Case Report

The Combination of Thrombotic Microangiopathy and Nodular Sclerosis in Light Chain Deposition Disease

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The authors reported the first case of nodular glomerulosclerosis, mesangiolysis, and thrombotic microangiopathy in a 69-year-old Thai man with chronic glomerulopathy from light chain deposition disease associated with multiple myeloma and kappa monoclonal gammopathy. He presented with subacute onset of generalized edema, hypertension, and renal insufficiency. Blood examinations revealed kappa monoclonal gammopathy. The diagnosis of multiple myeloma was confirmed by bone marrow aspiration and biopsy. The renal pathologies demonstrated specific findings for light chain deposition disease which were type II nodular glomerulosclerosis, strongly PAS-stained tubular basement membrane, monotypic-kappa light chain deposition along tubular and glomerular basement membranes, and granular electron dense deposits in electron microscopy. However, the authors also found the concomitant findings of mesangial and endothelial injuries which were mesangiolysis and thrombotic microangiopathy. Of interest, type II nodular sclerosis and thrombotic microangiopathy were caused by the same cell injury. These might shed new light on the pathogenesis of glomerular injury in monoclonal immunoglobulin deposition disease (MIDD).

Keywords: *Light chain deposition disease, Thrombotic microangiopathy, Mesangiolysis, Nodular glomerulosclerosis*

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Light chain deposition disease (LCDD) is a systemic disease characterized by the deposition of monoclonal immunoglobulin light chain in kidneys and various organs. The authors report a rare form of renal involvement by immunoglobulin light chain and thrombotic microangiopathy in an elderly man, who subsequently was found to have multiple myeloma.

Case Report

A previously healthy 69 year-old male presented with progressive leg and testicular swelling. His first laboratory exams at a local hospital revealed the serum creatinine of 2.26 mg/dL and urine protein semi-quantitation 4+/4+. The patient was referred to the King Chulalongkorn University Hospital for evaluation of the cause of his renal insufficiency. The initial physical examination showed hypertension (BP 170/110 mmHg) and generalized edema. He had neither palpable lymphadenopathy nor organomegaly. The serum creatinine was 2.6 mg/dL and subsequent rising to the level of 3.0 mg/dL and a 24-hr urinary protein level of 3.83 gm. A complete blood count revealed hemoglobin of 9.0 g/dL, WBC of 12,730/mL, and platelet count of 255,000/mL. A urine screen demonstrated active urine sediments and no Bence-Jones protein. His additional laboratory examination included serum albumin of 2.8 g/dL, globulin of 1.5 g/dL, blood sugar of 83 mg/dL, cholesterol of 226 mg/dL, triglycerides of 326 mg/dL, and normal liver and thyroid function tests. Tests for anti-nuclear antibody, antineutrophil cytoplasmic antibodies were negative, and complement levels (C3 and C4) were in the normal range. Testing for HIV, viral

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hepatitis and cryoglobulins were also negative. KUB ultrasonography delinated normal kidney sizes, normal parenchymal echogenicity, and minimal ascites. During work up, the patient was admitted due to pulmonary edema and increasing peripheral edema. His urine volume approached the level of oliguria. The echocardiography was performed and showed concentric ventricular hypertrophy (LVEF 70%) with mild diastolic dysfunction and pulmonary hypertension. An electrocardiography revealed a normal rhythm at a rate of 76/min, normal voltage with non-specific ST-T wave abnormalities. A chest radiography indicated slight cardiac enlargement and a moderate increase in bilateral pleural effusion compared with previous radiography.

Pathologic Findings

Light Microscopy

Light microscopy of the renal biopsy illustrated marked widening of glomerular mesangium with acellular material rending union-skin nodular appearance. The mesangial nodules were PAS positive and blue in Masson stain. The glomerular cellularity was increased at the peripheral loops accompanied by endocapillary proliferation and leukocyte infiltration. Segmental microanuerysm was present in all glomeruli but 5 which were global sclerosis. Half of them also showed focal discontinuity of the basement membranes of the glomerulus and the Bowman's capsule. Jones silver stains highlighted the broken basement membrane. Diffuse interstitial fibrosis and tubular atrophy were associated with minimal interstitial infiltration of mononuclear inflammatory cells. The renal tubule showed diffuse irregular thickening of the basement membrane. A few tubules contained red blood cells and RBC casts in lumina. One glomerular arteriole had intraluminal obstruction with fibrin thrombus and mucoid edema. One interlobular artery showed reduplication of the internal elastic lamina.

Immunofluorescence

Frozen sections exposed to fluorescein-labeled antibodies directed against IgG, IgM, IgA, C3, C1q, fibrinogen, and polyvalent immunoglobulins revealed moderately intense ribbon-like linear fluorescence in the glomerular and tubular basement membranes with the anti-kappa conjugates. The majority outline of the glomerular capillary loops was also stained with C3.

Electron Microscopy

The mesangiums were marked expansion. Some of them formed an onion-skin nodule. The patent capillary loops were present at periphery. These patent capillary loops were focally dilated and focally thickening of lamina densa with a "granular -powdery" ultrastructural appearance. Segmental wrinkling and collapsed capillary loops were encountered. Epithelial foot process effacement with microvillous transformation was diffusely present. No electron deposits were detected. The tubular basement membrane was irregularly thickened without electron dense deposits similar to those observed in the glomerular basement membrane.

To investigate the possibility of an associated hematologic or lymphoid malignancy, bone marrow aspiration and biopsy, whole body bone scan, and serum protein electrophoresis were performed. The bone scan showed multiple lytic lesions at the right clavicle as well as at both sides of the inferior pubic rami. Serum immuno-electrophoresis revealed an abnormal bulging band of kappa light chain. Urine remained negative for Bence-Jones protein and immuno-electrophoresis. A bone marrow examination revealed normal trilineage with focal deposition of amorphous material in vascular walls and markedly increased mature plasma cells. Some of the cells aggregated and built a sheet-liked formation. Many of which were stained with CD138. A final diagnosis of multiple myeloma with monoclonal light chain gammopathy was established and the patient was treated with Vincristine, Adriamycin, and Dexamethasone (VAD) regimen. After chemotherapy treatment, he developed tumor lysis syndrome and was dialysis dependent. The VAD regimen was stopped and dialysis was continued. A month later, the patient was re-admitted with acute respiratory distress syndrome, multi-organ failure, and death from septicemia. No autopsy was performed at the request of his family.

Discussion

Monoclonal immunoglobulin deposition disease (MIDD) is characterized by renal parenchymal deposition of complete or partial monoclonal immunoglobulin components and by exclusion of renal amyloid. The MIDD is subcategorized into 3 entities: 1) light chain deposition disease (LCDD); 2) light chain and heavy chain deposition disease (LHCDD); and 3) heavy chain deposition disease (HCDD). LCDD is the most common and most characterized form of MIDD; unlike light chain amyloidosis, kappa light chains predominate in LCDD. The depositions in all MIDDs are non-organized, non-Congophilic, but electron-dense deposits, which have a characteristic "granular -powdery" ultrastructural appearance as noted in our patient. The

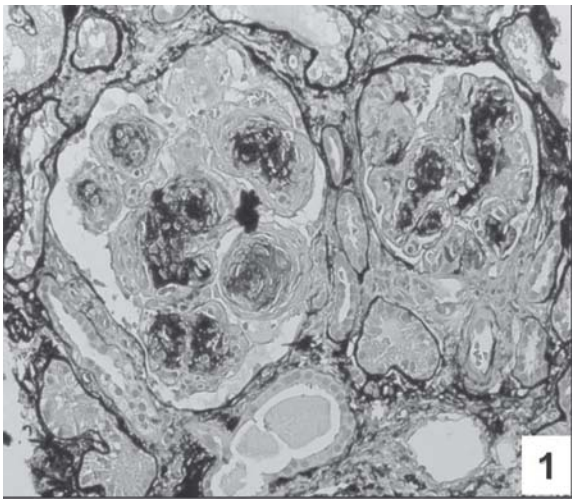

Fig. 1 Nodular glomerulosclerosis; nodules are fairly regular distribution (Jones silver, original magnification 200)

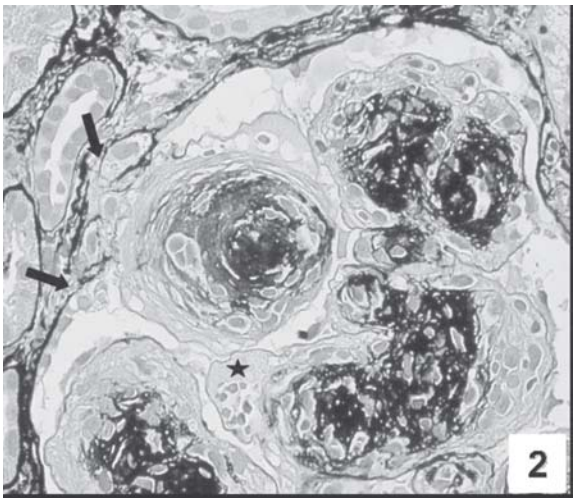

Fig. 2 "Type II lesion" as described by Kubo: characterized by peripheral lamellate nodule rending union-skin nodular appearance together with mesangiolysis and anuerysmal formation (star). Broken Bowman's capsule and peripheral adhesion is also seen (black arrow). (Jones silver, original magnification 400)

deposits in MIDD are located within basement membrane throughout the kidney, including glomerular, tubular, and the vessel wall depending on composition of the deposit and the subtypes of MIDD. In fact, light microscopic findings in MIDD are fairly heterogeneous varied from nearly normal, mesangial matrix expansion or cell proliferation, nodular sclerosis, membranous like, mesangiocapillary like, and crescent formation[1,2]. Hence, the diagnosis should inevitably rely on the immunofluorescense finding of monotypic kappa or lamda light chain deposit along tubular basement membranes. The most characteristic tubular findings are the deposition of a refractive, eosinophillic, PAS-positive, ribbon like material along the tubular basement membrane[1].

In a recent biopsy series from 121 patients who had monoclonal gammopathy, 14 of them had LCDD. By light microscopy, nodular mesangial sclerosis was the most common finding (13 of 14 cases). None of 121 patients had thrombotic microangiopathy[3]. In fact, microangiopathies are unusual findings in MIDD patients. To the authors' knowledge, this is the first report of thrombotic microangiopathy in an MIDD patient. The coexistence of 2 different entities will shed light on the pathogenesis of the light chain deposit since the mechanism of glomerular injury after light chain deposits remains inconclusive. This was supported by an unexpected result after injection of human monoclonal light chain into the mice done by Solomon[4]. He found a conspicuous amount of light chain deposits along basement membrane without consequent pathologic lesions. Thus, the amount of deposition does not reflect pathogenicity[5]. Kubo et al[6] described 2 types of glomerular nodules: 1) type I lesion is caused by nodular expansion of the mesangium; and 2) type II lesion is characterized by peripherally lamellate and is ascribed to repeated mesangiolysis as the findings in the presented patient (Fig. 2). Churg et al[7] hypothesized that "type II" lesion results from relatively mild but persistent or repeated mesangial and/or endothelial damage. The long standing condition can induce repeat local mesangiolysis[8], which is usually aided by other concomitant factors, such as changes of intraglomerular pressure. Thrombotic microangiopathy is renowned as an endothelial injury model of the kidney. Of interest, two entities are caused by injury of the same cell. In fact, the presented patient was a unique model and lead the way for the future testing of pathogenesis of glomerular injury in MIDD.

Conclusion

The combinations of thrombotic microangiopathies, mesangiolysis, and type II nodular sclerosis are unusual findings but might shed new light on the pathogenesis of glomerular injury in MIDD.

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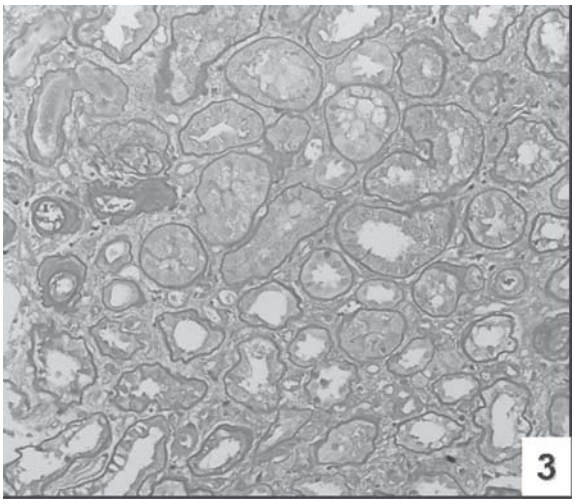

Fig. 3 The renal tubules show diffuse PAS-positive irregular thickening of the basement membrane (PAS, original magnification 200)

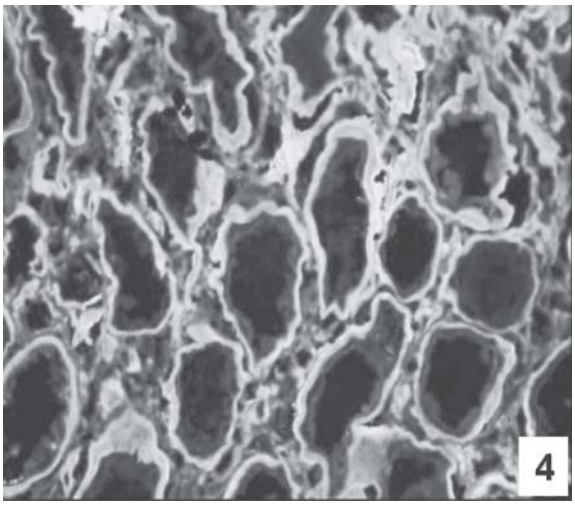

Fig. 4 Moderately intense ribbon-like linear peritubular deposits of monotypic kappa light chain as hallmark characteristic finding (IF, original magnification 400)

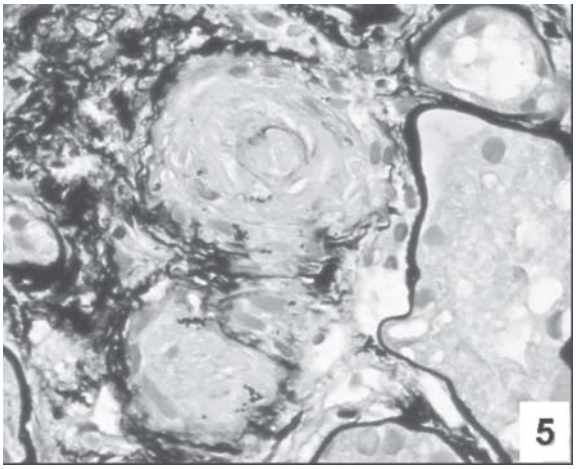

Fig. 5 Obliterated arteriole with intimal mucoid change: characteristic lesion of thrombotic microangiopathy (H&E, original magnification 400)

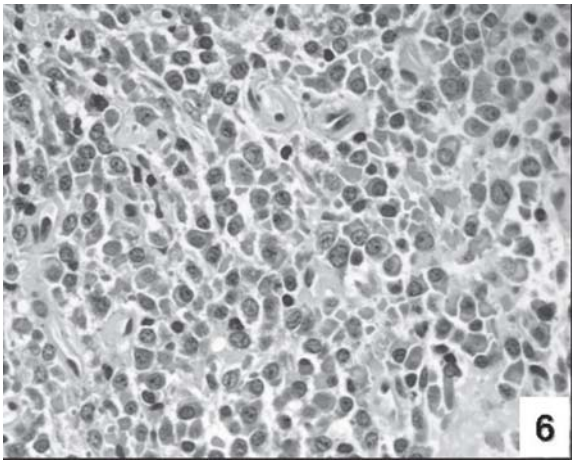

Fig. 6 Markedly increased mature plasma cells. Some of the cells aggregated and built a sheet-liked formation

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รายงานผู้ป่วย light chain deposition disease ที่มี thrombotic microangiopathy

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รายงานผู้ป่วยรายแรกที่มีการตรวจพบ thrombotic microangiopathy ร่วมกับ mesangiolysis และ nodular glomerulosclerosis ใน multiple myeloma ชนิดที่เป็น kappa monoclonal light chain gammopathy โดยผู้ป่วยรายนี้เป็นเพศชาย อายุ 69 ปี มาพบแพทย์ด้วยอาการบวมที่ขาทั้ง 2 ข้าง ความดันโลหิตสูง และไตวาย ผลตรวจทางห้องปฏิบัติการบ่งชี้ว่าผู้ป่วยมี kappa monoclonal gammopathy ในกระแสเลือด และพบลักษณะทางพยาธิวิทยาที่จำเพาะกับภาวะ light chain deposition disease จากการตรวจชิ้นเนื้อไตพิสูจน์โดยการพบ nodular glomerulosclerosis ชนิดที่เรียกว่า "type II lesion" ร่วมกับการสะสมของสารสีแดงที่ติดสี periodic acid Schiff ตามแนวของ tubular basement membrane และที่น่าสนใจคือการตรวจพบ mesangiolysis และ thrombotic microangiopathy ร่วมด้วย ซึ่งทั้งสองลักษณะช่วยบ่งชี้ว่าพยาธิสภาพของผู้ป่วยน่าจะเกิดจากการบาดเจ็บของเซลล์เยื่อบุผนังหลอดเลือด โดยสอดคล้องกับการตรวจพบ "type II lesion" ด้วยเหตุที่ตรวจพบลักษณะทางพยาธิสภาพร่วมกันระหว่าง type II nodular sclerosis และ thrombotic microangiopathy อาจช่วยเปิดเผยความลับของกลไกการบาดเจ็บของเซลล์เนื้อไตหลังจากการสะสมของสาร light chain ได้ในอนาคตข้างหน้า