Aortic Rupture in Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-Like Episodes

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Background: Microangiopathy has been well described in the brain and muscle of patients with mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS).

Objective: To describe a patient with the common A3243G/MELAS point mutation who had aortic rupture and whose mother also died of large vessel rupture.

Design: Case report.

Setting: Collaboration between a primary care hospital and 2 academic tertiary care hospitals.

Results: Histologically, there was marked disarray of the smooth muscle architecture of the aorta, and immunohistochemical staining with antibodies against the mitochondrial DNA-encoded cytochrome-C oxidase I subunit showed uniformly decreased immunostaining of the endothelial and smooth muscle cells of the aorta and vasa vasorum. Polymerase chain reaction and restriction fragment length polymorphism analysis showed that the mutation load was 40.5% in blood but 85.3% in the blood vessels.

Conclusions: The severe vasculopathy in this patient is probably directly related to the high mutation load in the blood vessels. Although aortic rupture is an unusual manifestation of MELAS, it is an important potential complication in patients undergoing minor surgical procedures.

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METHODS

Histopathologic Studies

Paraffin-embedded sections of the aorta were stained with Gomori trichrome stain. Immunohistochemical staining with antibodies against cytochrome-C oxidase (COX)I (representative of mitochondrial DNA–encoded proteins) and COX IV (representative of nuclear DNA–encoded proteins) was performed as previously described.6

Figure 1. Morphology of a cross-section of the ruptured aorta with Gomori trichrome staining under low magnification (A) and of the circled area seen at higher magnification (B). There was marked disruption of the smooth muscle and elastic layers of the tunica media.

Figure 2. Immunohistochemical staining for cytochrome-C oxidase (COX) I at lower (A) and higher (D) magnification and for COX IV at lower (B) and higher (C) magnification. There was decreased COX I but normal COX IV staining of the smooth muscle cells in the media and of the endothelial cells of the vasa vasorum in the adventitial layer.

Molecular Analysis

Total DNA was extracted from blood and paraffin-embedded slices of the aorta using the Puregene DNA Purification Kit (Gentra Systems, Minneapolis, Minn) according to the manufacturer’s protocol. Aortic tissue was deparaffinized using xylene.

Polymerase chain reaction amplification of mitochondrial DNA was performed using oligonucleotide primers corresponding to nucleotide positions 3116 to 3134 (forward) and 3353 to 3333 (reverse). Quantitation of the A3243G mutation load was performed as previously described.7

RESULTS

There was marked disruption of the smooth muscle and elastic layers of the aorta, which were evident adjacent to the rupture site but also in the rest of the intact aortic wall (Figure 1). Immunohistochemical studies showed that COX I staining of the smooth muscle cells was much less intense than COX IV staining (Figure 2), implying a lesser production of mitochondrial DNA–encoded proteins (COX I) than of nuclear DNA–encoded proteins (COX IV). Decreased COX I staining was also present in the vasa vasorum of the aorta. There was no evidence of aneurysmal dilatation of any large vessels (data not shown).

Quantitation of A3243G mutant genomes in blood showed a mutation load of 40.5%. The mutation load was much higher in 2 large aortic vessels, where it ranged from 83.3% to 87.3% (mean, 85.3%) (Figure 3). No other tissues were available for analysis.

COMMENT

To our knowledge, this is the first report of large-vessel involvement in MELAS, which resulted in catastrophic aortic rupture after a trivial surgical procedure. There is a strong possibility that the patient’s mother, who was an obligate carrier of the A3243G mutation and died of a ruptured vessel, also had large-vessel disease.
Histopathologic examination of the patient’s aorta demonstrated disruption of the smooth muscle layers. This may be directly attributable to mitochondrial dysfunction and decreased production of mitochondrial DNA-encoded proteins due to the underlying transfer RNA^5804L^ defect. In fact, we documented a high A3243G mutation load of about 85% in the aorta, suggestive of severe mitochondrial dysfunction in this tissue. Alternatively, because the COX I staining was also decreased in the vasa vasorum of the aorta, the abnormalities of the smooth muscle layers could have been caused by impaired blood supply to large vessels by the affected vasa vasorum.

Although the patient had high mutation loads both in large vessel walls and in blood (Shanske et al reported a mean ± SD mutation load of 23.47 ± 19.6 in the blood of patients with symptomatic MELAS), the A3243G mutation loads in easily accessible tissues, such as urine sediment and blood, do not correlate well with the mutation loads in less accessible tissues, such as brain and skeletal muscle. Therefore, it is impossible to predict the mutation load in blood vessels in patients with MELAS and the attending risk of large-vessel disease. A recent study by Takahashi et al described abnormal capacitive and oscillatory compliance on pulse wave analysis in a single adult patient with MELAS. Their patient and ours may represent the extreme spectrum of vascular involvement, but further studies are needed to establish the frequency and severity of large-vessel disease in patients with MELAS.

While large-vessel vasculopathy is a rare finding in MELAS, precautions should be taken before embarking on both trivial and major surgical procedures. Systemic vascular assessment may be prudent in these patients.

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REFERENCES


