AJKD
Case Report

MELAS Syndrome and Kidney Disease Without Fanconi Syndrome or Proteinuria: A Case Report

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Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS syndrome) represents one of the most frequent mitochondrial disorders. The majority of MELAS cases are caused by m.3243A>G mutation in the mitochondrial *MT-TL1* gene, which encodes the mitochondrial $tRNA^{Leu(UUR)}$. Kidney involvement usually manifests as Fanconi syndrome or focal segmental glomerulosclerosis. We describe a patient with MELAS mutation, cardiomyopathy, and chronic kidney disease without Fanconi syndrome, proteinuria, or hematuria. While the patient was waitlisted for heart transplantation, her kidney function deteriorated from an estimated glomerular filtration rate of 33 to 20 mL/min/1.73 m^2 within several months. Kidney biopsy was performed to distinguish decreased kidney perfusion from intrinsic kidney pathology. Histologic examination of the biopsy specimen showed only a moderate degree of tubular atrophy and interstitial fibrosis, but quantitative analysis of the m.3243A>G mitochondrial DNA mutation revealed high heteroplasmy levels of 89% in the kidney. Functional assessment showed reduced activity of mitochondrial enzymes in kidney tissue, which was confirmed by immunohistology. In conclusion, we describe an unusual case of MELAS syndrome with chronic kidney disease without apparent proteinuria or tubular disorders associated with Fanconi syndrome, but widespread interstitial fibrosis and a high degree of heteroplasmy of the MELAS specific mutation and low mitochondrial activity in the kidney.
Am J Kidney Dis. 68(6):949-953.

INDEX WORDS: Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS syndrome); kidney biopsy; renal; Fanconi syndrome; focal segmental glomerulosclerosis (FSGS); proteinuria; heteroplasmy.

Mitochondrial gene mutations cause visceral organ damage due to impaired oxidative energy production. Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS syndrome) is one of the most frequent maternally inherited mitochondrial disorders.[1] This disease is preferentially caused by point mutations in the mitochondrial *MT-TL1* gene, which encodes the mitochondrial $tRNA^{Leu(UUR)}$.[2] In approximately 80% of cases, MELAS syndrome is associated with m.3243A>G mutation; other frequent mutations are m.3271T>C and m.3253A>G.[3] The clinical phenotype associated with the MELAS mutations usually includes myopathy, seizures, stroke-like episodes, sensorineural hearing loss, and cognitive decline, but diabetes, polyneuropathy, and short stature also have been described.[4] Although kidney disease in MELAS syndrome is rather rare, it can present as Fanconi syndrome or focal segmental glomerulosclerosis. Worsening kidney function and progression to end-stage renal disease have been described in these patients as well.[5] Clinical features of these patients include signs of proximal tubular dysfunction and proteinuria, which is often in the nephrotic range. We describe an unusual case of MELAS mutation, cardiomyopathy, and chronic kidney disease in the absence of Fanconi syndrome, proteinuria, and hematuria.

CASE REPORT

A 37-year-old woman was given a diagnosis of hypertrophic cardiomyopathy in 2012. The endomyocardial biopsy specimen excluded inflammatory cardiomyopathy, cardiac sarcoidosis or amyloidosis, and various forms of lysosomal storage disease, but revealed hypertrophic myocytes with multifocal cytoplasmic vacuoles and diffuse interstitial fibrosis. Because the patient had sensorineural deafness, mild cognitive deficiencies, dysarthria, mild lactic acidosis, short stature, and diabetes, mitochondrial disease was suspected. Mitochondrial DNA (mtDNA; RefSeq NC_012920) analysis of endomyocardial biopsy specimens revealed a heteroplasmic mutation, m.3243A>G, which is

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Received October 30, 2015. Accepted in revised form June 13, 2016. Originally published online September 24, 2016.

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0272-6386
http://dx.doi.org/10.1053/j.ajkd.2016.06.027

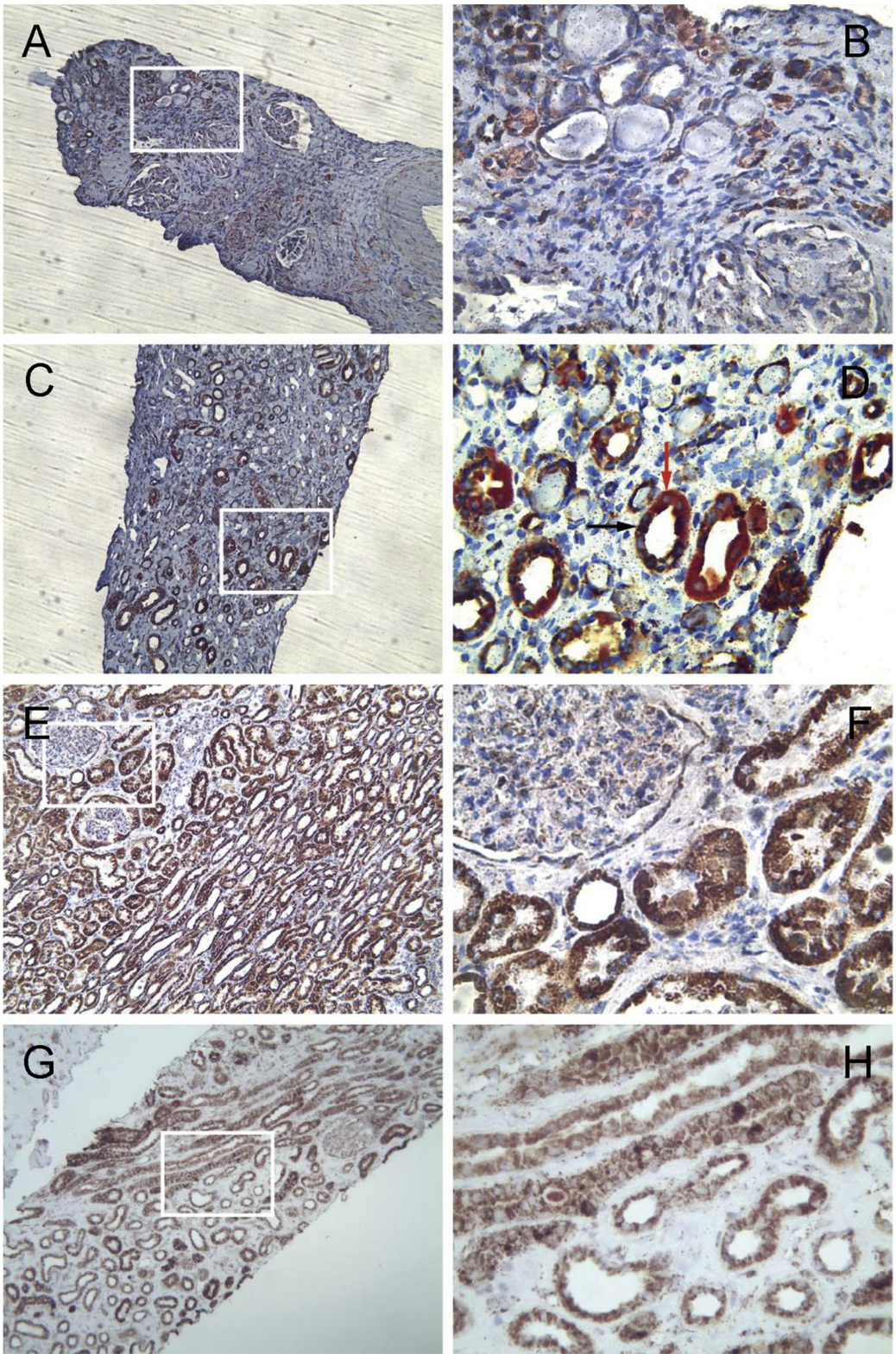

Figure 1. Immunohistochemical staining of complex I and porin in kidney biopsy specimens of (A-D) the patient with m.3243A>G mutation presented in this case report compared with (E-H) specimens of kidney controls. Complex I is stained in brown, and porin, in red. In the case of mitochondrial dysfunction, staining for complex I is absent, which is indicated by prominent red staining of porin. (A, C, E, G) Each area framed by a white rectangle (original magnification, ×100) is further magnified in the corresponding panel (B, D, F, H) to the right (original magnification, ×400). (D) In the patient with m.3243A>G, positive (black arrow) and negative (red arrow) epithelial cells are present within a single tubule complex I, as indicated by the red staining. (E, F) Healthy control tissue and (G, H) kidney tissue from a patient with hypertensive nephrosclerosis with moderate to severe interstitial fibrosis and tubular atrophy are stained brown, indicating the presence of complex I in the mitochondria.