



## A Case of Nephrotic Syndrome due to AHL Amyloidosis in a Patient with Renal Cell Carcinoma

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### Abstract

We report a highly unusual case of a patient with nephrotic syndrome due to AHL primary amyloidosis, with  $\alpha$  heavy chain fragments in serum and urine after a recent diagnosis of renal cell carcinoma. The patient was a 52 year-old male with solitary kidney, after nephrectomy of his left kidney, because of Renal Cell Carcinoma (RCC). He was admitted to our hospital, 8 months after nephrectomy, because of severe nephrotic syndrome (total urine protein (TPU) >8.5 gr/24h) with normal renal function. Biopsy of the remaining kidney showed AHL systemic amyloidosis, while immunofixation identified fragments of  $\alpha$ -heavy chains in urine and serum, as well as  $\lambda$  light-chains in urine. The diagnosis of primary amyloidosis in which the amyloid deposits are composed of both light and heavy chains, is an extremely unusual occurrence, while only a few cases are presented in the literature. Various studies have showed a rare association of renal cell carcinoma and amyloidosis, but this is related to secondary (AA type) amyloidosis. On the contrary, there are no data where renal carcinomas relate to systemic amyloidosis. Thus this case report is very interesting for two reasons; first for the concurrence between renal carcinoma and systemic amyloidosis and for the heavy chain fragments in serum and urine.

**Keywords:** Heavy and light-chain amyloidosis; AHL amyloidosis; Nephrotic syndrome;  $\alpha$ -heavy chain; Renal cell carcinoma

### Introduction

Amyloidosis encompasses a rare group of conditions characterized by extracellular deposition of fibrils, caused by abnormal folding of proteins which exhibits a beta sheet configuration on X-ray diffraction. These amyloid proteins can be histologically confirmed by their characteristic apple green birefringence under polarized light, when stained positively with Congo red dye. There have been identified approximately 15 to 20 precursor proteins of amyloid so far [1-6]. The most prevalent type of systemic amyloidosis is immunoglobulin (Ig)-related amyloidosis (referred to as 'primary amyloidosis') and even if it is difficult to document its incidence, it is considered to affect about 5 to 13 per million per year in western countries [7]. The most frequent presentation of amyloidosis is renal damage, which is characterized by proteinuria, with or without renal insufficiency. Our knowledge concerning the pathogenesis of primary amyloidosis is scanty, while our data for the infrequent entity of Heavy and Light-chain Amyloidosis (AHL), in which the amyloid fragments are composed of Ig heavy and light chains are even more limited [8-11]. Amyloidosis associated with immunoglobulin  $\alpha$ -heavy chain has been reported only in few cases [2,3,12,13]. Another thing that is unique, in the present patient, is that he was recently operated for clear cell carcinoma of his left kidney. These types of carcinomas had been correlated with paraneoplastic syndrome which is manifested with a variety of atypical symptoms (i.e. fatigue, anorexia, weight loss, or endocrine (i.e. hypercalcemia etc.) or non-endocrine disorders (i.e. amyloidosis) [14]. In these references, it is secondary amyloidosis (type AA amyloidosis) but not primary systemic one that is related to [15]. This report concerns a patient with nephrotic syndrome as a result of AHL amyloidosis (with  $\alpha$  heavy chain) which appeared after removal of his left kidney for renal cell carcinoma.

### Case Presentation

A 50-year-old man was admitted to our hospital for investigation of nephrotic syndrome (TPU >8.5 gr/dl, hypoalbuminemia (albumin=2.5 mg/dl) but normal renal function (Cr=0.9 mg/dl, eGFR=100 ml/min/1.73 m<sup>2</sup>, CKD-EPI, possible due to hyper filtration of the remaining kidney). The patient had a solitary right kidney, because eight months prior to his admission to our hospital he

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Received Date: 03 Jul 2018

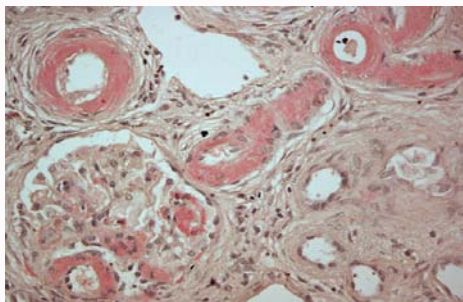
Accepted Date: 20 Jul 2018

Published Date: 30 Jul 2018

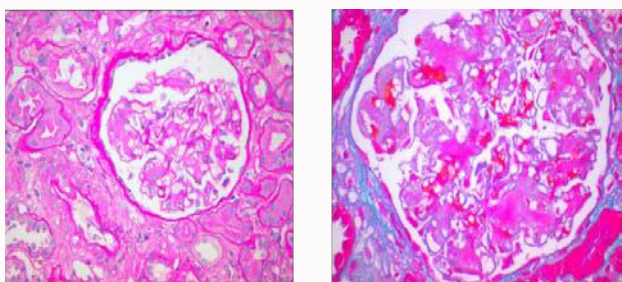
#### Citation:

Apostolou T, Smirli M, Vourlakou C. A Case of Nephrotic Syndrome due to AHL Amyloidosis in a Patient with Renal Cell Carcinoma. *Clin Case Rep Int.* 2018; 2: 1063.

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**Figure 1:** Depositions which represent morphological and immunophenotypic characteristics AL/AH amyloidosis and positive Congo red staining.



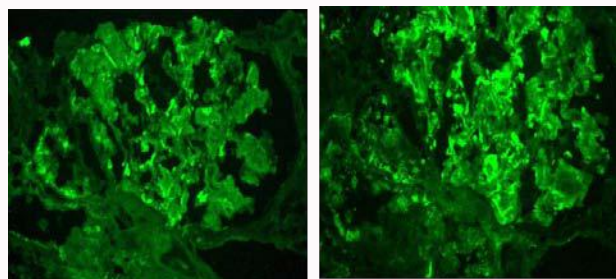
**Figure 2:** The mesangium of the glomerulus is expanded by amorphous, weakly periodic acid-Schiff-positive material that produced an early nodular appearance. This material is also evident in the vessel wall [PAS × 400].

had undergone nephrectomy in his left kidney due to clear cell renal carcinoma (Fuhrman Grade III). On physical examination, he had negligible pitting edema in lower extremities and there were no signs of organomegaly, lymphadenopathy, macroglossia or neuropathy. Laboratory data revealed normal serum IgA (161 mg/dl, normal values 72 mg/dl to 400 mg/dl), decreased IgG (369 mg/dl, normal values 690 mg/dl to 1,618 mg/dl) and highly increased IgM (457 mg/dl, normal values 40 mg/dl to 235mg/dl). Immunofixation detected a band of  $\alpha$ -heavy chain in the serum and urine, as well as  $\lambda$ -light chains in urine. Urine analysis showed proteinuria with no hematuria, with the amount of urine protein at 8.5 gr/day.

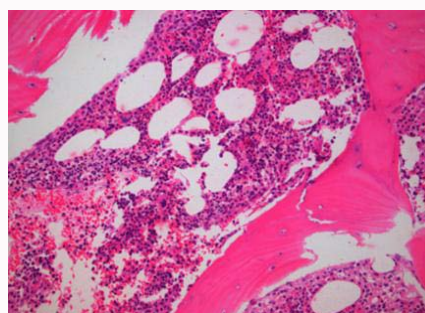
Because of his recent malignancy, we suspected that the possible cause of his nephritic syndrome might be secondary (membranous) glomerulonephritis. Thus he underwent methodical investigation with CT scanning of lungs, abdomen, as well as colonoscopy and gastroscopy, while he was subjected to ultrasound guided kidney biopsy. Due to the fact that the patient had  $\alpha$ -heavy chains in his immunofixation, gastroscopy that was performed also aimed to take biopsies from second, third, and fourth part of the duodenum and upper jejunum, so as to exclude the Possibility of Immunoproliferative Small Intestine Disease (IPSID) which sometimes accompanies a heavy chain findings [16]. The gastrointestinal endoscopy revealed only mild esophagitis while the gastroduodenal mucosal biopsy was negative for amyloid deposition.

The renal biopsy specimen indicated diffuse and global amyloid deposition both on peritubular spaces and the glomeruli, particularly in the mesangial region and the capillaries of glomeruli and Congo red stain positive (Figure 1). In addition, the mesangium of the glomerulus was expanded (Figure 2).

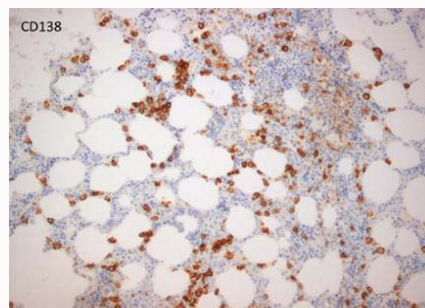
Immunohistological studies for renal amyloid using numeral antibodies (i.e.  $\beta$ -2 macroglobulin, transthyretin etc.) were not fully



**Figure 3:** Immunofluorescence shows strong reactivity for  $\lambda$  light chains. Reactivity for  $\kappa$  light chains was weak.



**Figure 4:** Bone marrow aspirates in AL/AH amyloidosis showing appropriate cellularity with associated normal trilineage hematopoiesis and without features of abnormal maturation or myelodysplasia.

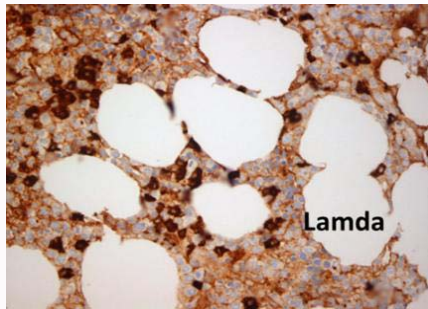


**Figure 5:** Plasmacytes detected with CD138 in proximately 12% to 15%.

available in our laboratory. From the available immunohistological studies, the amyloid deposits on immunofluorescence, stained strongly for  $\lambda$  and slightly for  $\kappa$ , IgM, IgG and IgA (Figure 3). Bone marrow aspiration biopsy showed a plasma cell count 12% to 15%, without amyloid deposition or any dysplasia as well as normal cellularity with trilinear adequate hematopoiesis (Figure 4 and 5). Moreover, monoclonal  $\lambda$  light chains expressed strongly in plasma cells with scattered aggregates or nodules whereas  $\kappa$  light chains' expression was weak (Figure 6). The diagnosis of AL/AHL amyloidosis was determined due to immunofixation findings in serum and urine of monoclonal  $\alpha$  heavy chain immunoglobulin, together with  $\lambda$  light chain immunoglobulins.

Neither electrocardiogram nor echocardiogram revealed any findings suggestive of amyloid heart disease. There was absence of "granular sparkling" myocardium and diastolic-systolic dysfunction, while proBNP, a prognostic factor of cardiac amyloidosis, was within the normal range. Chest and abdominal CT scans showed no enlarged lymph nodes.

Taking into consideration his diagnosis (AHL amyloidosis), he



**Figure 6:** Bone marrow core biopsy specimen with monoclonal  $\lambda$  light chain expression in plasma cells with scattered aggregates or nodules of monoclonal plasma cells in AL/AH amyloidosis (Immunoperoxidase wit).

was treated with chemotherapy (Bortezomib1, 3 mg/m<sup>2</sup> in days 1, 8 and 15, Lenalidomide 10 mg in 1-21 days and dexamethasone 40 mg in days 1, 8, 15 and 22). The whole therapy was administered for a 28 day-cycle, repeated 6 times. A dramatical decline in proteinuria as well as improvement of hypoalbuminemia and patient's lipidemic profile was observed after the end of chemotherapy, with complete remission of his nephrotic syndrome.

It is markedly important to mention that after the results of the kidney biopsy, we examined the tissue of the resected neoplastic left kidney so as to confirm whether amyloidosis was preexisted or not. Congo red staining and immunohistochemical staining were performed in the non-tumor region of his extracted left kidney and were negative for amyloid deposits. Taking into considerations all these findings, our patient was diagnosed with a clear cell carcinoma which was resected and few months later, he was presented with severe nephrotic syndrome due to a rare type of amyloidosis (AHL amyloidosis with  $\alpha$ -heavy chain in serum and urine).

## Discussion

AHL amyloidosis is considered to be a rather rare disorder compared to AL amyloidosis. There have been five cases of AHL reported up to now [2,3]. Light and electron microscopy are not always capable to determine the different types of amyloid. The most potent and sensitive method of distinguishing amyloidogenic fibrils is by Laser Micro Dissection (LMD) or Mass Spectrometry (MS)-based proteomic analysis, a method that can be done in formalin-fixed tissue-embedded paraffin specimens that helps to diagnose amyloidosis easier, even in archival material. However, these techniques have some limitations including the lack of a suitable reagent with the necessary specificity, as well as their unavailability in daily routine. Therefore mentioned methods are indispensable only when the other procedures are not diagnostic and unrevealing. In some problematic cases, where there is absence of immune reactivity for light or heavy chain, the right type of amyloidosis can be indirectly confirm by the demonstration of a monoclonal Ig protein in the blood, urine or in the bone marrow as in the present case [5,6,13,17,18].

In summary, the reported case is very interesting due to the concurrent presence of renal cell carcinoma and a rare type of systemic amyloidosis. It is also peculiar how systemic amyloidosis presented after 8 months of his nephrectomy given that the removed kidney was free of deposition of amyloid. To our knowledge, only limited cases of renal cell carcinoma associated with primary amyloidosis have been published and these are referring to the inverse relationship. In other words, there are references in literature where systemic amyloidosis

is preceded and RCC appears after a certain period [15]. On the other hand AA amyloidosis can be manifested as a possible consequence of stimulation by the carcinoma [14,15,19]. The exact mechanism of AA amyloid production in RCCs is not well understood but may involve protracted irritation of the immune system as the tumor grows. In any case a thorough histological examination is essential for the definite diagnosis of such entities [14,15,20]. Our patient for the time being and after almost two years remains well and free of proteinuria.

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