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Case Report

Undifferentiated connective tissue disease presenting with optic neuritis and concomitant axial spondyloarthritis: A rare case report

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ABSTRACT

Undifferentiated connective tissue disease (UCTD) represents a group of diseases which do not fulfill the criteria of rheumatologic diseases or may be considered as an early stage of any of these diseases. Axial spondyloarthritis (axSpA) is a disease accompanied by symptoms of inflammatory low back pain and peripheral symptoms, with more spine and sacroiliac joint involvement. In this report, we, for the first time, present a case of UCTD presenting with axSpA in whom the initial finding was optic neuritis, which is rarely seen in UCTD.

Keywords: Axial spondyloarthritis, enthesitis, heel pain, optic neuritis, systemic lupus erythematosus, ultrasonography, undifferentiated connective tissue disease.

Undifferentiated connective tissue disease (UCTD) is a systemic heterogeneous group of autoimmune diseases which do not fulfill the criteria of connective tissue diseases.[1,2] The term spondyloarthritis (SpA) refers to a group of diseases involving similar clinical and genetic features. According to the Assessment of SpondyloArthritis International Society (ASA), in the presence of low back pain for more than three months, axial SpA (axSpA) is diagnosed in the presence of at least one SpA findings in addition to sacroiliitis or in the presence of two or more SpA findings in addition to human leukocyte antigen-B27 (HLA-B27) positivity.[3,4]

To the best of our knowledge, UCTD concomitant with axSpA has not been published previously. In this article, we, for the first time, present a case of UCTD presenting with axSpA in whom the initial finding was optic neuritis, which is rarely seen in UCTD. We believe that this case is worthy of presentation due to two different uncommon occurrences.

CASE REPORT

A 41-year-old female patient was applied to the outpatient clinic with a complaint of heel pain. Her medical history revealed low back pain lasting for five months and she had morning stiffness about 1 h on her low back. She also suffered from non-scarring alopecia and oral and eye dryness. She had optic neuritis episodes three times within 19 years (1999, 2008 and January 2018), and no pathology was found on cranial and spinal magnetic resonance imaging (MRI). The patient refused cerebrospinal fluid examination. After the last optic neuritis episode on January 2018, rheumatologic investigation was performed. The results and routine testing results were normal, except for antinuclear antibody (ANA) positivity (1/320) (Table 1). The Schirmer's test result was also positive (right: 2 mm/min; left: 3 mm/min) and salivary gland biopsy revealed signs of Grade 1 inflammation according to the Chisholm-Mason classification which did not meet the diagnostic criteria of primary Sjögren's

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TABLE 1
Rheumatologic blood test results

Examination	Result	Examination	Result
Rheumatoid factor	<10.4 U/mL (-)	Anti-histone	(-)
Anti-cyclic citrullinated peptides	1.90 IU/mL (-)	Anti-cardiolipin IgG	5.77 U/mL (-)
C-reactive protein	<3.03 mg/L (-)	Anti-cardiolipin IgM	0 U/mL (-)
Sedimentation	6 mm	Anti-phospholipid IgG	0.77 U/mL (-)
cANCA	0.73 U/mL (-)	Anti-phospholipid IgM	1.9 U/mL (-)
pANCA	4.76 U/mL (-)	Anti-ds-DNA	(-)
IgA	266 mg/dL (N)	C3	1.72 g/L (N)
IgG	1480 mg/dL (N)	C4	0.295 g/L (N)
IgM	121 mg/dL (N)	ANA	1/320 (+)
Anti-SSA	(-)	U1-snRNP	(-)
Anti-SSB	(-)	Anti-Sm/RNP	(-)
Anti SCL 70	(-)	Anti-Sm	(-)
Anti Jo 1	(-)	Beta-2 glycoprotein IgG	(-)
Lupus anticoagulant ratio	1.07 (-)	Beta-2 glycoprotein IgM	(-)
Anti-ribosomal P0 protein	(-)	SSA/RO52KD	(-)
CENP-B	(-)	Nucleosome	(-)

cANCA: Cytoplasmic anti-neutrophil cytoplasmic antibodies; pANCA: Perinuclear anti-neutrophil cytoplasmic antibodies; Ds DNA: Double-stranded DNA; IgA: Immunoglobuline A; IgG: Immunoglobuline G; IgM: Immunoglobuline M; ANA: Antinuclear antibody; SSA: Sjögren's syndrome-related antigen A; snRNP: Small nuclear ribonucleoproteins; SSB: Sjögren's syndrome-related antigen B; Sm/RNP: Smith/Ribonucleoprotein; SCL: Scleroderma; CENP-B: Centromere protein B.

syndrome (SS) fully. Treatment with 50 mg/day of azathioprine, 400 mg/day of hydroxychloroquine sulfate, and 16 mg/day of methylprednisolone was started three months ago. However, she had no benefit from these medications with a poor effect on heel pain.

On physical examination at the time of referral to our clinic, sacroiliac compression test was bilaterally positive, and the Achille's tendon was painful, particularly on the left side with palpation. The pain was evaluated using the 0-10 Visual Analog Scale (VAS). The VAS score was 4 for low back, 5 for right heel, and 9 for left heel. Ultrasonographic (USG) evaluation of the Achille's tendons of the patient revealed tendinitis (thickening of the tendon, hypoechogenicity, disorganization of fibrillary pattern and 1+ Doppler signal) and cortical irregularity of calcaneus bone in the left heel (Figure 1). Due to the persistent low back and heel pain complaints, MRI of the sacroiliac joint was performed and active sacroiliitis was detected (Figure 2). The HLA-B27 test yielded a negative result.

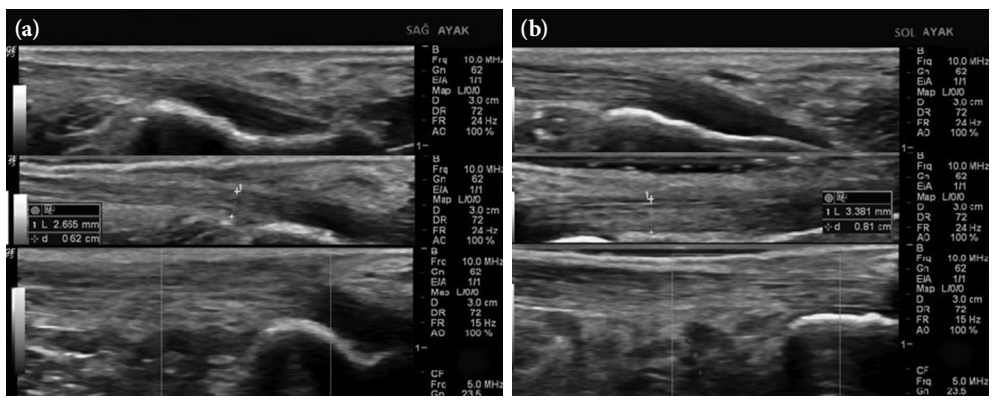

Figure 1. An ultrasonographic view of Achille's tendons: **(a)** right heel, **(b)** left heel. On left heel, tendinitis (thickening of the tendon, hypoechogenicity, disorganization of fibrillary pattern and 1+ Doppler signal) and cortical irregularity of calcaneus tendinitis were shown.

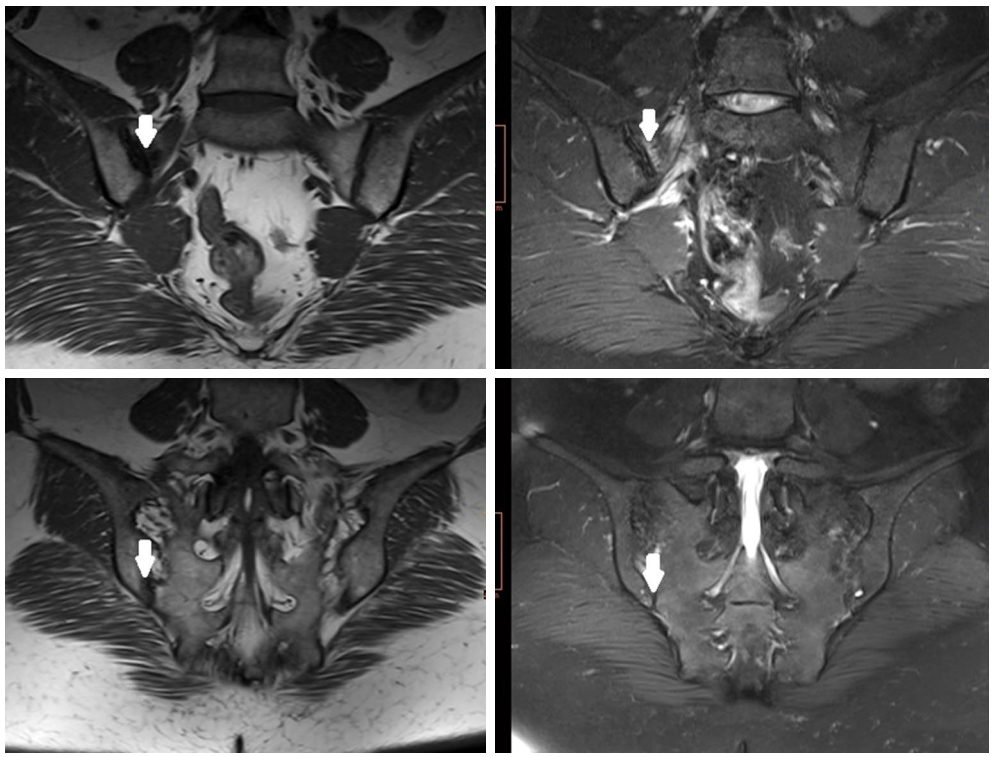

Figure 2. Sacroiliac magnetic resonance imaging showing active sacroiliitis.

Due to the numbness in her lower extremities, nerve conduction studies were performed, and peripheral sensory polyneuropathy was detected. Adding to the previous treatment of the patient, she was prescribed on diclofenac 75 mg twice a day. At three weeks of follow-up, this medication was switched to methotrexate 15 mg/week, as her symptoms did not relieve. At one month of follow-up, her complaints regressed, and morning stiffness decreased to 15 min with a VAS score of 1 for low back, 1 for right heel, and 3 for left heel. A written informed consent was obtained from the patient.

DISCUSSION

In the present case, she had inflammatory low back pain and heel pain with three optic neuritis episodes, oral and eye dryness, non-scarring alopecia, and peripheral sensorial neuropathy. She did not fulfill the systemic lupus erythematosus (SLE) and SS criteria as a result of laboratory and imaging methods and she was diagnosed with UCTD. She had also axSpA due to the presence of sacroiliitis on MRI and detection of enthesitis on USG.

Diagnosis of SLE is based on clinical findings and laboratory findings after all other differential diagnoses are excluded. The diagnosis can be clarified with a detailed medical history, physical examination, SLE-specific laboratory tests, and regular follow-up. The American College of Rheumatology (ACR) defined in 1997 or the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria described in 2012 are often used by clinicians due to the lack of specific diagnostic criteria.[5,6] As these criteria are insufficient in some cases, some other diagnostic criteria have been proposed in the literature. According to these criteria, if the patient has non-specific organ involvement for SLE (e.g., optic neuritis), and fulfills two or three criteria of ACR or SLICC (four criteria for the definite diagnosis should be positive), the patient is diagnosed with probable SLE.[7] Although this case did not fully meet the SLE criteria, she fulfilled three criteria according to SLICC: non-scarring alopecia, peripheral sensorial neuropathy, and ANA positivity. These findings were compatible with the probable SLE described in the literature. In addition, the literature data suggest that a patient having signs and symptoms suggestive of a connective tissue disease (CTD) without fulfilling the criteria of any defined CTD and having ANA positivity can be defined as having a UCTD. If the disease duration is less than three years, patients can be defined as having an early UCTD. A longer follow-up would allow correct classification of at least

some false-negative patients.[8] We believe that the patient would provide the SLE classification criteria during follow-up.

Classification criteria of the SS have been updated for years and the most recent 2016 ACR and European League Against Rheumatism (EULAR) criteria have been established.[9] Primary SS is not associated with other diseases, while secondary SS may be associated with other rheumatic diseases. In this case, although there was no supportive finding in the salivary gland biopsy, the Schirmer's test result positive. As the patient could not fulfill the primary SS classification criteria fully, she was diagnosed with secondary SS.

In our case, optic neuritis is the initial symptom of UCTD and other symptoms were added over time. We found a slightly similar case in the literature. Protti et al.[10] reported a case who had stiffness and pain in his arms. The ANA (1/640) Waaler-Rose (1/160), and Sjögren's syndrome-related antigen A (SSA) test results were positive. Since the patient had myelitis at the thoracic level in addition to optic neuritis, the diagnosis was made as neuromyelitis optica. Unlike this patient, our patient had no neurological findings, except for optic neuritis. In addition, the symptoms of inflammatory low back and heel pain in our patient make this case interesting.

In conclusion, inflammatory rheumatic diseases can be seen together, and diseases may overlap with each other. This case highlights the importance of detailed medical history and ultrasonographic assessment in addition to laboratory testing in rheumatic diseases. Based on our experience, we suggest that methotrexate may be a useful choice, when UCTD and axSpA are seen together.

Declaration of conflicting interests

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