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Adalimumab Mitigates Lumbar Radiculopathy in a Case of Ankylosing Spondylitis

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Patient: Male, 46-year-old
Final Diagnosis: Ankylosing spondylitis
Symptoms: Low back pain
Medication: —
Clinical Procedure: —
Specialty: Rehabilitation • Rheumatology

Objective: Rare coexistence of disease or pathology

Background: Ankylosing spondylitis (AS) is an immune-mediated chronic inflammatory condition grouped under spondyloarthritis (SpA), which is an umbrella term for a group of interrelated inflammatory rheumatic conditions with characteristic radiographic findings such as erosions and ankylosis of the sacroiliac joint. Unfortunately, there is an average delay of 8-9 years between the onset of the symptoms and diagnosis due to infrequent consideration of this disease in the differential diagnosis of patients with low back pain and unusual or incomplete presenting clinical symptoms.

Case Report: We describe the case of a 37-year-old male patient with no significant past medical history and surgical history of bilateral hip arthroplasty secondary to idiopathic aseptic necrosis of the bilateral femoral head and bilateral rotator cuff repaired surgery due to multiple motor vehicle accidents (MVA) with a chief concern of chronic low back pain. In this case of ankylosing spondylitis presenting with low back pain and radicular symptoms, his symptoms were resistant to multiple opioid medications, trigger point injections, and epidural steroid injections. Initiation of adalimumab subsequently relieved the patient's symptoms and restored his ability to perform daily activities.

Conclusions: This is an unusual presentation of AS with radiographic evidence of bilateral sacroiliitis. The neurological manifestations in AS are not uncommon, and they can occur during the quiescent stage of the disease. It should be emphasized that early diagnosis is essential to prevent progression of the disease and avoid unnecessary treatment for the patient.

Keywords: Adalimumab • HLA-B27 Antigen • Radiculopathy • Sacroiliitis • Spondylitis, Ankylosing

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Background

Ankylosing spondylitis (AS) is an immune-mediated chronic inflammatory condition grouped under spondyloarthritis (SpA) with a prevalence of 0.1% to 1.4% worldwide, and males are affected more frequently than females [1,2]. Spondyloarthritis (SpA) is an umbrella term for a group of interrelated inflammatory rheumatic conditions that include sacroiliitis, spondylitis, peripheral arthritis, enthesitis, dactylitis, acute anterior uveitis, associated psoriasis or inflammatory bowel disease, presence of HLA-B27, and no association with rheumatoid factor [3]. The SpA can be subdivided into axial SpA or ankylosing spondylitis (predominant symptoms of spine and sacroiliac joints) and peripheral SpA (predominant symptoms of peripheral arthritis, enthesitis, and or dactylitis) [3,4].

An early diagnosis of AS is critical because effective treatments are available, and they are more efficacious if used in the early stage of the disease [5-7]. Back pain is also the first symptom and most frequent manifestation in the AS [7,8]. Additionally, bilateral sacroiliitis is the hallmark of AS, and detecting radiographic sacroiliitis is pivotal for diagnosing AS [9,10]. Moreover, SpA accounts for only about 5% of chronic back pain, which is an extremely frequent symptom in pain management facilities and is widespread in the general population [11,12]. Therefore, subsequent referral to the rheumatologist of those patients with back pain with a higher probability of AS is needed to effectively rule out the disease.

To the best of our knowledge, an L4-5 nerve root radiculopathy associated with AS has not been previously reported. Increased

Table 1. Muscle strength grading and deep tendon reflexes (on last visit).

MRC*			
Upper limbs		**Right**	**Left**
	Wrist extension	5/5	5/5
	Wrist flexion	5/5	5/5
	Elbow extension	5/5	5/5
	Elbow flexion	5/5	5/5
	Shoulder abduction	5/5	5/5
Lower limbs		**Right**	**Left**
	Ankle dorsiflexion	5/5	5/5
	Ankle plantarflexion	5/5	5/5
	Knee extension	5/5	5/5
	Knee flexion	5/5	5/5
	Hip flexion	5/5	5/5
DTR**			
Lower limbs		**Right**	**Left**
	Patellar	2/4	2/4
	Ankle	2/4	2/4
Upper limbs		**Right**	**Left**
	Brachioradialis	2/4	2/4
	Biceps	2/4	2/4
	Triceps	2/4	2/4
	Triceps	2/4	2/4
Plantar response		Negative reflexes bilaterally	
Faber test		Positive on the left side only	
Straight leg raise		Negative bilaterally	
Schober test		Positive (lumbar flexion difference is 4 cm)	

* Medical Research Council muscle strength scale (Graded 0-5); ** NINDS (National Institute of Neurological Disorders and Stroke) Myotatic Reflex Scale for deep tendon reflexes (Graded 0-4). MRC – Medical Research Council; DTR – deep tendon teflexes.

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Table 2. Patient's laboratory tests summary (obtained on initial visit).

Test	Result	Reference range
Completement, total	>60	31-60 U/mL
Completement component C3	156	82-185 mg/dL
Completement component C4	36	15-53 mg/dL
Rheumatoid factor	<14	<14 IU/mL
C-reactive protein	2.2	<8.0 mg/L
Sjogren's antibody (SS-A)	<1.0 NEG	<1.0 NEG
Sjogren's antibody (SS-B)	<1.0 NEG	<1.0 NEG
Proteinase-3 antibody	<1.0 (no antibody detected	<1.0
Myeloperoxidase antibody	<1.0 (no antibody detected)	<1.0
HLA-B27 antigen	6.9 (Negative)	5.0-11.0 mcg/mL
ANA screen, IFA	Negative	Negative
HIV antigen/antibody, 4th generation	Non-reactive	Non-reactive
Hepatitis C antibody	Non-reactive	Non-reactive
Cyclic citrullinated peptide antibody	<16 (negative)	<20
VDRL	Non-Reactive	Non-reactive
Red blood cell count	4.18	4.20-5.80 Million/uL
Hemoglobin	12.7	13.2-17.1 g/dL
Hematocrit	35.4	38.5-50.0%
Glucose	115	65-99 mg/dL

SS-A – anti-Sjogren's-syndrome-related antigen A autoantibodies; SSB – anti-Sjögren's-syndrome-related antigen B autoantibodies; HLA – human leukocyte antigens; ANA – antinuclear antibodies; IFA – immunofluorescence assay; HIV – human immunodeficiency virus; VDRL – venereal disease research laboratory test.

suspicion may lead to earlier diagnosis and treatment, potentially reducing the duration of the symptoms and improving the functional ability of patient with AS.

Case Report

We present the case of a 37-year-old male patient with no significant PMH and a past surgical history of bilateral hip arthroplasty secondary to idiopathic aseptic necrosis of the bilateral femoral head and bilateral rotator cuff repaired surgery due to multiple motor vehicle accidents (MVA).

He came to our clinic for occasional low back pain in early 2018. Initially, he rated the pain as an 8 out of 10 on the numerical rating scale (NRS). It was described as a constant, aching sensation that radiated from his lower back to both feet with associated stiffness, numbness, and tingling in his feet. His pain was mostly concentrated in his lower back and gluteal regions. The intensity of his pain was more significant in the morning and when a posture was maintained for a prolonged duration.

On the initial visit, the physical examination elicited that the patient had limited thoracic and lumbar spinal range of motion throughout the sagittal and coronal planes, most apparent on the left side. As for the special test, the FABER test was positive on the left side, the straight leg raise was negative, and the Schober test was positive (Lumbar flexion difference is 4 cm). There were bilateral lumbar paraspinal spasms. Muscle strength, light touch, sensations, tactile discrimination, and deep tendon reflexes were normal in all extremities (**Table 1**). His complete blood count, complete metabolic panel, other antibody tests and inflammatory markers were within the reference ranges except for a mildly elevated total complement level and low hemoglobin level (**Table 2**).

On magnetic resonance imaging (MRI), there was evidence of an L4-5 mild broad-based disc bulge with superimposed small central disc protrusion/herniation and traced bilateral facet joint effusions along with sclerosis, joint space narrowing, and erosions of bilateral sacroiliac joints (**Figures 1, 2**). In addition, electromyography (EMG) was abnormal for chronic left L5 motor radiculopathy with signs of healing, but the nerve conduction studies were normal (**Table 3**). Therefore, a

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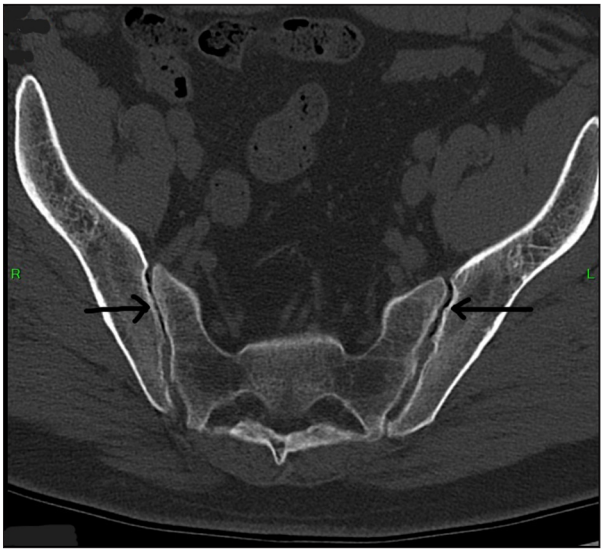

Figure 1. Axial view non-contrast CT scan of the pelvis showing bilateral Sacroiliitis and bony erosions (black arrows).

diagnosis of lumbar radiculopathy was corroborated based on clinical features, MRI findings, and EMG report.

Over the course of three and a half years, the patient had inadequate pain relief with multiple NSAIDs, pain medications (Oxycontin and Percocet), tizanidine, multiple sessions of osteopathic manipulative treatment (OMT), Physical therapy (PT), and multiple trigger point injections. He also underwent one left Intralaminar lumbar epidural steroid injection (L4/5) with 1-month relief of low back pain and resolution of radiating left leg pain and three bilateral SI joint injections, which provided >50% improvement in his low back pain for 2-3 weeks. In

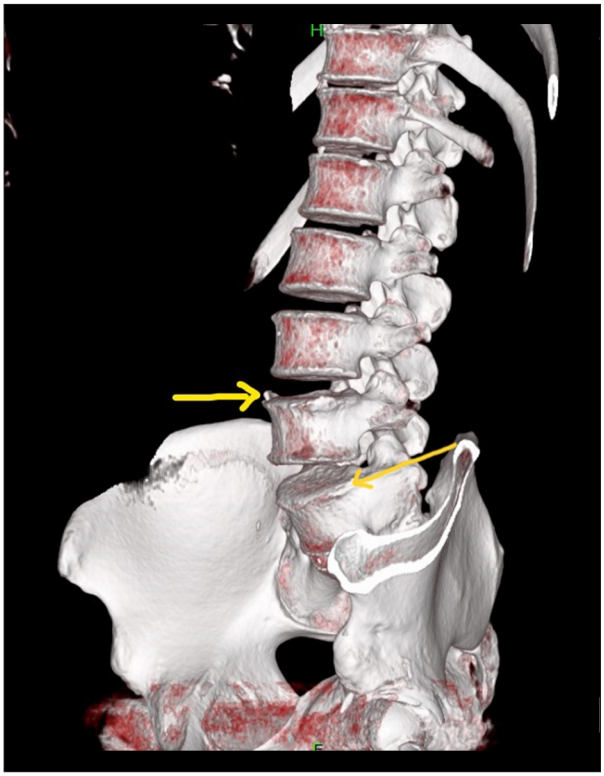

Figure 2. Sagittal view non-contrast CT scan of the lumbar spine using volume rendering technique (VRT) showing syndesmophytes over L4 and L5 vertebrae (yellow arrows).

Feb 2021, while the patient was waiting for the insurance approval for another intralaminar L4-5 lumbar epidural steroid injection, he developed bilateral eye redness and pain. At this

Table 3. Needle EMG (Electromyogram) results obtained on the follow-up visit.

Side	Muscle	Nerve	Root	Ins Act	Fibs	Psw	Amp	Dur	Poly	Recrt	Int Pat
Right	Vastus med	Femoral	L2-4	Nml	Nml	Nml	Nml	Nml	0	Nml	Nml
Right	Ant tibialis	Dp Br fibular	L4-5	Nml	Nml	Nml	Nml	Nml	0	Nml	Nml
Right	Fibularis long	Sup Br fibular	L5-S1	Nml	Nml	Nml	Nml	Nml	0	Nml	Nml
Right	Gastroc	Tibial	S1-2	Nml	Nml	Nml	Nml	Nml	0	Nml	Nml
Left	Vastus med	Femoral	L2-4	Nml	Nml	Nml	Nml	Nml	0	Nml	Nml
Left	Ant tibialis	Dp Br fibular	L4-5	Nml	Nml	Nml	Nml	Nml	1+	Nml	Nml
Left	Fibularis long	Sup Br fibular	L5-S1	Nml	Nml	Nml	Nml	Nml	1+	Nml	Nml
Left	Gastroc	Tibial	S1-2	Nml	Nml	Nml	Nml	Nml	0	Nml	Nml

Needle EMG study of bilateral lower extremity shows normal pattern except for left anterior tibialis and left fibularis longus which had increased polyphasic (L5 nerve root). Nml – normal; Vastus med – vastus medialis muscle; Ant tibialis – anterior tibialis muscle; Fibularis long – fibularis longus muscle; Gastroc – gastrocnemius muscle; Ins act – insertional activity; Fibs – fibrillation; Psw – positive sharp wave; Amp – amplitude; Dur – duration; Poly – polyphase; Recrt – recruitment; Int pat – interval pattern; Dp Br fibular – deep branch of fibular nerve; Sup Br fibular – superficial branch of fibular nerve.

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point, point, we considered his clinical symptoms to be an unusual presentation of AS possibly, and he was referred to an ophthalmologist and a rheumatologist, where he was diagnosed with AS. Adalimumab was initiated, and the patient experienced gradual improvement in his low back pain, radicular lower legs pain, and bilateral SI joints pain, with reduced need of pain medications. In a follow-up visit one month after initiating adalimumab, he rated his lower back and bilateral SI joint pain as 3-4/10 on the NRS. As a result, he could return to work and resume many of his activities.

Discussion

We present a rare case of lumbar radiculopathy associated with ankylosing spondylitis that was reversed with adalimumab. Despite conventional pain management, he experienced 3 years of intractable lower back pain with paresthesia throughout both lower limbs. After a diagnosis was corroborated using EMG, MRI, and clinical assessment, the patient was prescribed adalimumab and had relief of his symptoms within one month. To the best of our knowledge, attenuation of radicular pain with adalimumab in a case of ankylosing spondylitis has not been previously reported. Like our patient's presentation, Forestier et al stated that pain resembling sciatica is present in the early stage of the disease in 17 out of 200 patients. Most of these cases were described as having radiating pain in the distribution of the L5 nerve root [13,14]. Interestingly, L5 motor radiculopathy was characterized in the present case of AS.

The spine is progressively involved as the disease progresses, and previous studies using SSEP (somatosensory evoked potential) depict a prevalence of lumbosacral radiculopathy in AS to be 6.7-16.7%, although most cases were subclinical [15]. However, the neurological manifestations of AS are quite variable, ranging from minor joint instabilities to cauda equina syndrome, and they are rarely reported [16-18]. Bowie and Glasgo first described cauda equina syndrome as the rare complication of AS involving the dorsal and ventral roots of L3-S5 [19]. Similarly, Cumming and colleagues reported an association between AS and upper limb radiculopathy in addition to cauda equina syndrome during the late stages of the disease [20]. Those reports bear a resemblance to our patient's presentation, but our patient's neurological symptoms occurred at the early stage of the disease.

Several mechanisms have been postulated as causes of nervous system involvement in AS, such as arteritis, demyelination, cord, and nerve root compression from inflammation [16,21-24]. The intervertebral foramina may be radiologically normal, but the root pain is attributed to inflammatory changes and the development of characteristic bony spurs: syndesmophytes as in our patient's CT scan [25-28]. Additionally, the immune-mediated inflammatory responses in AS may contribute to enthesis and the erosive changes at the junction of the vertebrae and the annulus fibrosis. As a result, the extensive remodeling of the spine and spinal stenosis ensues due to bone overgrowth [16,25,28]. Given his diagnosis of AS with radicular symptoms, we presume that these immune-mediated mechanisms played a role in the present case.

On the other hand, lumbosacral radiculopathy is one of the most common symptoms presented to the outpatient clinic and is a leading referral diagnosis of EMG. The prevalence of lumbosacral radiculopathy is 3-5%, equally distributed between men and women in the general population [27-29]. Additionally, the back pain from lumbar radiculopathy and the inflammatory back pain from spondyloarthropathy have similar presentations in the early stage of AS [13,30]. Despite his relatively young age, it is plausible that his lower back pain was due to a history of multiple motor vehicle accidents. However, with a history of being recalcitrant to the opioid medications, multiple trigger point injections, epidural steroid injections, and osteopathic manipulative treatment for 3 years and his subsequent pain relief from initiation of adalimumab suggest that the probable cause of radiculopathy was AS.

Moreover, the criteria used for diagnosing AS, such as the modified New York criteria, require radiographic evidence of sacroiliitis [31]. This usually challenges the physicians and hampers the diagnosis because it takes years from the onset of the symptoms to the appearance of radiographic sacroiliitis. Sacroiliac joint inflammation occurs prior to the state that is detectable radiographically [31,32]. Many unnecessary investigations and treatments may have been performed during this prolonged diagnosis delay.

The diagnosis of AS is primarily clinical, and there are no specific laboratory investigations that can confirm the disease. HLA is strongly associated with the disease, and >80% of patients with AS are positive for HLA B27. Routine HLA testing is not clinically helpful because AS can occur in the absence of the HLA B27, as in the present case [2,33,34]. Further, only 1-5% of HLA-B27-positive individuals develop AS. Therefore, it is likely that there exists a combination of mechanisms involved in the disease pathogenesis [35].

NSAIDs (non-steroidal anti-inflammatory drugs) are the first-line recommended treatment for active AS [36]. Theoretically, NSAIDs inhibit the activity of COX (cyclooxygenase) enzymes, thereby inhibiting the synthesis of prostaglandins (PG) and thromboxane. PGE2 acts through PTGER4 (Prostaglandin E Receptor 4) to induce the production of IL (Interleukin)-23 and IL-17 and to promote the expansion of TH17 lymphocyte. Elevated TH17 lymphocyte counts and IL-17 levels are very well known in AS [35-37]. Reportedly, AS is highly associated with genetic variation in the PTGER4 gene, which leads

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to resistance to NSAIDs, like in our patient's poor response to multiple NSAIDs [38]. European League Against Rheumatism (EULAR) guidelines recommend that biologic disease-modifying antirheumatic drugs (eg, Tumor necrosis factor inhibitors and IL-17 inhibitors) should be considered in patients with persistently high disease activity despite conventional treatments with NSAIDs [38].

Timely initiation of the tumor necrosis factor (TNF) blocking agent is necessary for managing spondyloarthropathies because it can dramatically decrease disease activity, improving the patient's symptoms and radiographic sacroiliitis [36-39]. In our case report, use of adalimumab (TNF blocking agent) alleviated the recalcitrant low back pain with radicular symptoms and reduced the need for opioid medications.

Limitations of the Study

We aimed to present the unusual presentation of AS with lumbar radiculopathy signs and symptoms. However, there are limitations of our study: (1) the patient had previous multiple accidents that could contribute to the lumbar disc bulging, and (2) he should have had follow-up blood work to monitor complement level and MRI imaging to identify the improvement of radiographic sacroiliitis after initiation of adalimumab.

Conclusions

Current evidence demonstrates the beneficial effects of TNF inhibitor (adalimumab) in AS patient with symptoms of radiculopathy. It provides sustained clinical remission with the restoration of normal physical activities. Young patients with chronic worsening low back pain with symptoms of radiculopathy, reduced spine mobility, and minimal relief from opioid medications and epidural steroid injection should be referred to a rheumatologist to rule out AS. HLA-B27 is not a diagnostic feature for AS, and diagnostic delay can lead to unnecessary treatment, with poor quality of life, worse functional impairment, and more significant radiographic progression [40]. As such, physicians should be aware of the features of inflammatory low back pain.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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