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Concurrent occurrence of AA amyloidosis and IgA nephropathy: An association to gastrointestinal tuberculosis

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Abstract

Occurrence of AA amyloidosis and IgA nephropathy in tuberculosis is well known entity. To the best of our knowledge concurrent presence of AA amyloid and IgA nephropathy (IgAN) is not known. We here present a case of concurrent AA amyloidosis and IgA nephropathy secondary to gastrointestinal tuberculosis. This patient presented with nephrotic syndrome. The clinical and laboratory findings were suggestive of nephrotic syndrome and gastrointestinal tuberculosis. Renal histopathology concluded the diagnosis of concurrent renal AA amyloidosis and IgA nephropathy (M1E1S0T0C1). Patient was given six months anti-tuberculous treatment and he achieved complete remission of proteinuria and hematuria. Thus, it is important to address the cause of AA amyloidosis and secondary IgA nephropathy for better patients and renal outcome.

Keywords: AA amyloidosis, IgA Nephropathy, Concurrent, Gastrointestinal tuberculosis.

INTRODUCTION

Kidney involvement is most frequent and organ-threatening complication of AA amyloidosis. Chronic inflammatory diseases (rheumatoid arthritis (RA)), infections (tuberculosis (TB)) and malignancy are the most common causes of AA amyloidosis worldwide. [1, 2] Prevalence of AA amyloidosis in Western Europe is low. In an Indian study prevalence of AA amyloidosis is about 8% of total renal biopsies. [3] IgA nephropathy (IgAN) is the most common cause of glomerulonephritis. Mostly IgAN is primary; however, it could be secondary to various immunological disorder, malignancy and infection including tuberculosis. [4, 5] AA amyloidosis commonly presents with nephrotic syndrome, while tuberculosis associated IgAN have varied presentation ranging from hematuria, proteinuria and renal dysfunction to nephrotic syndrome. Treatment of underlying disease such as anti-tuberculous therapy for tuberculosis associated AA amyloidosis and IgAN is cornerstone of management. Concurrent occurrence of AA amyloidosis and IgAN in tuberculosis and its outcome is unknown. To the best of our knowledge, this is the first report of concurrent occurrence of AA amyloidosis and IgAN in gastrointestinal tuberculosis from India.

Case Presentation

A 30 years non-diabetic, normotensive man presented with history of low-grade night fever, loss of weight, and decrease in appetite for six months, followed by

progressive anasarca for two months. There was no associated history of hematuria, dysuria and urinary retention. There was no past medical history suggestive of gastrointestinal,

hepato-billary, cardiac and musculoskeletal system illness. On examination Blood Pressure was 116/72 mmHg, Temperature 101ºF, anasarca and ascites were demonstrable. Otherwise, clinical examination was normal. Detail biochemical laboratory investigations, ascites fluid analysis was done and summarised in the Table no-1. Urine routine analysis showed Albumin 3+++, RBC= 30-40/hpf, Pus cell= 3- 4/hpf and 24-hour urinary protein was 12.2 g/day. Biochemical result revealed hypoalbuminemia (Serum albumin– 1.6 g/dL), dyslipidemia (Total cholesterol- 277 mg/dL) and high erythrocyte sedimentation rate (ESR-64 mm/hour). Therefore, diagnosis of Nephrotic Syndrome was made. Radiological investigation revealed normal size kidney, ascites and multiple enlarged conglomerated mesenteric, pre and para-aortic lymph nodes. We further proceeded to search the cause of fever and did ascitic fluid analysis. Ascites fluid was exudative in nature probably secondary to tuberculosis. Microbiological confirmation of ascitic fluid for MTB done using the Xpert MTB/RIF, and Mycobacterium tuberculosis was detected. Cytological analysis of enlarged lymph node was not performed in view of patient refusal for invasive procedure (FNAC). Thus, final diagnosis of Nephrotic Syndrome and gastrointestinal tuberculosis was made.

Renal histopathology

Kidney biopsy was performed. On light microscopy total 13 glomeruli were seen; one globally sclerosed, remaining glomeruli show irregular expansion of mesangial matrix consequent to deposition of pale eosinophilic, PAS negative, Congo red positive material which was showing greenish birefringence under polarised microscope. Variable mild to moderate mesangial hypercellualrity and endocapillary proliferation was seen. Cellular crescent were seen over two glomeruli. Interstitial Fibrosis and Tubular Atrophy was present in 15-20% sampled cortex. Several arterioles show deposition of amyloid in wall. Direct immunofluorescence (DIF) revealed granular deposition of IgA 3+, C3 2+, Kappa and lambda 3+ into mesangium and capillary wall. IgG and C1q was negative. On immunohistochemistry (IHC) intense (3+) positivity for SAA was noted in area of amyloid. Electron microscopy show randomly oriented non-branching fibrillary structure measuring 8-10 nm in diameter into mesangium and capillary wall. On electron microscopy conventional EDD was seen in mesangium and capillary wall. Approximately 40-50% foot process effacement was noted. Renal histopathology concluded the diagnosis of concurrent renal AA amyloidosis and IgA nephropathy (Oxford MESTC score M1E1S0T0C1). (Figure no. 1,2,3)

Figure No. 1. Light microscopy.

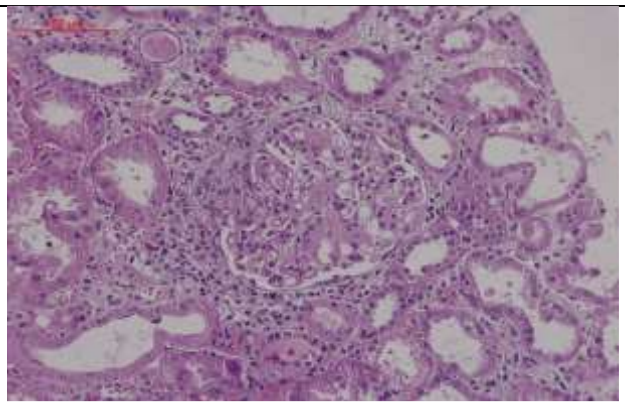

Figure 1A. H&E (X100) Showing irregular expansion of mesangial matrix and mild to moderate mesangial hypercellualrity and endocapillary proliferation.

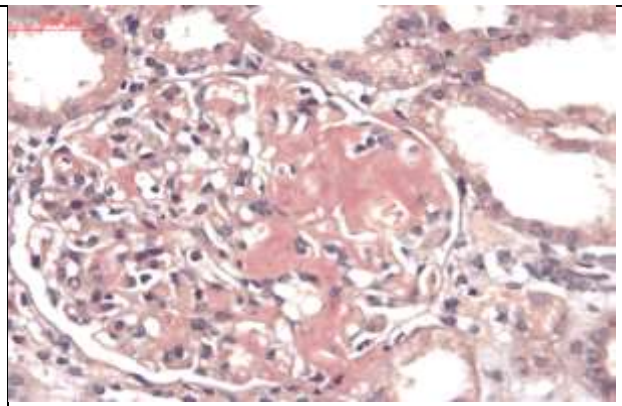

Figure 2B. Congo Red (X100) Showing deposition of Congo red positive amyloid material.

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Figure No. 2. Immunofluorescence microscopy.

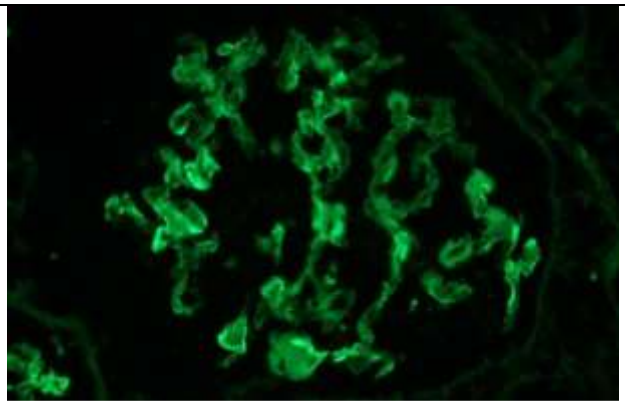

Figure 2A. Direct immunofluorescence (DIF) showing granular intense deposition of light chain (lambda 3+) into mesangium and capillary wall.

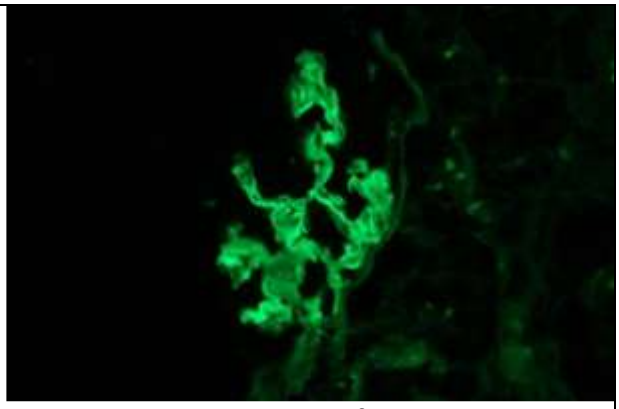

Figure 2B. Direct immunofluorescence (DIF) showing granular intense deposition of IgA (3+) into mesangium and capillary wall.

Figure No. 3. Electron microscopy.

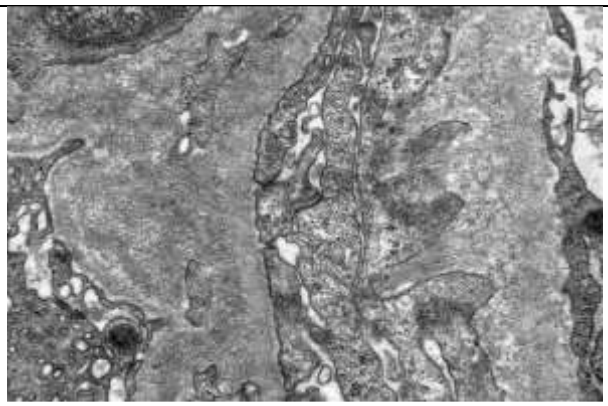

Figure 3A. (X8000) Electron microscopy showing randomly oriented non-branching fibrillary structure measuring 8-10 nm in diameter into mesangium and capillary wall.

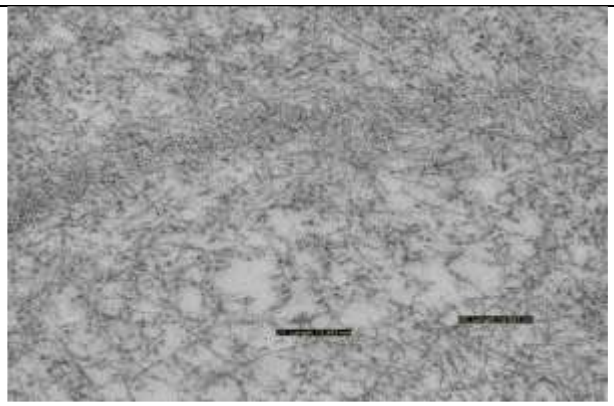

Figure 3B. (20000) Electron microscopy show randomly oriented non-branching fibrillary structure measuring 8-10 nm in diameter into mesangium and capillary wall

Therapy and follow-up

After complete evaluation patient received standard six-month anti-tuberculosis therapy as per World Health Organization (WHO) guidelines. [6] Treatment included body weight based HRZE for two months in intensive phase and HRE for four months in continuation phase. (H= Isoniazid; R= Rifampicin; Z= pyrazinamide; E=Ethambutol). All patients received antiproteinuric therapy with renin-angiotensin system blocker (ACEi/ARB), diuretic and other supportive treatment. Patient was closely monitored for adverse events and followed up monthly for first six month and three monthly for next six month. During follow up Haemogramm, liver function test, urine analysis and 24-hour urinary protein quantification were done. Our patient achieved complete remission of proteinuria (< 300 mg/day), hematuria (absence of RBC in urine sediments) and normalization of serum albumin by six month and was in remission with good health till last follow-up. (Table-2) We did not perform repeat kidney biopsy for assessment of histological changes

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after therapy, because patient denied consent for biopsy.

Discussion

Tuberculosis (TB) is one of the infectious diseases contributing alarming challenges to global health. In tuberculosis most often the lung (Pulmonary TB) is affected but it can also affect other parts of the body (Extra pulmonary TB) such as lymph node, genitourinary tract, gastrointestinal tract, brain bone and joints. In our case tuberculosis involved gastrointestinal tract. In tuberculosis kidney disease may be results of direct invasion of bacteria in the organ or indirect by producing chronic inflammatory state. Spectrums of kidney disease in tuberculosis are Classical Renal Tuberculosis, Tuberculous Interstitial Nephritis, Glomerular Disease and End- Stage Renal Disease. Glomerular disease in tuberculosis is complicated by AA amyloidosis, which in India is an important cause of renal disease. [1, 7] AA amyloidosis is extracellular deposition of insoluble form serum amyloid A (SAA), an Amyloid precursor produced in chronic inflammatory diseases (e.g., tuberculosis, rheumatoid arthritis, inflammatory bowel disease). Pathophysiology of AA amyloidosis is unknown. However, it is believed that an elevation of pro inflammatory cytokines like tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β) and IL6, stimulates production of large amounts of SAA by liver which latter on deposit in various tissues. There are a numerous reports of tuberculosis associated with various forms of glomerulonephritis. [4, 5, 8, 9] IgA nephropathy is the commonly encountered glomerulonephritis in tuberculosis. Recent evidences explain its pathophysiology. Although it is a well-known fact that cell mediated immune response is primary defense against mycobacterial infection. It is humoral immune response against A-60 mycobacterial antigen, which leads to excessive production of IgA antibodies. [10] Deposition of IgA containing immune complexes in kidney in turn may activate the alternative complement and lectin pathway with resultant local injury leading to IgA nephropathy. In present case, we noticed concurrent occurrence of AA amyloidosis and IgA nephropathy. AA amyloidosis commonly presents with nephrotic syndrome. However, presentation of secondary IgA nephropathy is variable ranging from hematuria, proteinuria, and renal dysfunction to nephrotic syndrome. Our case also presented with nephrotic syndrome, microscopic hematuria and constitutional symptoms suggestive of tuberculosis. The therapeutic key objective of AA amyloidosis and secondary IgA nephropathy is to reduce the excessive production of SAA and IgA antibody. This could be possible by modulating the inflammatory condition and eradication of the infection with appropriate anti-inflammatory drugs and antibacterial agent. We treated this case with anti-tuberculous drugs with an intension to first eradicate the infection. Treatment included standard body weight based daily anti-tuberculous treatment along with angiotensin receptor blocker and diuretic for six months. Surprisingly this therapy resulted in complete remission of proteinuria, hematuria, normalization of serum albumin and significant improvement in general health. Thus, it is important to address the possible underlying cause of AA amyloidosis and secondary IgA nephropathy depending on sign, symptoms and geographical region. Prompt correction of underlying condition has paramount value in management of AA amyloidosis and Secondary IgA nephropathy.

Conclusion

In conclusion, we are reporting a case of concurrent occurrence of renal AA amyloidosis and IgA nephropathy in association with gastrointestinal tuberculosis. Thus, it is important to have histological diagnosis and appropriate intervention of the underlying cause of AA amyloidosis and secondary IgAN is warranted for better patient and renal outcome.

Declarations

Consent for publication – Written consent for publication was obtained from Participant.

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Table No 1: Baseline investigation parameters of patient.

Parameters	Baseline Value	Parameters	Baseline Value
1.Haemogramm		**3.Serological**	
Total leucocyte counts (per µL)	9800	HIV	Non-reactive
Platelets counts ($x10^3$/µL)	183	Anti HCV	Non-reactive
Haemoglobin (g/dL)	12.8	HBsAg	Negative
2.Biochemical		**4.Immunological**	
ESR (mm/hour)	64	ANA	Negative
Serum creatinine (mg/dL)	0.8	RA	Negative
Urea (mg/dL)	28	Anti dsDNA	Negative
Serum total protein (g/dL)	3.4	PR3 ANCA	Negative
Serum albumin (g/dL)	1.6	MPO ANCA	Negative
AST/ALT (U/L)	38/31	C3 (mg/dL)	144
Total cholesterol (mg/dL)	277	C4 (mg/dL)	36
Triglyceride (mg/dL)	191	**5.Urine Analysis**	
LDL (mg/dL)	180	Routine & microscopy	Albumib3+++, RBC= 30-40/hpf, Pus cell= 3-4/hpf
HDL (mg/dL)	38		
Blood Sugar Fasting (mg/dL)	92	24hour protein (g/day)	12.2
TSH (mIU/L)	4.4	Urine culture	Sterile
6. SPEP & Immunofixation	No monoclonal Peak; Kappa &Lamda free light chain - Normal.		
7.Ascitic fluid anlysis			
Total Protein (gm/dL)	4.2	TLC (/µL)	900
SAAG ratio (g/dL)	<1.1	Neutrophils (%)	16
Glucose (mg/dL)	36	Lymphocyte (%)	84
ADA (U/L)	184	Zeilh-Neelsen stain	Negative for AFB
LDH (SU/L)	472	Ascitic fluid culture	Sterile
Xpert MTB/RIF- Mycobacterium tuberculosis detected, Rifampicin resistance- not detected.			
8.Radiological			

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CXR	Normal
Ultrasound Abdomen	RK=10.8*4.3cm, LK=12.3*4.6cm; Ascites and multiple enlarged, conglomerated lymph-nodes present.

ANCA= Anti Neutrophil Cytoplasmic Antibody, AST=Aspartate transaminase, ALT=Alanine transaminase

SAAG= Serum-Ascites Albumin Gap, RBC= Red Blood Corpuscles, PC= Pus cell

Table No 2: Follow up investigation parameters of patient.

Parameters	3 months	6 months	9 months	12 months
Total leucocyte counts (/µL)	9760	9910	8600	9200
Haemoglobin (g/dL)	13	12.8	13.4	14.1
ESR	33	12	Not done	Not done
AST/ALT	30/22	28/24	22/32	26/24
Serum albumin	3.0	4.4	4.1	4.0
Urine R/M	Albumin-2+ RBC- 8-12/hpf Pc- 2-3/hpf	Albumin -1+ RBC--1-2/hpf Pc- 2-3/hpf	Albumin- Nil RBC- Nil Pc- 2-3/hpf	Albumin- Nil RBC- Nil Pc- 2-3/hpf
24-hour protein (g/day)	2.2	.200	.260	.220

RBC= Red Blood Corpuscles, PC= Pus cell, AST=Aspartate transaminase, ALT=Alanine transaminase

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