypass graft (CABG) surgery at Dr Soetomo General Academic Hospital 14 months ago. The patient received acetylsalicylic acid, candesartan, bisoprolol, spironolactone and simvastatin regularly from standard treatment from the Cardiology Clinic.

The patient had had occasional pain in the lower right hip and stiffness in the fingers for two years without seeking treatment. No problems with the lungs, liver, or kidneys. No family members had similar joint diseases or symptoms, chronic cough, or currently or previously receiving TB treatment. Any history of drug or food allergies, smoking, alcohol, or alternative medicine was denied. The patient had never experienced skin numbness or been in contact with leprosy patients.

The general condition was weak, fully aware (Glasgow coma scale (GCS)456) with blood pressure of 109/72 mmHg, pulse of 98 beats per minute, and respiratory rate of 20 cycles per minute. The body temperature was 37.1°C (axillary), with a visual analog scale (VAS) score of 7. Head and neck examination was not anemic/icteric or showed dyspneal signs. No significant abnormalities were found on physical examination of the thorax, abdomen, and extremities.

#### Evaluation of gait, arms, legs, and spine (GALS)

1. Gait: Due to pain in the pelvis and back, the patient had difficulties changing positions from sitting to standing. The patient arrived at the Rheumatology Clinic in a wheelchair.
2. Arms: Right metacarpophalangeal (MCP) 1,2,3,4, and left MCP 2,3,4,5 had edema and pain, and right distal interphalangeal (DIP) 2,3,4 and left DIP 2,3,4 had deformity of unable



**Figure 3.** Time of sequences of patient' condition.



**Figure 4.** Follow-up X-ray examination of patient showing the lumbosacral (A and B) and the cervical (C and D).

for the handgrip. The shoulder and wrist joints are soreness and warmth, without any elbow pain. The shoulder and wrist have a restricted range of motion (ROM).

3. The bilateral hip joints were limited in leg flexion, extension, internal and external rotation. The knee joint had effusion and limited range of motion. There was no Achilles tendon tendinitis or plantar fasciitis on the soles and no effusion in the lower extremities.
4. Spine: there was some limitation of ROM in the cervical joints and reduced ROM for flexion. Occipital to wall test was 2 cm, tragus to the wall was 10 cm, chest expansion was 3.5 cm, and Schober test was 12.5 cm.

Observed skin efflorescence included multiple follicular papules clustered on an erythematous base, without pus or vesicles in the trunk, abdomen, superior extremities (predominantly extensor), and femoral areas. There were multiple nodules with erythematous base diameters of 0.5–1 cm in the bilateral auricular region, nasal root, palm, and sole.

**Laboratory parameter**

At the initial visit to the Rheumatology Clinic the hemoglobin 13.1 g/dL; hematocrit 38.9%; leukocytes 8.370/mm<sup>3</sup>; neutrophils 65.4%; lymphocytes 24.9%; platelets 368.000/mm<sup>3</sup>; erythrocyte sedimentation rate (ESR) 37; fasting blood glucose (FBG) 138 mg/dL; 2 hours post-prandial blood sugar (2HPP) 230 138 mg/dL; HbA1c: 6.8%; blood urine nitrogen (BUN) 8 mg/dL; serum creatinine 0.72 mg/dL; SGOT 18 U/L; SGPT 27 U/L; albumin 3.6 g/dl; uric acid 6,7; C-reactive protein (CRP) 4.2 mg/L; antinuclear antibody (ANA) test 6; 176 mg of total cholesterol, 117 mg of triglycerides, 47 mg of high-density lipoprotein (HDL), and 115 mg of low-density lipoprotein (LDL). Two weeks later, a blood test revealed FBG and 2HPP of 76 mg/dL and 172 mg/dL, respectively.

**Imaging**

The initial chest X-ray examination revealed a large and normal heart shape and a feature of right suprahilar fibroinfiltrate in the lungs (Figure 2A). A pelvic x-ray presented bilateral grade

2 hip joint osteoarthritis (sclerosis and osteophyte lateral acetabular roof), grade 2 right sacroiliitis, and grade 3-4 left sacroiliitis (Figure 2B). Knee AP/lateral x-ray showed diminished Hoffa fat pad and anterior suprapatellar fat pad leaving an impression of bilateral joint effusion (Figure 2C-F). Right/left AP/oblique radiograph of palms showed reduced trabeculation of the juxta-articular bone at metacarpal apex I-V, the base of the proximal phalanx digit I-V, and base of the middle phalanx digit II-V of both hands, with marginal erosion at the apex of the right metacarpal digit I and apex phalanx proximal digit I of both hands (Figure 2G and H). There were no anomalies in the foot x-ray taken from the both AP/oblique angles.

The Bath Ankylosing Spondylitis Disease Activity (BASDAI) score was 9.3, with the Ankylosing Spondylitis Disease Activity Score with CRP (ASDAS-CRP) was 4.2 and ASDAS with ESR (ASDAS-ESR) was 4.9.

The electrocardiogram (ECG) results 14-month before admission for coronary heart disease showed a sinus rhythm of 86 beats/min, normal frontal and horizontal axis, and anterolateral ischemia. Prior to CABG surgery, echocardiography revealed trivial mitral valve regurgitation and tricuspid regurgitation, normal heart chamber dimensions, normal left ventricular (LV) systolic function (ejection fraction by Teich 65%), abnormal relaxation of the LV diastolic function, normal right ventricular (RV) function, normokinetic LV, and concentric remodeling LV. Diagnostic coronary angiography (DCA) confirmed coronary heart disease with three-vessel disease and left main disease. The sequences of patient' condition are summarized in Figure 3.

Based on history taking and examinations, our patient was diagnosed with PSA with differential diagnosis of erythema nodosum leprosum (ENL), bilateral knee effusion, bilateral hip joint osteoarthritis, bilateral frozen shoulder, and coronary heart disease with a history of CABG and T2DM. Additional examinations, including AP/Lat x-ray of lumbosacral, cervical, and shoulder, dermatovenereologist consultations, and pulmonologist consultations were

requested. Laboratory tests also included interferon-gamma release assay (IGRA) and a complete urine test.

Both non-pharmacological and pharmacological therapies were employed to treat the patient. Dietary instruction comprised 1900 calories per day (68% carbohydrate, 12% protein, and 20% fat). The patient was planned to avoid food containing simple carbohydrates and educated about the activity/exercises including avoiding excessive activity during active inflammation marked by swelling/heat/severe pain in the joints. He also was requested to avoid physical and psychological stress. The patient was informed to reach the nearest health facility immediately if any shortness of breath, palpitations, or visual disturbances occurred. The patient received paracetamol 500 mg t.i.d. orally, intra-articular steroid injection for both shoulders MP 4 mg q.d., and metformin 500 mg t.i.d., glimepiride 2 mg q.d. per oral, calcium lactate 500 mg q.d. per oral, and continued his drugs from the cardiologist. The administration of TNFi was planned.

### Follow-up

After two weeks, the patient presented with diminished complaints of shoulder pain even the shoulder was still a bit difficult to move. The patient still needed help wearing clothes. It was still difficult and painful to stand up. Skin redness and papules on the skin were reduced. However, the lumps in the nose and ears were still present. The patient was fully aware (GCS E4V5M6), and had blood pressure of 105/63 mmHg, pulse of 93 beats per minute, breath of 20 times per minute, a temperature of 37.1°C. The ASDAS-CRP was 4.2, ASDAS-LED 4.9, VAS score 6, and BASDAI score 9.3. The latest random glucose test was 173 mg/dl with a positive IGRA test. The smear and gene expert from sputum and skin scraping were both negative.

Lumbosacral X-ray indicated lipping of the lumbar vertebrae bodies II-V, the feature of paramarginal syndesmophytes of lumbar vertebrae IV-V (Figure 4A and B). This characterized of lumbar spondylosis. No shoulder abnormalities were found in exo-endo rotation. The AP/lateral of cervical X-ray examination showed dense band calcification in

cervical vertebrae bodies II-VII posterior aspect. Osteophytes were seen in cervical vertebrae bodies V-VI. Other findings included straight curve, the impression of cervical spondylosis, posterior longitudinal ligament ossification at the level of cervical vertebrae II-VII, and paracervical muscle spasm (Figure 4C and D). Thoracic high-resolution computed tomography (HRCT) scan revealed no mass in the lungs, mediastinum, trachea, or right and left main bronchus. There were no abnormalities in the heart or major vessels. The right and left bronchus did not appear thickened or dilated with grade 1 wedge fracture of thoracic vertebrae XII and thoracic spondylosis.

The pulmonologist reported no symptoms of active pulmonary TB infection. The dermatologist reported that the patient had pityriasis rubra pilaris and exhibited no symptoms of erythema nodosum, indicating that steroid therapy and cetirizine should be continued. Follow up diagnosis was PSA, bilateral knee effusion, bilateral hip joint osteoarthritis, bilateral frozen shoulder, with a history of CABG, T2DM, and LTBI. The therapy was continued and INH 1 tablet q.d, pyridoxine once daily, sulfasalazine 500 mg b.i.d. were added; DMARD TNFi was postponed to wait for INH treatment to reach at least one month.

On week 5<sup>th</sup>, before DMARD TNFi admission, the hematocrit was 42.1%; leukocytes 8.260/mm<sup>3</sup>; neutrophils 57.6%; lymphocytes 32%; platelets 272,000/mm<sup>3</sup>; hemoglobin 13.1 g/dL; CRP 3.5 mg/dL; BUN 8 mg/dL; serum creatinine of 0.78 mg/dL; SGOT 27 U/L; SGPT 58 U/L; albumin of 3.7 g/dL; uric acid 6.0 mg/dL; Na, K, and Cl were 142 mEq/L, 3.3 mEq/L and 104 mEq/L, respectively. Other results included total cholesterol of 198 mg/dL, triglycerides of 192 mg/dL, LDL of 125 mg/dL, and HDL of 53 mg/dL. ASDAS-LED was 4.9. VAS score was 6, BASDAI score was 9.3 and ASDAS-CRP was 4.2. The patient received DMARD TNFi which was 50 mg etanercept injection, with a 2-week wait-time between injections. Other treatments were continued.

The patient returned for the 2<sup>nd</sup> etanercept injection at the seventh week. Our assessment indicated that the pain was much reduced and the patient was able to

sit and stand without assistance. The skin redness had subsided and the papules were decreased in size, with nodules in the nose and ear area still presented. ASDAS-CRP was 3.1, ASDAS-LED was 4.0, VAS score was 3, and BASDAI score was 6.0. In the eighth-week follow-up, the ASDAI score was 4.4, ASDAS-CRP was 1.8, ASDAS-LED was 2.8, and VAS scored 2. INH remained continued for six months, complemented by a weekly dosage of etanercept 50 mg, sulfasalazine 500 mg b.i.d, and pyridoxine one. We strictly monitored bDMARD side effects and symptoms of LTB reactivation.

### DISCUSSION

Spondyloarthritis is a group of interrelated chronic inflammatory rheumatic disorders with similar symptoms and a similar genetic predisposition yet manifest in different symptoms. The spondyloarthritis spectrum consists of axial spondyloarthritis and peripheral spondyloarthritis, such as PSA, reactive arthritis, enteropathic spondyloarthritis, undifferentiated spondyloarthritis, and juvenile-onset spondyloarthritis.<sup>3</sup> The pathogenesis of this disease is not fully understood and is multifactorial, but the literature shows the role of genes and the involvement of proinflammatory cytokines, including TNF alpha, IL-20, IL-17, and IL-23.<sup>2,7,8,9</sup>

Diagnosis of spondyloarthritis follows the Assessment of Spondyloarthritis international Society (ASAS) 2011 and 2009 ASAS criteria.<sup>3,10</sup> In our patient, according to the 2009 ASAS criteria, this patient's complaints met inflammatory low back pain criteria.<sup>10</sup> There were also complaints of swelling in the fingers and knee joints and inflammation of the peripheral joints, such as the shoulders, wrists, fingers, hips, knees, ankles, and toes. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) reduced pain complaints. Physical examination showed deformities in the right DIP II-III and left DIP II-IV and edema and tenderness in right MCP I-IV and left MCP II-V. There were decreased chest expansion and skin rashes. The radiological evaluation of the AP pelvic radiograph indicated bilateral sacroiliitis, grade 2 right sacroiliitis, and grade 3-4 left sacroiliitis. Laboratory evaluation found increased CRP. This

patient met the ASAS 2011 classification criteria which included inflammatory low back pain with radiological features of sacroiliitis with arthritis, dactylitis, psoriasis improved with NSAIDs and high level of CRP.<sup>3</sup> Therefore, the diagnosis was confirmed as spondyloarthritis.

After the spondyloarthritis classification criteria were met, the subgroup classification was determined in this patient. This is essential to decide the proper therapy and predict the prognosis for this patient.<sup>3</sup> PSA is one of the spondyloarthritis subgroups with a broad clinical range and various symptoms.<sup>4</sup> The definition of PSA is inflammatory arthropathy associated with psoriasis and negative rheumatoid factor. Patients with an asymmetric pattern of arthritis and additional clinical symptoms such as dactylitis, enthesitis, inflammatory low back pain with negative rheumatoid factors may be suspected of having PSA.<sup>4</sup> The 2006 Classification Criteria for Psoriatic Arthritis (CASPAR) is one of the most recent spondyloarthritis classification criteria adopted to assist the diagnosis of PSA. CASPAR is deemed positive in the presence of inflammatory articular disease with more than 3 points of five categories: (1) Evidence of psoriasis, which can be a feature of current psoriasis or a previous history of psoriasis based on a diagnosis from a rheumatologist or dermatologist, or a first/second-degree family history; (2) Typical nail dystrophy such as onycholysis, pitting nail, or hyperkeratosis is noted on current examination; (3) Negative rheumatoid factor; (4) Current dactylitis, i.e., swelling of all fingers, or the previous history documented by a rheumatologist; and (5) Specific radiological features such as juxta-articular new bone formation/ossification on plain radiographs of the hands or feet. Evidence of psoriasis weighs 2 points while the other categories weigh 1 point.<sup>11</sup> Our patient met the CASPAR criteria for PSA with evidence of current psoriasis (2 points), negative rheumatoid factor (1 point), and current dactylitis (1 point).

Based on Moll and Wright's 1973 criteria, PSA is divided into subgroups: asymmetric oligoarthritis, symmetric polyarthritis, predominant involvement of the distal interphalangeal joint (DIP),

and destructive arthritis (mutilation), and psoriatic spondylitis.<sup>4</sup> Our patient had axial involvement based on clinical symptoms, physical examination, and radiology. Symptoms included inflammatory back pain and axial joint stiffness. On physical examination, the patient showed limited ROM of the cervical joints and right-left lateral flexion of the dorsal spine; occipital to wall test of 2 cm, tragus to the wall of 10 cm, decreased chest expansion of 3.5 cm, and positive Schober's test (12.5 cm). The radiological examination showed radiological features of bilateral sacroiliitis, paramarginal syndesmophytes of lumbar vertebrae IV-V, lipping of lumbar vertebrae bodies II-V, posterior longitudinal ligament ossification on the level of cervical vertebrae II-VII, osteophytes on cervical vertebrae bodies V-VI, and lipping on cervical bodies III-VII. Radiologic features of the peripheral joints in this patient had reduced trabeculation of the metacarpal juxta-articular bones and bilateral phalanges, erosion of the metacarpal bones and bilateral phalanges, lateral acetabular roof osteophytes, bilateral hip joint osteoarthritis; diminished Hoffa fat pad and anterior suprapatellar fat pad with a suspicious impression of effusions in both knee joints.

There are various clinical variants of psoriasis based on skin lesions. The most common form is psoriasis vulgaris, characterized by nummular, oval-round, well-demarcated plaques. The initial lesions may be erythematous macules or papules, spread to the periphery areas, and coalesce to form plaques one to several centimeters in diameter. Scales are a typical form of psoriasis, silvery-white in color with varying thickness. Scales may be minimal in acute inflammation or exanthematic psoriasis, and erythema is the predominant symptom. Along with gradual peripheral spread, plaque can take on several configurations including gyrate psoriasis, annular psoriasis, and follicular psoriasis.<sup>12</sup> Follicular psoriasis is a rare variant and is very similar to pityriasis rubra pilaris which is difficult to distinguish clinically and histopathologically.<sup>13</sup> One of the important differential diagnoses of PSA is ENL, which is an immunologic complication in patients with lepromatous

leprosy (LL) and borderline lepromatous leprosy (BL) with clinical manifestations of skin lesions, neuritis, arthritis, dactylitis, eye inflammation, osteitis, orchitis, lymphadenitis, and nephritis.<sup>14</sup> The musculoskeletal manifestations of leprosy are variable and can resemble those of spondyloarthritis with skin lesions such as psoriasis. This similarity can potentially lead to misdiagnosis and treatment, so it is crucial to screen to exclude the possibility of leprosy in patients with suspected spondyloarthritis, especially in patients who are candidates for biologic agents and live in endemic areas.<sup>15</sup> Indonesia is an endemic area of leprosy whereas Papua is the area with the highest prevalence in Indonesia.<sup>16</sup>

The skin manifestations in this patient were multiple clustered follicular papules with erythema at the base without pus or vesicles and minimal scaly area in the trunk/abdomen/superior extremity (particularly the extensor)/femoral area. There were multiple nodules in the both auricula, nasal roots, hands, and soles. There were no hypopigmented or hypoesthetic lesions. Because our patient lives in Papua, which has the most significant prevalence of leprosy in Indonesia, we consulted this case with a dermatovenereologist for ENL suspicion. We also requested the microbiological study of AFB skin scrapings as an additional test to rule ENL. The skin scrapings for acid-fast bacillus test returned negative, and the dermatovenereologist ruled out ENL from the diagnosis.

Cardiovascular disease is a disorder that frequently occurs in rheumatic disease patients. The disease can present as the first manifestation of rheumatoid disease. The patients in those cases will consult with a cardiologist first about their cardiac symptoms.<sup>17</sup> Awalia et al., 2019 showed data that rheumatoid arthritis disease activity was associated with arterial stiffness in the absence of underlying cardiovascular disease.<sup>1</sup> Cardiovascular mortality and complications are common in PSA patients, and they are the primary cause of death. PSA is associated with atherosclerosis and an increased risk of heart disease, including obesity, insulin resistance, dyslipidemia, and hypertension. Several controlled studies

found increased intima-media thickness in the carotid artery and decreased flow-mediated endothelial-dependent vasodilation in the brachial arteries. Proinflammatory cytokines, particularly TNF- $\alpha$ , are suggested to have a role in the pathogenesis of vascular status alterations in PSA patients.<sup>4</sup>

This patient had pain in the right hip and occasionally stiffness in the fingers for the past two years. This problem was never reviewed or get it treated. The patient had chest pain and shortness of breath a year ago and was treated by a cardiologist. Based on the clinical symptoms, electrocardiography, echocardiography, and DCA, the patient had coronary heart disease, three-vessel disease, and left-main disease. At the time, the patient had no previous cardiovascular risk factors, such as diabetes, dyslipidemia, or hypertension. CABG was performed. Inflammatory polyarthritis symptoms emerged four months after the CABG treatment, and they got worsened over the next ten months, with skin lesions started to appear in the last month. Based on these findings, we believe that cardiovascular disease in this patient was an early extra-articular or concomitant manifestation of PSA that manifested when arthritic symptoms were still unknown.

The BASDAI and ASDAS scores were used to assess PSA disease activity with axial involvement.<sup>5</sup> ASDAS-CRP and ASDAS-LED are the two types of ASDAS (alternatives).<sup>18,19</sup> The disease activity in this patient was characterized as a disease with high activity based on the BASDAI and ASDAS scores in the first presentation, with a BASDAI score of 9.3 and ASDAS-CRP values of 4.2 and ASDAS-LED of 4.9. Therefore, this patient was recommended for DMARD. The prescription of a bDMARD, with TNFi as the first choice, is advised for patients with axial disease and a BASDAI score > 4. If the first-line bDMARD fails, another bDMARD or targeted synthetic (tsDMARD) can be used instead.<sup>6</sup> Given the evidence of axial involvement, bDMARD was proposed for pharmacological therapy in this patient. TNFi was the bDMARD that given. Local injectable corticosteroids were given to both shoulder joints to relieve discomfort and inflammation and

oral systemic corticosteroids in modest doses. We also used oral antidiabetics for blood sugar control, collaborating with the Cardiology team for coronary heart disease management as extra-articular symptoms and comorbidities. Because bDMARD required preparation and there were indications for csDMARD, our patient was given sulfasalazine as the chest X-ray revealed fibroinfiltrate and methotrexate might worsen or cause pulmonary abnormalities if administered.

The cost and availability of the drugs in specific places are factors to consider when choosing which drugs to offer. TNFi is the first choice because of its broad use and outstanding efficacy and safety in long-term use. Etanercept is a TNF used to treat rheumatoid arthritis, axial spondyloarthritis, PSA, juvenile idiopathic arthritis, and psoriasis, among other autoimmune diseases. Etanercept is administered subcutaneously at a dose of 50 mg per week. Choices of dose are 50 mg once a week or 25 mg twice weekly.<sup>18</sup>

Screening for hepatitis B and C with HBsAg and anti-HCV exams, as well as studies to rule out active TB infection or LTBI, need to be conducted prior to the start of TNFi medication.<sup>20</sup> TNFi treatment has been associated with an increased risk of latent TB reactivation in several clinical trials. The American Thoracic Society recommends screening and treating latent TB, and IGRA testing is one of the diagnostic modalities for LTBI in patients eligible for TNFi therapy. If LTBI is confirmed, the patient should be treated for at least four weeks before starting TNFi. Isoniazid for 9-12 months or isoniazid with rifampin for three months is recommended.<sup>21</sup> Until now, there are several choices of latent TB therapy regimens based on several guidelines; and ongoing and planned studies to find the best regimen to prevent progression from latent TB to active TB.<sup>22</sup>

Hepatitis B and C viruses were evaluated on this patient, and the results were negative. There was a fibroinfiltrate feature on the left suprahilar on his chest X-ray. Our patient was referred to the pulmonology department to rule out active TB infection, after which he was tested for sputum smear and gene expert tests. The results of both examinations

were negative. Due to the suspicion of bronchiectasis, the examination was followed with a thorax CT scan. Based on the imaging result, the mediastinum, lungs, heart, and major vessels were all within normal limits. The patient was tested for IGRA to rule out the presence of latent TB. The findings of the IGRA test were positive, indicating that this patient had latent TB. The patient received isoniazid and vitamin B6 therapy for four weeks before starting TNFi treatment. Due to financial concerns, our patient was administered TNFi, Etanercept 50 mg subcutaneously once every two weeks after receiving isoniazid for four weeks. The sulfasalazine treatment was continued.

After 12 weeks of treatment, the administration of TNFi was continued based on the response to therapy. The treatment can be continued if the ASDAS score improves by more than 1.1 or the BASDAI score improves by more than 2.0, plus a rheumatologist's assessment.<sup>18</sup> The treatment of TNFi to this patient resulted in an excellent therapeutic response. Before receiving etanercept injection, the patient had a BASDAI score of 9.3, ASDAS-CRP 4.2, and ASDA-LED 4.9. All these scores reduced to 3.1, 4.0, and 6.0, respectively, after one week of etanercept injection. Meanwhile, the ASDAS-CRP score was 1.8, the ASDAS-LED was 2.8, and the BASDAI score was 4.4 a week after the second etanercept injection. Compared to before receiving etanercept injection, the patient showed a significant improvement (improvement > 2.0) in disease activity level, going from very high to moderate level. Besides clinical improvement, we also have to consider the risk of latent TB reactivation in TNFi therapy. By administering TNFi, patients should be closely monitored for signs of reactivation of latent TB<sup>21</sup> and the TB could be diagnosed with GeneXpert MTB/RIF assay.<sup>23</sup>

The patient intended to return to Papua following the second Etanercept injection. TNFi therapy would be continued in Papua, and an internist would oversee and assess treatment progress, pharmacological side effects, and the risk of LTBI reactivation. Sulfasalazine 500 mg orally b.i.d., vitamin B6 1 tablet q.d, and paracetamol 500 mg t.i.d, if

necessary, oral antidiabetic medications were continued for nine months. In addition, multidisciplinary collaboration with cardiologists, pulmonologists, and medical rehabilitation was essential.

After three months of treatment at the Rheumatology Clinic of Dr. Soetomo General Academic Hospital, this patient improved clinically. The patient was able to walk unassisted for the first time, and the intensity and frequency of joint pain were significantly reduced compared to prior therapy. Patient compliance in treatment was assessed as good; medications were taken daily, and the patient always arrived on schedule for drug injections and follow-up evaluations. The patient intended to continue treatment in his or her hometown.

## CONCLUSION

We reported a 63-year-old male PSA patient with bilateral hip joint osteoarthritis, bilateral knee effusions, bilateral frozen shoulder, coronary heart disease with a history of CABG, DMT2 and latent TB. This case highlights the challenges to confirm the diagnosis and management of axial PSA with latent TB and coronary heart disease. Some consideration should be taken before the administration of TNFi therapy to effects.

## AUTHOR CONTRIBUTIONS

NN was responsible for conceptualization, data validation, clinical investigation and data curation, writing the original draft, and reviewing and editing the final manuscript. LDR was responsible in conceptualization, clinical investigation and reviewing and editing the final manuscript. All authors have read and agreed to the published version of the manuscript.

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## ETHICAL APPROVAL

Ethical clearance was not applicable for this case report.

## INFORMED CONSENT STATEMENT

Informed consent was obtained from the patient involved in the study.

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## CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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