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CASE REPORT

Acute cerebral infarction in a patient with nodular glomerulopathy—Atypical features and differential diagnosis

急性腦動脈梗於結節型腎病變 — 特殊病理表現與鑑別診斷

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關鍵詞
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結節性腎絲球病變;
腎病症候群;
動脈梗塞

Abstract Nodular glomerulopathy is a pattern of glomerular injury observed under light microscopy that could result from several diseases presented as nephrotic syndrome clinically. Compared with venous thrombosis, cerebral infarction resulting from arterial thrombosis is relatively rare in these patients. We report an interesting case of severe nephrotic syndrome complicated with acute cerebral infarction, and renal biopsy revealed nodular glomerulopathy under light microscopy. Immunofluorescent staining was positive for λ light chain (predominant) and κ light chain, mainly in mesangial areas, and electron microscopic study showed massive amorphous acellular deposits also in mesangial areas with some local extension to subendothelial space. Congo red stain gave negative results under polarized light. The case was concluded as an atypical presentation of light chain deposition disease both pathologically and clinically.

摘要 結節性腎絲球病變為腎絲球遭受傷害的所表現的一種形態，可能由某些特定疾病所導致，臨床表現為腎病症候群，相較於較常見的靜脈栓塞；以中風來表現的急性動脈梗塞是相對少見的。我們報告一位嚴重腎病症候群併發急性腦梗塞的病人，腎臟切片結果於光學顯微鏡下顯示為結節性腎絲球病變的型態，螢光染色顯示免疫λ和κ輕鏈陽性反應，而以λ輕鏈為主，主要沉積於腎間質區，電子顯微鏡下顯示大量免疫複合體沉積於腎間質區，部分延伸至腎絲球血管下。剛果紅染色於偏光鏡下為陰性反應，病理上確診為免疫球蛋白輕鏈沉積病變，其沉積型態與以往報告過的不同，於臨床上和病理上皆為較特殊的表現。

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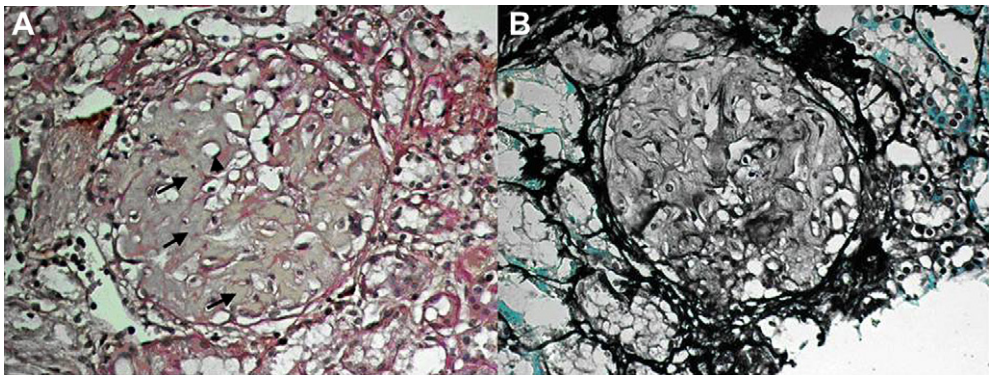

Figure 1. Light microscopy showed negative PAS stain [(A) PAS stain, 400×] and negative silver stain [(B) silver stain, 400×] amorphous, acellular deposits in mesangial area (arrows), with further narrowing of capillary lumen (arrow head).

Case presentation

A 72-year-old female patient first visited our clinic in September 2007 because of edema of lower legs and foamy urine for more than 2 months. She denied any systemic diseases except cholecystectomy 15 years ago for gall bladder stones.

Her blood pressure was 126/90 mmHg, pulse rate was 84 beats/min, body weight was 52 kg, and physical examination revealed only a moderate degree of edema over the lower extremities. Serial examination showed serum albumin of 1.80 g/dL, serum cholesterol and triglyceride of 556/349 mg/dL, and daily protein loss of 12 g. Other laboratory studies showed the following: blood glucose, 90 mg/dL; blood urea nitrogen, 14 mg/dL; serum creatinine, 0.91 mg/dL; phosphate, 3.9 mg/dL; ionized calcium, 4.84 mg/dL; aspartate transaminase, 28 U/L; alanine transaminase, 15 U/L; sodium, 138 mmol/L; potassium, 4.3 mmol/L; and uric acid, 4.8 mg/dL. Hematocrit was 39.1%, platelet count was 238,000/uL, and white blood cell count was 6,080/uL. Other findings included serum immunoglobulin gamma (IgG), 396 mg/dL; immunoglobulin A (IgA), 419 mg/dL; immunoglobulin M (IgM), 104 mg/dL; C3, 122 mg/dL; and C4, 29.1 mg/dL. Serum antinuclear antibody was negative. Prothrombin time was 10.1/11.1 s, and partial thromboplastin time was 27.9/29.5. Both hepatitis B surface antigen (HBsAg) and anti-hepatitis C (HCV) antibody were negative.

Ultrasonographic examination revealed kidneys of normal size with slightly irregular surface. Renal biopsy was performed and, under light microscopic examination, the renal core was found to contain 13 glomeruli. Most glomeruli showed increased amorphous acellular substance in the glomerular mesangium, without significant tubulointerstitial changes (Fig. 1). Immunofluorescence (IF) study showed negative staining for IgG, IgM, IgA, C3, C4, and fibrinogen, but positive staining for λ light chain (predominant) and κ light chain, mainly in mesangial areas (Fig. 2).

Electron microscopic (EM) study showed massive amorphous acellular deposits in mesangial areas with some local extension to subendothelial space, causing relative narrowing of the capillary lumen but without mesangial or endothelial proliferation. The glomerular basement membrane (GBM) was not thickened, and the foot processes were only focally effaced. Some lipid droplets could be seen in podocytes, compatible with severe proteinuria in clinical presentation (Fig. 3A and B). Under high-power examination, poorly organized materials and scattered coarse granules (Fig. 3C) were found, which, by definition, could only be classified as monoclonal immunoglobulin deposition disease, and was further classified as light chain deposit disease (LCDD) according to the immunofluorescent staining of light chain.

Albumin infusion along with diuretics (oral furosemide 40 mg/d and spironolactone 25 mg, three times a day) was given for symptomatic therapy of edema. The response was fair with urinary output of 1200 mL/d and a decrease in body weight of 6 kg within 1 week. Pentoxifylline, 400 mg twice daily, and rosuvastatin, 10 mg once daily, were also

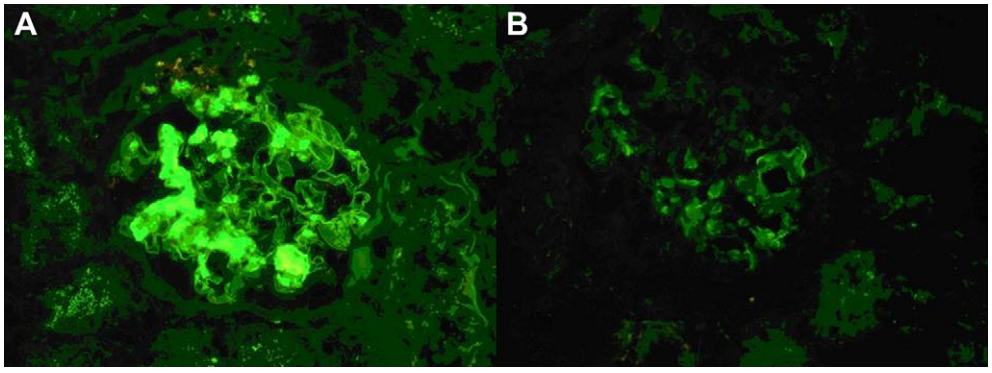

Figure 2. Immunofluorescence study revealed a strong positive reaction of λ light chain with mesangial distribution [(A) anti-λ, 400×] and weak positive reaction for κ light chain [(B) anti-κ, 400×].

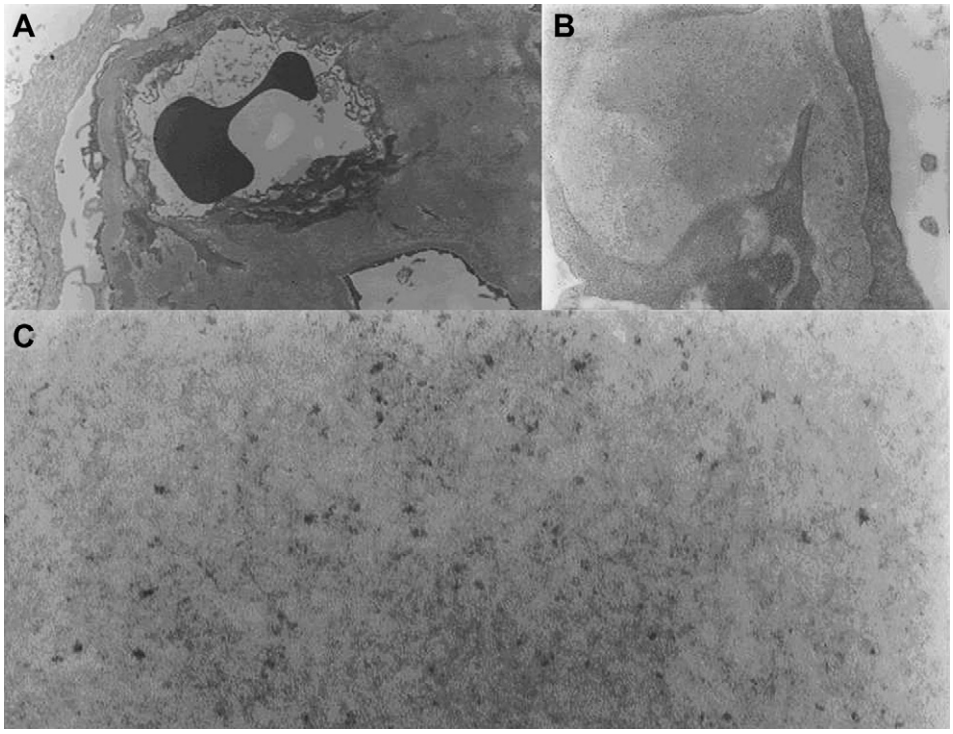

Figure 3. Electron microscopy showed compatible amorphous deposits in mesangial area extending to capillary loops with prominent subendothelial distribution [(A) 4,000×, (B) 30,000×]. No fibrillar organization deposit was found [(C) 100,000×].

given for prevention of thromboembolism and control of hyperlipidemia.

Unfortunately, she suffered acute onset of mutism and weakness over right limbs after a bath at home several days later. Inability to name things or even family members was observed. Owing to progressive worsening, she was sent to hospital again. Serial image study later revealed acute infarction over the left frontal lobe (Fig. 4), and her body weight was 48 kg. The clinical course stabilized after holding diuretics and giving hydration. However, Broca's aphasia and mild right limb weakness remained, and further rehabilitation was needed.

We carried out both serum and urine immunofixation electrophoresis and bone marrow aspiration for excluding possible multiple myeloma, and only nonspecific findings with plasma cells of less than 10% was found. Prednisolone (1 mg/kg/d) was given, and the daily protein loss decreased to 5.2 g. Aspirin was also given for prophylaxis of further thromboembolic events.

Discussion

This is an unusual case of nodular glomerulopathy complicated with acute cerebral infarction. Many factors contribute to hypercoagulability of nephrotic syndrome. They included the following: (1) decreased fibrinolytic activity because of marked urinary loss of related proteins (e.g. plasminogen) [1]; (2) compensatory increased high—molecular weight procoagulatory cofactors (e.g. Factors V, VII, and VIII) because of increased urinary loss of low—molecular weight factors; and (3) dysfunction or depletion of regulatory proteins of coagulation, such as Antithrombin III; debates exist although normal or high level have all been reported [2]. However, arterial occlusion is still relatively rare compared with venous thrombosis in adults with nephrotic syndrome and has been reported only sporadically [3,4]. As reviewed from the literature, the most important predisposing factors included severe hypoalbuminemia (<2.0 g/dL) and/or diuretics used; histological evidence of membranous nephropathy was frequently recognized as a predominant

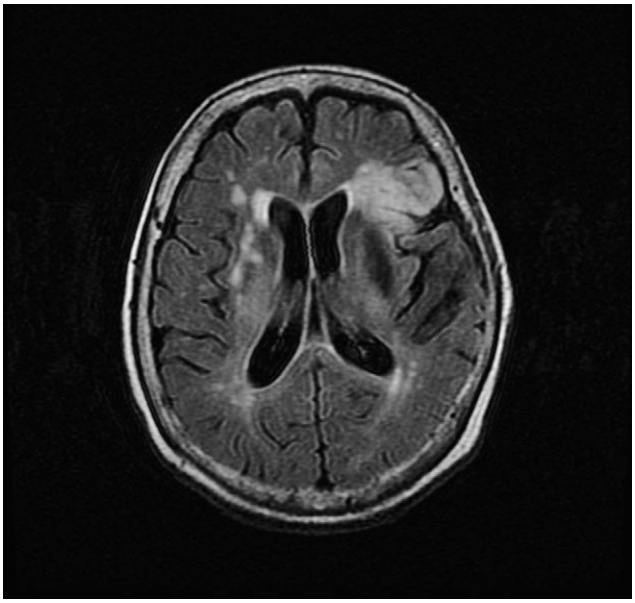

Figure 4. Diffusion-weighted magnetic resonance imaging study showed high signal intensity on left frontal lobe, compatible with acute cerebral infarction.

Table 1 Characteristics of common glomerular deposition diseases

Diseases	Etiology	Congo red stain	Light microscopic features	Immunofluorescence	Electron microscopy
Diabetic nodular sclerosis	Diabetes mellitus	Negative	Mesangial expansion and GBM thickening Arterial hyalization、Interstitial fibrosis Glomerulomegaly Nodular sclerosis with PAS stain (+) and silver stain (+)	Linear IgG along GBM Nonspecific trapping of IgM and C3 in sclerotic area	Homogenous thickening of GBM, occasional electron-dense hyaline material in mesangium
Amyloidosis	Lymphoproliferative disease Secondary to chronic inflammation	**Positive**	Acellular amorphous pink hyaline material Deposition mainly in mesangial area Occasionally feathery spikes because of GBM reaction in peripheral capillary loop Nodular lesion with PAS stain (−) and silver stain (−)	Smudgy deposition of light chain in mesangial area (AL amyloidosis) Predominant λ light chain	Organized, randomly oriented nonbranching fibrils; diameter, 8—12 nm
Fibrillary glomerulonephritis	Lymphoproliferative disease	Negative	Mesangial proliferation or diffuse endocapillary proliferation, occasionally with crescents, might GBM splitting Nodular lesion with PAS stain (+) and silver stain (+)	Predominant IgG and C3, chunky segmental staining along GBM and mesangium	Organized randomly arranged fibrils; diameter average, 20—22 nm
Immunotactoid glomerulonephropathy	Lymphoproliferative disease	Negative	Mild mesangial hypercellularity, might cause GBM splitting. Nodular lesion with PAS stain (+) and silver stain (+)	Predominant IgG and C3, chunky、irregular along capillary loops and in the mesangium	Regularly, parallelly arranged fibrils: diameter, 30—50 nm
Monoclonal immunoglobulin deposition disease	Lymphoproliferative disease	Negative	Nodular glomerulosclerosis, various degrees of mesangial proliferation and expansion, PAS stain (+) and silver stain (−)	Tubular basement membrane and GBM linear staining, usually κ light chain	Nonorganized granular deposits, usually along subendothelial region
MPGN、Lupus nephritis	Infection、autoimmune、idiopathic	Negative	Mesangial hypercellularity and mesangial matrix expansion, GBM duplication Nodular lesion with PAS stain (+) and silver stain (+)	C3, C1q, IgG, IgM deposition in capillary walls and mesangium	Nonorganized subendothelial electron-dense deposits

Bold term represents only amyloid fibrils have affinity with congo red stain.

type of nephrotic syndrome leading to thrombotic events, although other types of glomerulopathy (e.g. minimal change disease、focal segmental sclerosis) have been noticed.

There has been no case report on cerebral infarction complication in patients with LCDD-related nephrotic syndrome; perhaps, because it is a relatively rare cause of nephrotic syndrome, and the renal damage is heterogeneous, depending on the sites of light chain deposits. Patients with predominant tubular deposition may present with renal dysfunction and only mild proteinuria, whereas those with predominant glomerular deposition may present with marked protein loss because of severe glomerular destruction, such as that in our case. Our patient had severe hypoalbuminemia (1.8 g/dL) and relative hemoconcentration (39.1%) at the time of initial therapy. Prompt response to diuretic use and rapid body weight reduction were noted, which may possibly lead to the stroke event, as watershed infarction pattern in left hemisphere (Fig. 4), in spite of using antiplatelet agent. Hyperviscosity syndrome because of dysproteinemia of Waldenström's macroglobulinemia is also well known, but whether light chain paraproteins, as in our patient, are associated with the disorder is not known. Routine aggressive prophylactic anticoagulation therapies in such high-risk patients, including subcutaneous low—molecular weight or synthetic heparins, aspirin, dipyridamole, have been suggested. They should be justified with the risk of bleeding being considered and should be convenient for outpatient use.

Moreover, the histological findings on the kidneys of our patient are quiet interesting and worth further discussion. Monoclonal immunoglobulin deposition disease is an entity of diseases first described in the late 1950s, with nodular glomerular lesions resembling those of diabetic nephrosclerosis, but without fibrillar organization and Congo red affinity. These diseases include LCDD, heavy chain deposit disease (HCDD), and light and heavy chain deposit disease (LHCDD) [5], and must be differentiated from other "glomerular deposition diseases" [6], such as amyloidosis, and diabetic nephrosclerosis [7,8].

As summarized in Table 1, we could use Congo red, periodic acid-Schiff stain (PAS), and silver stains under light microscopy to differentiate nodular glomerulopathy. For example, the mesangial nodules could be stained with PAS and silver stains in diabetics, as may also be observed in membranoproliferative glomerulonephritis (MPGN), fibrillary glomerulopathy, and immunotactoid glomerulopathy patients. On the other hand, deposits in LCDD tend to be PAS stain positive and silver stain negative. Amyloid fibrils do not react with either PAS or silver stain. However, because of its special conformation of proteinaceous fibrils with β-sheet structure, it is resistant to proteolysis and shows affinity only to Congo red dye. It would show apple green birefringence under polarized light [9].

IF study could reveal further the characteristics of the deposits. Both λ and κ light chains are the precursor proteins of AL (it refers to amyloid light chain) amyloidosis and LCDD. However, λ light chain tends to form amyloid fibrils and is, thus, the dominant staining in AL amyloidosis. Instead, κ light chain is the dominant staining in LCDD. Finally, EM could help distinguish the ultrastructure of deposits, which varies with the characteristics of precursor proteins. In amyloidosis, fibrillary glomerulopathy, and immunotactoid glomerulopathy, paraproteins form fibrillar organization and can be further divided according to their diameters (Table 1). Others do not form definite organized deposits, and fine granular deposits were found along the GBM in LCDD.

Our case of LCDD shared many features with AL amyloidosis. First, LCDD usually shows nodular glomerulopathy positive for PAS stain but negative for silver stain. However, the amorphous deposits in our case were negative for both PAS and silver stains. Second, LCDD usually shows a predominant κ light chain staining (κ:λ = 3:2), instead of λ light chain staining, as in our case, under immunofluorescent staining. Third, the electron-dense deposits in LCDD are usually distributed granularly along the GBM and tubular basement membrane and to a lesser extent in mesangial areas, unlike those in our case, which showed prominent smudgy mesangial staining typical of amyloid deposits. Both Congo red negative staining and absence of fibrillar organization of the deposits pointed to the final diagnosis of LCDD.

Discrepancy between IF and EM findings in LCDD has been reported [10,11]. It may be a positive IF staining without deposits found on EM, because of focal distribution and small sample size, or there may be typical deposits found on EM but without IF staining because of loss of antigenic site [11]. The diversity of immunoglobulin structures that further undergo degradation and modification in tissue may also contribute to the aforementioned finding. However, our patient had dysproteinemia with compatible light chain deposition on both IF and EM studies, with mosaic features between AL amyloidosis and LCDD, which have never been reported.

Treatment of LCDD is aimed at ameliorating immunoglobulin production and the subsequent organ deposition. It is reasonable to give intensive chemotherapy or combined therapy with bone marrow transplantation if a comorbid malignancy was found. Multiple myeloma has been reported in up to 40% of cases of LCDD [12]. However, in most patients with LCDD, who are not associated with malignancy, therapy is controversial and data are limited [13]. Age and serum creatinine levels at presentation have been found to be the major predictors of prognosis, and recurrence is frequent after renal transplantation [14]. Therefore, renal transplantation could only be considered when the disease was well controlled. Owing to old age and comorbidity in our patient, we gave steroid alone, which seemed to be effective and achieved a decrease in proteinuria. Further studies are needed to determine the treatment of choice.

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