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【 CASE REPORT 】

A MELAS Patient Developing Fatal Acute Renal Failure with Lactic Acidosis and Rhabdomyolysis

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Abstract:
We herein present a patient with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), who developed serious acute renal failure with lactic acidosis, followed by rhabdomyolysis. Despite receiving intensive care, he suffered multiple cardiopulmonary arrests and died 10 days after presentation due to a sudden deterioration of his symptoms. Renal pathology revealed diffuse tubular necrosis with interstitial edema and tubular dilatation on light microscopy, and a severe degeneration of intracellular organelles on electron microscopy. These pathological findings could have resulted from multiple cardiopulmonary arrests; however, we must be aware of the extremely rare but sudden occurrence of these fatal conditions in MELAS patients.

Key words: MELAS, acute renal failure, lactic acidosis, rhabdomyolysis

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Introduction

Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) is a multi-organ disorder. Regarding renal involvement in MELAS patients, it tends to be chronic, but it is rarer than in other organ abnormalities. Such renal involvement can lead to a serious condition (1, 2); however, the trigger such involvement remains to be elucidated. We herein report a MELAS patient who suddenly developed acute renal failure with severe lactic acidosis, followed by rhabdomyolysis.

Case Report

A 30-year old man developed headache, vomiting, and aphasia at the age of 25. He had experienced right hearing disturbance since the age of 22; however, he had no past history of renal failure, rhabdomyolysis, or any cardiac events. His mother was diagnosed to have MELAS with A3243G mutations in mitochondrial DNA (heteroplasmy 5%). The findings of a routine blood examination and blood gas analysis were normal; however, the serum lactate level was 25.0 mg/dL (normal range: 4.2-17.0 mg/dL), pyruvate level was 1.4 mg/dL (normal range: 0.3-0.9 mg/dL), and the ratio of lactate/pyruvate was 17.9 (normal range: <10). In addition, the cerebrospinal fluid lactate level was 48.6 mg/dL (normal range: 9-16 mg/dL), pyruvate level was 1.6 mg/dL (normal range: 0.6-1.2 mg/dL), and the ratio of lactate/pyruvate was 30.4. Diffusion-weighted (DW) brain MR imaging demonstrated a large abnormal high-signal lesion in the left temporal, parietal, and occipital lobes. 99mTc ethylcysteinate dimer-single photon emission computed tomography showed a decrease in the tracer uptake of these lesions. Conventional Hematoxylin and Eosin staining and Gomori-Trichrome staining of biopsied biceps revealed a variation in the fiber size and many ragged-red fibers. Neither necrotic nor regenerating fibers were observed. We diagnosed the patient to have MELAS based on 3243G mutations in mitochondrial DNA (heteroplasmy 37%). As taurine had not been approved in Japan at that time (3), we administered 30 g of intravenous L-arginine daily (4). The administration of L-arginine was approved by the Review Board of Shonan Fujisawa Tokushukai Hospital. The patient provided written

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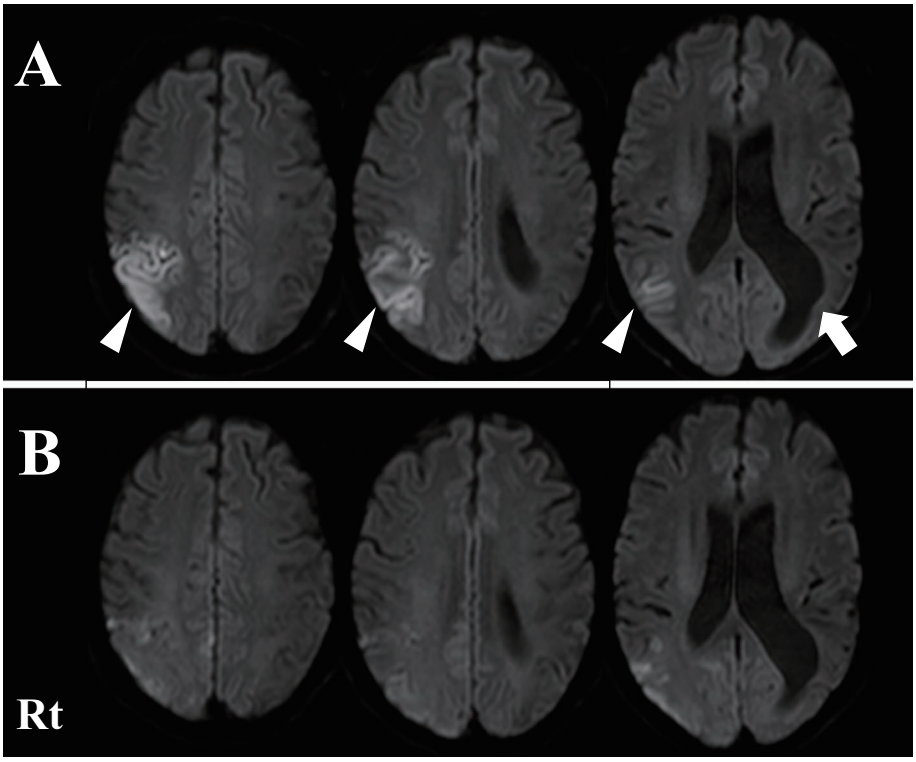

Figure 1. **Diffusion-weighted brain MR imaging. A: A high-signal lesion demonstrated in the right temporal and parietal lobes on admission (white arrowhead). Severe atrophy in the left temporal, parietal, and occipital lobes was observed after the last attack of MELAS at 25 years of age (white arrow). B: An abnormal MR signal almost completely disappeared on the day before a sudden deterioration in the patient's symptoms occurred. MELAS: mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes**

informed consent in accordance with the Declaration of Helsinki. The patient improved gradually, and we thus continued 12 g of oral L-arginine daily.

At 30 years of age, he developed a headache, vomiting, and apraxia. A routine blood examination including a blood gas analysis and brain natriuretic peptide (BNP) showed normal findings; however, the serum lactate and pyruvate levels were 25.2 mg/dL and 1.2 mg/dL (the ratio of lactate/pyruvate was 21.0). Although electrocardiogram (ECG) was normal, echocardiogram showed ventricular wall thickening, especially in the posterior wall [ejection fraction (EF) was 66.0%]. Brain MR imaging revealed a high-signal in DW and low-signal in apparent diffusion coefficient (ADC) in the right temporal and parietal lobes (Fig. 1A). We resumed the drip infusion of L-arginine (30 g per day). At 38 days of admission, most of the abnormal MR signals had disappeared (Fig. 1B) and a routine blood examination revealed mild blood urea nitrogen (BUN) elevation (37.3 mg/dL) with normal creatinine and electrolyte levels. His vital signs were normal, and we observed neither any signs of infection nor seizures. No mitochondrial toxins, including aminoglycoside, valproic acid, or dichloroacetate, were administered. However, he suffered cardiopulmonary arrest suddenly at night on the following day. The BUN, creatinine, potassium, and BNP levels were elevated to 100.2 mg/dL, 4.42 mg/dL, 7.4 mEq/L, and 79.4 mg/dL, respectively. Severe metabolic acidosis with an increased anion gap was revealed [pH 6.81, partial pressure of carbon dioxide (PCO_2) 50.6 mmHg, partial pressure of oxygen (PO_2) 30.4 mmHg, hydrogencarbonate (HCO_3^-) 7.5 mmol/L, and base excess (BE) -30.3 mmol/L, anion gap 15.5 mEq/L]. The serum lactate and pyruvate levels were 249.6 mg/dL and 7.7 mg/dL (the ratio of lactate/pyruvate was 32.4). Non-contrast abdominal CT imaging demonstrated neither any obstruction of the gastrointestinal tract nor hyperdensity in the portal vein. In addition, we did not detect any urinary tract obstruction. We successfully resuscitated the patient with cardiopulmonary resuscitation with the rapid intravenous infusion of a large quantity of bicarbonate; however, severe acute renal dysfunction with lactic acidosis continued and severe rhabdomyolysis followed [creatine kinase (CK) 153,293 IU/L, aspartate aminotransferase (AST) 2,551 IU/L, lactate dehydrogenase (LDH) 6,897 IU/L]. Despite receiving intensive care, including percutaneous cardiopulmonary support and continuous hemodialysis, he suffered multiple cardiopulmonary arrests and died 10 days later due to a sudden deterioration of his symptoms.

Autopsy findings

We performed an autopsy limited to the abdominal organs. The prefixed kidneys weighed 205 g (right) and 240 g (left). There were no marked abnormalities in the liver, pan-

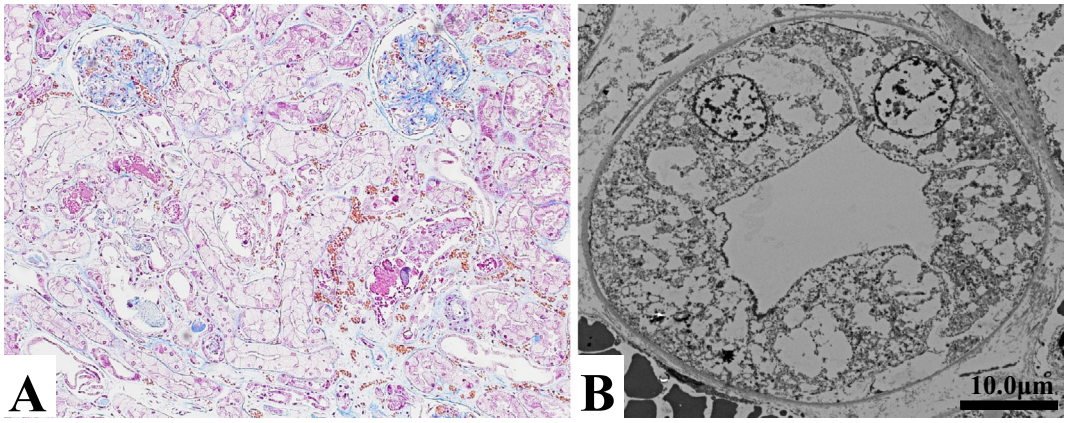

Figure 2. Pathology of the kidney. A: Diffuse tubular necrosis with interstitial edema and tubular dilatation as demonstrated by Masson's trichrome stain. However, no arterial capillary changes were observed (magnification 100×). B: Tubular necrosis with severe degeneration of subcellular organelles was revealed by electron microscopy (magnification 800×).

creas, or gastrointestinal tract macroscopically. Light microscopy of the kidney revealed no abnormality in the arterial capillaries; however, severe tubular necrosis with interstitial edema and tubular dilatation were observed (Fig. 2A). In addition, mild interstitial fibrosis was observed in the pancreas. Electron microscopy of the kidney revealed the severe degeneration of the intracellular organelles (Fig. 2B).

Discussion

MELAS is characterized by the mitochondrial dysfunction of multiple organs. The commonly affected extra-neuromuscular organs are the heart, pancreas, and hematopoietic system. On the other hand, the liver, endocrine glands, and kidney are less often affected (1). Most renal involvements in MELAS tend to be associated with chronic renal failure (5). We could find only a small number of reports on acute renal failure associated with MELAS (6-8). Acute exacerbations of MELAS could be triggered by febrile illness, mitochondrial toxins, cigarettes, and alcohol (9). Two patients, who developed acute renal failure and rhabdomyolysis after alcohol consumption, were reported previously (7, 8); however, we could not identify exacerbation factors in our case.

The renal pathology in MELAS has been reported as the dilatation of the renal tubules (10), granular swollen tubular epithelial cells (11), and global or focal-segmental glomerulosclerosis (10-13). Although this patient demonstrated a severe tubular pathology, we could not identify any arterial capillaries changes. Yanagihara et al. suggested that not only hemodynamic insufficiency due to vascular changes but mitochondrial damage due to MELAS could cause renal involvement (5). As we did not observe any vascular changes, intrinsic mitochondrial dysfunction might have been the trigger of a sudden deterioration in this case. However, electron microscopy did not reveal the accumulation of any abnormal mitochondria and it indicated that the renal tubular pathology might have resulted from multiple cardiopulmonary arrests.

Therefore, we could not clarify the trigger of the sudden development of fatal acute renal failure and rhabdomyolysis in this patient. However, this patient alerts us to the extremely rare but sudden development of these fatal conditions during the course of MELAS, despite obtaining an improvement in cerebral lesion. As there might be some unknown triggers of acute renal failure and rhabdomyolysis, further investigation with more MELAS patients is necessary.

The authors state that they have no Conflict of Interest (COI).

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