CASE REPORT

Renal amyloidosis in leprosy, an infrequent cause of nephrotic syndrome in Europe

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SUMMARY

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae*. The main clinical manifestations involve the skin and the peripheral nervous system. Several types of nephropathy have been described in leprosy. One frequent form of renal involvement is amyloidosis, especially in patients with lepromatous leprosy. In these patients, end-stage renal disease is an important contributor to morbidity and mortality. Here, we present the case of a patient with nephrotic syndrome caused by secondary amyloidosis, chronic peripheral neuropathy and a history of leprosy. The patient was correctly treated in her youth, which is the best way to avoid renal pathology, but she developed a nephrotic syndrome years later.

glomerulonephritis, secondary amyloidosis, interstitial nephritis, acute tubular necrosis, pyelonephritis and functional tubulopathies without histological lesions (changes in acidification and urinary concentration).¹ The most frequent cause of death in patients with leprosy is infections, kidney failure being the second one. Among patients with amyloidosis, renal failure is the leading cause of death, followed by infectious processes.

We here report the case of a patient with nephrotic syndrome in the context of secondary (AA) amyloidosis, probably related to leprosy. The aetiological diagnosis was delayed although the patient had clinical symptoms characteristic of the disease, probably due to the low prevalence of this entity in our environment. We think that the publication of this case is interesting to take notice of a rare but possible cause of amyloidosis in Europe.

BACKGROUND

Leprosy or Hansen's disease is a chronic infectious disease caused by *Mycobacterium leprae*. Different clinical presentations of leprosy are determined by the immune response of the host. Tuberculoid leprosy (paucibacillary) is characterised by a cellular immune response, preferentially with the formation of well-organised epithelioid granulomas that limit bacterial replication. In lepromatous leprosy (multibacillary), there is a state of anergy with an increased cellular response to infection mediated by antibodies.^{1–3} Between these two extremes, there are presentations of intermediate forms.

This is a disease that occurs almost exclusively in developing countries. The goal of elimination of leprosy at global level, defined as a reduction of disease prevalence to <1 case per 100 000 population, was achieved by the year 2000. In 2013, only 14 countries have reported >1000 new cases. These countries are Bangladesh, Brazil, Democratic Republic of the Congo, Ethiopia, India, Indonesia, Ivory Coast, Madagascar, Myanmar, Nepal, Nigeria, Philippines, Sri Lanka and United Republic of Tanzania.⁴ However, with the increasing migration, new cases can occur in any country. The transmission route remains questionable. It is believed that it could spread through the respiratory tract, contact with infected soil or through vectors.

The clinical manifestations are found mainly in the skin, the peripheral nervous system and the distal regions of the body, because the bacterium develops under optimal conditions at a temperature somewhat below body temperature. Renal involvement is not uncommon and includes different forms of expression, such as various types of

CASE PRESENTATION

The patient was a 50-year-old woman from Colombia who had moved to Spain in February 2001. A year later, she was referred to the Nephrology Department with generalised oedema of 2 months' evolution. She reported having had three pregnancies with three live births. Her last pregnancy, 19 years before, had been complicated by pre-eclampsia. She reported that she had no history of hypertension, diabetes mellitus or dyslipidaemia. Physical examination showed eyelid oedema, ascites and oedema of lower limbs up to groin, with a blood pressure of 100/65 mm Hg and the presence of an ulcerated lesion on her right foot. Although the patient did not have diabetes, a neuropathic arthropathy (Charcot foot) was diagnosed, and osteomyelitis was discarded. The relevant analytical data are shown in [table 1](#).

All immunological tests were strictly normal. With the diagnosis of nephrotic syndrome, a renal biopsy was performed. The sample for light microscopy contained 25 glomeruli. All of them exhibit mesangial expansion ([figure 1](#)) and Congo red-positive material deposition in glomerular capillaries and some vessel walls ([figure 2](#)) that were birefringent under polarised light. Interstitial fibrosis and mild tubular atrophy were also observed. Immunofluorescence was positive for AA protein ([figure 3](#)) and P component. A diagnosis of AA amyloidosis was performed, but it was not related to any primary pathological process. The use of diuretics and statins was started and continued in the care of the ambulatory patient.

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Table 1 Evolution of the most important analytical parameters of the patient

Year	2002	2003	2005	2008	2011	2015
Creatinine (mg/dL)	0.80	1.25	1.04	0.93	0.99	0.78
Urea (mg/dL)	14	52	44	48	31	40
Creatinine clearance (mL/min)	97	58	59	87	73	70
Albumin (g/dL)	1.2	2.5	3.4	3.5	3.5	3.9
Cholesterol (mg/dL)	265	240	235	237	208	184
Proteinuria (g/24 h)	10.6	6.6	2.0	1.1	0.2	0.1
Haemoglobin (g/dL)	11.0	13.1	14.0	14.0	14.6	14.9

OUTCOME AND FOLLOW-UP

During the follow-up since arriving in Spain in 2001, the patient suffered from painful thermal paresthesias, with stocking sensory loss and difficulty to walk. Physical examination revealed thickening of the ulnar nerves, a decrease in the size of feet and an abolition of Achilles reflexes. Sural nerve biopsy was performed in 2011, showing severe endoneurial fibrosis. This result is consistent with leprous neuropathy during the healing process. Asked in a targeted manner, she reported a history of Hansen's disease during her childhood and youth. She had been diagnosed when she was 6 years old and had been treated for 15 years with medication she could not remember. She began to note pain in her feet when she was 25 years old.

A thorough clinical and microbiological evaluation of the patient was performed, dismissing leprosy activity. Surprisingly, she had experienced gradual improvements in her kidney disease over the years, always maintaining a normal renal function. Nephrotic syndrome resolved spontaneously (table 1). In the last assessment, it was possible to quantify the serum amyloid A (SAA) protein level, which was found to be 7.5 mg/L (upper normal limit: 6.5 mg/L).

DISCUSSION

Renal involvement in leprosy is not uncommon and can manifest in different histopathological forms. The first report of a patient with leprosy and kidney damage was made by Hansen and Looft⁵ in 1894, with a diagnosis of 'nephritis'. Mitsuda and Ogawa⁶ confirmed the existence of renal disease in patients with leprosy in 1937 by autopsy findings. The incidence of renal disease is significantly higher in patients with lepromatous leprosy. A retrospective analysis of 461 cases of leprosy in Brazil showed a correlation between the prolonged duration of the

Figure 1 Glomerular mesangial expansion with an extracellular weakly eosinophilic deposit H&E. Original magnification, $\times 40$.

Figure 2 Mesangial deposition, Congo red positive. Original magnification, $\times 40$.

disease and high levels of creatinine, suggesting that the longer the length of the disease, the higher the possibility that kidney failure can appear.⁷

One of the most common forms of renal involvement in leprosy is amyloidosis, especially in patients with lepromatous leprosy. Its prevalence in the analysis of autopsies depends on the series, with a range between 3.9% and 31%.^{6 8–10} In these patients, chronic renal disease is the leading cause of death.⁸ Different forms of glomerulonephritis, such as proliferative endocapillary, mesangial proliferative and membranoproliferative, have also been described.^{11 12} The pathogenesis of renal lesions in leprosy is discussed. The bacterium does not seem to be directly involved,⁶ although it has been detected in the glomeruli and kidney tissue of some patient.^{1 8} There is a strong association between the development of amyloidosis and a history of recurrent episodes of erythema nodosum leprosum.⁸ In such episodes, there is a marked increase in serum concentration of SAA protein,¹³ the main component of amyloid deposit in secondary amyloidosis. In leprosy glomerulonephritis, glomerular lesions may be related to immune complexes produced during episodes of reactivation, especially in the context of outbreaks of erythema nodosum leprosum.^{14–16}

Our patient had an AA amyloidosis, chronic leprous neuropathy and a clear history of leprosy. Therefore, there seems to

Figure 3 Global and diffuse glomerular mesangial AA protein deposition. Note also the deposit in arterioles. Immunohistochemistry, AA protein. Original magnification, $\times 20$.

be a clear relationship between renal involvement and systemic infectious disease. Apparently, our patient had been treated successfully in her youth. It has been shown that aggressive early treatment is the best way to prevent kidney failure. However, years later, our patient had severe nephrotic syndrome, with no apparent previous kidney problems. Why did this reappear after years and why did it disappear without any specific therapeutic measures? We are not sure about the moment of the appearance of the nephrotic syndrome, as no previous medical records were available. Probably, our patient was suffering from renal amyloidosis for many years after the initial manifestations of leprosy, but the effective treatment of the infection conditioned the disappearance of immunological stimuli, in particular the synthesis of SAA protein, thereby promoting the slow dissolution of amyloid deposits in the kidney. In this regard, this possibility is suggested by the current slight increase in the levels of AA protein correlated with clinical improvement.

Learning points

- ▶ Leprosy is rare outside endemic countries, but with the increasing migration, it is possible to detect new cases in any country.
- ▶ The usual clinical manifestations are found in the skin, the peripheral nervous system and the distal regions of the body, which should guide us in the differential diagnosis.
- ▶ Renal involvement is not uncommon. The different possible forms of renal disease are glomerulonephritis, secondary amyloidosis, interstitial nephropathy, acute tubular necrosis, pyelonephritis and tubulopathies.
- ▶ Correct treatment of the disease is the best way to prevent AA amyloidosis in leprosy.

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