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Case Report

Kidney Involvement in Systemic Calcitonin Amyloidosis Associated With Medullary Thyroid Carcinoma

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A 52-year-old woman with widely disseminated medullary thyroid carcinoma developed nephrotic syndrome and slowly decreasing kidney function. A kidney biopsy was performed to differentiate between malignancy-associated membranous glomerulopathy and tyrosine kinase inhibitor–induced focal segmental glomerulosclerosis. Surprisingly, the biopsy specimen revealed diffuse glomerular deposition of amyloid that was proved to be derived from the calcitonin hormone (Acal), produced by the medullary thyroid carcinoma. This amyloid was also present in an abdominal fat pad biopsy. Although local ACal deposition is a characteristic feature of medullary thyroid carcinoma, the systemic amyloidosis involving the kidney that is presented in this case report has not to our knowledge been described previously and may be the result of long-term high plasma calcitonin levels. Our case illustrates that systemic calcitonin amyloidosis should be considered in the differential diagnosis of proteinuria in patients with medullary thyroid carcinoma.
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INDEX WORDS: Calcitonin amyloid (ACal); medullary thyroid carcinoma; systemic amyloidosis; kidney amyloidosis; amyloid-associated glomerulopathy; nephrotic syndrome; proteinuria; decreased kidney function; renal biopsy; case report.

In patients with malignant disease, the development of nephrotic syndrome can be caused by membranous glomerulopathy due to the deposition of antibodies. Alternatively, glomerular damage resulting in proteinuria may be related to specific types of medication, for example, tyrosine kinase inhibitors. Another cause of urinary protein loss is glomerular amyloidosis that is associated with excess production of immunoglobulin light chains (AL amyloid) in plasma cell neoplasms. Less frequently, malignancy-associated amyloidosis is caused by an excess of acute-phase proteins (serum amyloid A–associated [AA amyloid]) in, for example, renal cell carcinoma and Hodgkin lymphoma.[1,2] We present a patient with medullary thyroid carcinoma who developed nephrotic syndrome caused by systemic calcitonin amyloidosis involving the kidney.

CASE REPORT

In 2008, at the age of 45 years, a woman presented with partial paraplegia due to vertebral bone metastases of a previously undiscovered medullary thyroid carcinoma. At presentation, serum calcitonin level was 143,150 (reference range, 0.3-12) ng/L, carcinoembryonic antigen (CEA) level was 1,400 (reference range, 0.2-5.0) μg/L, and kidney function was normal, with creatinine level of 44 μmol/L (corresponding to estimated glomerular filtration rate of 134 mL/min/1.73 m^2 as calculated by the IDMS-traceable 4-variable MDRD equation).

Staging with ^{18}F-dihydroxyphenylalanine positron emission tomography and metaiodobenzylguanidine scans showed diffuse bone metastases. Total thyroidectomy was performed and pathologic examination revealed pT3N1a disease, with calcitonin amyloid (ACal) present in the tumor. Mutation analysis of the *RET* gene for multiple endocrine neoplasia type 2 gave negative results. After 2 cycles of postoperative radiotherapy with ^{131}iodine-metaiodobenzylguanidine, the patient was clinically stable.

On follow-up, clinical progression was initially slow, with calcitonin levels increasing steadily from 150,000 to 400,000 ng/L during the course of 4 years (until early 2013), after which point tumor marker progression accelerated (serum calcitonin, 1,076,000 ng/L; CEA, 4,325 μg/L). Systemic therapy with the tyrosine kinase inhibitor vandetanib (300 mg, once daily) was started; subsequently, calcitonin and CEA levels decreased to 39,915 ng/L and 1,375 μg/L, respectively. One month before the start of vandetanib therapy, a finding of proteinuria had been placed in the medical record after a routine urine dipstick test, but the finding was apparently not noticed at that time.

Two months after starting vandetanib therapy, the patient was admitted with nephrotic syndrome, with proteinuria with protein excretion of 3.8 g/24 h, weight gain, and peripheral edema. Potential causes that were considered were membranous glomerulopathy due to metastatic disease and tyrosine kinase inhibitor–related focal segmental glomerulosclerosis. Proteinuria was managed with a salt-restricted diet and the angiotensin-converting enzyme inhibitor enalapril. Vandetanib therapy was continued and

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in the following years, calcitonin levels fluctuated between 25,000 and 50,000 ng/L, while CEA levels slowly decreased from 500 to 300 μg/L. Imaging showed stable disease with regard to lymph node metastases in the neck. Proteinuria fluctuated between protein excretion of 2.3 to 5.0 g/L and 3.4 to 5.5 g/24 h. However, kidney function slowly decreased, with creatinine levels increasing to 136 μmol/L (estimated glomerular filtration rate, 36 mL/min/1.73 m^2). The evolution of calcitonin, CEA, creatinine, and proteinuria levels is shown in Fig 1.

At the end of 2015, a kidney biopsy was performed to clarify the underlying pathologic mechanism. Histologic examination of the specimen showed diffuse Congo Red positivity in glomeruli, with apple-green birefringence under polarized light. This amyloid was seen in every glomerulus present in the biopsy specimen, with additional subtle deposits in arterial walls. Amyloid also was visible by transmission electron microscopy and consisted of straight nonbranching fibrils in a haphazard arrangement. The fibrils showed mesangial and focal subendothelial localization along the glomerular basement membrane. Amyloid typing using immunofluorescence or immunostaining (with appropriate controls) revealed no predominance of κ or λ light chains and no AA amyloid or transthyretin. However, amyloid in all glomeruli showed strong immunoreactivity with calcitonin. Staining was highly specific to the amyloid and was even stronger than that of the control sample (C cells and amyloid in medullary thyroid carcinoma tissue). Histologic images are shown in Fig 2. Serum amyloid P scan did not show an abnormal pattern of uptake. However, an abdominal fat pad biopsy specimen obtained after this scan revealed the presence of Congo Red–positive amyloid in subcutaneous fat tissue, which also stained for calcitonin (Fig S1). As such, the nephrotic syndrome of this patient with metastatic medullary thyroid carcinoma turned out to be related to glomerular involvement of systemic amyloidosis with ACal.

DISCUSSION

Amyloidosis is characterized by the formation and extracellular deposition of insoluble fibrillary aggregates due to protein misfolding. Although these deposits have a uniform appearance and similar histomorphologic characteristics, the amyloid fibril protein can originate from a variety of soluble precursor proteins.[3-5] Among the most common and well-known amyloid proteins are AL and AA.[3,6,7] Amyloidosis can manifest as a systemic or generalized disease when the precursor is produced at one site (eg, in bone marrow or liver), distributed via the circulation, and deposited at distant sites such as the kidney and heart. In contrast, localized amyloidosis is defined by restriction of both precursor production and amyloid deposition in a single site or organ.[7,8]

Localized amyloidosis is a characteristic feature of medullary thyroid carcinoma because ACal fibrils are formed from the calcitonin hormone that is produced by the neoplastic C cells.[9] The calcitonin origin of these amyloid fibrils was recently confirmed with mass spectrometry–based proteomic analysis.[10] Unlike other forms of amyloidosis, ACal in medullary thyroid carcinoma is not known to be related to systemic amyloidosis. In the present case report, we identified glomerular ACal as the cause of nephrotic syndrome in a patient with medullary thyroid carcinoma. Additionally, the ACal was present in an abdominal fat pad biopsy specimen, further confirming the systemic nature of the calcitonin amyloidosis.[11] Unfortunately, insufficient remaining tissue was available to conduct mass spectrometry.

To our knowledge, this is the first case of systemic calcitonin amyloidosis described in the medical literature. To further investigate this unique finding, we conducted a search in our institute's records for patients with medullary thyroid carcinoma who had undergone autopsy between 1990 and 2015. Paraffin-embedded samples of routinely obtained kidney tissue were retrieved and histologic slides were stained with hematoxylin-eosin and Congo Red. In all 5 evaluated

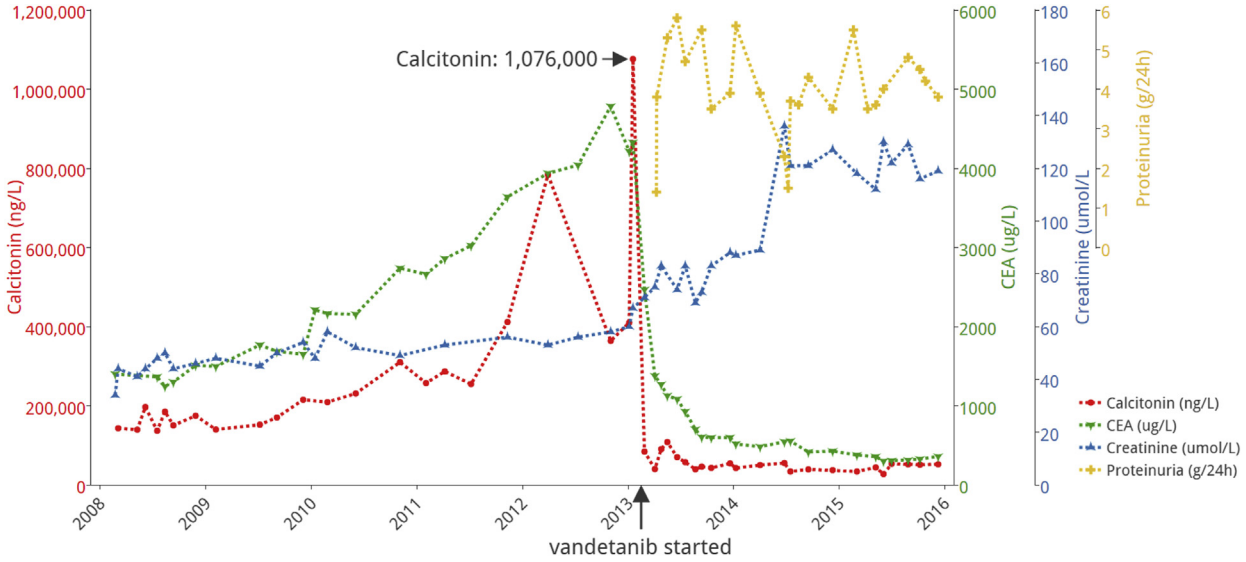

Figure 1. Serum calcitonin, serum carcinoembryonic antigen (CEA), serum creatinine, and proteinuria values over time. Conversion factor for serum creatinine in mg/dL to μmol/L, ×88.4.