

## Diffuse alveolar hemorrhage as a rare complication in a patient with mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)

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### Abstract

Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) is a syndrome with complex genetics and diverse manifestations. Diffuse alveolar hemorrhage is caused by alveolar microcirculation injury associated with lung illness or systemic disorders. To date, the relationship between diffuse alveolar hemorrhage and MELAS has not been reported. We report a MELAS patient who presented complications with diffuse alveolar hemorrhage.

### INTRODUCTION

Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) is a disorder characterized by an early onset of stroke-like episodes.<sup>1</sup> The pathophysiology of stroke-like episodes in MELAS remains controversial; mitochondrial cytopathy, mitochondrial angiopathy, a nonischemic neurovascular cellular mechanism, and a combination of these factors have all been suggested as etiologies.<sup>2</sup>

Ischemic stroke is more common than hemorrhagic stroke in MELAS patients.<sup>3</sup> Hemorrhage in MELAS has been reported in the brain and gastrointestinal system.<sup>3-7</sup> Pulmonary involvement is also unusual in MELAS, although it has been reported in one pediatric patient with pulmonary arterial hypertension.<sup>8</sup> Injury to the alveolar microcirculation can result in diffuse alveolar hemorrhage, which has a unique histopathology known as pulmonary capillaritis.<sup>9</sup> Pulmonary capillaritis includes interstitial neutrophilic infiltration, fibrinoid necrosis of the alveolar and capillary walls, and leukocytoclasia.<sup>9</sup> The common denominator in MELAS and diffuse alveolar hemorrhages is angiopathy. The angiopathy in MELAS causes the abnormal accumulation of mitochondria in the endothelium and smooth muscle cells of cerebral arterioles and capillaries.<sup>10</sup> Angiopathy in the capillaries of the lungs leads to pulmonary hemorrhage.<sup>11</sup>

Here, we describe a case of an adult patient with MELAS complicated by diffuse alveolar hemorrhage. To the best of our knowledge,

there have been no reports of diffuse alveolar hemorrhage as a complicating disorder of MELAS in adults.

### CASE REPORT

A 36-year-old man presented with left hemiparesis. The patient had no past medical or family history of migraine, seizure, stroke-like episodes, or dementia. However, he frequently complained of exercise intolerance, fatigue and hearing difficulties. The patient was mentally alert, thin, and of short stature (153 cm, 38 kg, BMI: 16.23 kg/m<sup>2</sup>). Neurologic examination revealed that the left hemiparesis motor power was of medical research council grade IV. Left deep tendon reflexes were increased. The Babinski sign was not observed.

A brain MRI including diffusion weighted image (DWI) showed high signal intensity in the right fronto-parieto-temporal lobe and insular areas with diffuse cerebral and cerebellar atrophy (Figure 1(a) and (b)). Intracerebral hemorrhage was not found in an MR gradient echo sequence (Figure 1(c)). Because the ischemic lesions did not respect usual vascular territories and the episode occurred before the patient reached 40 years of age, we studied protein C activity, protein C and S antigens, anti-thrombin III, lupus anticoagulant, anticardiolipin antibodies, antiphospholipid IgG and IgM antibodies, ANA and ANCA. In addition, we examined lactic acid and pyruvate levels, the lactic acid-to-pyruvate ratio and the mtDNA sequence.

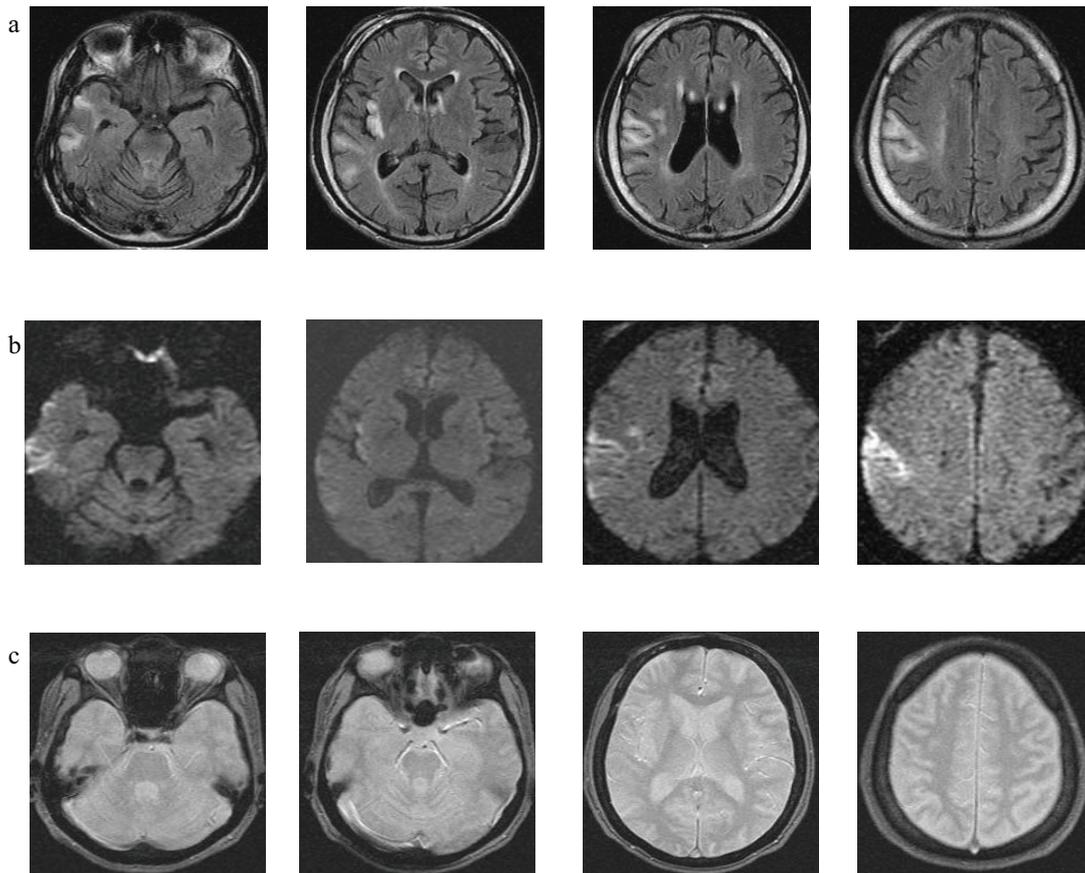


Figure 1 (a) Axial FLAIR MRI sequence; (b) DWI sequences; (c) MR gradient echo sequence. Hyperintense lesions of the right fronto-parieto-temporal lobe and insular area can be observed in (a) and (b). The cerebellum and brainstem are more atrophied than expected, given the patient’s age. There is no evidence of ICH in (c).

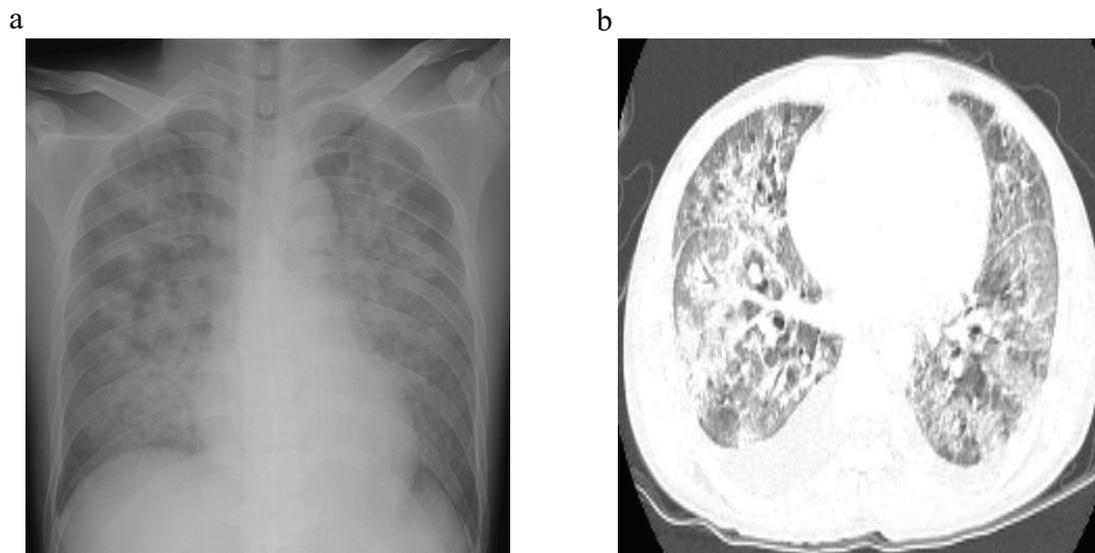


Figure 2. Chest X-ray (left) and CT scan (right) taken immediately after alveolar hemorrhage. Chest X-ray reveals diffuse consolidation in both lungs. The chest CT scan shows bilateral patchy areas of ground glass opacity and consolidation in both lung fields, with peribronchial predominance.

All laboratory test results were normal, except for the presence of an m.3242 A>G point mutation in the mitochondrial tRNA MT-TL1 gene.

On the sixth day after antithrombotic therapy with clopidogrel (75 mg/d), the patient had a sudden respiratory failure with dyspnea and endotracheal bleeding. Because his general condition had deteriorated rapidly, we could not perform a muscle biopsy. Despite the initially normal chest X-ray, a follow-up chest X-ray and chest CT revealed diffuse alveolar hemorrhage (Figure 2). Clopidogrel treatment was discontinued immediately after bronchoscopy. This patient was treated with hydrocortisone, methylprednisolone and antibiotics for 36 days, and coenzyme-Q 10 (600 mg/d) treatment was added. The diffuse alveolar hemorrhage and the patient's general condition were improved at four months after admission. Four months after discharge, he again complained of involuntary movement of the left hand, which was identified as myoclonus. The EEG displayed sharp waves with continuous slowing in the right temporal area. The follow-up DWI revealed the resolution of the previous lesions and the development of new lesions in the right temporo-parieto-occipital area and left cerebellar hemisphere. He was prescribed topiramate (100 mg/d), and the myoclonus disappeared one month later.

Both the patient and the institution approved the use of their records for our report.

## DISCUSSION

This case reveals interesting and potentially important observations with regard to diffuse alveolar hemorrhage as a complication of MELAS after antiplatelet treatment.

Intracranial hemorrhage (ICH) in MELAS was clinically associated with antithrombotic therapy<sup>3,4</sup> and pathologically related to fibrinoid necrosis of the small arteries and mitochondrial angiopathy.<sup>3,6</sup> The diffuse alveolar hemorrhage in this patient developed on the sixth day of treatment with clopidogrel. However, we did not obtain pathological specimens from patient through muscle biopsy because of the rapid progression of his illness. We also missed the opportunity to observe the abnormal accumulation of mitochondria in vascular endothelial cells through the strongly succinate dehydrogenase reactive vessels (SSVs), which are rich in mitochondria.<sup>12</sup>

Nevertheless, there are some features suggesting a relationship between diffuse alveolar

hemorrhage and MELAS in this patient. First, all laboratory results for coagulopathy, vasculitis or autoimmune connective disorders were normal. Furthermore, there was no evidence of underlying lung disease in the first chest X-ray on admission. Thus, we suggest that endothelial abnormality by mitochondrial dysfunction seems likely to have caused a small vessel angiopathy of the lung such as pulmonary capillaritis, which may be exacerbated by antithrombotic therapy.

In conclusion, MELAS is not only a neurologic disorder but also a systemic disease. Our case study is particularly interesting given the lack of similar reports of diffuse alveolar hemorrhage as a complication of MELAS.

## DISCLOSURE

Conflict of interest: None

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