

Multisystem AA Amyloidosis in Refractory Ankylosing Spondylitis: a Case-Based Review

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Case Report

Keywords: ankylosing spondylitis, amyloidosis, inflammation, renal, biologics

Posted Date: August 20th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10566690/v1>

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Additional Declarations: No competing interests reported.

Abstract

Background

Secondary (AA) amyloidosis is a rare but severe complication of chronic inflammatory diseases, including ankylosing spondylitis (AS). Although its incidence has declined in the biologic era, patients with long-standing, poorly controlled, or treatment-refractory disease remain at risk.

Case presentation:

We report a 40-year-old man with a 15-year history of refractory AS who presented with severe polyarthritis, marked systemic inflammation, nephrotic-range proteinuria, impaired renal function, anemia, and hypoalbuminemia. AA amyloidosis was confirmed by abdominal subcutaneous fat-pad aspiration and gastrointestinal biopsy demonstrating diffuse amyloid deposition, while alternative causes of systemic amyloidosis were excluded. Multisystem involvement included renal, gastrointestinal, and suspected early cardiac disease. After failure of anti-TNF, anti-IL-17, and JAK inhibitor therapy, treatment with tocilizumab resulted in marked improvement in disease activity and inflammatory markers, with stabilization of renal function despite persistent proteinuria.

Conclusion

This case highlights that AA amyloidosis, although uncommon, remains a serious complication of long-standing AS with persistent inflammation. Early recognition, close monitoring, and strict adherence to a treat-to-target strategy are essential to prevent irreversible organ damage. Furthermore, the favorable response observed with IL-6 inhibition supports its potential role as an effective therapeutic option in refractory AS-associated AA amyloidosis.

Introduction

Secondary (AA) amyloidosis is a complication of chronic inflammatory diseases, resulting from prolonged elevation of serum amyloid A (SAA), an acute-phase reactant produced by the liver in response to inflammatory cytokines. Persistent inflammation leads to misfolding and extracellular deposition of amyloid fibrils in various organs, most commonly the kidneys, causing progressive organ dysfunction and increased morbidity and mortality.^{1,2} Rheumatic diseases are among the most frequent underlying conditions associated with AA amyloidosis. While rheumatoid arthritis has traditionally been the leading cause, the incidence of AA amyloidosis in other chronic inflammatory disorders, including spondyloarthritis (SpA), has declined with the widespread use of effective biologic therapies. Nevertheless, patients with long-standing, poorly controlled, or treatment-refractory disease remain at risk, particularly when systemic inflammation persists despite multiple lines of therapy.^{3,4} In ankylosing spondylitis (AS), AA amyloidosis is a rare complication. Renal involvement is the predominant

manifestation, whereas gastrointestinal and cardiac involvement are uncommon. Multisystem amyloid deposition is usually associated with delayed diagnosis or inadequate disease control, emphasizing the importance of early recognition and prompt suppression of systemic inflammation.^{5,6}

Here, we report a case of multisystem AA amyloidosis in a patient with long-standing, treatment-refractory ankylosing spondylitis. Informed consent was obtained and signed from the patient regarding the use of patient health information for the purposes of writing a case report publication.

Case report

A 40-year-old male was diagnosed with AS at the age of 25, based on inflammatory back pain, MRI-confirmed bilateral sacroiliitis, peripheral arthritis (bilateral gonitis and left ankle arthritis), HLA-B 27 positivity and elevated inflammatory biomarkers. Diagnosis was established according to the ASAS Classification Criteria for Axial Spondyloarthritis.⁷ Initial treatment included conventional disease-modifying antirheumatic drugs (cDMARDs), namely sulfasalazine and methotrexate, as well as systemic and intra-articular glucocorticoids.

The patient was subsequently lost to follow-up for two years, during which time he used only glucocorticoids and underwent left total hip replacement due to osteonecrosis. In 2015, five years after the diagnosis, biologic therapy was initiated, because of persistently high disease activity (BASDAI 7.6, ESR 110 mm/h, CRP 77 mg/L). The patient demonstrated primary inefficacy to several biologic agents, including golimumab (BASDAI 7.9, ASDAS 6.2, ESR 77 mm/h, CRP 99 mg/L), etanercept (BASDAI 7.4, ASDAS 5.0) and adalimumab (BASDAI 7.6, ASDAS 5.0). He was again lost to follow-up and subsequently underwent right total hip arthroplasty due to advanced coxarthrosis. Secukinumab was later initiated because of high disease activity (BASDAI 8.8, ASDAS 6.0, ESR 77 mm/h, CRP 96 mg/L); however, during the COVID-19 pandemic, the patient discontinued regular follow-up and, over the following four years, used only nonsteroidal anti-inflammatory drugs.

In October 2024, the patient was urgently admitted to the Institute of Rheumatology with complaints of fatigue, malaise, weight loss, pain and swelling of the knees, ankles, small hand joints, elbows, accompanied by all-day stiffness. Physical examination revealed polyarthritis, bilateral positive Mennell sign, without periorbital or pretibial edema. Disease activity indices were elevated (BASDAI 7.4, ASDAS 5.8). Laboratory investigations showed pronounced inflammatory activity (ESR 160 mm/h, CRP 105 mg/L, fibrinogen 6.4 g/L), severe anemia (Hgb 71 g/L), hypoproteinemia, and renal impairment (urea 12 mmol/L, creatinine 247 µmol/L, uric acid 500 µmol/L), with reduced creatinine clearance (33 ml/min) and nephrotic-range proteinuria (7.7 g/day). Serum amyloid A levels were markedly elevated at 239 mg/L (reference range 0.0-6.8 mg/L). Radiography of the cervical and lumbar spine demonstrated apophyseal joint ankyloses and bilateral sacroiliac ankylosis, along with an L3 compression fracture. Abdominal ultrasonography revealed reduced kidney size with hyperechoic parenchyma and accentuated pyramids.

Renal biopsy could not be performed because of advanced spinal ankylosis. Abdominal subcutaneous fat pad aspiration demonstrated histopathological findings consistent with amyloidosis. Fecal

calprotectin was elevated (544.2 µg/g), and colonoscopy with terminal ileoscopy with biopsy revealed chronic inflammation of both the small and large intestine with diffuse amyloid deposition (Fig. 1). NT-proBNP levels were increased (797 pg/mL), and echocardiography raised suspicion of early amyloid cardiomyopathy; however, cardiac scintigraphy did not show increased myocardial pyrophosphate uptake. Additional investigations including immunoelectrophoresis and iliac bone biopsy, excluded plasma cell dyscrasias. Whole-exome sequencing identified a heterozygous variant of uncertain significance (c.2084A > G ; p.Lys695Arg), whose clinical relevance remains unclear. A diagnosis of multisystem secondary AA amyloidosis as a complication of prolonged inflammation in AS was established.

The patient was treated with systemic and intra-articular corticosteroids, methotrexate and sulfasalazine were reintroduced, along with angiotensin-converting enzyme inhibitors, beta-blockers, allopurinol. Given persistent high inflammatory activity with ongoing polyarthritis, impaired renal function and multisystem AA amyloidosis, escalation to advanced therapy was considered. Treatment with upadacitinib was initiated in December 2024. Due to persistently elevated inflammatory markers and high disease activity indices, therapy was switched to tocilizumab in April 2025. Following initiation of IL-6 inhibition, a significant improvement in BASDAI and ASDAS scores was observed, inflammatory markers decreased and renal function remained stable, although nephrotic-range proteinuria persisted (Fig. 2, Fig. 3).

Discussion

Secondary (AA) amyloidosis is an uncommon but potentially life-threatening complication of ankylosing spondylitis (AS), generally arising in the context of long-standing, inadequately controlled inflammation.^{5,6} Persistent elevation of serum amyloid A (SAA), primarily driven by IL-6, IL-1β and TNF-α, leads to extracellular deposition of amyloid fibrils in multiple organs.^{3,4} The kidneys are most frequently affected, whereas gastrointestinal and cardiac involvement are considerably rarer.⁶ Our patient illustrates multisystem AA amyloidosis with nephrotic-range proteinuria, diffuse intestinal amyloid deposits, and early cardiac involvement, highlighting the severe consequences of chronic systemic inflammation in refractory AS.

Epidemiological data suggest that AA amyloidosis in AS is rare, with historical incidence estimates of 2–3% in populations without access to modern biologic therapies, decreasing to < 1% in countries where biologic agents are widely used.⁵ According to a recent systematic review, prevalence rates of AA amyloidosis in AS ranged from approximately 6.1–8.5% in studies conducted before 2010, but declined to 1.1–1.3% in studies reported after 2010, likely reflecting the impact of biologics on disease control.⁸ Population-based longitudinal studies identify male sex, long disease duration, persistent high disease activity, delayed therapy initiation, treatment interruptions and previous joint replacements as major risk factors for development of AA amyloidosis in ankylosing spondylitis.⁹ In a large population-based cohort, AS was associated with a more than six-fold increased risk of developing AA amyloidosis compared with match controls, and patient with amyloidosis had an approximately 14-fold higher risk of progression to end-stage renal disease requiring dialysis.¹⁰ Dönmez et al. reported that secondary AA amyloidosis in

ankylosing spondylitis typically develops after prolonged disease duration, most commonly presenting with renal involvement and proteinuria as the first clinical sign. Their cohort consisted predominantly of male patients with poorly controlled disease, peripheral arthritis and persistently elevated inflammatory markers.¹¹ In our case, the patient exhibited multiple of these risk factors: male sex, 15-year disease duration, refractory peripheral arthritis, intermittent follow-up, previous joint replacements and periods of suboptimal therapy due to primary inefficacy and loss to follow-up.

Renal involvement represents the predominant and often earliest manifestation of AA amyloidosis in ankylosing spondylitis, most commonly presenting with proteinuria that may progress to nephrotic syndrome and chronic kidney disease.^{12,13} In the 48-month follow-up reported by Domingos et al., patients with AS-associated AA amyloidosis developed nephrotic-range proteinuria and progressive renal dysfunction, emphasizing the central role of sustained inflammation in renal amyloid deposition.¹² Similarly the monocentric study by Barbouch et al. confirmed that renal involvement is the most frequent clinical presentation of AA amyloidosis in AS, often determining long-term prognosis and survival.¹³ Population-based data further support the clinical relevance of renal amyloidosis in spondyloarthritis, with the TREND-EspA study showing that amyloidosis-related hospitalizations in SpA patients are predominantly driven by renal complications despite the declining incidence in the biologic era.¹⁴ In our patient, nephrotic-range proteinuria (7.7 g/day), hypoproteinemia and impaired renal function were the initial clues to renal involvement. Although renal biopsy could not be performed due to advanced spinal ankyloses, the clinical and laboratory profile closely mirrors patterns described in published series.^{12,13} Notably, renal amyloidosis developed despite previous exposure to multiple biologic agents, highlighting the persistent risk in patients with refractory disease and prolonged periods of uncontrolled inflammation.

Gastrointestinal involvement is uncommon but can significantly impact patient outcomes. Ozcakar et al. described a patient with AS who developed extensive amyloid deposition throughout the gastrointestinal tract, leading to chronic inflammation, malabsorption and elevated inflammatory biomarkers.¹⁵ Similarly in our case, colonoscopy and terminal ileoscopy revealed diffuse amyloid deposits throughout the small and large intestine, with markedly elevated fecal calprotectin (544.2 µg/g), reflecting active intestinal inflammation. Although gastrointestinal symptoms were mild, these findings underscore that even subclinical, gastrointestinal involvement may contribute to systemic inflammation and further elevate SAA levels, perpetuating amyloid deposition in other organs such as the kidneys and heart. Rare, but serious gastrointestinal complications such as spontaneous bowel perforation have been described in patients with AA amyloidosis secondary to AS, including a report of colonic perforation and resultant peritonitis attributed to amyloid deposition in the bowel wall.¹⁶

Cardiac involvement in AS-associated AA amyloidosis is rare and is usually described in isolated case reports. Barakat et al. reported a patient with multisystem AA amyloidosis complicating AS with cardiac manifestations, including evidence of restrictive cardiomyopathy and heart failure confirmed by echocardiography and cardiac biomarkers.¹⁷ In our patient, early echocardiographic changes and elevated NT-proBNP levels (797pg/ml), suggested incipient amyloid cardiomyopathy. Cardiac

scintigraphy was negative, while cardiac magnetic resonance imaging could not be performed because of bilateral hip replacements. These findings are consistent with Barakat et al., suggesting that early cardiac amyloid involvement may be subtle and not always detected by conventional imaging.

Therapeutically, biologic agents targeting IL-6, TNF- α , and JAK pathways have demonstrated efficacy in controlling systemic inflammation and stabilizing organ function.^{18, 19} Domingos et al. reported a sustained clinical and renal improvement in a patient with ankylosing spondylitis complicated by AA amyloidosis and nephrotic syndrome, with etanercept maintaining renal function and reducing proteinuria over 48 months.¹² A multicenter follow-up of 15 patients with AA amyloidosis secondary to inflammatory arthritides, including AS, showed stabilization or significant reduction in proteinuria and maintenance of renal function with anti-TNF therapy.²⁰ In our patient, previous anti-TNF therapy (golimumab, etanercept, adalimumab) and IL-17 blockade (secukinumab) were ineffective, even before the development of AA amyloidosis. After the diagnosis of AA amyloidosis was established, therapy with upadacitinib was initiated. Although JAK inhibitors effectively control AS, upadacitinib failed to improve clinical or laboratory manifestations of AA amyloidosis in our patient, and its efficacy in this setting remains uncertain.⁴ Following inadequate response to upadacitinib, treatment with Tocilizumab, an IL-6 receptor inhibitor, was initiated. This led to stabilization of renal function, reduction of ESR and CRP, and significant improvement in disease activity indices (BASDAI and ASDAS). This outcome aligns with earlier reports, including Eriksson et al., who described two patients with refractory AS-associated AA amyloidosis, treated with tocilizumab, resulting in rapid suppression of systemic inflammation, normalization of SAA levels, marked reduction of proteinuria, and stabilization of renal function.¹⁹ In addition, recent reports highlight the broader efficacy of IL-6 blockade in AA amyloidosis secondary to chronic inflammatory diseases. Tortosa-Cabañas et al. described patients in whom tocilizumab not only suppressed systemic inflammation but also contributed to regression of amyloid deposits, emphasizing the potential for organ preservation beyond symptomatic control.²¹ Similarly, Ugurlu et al. reported a series of patients with AA amyloidosis of diverse etiologies, demonstrating that IL-6 inhibition led to normalization of SAA levels, reduction in proteinuria, and stabilization or improvement of renal function over time.²² These findings are further supported by review data, confirming that targeting IL-6 represents a rational therapeutic strategy in refractory cases of AA amyloidosis, particularly when conventional and anti-TNF therapies fail to control systemic inflammation.²³

To further contextualize our findings, we reviewed the PubMed literature for published cases of multisystem AA amyloidosis associated with AS. Only a limited number of reports describing multiorgan involvement were identified. The main clinical characteristics, treatment and outcomes of representative cases are summarized in Table I.^{16, 17, 24, 25}

Limitations. This report has several limitations. As a single-patient case, the findings cannot be generalized. In addition, the long and complex disease course was partly assessed retrospectively, which may have limited the completeness of some clinical data. Although AA amyloidosis was histologically confirmed, the extent of individual organ involvement could not be established with equal diagnostic

certainty in all sites. Finally, the observed response to targeted therapies does not allow conclusions regarding comparative treatment efficacy.

In **conclusion**, multisystem AA amyloidosis, although rare, remains a serious complication in long-standing AS. Vigilant disease monitoring, adherence to treat-to-target strategies, and timely escalation to biologic therapy - particularly IL-6 inhibition - can stabilize systemic inflammation, preserve organ function, and improve patient outcomes.

Abbreviations

AA - Secondary amyloidosis SAA - Serum amyloid A SpA - Spondyloarthritis AS - Ankylosing spondylitis MRI – Magnetic resonance imaging cDMARDs - Conventional Disease-Modifying Antirheumatic Drugs BASDAI – Bath Ankylosing spondylitis Disease activity index ASDAS - Ankylosing spondylitis Disease activity score ESR – Erythrocyte sedimentation rate CRP – C-reactive protein IL – interleukin TNF – Tumor necrosis factor JAK – Janus kinase

Declarations

Author Contribution

MAP conceived the study, collected and interpreted the clinical data, performed the literature review, drafted the manuscript, and prepared the figures and tables. JČ, MB, AV, PO, SŽ, TŽR, and MSB contributed to patient management, acquisition and interpretation of clinical data, and critically revised the manuscript for important intellectual content. MŠB supervised the work. All authors reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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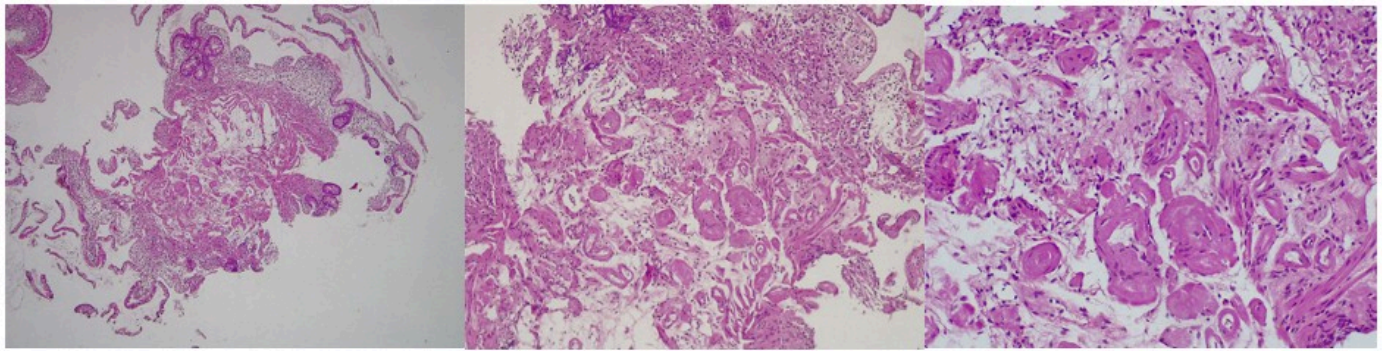
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Table

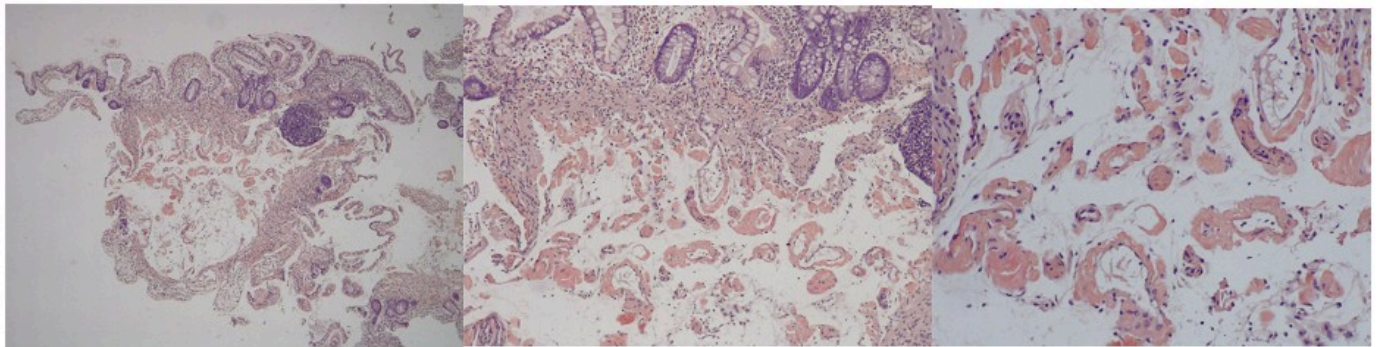
Table I: Representative published cases of multisystem AA amyloidosis associated with ankylosing spondylitis

Author (year)	Organ involvement	Diagnostic confirmation	Treatment	Outcome
Ha et al. (2009) ²⁴	Cardiac, skin	Rectal and skin biopsy	Methotrexate, corticosteroids, etanercept	Clinical and echocardiographic improvement
McMahan et al. (2010) ²⁵	Gastrointestinal, renal, thyroid, autonomic nervous system	Small bowel, colon and rectal biopsies	Etanercept + supportive therapy	Improvement in diarrhea, weight gain, stable renal function
Kovacsovics-Bankowski M et al (2000) ¹⁶	Gastrointestinal, renal	Renal biopsy	Supportive therapy; chronic hemodialysis	One patient remained dialysis-dependent; the other developed colonic perforation
Barakat et al. (2024) ¹⁷	Renal, thyroid, cardiac	Thyroid and accessory salivary gland biopsy	Anti-TNF therapy	Improvement of inflammatory syndrome
Present case	Renal, gastrointestinal, early cardiac	Fat-pad aspiration and intestinal biopsy	Upadacitinib → Tocilizumab	Stable renal function and marked improvement in disease activity

Figures



(a)



(b)

Figure 1

(a) Pathohistological findings (H/E) of terminal ileum biopsy showing non-homogeneous inflammatory infiltrate predominantly composed of mononuclear cells, with mild crypt disorganization.

(b) Congo-red staining demonstrating amyloid deposition in the lamina propria and around small vessels.

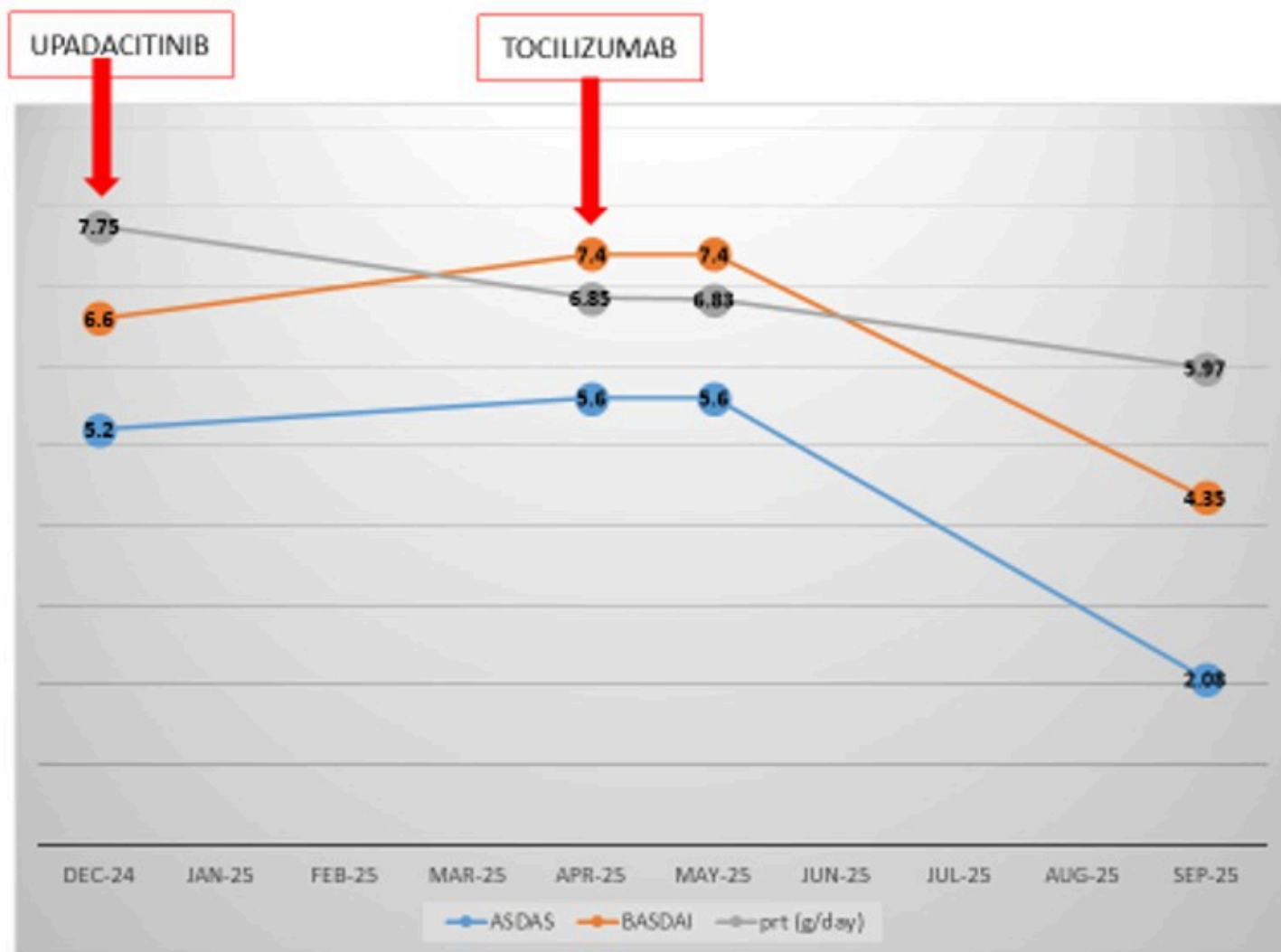


Figure 2

Disease activity indices and proteinuria on tsDMARD and bDMARD

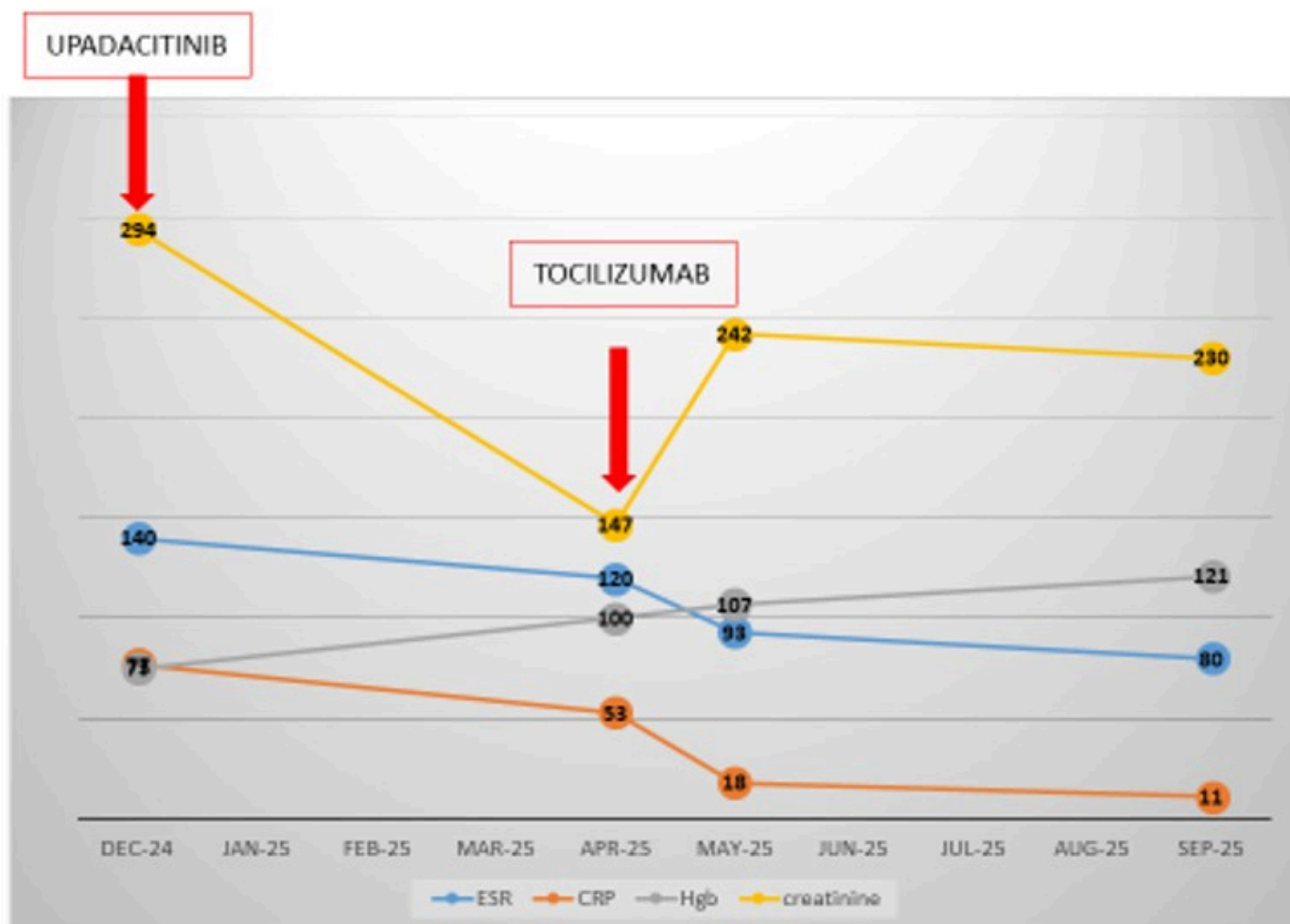


Figure 3

Laboratory findings on tsDMARD and bDMARD