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Are we Treating or Curing Tuberculosis? Profile of Secondary Renal Amyloidosis in Patients Receiving Anti Tubercular Treatment

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Abstract

Introduction. Secondary renal amyloidosis due to tuberculosis is a debilitating disease with considerable mortality and morbidity due to renal failure and other manifestations of both amyloidosis and renal failure. Most patients with amyloidosis have been adequately treated with DOTS (Directly observed treatment, Short Course strategy). The aimof our study was to analyze the epidemiological and demographic profile of patients undergoing renal biopsy and found to have renal amyloidosis secondary to tuberculosis.
Methods. In this study, retrospective renal biopsy data was collected from 2009-2012 and patients with amyloidosis were identified and their clinical and biochemical parameters were analyzed.
Results. Incidence of amyloidosis was 4.66% (n=24/514) among total renal biopsies. Among this, secondary amyloidosis constituted 87.5% of total amyloidosis. The commonest etiology in these patients was pulmonary tuberculosis (73.5%). All patients with tuberculosis had previously received DOTS treatment. 47.5% of patients with amyloidosis had renal impairment and 10.5% developed end-stage renal disease over 12 months and were dialysis dependent.
Conclusions. Amyloidosis due to tuberculosis is a well-established, yet under-diagnosed complication of tuberculosis. The duration and treatment status of tuberculosis does not influence the occurrence of amyloidosis, as most of the patients were treated appropriately with DOTS. There are no predictive factors in patients who will develop secondary amyloidosis. At present there is no specific treatment apart from supportive therapy. The prognosis is poor, as most of these patients inexorably progress towards end-stage renal disease (ESRD) with significant mortality and morbidity. To conclude, at present we are only treating tuberculosis, we are yet to cure tuberculosis.

Key words: secondary renal amyloidosis, pulmonary tuberculosis, end-stage renal disease (ESRD), DOTS, supportive treatment

Introduction

Tuberculosis is an overwhelming public health problem of the 21st century in India. The incidence of tuberculosis in India is 1.96 million new cases annually and the prevalence was 3.8 million cases in 2000 [1]. The annual mortality due to tuberculosis is 3,30,000 deaths per year [1]. Among various long-term complications of tuberculosis, secondary amyloidosis is perhaps the rarest and one of the most debilitating [2-4]. Apart from the sequelae of tuberculosis, the patient suffers from various manifestations of amyloidosis like edema, anemia, renal failure, malnutrition (due to proteinuria and losses from gastrointestinal tract), cardiac failure and autonomic neuropathy [5-7]. In this study, retrospective data was collected from 2009 to 2012 of all patients undergoing renal biopsies. Renal amyloidosis cases were identified and their clinical and biochemical parameters were analyzed.

Material and methods

We have analyzed the demographic and epidemiological profile of patients undergoing renal biopsy and found to have renal amyloidosis secondary to tuberculosis.
Retrospective renal biopsy registry data from 2009 to 2012 was analyzed.
All renal biopsies found to have amyloidosis were identified and retrospectively analyzed. All renal biopsies were found to be adequate [7] .They were reported by a fixed panel of pathologists. The biopsies were analyzed with standard light microscopy stains like hemotoxylin & eosin, congo red, Masson's trichome, Periodicacid-Schiff, silver methenamine stain. All congo red positive samples were subsequently examined with polarizing microscope and apple green birefringence was confirmed in all of the samples. Immunohistochemical staining to differentiate primary from secondary amyloidosis was not performed. Demographic, clinical, treatment history

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and biochemical data of these patients were analyzed using standard analytical methods.
Ethical approval was not needed because of the retrospective nature of the study.

Results

A total of 514 biopsies were available for analysis from 2009 to 2012, out of which a total of 24 patients (4.66% of the total biopsies) were found to have renal amyloidosis (Figure 1). Among these patients, secondary renal amyloidosis was found in 21 patients (87.5% of total amyloidosis patients). The remaining 3 patients (12.5% of total amyloidosis patients) had primary amyloidosis, 1 patient had AL amyloidosis and the remaining 2 patients had multiple myeloma.

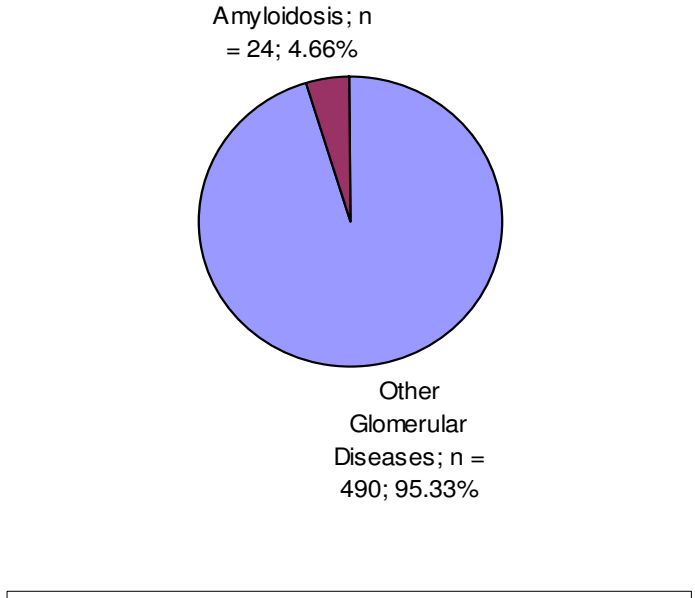

Fig. 1. Percentage of patients having amyloidosis among total renal biopsies

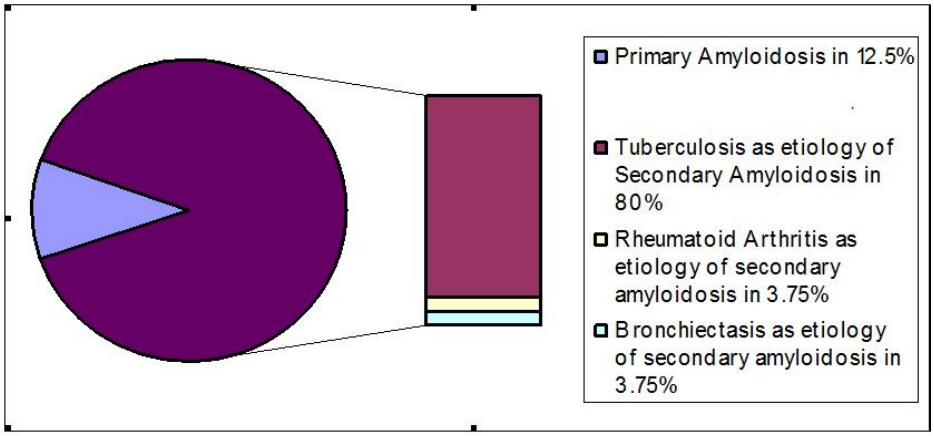

Fig. 2. Various etiologies of amyloidosis

Among the 21 patients deemed to have secondary renal amyloidosis, 19 patients had definite history of tuberculosis in the past, 1 patient had evidence of rheumatoid arthritis and 1 patient had bronchiectasis (Figure 2).
The demographic profile of the patients with secondary amyloidosis due to tuberculosis is given in Table1.
All patients had received anti-tuberculosis treatment according to DOTS, at sometime during the course of their illness. Among these, 6 out of 19 patients (31.5% of total secondary amyloidosis patients) were defaulters and 3 out 6 of the defaulters had received 2 or more courses of anti-tuberculosis treatment. The remaining 13 patients were declared to be cured of tuberculosis. Except for 1 patient who had active pulmonary TB, receiving Anti Tubercular Treatment (ATT) at the time of diagnosis, none of the patients had any clinical features suggestive of active TB at the time of diagnosis of amyloidosis.
The clinical profile of these patients is given in Table 2.
None of the patients had significant hematuria, hyperlipidemia or evidence of any other glomerular diseases.
Nine (9) patients (47.2%) had deranged renal functions, defined as serum creatinine of more than 1.3 mg/dl at the

Table 1. Demographic profile of patients with secondary amyloidosis due to tuberculosis

Age of patients	
a) Mean age	38 years
b) Range of age	13 years to 66 years
Sex	
Male: Female	11: 8 (n = 19)
History of tuberculosis prior to presentation	
a) Mean duration of history of tuberculosis	3.5 years
b) Range of duration of history of tuberculosis	2 months* to 16 years

*1 patient was diagnosed with pulmonary tuberculosis 2 months prior to the diagnosis of amyloidosis and he was already on anti tuberculosis treatment

time of presentation. Two (2) patients presented with uremic symptoms, requiring dialysis at the time of presentation. Glomerular amyloid deposition was present in 17 patients (90%), tubular deposition in 2 (10.5%) patients and arteriolar deposition in 3 (15.7%) patients.

Table 2. Clinical and biochemical profile of patients; n = 19

1) Site of tuberculosis		
i) Pulmonary		14 (73.68%)
ii) Extrapulmonary		5 (26.31%)
a) Lymphadenopathy		1 (5.25%)
b) Gastrointestinal tract		1 (5.25%)
c) Bone and joint		1 (5.25%)
d) Disseminated tuberculosis		2 (10.5%)
2) Clinical features at presentation		
a) Edema		16 (84.2%)
b) Anemia		11 (57.9%)
c) Fatigue and malaise		11 (57.9%)
d) Fever		2 (10.5%)
e) Anorexia		3 (15.7%)
f) Dyspnea on exertion		7 (36.8%)
g) Ascites		12 (63.1%)
h) Autonomic dysfunction		1 (5.2%)
i) Cardiac failure		2 (10.5%)
j) Uremic symptoms (Any combination of: Oliguria, asterexis, anorexia, pericardial rub, nausea & vomiting)		2 (10.5%)
k) Hypertension		3 (15.7%)
3) Degree of renal dysfunction at presentation		
a) Mean Serum Creatinine (mg/dl)	1.66	(Range: 0.9-5.8)
b) Mean 24 hour Proteinuria (grams)	2.8	(Range: 1.6-6.2)
c) Mean hemoglobin (g/dl)	10.6	(Range: 7.7-13.4)
d) Mean serum albumin (g/L)	2.6	(Range: 1.8-3.6)
4) Patients developing ESRD over 12 months		2 (10.5%)

Discussion

In this study, the incidence of amyloidosis in patients with glomerular disease was found to be 4.66%, which was concordant with data from similar studies [2-4,11-13]. Not surprisingly, tuberculosis was the most common etiology of amyloidosis in our study and primary amyloidosis was rare in our study as in similar studies from Indian sub-continent with AL amyloidosis and multiple myeloma being fairly uncommon causes of amyloidosis [2,12,13]. Tuberculosis is an overwhelming public health problem in India. It causes significant mortality and morbidity, often afflicting the most productive age group, thus affecting the physical health and also the socio-economic status of the family and the community [1]. Amyloidosis is a serious and debilitating complication of tuberculosis and its incidence and prevalence among tuberculosis patients in India is not known. Pulmonary tuberculosis was the commonest site of tuberculosis and extra-pulmonary sites being uncommon in our study. In western countries chronic rheumatologic diseases [5,6,9] are common etiologies of secondary renal amyloidosis, however they are distinctly uncommon causes of amyloidosis in our country as found in our study and in other similar studies [2,4,11,13]. This could be due to low incidence of rheumatologic diseases in India when compared to western countries and also the long duration of illness required (often more than 20 years) to cause secondary amyloidosis. None of the patients had chronic bronchiectasis, which has been often implicated

in pulmonary tuberculosis as the source of persistent inflammation despite apparent cure of TB [4,11,14].
The duration of tuberculosis required to cause amyloidosis ranged from 2 months to 16 years, thus implying that even remote history of tuberculosis is enough to trigger amyloidosis; the flip side being that patients having tuberculosis for a short duration can also suffer from amyloidosis. As already mentioned, all of the patients had received some form of anti-tuberculosis treatment (DOTS) prior to the diagnosis of amyloidosis and up to 70% of the patients were declared to be cured of tuberculosis, after which they subsequently went on to develop amyloidosis. This raises a few pertinent questions regarding tuberculosis and its treatment. Firstly, do dormant mycobacterium bacilli continue to be a focus of inflammatory stimuli without producing clinical disease? Secondly, the often quoted time interval of decades [5,7,10] required prior to the development of amyloidosis was not seen in patients suffering from amyloidosis secondary to tuberculosis; so, does this imply that mycobacterial infection causes more rapid and higher levels of serum amyloid A protein (SAA) production leading to early amyloidosis?
Amyloidosis is a systemic disease affecting many organs and can be fatal or extremely debilitating due to the involvement of gastrointestinal tract, cardiovascular system and kidneys [6,7,17,18]. Amyloidosis formation is a nucleation-initiation process [8,9], in some cases of disseminated tuberculosis and destroyed lung due to tuberculosis, large quantity of SAA is constantly produced. These act as a constant source of inflammation and may accelerate deposition of amyloid fibrils on a pre-existing nidus and may perpetuate amyloidosis, even after apparent cure [9-11]. This, however, remains conjectural at present and needs to be proven.
Diagnosis of amyloidosis in a patient with remote history of tuberculosis also causes dilemma with respect to treatment of these patients. The obvious treatment of secondary amyloidosis is to treat the underlying inflammatory disorder, which may include specific measures like using DMARD's/biological agents in patients with rheumatoid arthritis [20-23], treatment of chronic osteomyelitis etc, depending on the specific underlying cause. These measures are known to slow or even completely stop the progress of amyloidosis. However most of the patients in our study did not have any evidence of active tuberculosis, so there is often no justification in starting anti-tuberculosis treatment. It is ironical that even though we have effective treatment for tuberculosis, we cannot offer any definitive treatment in secondary amyloidosis. Hence, we are often left with the only option of offering supportive treatment and to closely monitor the patient for progression of the disease.
A significant number of these patients inexorably progress towards ESRD, requiring some form of renal replacement therapy. These patients often have difficulty in tolerating hemodialysis [24-26] due to frequent episodes of hypotension due to cardiomyopathy and autonomic neuropathy. Continuous ambulatory peritoneal dialysis (CAPD) is often the preferred modality in these patients [24-28]. Renal transplant can also be offered to these patients; however the incidence of recurrence of amyloidosis in the transplanted kidney and duration of graft survival has not been studied in any large studies [29-31]. There is also the possibility of re-activating tuberculosis in these patients after initiation of immunosuppressants. Apart from routine measures used in chronic kidney disease (CKD) patients, drugs like colchicines [5,6,19] often used in familial amyloidosis, have not been found to be useful in this group of patients. Newer drugs like dimethylsulfoxide and eprosidate are yet to be tried in this group of patients [6,9,19,32].
In India, it is a well-established fact that tuberculosis is the commonest etiology of amyloidosis. The clinical features and pattern of organ involvement have been well-established in many studies [4,11,12]. The latency between the infection with tuberculosis and initiation of the amyloidosis is not known clearly. Patients may be totally asymptomatic till the establishment of pedal edema. It is the importance of diagnosing amyloidosis, which needs to be highlighted. As shown in our study, edema may be absent in a few patients (15%) and hypertension may be present in a few patients (15%). Highlighting these exceptions to the general practitioners and to inculcate a high index of suspicion in them towards diagnosing amyloidosis will go a long way in managing these patients. Given the tremendous public health importance of tuberculosis and its re-emergence in a more severe form due to its association with HIV and the emergence of multidrug and extensively drug-resistant tuberculosis (MDR&X-DR TB), any disease sequelae due to tuberculosis should be taken seriously. Even though there is no definite data on the incidence and prevalence of secondary amyloidosis in tuberculosis patients, it should be given due importance because of the sheer number of patients afflicted with TB in India [1].
Limitations of this study include retrospective nature of the data, with limited follow-up. Patients with non-renal manifestations were not included in this study. The criteria for renal biopsy was not uniform, patients with sub-nephrotic range proteinuria were not universally biopsied, hence possibly leading to under-diagnosing those patients with sub-nephrotic proteinuria and non-glomerular amyloidosis deposition.

Conclusions

Amyloidosis due to tuberculosis is a well-established, yet under-diagnosed complication of tuberculosis. The duration and treatment status of tuberculosis does not influence the occurrence of amyloidosis, as most of the patients were treated appropriately with DOTS. Education regarding the typical and atypical manifestations of amyloidosis is important in establishing the diagnosis.

As shown in our study, in many patients amyloidosis develops after apparent cure of tuberculosis, and even in patients currently receiving treatment for tuberculosis. There are no predictive factors in patients who will develop secondary amyloidosis

Once established, there is no specific treatment for amyloidosis due to tuberculosis, there is no role of anti-tuberculosis treatment in a large majority of patients, as they usually do not have evidence of active tuberculosis. Only supportive treatment and management of CKD can be offered to these patients. Large multicentric studies with long follow-up are needed to identify the subset of tuberculosis patients who are prone to develop amyloidosis in future, and to answer the various questions raised in this study regarding management of these patients. To conclude, at present we are only treating tuberculosis, we are yet to cure tuberculosis.

Conflict of interest statement. None declared.

References

1. Mohan A, Sharma SK. History. In: Sharma SK, Mohan A (editors). Tuberculosis. New Delhi, *Jaypee Brothers Medical Publishers, 2nd edition* 2009;5-13.
2. Jai Prakash, Takhellambam Brojen, Surendra Singh Rathore, *et al*. The Changing Pattern of Renal Amyloidosis in Indian Subcontinent: Two Decades of Experience from a Single Center. *Ren Fail* 2012; Vol. 34, No.10: Pages 1212-1216.
3. SK Agarwal, SC Dash. Spectrum of Renal Diseases in Indian Adults. *J Assoc Physicians India* 2000; 48(6): 594-600.
4. Chugh KS, Datta BN, Singhal PC, *et al*. Pattern of renal amyloidosis in Indian patients. *Post Graduate Medical Journal* 1981; 57: 31-35.
5. Helen J Lachmann, Hugh JB Goodman, Janet A Gilbertson, *et al*. Natural History and Outcome in Systemic AA Amyloidosis. *N Engl J Med* 2007; 356: 2361-2371.
6. Bouke PC, Hazenberg. Amyloidosis. *Rheumatic Disease Clinics of North America* 2013; 39(2): 323-345.
7. Dember L. Amyloidosis associated Kidney Disease. *J Am Soc Nephrol* 2006; 17: 3458-3471.
8. Merlini G, Bellotti V. Molecular mechanisms of amyloidosis. *N Engl J Med* 2003; 349: 583-596.
9. Giampaolo Merlini, David C Seldin, Morie A Gertz. Amyloidosis: Pathogenesis and New Therapeutic Options. *J Clin Oncol* 2011; 29(14): 1924-1933.
10. Gillmore JD, Lovat LB, Persey MR, *et al*. Amyloid load and clinical outcome in AA amyloidosis in relation to circulating concentration of serum amyloid A protein. *Lancet* 2001; 358: 24-29.
11. Ramakant Dixit, Rakesh Gupta, Lokendra Dave, *et al*. Clinical profile of patients having pulmonary tuberculosis and renal amyloidosis. *Lung India* 2009; Vol 26(2): 41-45.
12. Shah VB, Phatak AM, Shah BS, *et al*. Renal amyloidosis-A clinicopathological study. *Indian J Pathol Microbiol* 1996; 39(3): 179-185.
13. Mehta HJ, Talwalkar NC, Merchant MR, *et al*. Pattern of renal amyloidosis in western India-A study of 104 cases. *J Assoc Physicians India* 1990; 38(6): 407-410.
14. Tank SJ, Chima RS, Shah V, *et al*. Renal amyloidosis following tuberculosis. *Indian J Pediatr* 2000; 67: 679-81.
15. Simons JP, Al-Shawi R, Ellmerich S, *et al*. Pathogenetic mechanisms of amyloid A amyloidosis. *Proceedings of the National Academy of Sciences* 2013; 110(40): 16115-16120.
16. Le Roux DM, Pillay K, Nourse P, *et al.* Systemic amyloidosis complicating multidrug-resistant tuberculosis in childhood. *Pediatric Infectious Disease Journal* 2012; 31(9): 994-997.
17. Dubrey SW, Comenzo RL. Amyloid diseases of the heart: current and future therapies. *QJM*: *An International Journal of Medicine* 2012; Vol 105, Issue 7: 617-631.
18. Ambruzs JM, Walker PD, Larsen CP. The histopathologic spectrum of kidney biopsies in patients with inflammatory bowel disease. *Clin J Am Soc Nephrol* 2014; 9(2): 265-270.
19. Nelson Leung, Samith H Nasr and Sanjeev Sethi. How I treat amyloidosis: the importance of accurate diagnosis and amyloid typing. *Blood* 2012; 120: 3206-3213.
20. Gottenberg JE, Merle-Vincent F, Bentaberry F, *et al*. Anti–tumor necrosis factor α therapy in fifteen patients with AA amyloidosis secondary to inflammatory arthritides: A follow up report of tolerability and efficacy. *Arthritis & Rheumatism* 2003; 48: 2019-2024.
21. Elkayam O, Hawkins PN, Lachmann H, *et al*. Rapid and complete resolution of proteinuria due to renal amyloidosis in a patient with rheumatoid arthritis treated with infliximab. *Arthritis & Rheumatism* 2002; 46: 2571-2573.
22. Ippei Miyagawa, Shingo Nakayamada, Kazuyoshi Saito, *et al*. Study on the safety and efficacy of tocilizumab, an anti-IL-6 receptor antibody, in patients with rheumatoid arthritis complicated with AA amyloidosis. *Modern Rheumatology* 2013; 1-5.
23. Castellano I, Gomez-Martino JR, Hernandez MT, *et al*. Remission of nephrotic syndrome caused by renal amyloidosis secondary to pulmonary tuberculosis after tuberculostatic treatment. *Nefrologia* 2001; 21: 88-91.
24. Guillaume Bollee, Bruno Guery, Dominique Joly, *et al*. Presentation and Outcome of Patients with Systemic Amyloidosis Undergoing Dialysis. *CJASN* 2008; (2): 375-381.
25. Gertz MA, Kyle RA, O'Fallon WM. Dialysis support of patients with primary systemic amyloidosis: A study of 211 patients. *Arch Intern Med* 1992; 11: 2245-2250.
26. Martinez-Vea A, Garcia C, Carreras M, *et al*. End-stage renal disease in systemic amyloidosis: Clinical course and outcome on dialysis. *Am J Nephrol* 1990; 4: 283-289.
27. Sanai T, Nanishi F, Nagata M, *et al*. Role of amyloidosis in determining the prognosis of dialyzed patients with rheumatoid arthritis. *Rheumatol Int* 2007; 363-367.
28. Kuroda T, Tanabe N, Sato H, *et al*. Outcome of patients with reactive amyloidosis associated with rheumatoid arthritis in dialysis treatment. *Rheumatol Int* 2006; 12: 1147-1153.
29. Claudio Ponticelli, Gabriella Moroni and Richard J. Glassock. Recurrence of Secondary Glomerular Disease after Renal Transplantation. *Clin J Am Soc Nephrol* 2011; 6: 1214-1221.
30. Pinney JH, Lachmann HJ, Sattianayagam PT, *et al*. Renal Transplantation in Systemic Amyloidosis-Importance of Amyloid Fibril Type and Precursor Protein Abundance. *American Journal of Transplantation* 2013; 13: 433-441.
31. Vivekanand Jha, Vinay Sakhuja, Kim Vaiphei, *et al*. An Unusual Case of Recurrence of AA Amyloidosis in the Renal Allograft. *Renal Failure* 2004; 26(1): 89-92.
32. Dember LM, Hawkins PN, Hazenberg BP, *et al.* Eprodisate for the Treatment of Renal Disease in AA amyloidosis Trial Group. *N Engl J Med* 2007; 356: 2349-2360.