Scholars Journal of Medical Case Reports
Abbreviated Key Title: Sch J Med Case Rep
ISSN 2347-9507 (Print) | ISSN 2347-6559 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Nephrology

Renal AA Amyloidosis in Ankylosing Spondylitis: A Case Report

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DOI: 10.36347/sjmcr.2024.v12i06.026 | **Received:** 28.04.2024 | **Accepted:** 06.06.2024 | **Published:** 11.06.2024

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Abstract **Case Report**

Ankylosing spondylitis (AS) is a chronic inflammatory joint disease of seronegative spondyloarthropathies (SpA). Secondary amyloid A amyloidosis (Amyloidosis AA) is an uncommon complication of ankylosing spondylitis (AS). Amyloidosis AA is a systemic disease characterized by amyloid deposition in many organs including kidneys. An amyloid fibril formation starts with inappropriate folding of amyloidogenic precursor proteins. The amyloid fibrils have a typical appearance on light microscope that could be easily identified. The classification of secondary amyloidosis is based on the precursor proteins that form amyloid fibrils along with systemic and local distribution of amyloid deposition. Renal involvement is most frequent in systemic amyloidosis. The clinical manifestation of renal amyloidosis differs depending on the type of amyloid protein with the location and amount of amyloid deposition. The treatment of amyloidosis should be focused on managing symptoms and stabilizing amyloid protein.

Keywords: Amyloidosis AA, Ankylosing Spondylitis (AS), Secondary Amyloidosis, Renal Involvement.

INTRODUCTION

Ankylosing spondylitis (AS) is an inflammatory rheumatic disorder that represent the end phenotype of the spondyloarthropathy (SpA) group of diseases [1]. The preliminary clinical manifestations are back pain and progressive spinal rigidity along with inflammation of the shoulders, hips as well as peripheral joints [2]. There is a correlation between the prevalence of AS and positive HLA B27 frequency [3]. It was reported that the estimated overall prevalence of AS in general population is 1.5%, which approaches to 5-6% among HLA B27 positive population [4]. The frequency and severity of extra-articular manifestations in AS usually vary widely that represents a significant concern [5]. The most prevalent extra-articular manifestations represented by uveitis, psoriasis, inflammatory bowel disease, lung, heart, bone and kidney involvement [5]. It is commonly believed that renal involvement in AS is rare [6], however AS has been linked to a higher incidence of renal disease in comparison to the general population, which sometimes overlooked [1]. The exact mechanism of kidney disease in AS remains poorly understood as kidney biopsy results are only rarely reported.

Amyloidosis is a condition associated with extracellular deposition of insoluble fibrils that can cause a wide range of symptoms [7]. Amyloidosis can be divided into systemic or local diseases depending on the precursor protein which form amyloid fibril along with the type, location and extent of deposition [7]. The most frequent types of amyloids include- immunoglobulin light chain (AL), amyloid A (AA), transthyretin (ATTR) and amyloid beta peptide (AB) [8]. Systemic amyloidosis further categorized into primary and secondary amyloidosis, are often associated with a risk of developing neoplastic diseases [7]. Systemic amyloidosis typically affects tissues like- kidney, heart, peripheral nerves and musculoskeletal tissue [7]. Amyloid A (AA) amyloidosis, is a secondary systemic amyloidosis which is an uncommon multi-organ disorder caused by the extracellular tissue deposition of an AA protein, a non-immunoglobulin protein [3]. AA protein

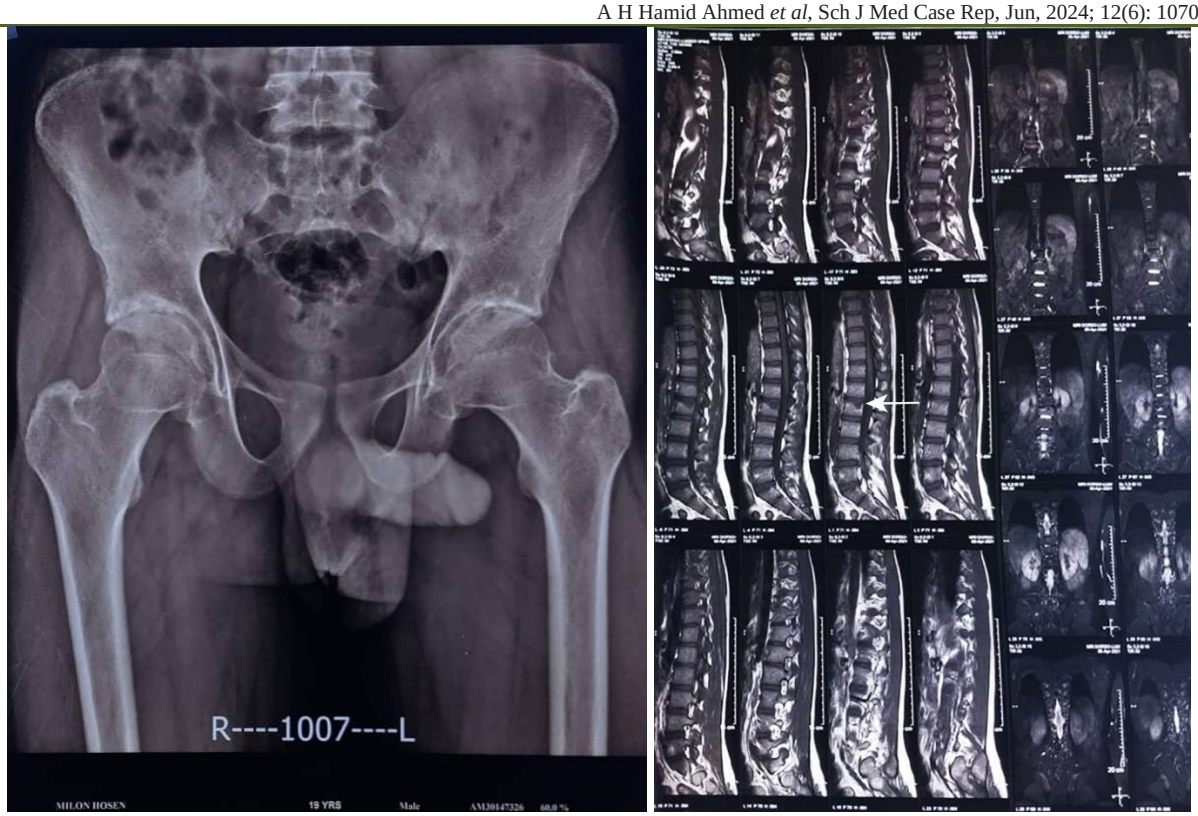
is an acute-phase reactant protein, mostly generated in the liver and has a controlling role in the metabolism of lipoproteins during inflammation [9]. During chronic inflammation, the protein fibrils deposit and aggregate in the extra-cellular matrix of tissues, resulting in disruption of normal architecture and function of the surrounding cells. Although AA amyloidosis commonly manifests as renal involvement, it could also affect other organs such as liver, spleen, adrenals, lungs and heart [10]. Thus, renal AA amyloidosis emerges as a systemic consequence of severe chronic inflammatory disorder. Here we discuss a case of renal (AA) amyloidosis secondary to ankylosing spondylitis in a 24 years old male.

CASE REPORT

A 24 years old young male presented with the complaints of bilateral leg swelling for 2 months which was insidious in onset, recurrent, pitting, associated with reduced urine output. The urine was frothy and its color was normal. His swelling was not associated with cold intolerance, chest pain, shortness of breath (SOB) and was improved after taking diuretics. He stated that, he has been suffering from inflammatory low back pain for last 7 years for which he was evaluated with relevant investigations like- HLA B27 (positive) along with X-Ray lumbo-sacral spine and magnetic resonance imaging (MRI) of spine which revealed bilateral sacroillitis (Figure- 1a and 1b); ultimately, he was labelled as a case of ankylosing spondylitis (AS). During his disease course, he has been treated with multiple non-steroidal anti-inflammatory drugs (NSAIDs such as indomethacin, etodolac, etoricoxib) on several occasions, along with disease modifying anti-rheumatic drugs (DMARDs like- methotrexate, sulfasalazine and Adalimumab) on separate occasions with partial improvement of his back pain. Later he discontinued all drugs due to financial constrain. There was no history of painful red eye, skin rash, nail change, oral ulcer, fever, cough etc. Apart from his rheumatological disease, his other medical, family and psychosocial history didn't have any relevant findings.

On physical examination, he was mildly pale looking, pulse rate was 96 beats per minute (bpm) and regular, blood pressure (BP) was 110/75 mm of Hg with no postural drop, respiratory rate (RR) was 18 breaths/minute, body temperature was normal (98.6°F), leuconychia was present, peripheral oedema was ++, bed side heat coagulation test reveals ++++ proteinuria (Figure- 2). On musculo-skeletal (MSK) system examination; mild tenderness was present all over the spine, modified schöber's test was positive, axial movement was normal except mild restriction in lumber region. Ascites was present as evident by positive shifting dullness, but no abdominal organomegaly. There was no cardiovascular and neurological abnormality observed.

The laboratory investigations report such as- urine routine microscopic examination (RME) showed: 4+ peoteinuria with no active urinary sediments, urinary total protein (UTP) was 15 gm/24 hours, urinary protein creatinine ratio (uPCR) was 15, haemoglobin (Hb) level was 10.5 g/dl, erythrocyte sedimentation rate (ESR) was 125 mm in 1st hour, C-reactive protein (CRP) was 16 U/ml, serum creatinine was 0.51 mg/dl and the creatinine clearance rate was 98 ml/minute. His serum electrolytes levels were within normal limit, transferrin saturation (TSAT) was 40.7%, serum albumin level was 16 g/L, corrected serum calcium level was 8.12 mg/dl, serum cholesterol level was 275 mg/dl, thyroid function was normal, hepatitis serologies were negative, anti-nuclear antibody (ANA) was not detected, serum complement levels (C_3, C_4) were within normal limit, he was tested negative for rheumatoid arthritis as his rheumatoid factor (RF) and ant-cyclic citrullinated peptide (anti-CCP) were negative (Table- 1). After evaluation, renal biopsy was done following standard procedure which showed: out of 8 glomeruli, 3 global sclerosis and 4 segmental sclerosis, cellularity was not increased, glomerular basement membrane (GBM) was not thick, increased mesangial matrix, mild tubular atrophy, the direct immunofluorescence (DIF) was negative for any immunoglobulin and complement (not shown), Haematoxylin and eosin stain showed amorphous and granular deposits on light microscopy (LM) (Figure- 3A), Silver stain showed deposition in the glomeruli and wall of blood vessels with normal basement membrane (Figure- 3B), Congo red stain showed positive deposits in the glomeruli and wall of blood vessels (Figure- 3C), Crystal violet stain was also positive in above mentioned areas (Figure- 3D). Thus, the diagnosis of renal amyloidosis was established. Primary AL amyloidosis was excluded by serum protein electrophoresis, immune-electrophoresis and serum free light chain assay. Serum protein electrophoresis showed polyclonal gammopathy, immuno-electrophoresis showed normal pattern-no monoclonal band identified, kappa light chain was 209.78 mg/dl, lamda light chain was 107 mg/dl, kappa to lamda ratio was- 1.92 (Figure- 4a, 4b; Table- 2).



(a) (b)

Figure- 1: (a) X- Ray sacroiliac joints showing abnormalities (sclerosis) of both sacroiliac joints (bilateral sacroiliitis). (b) MRI spine showing- focal area of marrow edema at L_2 upper end plate with schmrol's node (White arrow). Marrow edema is noted L_5 lower end plate

Figure- 2: Bed side heat coagulation test showing ++++ proteinuria

Table- 1: Laboratory investigations

Parameters	**Patient's findings**	**Reference values**
HLA B27	Positive	Negative
Urine routine microscopic examination (R/M/E)		
Protein	++++	Nil
RBC	0-2	0-5
WBC	4-6	Nil
Cast	Nil	Nil
Urinary total protein (UTP)	15 gm/24 hours	<0.2 gm/24 hours
Urinary protein creatinine ratio	14.9	<0.2: normal, >0.2: proteinuria
C-reactive protein (CRP)	16 U/ml	<5 U/ml
Haemoglobin (Hb)	10.5 g/dl	Male: 15.2±2 g/dl Female: 13.5±1.3 g/dl

Parameters	Patient's findings	Reference values
Erythrocyte sedimentation rate (ESR)	125 mm in 1st hour	0-10 mm in 1st hour
S. Creatinine	0.5 mg/dl	Male: 0.7-1.3 mg/dl Female: 0.5-1.2 mg/dl
Creatinine clearance rate	98 ml/ minute	Male: 97-137 ml/minute Female: 88-128 ml/minute
T-SAT	40.70%	
S. Ferritin	574 ng/ml	26-388 ng/ml
S. Albumin	16 g/L	32-48 g/L
S. Calcium	8.1mg/dl (corrected)	8.3 -10.2 mg/dl
S. Cholesterol	275 mg/dl	<200 mg/dl
S. TSH	4.35uIU/ml	0.3-4.5 uIU/ml
FT_4	1.52 ng/dl	0.89-1.72 g/dl
HBsAg	Negative	Negative
Anti HCV	Negative	Negative
ANA	Negative	Negative
C_3	0.97 g/l	0.90-1.80 g/L
C_4	0.4 g/l	0.1-0.5 g/L
RF	Negative	Negative
Anti CCP	Negative	Negative

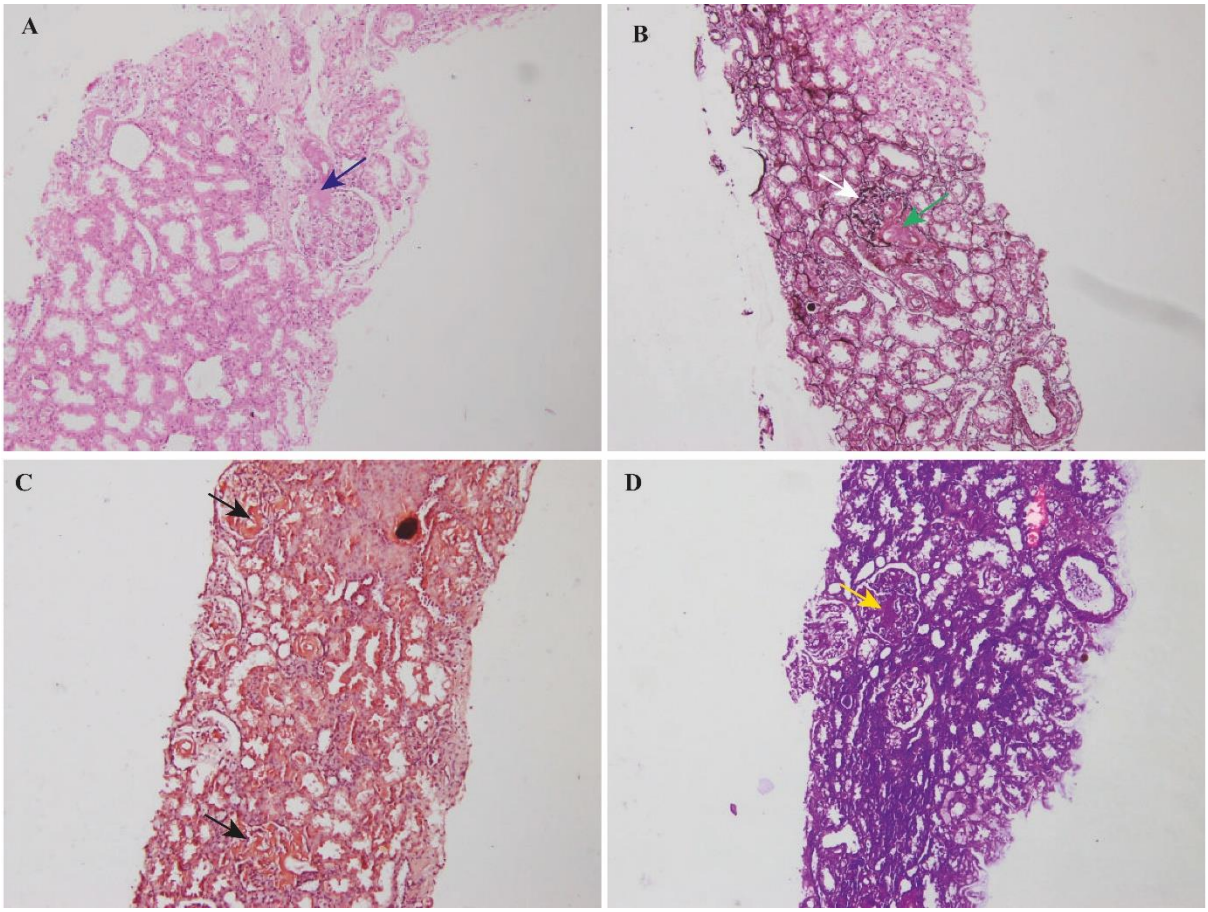


Figure- 3: Microscopic findings of renal tissue (A) Haematoxylin and Eosin stain- showed amorphous and granular deposits on light microscopy (blue arrows); (B) Silver stain showing deposition in the glomeruli and wall of blood vessels (green arrow), normal basement membrane (white arrow); (C) Congo Red stain showed positive deposits in the glomeruli and wall of blood vessels (black arrows); (D) Crystal Violet stain was also positive in above mentioned areas (yellow arrow)

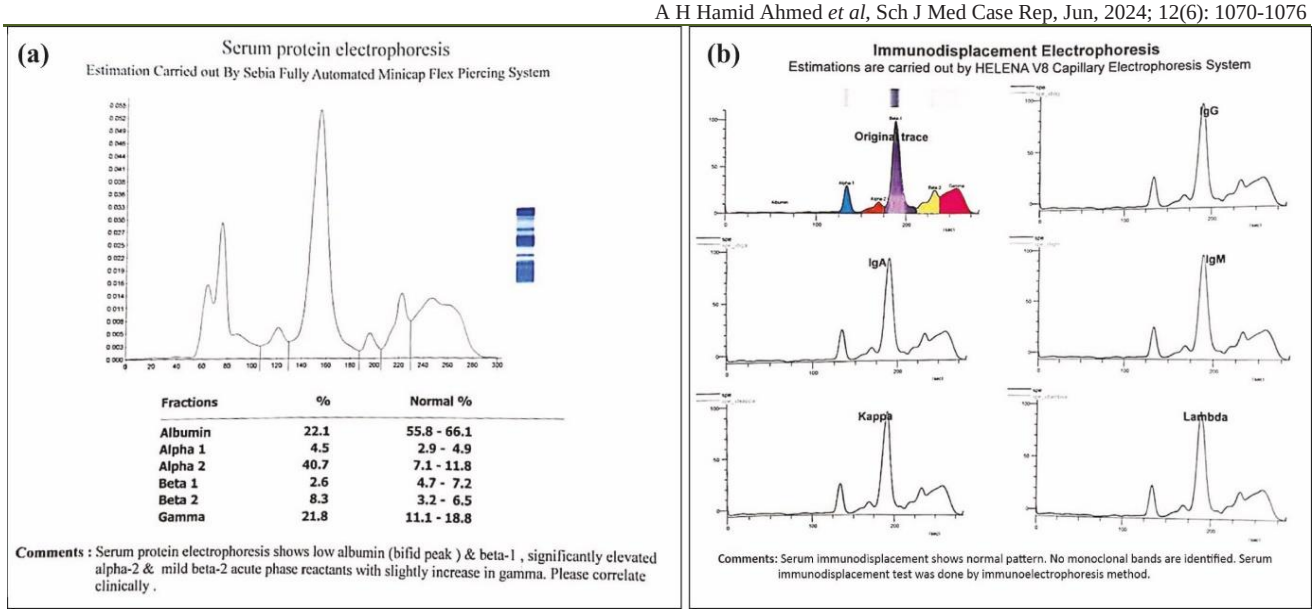


Figure- 4: (a) Serum protein electrophoresis, (b) Immune electrophoresis

Table- 2: The serum free light chain assay

Test	Result	Reference value
Kappa Light Chain	209.78 mg/dl	200-440 mg/dl
Lamda Light Chain	107.99 mg/di	110-240 mg/dl
Kappa: Lamda	1.92	0.31-1.56

DISCUSSION

Ankylosing spondylitis (AS) is a chronic inflammatory joint disease that falls in the category of seronegative spondyloarthropathy (SpA). The condition mostly affects young male and is strongly linked to the HLA B27 histocompatibility antigen [1]. The majority of affected joints are the sacroiliac and vertebral ones, but peripheral arthritis affects at least one-third of AS patients [1]. Secondary amyloidosis (amyloidosis AA) is a consequence of chronic inflammatory diseases like-ankylosing spondylitis (AS), rheumatoid arthritis (RA), inflammatory bowel disease (IBD) and other auto-inflammatory conditions [11]. There are different types of amyloidosis, albeit main subtypes are- primary AL (amyloid light chains) amyloidosis, secondary amyloid A (AA) amyloidosis, familial amyloidosis and β_2-macroglobulin-related amyloidosis [12]. The well-established but rather uncommon finding of secondary renal amyloidosis as a consequence of AS is seen in 4–9% of all patients with AS [13]. Amyloidosis typically develops as a late consequence of active longstanding AS [14]. The diagnosis of an amyloidosis depends on particular organ involvement along with histological evidence of target organ tissues showing deposition of inappropriately folded proteins (amyloid fibrils) resulting to organ dysfunction [12]. Renal involvement in ankylosing spondylitis (AS) is uncommon and frequently disregarded, because it tends to manifest itself later in the natural progression of the disease [15]. In renal involvement, there are three distinct etiologies that need to be distinguished: AA amyloidosis, NSAID-induced tubulointerstitial nephritis, and IgA nephropathy [1, 15]. These conditions differ significantly in terms of management and prognosis of the disease. Because of their low prevalence, very little information is available about their distribution. Amyloidosis AA (60%) and IgA nephropathy (30%) account for 90% of the cases reported in the literature [10, 16-17]. The initial sign of amyloidosis AA in renal injury accompanied by proteinuria [18]. Proteinuria, which can range from sub-nephrotic to massive, is the typical sign of a renal lesion that is caused by both the physical distortion of the glomerular structures and the direct cytotoxicity of the amyloid precursor following the interaction with membrane receptors and endocytosis [17]. In AA amyloid kidney disease, the site of protein deposition varies that may affect the course and clinical presentation of the disease [19]. There is usually less severe proteinuria when amyloid deposition is localized to the tubule interstitium, Conversely, glomerular involvement causes nephrotic-range proteinuria and a faster loss in renal function (rapid decline of eGFR) [18]. Therefore, in the setting of an underlying chronic inflammatory illness, any patient presenting with new proteinuria coupled with a deterioration in renal function should be suspected of having AA amyloid kidney disease [20].

Our patient presented with generalized body swelling and reduced urine output for 3 months. He has been diagnosed as a case of ankylosing spondylitis 7 years back on the basis of positive HLA B27 with bilateral sacroilitis on X-Ray and MRI spine. Since then, he was treated with several NSAIDs and DMARDs. But he could not continue any of medications due to financial

constrain. On presentation, his urine RME showed ++++ proteinuria and uPCR was 15. His massive proteinuria was accompanied by amyloid nephrosis syndrome that includes- hypoalbuminemia, hypercholesterolemia, and pitting oedema. There was no organomegaly, his blood pressure remained within normal limit and the sizes of both kidneys were sonographically normal. His renal function was normal with optimum creatinine clearance rate. Renal biopsy showed positive Congo red stain deposits in glomerular mesangium and wall of the blood vessels with absence of any immunoglobulin and complement deposition on DIF.

In this patient, we would like to emphasize the need for careful clinical and laboratory evaluation, diagnosis, regular follow-up, and tailoring subsequent treatments, as well as being alert to amyloidosis and its impending morbidity and mortality. Overt amyloidosis is often referred to as a late complication of AS, as it has been reported in patients with active and long-standing AS disease [14]. On the other hand, renal AA amyloidosis in our patient evolve within 7 years of diagnosis AS, although he has got DMARDs and biologics in irregular pattern during his disease course. Since the clinical presentation in this patient was insidious, the diagnosis of secondary amyloidosis (amyloidosis AA) was dependent solely on high degree of clinical suspicion and performing tissue biopsy.

CONCLUSION

Ankylosing spondylitis (AS) is a chronic inflammatory joint condition, which is one of the seronegative spondyloarthropathies (SpA). According to current theories, renal involvement in AS is rare. It is generally known that AS can cause secondary renal amyloidosis (amyloidosis AA), yet this is a relatively uncommon occurrence. Proteinuria, which can range from sub-nephrotic to massive, is the typical sign of renal lesion. Glomerulonephritis, amyloidosis, and NSAID nephropathy should all be taken into consideration in patients with ankylosing spondylitis. In our patient after reaching a diagnosis of secondary renal amyloidosis (amyloidosis AA) following AS, we prescribed him biologics in the form of either intravenous tocilizumab or subcutaneous etanercept. But unfortunately, he could not take any treatment due to financial constraint. Therefore, we could not observe the response of biologics in this case.

Authors Contribution

Each author contributed to the article's drafting or critical revision for significant intellectual content, and they all gave their approval for the publication of the finished edition.

Conflicts of Interest: All authors stated that they have no conflict of interest.

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