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Hypertension, renal failure, and edema in a 38-year-old man: light chain deposition disease; a case report and review of the literature

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ABSTRACT

Background: Monoclonal immunoglobulin deposition disease (MIDD) is a rare disease, usually manifesting between the 5th and 6th decades of life but can also occur earlier. Characteristic feature of MIDD is a non-fibrillar, Congo red negative deposition of monoclonal immunoglobulins in various organs, including the kidneys. Depending on the composition of the deposits, MIDD is classified into 3 types; light chain deposition disease (LCDD), which is the most common form, heavy chain deposition disease (HCDD) and light and heavy chain deposition disease (LHCDD). Kidney involvement is common in MIDD. Renal biopsy reveals nodular sclerosing glomerulopathy on light microscopy and diffuse linear staining of glomerular and tubular basement membranes on immunofluorescence (IF) microscopy.

Case presentation: A 38-year-old male patient recently diagnosed with hypertension presented with lower extremity edema, shortness of breath, and fatigue. The workup that was performed in a different hospital prior to this admission, demonstrated the presence of significant proteinuria and renal failure. He was intermittently dialyzed and a renal biopsy was obtained, which showed LCDD. Further laboratory workup revealed an increase of IgM, kappa chain and ß2 microglobulin chain, in addition to proteinuria and renal insufficiency. Bone marrow biopsy demonstrated an involvement of 30% with plasma cells. The flow cytometry test showed monotypic plasma cells expressing intracytoplasmic kappa light chain restriction with kappa to lambda ratio of 35/1. The diagnosis of LCDD was established. Treatment with steroids and bortezomib was initiated.

Conclusions: MIDD is an unusual disease and LCDD is the most common form of MIDD. The peak incidence is around the 5th and 6th decade of life, however, LCDD can also be found in younger patients. Renal involvement, proteinuria, hematuria, and hypertension are markers of the initial clinical presentation. Nodular sclerosing glomerulopathy is found in about 60% of the affected patients. Early diagnosis and early treatment improve the prognostic course of LCDD.

Case Report

Implication for health policy/practice/research/medical education:
Monoclonal immunoglobulin deposition disease (MIDD) is unusual disease and light chain deposition disease (LCDD) is the most common form of MIDD. The peak incidence is around the 5th and 6th decade of life, however, LCDD can also be found in younger patients. Renal involvement, proteinuria, hematuria, and hypertension are markers of the initial clinical presentation. Nodular sclerosing glomerulopathy is found in about 60% of the affected patients. Early diagnosis and treatment improve the prognostic course of LCDD.

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Introduction

Monoclonal immunoglobulin deposition disease (MIDD) is a rare systemic disease, characterized by non-fibrillar, Congo red negative deposition of monoclonal immunoglobulins in basement membranes. MIDD usually manifests in the 5th to 6th decade of life; however the presentation can also occur in patients <50 years of age in one-third of the cases (1). The location of immunoglobulin deposition determines the clinical presentation. Kidney involvement is the most common site of manifestation, however, other organs may be affected (cardiac, hepatic and neural involvement have been described) (2,3). MIDD is sub-classified into three types: light chain deposition disease (LCDD), heavy chain deposition disease (HCDD) and light and heavy chain deposition disease (LHCDD). All types manifest with similar clinical and histopathological features and can be distinguished by quantification of light and heavy chain serum levels or by immunological testing. LCDD is the most common type accounting for 80% of the cases. In LCDD, the monoclonal light chains are predominantly of the κ category (92%), and the majority consists of the VκIV type (1,3). LCDD typically occurs in association with multiple myeloma (MM) or other lymphoproliferative disorders. In more than 90% of the affected patients, non-selective proteinuria may occur; however, during the early stages of the disease, proteinuria may be absent. In 23-57% of the patients, nephrotic range proteinuria can be seen. Gross hematuria is rarely seen, while, microscopic hematuria is observed in 60% of the cases (1,4).

Case presentation

A 38-year-old male patient with a past medical history of diagnosed hypertension about 3 months ago was admitted with progressive lower extremity edema, shortness of breath, and fatigue. Family history was remarkable for his brother diagnosed with chronic kidney disease due to lupus nephritis. He denied smoking and the use of alcohol as well as illegal drugs. Physical examination showed a hemodynamically stable patient with pale conjunctiva, mild periorbital puffiness, and mild non-pitting edema on both lower extremities extending above the knee. Cardiovascular, respiratory, abdominal and neurological examinations were unremarkable. Over the last 3 months, he developed anasarca and was discharged one week prior to this admission from another hospital, where further work-up demonstrated a significant proteinuria and renal insufficiency requiring 4 rounds of hemodialysis through a tunneled catheter.

Initial laboratory workup demonstrated a normocytic normochromic anemia, borderline elevated potassium and increased blood urea nitrogen (BUN) and creatinine (Table 1). The urine analysis is shown in Table 2. Further laboratory workup revealed an elevated urine protein, IgM, kappa light chain and ß2 microglobulin chain (Table 3). A renal biopsy was performed (Figures 1-3). A total of eight glomeruli were available, one of which was globally sclerosed. The non-sclerosed glomeruli exhibited a distinctive hypocellular amphophilic periodic acid-Schiff (PAS) positive expansion of the mesangial matrix. The glomerular capillary basement membranes were diffusely thickened and the glomerular capillary loops were focally obliterated. There were no necrotizing or proliferative lesions. The

Table 1. Initial laboratory workup

Initial laboratory Work up	
White blood cell count	7.11 × 10^3 /uL
Hemoglobin	8.4 g/dL
Hematocrit	25.4%
Platelet count	294 × 10^3/uL
Sodium	144 mmol/L
Potassium	5.6 mmol/L
Chloride	104 mmol/L
CO_2	23 mmol/L
Serum glucose	102 mg/dL
BUN	98 mg/dL
Creatinine	11.53 mg/dL
Calcium	8.6 mmol/L
Albumin	3.0 g/dL
Protein	5.5 g/dL
AST	5 I.U./L
ALT	15 I.U/L

Table 2. Urine analysis on admission

Urine analysis	
Urine appearance	Hazy
Glucose	Negative
Bilirubin	Negative
Specific gravity	1.015
Blood	Moderate
Urine PH	6.0
Protein	3+
Nitrite	Negative
Leuk esterase	Trace
Casts	2-5 Hyaline/ LPF
WBC in urine	3-5/HPF
RBC in urine	0-3/HPF
Bacteria	Trace

tubulointerstitial compartment demonstrated mild to moderate atrophy and fibrosis as well as mild chronic inflammation. A few tubules contained refractory proteinaceous casts. The interstitial infiltrate was mostly lymphocytic in nature. The vessels appeared thickened and hyalinized. The Congo red stain displayed the presence of focal areas suggestive, but not conclusive for interstitial apple green birefringence. The Immunofluorescence studies revealed intense linear smooth positivity for kappa (4+) along the tubular basement membranes, glomerular capillary basement membranes, and the mesangium. In addition, a few proteinaceous

Table 3. Laboratory workup for renal function impairment.

Extended laboratory workup		
Urine creatinine	64 mg/dL	15-392
Urine protein	450.2 mg/dL	14-138
24-hours total U protein	8526 mg/24hrs	0-150
24-hours U α-1 globulin	4%	0
24-hours U α-2 globulin	24%	0
24-hours U albumin	39%	<100
24-hours U ß globulin	18%	0
24-hours U γ globulin	15%	0
HCV antibody	Negative	Negative
HCV Ab EIA	Negative	Negative
HBV Core Ab	Negative	Negative
HBV Bs Ab	Negative	Negative
C3 complement	93 mg/dL	90-180
C4 complement	24 mg/dL	10-40
ANA	Negative	Negative
DNA Ds	1 I.U/mL	0-9
cANCA	<1:20	<1:20
pANCA	<1:20	<1:20
Aldosterone	<1.0 ng/dL	0-30
Serum electrophoresis		
- Total protein	5.30 g/dL	6.00-8.00
- α-1 globulin	0.38 g/dL	0.10-0.40
- α-2 globulin	1.21 g/dL	0.60-1.00
-Albumin	2.41 g/dL	3.00-4.50
- ß globulin	0.82 g/dL	0.60-1.20
- γ globulin	0.47 g/dL	0.60-1.80
Immunoglobulins		
- IgA	37 mg/dL	70-400
- IgG	266 mg/dL	700-1700
- IgM	385 mg/dL	20-240
Protein/ creatinin ratio	7.0	
Metanephrine in plasma	<10 pg/mL	0-62
Normetanephrine plasma	178 pg/mL	0-145
Lambda light chain	14.1 mg/L	5.7-26.3
Kappa light chain	84.1 mg/L	3.3-19.4
ß2 microglobulin chain	13.5 mg/L	0.6-2.4
Kappa Lamda ratio	5.96	0.26-1.65

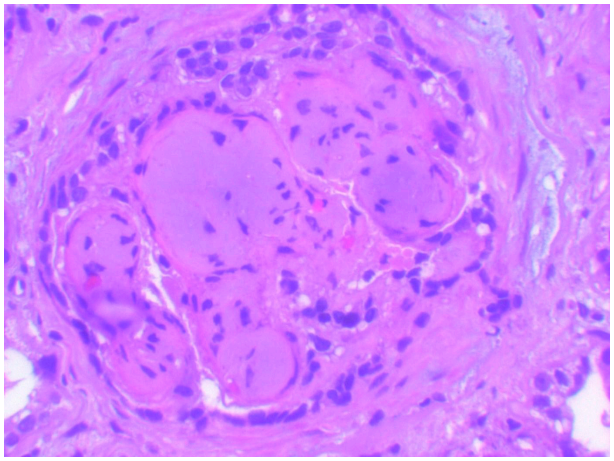

Figure 1. Hypocellular nodular mesangial expansion with complete obliteration of capillary loops

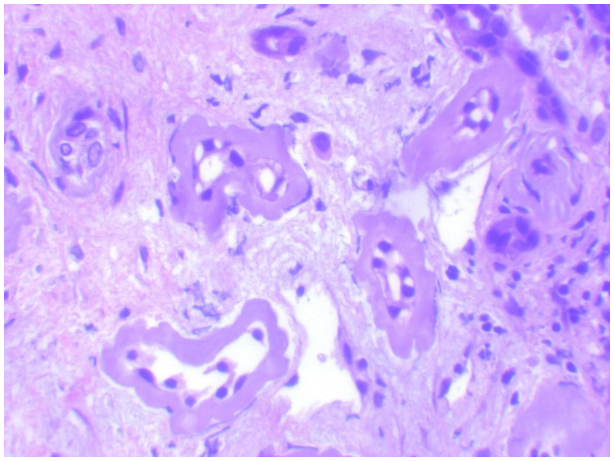

Figure 2. Eosinophilic amorphous deposits that involve the tubular basement membranes.

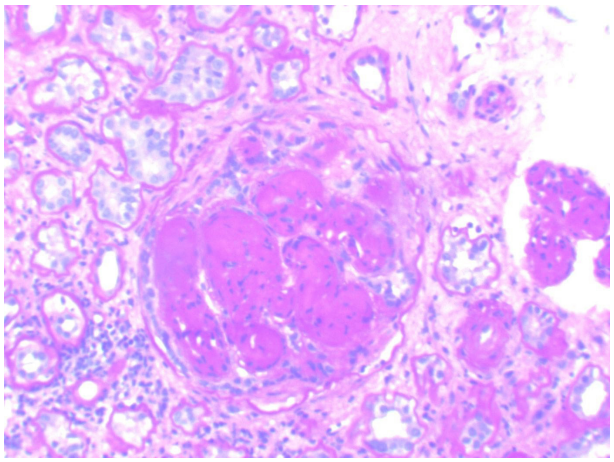

Figure 3. PAS positive staining of the mesangial nodules

casts stained strongly for kappa light chain (4+). The remaining Immunofluorescence stains were negative. The renal biopsy findings were interpreted as consistent with LCDD.

Bone marrow biopsy showed focal involvement of 30% with plasma cells and the flow cytometry demonstrated monotypic plasma cells expressing intracytoplasmic kappa light chain restriction with kappa to lambda ratio of 35/1. These finding were consistent with the diagnosis of LCDD.

The patient was started on steroids and bortezomib and was discharged to continue chemotherapy and intermittent hemodialysis.

Discussion

MIDD is an infrequent disease defined by the deposition of monoclonal light and/or heavy chains of immunoglobulins. Reports about MIDD show variable incidence, however, it remains rare (0.33% of all kidney biopsies over 18-years) (5). MM is considered as the most common underlying cause for MIDD. Sometimes, the manifestation of LCDD leads to the diagnosis before the occurrence of other clinical features of dysproteinemia and is the presenting characteristic preceding the diagnosis of MM. As a general rule, MIDD presents in the 5th to 6th decade of life, however, earlier manifestation in about 30% of the cases has been reported. Male predominance has been described (1,3). Hypertension and kidney failure are initial features that accompany LCDD (80% and >90%, respectively). However, dialysis at presentation is seen in only 16%. LCDD can occur in few cases in combination with cast nephropathy and is usually a severe form, compared with LCDD alone (1). Monoclonal immunoglobulin deposition in the glomerular basement membranes (GBM) and tubular basement membranes (TBM) is the histopathological feature of renal involvement. The light microscopy examination of the kidney biopsy shows acellular, nodular glomerulosclerosis. The glomeruli appear enlarged with nodular infiltration of the mesangial matrix as well as with cellularity. These nodules

are eosinophilic and PAS positive, but negative with Jones' methenamine positive and Congo red stains. Nodular glomerulosclerosis in LCDD on light microscopy seems to be similar to nodules presented in other glomerular diseases, including diabetic nephropathy, membranoproliferative glomerulonephritis, amyloidosis, and fibrillary glomerulonephritis. Nevertheless, nodules of MIDD do not color with Congo red and silver stain, which differentiates it from amyloidosis (Congo red positive) and diabetic nephropathy (Jones' methenamine positive), respectively (5). The GBMs appear thickened, radiant, and taut. The extraglomerular diversities involve "ribbon like" expansion of TBMs and the vessel surface (6). The interstitium demonstrates varying amount of infiltrate and interstitial fibrosis.

Hematuria may be seen due to the presence of tubular RBC casts associated with the interaction of penetrated RBCs with Tamm-Horsfall protein. These RBCs can produce an inflammatory response causing damage of the tubulointerstitium (7).

Monoclonal immunoglobulins which deposit in GBMs and TBMs are pathognomonic of MIDD. In LCDD, kappa light chain depositions are found more than lambda light chain (κ:λ= 4:1). Electron microscope analysis reveals flocculent to granular to powdery electron-dense deposits in the GBMs (100%), mesangium (96%), TBMs (96%), interstitium (18%), and vascular basement membranes (78%) (6).

Treatment goal in MIDD is to control plasma cell proliferation, maintain kidney function and enhance survival by using chemotherapeutics and autologous hematopoietic cell transplantation. Therapy of non-myeloma LCDD remains unclear; chemotherapy with alkylating drugs and steroids showed limited improvement. Bortezomib has been tried with success in subjects with LCDD with other chemotherapeutics (8). The age at presentation and serum creatinine are valuable prognosticators of kidney survival, while, age and the presence of MM are predictors of overall survival (9).

Recurrence of the disease may occur despite renal transplantation. In more than 70% of the cases a loss of the graft can be seen. Accordingly, transplantation should be achieved only after accomplishing complete remission (10).

Conclusions

In summary, MIDD is a rare disease. LCDD accounts for more than 80% of the cases. MIDD is more frequent in middle-aged than in elderly patients. However, clinical attention should be paid to a possible earlier occurrence. Typical presentation includes kidney failure, hematuria, proteinuria, and hypertension. Nephrotic syndrome is found less in LCDD compared to HCDD. Histopathologic features include nodular sclerosing glomerulopathy, which is seen in about 60% of the patients. Awareness for this disease increases the chances of recovery. Early diagnosis and treatment may result in favorable prognostic course of LCDD.

Authors' contributions

All authors wrote the paper equally.

Conflict of interests

The authors declared no competing interests.

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