Case Report

DOI: 10.7860/JCDR/2024/74336.20332

Early Onset Renal Amyloidosis in a Case of Rheumatoid Arthritis: A Case Report

Internal Medicine Section

RASHMI MISHRA[1], MAHAK GOLANI[2], NARESH KUMAR[3], GRISHA MAICH[4], ARUN BARGALI[5]

ABSTRACT

Amyloidosis refers to a group of disorders characterised by the deposition of misfolded amyloid proteins in various tissues, leading to organ dysfunction. Secondary (AA) amyloidosis is most commonly associated with chronic inflammatory conditions such as Rheumatoid Arthritis (RA), where persistent inflammation triggers the overproduction of Serum Amyloid A (SAA) protein, which subsequently deposits as amyloid fibrils. Renal involvement is frequent in AA amyloidosis, often manifesting as nephrotic syndrome due to amyloid deposition in the glomeruli. Present case is of a 38-year-old female with a five-year history of RA, who was on methotrexate and sulfasalazine, and presented with frothy urine and progressive anasarca over two months. She exhibited a high-grade fever, cough, shortness of breath and right-sided chest pain. Examination revealed bilateral pedal oedema, facial puffiness, and signs of pleural effusion and ascites. Urine examination indicated nephrotic-range proteinuria, and pleural fluid analysis revealed a transudative effusion. A kidney biopsy confirmed AA amyloidosis, with positive Congo red staining and apple-green birefringence. This case highlights the unusual early onset of AA amyloidosis in RA, developing only five years postdiagnosis, significantly earlier than the typical median of 19 years. Despite well-managed RA and minimal disability, the patient developed nephrotic syndrome and subsequent immunosuppression, culminating in empyema. This case underscores the unpredictable progression of RA-related complications and highlights the critical need for vigilant monitoring and proactive management strategies.

Keywords: Empyema, Pleural fluid, Proteinuria

CASE REPORT

A 38-year-old female homemaker, diagnosed with RA for the past five years and currently on Methotrexate (15 mg weekly) and Sulfasalazine (500 mg twice a day), had no other co-morbidities. She presented to the emergency department with complaints of frothy urine and gradually worsening anasarca over the course of two months. The swelling began in her legs and face and gradually involved her entire body. She developed a high-grade fever for 10 days prior to presentation, documented to be as high as 102°F, associated with chills and rigors, as well as a cough with scanty yellow-coloured sputum, shortness of breath, and right-sided chest pain that increased with inspiration. She followed a primarily vegetarian diet and has no history of alcohol or nicotine use. Her obstetric history was unremarkable.

On examination, her blood pressure was 110/72 mmHg. She had tachycardia and was tachypneic, with an oxygen saturation of 84% on room air, which improved to 97% on 4 L/min of oxygen via nasal prongs. She exhibited pallor, bilateral pitting pedal oedema, and facial puffiness. On respiratory examination, decreased air entry was noted in the right-side of the chest, with stony dullness on percussion, suggestive of a pleural effusion. On abdominal examination, there was no organomegaly, but shifting dullness was present, suggestive of ascites. Cardiac and neurological examinations were within normal limits.

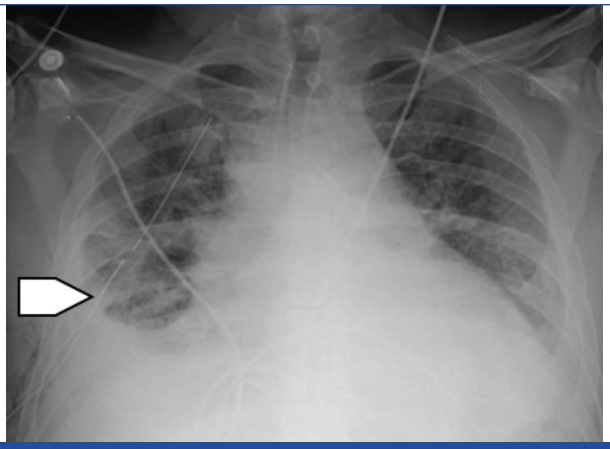
Investigations upon presentation [Table/Fig-1] included elevated procalcitonin levels (52.0 ng/mL) (Normal: <0.05 ng/mL) and an increased D-dimer level (3759 ng/mL) (Normal: <500 ng/mL). The urine examination revealed 3+ protein, with no red blood cells or pus cells. A 24-hour urinary protein test showed 4.5 g/day. Pleural fluid analysis revealed 30,720 cells (90% polymorphonuclear leukocytes, 10% lymphocytes), but it was transudative (protein 2 g/dL), and the Adenosine Deaminase (ADA) was normal. The Anti-Nuclear Antibody (ANA) profile and anti-dsDNA tests were negative. C-reactive Protein (CRP) was elevated at 84 (normal: <1.0 mg/L), and Erythrocyte Sedimentation Rate (ESR) was 56 (normal: <20 mm/hour). Her chest

Investigation	Report	Normal range
Haemoglobin (gm/dL)	7.9	11-13
Haematocrit (%)	27.7	35-43
TLC (WBCs/µL)	16,780	4000-11000
DLC	N68 L27 M4 E1	
PLC (lac/µL)	4.12	1.5-4.0
Total bilirubin (mg/dL)	0.1	<0.3
AST (IU/L)	26	15-35
ALT (IU/L)	22	15-35
ALP (IU/L)	300	30-130
Total Protein (g/dL)	4.7	5.5-7.5
Serum Albumin (g/dL)	2.0	3.5-5.5
Urea (mg/dL)	32	15-40
Creatinine (mg/dL)	1.2	0.6-1.1
Sodium (meq/L)	144	135-145
Potassium (meq/L)	5.2	3.5-5.5
Calcium (meq/L)	8.3	8.0-10.0
Phosphate (meq/L)	4.0	2.5-4.5

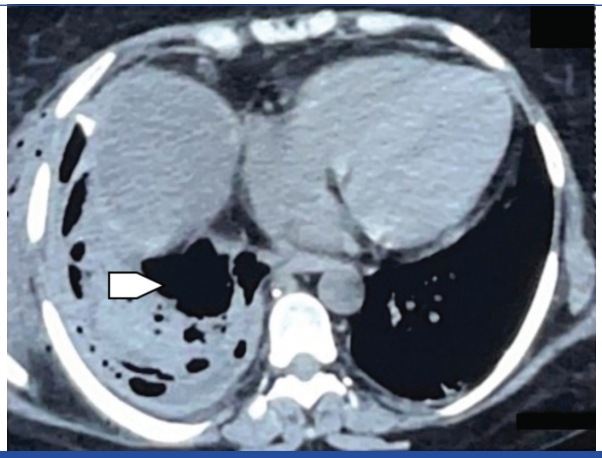
[Table/Fig-1]: Investigations on presentation.
TLC: Total leukocyte count; DLC: Differential leukocyte count; PLC: Platelet count; AST: Aspartate transaminase; ALT: Alanine transaminase; ALP: Alkaline phosphate

X-ray [Table/Fig-2] suggested a right-sided heterogeneous loculated opacity. The Computed Tomography (CT) chest [Table/Fig-3] showed multifocal areas of consolidation in the bilateral lung parenchyma, predominantly in the lower lobes, with fissural and interstitial septal thickening, along with surrounding ground-glass opacities. Moderate free fluid was present in the right pleural cavity with multiple air foci within it and pleural thickening, suggestive of empyema.

She was started on intravenous antibiotics (meropenem 500 mg thrice a day and clindamycin 600 mg thrice a day) and i.v. albumin for her empyema and hypoalbuminaemia. In view of nephrotic-range proteinuria, a renal biopsy was planned. The possibility of

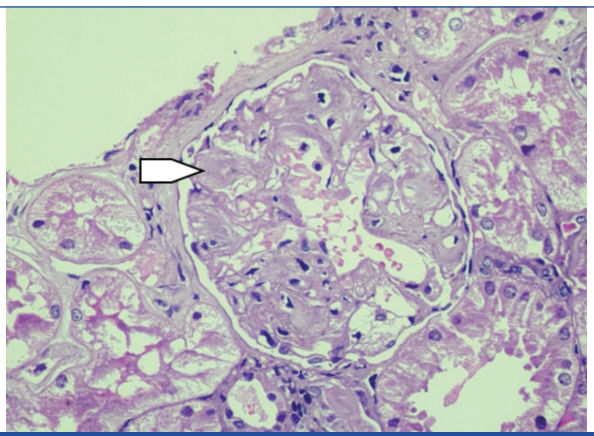


[Table/Fig-2]: Chest X-ray showing right-side costophrenic angle blunting with irregular margin (white arrow).



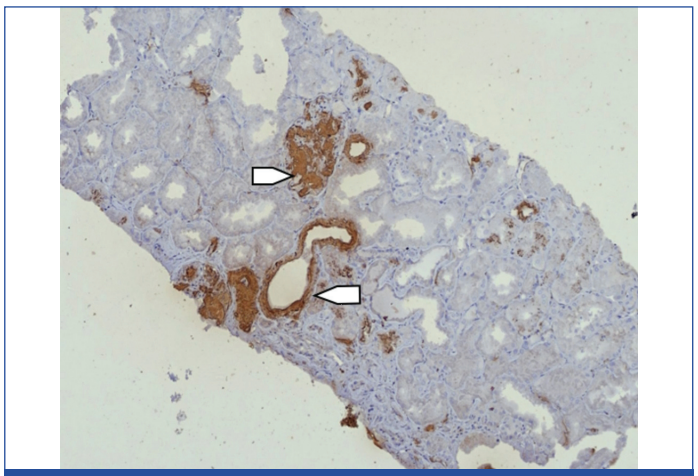
[Table/Fig-3]: Free fluid in right pleural cavity with multiple air foci (white arrow) within associated with pleural thickening suggestive of empyema.

tuberculosis with a superadded infection was considered, and an ultrasound-guided kidney biopsy was performed, which showed enlarged glomeruli and deposition of a pink amorphous substance in the mesangium and focally in the peripheral capillary walls [Table/Fig-4].



[Table/Fig-4]: Deposition of pink amorphous material (white arrow) in glomeruli (H&E,100x).

The substance was negative on Periodic Acid-Schiff (PAS) and silver stain, positive on Congo red stain, and showed apple green birefringence under polarised light. Large blood vessels showed duplication of the internal elastic lamina, suggesting secondary amyloidosis involving the glomeruli and blood vessels. For confirmation, Immunohistochemistry (IHC) showed SAA deposits [Table/Fig-5], which ruled out the possibility of primary amyloidosis. The two possible aetiologies of nephrotic syndrome in this case were secondary amyloidosis due to either tuberculosis or RA. Despite extensive work-up, there was no concrete evidence of tuberculosis. Her rheumatoid factor and anti-Cyclic Citrullinated Peptide (anti-CCP) were strongly positive. The diagnosis of AA amyloidosis (secondary to RA) presenting as nephrotic syndrome with right-sided empyema and sepsis was made. Despite being on antibiotics and having an intercostal chest tube for drainage, she failed to improve and succumbed to her illness on day 18 of admission.



[Table/Fig-5]: Immunostaining for Amyloid A shows SAA amyloid positivity in glomeruli and capillary wall (white arrows, 10x).

DISCUSSION

AA amyloidosis (secondary amyloidosis) is a rare but serious complication of long-term inflammatory disorders, resulting from extracellular fibril deposition derived from the SAA protein. SAA is an acute phase reactant produced by hepatocytes in response to proinflammatory cytokines, particularly interleukin-6 (IL-6). Prolonged high concentrations of SAA lead to its aggregation into cross-β-sheet fibrillar deposits [1]. The causes of AA amyloidosis include chronic infections, chronic inflammatory diseases, hereditary diseases, haematologic disorders, tumours and idiopathic origins [2,3]. A study by Lachmann HJ et al., in the United Kingdom evaluated 374 patients with AA amyloidosis and found that the most common cause was chronic inflammatory arthritis, with RA accounting for 33% of cases [4]. The prevalence of AA amyloidosis in RA patients ranges from 4-26%, with a median duration of 19 years from the onset of RA symptoms to the development of amyloidosis [5].

In AA amyloidosis, chronic inflammation induces overproduction of SAA. Persistently high levels of SAA lead to its misfolding and deposition as amyloid fibrils in various organs. The kidneys are the major organs affected, with glomerular amyloid deposition causing proteinuria. Other organs that may be involved include the gut, liver, spleen and adrenal glands [2]. The clinical presentation of renal amyloidosis varies based on the type of amyloid involved, the location and quantity of amyloid deposits within the kidney, and the extent of involvement in other organs. Proteinuria is the most frequent manifestation, ranging from mild to severe nephrotic levels, depending on the degree of glomerular involvement. Crescentic glomerulonephritis, including anti-glomerular basement membrane disease, has also been observed in patients with AA amyloidosis [6].

Nephrotic syndrome can cause immunosuppression and increase the risk of infections even in the absence of immunosuppressive therapy. Factors contributing to immunosuppression in nephrotic syndrome include decreased serum immunoglobulin G, transferrin, deficiency of factors B and I in the alternative complement pathway, T cell function defects, and fluid accumulation in cavities leading to the dilution of local humoural defences by oedema [7]. A study in India involving children with nephrotic syndrome who were not on glucocorticoid therapy found that the most common infection was upper respiratory infection (28.07%), followed by urinary tract infection, peritonitis, pneumonia and severe acute gastroenteritis, with empyema being the least common (5.2%) [8].

Author's Name, Year (Reference no.)	Study aim	Drug used	Outcome	Miscellaneous
Nakamura T et al., 2010 [12]	Clinical benefit of etanercept, 14 patients	Etanercept	Proteinuria decreased from 2.24±0.81 to 0.57±0.41 g/day (p-value <0.01) SAA fell from 250±129 to 26±15 µg/mL (p-value <0.01).	Creatinine levels did not benefit with treatment
Kuroda T et al., 2012 [13]	Therapy with anti-Tumour Necrosis Factor (TNF) and anti-Interleukin-6 (IL-6) biologic agents in RA patients with reactive AA amyloidosis	53 patients were treated with biologic agents (biologic group) and 80 were not (non biologic group)	Survival rate- significantly higher in the biologic group. 9 patients in the biologics group and 33 in the non biologic group started dialysis.	
Courties A et al., 2014 [14]	Efficacy and safety of Tocilizumab (TCZ) in AA amyloidosis in a multicentre study	12 patients	TCZ was effective for six patients. Renal amyloidosis progressed in three patients, stabilised in three and three showed improvement, with sustained decrease in proteinuria level.	
Current study, 2024	To study the cause of early onset amyloidosis	One patient	Rheumatoid Arthritis (RA) on Disease-modifying antirheumatic drugs (DMARD) still resulted in early onset amyloidosis. The patient presented with empyema and eventually succumbed to sepsis.	

[Table/Fig-6]: Comparative analysis of previous literature on Rheumatoid Arthritis (RA) and amyloidosis [12-14].

The diagnosis of AA amyloidosis requires a positive histological examination. The gold standard is the demonstration of apple green birefringence under polarised light with Congo red staining. Renal biopsy diagnosis AA amyloidosis in 7-40% of cases, while abdominal fat pad and rectal biopsies have lower sensitivities [2,9]. The treatment of RA with multiple Disease-Modifying Antirheumatic Drugs (DMARDs) can lead to partial resolution of amyloid deposits, stabilising or improving organ function. Controlling the underlying disease is essential to prevent adverse outcomes and enhance survival rates in AA amyloidosis [10]. Poor prognostic factors include older age, low serum albumin concentration, end-stage renal disease at baseline, and increased SAA concentration. While renal function may take months to years to improve with successful anti-inflammatory therapy, relapses in renal dysfunction can occur rapidly with increased disease activity [11]. [Table/Fig-6] highlights the salient findings of the previously published literature [12-14].

In present case patient developed AA amyloidosis only five years after the diagnosis of RA, which is significantly earlier than the median duration of 19 years as reported in the literature. Additionally, the patient had limited disability and no deformities, indicating controlled disease activity. In contrast, AA amyloidosis in RA is generally associated with a longer duration of disease, higher disease activity, and significant functional disability. A study by Wakhlu A et al., in North India found that one-fourth of RA patients had amyloid deposits after a mean disease duration of 10 years, with 25% developing clinical amyloidosis [5]. This early onset of amyloidosis despite adequate treatment and controlled RA activity underscores the unpredictable nature of the disease and the need for vigilant monitoring.

CONCLUSION(S)

The case underscores the unusual early onset of AA amyloidosis in a young female with RA, developing only five years postdiagnosis, significantly earlier than the typical median of 19 years. Despite controlled disease activity and limited disability, the patient presented with nephrotic syndrome and associated immunosuppression, resulting in empyema. This highlights the unpredictable nature of RA complications and the necessity for vigilant monitoring and proactive management.

REFERENCES

[1] Papa R, Lachmann HJ. Secondary, AA, Amyloidosis. Rheum Dis Clin North Am. 2018;44(4):585-603.
[2] Westermark GT, Fändrich M, Westermark P. AA Amyloidosis: Pathogenesis and targeted therapy. Annu Rev Pathol Mech Dis. 2015;10(1):321-44.
[3] Brunger AF, Nienhuis HLA, Bijzet J, Hazenberg BPC. Causes of AA amyloidosis: A systematic review. Amyloid. 2020;27(1):01-12.
[4] Lachmann HJ, Goodman HJB, Gilbertson JA, Gallimore JR, Sabin CA, Gillmore JD, et al. Natural history and outcome in systemic AA amyloidosis. N Eng J Med. 2007;356:2361-71.
[5] Wakhlu A, Krisnani N, Hissaria P, Aggarwal A, Misra R. Prevalence of secondary amyloidosis in Asian North Indian patients with rheumatoid arthritis. J Rheumatol. 2003;30(5):948-51.
[6] Gurung R, Li T. Renal amyloidosis: Presentation, diagnosis, and management. Am J Med. 2022;135:S38-S43.
[7] Chevrel G, Jenvrin C, McGregor B, Miossec P. Renal type AA amyloidosis associated with rheumatoid arthritis: A cohort study showing improved survival on treatment with pulse cyclophosphamide. Rheumatology. 2001;40(7):821-25.
[8] Alwadhi R, Mathew J, Rath B. Clinical profile of children with nephrotic syndrome not on glucorticoid therapy, but presenting with infection. J Paediatrics Child Health. 2004;40(1-2):28-32.
[9] Westermark GT, Sletten K, Westermark P. Massive vascular AA-Amyloidosis: A histologically and biochemically distinctive subtype of reactive systemic amyloidosis. Scand J Immunol. 1989;30(5):605-13.
[10] Park SJ, Shin JI. Complications of nephrotic syndrome. Korean J Pediatr. 2011;54(8):322.
[11] Hazenberg BPC. Where has secondary amyloid gone? Ann Rheum Dis. 2000;59(8):577-79.
[12] Nakamura T, Higashi SI, Tomoda K, Tsukano M, Shono M. Etanercept can induce resolution of renal deterioration in patients with amyloid A amyloidosis secondary to rheumatoid arthritis. Clin Rheumatol. 2010;29(12):1395-401.
[13] Kuroda T, Tanabe N, Kobayashi D, Sato H, Wada Y, Murakami S, et al. Treatment with biologic agents improves the prognosis of patients with rheumatoid arthritis and amyloidosis. J Rheumatol. 2012;39(7):1348-54.
[14] Courties A, Grateau G, Philippe P, Flipo RM, Astudillo L, Aubry-Rozier B, et al. AA amyloidosis treated with tocilizumab: Case series and updated literature review. Amyloid. 2015;22(2):84-92.

PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Medicine, Maulana Azad Medical College, New Delhi, India.
2. Senior Resident, Department of Medicine, Maulana Azad Medical College, New Delhi, India.
3. Professor, Department of Medicine, Maulana Azad Medical College, New Delhi, India.
4. Postgraduate Student, Department of Medicine, Maulana Azad Medical College, New Delhi, India.
5. Postgraduate Student, Department of Medicine, Maulana Azad Medical College, New Delhi, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Rashmi Mishra,
BL Taneja Block, Maulana Azad Medical College, New Delhi-110002, India.
E-mail: rashmi.virgo02@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jul 19, 2024
- Manual Googling: Sep 03, 2024
- iThenticate Software: Oct 08, 2024 (10%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? No
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Jul 18, 2024**
Date of Peer Review: **Sep 04, 2024**
Date of Acceptance: **Oct 09, 2024**
Date of Publishing: **Nov 01, 2024**