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Case study

Diagnosis of mitochondrial neurogastrointestinal encephalopathy disease in gastrointestinal biopsies

Antonio R. Perez-Atayde MD*

Department of Pathology, Boston Children's Hospital and Harvard Medical School, Boston, MA 02115, USA

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Summary A 14-year-old boy with mitochondrial neurogastrointestinal encephalopathy (MNGIE) disease had a lifelong history of failure to thrive and gastrointestinal symptoms including vomiting, pain, and diarrhea, leading to progressive cachexia. At the age of 9 years, after an extensive workup, the diagnosis of Crohn disease was strongly suspected, and he underwent colonoscopy with multiple biopsies. At 11 years of age, vision change and poor balance lead to a diagnosis of leukodystrophy by magnetic resonance imaging. Investigations for metachromatic leukodystrophy, adrenal leukodystrophy, and globoid cell leukodystrophy were all negative. A diagnosis of MNGIE disease was suspected when he continued deteriorating with gastrointestinal symptoms, multiple neurologic deficits, and encephalopathy. Markedly diminished thymidine phosphorylase activity and increased thymidine plasma levels confirmed the diagnosis of MNGIE. At autopsy, megamitochondria were observed by light microscopy in submucosal and myenteric ganglion cells and in smooth muscle cells of muscularis mucosae and muscularis propria, along the entire gastrointestinal tract from the esophagus to the rectum. Megamitochondria in ganglion cells were also observed in a retrospective review of the endoscopic intestinal biopsies taken at age 9 and 13 years and in the appendectomy specimen obtained 1 month before his demise. This study corroborates the presence of megamitochondria in gastrointestinal ganglion cells in MNGIE disease, better illustrates their detailed morphology, and describes for the first time similar structures in the cytoplasm of gastrointestinal smooth muscle cells. Pathologists should be able to recognize these structures by light microscopy and be aware of their association with primary mitochondriopathies.

1. Introduction

The diagnosis of mitochondrial neurogastrointestinal encephalopathy (MNGIE) disease is usually suspected late in the clinical course when the disease is relatively fully expressed with progressive gastrointestinal dysmotility, progressive failure to thrive, ptosis, external ophthalmoplegia, mixed sensorimotor demyelinating neuropathy, hearing loss, and asymptomatic leukodystrophy with increased T2 signal abnormalities in the white matter by magnetic resonance imaging. The order in which these manifestations appear is unpredictable, but severe gastrointestinal dysmotility with weight loss, episodic abdominal pain, and diarrhea are often the earliest manifestations, and patients remain undiagnosed for many years enduring extensive workup for an etiology, in particular Crohn disease.

In 1998, we described megamitochondria seen by light microscopy as brightly eosinophilic inclusions in the cytoplasm of submucosal ganglion cells in a rectal suction

* Corresponding author.
E-mail address: antonio.perezatayde@childrens.harvard.edu.

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biopsy, as a characteristic feature of MNGIE disease [1]. Recently, similar structures have been observed within gastrointestinal ganglion cells in children with Alpers disease [2]. In addition, prior reports have described abnormal mitochondria by electron microscopy in intestinal smooth muscle cells of patients with MNGIE and mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) and in ganglion cells in a patient with MELAS, but megamitochondria were not observed by light microscopy in any of these reports [3–7]. To validate our prior report [1] and to describe additional findings, I now describe a second case of MNGIE that strikingly showed by light microscopy numerous characteristic megamitochondria in the cytoplasm of gastrointestinal ganglion cells. They were present long before the onset of neurologic symptoms and before the diagnosis of MNGIE was biochemically established. In addition, this report describes for the first time identical inclusions within the cytoplasm of smooth muscle cells of the muscularis mucosae and muscularis propria of the gastrointestinal tract.

2. Case report

This 14-year-old boy was the product of a 38 weeks' gestation born after an uncomplicated pregnancy and labor and normal spontaneous vaginal delivery. As a neonate, he developed transient jaundice treated with phototherapy. Early-onset failure to thrive continued during his entire life despite vigorous appetite. He had intermittent episodes of vomiting, abdominal pain, and loose stools. At age 9 years, his weight and height began to plateau, and an extensive workup ruled out pancreatic insufficiency, thyroid disease, celiac disease, and parasitic infection. The diagnosis of Crohn disease was considered likely, and although endoscopy and colonoscopy were grossly normal and multiple intestinal biopsies were microscopically unremarkable, the biopsy sample from the terminal ileum showed focal active ileitis. Against this diagnosis, however, the antineutrophil cytoplasmic antibody, upper gastrointestinal series, small bowel follow-through, hematocrit, albumin and blood sedimentation rate were all normal. At that time, the neurologic examination was unremarkable without focal deficits. At 11 years of age because of persistent vomiting, vision change, and poor balance noted by his mother, a head magnetic resonance imaging was done that revealed leukodystrophy with extensive T2 signal abnormality in the periventricular white matter and generalized demyelination. Workups for metachromatic leukodystrophy, adrenal leukodystrophy, and globoid cell leukodystrophy had all negative results. He progressively developed muscle wasting, weakness, bilateral foot drop, loss of deep tendon reflexes, mild intention tremor, deterioration of gait and balance, ptosis, and abnormal behavior with anger outbursts. Nerve conduction tests showed severe axonal demyelinating mixed sensory-motor neuropathy. Because of these neurologic deficits, signs of encephalopathy with behavioral and personality changes, and chronic gastrointestinal symptoms, a diagnosis of MNGIE syndrome was suspected. The thymidine phosphorylase (TP) enzyme activity in buffy coat was 16.2 nmol/hour/mg protein (normal activity, 667 ± 212 nmol/hour/mg protein; range, 200-1340 nmol/hour/mg protein; patients with MNGIE: 0-43 nmol/hour/mg protein). A thymidine plasma level was 8.4 μmol/L (normal, <0.05 μmol/L; patients with MNGIE, 8.68 ± 5.23 μmol/L) (M. Hirano, personal communication, Columbia University). These findings are considered diagnostic of MNGIE disease [8,9].

The patient became progressively cachectic despite vigorous oral intake, percutaneous endoscopic feeding, and parenteral nutrition. Decreased pulmonary function tests were attributed to progressive thoracic muscle weakness. A bone marrow transplant was considered, but after placement of a feeding jejunostomy tube, the patient developed ruptured appendicitis, peritonitis, sepsis, acute respiratory distress, and hemodynamic instability requiring pressors. *Candida albicans* was cultured from an abdominal drain, and he was found to have an enterocutaneous fistula draining from the umbilicus. Because of progressive deterioration and after family consent, support was withdrawn and the patient died. An autopsy was granted.

The patient had 2 healthy siblings, and there was no family history of consanguinity.

3. Pathologic findings

At autopsy, there were features consistent with the clinical diagnosis of chronic intestinal pseudo-obstruction with diminished diameter of small bowel and markedly dilated stomach with hypertrophic muscular wall. The outer layer of muscularis propria of the small intestine was very thin with degeneration, loss of smooth muscle cells, and replacement fibrosis (Fig. 1). Degenerating smooth muscle cells had cytoplasmic vacuoles but not megamitochondria.

Frequent megamitochondria were identified in the submucosal and myenteric ganglion cells as well as in smooth muscle cells of the muscularis mucosae and muscularis propria of the entire gastrointestinal tract including the esophagus, stomach, duodenum, jejunum, ileum, colon, and rectum. Megamitochondria were visible by light microscopy as round brightly eosinophilic inclusions that were refractile to light by lowering the microscope condenser lens (Figs. 2–6). Megamitochondria were present in approximately 30% of ganglion cells in all gastrointestinal segments examined. The number of megamitochondria per cell varied from one to few to numerous and the size from very small, almost imperceptible to larger inclusions 3 to 5 μm in diameter resembling red blood cells (Figs. 2 and 3). Although the cytoplasm of ganglion cells with few or small megamitochondria appeared unremarkable, those with