Case Reports in Nephrology and Dialysis

Case Rep Nephrol Dial 2022;12:178–184
DOI: 10.1159/000524665
Received: May 1, 2021
Accepted: January 29, 2022
Published online: October 4, 2022

Single Case

Primary Sclerosing Cholangitis and Amyloid A Amyloidosis: Association or Coincidence?

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Keywords
AA amyloidosis · Primary sclerosing cholangitis · Nephrotic syndrome

Abstract
AA amyloidosis may complicate several chronic inflammatory conditions. From a clinical point of view, causality between inflammatory pathology and AA amyloidosis can be assumed because of the data described in the literature; some of the best known include rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, and chronic infections. Singles cases of inflammatory diseases have been found at AA amyloidosis. Causality becomes more plausible if at least two different cases with AA amyloidosis are both found to have the same rare inflammatory disease. We describe the case of a patient with primary sclerosing cholangitis (PSC) with development of AA amyloidosis conditioning a nephrotic syndrome, likely secondary to failure to control the chronic inflammatory process. Only two cases in the literature describe the association of this rare disease and the appearance of AA amyloidosis. The treatment of AA amyloidosis consists in treating the underlying inflammatory disorder; to date, few effective treatments are available for PSC. Therefore, and in view of the limited data in the literature, we believe it is important to describe its association.

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Case Rep Nephrol Dial 2022;12:178–184
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Introduction

AA amyloidosis is a disorder characterized by deposition in extracellular tissues of fibrils. Fibrils are composed of fragments of serum amyloid A (SAA) protein. AA amyloidosis can complicate some chronic inflammatory conditions (e.g., rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease) [1]. The annual incidence and prevalence in the general population of AA amyloidosis has decreased over time, presumably due to advances in the treatment of the underlying disorders [2].

AA amyloidosis affects various organs including the heart and kidney, with the most affected organ in 90% of cases being the kidney. Renal involvement is usually characterized by deposition of amyloid in the glomerulus with onset of nephrotic syndrome. Tissue biopsy is required to demonstrate the presence of amyloid, although the diagnosis of AA amyloidosis may be suggested by clinical features and the presence of rheumatic or chronic inflammatory disease [3].

If untreated, AA amyloidosis is a severe disease with a high mortality due to end-stage kidney disease and heart failure. Patients with permanently elevated circulating levels of SAA protein are at increased risk for these complications. A gradual improvement in survival rates has been shown among patients with AA amyloidosis, presumably reflecting, in part, better treatment strategies for associated inflammatory disorders, as well as earlier detection [4].

We describe a patient who developed AA amyloidosis with nephrotic syndrome in association with primary sclerosing cholangitis (PSC). It is likely that the pathogenesis of amyloid AA deposition could be due to the progressive and unresolved inflammatory process.

Case Report

A 64-year-old Caucasian woman, nonsmoker, referred to our clinic in January 2021 due to the onset of previously unknown nephrotic syndrome. Her clinical history was positive for appendectomy and tonsillectomy in childhood, TIA with pervious foramen ovale, diverticulosis of the colon, and gastroesophageal reflux disease.

In 2005, the patient developed an episode of acute pancreatitis – cholangitis for which she performed endoscopic retrograde cholangiopancreatography with evidence of multifocal, short strictures, alternating with dilatation. Subsequently, the diagnosis of sclerosing cholangitis was established and the following tests were performed: no eosinophilia in blood tests, negative antibody tests (antinuclear, antismooth muscle, antimitochondrial, perinuclear antineutrophil cytoplasmic antibodies), negative viral markers (HBV, HCV, HIV), increased inflammatory indexes (CRP 3 mg/dL, normal <0.5, and ESR 43 mm/h, normal <30), increased cholestasis enzymes (alkaline phosphatase 244 UI/L, normal <105, and gamma-glutamyltransferase 269 U/L, normal <48), hypergammaglobulinemia with IgG4 within normal limits, normal urine test. Secondary causes of sclerosing cholangitis were excluded, on endoscopic examinations no signs of inflammatory bowel disease. In fact, histological examination of the sigma and rectum has revealed the presence of intestinal mucosa with preserved architecture that did not show histological signs compatible with the diagnosis of ulcerative rectocolitis. A diagnosis of PSC was made.

The course of the disease was characterized by persistent elevation of the liver function tests, episodes of fever, abdominal pain, and arthralgia. In the suspicion of episodes of acute ascending cholangitis, the patient was treated with cycles of antibiotic therapy (mainly quinolones) with regression of abdominalgia. However, in view of the symptoms and signs of systemic involvement, the patient was evaluated by a rheumatologist with exclusion of inflammatory arthropathy.

Case Rep Nephrol Dial 2022;12:178–184
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The patient received treatment with ursodeoxycholic acid (UDCA) even though it is not a registered therapy for PSC. The latest follow-up magnetic resonance cholangiopancreatography in December 2020 showed disease progression with signs of acute inflammation on chronic involvement. The picture depicted evolution of PSC with increased stenosis and dilatation and widespread thickening of the biliary tract wall.

Since December 2020, 15 years after the diagnosis of PSC, a proteinuria in the nephrotic range (proteinuria 3.7 g/day) and traces of emazies (20 globules/μL) appeared on routine urine chemistry examination. Subsequent urine tests did not confirm the presence of microhematuria and urinary sediment did not identify signs of glomerular hematuria.

The hematochemical examinations showed hypoalbuminemia (2 g/dL, normal <4) and normal renal function (creatinine 0.9 mg/dL, normal 1). In contrast, no edema was present on physical examination and diuresis remained normal. To identify the cause of the nephrotic syndrome, the patient underwent a nephrological examination with an indication to perform a renal biopsy.

To frame the nephrotic syndrome, we performed the following investigations: ANA resulted negative, complement within normal limits, increased inflammatory indices, confirmation of hypergammaglobulinemia with normal IgG4, at protein electrophoresis no evidence of monoclonal components, finally there was no alteration of free light chains, urinary Bence Jones negative. The suspected diagnosis was membranous nephropathy. Some cases in the literature have suggested a strong association between membranous nephropathy and liver diseases associated with immune dysfunction, such as PSC [5, 6].

She underwent a renal biopsy that showed glomerular and vascular deposition of amorphous, hyaline, acellular material, slightly positive to PAS stain (Fig. 1a), negative to Jones stain (Fig. 1b), and positive to Congo Red (Fig. 1c) with birefringence under polarized light (Fig. 1d), compatible with amyloidosis. Immunofluorescence was negative for all the antisera. Immunohistochemistry directed against serum AA protein was positive in the vascular wall of vasa

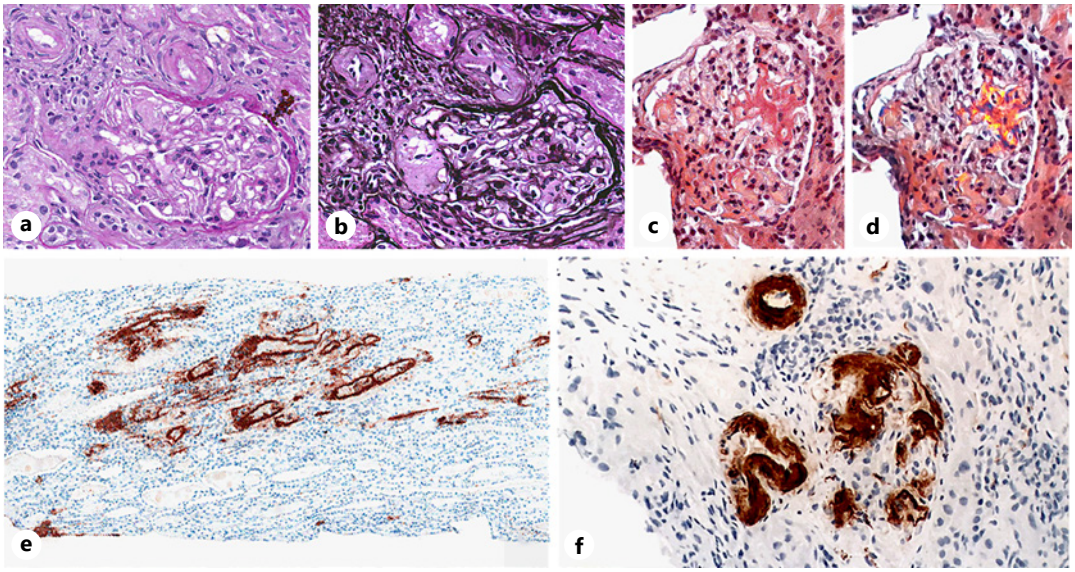

Fig. 1. Renal biopsy showed glomerular and vascular deposition of amorphous, hyaline, acellular material, slightly positive to PAS stain (**a**, ×20), negative to Jones stain (**b**, ×20), and positive to Congo Red (**c**, ×20) with birefringence under polarized light (**d**, ×20), compatible with amyloidosis. Immunofluorescence was negative for all the antisera. Immunohistochemistry directed against serum AA protein was positive in the vascular wall of vasa recta in the medulla (**e**, ×4) and in the arteriolar wall as well as in mesangial areas and capillary walls of glomeruli (**f**, ×20).

Case Rep Nephrol Dial 2022;12:178–184
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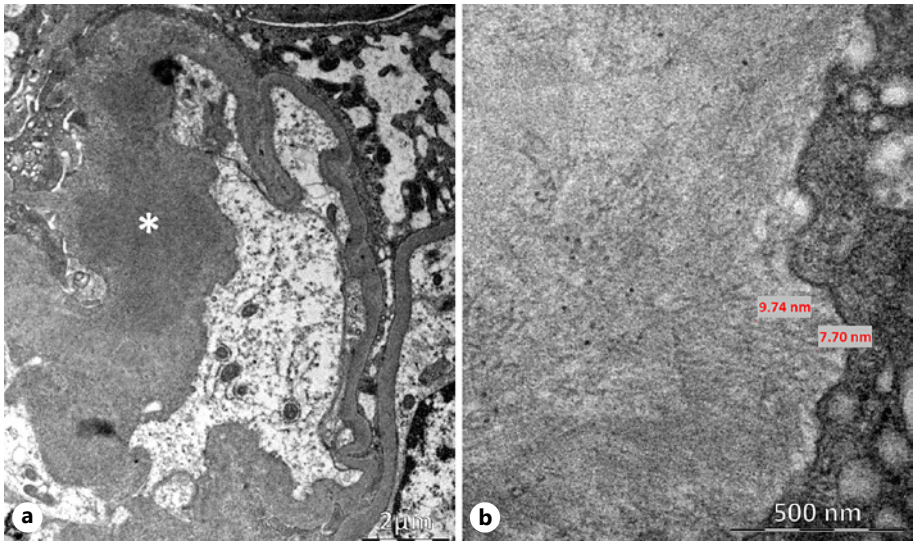

Fig. 2. Transmission electron microscopy demonstrated the presence of mainly subendothelial deposits (**a**, ×5,800, white asterisk) composed of randomly arranged, nonbranching fibrils with a diameter of 8–10 nm (**b**, ×46,000), compatible with the diagnosis of amyloidosis.

recta in the medulla (Fig. 1e) and in the arteriolar wall as well as in mesangial areas and capillary walls of glomeruli (Fig. 1f).

Finally, electron microscopy confirmed the presence of structured deposits, mainly located in the subendothelial area (Fig. 2a), composed by randomly oriented, nonbranching fibrils with a diameter of 8–10 nm (Fig. 2b). Based on these findings, a final diagnosis of amyloidosis, AA type, with glomerular and vascular involvement was made.

AA amyloidosis can complicate chronic inflammatory diseases including rheumatoid arthritis, IBD, ankylosing spondylitis, and others. On endoscopic examinations performed throughout the patient's medical history (last in 2018), there are no biopsy signs of inflammatory bowel disease. On rheumatologic evaluation, there are no signs of inflammatory arthropathy.

ACE inhibitor therapy was initiated for antiproteinuric purposes. From the hepatological point of view, there was no indication to modify the current therapy.

Discussion

In this study, we present a patient with PSC complicated by systemic AA amyloidosis. As mentioned, AA amyloid results from the deposition in tissue of SAA protein, which is a major acute-phase reactant [7].

Amyloid AA can be induced by chronic inflammatory stimuli. Among the main pathogenic factors in AA amyloidosis, we recognize the overproduction of SAA as a consequence of acute and chronic inflammation. Indeed, in these disorders there is increased synthesis of proinflammatory cytokines [8]. Proteolytic processing of SAA into AA occurs with a cleavage at position 76, thus releasing the carboxy-terminal third of the molecule [9]. The intrinsic fibrillogenic properties of the molecule are also relevant, in particular the characteristics at the amino-terminal end of the molecular sequence [10]. All forms of AA amyloidosis are associated with increased levels of SAA in the blood. Admittedly, in rheumatic disease, SAA levels are increased in both patients with and without amyloidosis. This indicates that genetic and environmental factors must be involved in the pathogenesis [11, 12].

Case Rep Nephrol Dial 2022;12:178–184
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Finally, the size and type of fragments can also influence the site of deposition; in fact, smaller fragments are more likely to be deposited in the glomeruli, whereas larger fragments may be preferentially deposited in blood vessels [13]. AA amyloidosis if not treated effectively is associated with high mortality [14]. The preferred therapy of AA amyloidosis is the management of the underlying inflammatory disease and thus the almost complete suppression of SAA protein production.

Treatment needs to be specific for the underlying disease. Successful treatment of the underlying inflammatory process results in reduced hepatic production of the acute phase proteins and reduction of circulating SAA to normal healthy levels [15].

PSC is a chronic progressive disease of unknown etiology characterized by inflammation, fibrosis, and stenosis of medium- and large-caliber ducts. There is more evidence suggesting that abnormal immunity underlies the pathogenic mechanism of PSC [16].

The disease is complicated by evolution into cholestasis and liver failure. Median survival without liver transplantation is between 10 and 12 years. The main goals of treatment of PSC are to delay pathologic evolution and to manage the progressive disease and its complications. To date, there is no proven treatment that slows disease progression. However, excellent results can be achieved after liver transplantation [17].

A variety of immunosuppressive agents have been studied in these patients (glucocorticoids, azathioprine, cyclosporine, etc). Unfortunately, this therapeutic approach has not altered the natural history of this disease [18]. The most widely used therapeutic approach is UDCA at the maximum tolerated dose. UDCA is considered to exert its effects through protection of cholangiocytes and hepatocytes from bile acid-induced apoptosis. However, it has not shown a benefit in survival or in the need for liver transplantation [19]. Only 2 cases of PSC associated with amyloidosis AA are described in the literature to our knowledge [20, 21].

Van Steenbergen et al. [21] described in 2010 the case of a 44-year-old woman diagnosed with PSC not associated with chronic bowel inflammatory disease. The patient presented an evolving clinical picture with systemic symptoms and ultrasonographic evidence of cirrhosis. Therefore, she was treated with UDCA and immunosuppressive therapy with steroid and azathioprine with laboratory and subjective benefit. However, she progressively presented with a worsening histological picture. Four years after the diagnosis, nephrotic syndrome appeared. At the renal biopsy picture compatible with amyloidosis AA, PSC was considered the cause of reactive amyloidosis. For this reason, the patient underwent liver transplantation with subsequent regression of the nephrotic syndrome [21]. The second case by Kato et al. [20] describes a 69-year-old Japanese woman diagnosed with PSC and AA amyloidosis.

Histological samples from the liver, salivary glands, and stomach mucosa were positive for Congo Red staining. The patient had no other associated chronic inflammatory diseases. Again, the etiology of amyloidosis was attributed to PSC. These limited data suggest the existence of an association of PSC and amyloidosis AA.

Moreover, in a systematic review published in 2020, the disorders causing AA amyloidosis are described and ranked by strength of evidence of association with the underlying disease. The authors classify PSC and AA amyloidosis among diseases with an "unclear" association, that is, two or more publications describing the association between the disease and the development of AA amyloidosis, in which the diagnosis of AA amyloid is at least possible.

The connection becomes more plausible if at least two different cases with AA amyloidosis are both found to be associated with the same rare inflammatory disease [1]. The inability of available treatments to control the inflammatory process could be at the basis of the possible pathogenetic mechanism of this association.

As in other inflammatory diseases associated with AA amyloidosis, the single presence of elevated levels of circulating SAA secondary to the inflammatory state does not justify the

development of the disease. It is likely that other factors such as environmental and genetic ones are required. Moreover, since PSC is a rare disease, it is presumable that the number of patients who develop this association is limited. For these reasons, we consider that the description of this case may increase the strength of the association between PSC and amyloidosis AA.

We also suggest that urine chemistry and renal function should be included in the follow-up examinations of patients with this disease but also with other chronic inflammatory diseases. The appearance of urinary abnormalities could suggest the diagnosis of amyloidosis at an early stage, thus modifying the management and therapeutic approach to the underlying disease if possible.

Acknowledgments

We thank the patient who consented to the use of her data for the publication of this case report.

Statement of Ethics

The paper is exempt from Ethical Committee approval. The patient has given her written informed consent to publish the case (including publication of images). Our institute San Gerardo Hospital does not require Ethical Committee approval for the submission of case report. Ethics approval was not required in accordance with local guidelines.

Conflict of Interest Statement

The authors declare no conflicts of interest.

Funding Sources

This research did not receive any funding sources.

Author Contributions

Rosanna Lacetera, Letizia Roggero, and Martina Uzzo: conceptualization, writing, and original draft preparation. Vincenzo L'Imperio for pathological diagnosis. Paolo Vercelloni, Renato Alberto Sinico, Federico Pieruzzi, Marco Carbone, and Pietro Invernizzi read and agreed the published version of the manuscript. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

The data that support the findings of this study are openly available in the computerized file (Galileo software) in San Gerardo Hospital in Monza. Further inquiries can be directed to the corresponding author.

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