Int J Clin Exp Pathol 2015;8(7):8624-8627
www.ijcep.com /ISSN:1936-2625/IJCEP0009354

Case Report

Wild-type ATTR amyloidosis of the ureter in a 56-year-old woman with rheumatoid arthritis and Sjögren's syndrome

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Received April 20, 2015; Accepted June 26, 2015; Epub July 1, 2015; Published July 15, 2015

Abstract: We present a case of acute pyelonephritis with right hydronephrosis in a middle-aged woman, who had suffered from rheumatoid arthritis and Sjögren's syndrome. She had successfully treated with antibiotics, however, ureteral stenosis sustained. She underwent ureteroscopy and stenting of right ureter. Biopsy specimen revealed submucosal amyloid deposition in the interstitium overlying a benign urothelium. Amyloid protein was positive for transthyretin (TTR) by immunohistochemistry and amyloid deposition was not demonstrated in other organs. The patient's TTR genes were wild type and she was diagnosed with wild-type ATTR (ATTR wt) amyloidosis. This is the first report about symptomatic ATTR wt amyloidosis, which was also called 'systemic senile amyloidosis (SSA)' in the ureter. We should aware that SSA can occur at younger age and cause symptomatic ureteral stenosis. Further investigation is needed to clarify the association of autoimmune diseases to develop ATTR wt amyloidosis.

Keywords: Rheumatoid arthritis, senile systemic amyloidosis, Sjögren's syndrome, ureteral amyloidosis, wild-type transthyretin amyloidosis

Introduction

Amyloidosis results from the extracellular tissue deposition of fibrils composed of a variety of proteins. Most of the proteins are derived from any of a variety of serum proteins or sometimes locally produced proteins by tissue infiltrating cells [1]. Localized amyloidosis of the genitourinary tract is uncommon and an extremely rare cause of hydronephrosis and renal failure. Monge *et al.* reviewed 169 reported cases of localized amyloidosis of the genitourinary tract and reported that the involved organs were the bladder (48.5%), ureter (25.4%), urethra (20.1%), and renal pelvis (5.9%) [2]. The disease is characterized by AL amyloidosis without systemic disease, and symptomatic wild-type ATTR (ATTR wt) amyloidosis of ureter has never been described previously [2]. Here we present a case of right ureteral amyloidosis in a middle-aged woman, who had suffered from rheumatoid arthritis and Sjögren's syndrome. Her amyloid protein was neither amyloid A (AA) nor immunoglobulin light chain (AL), but transthyretin by means of immunohistochemistry. The patient's TTR genes were wild type and she was diagnosed with ureteral ATTR wt amyloidosis. We discuss about the developmental mechanism of ureteral TTR amyloid deposition in this case.

Case report

A 54-year-old Japanese woman was admitted to our hospital for fever and nausea. She had been diagnosed with Sjögren's syndrome 7 years earlier and she also suffered from recently onset rheumatoid arthritis, which was controlled by non-steroidal anti-inflammatory drugs. On admission, her body temperature

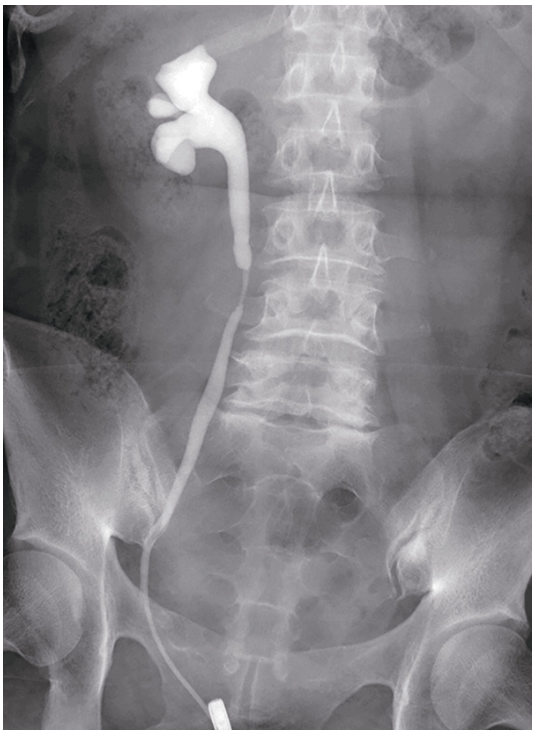

Figure 1. Retrograde pyelography of the right ureter showed mild hydronephrosis and an area of distal narrowing of the right ureter.

was 38.6°C, pulse 110/min, blood pressure 118/66 mmHg, and respiratory rate 25/min. The right renal angle was tender with guarding in the right lumbar region. Laboratory data were as follows: white blood cells 16,000/mm^3; platelets 157,000/mm^3; blood urea nitrogen 34 mg/dL; serum creatinine 1.9 mg/dL; C-reactive protein 25.25 mg/dL. Urinalysis revealed pyuria with proteinuria and microhematuria. Computed tomography of the abdomen revealed hydronephrosis on the right side, and the ureter was dilated down to the distal section. Clinical symptoms and the presence of pyuria and fever led to the diagnosis of acute right pyelonephritis, and the patient was successfully treated with meropenem. Retrograde pyelography revealed mild hydronephrosis and an area of distal narrowing on the right side (**Figure 1**). A urinary wash of the lesion revealed no malignant neoplasm, and the patient was discharged. Sixteen months later, she underwent ureteroscopy and stenting because of worsening right-sided hydronephrosis. The biopsy specimen from the lesion revealed submucosal proteinaceous material deposited in the interstitium overlying a benign urothelium that stained positive for Congo red and had an apple green appearance under cross-polarized light, consistent with amyloidosis (**Figure 2A**, **2B**). Immunostaining for AL kappa, lambda, and AA protein was negative. Staining for TTR was positive (**Figure 2C**), and her amyloidosis was confirmed to be ATTR wt amyloidosis by genotyping for TTR gene mutations. The biopsy specimens of salivary grand, gastric, duodenal, and rectal mucosa were negative for amyloid deposition. The results of ECG and echocardiogram were normal. The patient was diagnosed with ATTR wt amyloidosis of the right ureter. There was no recurrence or systemic involvement of the amyloidosis.

Discussion

TTR, which has a β-sheet-rich structure, is an amyloidogenic protein that causes two types of amyloidosis. One is ATTR wt amyloidosis, also called senile systemic amyloidosis (SSA), caused by wild-type TTR, and the other is familial amyloid polyneuropathy (FAP), caused by mutant TTR [3]. SSA is a common age-related amyloidosis that involves accumulation of wild-type transthyretin, with cardiac dysfunction being a predominant result. However the Nomenclature Committee of the International Society of Amyloidosis recommend to use "wild-type ATTR (ATTR wt) amyloidosis" instead of SSA, because this is a systemic disease not only a cardiac disease that occurs particularly in old age, but the disease can occur at younger age [1]. TTR circulates as a tetramer, but these tetramers can dissociate to monomers that misassemble into amyloid fibrils with age [4]. Ueda *et al.* reported that amyloid deposits in ATTR wt amyloidosis tended to develop predominantly in tissues with high mechanical stress, such as the cardiac ventricle, alveolar wall of the lungs, bladder wall, and vascular walls [5]. Recently, ATTR wt amyloid deposition was demonstrated in various ligaments and tendons of patients with some orthopedics diseases and the authors concluded that TTR amyloid deposition is a result of mechanical wear and degeneration during everyday activity [6, 7].

The reason why TTR amyloid was deposited in the right ureter in a 54-year-old woman is unknown; however, we consider that the ureter is susceptible to TTR amyloid deposition

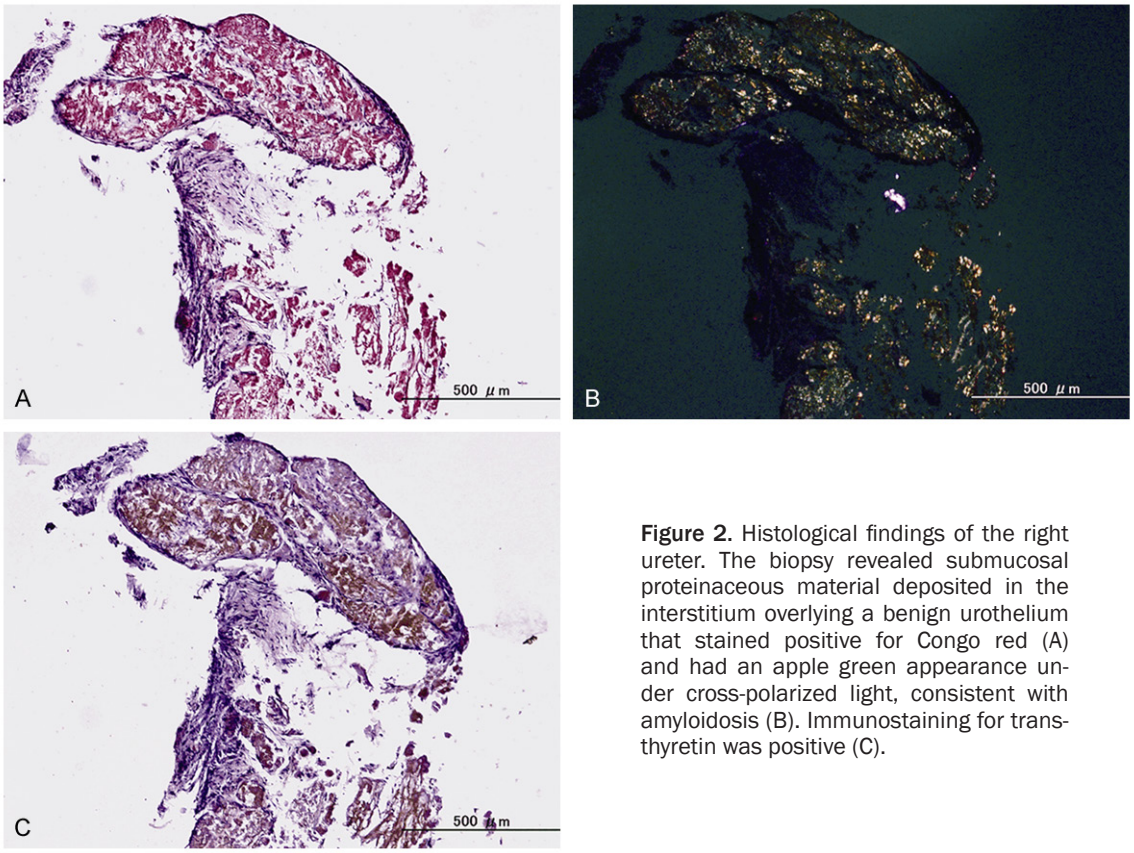

Figure 2. Histological findings of the right ureter. The biopsy revealed submucosal proteinaceous material deposited in the interstitium overlying a benign urothelium that stained positive for Congo red (A) and had an apple green appearance under cross-polarized light, consistent with amyloidosis (B). Immunostaining for transthyretin was positive (C).

because the ureter is a tube made of smooth muscle fibers that propels urine from the kidneys to the urinary bladder, and it is always affected by postural movement of the kidneys. In a post-mortem study into SSA, ureteral amyloid deposits were observed in both of the two cases examined [5]. The TTR amyloid deposits in this case were localized to the ureter, and were not found in the other organs examined. Whether all ATTR wt amyloidosis is part of SSA is still controversial. Kyle *et al.* reported that TTR amyloid deposits localized to the tenosynovium rarely develop into SSA [6]. However, some patients with carpal tunnel syndrome later develop SSA [7]. In view of these results, our case may progress to systemic disease in the future, and we should carefully follow her clinical course.

No research has investigated the relationship between underlying disease and ATTR wt amyloidosis. The patient in our case had Sjögren's syndrome and rheumatoid arthritis. Sjögren's syndrome is complicated with a localized form of AL amyloidosis in the skin and lungs [8], and rheumatoid arthritis is complicated with systemic AA amyloidosis. Although the association of these disorders with ATTR wt amyloidosis in our case is difficult to explain, however recent report demonstrated that TTR was highly expressed in rheumatoid arthritis patients as same as amyloid A protein, especially in severe rheumatoid arthritis [9]. Increase TTR expression related to RA might be associated to the development of amyloidosis. Most of the reported cases about ureteral amyloidosis in the English literature were localized AL amyloidosis [2]. This is the first report about symptomatic ATTR wt amyloidosis in the ureter. The treatment of ATTR wt amyloidosis have never been established. However, TTR tetramer stabilizers for the treatment of FAP, might be effective for ATTR wt amyloidosis in the future [10].

Disclosure of conflict of interest

None.

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