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CASE REPORT

Membranous glomerulonephritis with an *LMNA* mutation

Kumi Fujita[1] · **Kazuhiro Hatta**[2]

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Abstract
We had encountered the case of membranous glomerulonephritis (MGN) with dilated cardiomyopathy due to LMNA gene mutation. LMNA mutation was known as a cause of 'laminopathy' such as dilated cardiomyopathy, muscular dystrophy, neuropathy and so on. LMNA gene might be a candidate of genetic basis in cryptogenic MGN.

Keywords Membranous glomerulonephritis · Dilated cardiomyopathy · Lamin A/C · LMNA

Introduction

We witnessed the case of a patient with membranous glomerulonephritis (MGN) with dilated cardiomyopathy caused by an *LMNA* mutation. *LMNA* mutations are known to cause "laminopathies," such as dilated cardiomyopathy, muscular dystrophy, and neuropathy [1]. *LMNA* mutations might be a genetic cause of cryptogenic MGN.

Case report

A 65-year-old man was admitted to our hospital for renal biopsy to identify the cause of proteinuria. The patient had been diagnosed with dilated cardiomyopathy (DCM) following an episode of syncope 8 years earlier and was treated with amiodarone and valsartan. A cardioverter defibrillator was implanted in him 7 years ago and he had undergone catheter ablation 1 year ago. He had experienced hypereosinophilia 2 years ago. Although the cause of hypereosinophilia was considered to be drug-induced allergy, medication had not been changed, because of the necessity to control cardiac disease.

His cardiac function worsened, and subsequently, he developed proteinuria. 1 year ago, during admission his serum creatinine was 1.6 mg/dL.

The patient's height, weight, blood pressure, pulse rate, and body temperature were 162 cm, 57.8 kg, 108/68 mmHg, 60 bpm, and 36.2 °C, respectively. His consciousness was alart. Auscultation of his heart sounds revealed a gallop rhythm. No remarkable abnormalities were found in the lungs or abdomen. Pitting edema was present in his lower extremities.

The results of laboratory investigations were as follows: hemoglobin, 11.7 g/dL; hematocrit, 36.0%; platelets, 323,000/μL; white blood cells, 12,400/μL (lymphocytes 9.5%, monocytes 3.5%, eosinophils 42.5%, segmented neutrophils 43.5%, band neutrophils 1.0%); C-reactive protein, 0.6 mg/dL; blood urea nitrogen, 25.4 mg/dL; serum creatinine, 1.6 mg/dL; total cholesterol, 187 mg/dL; total protein, 6.4 g/dL; albumin, 2.8 g/dL; lactate dehydrogenase, 289 IU/L; aspartate aminotransferase, 29 IU/L; alanine aminotransferase, 20 IU/L; total bilirubin, 0.4 mg/dL; alkaline phosphatase, 387 IU/L; Na, 141 mmol/L; K, 4.5 mmol/L; and Cl, 106 mmol/L; BNP, 483.1 pg/mL; IgG, 1640 mg/dL; IgA, 243 mg/dL; IgM, 98 mg/dL; IgE, 2500 IU/ml; CH50, 36.0 U/mL; C3, 97.4 mg/dL; C4, 56.2 mg/dL; and anti-dsDNA antibody, 31 IU/mL. HBs antigen and HCV antibody were negative.

Urinalysis revealed 3+ proteinuria (1.79 g/day), 2+ hematuria, and 10–20 erythrocytes per high-power field. RBC cast was absent. Urinary beta 2-microglobulin, 28.0 μg/L; urinary NAG, 30.0 IU/L.

Renal biopsy was performed (Fig. 1). 50 glomeruli could be evaluated, 17 of which showed global sclerosis.

✉ Kumi Fujita
fujiko@tenriyorozu.jp

[1] Department of Diagnostic Pathology, Tenri Hospital, 200 Mishima-cho, Tenri, Nara, Japan

[2] Department of General Medicine, Tenri Hospital, 200 Mishima-cho, Tenri, Nara, Japan

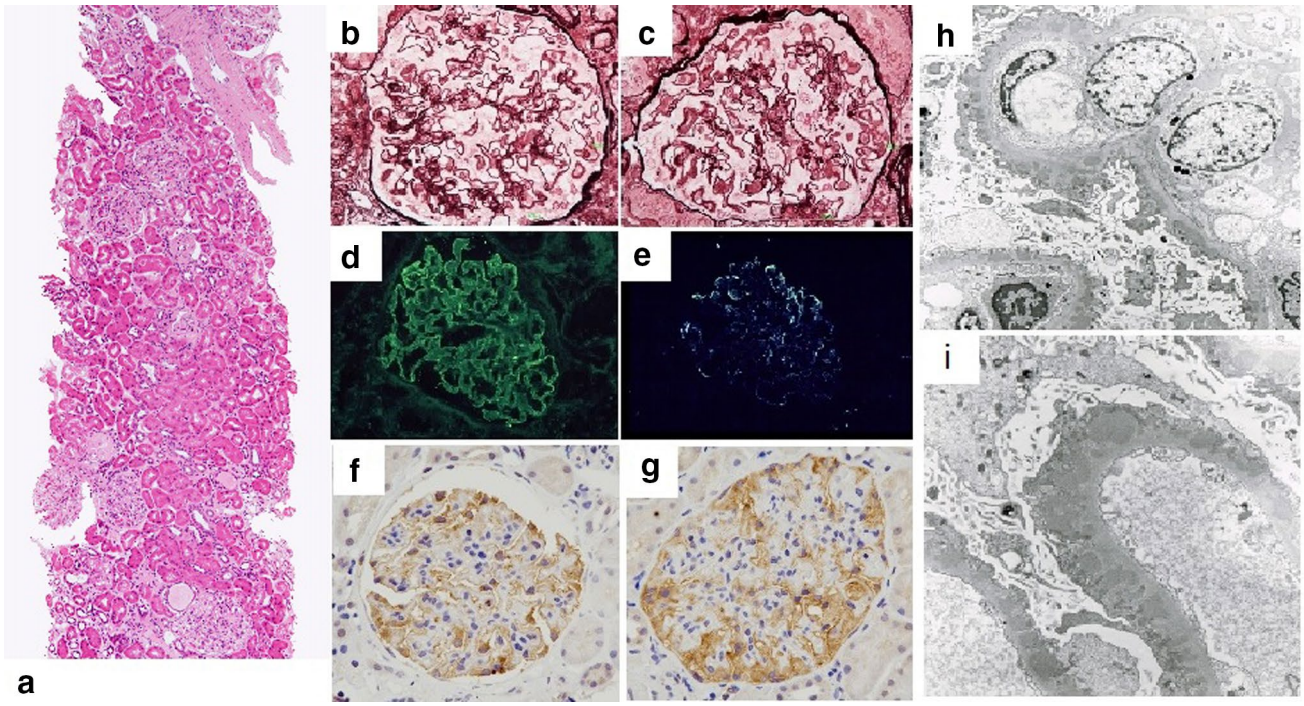

Fig. 1 **a–c** Micrographs of the glomeruli showing subepithelial spike formations. (**a** HE stains, **b, c** PAM stains), **d, e** immunoglobulin G and C3 deposition along the capillaries identified by immunostaining, **f, g** PLA2R1 was positive along capillaries identified immunohistochemically, **h, i** electron-dense deposits in the subepithelial and intramembranous region (3000×)

Histological findings included diffused spike appearance in the subepithelial lesions and focal mesangial cell proliferation in the glomeruli. Inflammatory cell infiltration was sparse and eosinophils were almost never observed. Arteriolosclerotic changes were also observed. Immunofluorescence staining was strongly positive for IgG with a granular pattern and weakly positive for C3. PLA2R1 was positive along capillaries identified immunohistochemically. Electron microscopy revealed multiple, large electron-dense deposits in the subepithelial lesions with a few intramembranous deposits. He was diagnosed with primary membranous glomerulonephritis. Administration of 0.6 mg/kg/day prednisolone was started. His renal function remained stable, but the proteinuria persisted. His hypereosinophilia had got solved soon after prednisolone administration. One year later, genetic evaluation for cardiomyopathy was performed and mutation of the *LMNA* gene was established (Fig. 2).

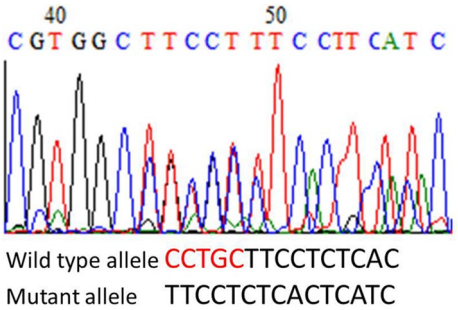

Fig. 2 The DNA sequencing chromatogram revealed a deletion of CCTGC in the mutant allele

Discussion

LMNA (1q21.2–q21.3) encodes lamin A/C protein that belongs to the family of intermediate filaments. The protein lines the inner nuclear membrane of somatic cells, and is associated with the stabilization of nuclear membrane and regulation of cell division.

LMNA mutations cause various diseases, which are collectively called "laminopathy" and include dilated cardiomyopathy, muscular dystrophy, neuropathy, progeria, and partial lipodystrophy [1]. This patient presented with dilated cardiomyopathy associated with *LMNA* mutation and complicated by glomerulonephritis with, mainly, membranous lesions. MGN is divided into primary and secondary types. Secondary MGN can be due to various factor such as collagen vascular diseases, viral infections, drugs, and malignancies. Though the titer of anti-dsDNA antibody in this patient was slightly high, he did not fulfill the diagnostic criteria of systemic lupus erythematosus. No evidence of

infection or malignancy were found. His medication history included amiodarone and valsartan, which have been hardly reported to cause glomerulonephritis. We could identify only few papers describing the possibility of membranous glomerulonephritis induced by the drugs [2]. We speculate that there are too few cases to clarify the relation between the drugs and glomerular lesions. Major histological findings in drug-induced renal diseases, such as tubulointerstitial nephritis or eosinophilic infiltration were not observed in our patient, although hypereosinophilia could be a manifestation of drug allergy.

MGN due to unknown etiology is classified as primary MGN. Phospholipase A2 receptor (PLA2R) expressed in podocytes was found to be the target antigen in about 70% of cases of primary MGN [3]. The importance of HLA-DQA11 in the onset of primary MGN was also described by Stranescu et al. [4]. Our case was proved PLA2R1 expression, and was considered to be primary MGN. The genetic background of primary MGN is still not completely understood in many cases. This is the first case report of cryptogenic MGN in a patient with an *LMNA* mutation.

Reported cases of glomerulonephritis with *LMNA* mutations were rare. However, partial lipodystrophy, which is a laminopathy, was reported to be associated with glomerulonephritis. The type of glomerulonephritis associated with partial lipodystrophy is believed to be type 2 membranoproliferative glomerulonephritis (MPGN), or C3 nephropathy, according to recent reports. Only one case report by Chartier S et al. had suggested a relationship between partial lipodystrophy and type 3 MPGN [5]. Owen KR et al. had reported the case of a patient with type 2 MPGN with an *LMNA* mutation [6]. Activation of the alternative complement pathway by C3 nephritic factor had been hypothesized as an important factor for the coexistence of lipodystrophy and MPGN [7]. Javor et al. argued for association with lipodystrophy and focal segmental glomerulosclerosis, but they could not comment on the etiology of the phenomenon completely [8].

Although lipodystrophy was not found in this case, the glomerulonephritis in this case might be similar to that associated with lipodystrophy based on an *LMNA* mutation. *LMNA* gene might be candidate of genetic basis in cryptogenic MGN. The association of glomerulonephritis and dilated cardiomyopathy has been hardly reported. Further studies to investigate the possibility of an *LMNA* mutation as an etiology of membranous glomerulonephritis or other types of renal disease might be valuable.

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Compliance with ethical standards

Conflict of interest All the authors have declared that no conflict of interest exists.

Human and animal rights All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from the patient for being included in the study.

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