Case Report

A Concurrence of Light and Heavy Chain Deposition Disease and Diabetic Nephropathy

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A 56-year-old female patient was clinically characterized by heavy proteinuria, anemia, hypertension, and no detectable monoclonal protein in serum or urine. She had a history of diabetes with retinopathy and hypertension. Histological investigation of renal biopsy specimens revealed nodular glomerulosclerosis. Light microscopic examination did not allow discrimination between diabetic glomerulosclerosis and monoclonal immunoglobulin deposition disease (MIDD). Immunofluorescent examination showed linear capillary wall and tubular basement membrane staining with kappa, and IgG staining. Electron-microscopic examination confirmed the amorphous material along the glomerular basement. Based on these findings, the diagnosis of light chain and heavy chain monoclonal immunoglobulin deposition disease (LHCDD) and diabetic nephropathy was made. At the present after the 7th course of melphalan and prednisolone treatment, her renal function and proteinuria have progressively improved.

Keywords: *Light and heavy chain deposition disease (LHCDD), Nodular glomerulosclerosis, Monoclonal protein, Diabetic glomerulosclerosis*

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Light and heavy chain monoclonal immunoglobulin deposition disease (LHCDD) was first reported in 1980 by Preud'homme *et al*[1]. LHCDD belongs to the disease entity of monoclonal immunoglobulin deposition disease (MIDD) together with light chain deposition disease (LCDD) and heavy chain deposition disease (HCDD) and is a variant of LCDD, showing similar clinicopathological pictures of LCDD. Reports of LHCDD are a rare entity with less than two dozen reported cases, in which the renal pathology files were reviewed retrospectively, and 5 cases of LHCDD, were identified among the 7241 cases (0.07%) processed during that time period[2]. Renal involvement is a constant feature of LHCDD and renal manifestations often dominates the clinical presentation. The patients have proteinuria and renal insufficiency. Renal function deteriorates rapidly in most patients to end stage renal disease. The number of LHCDD cases is too few to draw conclusions about treatment. Here, the authors report a case of renal biopsy proven LHCDD without monoclonal proteinuria or marrow plasmacytosis in the setting of a diabetic patient. Renal function of the patient remained stable while clinical hypervolemia, hematuria, and proteinuria were partially improved by conventional chemotherapy treatment.

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Case Report

A 56-year-old female patient visited the outpatient clinic with a 3-week history of anorexia, lassitude, foamy urine, and generalized edema. The past medical history was notable for diabetes with proliferative diabetic retinopathy and hypertension. Her medications included enalapril 20 mg daily, felodipine 10 mg daily, glimepiride 2 mg daily, metformin 500 mg twice daily, fenofibrate 200 mg daily and simvastatin 40 mg daily. Her blood pressure was 183/108 mmHg with a pulse of 68/min, and fundi showed retinopathy consistent with diabetes. Physical examination showed a hypervolemic patient and mild pale conjunctivae. There was no lymphadenopathy, and her heart, lungs,

abdomen, and skin were normal. The lower legs showed moderately pitting edema. The initial laboratory work-up showed hemoglobin 9.3 g/dL, white blood cell count 8,370/mm^3, platelet count 188,000/mm^3, serum creatinine 2.1 mg/dL, serum albumin 2.0 g/dL, globulin 2.8 g/dL, serum cholesterol 249 mg/dL, serum triglyceride 463 mg/dL, serum calcium 7.8 mg/dL and plasma glucose 170 mg/dL. Urinalysis revealed red blood cells 10-15 and white blood cells 0-1 per high power field, 3+ albumin, and a 24-hour urine protein was 8.1 g/day. Serological investigations were negative for antinuclear antibodies, antineutrophil cytoplasmatic antibodies, hepatitis B and C. Complement factors CH50, C3, and C4 were all normal. Further laboratory tests were as follows: urine was positive for urine Bence Jones protein, serum, and urinary protein electrophoresis showed no qualitative abnormality. Quantitative assessment of IgG, IgA and IgM in blood was normal (IgG 10.4 g/L, IgA 2.4 g/L, IgM 0.9 g/l). Renal sonography showed normal-sized kidneys without signs of obstructive uropathy. No lytic lesion was detected on the skeletal survey. Bone marrow examination revealed erythroid hyperplasia with normal range of plasma cells. A percutaneous renal biopsy was performed.

Renal biopsy findings

Light microscopy

Glomeruli showed markedly increase in mesangial matrix with moderately increased in mesangial cellularity with nodular formation (Fig. 1). Glomerular basement membranes were thick. There were segmental endocapillary proliferation and splitting of capillary basement membranes. No spike was discernable. There were no glomeruli with segmental sclerosis. There was interstitial fibrosis involving approximately 20% of the biopsy tissue with proportional tubular atrophy. Tubular basement membranes were thick with reduplication. Arterioles showed mild hyalinosis and interlobular arteries showed marked intimal fibrosis.

Immunofluorescence

There were 2+ diffuse linear capillary wall and tubular basement membrane kappa staining (Fig. 2), and 1 to 2+ IgG staining (Fig. 3) in the same pattern with kappa. IgA, IgM, Lambda, C1q and fibrinogen were negative.

Electron microscopy

Glomerular basement membranes (GBMs) were corrugated and markedly increased in thickness due to numerous amorphous and punctuate materials

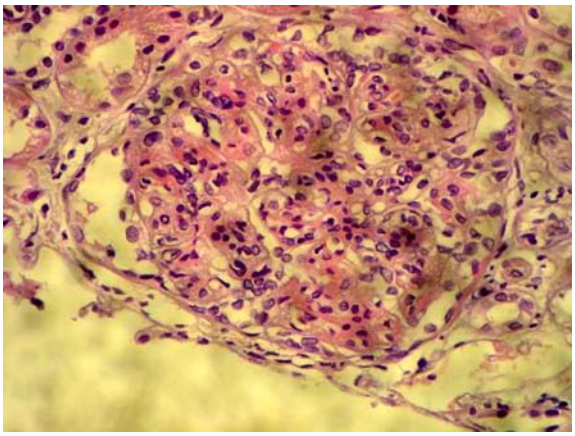

Fig. 1 A glomerulus with increased in mesangial matrix and cellularity with nodular formation. There is segmental capillary proliferation, H&E, x400

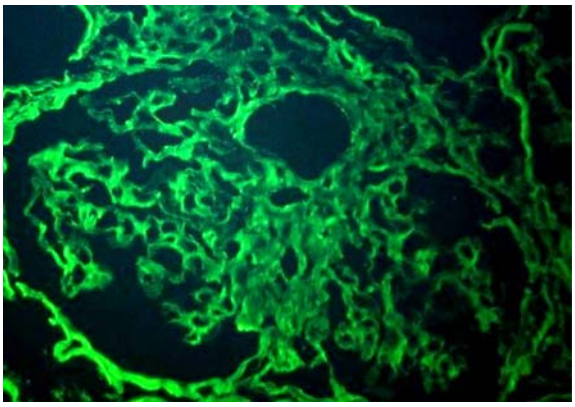

Fig. 2 Linear capillary wall and tubular basement membrane staining with anti-kappa light chain, x400

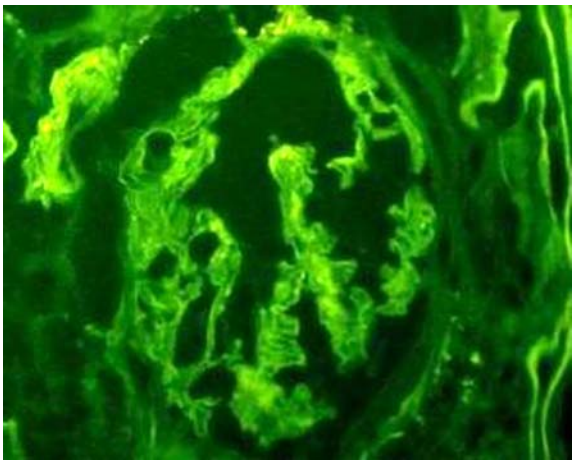

Fig. 3 Linear capillary wall and tubular basement membrane staining with anti-IgG, x400

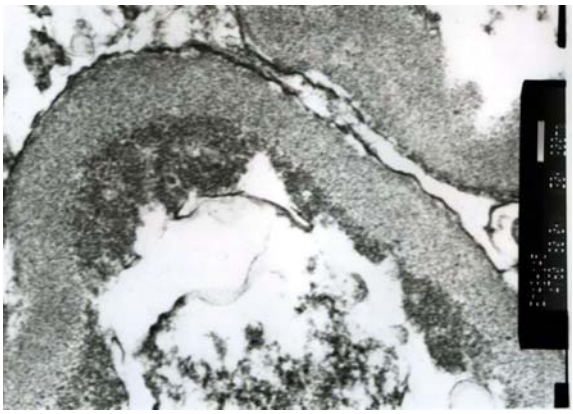

Fig. 4 Amorphous materials in mesangial and subendothelail areas, TEM, x9000

along subendothelial areas (Fig. 4). No fibril was seen. There was complete foot process effacement. Mesangium was markedly wide with occasional amorphous material. Based on pathological findings, the diagnosis of LHCDD and diabetic nephropathy were made.

Clinical outcome

The clinical course of the patient is summarized in Figure 5. After diagnosis, her renal function progressively deteriorated. She was treated initially with prednisolone 30 mg/day and mephalan 0.2 mg/kg/day every 5 days per month for 7 months. After the 2nd course of melphalan and prednisolone, her renal function remained stable while heavy proteinuria, hematuria and clinical hypervolemia were partially improved. At the present after the 7th course of melphalan and prednisolone, serum creatinine concentration was 2.5 mg/dL and 24 hr urine protein was 1.5 g/day. No extrarenal manifestations related to immunoglobulin deposits occurred or recurred in the presented patient, especially no further alteration of liver enzyme.

Discussion

The diagnosis of MIDD in this patient was suspected in the setting of nephrotic-range proteinuria, positive urine Bence Jones protein and nodular glomerulosclerosis. Nodular glomeruloscleosis is the

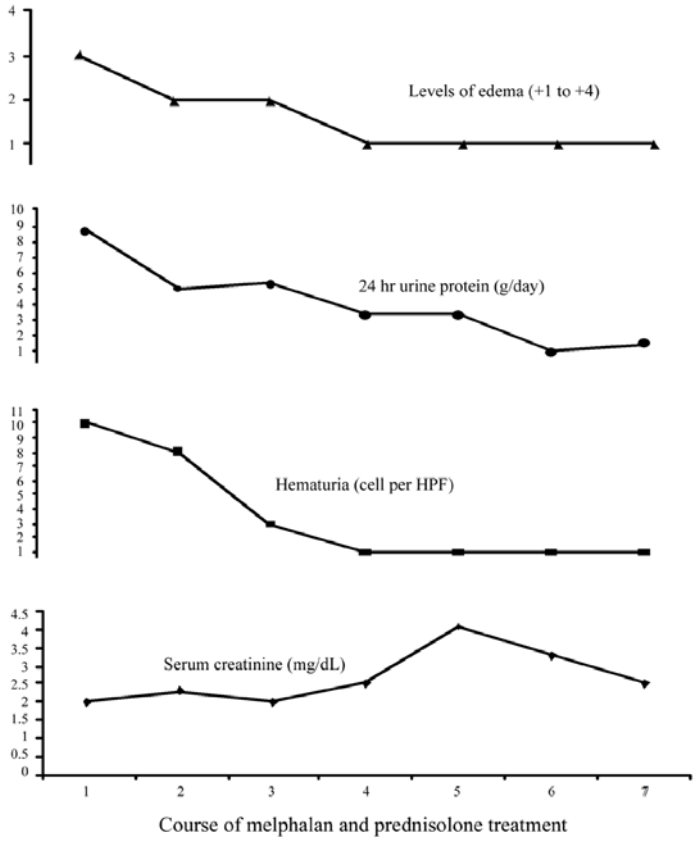

Fig. 5 Clinical course of patient was treated with chemotherapy (melphalan and prednisolone) once a month until 7th course

most characteristic of renal MIDD. However, nodular glomerulosclerosis has been described in association with diabetic nephropathy, multiple myeloma, membranoproliferative glomerulonephritis (MPGN), amyloidosis, fibrillary glomerulonephritis, and carbon disulfide (CS_2) poisoning. Other histological findings such as fairly regular distribution of the nodules, poorly argyrophilic nodule, no exudative lesions as "fibrin caps", and extensive hyalinosis of the efferent arterioles are also considered additional features of MIDD than diabetic nephropathy. However, the diagnosis of MIDD cannot be established by a simple light microscopic examination. First, Immunofluorescence examination of kidney is a key step in the diagnosis of MIDD. In LHCDD, Immunofluorescence analysis of the tissue deposits have revealed one class of heavy-chain (IgG) and one class of light-chain (kappa) staining in a diffuse linear pattern along the GBMs, in the nodules and a long the tubule basement membranes and vessel wall. As opposed to amyloidosis, approximately 80% of LCDD cases are composed of kappa rather than lambda light chains, they do not bind Congo red stain or thioflavine T. They do not contain the P component. Second, on the presence at the electron microscopy level, the deposits are electron-dense-amorphous material in the mesangial nodule and along the glomerular and tubular basement membranes.

Monotypic immunoglobulin is produced by a monoclonal B-cell clone, the burden of which may be variable. It may be associated with myeloma or other conditions, such as lymphoma or Waldenstrom's macroglobulinemia, but many patients have no evidence of any overt plasma cell dyscarsia[3]. Recently, Sakakima et al reported LHCDD patient with no monoclonal protein but also positive abnormal plasma cell surface markers without definite malignant hematological disease[4]. If these patients had long-term follow up, they may develop a symptomatic multiple myeloma. Some patients of MIDD have not demonstrated monoclonal protein by SPEP or UPEP as the presented patient[3]. At the time of renal biopsy, up to 30% of patients with renal MIDD have no detectable monoclonal protein in serum or urine[5,6]. This is because these monoclonal proteins may be detectable only intermittently or that they are found in serum and/or urine only in low concentrations. Additionally, abnormally structured immunoglobulins were rapidly degraded post synthetically or high affinity of these proteins for tissue deposit[5,6].

The clinical findings in the present case are similar to those reported previously in LHCDD[3]. Renal insufficiency, nephrotic-range proteinuria, hematuria and hypertension are the common finding in patients with LHCDD. MIDD is a systemic disease, but visceral light chain deposits may be totally asymptomatic. Liver deposits were constant in patients whose liver was examined[7]. Current data suggest that liver function abnormality may be more frequent in nonamyloid deposition, but liver failure and portal hypertension are rare. The presented patient showed mild alteration of liver function test but no evidence of portal hypertension.

Present treatment is based on eliminating the clonal plasma cells responsible for the production of the deposited protein. Chemotherapy for multiple myeloma has been applied for cases of MIDD. However, there is no consensus regarding chemotherapy, with potential severe side effects. Treatment with mephalan and prednisolone, as in amyloid, has led to stabilized or improved renal function in LCDD especially some patients with moderate impairment of renal function. In a large series of patients with renal MIDD, conventional chemotherapy (steroids plus melphalan or a cytotoxic agent) stabilized or improved renal function in 10 of 15 patients (67%) with pure MIDD who presented with creatinine of < 5.0 mg/dl[2]. However, recent advances in high dose therapy with stem cell support in young patients with LHCDD have improved renal and extrarenal manifestation due to L(H)C deposits and may prevent their progression without resulting in morbidity and mortality[8-9]. However, there are too few cases to draw conclusions about treatment. The presented patient was treated with melphalan and predisolone because she was pure MIDD with serum creatinine 2.1 mg/dL. She also had other co morbid diseases such as diabetes and hypertension, which may not be able to tolerate a high dose of chemotherapy and stem cell transplantation.

The prognosis for patients with LCDD is uncertain but appears to be better than that for amyloidosis. In most reported series, prognosis is poor especially in those who had renal failure. Reported median survival rates can range from 18 months to more than 5 years[10]. One series of patients, 5-year survival-free end stage renal disease was 37% and 82% of the patients, initially having a serum creatinine rate over 3.9 mg/dL progressed to end stage renal disease[7]. The only predictor of renal patient survival seems to be the initial serum creatinine at the time of biopsy. However, few data about survival in LHCDD, Lin et al reported a series of LHCDD in which mean renal and patient survival was 8 and 13 months, respectively, but

follow-up time of the present report was limited to 9.1 months[2].

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รายงานผู้ป่วย light and heavy chain deposition disease ร่วมกับ diabetic nephropathy

บัญชา สถิระพจน์, ไพสิฐ เผือกสกนธ์

ผู้ป่วยหญิงไทย อายุ 56 ปี มาโรงพยาบาลด้วยอาการปัสสาวะมีฟอง ขาบวม ซีด และความดันโลหิตสูง มีโรคประจำตัวเดิมคือ โรคเบาหวาน และความดันโลหิตสูง ได้ทำการตัดชิ้นเนื้อไตพบลักษณะทางกล้องจุลทรรศน์ธรรมดาเป็น nodular glomerulosclerosis ซึ่งไม่สามารถให้การวินิจฉัยแยกโรคระหว่าง diabetic glomerulosclerosis และ monoclonal immunoglobulin deposition disease (MIDD) ได้ จึงย้อมพิเศษทาง immunofluorescene พบ kappa และ IgG ติดเป็นแนวต่อเนื่องตาม capillary และ tubular basement membrane และตรวจทางกล้องจุลทรรศน์อิเล็กตรอนพบ amorphous material บริเวณ glomerular basement ดังนั้นจากลักษณะทางพยาธิสภาพของไตข้างต้นเข้าได้กับ light chain and heavy chain monoclonal immunoglobulin deposition disease ร่วมกับ diabetic nephropathy จึงได้ให้การรักษาด้วยยา melphalan และ prednisolone จำนวน 7 ครั้ง สามารถลดปริมาณไข่ขาวในปัสสาวะ และชะลอการเสื่อมของหน้าที่ไตได้
