International Journal of Innovation and Applied Studies
ISSN 2028-9324 Vol. 16 No. 4 Jun. 2016, pp. 894-901

http://www.ijias.issr-journals.org/

The impact of tuberculosis in the development of secondary amyloidosis

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ABSTRACT: In this work, we tried to find the clinical and therapeutic features and diagnostic difficulties of amyloidosis in pulmonary tuberculosis. For early diagnosis and timely assessment. To evaluate, in a prospective study, adult patients of pulmonary tuberculosis attending our service with subsequent diagnosis of renal amyloidosis AA constituted study population. Clinical profile of biopsy proven amyloidosis cases was analyzed. There were 13 patients (10 males, 3 females, age range 21–80 years) having PTB with edema, proteinuria, and renal amyloidosis AA confirmed by renal biopsy. The total duration of illness ranged from 3 months to 12 years (mean 4 years). All patients had significant proteinuria. Nephrotic syndrome was seen in 11; hypoalbuminemia in 12, and 7 patients progressed to chronic renal failure. 5 patients had moderate to far advanced pulmonary lesions on chest radiography All patients were managed according anti tuberculosis protocol. Tuberculosis is the commonest cause of secondary amyloidosis in developing countries. Renal amyloidosis AA should be suspected clinically in patients presenting edema and proteinuria. It is often believed that secondary amyloidosis occurs months to years after the onset of the predisposing infectious or inflammatory cause. However, as our report will illustrate, secondary amyloidosis can occur as early as 3 months after the diagnosis of active tuberculosis. Further studies will be needed to look for some factors occurred despite good management of tuberculosis.

KEYWORDS: Pulmonary tuberculosis, AA amyloidosis, disease duration, Inflammatory diseases, Kidney biopsy.

1 INTRODUCTION

The tuberculosis (TB) remains a public health problem in Morocco: Every year 27. 000 new cases are reported, including 5,000 cases alone in Casablanca (20% of cases) (by the minister of public health of Morocco 2012). TB is an infectious disease that usually affects the lungs, although it can affect almost any part of the body.

However, TB is the major cause of AA amyloidosis which occurs secondary to chronic inflammation, in which amyloid A (AA) fibrils are derived from high circulating concentration of the acute-phase protein serum amyloid A (SAA) [1]. Rheumatoid arthritis is currently the most frequent underlying inflammatory disease in developed countries, in contrast to developing countries, where tuberculosis (TB) is still the commonest underlying cause for renal amyloidosis [2]. The diagnosis of amyloidosis is suspected on the basis of clinical features and is established by biopsy and appropriate staining procedure looking for amyloid deposition on tissue. Amyloidosis could be or very often present during a long time without clinical manifestations. In TB, edema (swelling) may have other causes including anemia and malnutrition. This may result in missing amyloidosis in patients with TB.

Secondary amyloidosis can occur as early as 2–4 weeks after the diagnosis of active tuberculosis. This should be kept in mind when dealing with patients with tuberculosis who have otherwise unexplained edema, even those with active disease.

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Since our experience is that tuberculosis remains the major antecedent of renal amyloidosis we thought it is important to record our data.

In this work, we tried to look for the clinical; therapeutic features and diagnostic difficulties of amyloidosis in pulmonary tuberculosis (PTB) for early diagnosis and timely assessment.

2 MATERIALS AND METHODS

This is a prospective study. The study was conducted in Pathological department of Children's Hospital of Rabat from 2010 to 2012.

2.1 PATIENTS

In a precedent study, 30 cases of AA amyloidosis were analyzed, 10 cases (33, 33%) had tuberculosis in their antecedents. This subgroup, adult patients of PTB attending our service with subsequent diagnosis of renal amyloidosis AA, constituted study population Information regarding each patient was obtained from each patient's file.

2.2 BIOPSY AND HISTOPATHOLOGY

The 2 renal biopsies (n = 13) were jointly reviewed by 2 pathologists. Biopsy specimens for light microscopic analysis were fixed either in formalin, embedded in paraffin, and sectioned at 2 to 3 µm. The diagnosis of amyloidosis was confirmed by the presence of classical green birefringence in Congo red stained sections viewed under polarized light. In order to differentiate primary from secondary variety of amyloidosis, the deposits were tested by immunohistochemistry procedure using the anti-SAA antibodies(FLEX Monoclonal Mouse Anti-human Amyloïde A Clone nc1 Ready-to-use DakoAutostainer/ Autostainer Plus).

Immunofluorescence (IF) specimens were studied on frozen sections with fluorescein isothiocyanate (FITC)-conjugated, monospecific, anti–light chains (κ and λ), anticomplement factors (C3 and C1q), and antifibrinogen (1:10 dilution; DakoCytomation).

2.3 CLINICAL FINDINGS

For each patient under investigation general clinical features shown on presentation were recorded. These included : age, sexe, amyloidogenic disease(s), geographic origin, interval between the onset of the pulmonary disease and the earliest clinical evidence of renal amyloidosis was estimated. The first detection of protein in urine, or appearance of edema, was taken as evidence of renal involvement by amyloidosis. history of anti-TB treatment, extent of proteinuria , and other biochemical profiles.

3 RESULTS

In this study, 13 patients were prospectively investigated for the presence of pulmonary tuberculosis and amyloidosis. General and clinical characteristics of the patients investigated are represented in the Table 1.

Table 1: General and clinical findings of patients with pulmonary tuberculosis and renal amyloidosis.

Patients Characteristics	
Sex (Number of patients (%))	
Males	10 (77)
Females	3 (22)
Other disease	
Yes	6
No	7
Tabagisme	
Yes	5
No	8
Years of age (Mean +/- SD)	(48±15, 11)
Clinicalsymptoms(Mean +/- SD**)**	
Proteinuria	(6, 33±2, 55)
Hypoalbuminemia	(16, 13±7, 45)
Hypoprotidemia	(51±9, 96)
Urea	(0, 67±0, 44)
Creatinine	(33, 20±34, 65)
Leukocytosis	(13, 69±19, 76)

Renal amyloidosis was confirmed by the appearance of an apple green birefringence from alkaline Congo red staining under polarized light (Figure 1A). AA amyloidosis was demonstrated by positive immunohistochemical (Figure 1B). Systematic study by anti–light chains (κ and λ), did not allow to identify amyloid deposits AL.

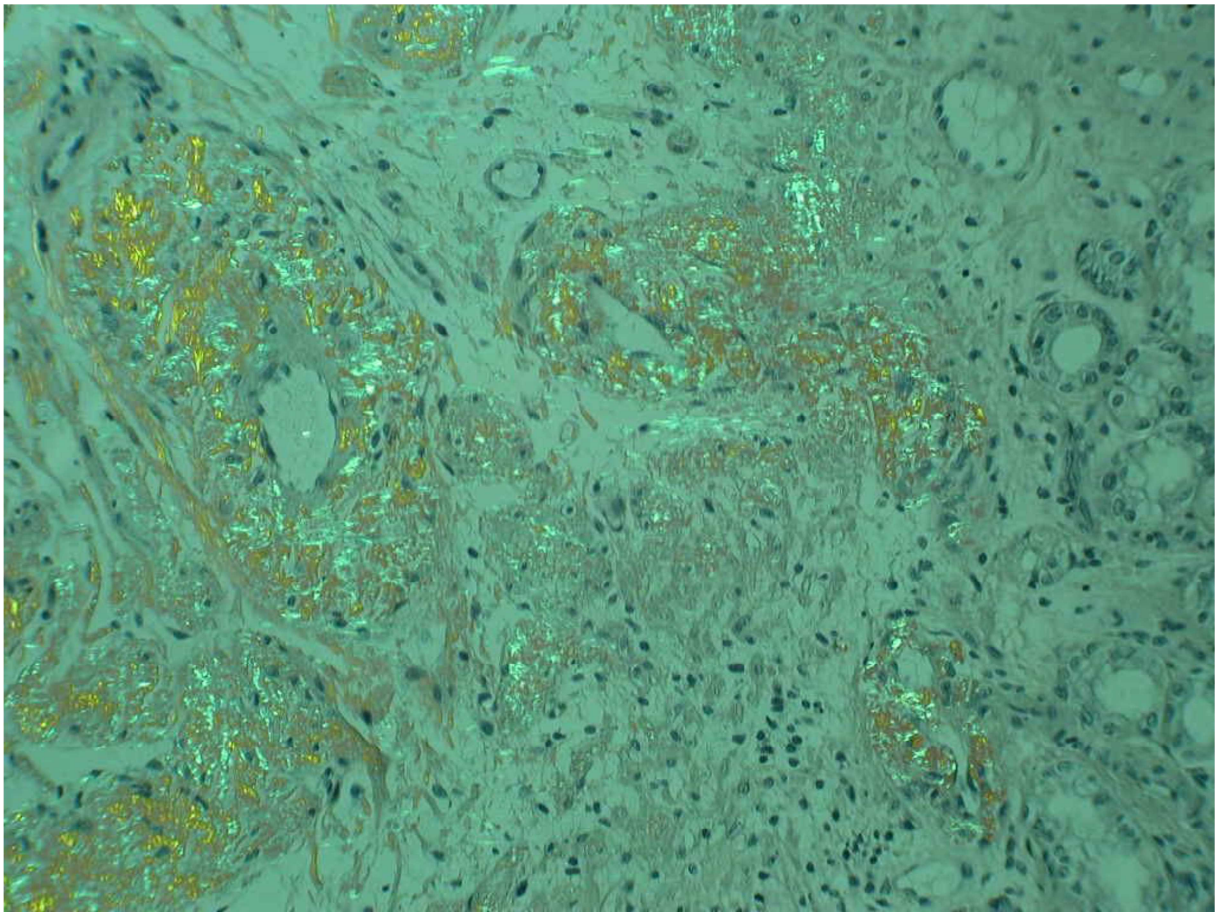

Fig.A.1 : Amyloid deposition in the renal biopsie was detected in Congo redstaining, by green birefringence under polarized microscopy (Magnification ×400)

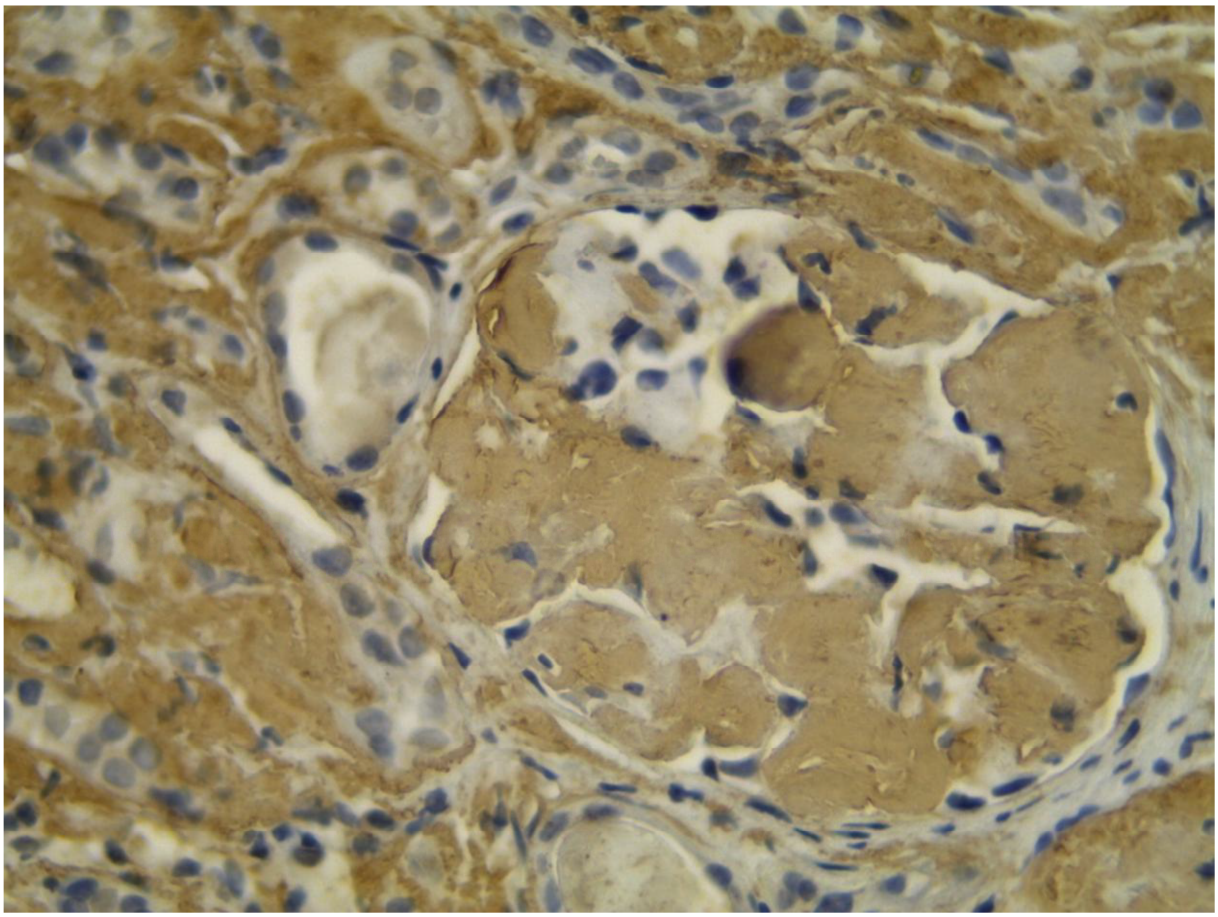

Fig.B.1 : Amyloid deposition in the renalbiopsie by immunohistochemicalstaining. The anti-SAA antiserum was used as primary antibody (dilution 1:1,000). (Magnification, ×200.)

Their ages ranged from 21 to 80 years with a mean age of 48±15, 11 years old, most positive cases were identified among age range 40–59 years constituting 8/13 followed by 20–39, and > 60. There were 10 males (77%) and 3 females (22%); the male to female ratio was 3. Six patients had in their medical history another amyloidogenic disease (like Crohn disease, Rheumatoid arthritis, Psoriatic arthritis, Bronchiectasis) and AA amyloidosis was then considered as a consequence of these 2 diseases.

All 13 had edema except one patient. Five patients have the symptoms (asthenia, emaciation).

No one showed chest pain, or fever and cough except one patient. Most patients of this group lived in rural areas.

The time interval between diagnosis of PTB and the first evidence of renal amyloidosis varied from 3 months to 12 years, with a mean of only 4 years or 53 months. The median interval between onset of symptoms and evidence of amyloid was 7 months.

Urinalysis revealed proteinuria of varying degrees present for all patients. It was nephrotic (>3 g/24 hours) in 11 (85%) patients, and 2 of them had a 24-hour proteinuria of >10 g. 12 patients (92 %) had hypoalbuminemia, and 9 patients (69%) had hypoprotidemia. Blood urea 0, 10 - 0, 55 g / L and serum creatinine 5 - 12 mg / L were observed in 8 (62 %) patients.7 patients (54 %) progressed to chronic renal failure.

5 patients had moderate to far advanced pulmonary lesions on chest X-ray (Figure 2) and for the remaining cases Chest X-ray were normal.

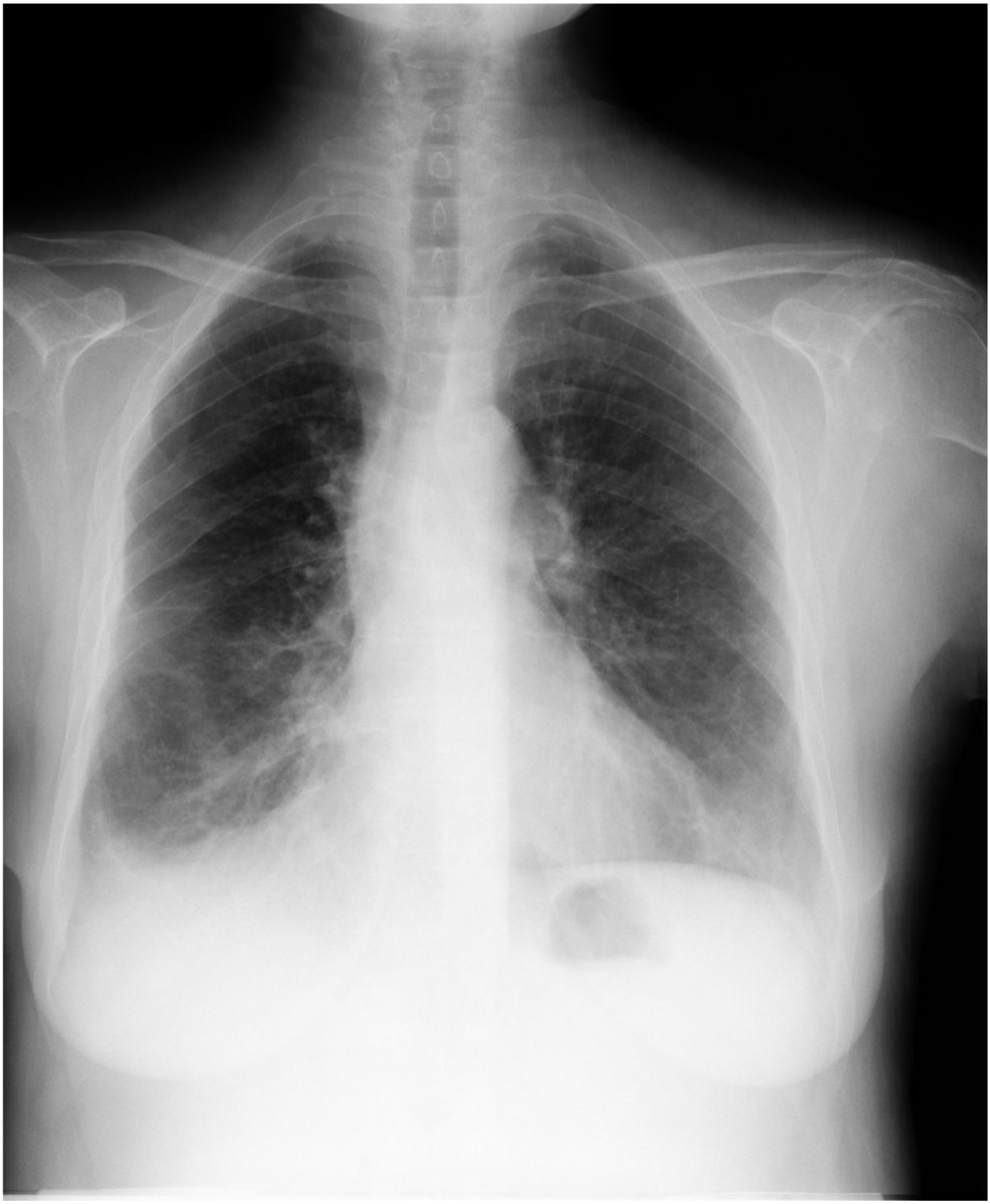

Fig. 2: Appearance advanced pulmonary lesions on chest X-ray (minor pleurisy)

All patients received an anti TB treatment based on rifampicine, ethambutol, isoniazide, pirazynamide (RHZE).At the end of anti - TB treatment, the patient were apyretic.

4 DISCUSSION

In earlier decades it was widely recognized that 80-90% of amyloid disease was found in association with a past history of tuberculosis or chronic suppurative disease [3]. In a series of 203 cases of secondary amyloidosis diagnosed by renal biopsy at our Institute, tuberculosis of various organs accounted for 59.1% of all cases [4]. More recently, 78 of 104 (72.4%) cases of secondary amyloidosis diagnosed at autopsy and on renal biopsy at a hospital in Western India were due to tuberculosis [5]. Tuberculosis still remains the commonest cause of secondary renal amyloidosis in developing countries including Morroco [6–7]. Then, in Western countries, TB was the most important cause accounting for 50–80% of secondary causes of amyloidosis [8–9]. However, rheumatoid arthritis is the common cause these days.

The decline in the incidence of amyloidosis secondary to tuberculosis has been largely due to the introduction of effective anti-TB therapy and clear diminution in TB rate [10]. In our study, the incidence of tuberculosis could be explained both by the geographical origin and socio-economic conditions of our patients. Indeed, most of them live in rural areas and often have a chronic infectious disease in their history.

AA amyloidosis is a relatively rare disease which may complicate chronic inflammatory diseases, chronic infection, familial Mediterranean fever, and occasionally malignant diseases. The pathogenesis of secondary amyloidosis is related to the release of proinflammatory cytokines such as interleukin (IL)-1, IL-6, and TNF-a, which stimulate the synthesis of serum amyloid in the liver and its subsequent deposition in various organs [11]. It is also to be noted that not all patients with chronic inflammatory disorders develop AA amyloidosis, and other factors such as genetic or environmental influences, specific properties of the precursor protein, macrophage activity, and the presence of amyloid enhancing factor beside local tissue factors also play a role in amyloid fibril accumulation [12].

It is often believed that secondary amyloidosis occurs months to years after the onset of the predisposing infectious or inflammatory cause. Heptinstall and Joekes drew attention to this long interval between active inflammation and detection of amyloidosis in a review of 11 cases of renal amyloid [13]. In the present study, the interval between the onset of predisposing disease and first evidence of amyloidosis varied from 3 months to 12 years, with a mean of 4 years. 20% patients were detected to have amyloidosis in less than three months period after the diagnosis of PTB. A very early onset amyloidosis after the diagnosis of active TB has also been reported by El-Hennawy et al [14] and Malhotra et al [15] in recent years.

Since the clinical onset of amyloidosis is preceded by a variable preclinical stage, the true interval between the preceding disease and the onset of amyloidosis is not known exactly. It is known that proteinuria is most consistent feature of renal amyloidosis. It may be moderate but is generally abundant. The reported incidence of this complication varied from 32–68% [16]. Indeed, in our study all patients showed variable proteinuria, and it was nephrotic (>3 g/24 hours) in 11 (85%) patients. We noted also all patients had edema with or without generalized puffiness. Therefore, these features (edema and proteinuria) should arouse suspicion of amyloidosis in any TB patient and consideration of renal biopsy for confirmation.

Elsewhere, persistent inflammation is continuous source of SAA with subsequent amyloid deposition in the kidneys with other factors, this mechanism also explains increased risk of renal amyloidosis in patients having extensive PTB – moderately advanced/far advanced/destroyed lung disease – where permanent structural damage causes persistent inflammation despite adequate anti-TB therapy.

The gold standard therapy for amyloidosis is treating the underlying condition which can lead to a reduction in urinary protein excretion and stabilization of renal function in patients whose serum SAA concentration remains within a normal range [17]. In a study, 9–10% of all patients with various stages of PTB despite effective anti-TB therapy eventually developed proteinuria due to renal amyloidosis after a certain period of time. It has also been postulated that once amyloidosis has extensively involved the kidneys, anti-TB treatment will not cause any regression in the course of renal amyloidosis [18]. In our study, all adequately treated patients of PTB also developed renal amyloidosis despite adequate treatment. Regarding clinical course in our patient contrary to the complete regression of the tuberculous, we noted a worsening of the 24-hour proteinuria.

Most patients with renal amyloidosis ultimately progress to chronic renal failure Cases of regression of amyloidosis are exceptional because once established, the prognosis remains poor and progression to renal failure is inevitable [9]. This could explain the worsening of the glomerular nephropathy in our patients after TB treatment. However, to the best of our knowledge, there has never been histological evidence of disappearance of amyloidosis.

5 CONCLUSION

To conclude, these cases illustrate that secondary amyloidosis can occur as early as 3 month after the onset of symptoms of tuberculosis. This is contrary to general belief that renal amyloidosis develops only in chronic cases of PTB with duration of illness often ten or more years. This diagnosis should be suspected in all patients with tuberculosis who have otherwise unexplainedoedema or proteinuria and especially those with extensive lesions on chest radiography, should be evaluated for amyloidosis by renal biopsy.

Amyloidosis prognosis is very poor as once started, it evolves by its own and inevitably leads to chronic renal failure. An increase in awareness of the clinical features of amyloidosis in TB is important for its early diagnosis and timely assessment. So, therapeutic advances are needed, particularly the development of drugs targeting early phases of amyloidogenesis.

Futher analysis will be needed to look for some factors may be implicated in occurrence of amyloidosis (environnemental, genetical factors ?)

ACKNOWLEDGMENT

I want to thank all Laboratory of Anatomy Cytologyteams and members Department of Nephrology.

REFERENCES

[1] Buxbaum J. The Amyloidosis. In: Klippel JH, Dieppe PA, editors. Rheumatology.2nd ed. vol. 13. London: Mosby International; 1998. 615–28.
[2] Gertz MA, Kyle RA. Secondary systemic amyloidosis: Response and survival in 64 patients. Medicine. 1991;70:246–56
[3] Pepys M.B. Amyloidosis Oxford: Oxford University Press (1996). 151
[4] Chugh KS, Singhal PC, Sakhuja V, and al. Pattern of renal amyloidosis in Indian patients. Postgrad Med J 1981;57:31–5.
[5] Mehta HJ, Talwalkar NC, Merchant MR, and al. Pattern of renal amyloidosis in western India: A study of 104 cases. J Assoc Physicians India 1990; 38 (6):407– 10.
[6] Hazenberg BP, van Rijswijk MH. Amylose AA. In: Grateau G, Benson MD, Delpech M, editors. Les amyloses. Paris: Flammarion Médecine-Sciences; 2000. p. 377—427.
[7] Shah VB, Phatak AM, Shah BS, and al. Renal amyloidosis: A clinicopathologic study. Indian J PatholMicrobiol.1996; 39:179–85.
[8] Ndiaye M, DiopA,Lemrabott AT and al. Renal AA amyloidosis secondary of tuberculousPanniculitis. Key Research Journal of Applied Medicine 2013 : 1 (1); 1-4
[9] Stankovic K, Grateau G. Amylose AA. Néphrologie et thérapeutique. 2008; 4, 281-287.
[10] Boussema E, Labeeuw M, Colon S, and al. Diseases associated with renal amyloidosis: A propos of 216 cases. Ann Med Interne (Paris) 1991;142:331–334
[11] Charles P, Elliott MJ, Davis D, and al. Regulation of cytokines inhibitors and acute phase proteins following anti-TNF-alpha therapy in rheumatoid arthritis. J Immunol. 1999;163:1521–1528.
[12] Cunnane G. Amyloid proteins in pathogenesis of AA amyloidosis (commentary) Lancet. 2001;358:4–5.
[13] Heptinstall RH, JoekesAM. Renal amyloid. A report on eleven cases proven by renal biopsy. Ann Rheum Dis 1960;19:126–1 34.
[14] El-Hennawy AS, Goldstein M, Nicastri A. Renal amyloidosis secondary to tuberculosis of cecum. Nephron. 2002;92:708–710.
[15] Malhotra P, Agarwal R, Awasthi A, and al. How long does it take for tuberculosis tocause secondary amyloidosis? Eur J Intern Med. 2006;16:437–439
[16] Chug KS, Singhal PC, Sakhuja V, and al. Pattern of renal amyloidosis in Indian Patients. Postgrad Med J. 1981;57:31–35.
[17] Nik-Akhtar B, Khorsandi H, Nejatbaksh A. Incidence of renal amyloidosis in pulmonary tuberculosis. J Trop Med Hyg. 1977;80:147–148
[18] Lachmann HJ, Goodman HJ, Gilbertson JA and al. Natural History and Outcome in Systemic AA Amyloidosis. N Engl J Med 2007;356:2361–2371.