Sawlani and Masood
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CASE REPORT Open Access

# Beyond the spine: a case of ankylosing spondylitis complicated by secondary amyloidosis

Anjlee Sawlani[1*] and Rida Masood[1]

## Abstract

**Background** Ankylosing spondylitis (AS) is a chronic inflammatory condition primarily affecting the spine and sacroiliac joints, often associated with human leukocyte antigen B27 (HLA-B27) positivity. While musculoskeletal symptoms are typical manifestations, AS can also lead to systemic complications, including secondary systemic amyloidosis (SSA), also known as Amyloid A (AA) amyloidosis, involving multiple organs.

**Case presentation** We present a case of a 45-year-old Asian male with a complex medical history, including diabetes and hypertension, who developed AS complicated by SSA. The patient exhibited a diverse range of symptoms, including cardiac, renal, gastrointestinal, and musculoskeletal manifestations. He reported shortness of breath on exertion, orthopnea, pedal edema, generalized weakness, back pain, neck pain, low-grade fever, decreased appetite, frothy urine, and significant weight loss over the past year. Diagnostic evaluations revealed HLA-B27 positivity and histologically confirmed AA amyloidosis, providing a comprehensive understanding of the systemic involvement.

**Conclusion** This case report highlights the intricate interplay between AS and SSA, particularly AA amyloidosis, with a focus on its systemic impact beyond musculoskeletal symptoms. The tragic outcome, marked by severe cardiac involvement, underscores the challenges in managing such complex cases. This report emphasizes the importance of early diagnosis and treatment of AS to prevent severe complications, along with vigilant monitoring and individualized treatment plans, as well as the need for further research to enhance our understanding and improve management strategies for AS-related amyloidosis.

**Keywords** Ankylosing spondylitis, Secondary amyloidosis, Systemic amyloidosis, HLA B27, Chronic inflammatory disorders

## Background

SpA encompasses a spectrum of disorders characterized by inflammation affecting both the spine and peripheral joints, often associated with HLA-B27 [1]. This diverse group of conditions presents a wide range of clinical symptoms, including uveitis, psoriasis, and inflammatory bowel disease [1, 2]. AS, the most common and severe subtype of SpA, predominantly affects axial joints, notably the sacroiliac joints. Additional involvement can occur in the spine, peripheral joints, and enthuses [2]. Beyond its well-recognized musculoskeletal manifestations, AS can lead to rare complications, challenging diagnosis, and affecting approximately 5% of individuals with poorly controlled chronic inflammatory disorders [2, 3].

One such complication is SSA, a long-term consequence associated with various chronic inflammatory conditions, including rheumatoid arthritis, ankylosing spondylitis, and Crohn's disease [3]. SSA is characterized by organ damage resulting from the deposition of amyloid fibrils in the extracellular space [4]. SAA, an

*Correspondence:
Anjlee Sawlani
anjleesawlani56@gmail.com
[1] Dow Mediical College, Karachi, Pakistan

acute-phase reactant primarily produced by hepatocytes in response to chronic inflammation, is resistant to proteolysis and forms rigid, unbranched fibrils capable of causing mechanical disruption and local oxidative stress in organs [4, 5]. While the kidneys are commonly affected, it is essential to investigate the potential involvement of other organs, such as the heart, liver, gastrointestinal tract, and peripheral nervous system. Symptoms like proteinuria, malabsorption, intestinal obstruction, hepatomegaly, polyneuropathy, and restrictive myocarditis should prompt evaluation for SSA in individuals with chronic inflammatory diseases [5, 6].

In this case report, we present a male patient who had an underdiagnosed AS, which was further complicated by SSA. The report emphasizes that early identification of clinical amyloidosis in AS facilitates effective management through established treatment protocols. Specific screening guidelines for amyloidosis should include regular and frequent monitoring, such as biannual SAA tests, urine protein analysis, and annual imaging studies like echocardiography or MRI to detect early signs of amyloidosis [7]. Thus, assessing patients for amyloidosis during the early stages of the disease is highly recommended.

## Case presentation

### Patient information

A 45-year-old Asian male with known comorbidities, including diabetes diagnosed 2 years prior, hypertension diagnosed 5 years prior, and a 10-year history of chewing betel nuts, presented with complaints of shortness of breath on exertion and orthopnea, accompanied by pedal edema. Over the past year, he reported generalized weakness, back pain, neck pain, low-grade fever, decreased appetite, and frothy urine, along with a significant weight loss of 8 kg. The patient's back pain had an insidious onset, persisting for approximately 6 to 8 months, and worsened during periods of rest and physical inactivity, especially in the early morning. The pain and stiffness improved notably with physical activity. Additionally, the patient experienced a temporary response to non-steroidal anti-inflammatory drugs (NSAIDs) prescribed by a local physician, which partially alleviated the back pain.

The patient had no prior history of endoscopy, colonoscopy, blood transfusion, or hospital admission for similar complaints. His medication history included empagliflozin, bisoprolol, atorvastatin, and spironolactone for managing his comorbidities, and he reported adherence to his prescribed medications. His latest HbA1c measurement indicated good glycemic control, with a level of 6.9%. Additionally, his mean blood pressure, measured with home readings, was 134/87 mmHg.

### Clinical findings

During the physical examination, the patient had a temperature of 37 °C, a blood pressure of 90/60 mmHg, and a heart rate of 58 beats per minute. The musculoskeletal examination revealed positive findings on Schober's and modified Schober's tests, indicating restricted lumbar spine flexion. The patient also demonstrated restricted lateral flexion of the neck, with an occiput-to-wall distance measurement of 2 cm. A stooped posture, slightly decreased power in the lower limbs, and diminished ankle reflexes were also noted.

The patient exhibited a Marfanoid habitus, characterized by long limbs with an arm span measuring 1.06 times the height, a high-arched palate, and a crowded oral maxilla. Abdominal examination showed a distended abdomen with a full umbilicus. Palpation revealed that the liver was palpable 3 fingers below the costal margin, with a span of 11 cm. Audible bowel sounds were present.

Cardiovascular examination findings included audible S1 and S2 heart sounds. A holosystolic murmur was detected at the left 5th intercostal space along the midclavicular line, radiating to the left axilla. Additionally, a high-pitched pansystolic, non-radiating murmur was heard at the lower left sternal border, accompanied by a loud P2. Chest examination showed an increased anteroposterior diameter, decreased breath sounds bilaterally, and restricted chest expansion.

### Diagnostic assessment

Extensive investigations revealed findings contributing to the patient's differential diagnosis. Blood test results indicated microcytic, hypochromic anemia, with a hemoglobin level of 9.8 g/dL and a mean corpuscular volume (MCV) of 70.6 fL. The total leukocyte count (TLC) was within the normal range at 7100/mm$^3$, while the platelet count was elevated at 436, suggestive of mild thrombocytosis. The vitamin D (25-OH) level was 58.9 ng/mL, falling within the normal range. The C-reactive protein (CRP) level showed an elevation at 84.9 mg/L, the erythrocyte sedimentation rate (ESR) measured 42 mm/h, and SAA level was measured at 44 mg/L, indicating a moderate to severe elevation above the normal reference range(normal < 3 mg/L), all indicative of an inflammatory response. Lactate dehydrogenase (LDH) exhibited an elevation at 307 U/L, whereas ferritin levels remained within the normal range at 76 ng/mL. The diagnostic workup also revealed evidence supporting a diagnosis of SSA. In the protein profile, the total protein measured 6.72 g/dL, with a decreased level of albumin at 2.87 g/dL. The fractions revealed alpha-1 at 0.20 g/dL, alpha-2 at 0.80 g/dL, beta at 0.96 g/dL, and an elevated level of gamma at 1.89 g/dL. During serum protein electrophoresis, a sharp,

discrete, well-defined spike was identified in the gamma region. This monoclonal protein peak accounted for 0.63 g/dL, representing 33.2% of the total protein in the gamma region. The A/G ratio was calculated at 0.75.

In the coagulation profile, both prothrombin time (PT) and activated partial thromboplastin time (APTT) were within normal limits at 17.2 s and 25 s, respectively, with an international normalized ratio (INR) of 1.63. Thyroid function tests revealed normal levels, with a thyroid-stimulating hormone (TSH) level of 2.53 μIU/mL, a thyroxine (T4) level of 1.19 ng/dL, and a triiodothyronine (T3) level of 2.22 pg/mL. Liver function tests, including total bilirubin (0.4 mg/dL), serum glutamic-pyruvic transaminase (SGPT, 10 U/L), and alkaline phosphatase (213 U/L), were within normal reference ranges, indicating normal liver function.

Blood urea nitrogen (BUN) was elevated at 82 mg/dL, while serum creatinine was also elevated at 1.8 mg/dL, suggesting potential renal impairment. Spot urine analysis revealed a creatinine level of 91 mg/dL and a protein level of 629 mg/dL, resulting in a protein-to-creatinine ratio of 6.91, indicating significant proteinuria. Electrolyte levels, including sodium (136 mmol/L), potassium (4.8 mmol/L), and chloride (105 mmol/L), were within normal ranges. Calcium (8.8 mg/dL), magnesium (2.3 mg/dL), and phosphate (3.5 mg/dL) levels were all within normal limits.

Urine dipstick analysis showed a specific gravity of 1.010 and a pH of 6.5. Protein levels were markedly elevated at 3+, indicating significant proteinuria. Glucose was also elevated at 3+, suggesting glycosuria despite a well-controlled HbA1c, which may indicate an acute metabolic stress state. Red blood cells were present at 1–3 per high power field (HPF), and pus cells were observed at 2–4 per HPF, indicating potential hematuria and inflammation, respectively. Granular casts were abundant, marked as+++/HPF, suggesting renal tubular damage. Additionally, amorphous urate crystals were detected at++, indicating a moderate presence of urate crystals in the urine sediment.

Abdominal ultrasound revealed liver enlargement measuring 15.8 cm in span, with smooth margins and a modified echotexture. Transthoracic echocardiography showed symmetric hypertrophy of the left ventricle with preserved systolic function and dilation of both the left and right atria, as well as a mildly enlarged right ventricle. These findings were consistent with cardiac amyloidosis. The Doppler study indicated left ventricular diastolic dysfunction with an increased E/A ratio of 2.08 and an isovolumic relaxation time (IVRT) of 85 ms. Mild tricuspid and mitral regurgitation were also noted.

A comprehensive colonoscopy was performed, successfully passing the scope up to the descending colon. The examination revealed unremarkable mucosa throughout the examined regions. A biopsy was taken from the rectum to evaluate for amyloidosis, but Congo's red stain for amyloid was negative. Following this, a renal biopsy confirmed the presence of amyloidosis. The renal biopsy findings, including positive Congo red staining for amyloid deposits and the absence of features typical of diabetic nephropathy (such as nodular glomerulosclerosis), were crucial in differentiating renal amyloidosis from diabetic nephropathy. The patient exhibited systemic symptoms consistent with amyloidosis and had elevated serum amyloid A levels, further supporting the diagnosis of systemic amyloidosis over diabetic nephropathy. Concomitant hereditary amyloidosis was excluded due to the absence of a family history suggestive of hereditary forms, and the clinical presentation and diagnostic findings were more consistent with acquired systemic amyloidosis secondary to chronic inflammatory conditions.

Genetic analysis by polymerase chain reaction (PCR) revealed the presence of the HLA-B27 allele, indicating a potential association with certain autoimmune conditions, particularly ankylosing spondylitis (AS). Magnetic resonance imaging (MRI) of the lumbar-sacral spine showed loss of lumbar lordosis and Modic type 2 changes at multiple levels, along with obliteration of the sacroiliac joints (SI joints) and no active inflammation. A hyperintense signal was observed on the superior and anterior plates of the L4 and L5 vertebrae and the inferior aspect of the L5 vertebra. These findings were consistent with Romus and Anderson lesions of ankylosing spondylitis, with ossification of the anterior longitudinal ligament bridging adjacent upper and lower vertebrae, potentially forming syndesmophytes.

This was the first time the patient was diagnosed with AS during hospitalization, based on the Modified New York Criteria [8]. The patient met the clinical criteria of insidious low back pain that improves with exercise but not with rest, limited motion of the lumbar spine, and reduced chest expansion. Radiographic evidence supported the presence of bilateral sacroiliitis, fulfilling the radiological criteria.

Following admission, the patient was prescribed tizanidine 2 mg orally and pregabalin 75 mg orally to manage muscular spasms and alleviate musculoskeletal symptoms. Rivaroxaban 2.5 mg orally was also administered for its anticoagulant properties, aiming to reduce the risk of thromboembolic complications associated with secondary systemic amyloidosis (SSA). Supplementary medications included folic acid tablets to counteract potential adverse effects of the prescribed drugs, Neurobion tablets to promote nerve health, Qalsan D tablets providing calcium and vitamin D supplements to enhance bone health, and Nuberol Forte capsules

(paracetamol-orphenadrine citrate) for pain relief and its anti-inflammatory properties. The decision to withhold NSAIDS during hospitalization was based on concerns about potential renal damage, considering the patient's comorbidities and renal amyloidosis. Additionally, the lack of symptom improvement despite prior NSAID use at home prompted the need for more targeted therapy to address the underlying inflammatory process.

Consequently, a decision was made to initiate infliximab therapy to treat musculoskeletal symptoms, after ruling out latent tuberculosis through an interferon-gamma release assay. Treatment began with an intravenous infusion of 5 mg/kg at 0 and 2 weeks, which resulted in improved renal function tests and a reduction in inflammatory markers. A comprehensive treatment approach was employed to manage ankylosing spondylitis symptoms, with ongoing monitoring and adjustments based on the patient's cardiac functions. Despite the positive response, when the decision was made to administer a third dose at 6 weeks, the patient, eager for discharge, returned after 8 weeks with signs of heart failure. Due to the deteriorating clinical status, intubation and mechanical ventilation were planned. Tragically, the patient passed away within an hour of hospital readmission. The reporting of this study conforms to CARE guidelines [9]. Written informed consent was obtained from the patient's family to publish his anonymized data and the case report did not require ethics committee approval.

## Discussion

This report presents a case indicative of AS-related SSA, with findings suggestive of AA amyloidosis. The patient's complex presentation included signs of congestive heart failure, restrictive cardiomyopathy, proteinuria, renal tubular damage, hepatomegaly, malabsorption, and a low serum albumin level. The relationship between AS and SSA remains an area of ongoing investigation. Recent studies suggest that patients with AS may be at a higher risk of developing SSA [10].

AS primarily targets axial joints, especially the sacroiliac joints, and also affects the spine, peripheral joints, and entheses. AS can present with uncommon complications beyond the spine, posing challenges for diagnosis [2–4]. A significant concern is SSA, a long-term complication associated with various chronic inflammatory conditions. Individuals with AS have a higher incidence (1.1%) of clinically visible secondary amyloidosis. Among those with AS who develop renal complications, secondary amyloidosis is the most prevalent cause, accounting for 62% of these cases [8, 10]. In addition to the kidneys, systemic amyloidosis may also impact the heart, liver, gastrointestinal tract, and peripheral nervous system [11, 12].

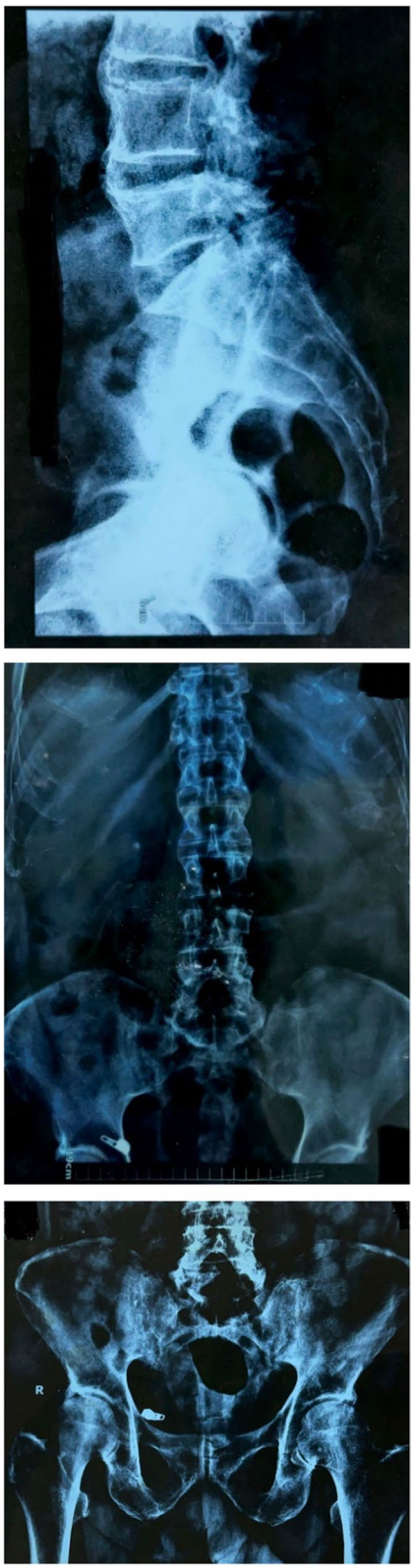


**Fig. 1** X-ray of lumbar spine

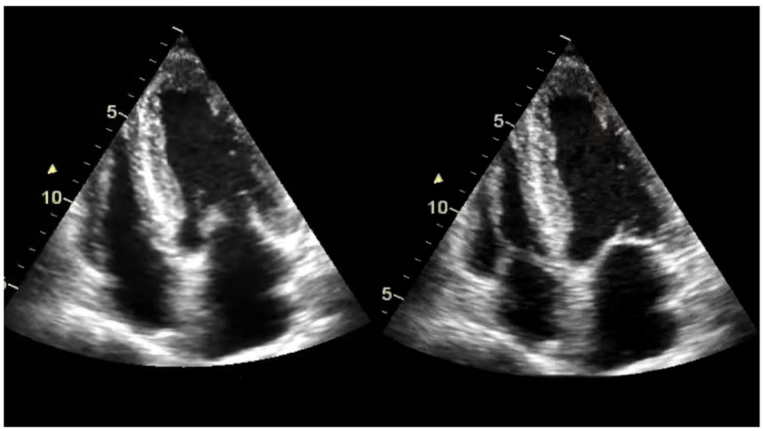


**Fig. 2** Echocardiogram exhibits symmetric hypertrophy of both the left and right ventricles, accompanied by biatrial dilation

Patients diagnosed with AS have approximately twice the risk of mortality compared to the general population. This elevated risk is primarily related to increased cardiovascular risks, with myocardial infarction rates around 2–3 times higher than in the general population. Although AA amyloidosis can cause cardiovascular issues, significant amyloid deposition in the heart is unusual and seldom leads to death [3, 4]. The primary cause of these effects is organ damage resulting from the accumulation of amyloid fibrils in the extracellular space. Hepatocytes produce these fibrils in response to chronic inflammation, leading to mechanical disruption and local oxidative stress within organs [5, 6]. The spleen and liver are typically the initial sites of AA amyloid deposition. However, even with substantial amyloid infiltration, splenic and hepatic involvement often remains asymptomatic for extended periods or results in only mild abnormalities in liver function [13]. AA amyloid fibril deposition in the mesangium and glomerular capillary walls of the kidneys typically results in proteinuria, nephrotic syndrome, and progressive renal failure. Proteinuria, often the earliest and most common sign of AA amyloidosis in patients with chronic inflammatory conditions, occurs in up to 95% of cases and plays a crucial role in determining prognosis [7, 13]. The overall incidence of AA amyloidosis in post-mortem examinations conducted in Western nations has been reported to vary between 0.5% and 0.86% [14]. A previous study found that individuals with AS and amyloidosis were generally older, had a longer duration of illness, limited spinal mobility, and lower hemoglobin levels [15].

Prior to the development of targeted anti-cytokine therapy, standard synthetic disease-modifying antirheumatic drugs (DMARDs) such as azathioprine, cyclophosphamide, and methotrexate were commonly used to manage significant proteinuria and prevent renal failure in individuals with AA amyloidosis [16]. Recent studies have shown that TNF-blocking medications are beneficial in reducing the risk of AA amyloidosis formation and improving renal outcomes in individuals with inflammatory arthritis. The most effective treatment for AA

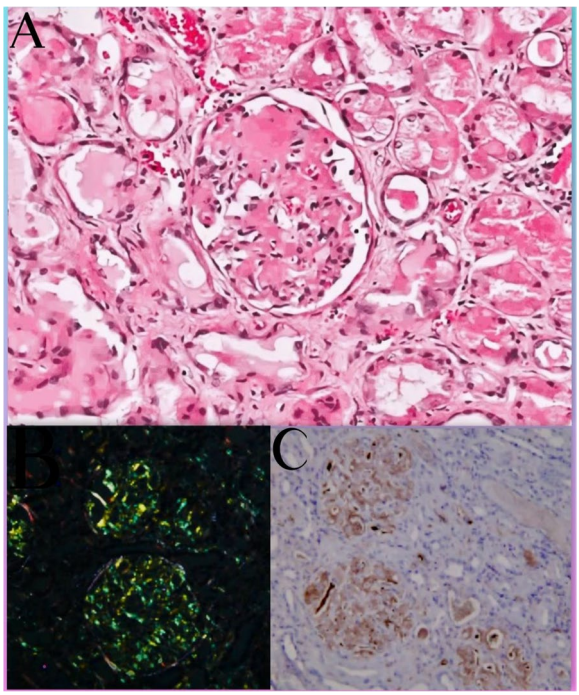


**Fig. 3** Pathological observations from the biopsy of renal tissue. **A** Renal amyloidosis is evident, with substantial mesangial expansion and eosinophilic, noncellular material extending into the glomerular capillary loops, visualized by H&E staining. **B** Apple-green birefringence under cross-polarized light confirms the presence of amyloid deposits, indicating positive staining. **C** Immunohistochemical staining shows a positive reaction, with brown coloration indicating the presence and distribution of amyloid-specific proteins within the renal tissue

amyloidosis involves managing the underlying inflammatory disease and reducing SAA levels. TNF-alpha promotes the synthesis of interleukin-1 (IL-1), interleukin-6 (IL-6), and SAA in the liver as part of the acute inflammatory response, which contributes to the development of amyloidosis [16, 17]. Additionally, TNF receptors increase the accumulation of advanced glycation end products, enhancing interactions with amyloid fibrils. These interactions lead to tissue damage and cytotoxic effects in amyloidosis [18, 19]. Anti-TNFα medications can reduce systemic inflammation and promote clinical remission in secondary amyloidosis [17, 20]. TNF-α inhibitors have been found to be notably effective and may be the preferred choice for managing the rapid progression and severe functional impairments associated with ankylosing spondylitis [21]. Given that back pain was a primary presenting complaint for the patient, the decision was made to initiate anti-TNF therapy to address the inflammatory progression related to ankylosing spondylitis.

Studies have shown that TNF-α inhibitors may exacerbate heart failure, particularly affecting both systolic and diastolic heart function, especially when administered at higher doses [22]. This case report underscores the treatment dilemma encountered when clinical amyloidosis is present in ankylosing spondylitis (AS). The patient's progression to heart failure and subsequent death after the third dose of infliximab highlights the need for treating physicians to be vigilant regarding the presence of cardiac amyloid involvement. Unfortunately, postmortem

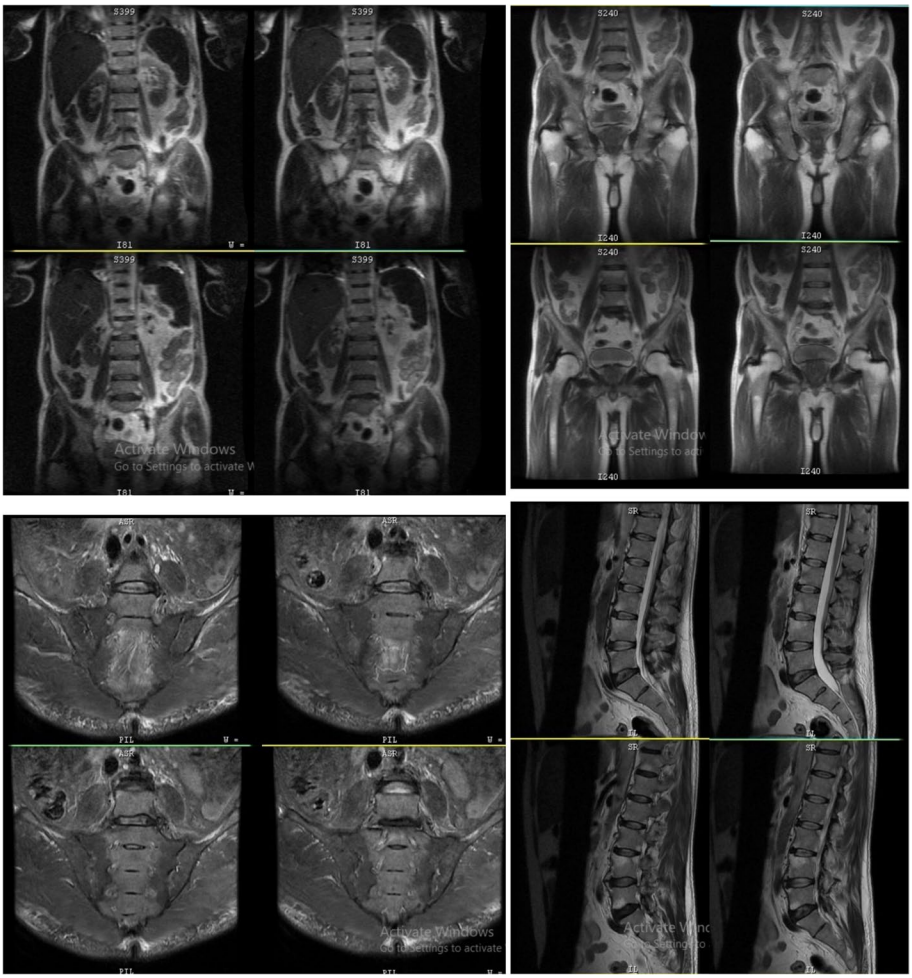

**Fig. 4** MRI of the lumbar-sacral spine. MRI revealed findings suggestive of the loss of lumbar lordosis and Modic type 2 changes at multiple levels, along with obliteration of the sacroiliac joints (SI Joints) and no active inflammation. The MRI of the lumbar-sacral spine revealed findings suggestive of the loss of lumbar lordosis and Modic type 2 changes at multiple levels, along with obliteration of the sacroiliac joints (SI Joints) and no active inflammation. A hyper-intense signal was observed superior and anterior plates of the L4 and L5 vertebrae and the inferior aspect of the L5 vertebra. These findings indicated Romus and Anderson lesions of ankylosing spondylitis, with ossification of the anterior longitudinal ligament bridging the adjacent upper and lower vertebrae, potentially forming syndesmophytes

studies to determine the precise cause of death were not conducted due to the family's refusal.

It is recommended to evaluate patients for amyloidosis at the early stages of AS. A comprehensive treatment approach should address ankylosing spondylitis symptoms while closely monitoring cardiac function. Given the increased risk of hospitalization and mortality associated with infliximab in patients with cardiac amyloidosis [23], alternative treatment options and supportive therapies should be considered. Management should include a thorough assessment of subclinical cardiac amyloidosis by a cardiologist. Future studies are needed to explore new therapeutic options beyond infliximab for treating amyloidosis, particularly when cardiac involvement is a concern, as suggested by Mallus and Rizzello [24] (Figs. 1, 2, 3, and 4).

## Conclusion

Our case study delves into the intricate relationship between AS and SSA, particularly AA amyloidosis, which impacts multiple organs. The patient's complex clinical presentation—including cardiac, renal, gastrointestinal, and musculoskeletal symptoms—illustrates the extensive consequences of this rare complication beyond the musculoskeletal manifestations of AS. Key diagnostic findings, such as HLA B27 positivity and clinical features and investigations suggestive of of AA amyloidosis.

We recognize the tragic outcome of this case, which underscores the challenges and risks associated with managing secondary amyloidosis, particularly in patients with cardiac involvement. Despite the difficulties in balancing treatment efficacy with patient safety, this case provides important clinical and therapeutic insights into managing ankylosing spondylitis and secondary amyloidosis. It emphasizes the need for careful monitoring and individualized treatment strategies, offering crucial lessons for clinicians.

While early detection generally offers benefits, it does not guarantee a successful outcome in every instance. Therefore, further research and additional case studies are necessary to better understand the variability in patient responses to treatment. As our comprehension of this complex relationship evolves, ongoing research will be vital for refining treatment strategies and addressing the systemic impact of AS-related amyloidosis comprehensively.

### Abbreviations

| | |
|---|---|
| SpA | Spondyloarthritis |
| AS | Ankylosing spondylitis |
| SSA | Secondary systemic amyloidosis |
| SAA | Serum amyloid A |
| Anti-TNFα | Anti-tumor necrosis factor-alpha |
| NSAIDS | Non-steroidal anti-inflammatory drugs |
| DMARDS | Disease-modifying anti-rheumatic drugs |

### Acknowledgements

Not applicable.

### Authors' contributions

Both authors contributed significantly to the development and completion of this case report. Rida Masood was involved in the initial patient assessment, including history-taking and physical examination. They participated in the diagnosis and treatment planning, contributing to the interpretation of diagnostic tests and imaging studies. Anjlee Sawlani also played a key role in drafting the manuscript, synthesizing clinical information, and providing critical insights into the discussion section, and literature review, ensuring that the case report was contextualized within existing research and clinical practices. Both authors read and approved the final manuscript.

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Not applicable.

### Availability of data and materials

All relevant data, including diagnostic pictures, and any other materials referenced in this case report, are provided as supplementary files with the submission. Should additional information be required, the corresponding author can be contacted for further assistance.

## Declarations

### Ethics approval and consent to participate

In accordance with the ethical standards, written informed consent was obtained from the patient's family for the publication of this case report and any accompanying images. All personal identifying information has been removed to protect patient confidentiality.
As per institutional guidelines, IRB approval was not required for the publication of this case report.

### Consent for publication

The patient's family provided written informed consent for the publication of this case report and any accompanying images. The consent process involved explaining the purpose of the report, its potential reach, and the measures taken to ensure patient confidentiality. The patient's family was assured that their identity would remain anonymous, with all personal identifying information removed or altered.

### Competing interests

The authors declare that they have no competing interests.

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