



## Case Report

# One Illness Always Conceals Another: A Rare Case of Renal AA Amyloidosis Secondary to Progressive Systemic Sclerosis.

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## Abstract

Amyloidosis is a disparate group of diseases characterized by the extracellular deposition of abnormal proteins in diverse organs, leading to the progressive deterioration of one or several of them. There are several types of amyloidosis, but the three most frequently encountered are, in order of frequency, primary light chain (AL), secondary chain (AA), and wild-type transthyretin (ATTR), depending on the type of precursor protein found in the organs and whether or not another disease coexists. Secondary AA amyloidosis, which mainly affects the kidneys, may develop due to an underlying infection or long-term chronic inflammatory conditions. Additionally, chronic elevation of serum amyloid A (SAA) levels continues to be a significant risk factor for the development of AA amyloidosis in rheumatic diseases, and the prognosis can be unforeseeable. According to the literature, there are very few reported cases of AA amyloidosis secondary to progressive systemic sclerosis (PSS). Here we present a rare case of renal AA amyloidosis secondary to PSS and a literature review.

**Keywords:** Systemic Amyloidosis; AA Amyloidosis; Progressive Systemic Sclerosis; Auto inflammatory Syndrome.

## Introduction

First described in an autopsy case published in 1639 by Nicolaes Fonteyn (Dutch physician and poet), AA amyloidosis is a rare but serious systemic complication that can develop in any long-term inflammatory disorder [1]. Formerly considered a frequent and serious complication of rheumatoid arthritis (RA), ankylosing spondylitis (AS), inflammatory bowel disease (IBD), and auto inflammatory conditions, it is characterized by the accumulation of abnormal proteins, commonly known as amyloid fibrils, in various

organs and tissues of the body, culminating in the production of insoluble and toxic clumps, which can lead to organ dysfunction and potentially life-threatening complications [1,2]. While it can affect multiple organs, amyloidosis preferentially involves kidneys, leading to proteinuria as the first clinical manifestation and renal impairment [3]. There are different subtypes of amyloidosis, but the main subtypes are primary AL amyloidosis (light chains), secondary amyloid A (AA) amyloidosis, familial/ATTR amyloidosis, and  $\beta$ 2-microglobulin-related amyloidosis [3]. Primary amyloidosis (AL) is characterized by the deposition of light chain proteins involving the subtypes Kappa ( $\kappa$ ) or Lambda ( $\lambda$ ). In contrast, secondary amyloidosis (AA) is associated with

serum amyloid A protein (SAA), a hepatic acute phase protein, derived from chronic inflammatory conditions [2,3]. In recent years, the intricate connection between autoimmune diseases and amyloidosis has garnered increased attention in the medical community. Autoimmune diseases involve the body's immune system mistakenly attacking its tissues, leading to chronic inflammation. This persistent inflammatory environment can trigger the deposition of amyloid fibrils, complicating the clinical picture and treatment approach [4]. Progressive systemic sclerosis (PSS), a rare autoimmune disorder, is one such condition that can predispose individuals to secondary AA amyloidosis. Herein, we present a scarce case of renal AA amyloidosis secondary to PSS.

### Case Presentation

A 55-year-old female patient of Moldavian origin was referred to our internal medicine department for asthenia, substantial weight loss over a short period (6-7kg in three months), dysphagia, and leg and abdominal pains. She has no other associated complaints. Her medical history is marked by diffuse systemic scleroderma, known for 10 years and not followed up since, with associated cutaneous and pulmonary interstitial involvement, Raynaud's phenomenon, gastro-oesophageal reflux, and tension headaches. Home medication revealed Level I analgesics and proton pump inhibitors (PPIs). No other medications were reported. Her clinical parameters on arrival were entirely satisfactory; a blood pressure of 130/60mm Hg, a heartbeat rate of 85 per minute, a temperature of 36.6°C, an oxygen saturation of 97% on room air, and a respiratory rate of 20 per minute. Clinical examination showed unremarkable cardiorespiratory auscultation, abdominal examination with very slight epigastric tenderness, a reassuring neurological examination, and the lower limbs showed oedema. The skin examination revealed sclerodactyly, Morphoea on the lower limbs, and ulcerations of the extremities. A laboratory examination revealed as follows; Haemoglobin of 10.5g/dL, platelets of 336,000/mm<sup>3</sup>, white blood cells of 11,450/mm<sup>3</sup> predominantly neutrophilic, C-reactive protein of 168g/dL, coagulation was normal, urea of 89, creatinine of 4.4g/dL, renal glomerular filtration (GFR) of 35mL/min/1.73m<sup>2</sup>, troponin, NT-ProBNP, ionogram and liver function were unremarkable. All viral, bacterial, and other infections were excluded. Tests for tuberculosis came back negative. Stool tests and fecal calprotectin returned negative.

Bearing the patient's condition, complementary investigations were realized. On a biological level, anti-nuclear factors returned positive at a 1:640 (Normal 1:80) titer with a centromere pattern and positive SS-A and Jo-1 antibodies. To note, Scl-70 and anti-RNP antibodies were negative. On the imaging level, the thoracoabdominal scan revealed no evidence of infection or other notable abnormalities, and cardiac ultrasound proved reassuring. Upper endoscopy and barium radiography revealed chronic gastritis and oesophageal dysmotility, probably secondary

to her PSS (a frequent and early-onset complication). A 24-hour urine collection revealed significant proteinuria (>3g, repeatedly twice). Given these results, a suspicion of nephrotic syndrome due to renal amyloidosis was raised and a renal biopsy was performed. Congo red staining revealed amyloid deposits in the glomeruli (figure 1). A diagnosis of AA amyloidosis secondary to systemic scleroderma was made. A treatment with corticosteroids and Tocilizumab (IL-6) began. Therapy with corticosteroids followed by tocilizumab led to clinical and biological improvement.

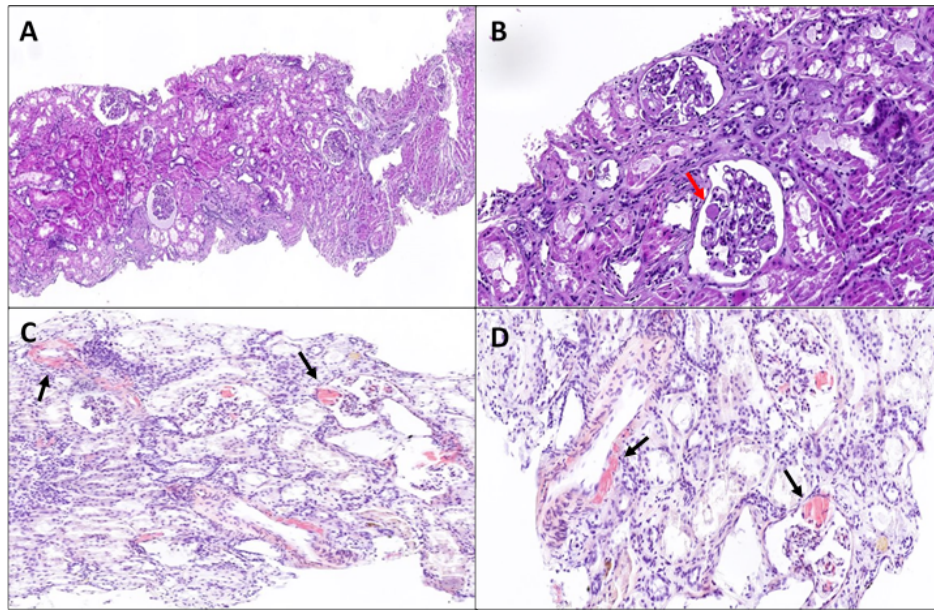
### Discussion

The percentage of AA amyloidosis varies widely between geographical regions, as does the lack of data in the literature [5]. A Swedish study identifying patients based on hospital discharge and outpatient registers between 2001 and 2008 has estimated the incidence of AA amyloidosis at 0.2 per 100,000, based on rheumatic arthritis (RA)-related death rates [6]. In 2013, an epidemiological study of systemic amyloidosis in England was carried out and suggested that only 48% of UK patients with amyloidosis were registered at the NAC, yielding an estimated incidence of AA amyloidosis in the UK of 0.166 per 100,000 in 2008 [7].

In our view, the most commonly encountered causes of secondary AA amyloidosis are rheumatoid arthritis (RA), followed by ankylosing spondylitis (AS), chronic juvenile arthritis (CJA), inflammatory diseases of the digestive tract (IBD), infectious diseases such as tuberculosis, and familial Mediterranean fever (FMF), in which other auto-inflammatory diseases may be associated [8,9]. According to the literature, there are very few studies reporting cases of AA amyloidosis secondary to progressive systemic scleroderma (PSS), the last cases being reported more than 20 years ago [10,11].

The prevalence of AA amyloidosis may vary depending on the mode of diagnosis: autopsy, digestive biopsy, renal biopsy, aspiration of subcutaneous fat from the abdomen for the most part, but also on the presence of clinical signs and the nature of the underlying disease [12]. The identification of antinuclear antibodies (ANA) with a centromeric motif and the positivity of SS-A and Jo-1 antibodies are consistent with autoimmune features associated with PSS. However, the absence of anti-Scl-70 and anti-RNP antibodies emphasizes the variability of immunological profiles in this disease [12].

AA amyloidosis can affect several organs but preferentially affects the kidneys, leading to proteinuria, oedema, and glomerular nephropathy, as in our patient, all of which may lead to very severe renal impairment if untreated [13,14]. Congo red staining remains the gold standard for diagnosis, revealing the presence of amyloid deposits in the tissues concerned, as in our patient's case in the kidneys (Figure 1).



**Figure 1:** Light microscopic images of renal biopsy of the patient. Haematoxylin-eosin coloration (A, size 50x; B, size 100x) showed amorphous material in the glomerulus (B, red arrow). Congo Red stain (C, size 100x and D, size 200x) revealed amyloid in the glomerulus and arteries (black arrow).

The relationship between autoimmune diseases and amyloidosis is fascinating. Studies have suggested that autoimmune disorders involve dysregulated immune responses and chronic inflammation. This chronic inflammatory environment can promote the deposition of amyloid fibrils, particularly of the AA type, derived from serum amyloid A protein [2]. Therefore, the development of secondary AA amyloidosis in patients with autoimmune diseases, and especially long-standing progressive systemic sclerosis such as ours, is not infrequent.

The therapeutic management of secondary amyloidosis represents a complex and multifaceted challenge. The most effective therapeutic approach involves control of the subjacent inflammatory disease and complete suppression of SAA production [15]. Like C-reactive protein (CRP), SAA is an acute-phase reagent synthesized by hepatocytes but also by other cells, notably macrophages and endothelial cells, through the regulation of pro-inflammatory cytokines, especially tumour necrosis factor (TNF) alpha, and IL-6 [15]. Before the age of targeted anti-cytokine therapies, the main ones used were corticosteroids, Disease-Modifying Anti-Rheumatic Drugs (DMARDs) such as azathioprine, cyclophosphamide, or methotrexate, and the anti-TNFs frequently used to avoid high proteinuria and renal failure in patients with AA amyloidosis [16]. Enhanced comprehension of the mechanisms underlying amyloid deposits has led to new treatment strategies, in particular those targeting the formation of amyloid protein. As IL-6 is one of the main triggers of SAA release, some

studies have reported some effectiveness of tocilizumab (anti-IL6) in the treatment of AA amyloidosis in rheumatoid arthritis and juvenile idiopathic arthritis [4,17]. A recently published study by Kuwana et al. showed very good efficacy and safety of Tocilizumab in the treatment of systemic sclerosis [18]. Our patient was treated with corticosteroids and then anti-IL6 with a spectacular clinical and biological response.

### Conclusion

In conclusion, this case highlights the importance of a multidisciplinary approach and comprehensive assessment in patients with autoimmune diseases presenting with renal symptoms. The diagnostic pathway involves a combination of laboratory findings, imaging studies, endoscopic procedures, and biopsies. Congo red staining remains the gold standard of diagnosis given its superior sensitivity and specificity in distinguishing amyloid from other protein deposits. Nevertheless, the rarity of secondary amyloidosis in systemic sclerosis warrants heightened clinical suspicion to ensure rapid diagnosis and management. Clinicians must remain vigilant for the potential development of proteinuria and renal signs in patients with systemic sclerosis. Improvements in diagnostic techniques, targeted therapies and a better understanding of the underlying mechanisms will be essential to improve outcomes and reduce the morbidity and mortality associated with this challenging combination of diseases.

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