Cast Nephropathy in the Setting of Diffuse Carcinomatosis of Unknown Origin

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Cast nephropathy, previously named myeloma kidney, refers to either acute or chronic kidney injury produced by monoclonal urinary immunoglobulin light chains (Bence-Jones proteins). The characteristic renal histological appearance shows fractionated, eosinophilic intratubular casts surrounded by a giant cell reaction. Although this histological picture is virtually diagnostic of myeloma or plasma cell dyscrasia, it has rarely been described in conditions other than multiple myeloma. Specifically, such an appearance has been published in association with heavy albuminuria [1] and pancreatic and thyroid malignancies [2-4]. We report a case of typical cast nephropathy in a patient with diffuse metastatic adenocarcinoma of unknown origin in the absence of any monoclonal gammopathy.

PATIENT DESCRIPTION

A 79 year old Caucasian male was admitted in November 2013 for the investigation of rapidly progressive renal failure, serum creatinine having increased from a basal level of 1.0 to 2.0 mg/dl and within a month to 3.8 mg/dl. Two years previously, renal sonography showed two kidneys of normal size and structure without hydronephrosis and an enlarged prostate with protrusion of the middle lobe into the bladder. The ultrasound also demonstrated multiple hypoechogenic lesions in the liver. Abdominal computed tomography confirmed the presence of the hepatic lesions which were enhanced by contrast dye, and also revealed a hypodense mass with diameter of 20 mm and 70 Hounsfield units in the tail of the pancreas. Biopsy of one of the liver masses showed tumor cells compatible with metastatic adenocarcinoma. The cells stained positive for CK7 and MNF116, and negative for prostatic specific antigen (PSA), TTF1 and CK20. They were also negative for neuroendocrine markers (chromogranin, synaptophysin, neuron-specific enolase) as well as for CDX2 and CEA. An attempted biopsy of the pancreatic mass yielded inadequate tissue. Based on these results, the origin of the carcinoma could not be determined. The patient refused chemotherapy. In January 2013, transrectal ultrasound and prostatic biopsy were performed. Peak PSA blood level reached 9.0 ng/ml. The biopsy showed prostatic adenocarcinoma, Gleason score 7(3+4) present in five of six cores involving 35% of core tissue. Treatment with the luteinizing hormone blocker buserelin was started, resulting in a reduction of PSA to 0.05 ng/ml but no regression of metastases.

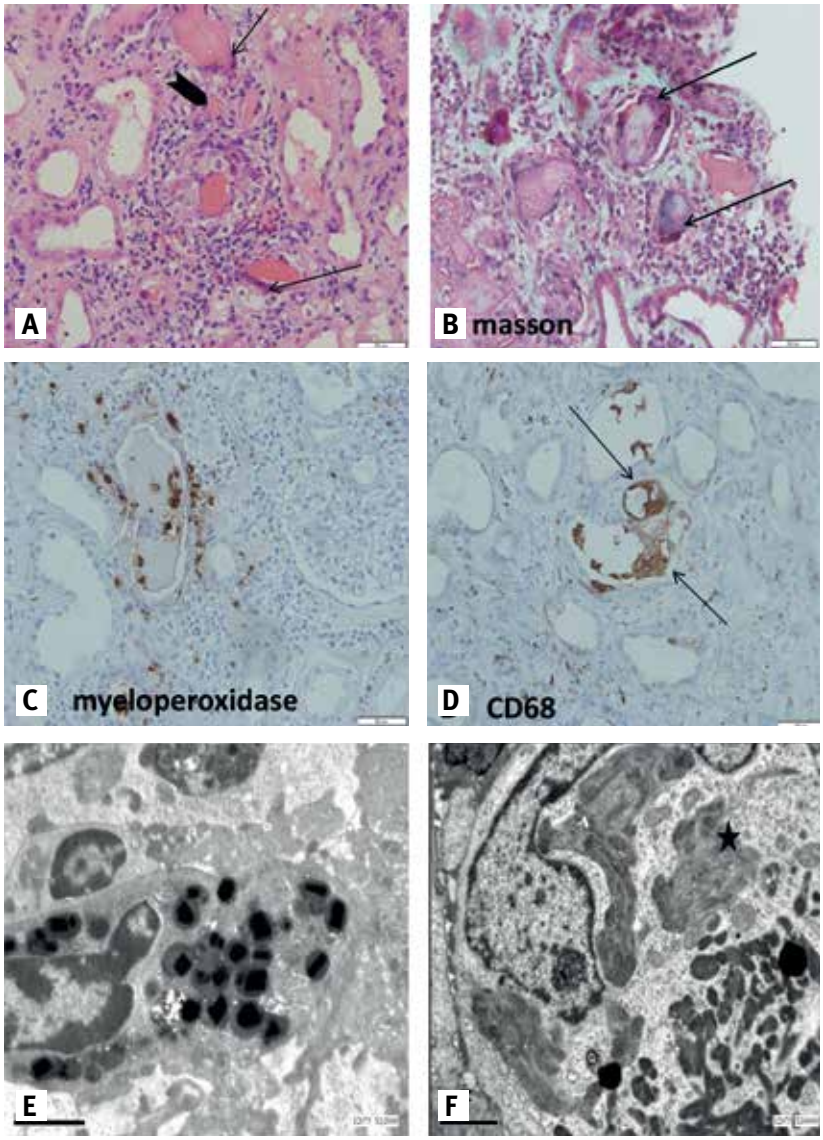
On his current admission, the patient appeared well, blood pressure was 140/80 (on treatment), and a mass was palpable in the left lobe of the liver. Laboratory data showed hemoglobin 9.0 g/dl, creatinine 3.8 mg/dl, calcium 9.1 mg/dl, phosphorus 4.2 mg/dl, total protein 6.5 g/dl with albumin 3.1 g/dl, alkaline phosphatase 115 U/L (range 30–120), aspartate aminotransferase 26 U/L, alanine aminotransferase 10 U/L, gammaglutamyl transferase 100 (7–49) U/L, and lactate dehydogenase 871 U/L (230–460). Tumor marker CA 19-9 was elevated at 249 U/ml.

Serum antinuclear antibody, complement C3, C4, cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA), peripheral-ANCA, quantitative immunoglobulin (Ig), IgG4, HBsAg, hepatitis C virus and human immunodeficiency virus were all negative or within normal limits. Serum electrophoresis and immunofixation was normal without any demonstrable monoclonal peak. Free light chain assay showed kappa 88 mg/L (3.3–19.4) and lambda 91.2 mg/L (5.7–26.3), with a normal kappa/lambda ratio of 0.96 (0.26–1.65). Bone marrow examination was normal regarding all three blood lines with no atypical plasma cells.

Urine 24 hour protein collection yielded 5 g of protein per day; albumin/creatinine ratio was 731 µg/mg and creatinine 1735 mg/day. Bence-Jones proteinuria was negative.

A repeat renal sonography showed the kidneys to be of normal size and structure with mildly hyperechogenic parenchyma and no hydronephrosis. Renal biopsy was performed. On light microscopy there were 20 glomeruli, 3 of which were totally hyalinized. The remainder showed a mildly increased thickness of the glomerular basement membrane (GBM) and mild focal mesangial proliferation. The interstitium was studded by many foci of both an acute and chronic inflammatory infiltrate. There were many intratubular fractionated eosinophilic casts surrounded by macrophages and a giant cell reaction [Figure 1 A & B].

[A,B] Renal biopsy, light microscopy, showing intratubular fractionated eosinophilic casts (arrowhead) surrounded by macrophages and a giant cell reaction (arrow). **[C,D]** Immunohistochemical staining of the same biopsy showing positive staining for myeloperoxidase (C) and for CD68 (D) (both specific for macrophages). **[E]** Electron microscopy showing bizarre crystal-like structures within tubular cell lysosomes. **[F]** Electron microscopy showing foci of fibrillar material (asterisk) within these tubular cells



Immunohistochemically, these cells stained positively for CD68 [Figure 1C] and myeloperoxidase [Figure 1D]. Immunofluorescence was essentially negative with non-specific lambda and kappa staining of the casts. Electron microscopy demonstrated widespread effacement of visceral epithelial cell foot processes in keeping with the presence of nephrotic range proteinuria. The GBM was of normal appearance with no electron dense deposits. Tubular cells were seen to contain crystal-like structures situated within lysosomes [Figure 1E]. In addition, within the cytoplasm of these cells were irregular foci of fibrillar material (size not compatible with amyloid) some of which were surrounded by a membrane [Figure 1F].

COMMENT

Our patient presented with rapidly deteriorating renal function in the context of diffuse metastatic adenocarcinoma of unknown origin. Although it is tempting to assume that the biopsy-proven carcinoma of the prostate was the primary tumor, immunostaining of the hepatic metastasis did not support this conjecture nor did the failure of regression of lesions on buserelin treatment. The most obvious cause of renal failure in such a setting is obstructive uropathy. However, repeated imaging modalities in a normovolemic state did not demonstrate any dilatation of the urinary tract.

Renal biopsy was distinct as it showed the characteristic features of cast nephropathy. The term, cast nephropathy, is typically indicative of multiple myeloma or plasma cell dyscrasia as it is monoclonal urinary immunoglobulin light chains that produce the renal injury. Light chains precipitate in the distal and collecting tubules in conjunction with Tamm-Horsfall mucoprotein (uromodulin) which constitutes the matrix of all urinary casts. The binding and precipitation result in the formation of obstructing intratubular casts which may trigger a giant cell reaction and lead to interstitial inflammation and fibrosis. Hypovolemia is an established contributing factor to cast nephropathy. Other important determinants of the ability of a particular light chain to form intratubular casts are the affinity of its binding to uromodulin and its isoelectric point.

Although cast nephropathy is almost pathognomonic of myeloma, the histological picture has rarely been described in association with conditions lacking the presence of monoclonal light chains. Among these are heavy albuminuria and notably pancreatic and thyroid malignancies [1-3]. Min et al. [1] reported a case of acinar cell carcinoma of the pancreas and myeloma-like lesions of the kidney in which serum electrophoresis was normal. A remarkably similar case was described by Reducka and colleagues [4]. In that case, the protein electrophoretic patterns of a frozen

extract of tumor (acinar cell carcinoma) and kidney were different from those of a normal pancreas and kidney. However, a common morphologic association between the pancreatic neoplasm and renal tubular casts could not be found. Hobbs et al. [2] published a case of ductal adenocarcinoma of the pancreas and cast formation in which the urine concentrate and tumor extract had identical electrophoretic bands. Notably, the ultrastructural examination of the acinic cell tumor in Reducka's case revealed zymogen granules of variable size and dense bundles of tightly packed keratin filaments. In Min's case report, fibrillar cytoplasmic inclusions consisting of parallel stacks of microtubules were described. In a clinicopathologic review of acinar cell carcinoma of the pancreas by Klimstra et al. [5], in many of the tumors electron microscopy showed cytoplasmic pleomorphic granules often of bizarre shapes which contained parallel arrays of electron dense filamentous material. These findings are remarkably similar to those demonstrated in our case.

Although pancreatic adenocarcinoma was considered the primary tumor in our patient, this could not be determined with certainty. Furthermore, the rather long survival of our patient with diffuse metastases is at odds with this diagnosis. In view of the above, it appears that under certain conditions, cast formation might be related to the filtration and deposition of an abnormal protein produced by the tumor, in particular pancreatic tumors. This pathogenic mechanism also appears to have been the case in our patient.

The positive immunofluorescence staining for both lambda and kappa light chains in our patient probably reflects the presence of polyclonal light chains in this nephrotic urine.

This case serves to highlight the fact that myeloma-like cast nephropathy may occur in association with malignancies other than plasma cell dyscrasias. In the absence of the usual clinical and laboratory parameters of plasma cell dyscrasia, cast nephropathy does not necessarily denote myeloma.

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