Indonesian Journal of Rheumatology

Journal Homepage: https://journalrheumatology.or.id/index.php/IJR

Management of Non-Radiographic Axial Spondyloarthritis Cases with IL-17A Inhibitors

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ARTICLE INFO

Keywords:
Non-radiographic
Axial spondyloarthritis
IL-17A inhibitor

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.66446/IJR.v18i1.60

A B S T R A C T

Background: Non-radiographic axial spondyloarthritis (nr-axSpA) is a key subgroup within the spondyloarthritis (SpA) spectrum, recognized via the Assessment of Spondyloarthritis International Society (ASAS) classification criteria. Treatment options for nr-axSpA are similar to ankylosing spondylitis (AS) and include nonsteroidal anti-inflammatory drugs, tumor necrosis factor (TNF)-α inhibitors and interleukin (IL)-17A inhibitors. Secukinumab, a fully human monoclonal antibody, targets and neutralizes IL-17A, and is the first IL-17A inhibitor approved for AS treatment. **Case Presentation**: This case involves a 34-year-old male with nr-axSpA. The patient presented with chronic back pain and stiffness, mainly in the sacroiliac joints. Initial treatments were inadequate, leading to the administration of secukinumab. The patient showed significant clinical improvement following secukinumab treatment, indicating its efficacy in managing nr-axSpA. **Conclusion**: This case demonstrates the potential benefits of secukinumab in treating nr-axSpA. As the first IL-17A inhibitor approved for AS, secukinumab offers a promising therapeutic option for nr-axSpA patients, providing substantial symptom relief and enhancing quality of life. Further research is needed to assess the long-term efficacy and safety of secukinumab in this patient population.

1. Introduction

Spondyloarthropathy (SpA), also known as seronegative spondyloarthropathy or spondyloarthritis, is a collection of several diseases with different manifestations but almost the same characteristics, such as asymmetric peripheral arthritis or arthritis that predominates in the lower extremities, anterior uveitis, and sacroiliitis. Negative rheumatoid factor results with a history of family SpA in the family and generally positive human leukocyte antigen B27 (HLA-B27) results are also present.[1] Patients with this diagnosis can be classified as axial or peripheral SpA. The term axial spondyloarthritis (axSpA) describes a group of chronic inflammatory rheumatic diseases that primarily involve the axial skeleton. Classified into two main subtypes, namely radiographic axial spondyloarthritis (rx-axSpA) or ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA) based on the presence or absence of conventional radiographically detectable changes in the sacroiliac joints and/or spine. Nr-axSpA is a subset of axSpA in which nr-axSpA does not cause substantial erosive damage to the sacroiliac joint.[1,2]

Globally, the prevalence of SpA is 0.5%-2% of the population. The prevalence of SpA in each continent varies, such as in Southeast Asia, it is 0.20%; in the North Pole, it is 1.61%; in America, it is 1.35%. In Europe, it is 0.54% of the population, and in South Asia, it is 0. 22% of the population has this condition.[1] Approximately 1.5 million Americans are affected by axSpA, with an estimated prevalence of 0.9%–1.4%.About half of patients with axSpA are patients with nr-axSpA. AS is more common in men, while nr-

axSpA is the same in men and women.[3] AS is among the SpA subgroups with the greatest prevalence. The prevalence of AS in the population aged > 20 years ranges from 68 per 100,000 in the Netherlands to 197 per 100,000 in the United States. This prevalence appears to parallel the frequency of HLA-B27, especially in Caucasian populations with a fairly large prevalence of HLA-B27.[1]

The diagnosis of SpA is based on the history, physical examination, and supporting examinations, including laboratory examinations and radiological examinations (conventional radiography and/or MRI) of the spine, sacroiliac joints, and other joints involved. An MRI examination should be carried out after the radiography results. Classification criteria can be used as a guide to establish a diagnosis so that every case suspected of being SpA should be classified into one of these subgroups. For the axSpA diagnostic criteria, use the Assessment of Spondyloarthritis International Society (ASAS) 2010 criteria.[1]

In the management of SpA cases, the first line therapy given continuously is Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), there is no specific NSAID choice that is recommended so any NSAID choice can be used. If additional manifestations are found that are dominant in the periphery, local glucocorticoid injections can be given for arthritis in two joints or less. If manifestations occur in more than two joints, sulfasalazine (first choice) or methotrexate can be given. If axSpA remains active despite using NSAIDs (after 4 weeks), then the choice is a combination of NSAIDs and , tumor necrosis factor (TNF)-α inhibitors or a combination of NSAIDs and interleukin (IL)-17A inhibitors (Secukinumab, Ixekizumab).[1]

Non-radiographic axial spondyloarthritis (Nr-axSpA) is often missed in non-specialist services, which can delay diagnosis and treatment. There is no special examination to confirm the diagnosis. Pharmacological therapy for Nr-axSpA, or SpA in general, is still in the process of development. Recently, the use of IL-17A inhibitor showed significant clinical improvement in patients with axSpA. So, the author is interested in highlighting this case. This report highlights the challenges in diagnosing nr-axSpA in non-specialist settings, the absence of specific diagnostic tests, and the ongoing development of pharmacological therapies for nr-axSpA. By presenting a case demonstrating significant clinical improvement with IL-17A inhibitor, the report seeks to underscore the potential benefits of this treatment approach for patients with axial spondyloarthritis.

2. Case Presentation

A 34-year-old male patient, Balinese, currently working as a hotel employee, complained of pain in the waist. The pain is felt to be so intense that it interferes with the patient's daily activities. The patient has been suffering from pain in the waist since 2018, which has become increasingly worse in the last month. The pain is felt to persist in the waist and is often felt along the spine from the back to the hips. Movement is limited due to stiffness in the spine. The pain usually subsides with light activity or light exercise. The pain gets worse, especially at night and in the morning and if you stay in the same position for a long time. The patient said he had a body posture that was bent like the letter C. Apart from that, the patient also complained of frequent tingling in both legs. The eyes are often red and sore with no specific triggering factor. The patient in 2018 also had a pattern of defecation with a frequency of once a week. Currently, the patient defecates twice a week.

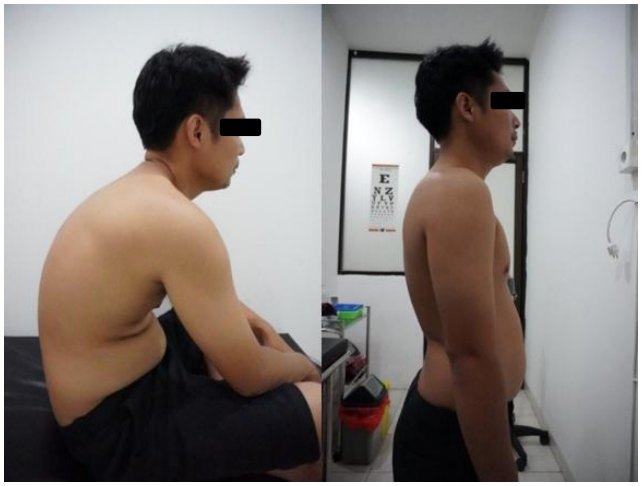

Figure 1. Clinical presentation of the patient

The patient experienced no complaints of coughing, shortness of breath, fever, night sweats or weight loss. There were no complaints of hair loss, redness of the face when exposed to the sun, sores on the mouth or lesions on the skin. There were no complaints of pain in other joints. The patient denied a history of chronic diseases such as diabetes and high blood pressure, and the patient also denied a history of other systemic diseases. There is no history of autoimmune disease in the patient or in the family. The patient has been regularly taking pain medication in the form of meloxicam 15 mg once a day for the past year and is said to have improved, but then the pain recurred.

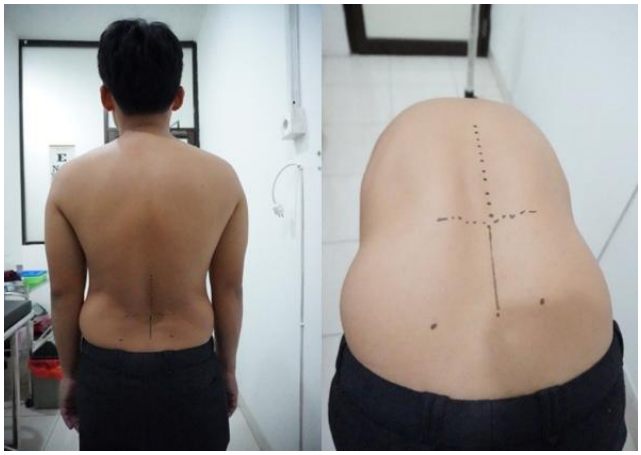

Figure 2. Modified Schober test on the patient

On physical examination, it was found that the patient appeared to be in severe pain, blood pressure of 120/70 mmHg, pulse rate of 98 times per minute, a respiratory rate of 18 times per minute, temperature of 36.5ºC, with a Visual Analog Scale (VAS) pain scale of 8/10. Other general physical examinations were found to be within normal limits. In examining the scope of the spine, it was found that there were limitations in flexing and extending the vertebrae and limitations were found in carrying out lateral bending examinations. The patient also underwent a modified Schober test and obtained positive results with a change in distance after vertebral flexion of 3 cm. (Figure 2)

Laboratory examination showed White Blood Cell (WBC) 7.91 x103/µL, hemoglobin (Hb) 14.6 g/dL, hematocrit (HCT) 43.3%, platelets (PLT) 266 x103/µL. On kidney function examination, BUN was found to be 11.3 mg/dl, creatinine 0.83 mg/dl with e-GFR 114.80. Lipid profile examination was found to be normal where Total Cholesterol was 143 mg/dl, LDL Cholesterol was 79 mg/dl, HDL Cholesterol was 44 mg/dl, Triglycerides were 116.1 mg/dl and uric acid examination was normal at 5.44 mg/dl. At baseline, the erythrocyte sedimentation rate (ESR) was 12 mm/hour. Following the fifth dose of secukinumab, the ESR decreased to 11 mm/hour.

On the AP pelvic x-ray examination, there were no signs of sacroiliitis and no fractures or dislocations of the bones and joints were visualized.

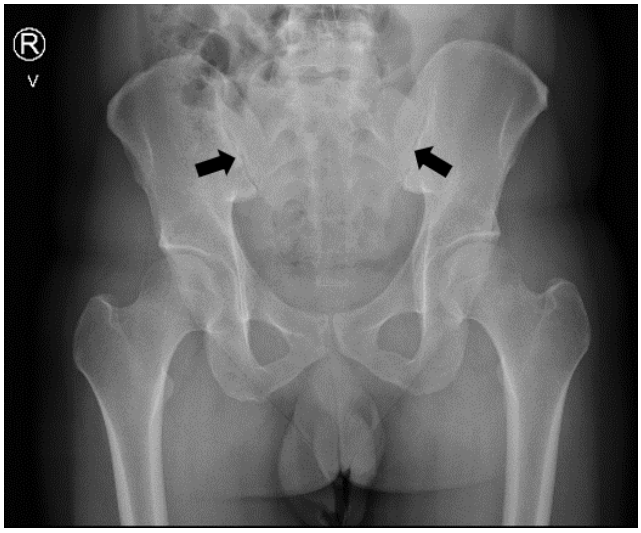

Figure 3. Anteroposterior pelvic X-ray examination.

On an MRI examination of the pelvis, narrowing of the Sacro Iliac Joint (SIJ) on the right and left anterior aspect with fatty marrow changes (Modic 1) on the sacrum and surrounding os ilium can be seen as a picture of ankylosing spondylitis fatty marrow changes on the superoanterior endplate of CV S1 with a shiny appearance. corner sign (+), S3-coccyx 3 (Modic 2), multiple lymphadenopathies of the para iliac, presacral, and left right inguinal regions.

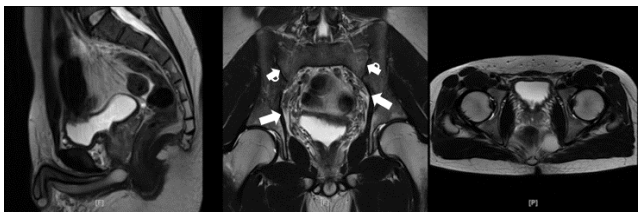

Figure 4. Pelvic MRI.

The patient received IL-17A inhibitor (secukinumab) 150 mg subcutaneously once a week for 5 weeks. The patient also received therapy with meloxicam 15 mg once a day, pregabalin 75 mg once a day and omeprazole 20 mg once a day.

After receiving the fifth sucukinumab therapy, the response to therapy was monitored based on a pain scale and it was found that there was a decrease in the quality of pain in patients with a VAS score of 1 to 2.

3. Discussion

This case report describes a 34-year-old man with a diagnosis of nr-axSpA treated with IL-17A Inhibitor. Nr-axSpA is a subset of axSpA in which nr-axSpA does not cause substantial erosive damage to the sacroiliac joints.[1]

Human leukocyte antigen-B27 (HLA-B27), one of the proteins of major histocompatibility complex (MHC) class I, is considered an important genetic factor in the pathogenesis of SpA. High HLA-B27 (90–95%) in AS patients suggests that HLA-B27 is strongly associated with axial SpA. In contrast, it was found to be lower (22-36%) in PsA with more peripheral joint involvement. Genome-wide Association Studies (GWAS) identified endoplasmic reticulum aminopeptidase 1 (ERAP1) as a risk factor for AS and PsA. ERAP1 is one of the aminopeptidases expressed in the Endoplasmic Reticulum (ER). ERAP1 plays a role in cutting peptides in the endoplasmic reticulum (ER) into 8-10 amino acids to form antigens by MHC class I molecules, such as HLA-B27. It is suggested that ER stress caused by HLA-B27 and ERAP1 can trigger the IL-23/IL-17 pathway activation. In addition to these genetic factors, mechanical stress and dysbiosis of the gut microbiota are also said to play a role in the pathogenesis of SpA.[4]

In the case, it was found that there were complaints of low back pain for more than 3 months, which had been felt since 2018. With a gradual onset of pain, especially felt at night until the morning, the nature of the pain did not improve with rest but subsided with light activity. This is in accordance with the criteria for inflammatory low back pain according to ASAS, namely chronic low back pain for more than 3 months with 4 out of 5 criteria including onset of patient age less than 45 years, onset slowly, improvement with activity or physical exercise, not improvement with rest. and pain at night. This parameter has a sensitivity of 77% and a specificity of 91.7%.[1]

The axSpA classification criteria according to ASAS 2010 are that patients with clinical low back pain are patients aged less than 45 years with low back pain lasting more than 3 months accompanied by a radiological diagnosis of sacroiliitis (x-ray or MRI) plus one or more features of SpA or HLA-B27 positives were accompanied by two or more other features of SpA. Features of SpA include inflammatory low back pain, arthritis, enthesitis, uveitis, dactylitis, psoriasis, chron/colitis, good response to NSAIDs, family history of SpA, positive HLA-B27 and high C-reactive protein (CRP) levels. The radiological diagnosis of sacroiliitis is in the form of acute or active inflammation on an MRI examination that depicts sacroiliitis due to SpA or the radiological appearance of sacroiliitis based on the New York criteria, namely grade > 2 bilaterally or grade 3-4 unilaterally.[1,5]

Assessment of Spondyloarthritis International Society (ASAS) criteria are classification criteria and are not diagnostic criteria. The use of ASAS classification criteria can result in misdiagnosis because spondyloarthropathy has broad inclusion criteria. Objective signs indicating the presence of an inflammatory process can assist in the diagnosis process, including radiological examination with no structural damage to the sacroiliac joint on x-ray (which, if present, would indicate a diagnosis of AS) but signs of active inflammation in the sacroiliac joint. MRI, laboratory examinations that show systemic inflammatory processes such as increased ESR and/or CRP and extraspinal manifestations and peripheral manifestations such as active uveitis, psoriasis, inflammatory bowel disease (IBD), dactylitis, peripheral arthritis and enthesitis.[1]

In cases where the axSpA criteria are met, they include age less than 45 years with low back pain lasting more than 3 months confirmed by a positive modified Schober test as well as limitations or obstacles when flexing and extending the vertebrae

and limitations when carrying out lateral bending examinations. No picture of sacroiliitis was found on conventional radiological examination (pelvic x-ray). However, the picture of sacroiliitis in the case was shown by the results of an MRI of the pelvis in the form of narrowing of the right and left sacroiliac joints in the anterior aspect with fatty marrow changes (Modic 1) on the sacrum and surrounding ilium. can be a picture of ankylosing spondylitis, fatty marrow changes in the super interior endplate of CV S1 with a shiny corner sign (+), S3-coccyx 3 (Modic 2), multiple lymphadenopathies in the para iliac region, presacral and left right inguinal. Although conventional radiography did not demonstrate definite sacroiliitis, MRI findings together with the patient's clinical features fulfilled the ASAS classification criteria for nr-axSpA.

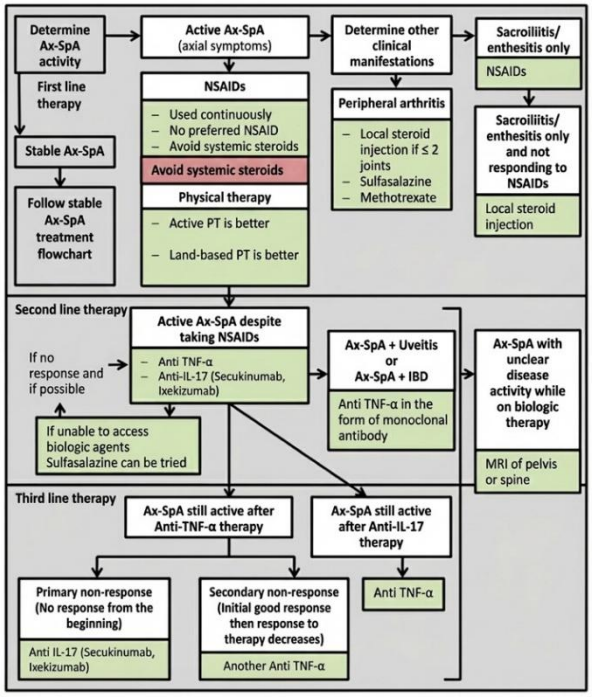

Figure 5. Medical therapy options for active axial spondyloarthritis.[1]

Radiological examination in the form of conventional radiography (x-ray) of the SIJ is the first modality recommended for diagnosing axSpA. It remains the main choice for assessing structural changes in the spine and SIJ.[1]

Magnetic resonance imaging (MRI) of the sacroiliac joints is recommended when the diagnosis of axial spondyloarthritis is uncertain despite normal or inconclusive radiographic findings. Routine MRI protocols include semicoronal T1-weighted (T1W) and short tau inversion recovery (STIR) or fat-saturated T2-weighted (T2FS) sequences to evaluate inflammatory and structural lesions of the sacroiliac joints. MRI of the spine may also be performed when clinically indicated. According to the ASAS, a positive MRI is defined by the presence of characteristic inflammatory and/or structural lesions consistent with axSpA.[1]

According to ASAS and National Institute for Health and Care Excellence (NICE), axSpA is classified into two subtypes, rx-axSpA, which is proven by sacroiliitis on conventional pelvic radiography. This term is synonymous with AS according to the modified New York criteria and nr-axSpA proven without evidence of sacroiliitis on conventional radiographic examination of the pelvis. Grade I bilateral or grade II unilateral. In nr-axSpA, an MRI examination can show a picture of sacroiliitis. The presence of clinical US findings defines Nr-axSpA. Still, it does not show definitive sacroiliitis on conventional radiography (x-ray), such as findings of erosive damage, widening or narrowing of the joint space, sclerosis, and bone fusion at the sacroiliac joint.[1] In this case, there were no abnormalities or features of sacroiliitis on conventional pelvic x-ray examination, so the case was diagnosed with nr-axSpA.

Other symptoms of SpA that are also found in cases include suspicion of uveitis with symptoms that the eyes are often red and sore. Suspicion of gastrointestinal abnormalities with a history of the patient's defecation frequency of 1-2 times a week. The patient has never had further examination for complaints about the eyes and gastrointestinal tract. The patient was also examined for markers of inflammation in the form of an ESR examination which was found to be normal. Laboratory investigations such as ESR and CRP are not specific for the diagnosis of AS. In general, this inflammatory marker is increased in approximately 75% of cases,

but levels that are not increased cannot rule out the diagnosis of this disease.[6]

Based on the SpA management algorithm according to ASAS-EULAR, if axial spondyloarthritis remains active even after using NSAIDs after 4 weeks, then the choice is a combination of NSAIDs and TNF-α inhibitors, IL-7A inhibitor therapy or a combination of NSAIDs and anti-IL-17A (Secukinumab, Ixekizumab).[1,2,7] Surgery such as total hip arthroplasty should be considered in patients with refractory pain and radiologically assessable structural damage. Spinal corrective osteotomy also needs to be considered in severe spinal deformities.[1]

Genome-wide association studies, network analyzes and preclinical models have identified a key role for the IL-23/-17 pathway in the pathogenesis of SpA, including axSpA. Therapy that targets this pathway, one of which in patients with psoriasis, shows better clinical improvement compared to TNF-α inhibitors.[8] Although TNF-α inhibitors can improve symptoms, improve functional mobility and reduce disease activity, almost 40% of axSpA patients did not respond sufficiently to TNF-α inhibitors. TNF-α inhibitors has been proven to be able to suppress the inflammatory process, but in patients with axSpA it not only involves an inflammatory process but also a process of bone loss and new bone formation. Clinical evidence shows that the administration of TNF-α inhibitors to AS patients does not significantly affect the IL-23/-17 axis. The focus of therapy currently being developed is on IL-23 and IL-17 which are considered disease-modifying targets in the treatment of SpA. Administration of IL-7A inhibitors provides a good therapeutic response by significantly alleviating symptoms, improving skin lesions in psoriatic patients and reducing pain and inflammatory lesions in the joints.[9]

The recommended dose of secukinumab is 150 mg given at weeks 0, 1, 2, 3 and 4 followed by 4 weekly (USA) or monthly (Europe) doses starting at week 4 or, alternatively, in the US, starting on a schedule of 4 weekly without loading dose. Each injection should be given in a different location (upper arm, stomach or thigh) than the previous injection. Discontinuation of secukinumab should be considered if no response is seen after 16 weeks of treatment; patients with an initial partial response may subsequently improve with continued treatment after 16 weeks.[10]

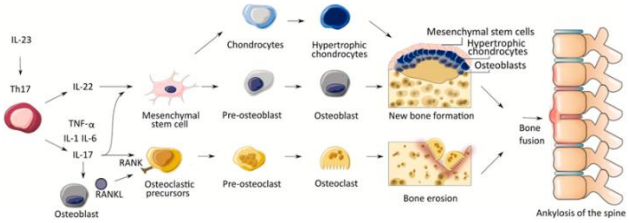

Figure 6. Overview of bone erosion and new bone formation in axSpA.[9]

In this case, the patient had received 15 mg meloxicam therapy once a day for approximately 1 year and had improved, but symptoms worsened in the last 1 month. Because the patient still experienced recurrent pain and did not respond to NSAID administration, in accordance with the SpA management algorithm according to ASAS-EULAR the patient was then given IL-17A inhibitor (secukinumab) injection therapy 150 mg subcutaneously once a week for 5 weeks.

Monitoring of axSpA disease activity is carried out at least twice a year or every 6 months using the Ankylosing Spondylitis Disease Activity Score (ASDAS) or the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). In patients receiving biologic therapy, if disease activity is uncertain, magnetic resonance imaging (MRI) of the spine or sacroiliac joints is recommended. The therapeutic target in axial spondyloarthritis is to reduce disease activity by achieving an ASDAS <1.3 (inactive disease) or at least an ASDAS <2.1 (low disease activity). Other treatment goals include pain control (a reduction of at least 2 points on the Visual Analog Scale [VAS]) and improvement in physical function.[1] In the present case, the baseline BASDAI score was 7.4, indicating high disease activity, and improved to 3.0 following the fifth dose of secukinumab. The baseline ASDAS-ESR was 3.5, indicating very high disease activity, and improved to 1.6 after the fifth dose of secukinumab, indicating low disease activity. The patient's pain also

markedly improved, with the VAS score decreasing to 1–2.

This report still has several limitations. The case report focuses on a single patient's experience, limiting the generalizability of the findings, as the outcomes and responses to treatment may not apply to others with similar conditions. The pain assessment relies on the subjective Visual Analog Scale (VAS), which can vary based on individual pain thresholds and perceptions, potentially affecting the reported efficacy of the treatment. Furthermore, the report provides a short-term view of the patient's response to secukinumab after five weeks, lacking information on long-term outcomes or potential side effects, which are crucial for chronic conditions like ankylosing spondylitis. While MRI findings suggest ankylosing spondylitis, the absence of genetic testing (such as HLA-B27) and comprehensive imaging of other joints may limit the diagnostic thoroughness. The report also omits comprehensive functional assessments or quality-of-life measures post-treatment, which are essential for evaluating the therapy's full impact. The patient's significant pain reduction might be influenced by the placebo effect or other uncontrolled factors, potentially overestimating the efficacy of secukinumab. The report does not discuss potential interactions between secukinumab and other medications (meloxicam, pregabalin, omeprazole) or any adverse effects experienced during the treatment. Lastly, the patient's occupation and cultural background are mentioned but not explored about their condition and treatment. However, these factors could influence the patient's experience and response to therapy.

4. Conclusion

We report the case of a 34-year-old man with nr-axSpA, characterized by the absence of radiographic sacroiliitis on anteroposterior (AP) pelvic radiography despite MRI findings consistent with active sacroiliitis. The diagnosis of SpA in upright cases was based on the 2010 ASAS classification criteria. The patient had received NSAID therapy for one year and had improved but due to relapse the patient was then given IL-17A inhibitor (secukinumab) based on the SpA management algorithm according to ASAS-EULAR. The patient's condition improved and it was planned to continue administering IL-17A inhibitors to the patient. SpA is often overlooked in non-specialist services, which can result in delays in diagnosis and treatment. There is no special examination to confirm the diagnosis. SpA can present with various symptoms and difficulties in disease identification, leading to delayed and inaccurate diagnosis.

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