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Case Report

Nephrotic Syndrome as a Complication of Systemic Calcitonin Amyloidosis From Long-Standing Metastatic Medullary Thyroid Cancer

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ABSTRACT

Background/Objective: Medullary thyroid cancer often results in elevated calcitonin levels, which can cause localized formation of calcitonin amyloid, though rarely complications of systemic calcitonin amyloidosis have been reported. The objective of this report is to encourage awareness of calcitonin amyloid causing nephrotic syndrome in patients with metastatic medullary thyroid cancer.
Case Report: A 65-year-old woman with weakness, fatigue, anasarca, anemia, thrombocytopenia, venous and arterial thrombi, and a cavitary right lung lesion was transferred for care. She had a 14-year history of metastatic medullary thyroid cancer, status post-thyroidectomy and tyrosine kinase inhibitor therapy, adrenocorticotropic hormone-dependent Cushing syndrome in remission, and recently diagnosed nephrotic syndrome. On admission, she had lower extremity edema and scattered ecchymoses. Labs showed creatinine 0.62 mg/dL (0.7-1.3 mg/dL), morning cortisol >119.6 ug/dL (4-23 ug/dL), adrenocorticotropic hormone 426 pg/mL (6-50 pg/mL), 24-hour urine cortisol 6115.2 mcg/24 h (4-50 mcg/24 h), calcitonin 39 373 pg/mL (≤5 pg/mL), and carcinoembryonic antigen level 484.8 ng/mL (0-4.9 ng/mL). Kidney biopsy showed amyloidosis, which stained positive for calcitonin.
Discussion: Systemic calcitonin amyloidosis is not well-documented in medullary thyroid cancer. To our knowledge, there are 2 previous case reports describing nephrotic syndrome secondary to calcitonin amyloid in the setting of medullary thyroid cancer.
Conclusion: This case supports a small body of evidence that metastatic medullary thyroid cancer can result in systemic calcitonin amyloidosis and its complications, including nephrotic syndrome. Clinicians should consider nephrotic syndrome as a potential complication in patients with metastatic medullary thyroid cancer, particularly in those with long-standing calcitonin elevation and characteristic symptoms.

Introduction

Elevated calcitonin levels are commonly seen in medullary thyroid cancer (MTC), often rising in proportion to the parafollicular C cell mass.[1] This can result in amyloid formation called calcitonin amyloid (ACal). While other forms of amyloid are known to spread and cause systemic complications, ACal generally remains localized in the thyroid and adjacent lymph nodes.[2] We present a case demonstrating ACal as a cause of nephrotic syndrome in a patient with metastatic MTC, adding to a small number of cases

Abbreviations: ACal, calcitonin amyloid; ACTH, adrenocorticotropic hormone; CEA, carcinoembryonic antigen; CT, computed tomography; MTC, medullary thyroid cancer; TKI, tyrosine kinase inhibitor.

Statement of Patient Consent: Consent for publication has been obtained from patient's husband, as proxy for patient who is now deceased.

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suggesting that clinicians should consider nephrotic syndrome as a potential complication of metastatic MTC, particularly in patients with long-standing calcitonin elevation.

Case Report

A 65-year-old woman with weakness, fatigue, anasarca, anemia, thrombocytopenia, venous and arterial thrombi, and a right middle lobe cavitary lung lesion on computed tomography (CT) of the chest was admitted for care via transfer from an outside hospital. Her medications at time of transfer included levothyroxine, furosemide, metoprolol tartrate, vancomycin, meropenem, and voriconazole. Her past medical history included metastatic MTC status post debulking surgery and tyrosine kinase inhibitor (TKI) therapy, Cushing syndrome in remission, postsurgical hypothyroidism, and newly diagnosed nephrotic syndrome.

Her medical history was known to us, as she received endocrine and prior oncology care at our institution. She had been diagnosed with metastatic MTC 14 years earlier. Her disease was complicated by metastases to the neck, mediastinum, and liver, and severe Cushing syndrome attributed to ectopic adrenocorticotropic hormone (ACTH) production, based on afternoon ACTH 770 pg/mL (7-50 pg/mL) and failure of cortisol to suppress on overnight 8 mg dexamethasone suppression test. Calcitonin and carcinoembryonic antigen (CEA) were 44,488 pg/mL (≤5 pg/mL) and 685.5 ng/mL (0-4.9 ng/mL), respectively. Rearranged during transfection proto-oncogene testing was negative. She underwent total thyroidectomy with central and extensive mediastinal lymph node dissection shortly after diagnosis. Her Cushing syndrome resolved after surgery; calcitonin and CEA levels decreased to 36,176 pg/mL (≤5 pg/mL) and 245.5 ng/mL (0-4.9 ng/mL), respectively. She underwent a second radical neck dissection and was started on TKI therapy. She received sorafenib for 7 years before calcitonin and CEA levels rose and new liver lesions were noted on CT scan. She transitioned to cabozantinib but developed grade 4 toxicity after 1 month and it was discontinued. She was reluctant to try further TKI therapy and chose active surveillance. During a 5-year period of active surveillance, calcitonin and CEA levels remained elevated but stable for approximately 2 years before uptrending (Fig. 1). 24-hour urine cortisol remained within normal limits, including on a collection 1 month before admission, and CT scans showed known liver metastases with no changes.

Nephrotic syndrome was diagnosed 2 months before hospital admission, when she developed bilateral leg swelling and was found to have urine protein-creatinine ratio >10,000 mg/g (<200 mg/g) and serum albumin 1.9 g/dL (3.5-5.0 g/dL). A kidney biopsy was performed 1 week before admission; results were not immediately available.

On admission, physical exam showed 3+ bilateral lower extremity pitting edema, scattered ecchymoses, and diminished breath sounds in the right lung base. Labs showed hemoglobin 7.2 g/dL (11.8-16.0 g/dL), platelet count 10 K/UL (150-400 K/UL), lactate dehydrogenase 534 U/L (171-308 U/L), and creatinine 0.62 mg/dL (0.7-1.3 mg/dL). PLASMIC score was 6 and plasma exchange was started but discontinued when haptoglobin measured 285 mg/dL (44-184 mg/dL), rare schistocytes were seen on blood

Highlights

- Calcitonin amyloid (ACal) can develop from calcitonin elevation in medullary thyroid cancer (MTC).
- ACal usually remains localized in the thyroid gland and adjacent lymph nodes.
- Prolonged calcitonin elevation in metastatic MTC may cause systemic ACal amyloidosis
- Consider nephrotic syndrome in patient with typical symptoms and history of MTC.
- Consider ACal as a cause of nephrotic syndrome if history of metastatic MTC.

Clinical Relevance

It is well-known that increased calcitonin production in medullary thyroid cancer (MTC) can lead to localized calcitonin amyloidosis. This case contributes to a small body of evidence that metastatic MTC can also result in systemic calcitonin amyloidosis and resulting complications, including nephrotic syndrome.

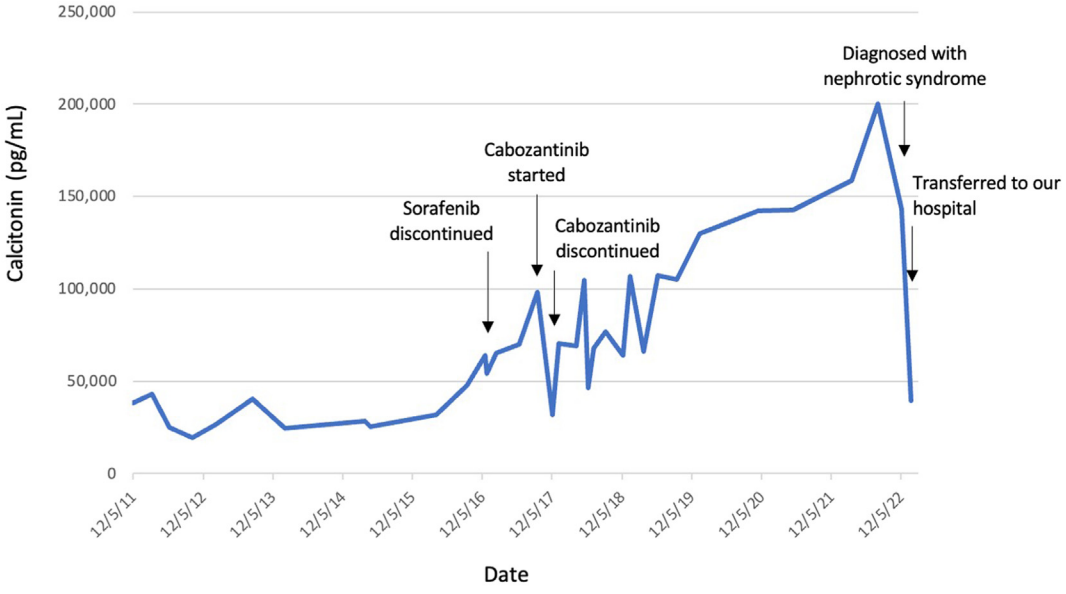

Fig. 1. Calcitonin over the long course of the patient's illness leading up to her diagnosis of nephrotic syndrome.

smear, and Von Willebrand factor protease activity returned at 0.33 IU/mL (0.68-1.63 IU/mL). Heparin-induced thrombocytopenia antibody and direct Coombs test were negative. D-dimer was 2291 ng/dL (<243 ng/dL), PT was 12.6 s (9.2-13.5 s), PTT was 24 s (27-37 s), and fibrinogen was 594 mg/dL (180-460 mg/dL).

Morning cortisol was >119.6 ug/dL (4-23 ug/dL), morning ACTH was 426 pg/mL (6-50 pg/mL), and 24-hour urine cortisol was 6115.2 mcg/24 h (4-50 mcg/24 h). Calcitonin and CEA were 39,373 pg/mL (≤5 pg/mL) and 484.8 ng/mL (0-4.9 ng/mL), respectively. Repeat CT scan showed new diffuse enlargement of the bilateral adrenal glands, previously seen liver metastases, bilateral pleural effusions, multifocal ground-glass and consolidative opacities in lung bases, ascites, and diffuse anasarca. Etomidate and ketoconazole were used to treat cortisol excess, as the patient was deemed too unstable for bilateral adrenalectomy by the surgical consult team.

Infectious work up revealed *Nocardia* bacteremia, *Pneumocystis jiroveci* pneumonia, and *Clostridium difficile* colitis, and the patient was treated with antibiotic therapy. The patient's renal function and hypervolemia worsened, and she was treated with intravenous furosemide, but later developed septic shock requiring pressors and was transitioned to continuous renal replacement therapy. Urine protein electrophoresis showed multiple bands (albumin predominating) and serum protein electrophoresis showed albumin 1.9 g/dL (3.35-5.40 g/L), beta globulin 0.39 g/dL (0.7-1.2 g/dL) and gamma globulin 0.14 g/dL (0.59-1.47 g/dL) with a restricted band in the gamma region. Serum and urine immunofixation did not show monoclonal proteins and serum kappa-lambda free light chain ratio was 0.83 (0.26-1.65). Testing for hepatitis B and C, human immunodeficiency virus, syphilis, cryoglobulin, antinuclear antibody, anticardiolipin antibodies, anti-beta2 glycoprotein I antibodies, and anti-phospholipid A2 receptor levels was negative. Complement factors 3 and 4 were 58 mg/dl (79-160 mg/dl) and 12 mg/dL (17-48 mg/dl), respectively.

The prior kidney biopsy results returned and revealed widespread involvement by amyloidosis with positive Congo red staining with green birefringence when examined under polarized light (Fig. 2). Routine immunofluorescence microscopy showed weak reactivity of the amyloid for protein-A and for gamma heavy chain, and negative reactivity for both immunoglobulin light chains and transthyretin. The amyloid deposits showed characteristic fibrillary appearance by electron microscopy (Fig. 3). The kidney biopsy subsequently stained positive for calcitonin by immunohistochemistry (Fig. 2-D), and mass spectrometry performed on the micro-dissected Congo red-positive material from the kidney biopsy demonstrated the presence of calcitonin.

Despite ongoing treatment, the patient remained critically ill and her condition progressively worsened in the setting of her multiple comorbidities and infections. Her family ultimately decided to transition her to comfort-directed care and she passed away peacefully.

Discussion

In this complex case, a patient with long-standing metastatic MTC treated with debulking surgery and TKI therapy developed nephrotic syndrome and presented with anasarca, anemia, thrombocytopenia, venous and arterial thrombi, and multiple infections. She was found to have recurrence of ACTH-dependent Cushing syndrome and imaging showed bilateral enlargement of the adrenal glands, consistent with stimulation from elevated ACTH, but no visible evidence of MTC progression. Calcitonin and CEA levels measured significantly lower than prior, suggesting possible de-differentiation of MTC, as de-differentiation of MTC leading to loss in calcitonin production has been described.[3] Hypercortisolemia was thought to contribute to the multiple infectious complications. Initial labs raised concern for thrombotic thrombocytopenic purpura or other thrombotic microangiopathy as cause of the patient's anemia, but subsequent lab results made these diagnoses unlikely and excluded heparin-induced thrombocytopenia, autoimmune hemolytic anemia, and disseminated intravascular coagulation. Immune thrombocytopenia was considered as a possible cause of the thrombocytopenia. Glucocorticoid therapy was deferred due to elevated morning cortisol level and the patient was treated with intravenous immunoglobulin. Ultimately, the causes of the anemia and thrombocytopenia remained unclear.

Interestingly, the patient's kidney biopsy showed widespread involvement by ACal, supporting systemic calcitonin amyloidosis as the cause of her nephrotic syndrome. While it is well-known that increased calcitonin production in MTC can lead to localized calcitonin amyloidosis, systemic calcitonin amyloidosis from MTC is not well-documented, apart from 2 prior case reports. The first, published in 2017, described a 45-year-old woman with metastatic MTC who underwent total thyroidectomy and radiotherapy with ^{131}iodine-meta-iodobenzylguanidine.[4] She initially appeared clinically stable, though calcitonin levels rose over a 5-year period. She was started on vandetanib and calcitonin levels improved, but she then developed proteinuria and was diagnosed with nephrotic syndrome. Kidney biopsy revealed diffuse glomerular deposition of amyloid derived from calcitonin and abdominal fat pad biopsy revealed amyloid, supporting systemic calcitonin amyloidosis as the cause of her nephrotic syndrome.

A second case published in 2020 described a 55-year-old woman with a history of MTC status post partial thyroid resection, cervical lymph node resection, and 2 cycles of chemotherapy who developed metastasis of her MTC, rise in calcitonin level, proteinuria, and renal dysfunction 9 years later.[5] Kidney biopsy showed glomerular and arteriolar amyloid deposition, with immunohistochemistry showing that the amyloid deposits stained strongly positive for calcitonin. Laser microdissection and mass spectrometry showed sequences for procalcitonin and calcitonin, indicating ACal, again suggesting systemic calcitonin amyloidosis from MTC as the cause of the patient's nephrotic syndrome.

In these cases, it was theorized that systemic calcitonin amyloidosis resulted from high calcitonin levels circulating over a prolonged period.

We believe our case represents the third documented case of nephrotic syndrome due to systemic calcitonin amyloidosis from metastatic MTC and long-standing calcitonin elevation. This finding is significant, as it suggests that while uncommon, MTC may cause systemic amyloidosis and resulting complications, including nephrotic syndrome, and this may be underdiagnosed. While TKIs are sometimes considered a cause of nephrotic syndrome in patients who have received TKI therapy for MTC, systemic ACal should be considered as a potential etiology as well. Clinicians caring for patients with histories of metastatic MTC should consider nephrotic syndrome as a potential complication, particularly in patients with long-standing calcitonin elevation and who present with characteristic symptoms.

Disclosure

Dr Jean Francis receives advisory board fees from Alexion and honoraria from Uptodate.

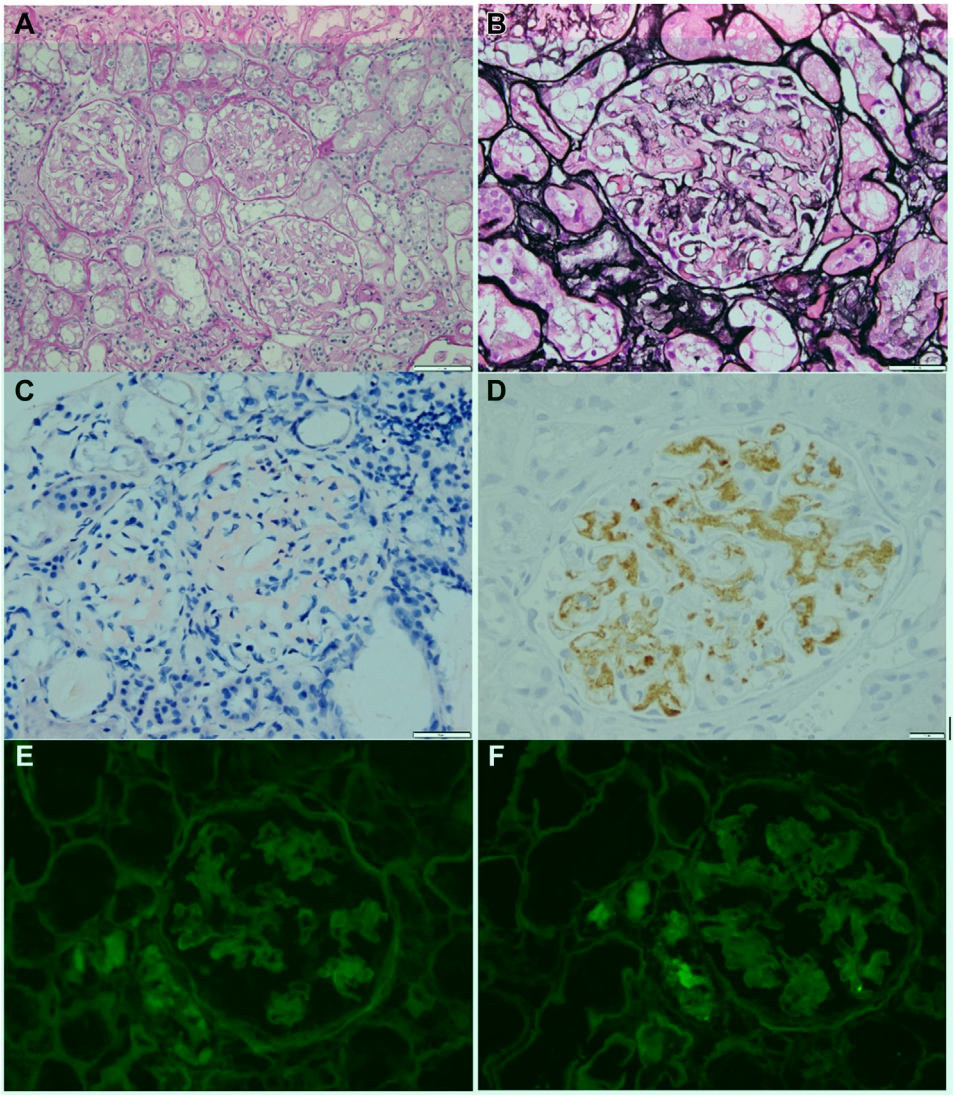

Fig. 2. Kidney biopsy specimens. The glomeruli are involved by amyloidosis, calcitonin type (ACal). Three glomeruli reveal widening of the mesangium and focal thickening of the peripheral capillary walls by acellular, amorphous material with weak staining by the periodic acid-Schiff reaction (*A*). The infiltrating material is silver negative (*B*) and Congo red positive (*C*), characteristic for amyloid deposition. The amyloid is reactive for calcitonin (*D*), and it is negative for kappa (*E*) and lambda (*F*) light chains (A-periodic acid-Schiff stain; B-Jones' silver methenamine stain; C-Congo red stain; D-Immunohistochemistry for calcitonin; E and F-immunofluorescence microscopy using fluorescein isothiocyanate-labelled anti-kappa and anti-lambda antibodies, respectively). *ACal* = calcitonin amyloid.

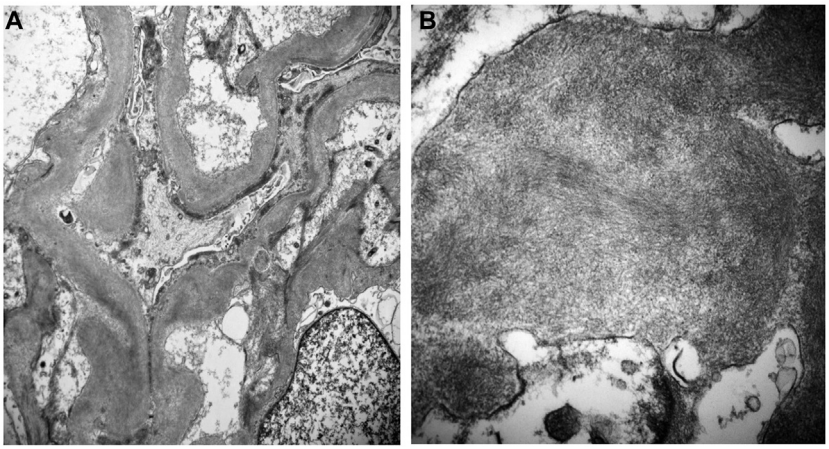

Fig. 3. Electron microscopy of the kidney biopsy. (*A*), A low magnification electron micrograph reveals widespread widening of the peripheral glomerular capillary walls by amyloidosis. (*B*), The infiltrating amyloid shows the characteristic fibrillary substructure. The fibrils measure on average 8.9 nm (Electron microscopy; Original magnification: A = 10,000 x; B = 50,000 x).

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