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CASE REPORT

Spondyloarthritis and nonbacterial thrombotic endocarditis as paraneoplastic manifestations in treatment-naive Burkitt lymphoma

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Abstract

Non-radiographic axial spondyloarthropathy (nr-axSpA) is a clinical diagnosis of symptoms matching inflammatory back pain criteria without radiological lesions at the sacroiliac joint. The frequency of an early nr-axSpA-like presentation in lymphoma patients has not been clarified. Here we report a woman in her 20s with a fever and musculoskeletal discomfort. Detailed investigations revealed that she was suffering from Burkitt lymphoma in which nr-axSpA-like symptoms were a musculoskeletal manifestation of the disease, irrelevant to the anti-neoplastic treatment.

KEYWORDS
axial SpA, Burkitt lymphoma, nonbacterial thrombotic endocarditis, non-Hodgkin lymphoma, non-radiographic axSpA, seronegative spondyloarthropathy

1 | INTRODUCTION

Seronegative spondyloarthropathy (SpA) is an umbrella term for rheumatology diseases encompassing ankylosing spondylitis (AS), psoriatic arthritis (PsA), inflammatory bowel disease (IBD) associated arthritis, reactive arthritis (formerly Reiter syndrome; ReA), and undifferentiated SpA. Moreover, the presumptive diagnostic workup often originates from an observation of inflammatory back pain (IBP).[1] Patients with a subsequent diagnosis of IBP must initially fulfill clinical features of a chronic (>3 months) back pain of unknown origin that begins before 45 years of age.[2] Considering both the clinical manifestations and image evidence, SpA can be categorized into axial SpA (axSpA) and peripheral SpA. axSpA is composed of at least 2 disease modalities, AS and non-radiographic axSpA (nr-axSpA), which does not meet the modified New York criteria.[3]

Non-Hodgkin's B cell lymphoma (B cell NHL) distinguishes itself from Hodgkin's lymphoma due to the absence of Reed-Sternberg cells. Classical clinical manifestations of NHL include non-tender diffuse lymphadenopathy with symptoms reflecting involved sites. Incidence of traditional "B" symptoms (fever, drenching sweats, clinically established body weight loss) ranges from 15% to 50%.

The link between any predisposed SpA, especially AS, and the subsequent risk of a confirmed diagnosis of hematological diseases has long been a controversial issue. Chronic inflammation and/or the administration of immune suppressants are potential pathophysiological mechanisms. A recent study utilizing a population-based cohort of beneficiaries with AS reported an elevated risk of developing NHL, chronic lymphocytic leukemia, and multiple myeloma among elderly patients with AS.[4] On the other hand, a case report of a patient who developed non-Hodgkin T cell lymphoma with an underlying AS treated by tumor necrosis factor (TNF)-α inhibitor

demonstrated the potential causality of immunosuppressive status to the eventual hematologic malignancy (HM).[5] However, there remains a paucity of substantial populational studies to evaluate the relative risk of developing HM in TNF-α inhibitor exposed or naive patient cohorts.

Despite the abundant efforts to explore the incidence of lymphoma and the prior diagnosed spondyloarthropathies, the early occurrence of these axSpA-like manifestations in HM, especially B cell NHL, has been overlooked. Herein, we report a young woman in her 20s with Burkitt lymphoma who initially presented with axSpA-like symptoms (bilateral hip pain and lower back pain for more than 3 months), FUO (fever of unknown origin), and elevated C-reactive protein (CRP). The awareness of a bone marrow infiltrating disease arose after a 3-phase bone scan was done.

2 | CASE PRESENTATION

The first case was a female in her 20s with a medical history of discoid lupus erythematosus and was treated with Plaquenil 6 years before admission. She had leg, hip, and low back pain with slight narrowing of L4-L5 disc space on X-ray and received a rehabilitation program 1 month before admission. A weight loss of 5 kg was noted in the past 4 months. She was admitted due to severe sacroiliac joint pain and fever for 3 days. She was febrile (37.8°C) and positive for the Patrick test. Laboratory tests showed highly elevated CRP (188.02 mg/L), neutrophilia without leukocytosis, and elevated D-dimer (3.4 mg/L). Seronegative spondyloarthropathy was the first impression without specific radiographic findings.

Transthoracic echocardiography (TTE) was arranged under suspicion of concomitant infective endocarditis. TTE showed oscillating vegetations on the surface of the mitral valve with ruptured chordae tendineae and mild mitral valve regurgitation. Empirical antibiotics for infective endocarditis were prescribed, but the fever persisted. However, blood cultures were negative. Further examination by transthoracic echocardiography revealed verrucous vegetations on the mitral leaflets surface and aortic cusp with focal thickening, supporting the diagnosis of nonbacterial thrombotic endocarditis (NBTE). Autoantibodies, including antiphospholipid, were all negative.

A 3-phase bone scan revealed a possible bone marrow infiltrating disease or increased hematopoietic activity in bilateral pelvic bones and the right side of the pelvic cavity. Magnetic resonance imaging (MRI) revealed disease involvement in the pelvis, sacrum, and bilateral femur, and a positron emission tomography (PET) scan revealed lymph node involvement in the abdomen and inguinal region (Figure 1). Pathologic report of iliac bone marrow aspiration revealed a highly aggressive Burkitt lymphoma. A diagnosis of NBTE associated with Burkitt lymphoma was made. Fever and hip pain resolved after chemotherapy.

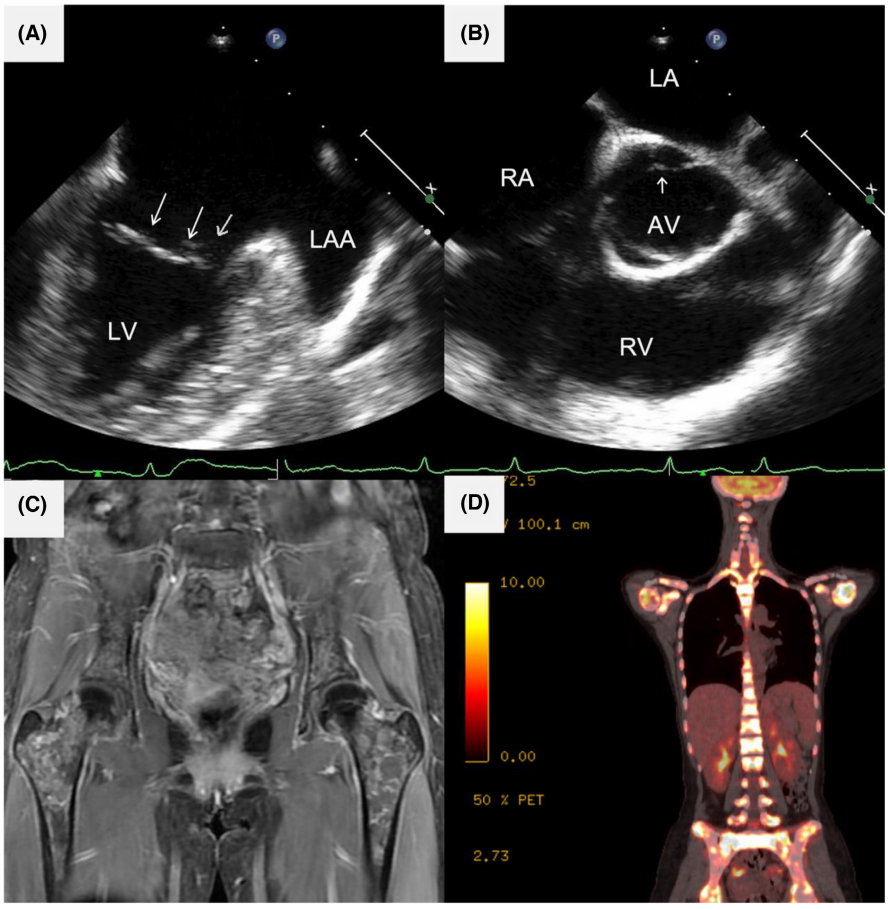

FIGURE 1 (A) Transesophageal echocardiography (TEE) in mid-esophageal 2-chamber view. White arrows indicate verrucous lesions on the focally thickened mitral leaflets. (B) TEE in mid-esophageal short-axis view. The white arrow indicates the verrucous lesions on the aortic valve. (C) T2-weighted magnetic resonance imaging indicates heterogeneously enhanced lesions over the bone marrow of bilateral pelvic bone, femur, and sacrum. (D) Fluorodeoxyglucose (FDG) positron emission tomography / computed tomography scan demonstrating increased nodal FDG uptake in para-aortic, mesenteric, bilateral obturator, bilateral external iliac, and right inguinal regions. LV, left ventricle; LAA, left atrial appendage; RA, right atrium; LA, left atrium; AV, aortic valve; RV, right ventricle.

3 | DISCUSSION

Non-radiographic axial spondyloarthritis of unspecified sites in spine (M45.A0) was newly added into the diagnostic group of AS (M45) in 2021. To establish a confirmed diagnosis of nr-axSpA, chronic low back pain of more than 3 months and age at onset of less than 45 years should be initially confirmed. The modified New York criteria and human leukocyte antigen (HLA)-B27 positivity conjunctively form the current consensus of SpA diagnosis and classification. The existence of IBP symptoms, specified by morning stiffness over 30 minutes, nocturnal or early morning pain, and alleviation of symptoms after exercise, will prompt the following diagnostic algorithm. Furthermore, the presence of more than one SpA feature will lead to imaging modalities and serological tests. These features encompass arthritis, enthetiitis, anterior uveitis, IBD, symptom relief after nonsteroidal anti-inflammatory drug (NSAID) use, family history of SpA, and elevated acute-phase reactants (CRP/erythrocyte sedimentation rate). The presence of HLA-B27 and/or image-proven sacroiliitis augment the diagnostic sensitivity of axSpA to about 80%–90%. Regarding the imaging modalities, Assessment in Spondyloarthritis International Working Group criteria specified the X-ray and MRI features leading to SpA diagnosis. According to the modified New York criteria, a SpA-positive X-ray is characterized by bilateral grade 2–4 or unilateral grade 3–4 sacroiliitis. MRI has the advantage of identifying inflammatory lesions, including bone marrow edema and osteitis, or fatty lesions, which can predict the progression of axSpA. Of note, these MRI features have variable sensitivity and specificity among different studies, thus, should not be used as the sole inclusion criteria for SpA.

For nr-axSpA, it is important to achieve an early diagnosis in order to halt the progression (measured by modified Stoke Ankylosing Spondylitis Spine Score [mSASSS]) into radiographic axSpA via medical interventions, such as TNF inhibitors.[6] On the other hand, well differentiating other similar pathological lesions by current imaging modalities is still challenging. These lesions include degenerative changes, Scheuermann disease, osteitis condensans illi, diffuse idiopathic skeletal hyperostosis and ossification of the posterior longitudinal ligament, fractures, septic arthritis, metabolic diseases, crystal deposition arthropathy, SAPHO (synovitis, acne, pustulosis, hyperostosis, osteomyelitis) syndrome/ chronic recurrent multifocal osteomyelitis, Charcot spine, Beçhet's disease, rheumatoid arthritis, hemoglobinopathies, and sarcoidosis.[7] Moreover, infiltrative bone tumors, benign or malignant, can manifest non-specific imaging features that mimic bone marrow edema in SpA. Among them, malignant bone lesions, encompassing lymphoma, leukemia, multiple myeloma, plasmacytoma, Ewing sarcoma, and metastasis, should be carefully ruled out.

The mainstay of nr-axSpA treatment composes of pharmacological and physical therapeutic aspects. NSAIDs can achieve a response (measured by Bath Ankylosing Spondylitis Disease Activity Index score) rate of 35% in nr-axSpA patients.[8] Biologic disease-modifying antirheumatic drugs (bDMARDs) are several TNF inhibitors, including adalimumab, golimumab, cetrolizumab, and etanercept. The Assessment in SpondyloArthritis International Society 40% improvement (ASAS40) was met in a range of 32% to 57% nr-axSpA patients treated with bDMARDs.[9]

Our case initially presented with FUO, elevated CRP, and nr-axSpA-like symptoms. Lumbar radiography showed sacroiliac joint irregularity, but the radiologist claimed it was unremarkable with any presumptive SpA disease on the basis of modified New York criteria. Due to the negativities of all serologic tests for potential rheumatological diseases and the persistent symptoms, a 3-phase bone scan as well as MRI on sacroiliac joints were done and support the underlying bone marrow infiltrating diseases, including lymphoma, leukemia, and multiple myeloma. Notably, about 74% of multiple myeloma patients feature CRAB (hypercalcemia, renal disease, anemia, lytic bone lesions) symptoms. According to the International Myeloma Working Group, the confirmed diagnosis of multiple myeloma requires more than 10% bone marrow plasma cells or biopsy-proven plasmacytoma and at least 1 multiple myeloma -defining event (myeloma-related organ or tissue impairment and any of the following biomarkers: bone marrow plasma cells >60%; serum free light chain ratio <100:1, more than one focal lesion on MRI).[10] On the other hand, referring to the World Health Organization's classification of myeloid neoplasms and acute leukemia, the diagnosis and classification of leukemia demand peripheral blood smear, bone marrow examination for blast components and immunophenotypes, as well as laboratory studies for cytogenetic anomalies and molecular mutations.[11] Furthermore, according to current National Comprehensive Cancer Network guidelines, the establishment of lymphoma diagnosis requires excision or incisional biopsy to achieve histologic classification, grading, and adequate immunophenotyping. Because bone marrow biopsy served as the shared essential step to confirm the aforementioned diseases, thus, our patient underwent bone marrow examination and was eventually diagnosed with Burkitt lymphoma.

4 | CONCLUSION

This case should raise awareness of a confusing early presentation of SpA symptoms in certain hematological malignancies, which could lead to misdiagnosis. Given that no single imaging modality is adequate for nr-axSpA or hematological malignancy diagnosis, timely consideration of advanced examinations, such as bone marrow biopsy or fluorodeoxyglucose-PET/computed tomography scan, will be helpful for clarifying the etiologies of axSpA-alike symptoms.

AUTHOR CONTRIBUTIONS

Category 1: Conception and design of study: J.J.Tsai. Acquisition of data: J.J.Tsai & H.C.Lee. Analysis and/or interpretation of data: C.Y.Wang, H.C.Lee, R.J.Lin,J.J.Tsai. Category 2: Drafting the manuscript: C.Y. Wang, R.J.Lin. revising the manuscript critically for important intellectual content: J.J.Tsai & H.C.Lee. Category 3: Approval of the version of the manuscript to be published (the names of all authors must be listed): C.Y.Wang, H.C.Lee, R.J.Lin, J.J.Tsai.

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CONFLICT OF INTEREST STATEMENT

For all the enlisted authors, our objectivity **has not** been compromised by any desire for financial gain, prominence, professional advancement or a successful outcome.

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