



A Rare Case of Mitochondrial Neurogastrointestinal Encephalomyopathy

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ABSTRACT

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is a rare autosomal recessive disease due to mutations in the thymidine phosphorylase gene, leading to mitochondrial alterations and dysfunctions in oxidative phosphorylation. MNGIE is a multisystem disorder with gastrointestinal symptoms arising in large part from gut dysmotility and neurological manifestations including peripheral neuropathy. We discuss a patient with chronic vomiting, diarrhea, and weight loss with a prior unrevealing extensive workup who was hospitalized for severe protein-calorie malnutrition. The patient was found to have gastrointestinal dysmotility on a gastric emptying scan and persistently elevated lactate levels and was subsequently diagnosed with MNGIE after confirmatory testing.

INTRODUCTION

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is a rare and fatal metabolic disorder.¹ It was first described in 1976 in a 22-year-old man with ptosis, ophthalmoplegia, dysphagia, and myopathy. The disease is caused by an accumulation of mutations in the mitochondrial genome, leading to dysfunction in oxidative phosphorylation. This etiology was first elucidated in 1999.¹ The prevalence of MNGIE is estimated to be 1–9 in 1,000,000 worldwide.¹ Between 1988 and 2011, only 102 patients had been documented.² The onset of symptoms can occur between the first and second decade of life. However, owing to its complex clinical presentation and rarity, diagnosis is often delayed 5–10 years.¹ Patients are frequently misdiagnosed with a variety of gastrointestinal (GI) and neurologic conditions, including inflammatory bowel disease, chronic intestinal pseudo-obstruction, and chronic inflammatory demyelinating polyneuropathy. Here, we present a case of this exceedingly rare disease.

CASE REPORT

A 24-year-old man with chronic nausea, vomiting, diarrhea, and weight loss of 3-year duration was admitted to the hospital for intractable vomiting and failure to thrive. On presentation, the patient endorsed intermittent postprandial nonbloody emesis and diarrhea up to 6 times per day. The patient experienced a decrease in weight from 130–75 lbs since symptom onset. Before admission, the patient underwent extensive serologic, radiographic, and endoscopic testing without a clear etiology being identified. Workup was notable for an elevated C-reactive protein level of 27 mg/dL (normal <10 mg/dL) and a fecal calprotectin of 296 µg/g (normal <120 µg/g). A stool infectious panel, antinuclear antibody, and celiac disease panel were unremarkable. Fecal fat and elastase were unremarkable as well. Magnetic resonance enterography and mesenteric Doppler were unrevealing. The patient also underwent 2 previous esophagogastroduodenoscopies (EGDs) and colonoscopies. Initial endoscopic findings were notable for antral gastritis with unremarkable duodenal and colonic mucosa. Pathology reflected chronic body and antral gastritis, which was negative for *Helicobacter pylori*. Random colon biopsies noted chronic colitis with lymphoid aggregates and reactive changes. A colonoscopy 1 month before admission was limited by poor bowel preparation, although no evidence of inflammation was found on rectal biopsies (Figure 1). A concomitant EGD found nonerosive chronic gastritis in the cardia, body, and antrum (Figure 2).

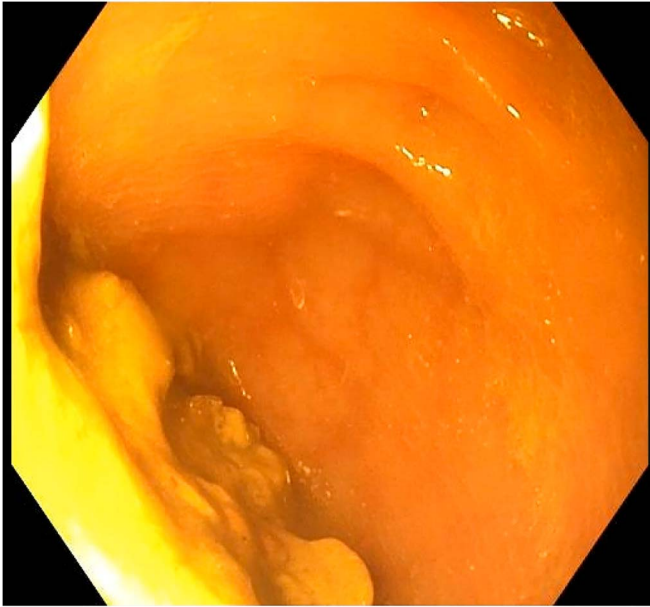


Figure 1. Colonoscopy with a view of the rectal mucosa. The procedure was limited by the presence of solid stool.

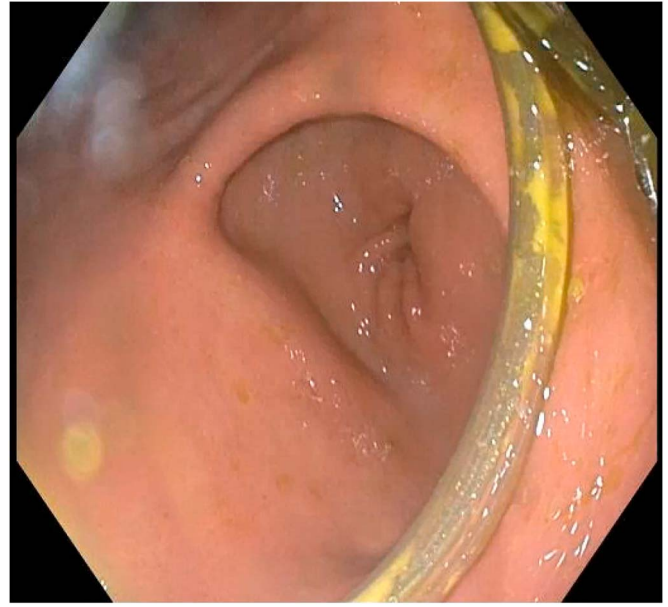


Figure 3. Esophagogastroduodenoscopy showing the stomach antrum with the jejunal portion of a gastrojejunal enteric tube looped in the stomach.

On admission, the patient was noted to be ill-appearing and cachectic with pale skin. Initial workup revealed an elevated lactate level of 6.8 mmol/L (normal 0.5–2.0 mmol/L) and an anion gap of 17 with an unremarkable basic metabolic panel, complete blood count, and liver enzymes. Albumin levels ranged from 2.3 to 3.3 g/dL (normal 3.5–5.3 g/dL), with a low prealbumin level of 9.7 mg/dL (normal 17.0–35.0 mg/dL). Computed tomography of the chest, abdomen, and pelvis noted wall thickening of the mid-distal esophagus with mucosal enhancement. The patient underwent surgical gastrojejunostomy tube placement, which was later converted to separate gastrostomy and jejunal tubes. An inpatient EGD was performed with findings of nonerosive chronic antral gastritis (Figure 3). A gastric emptying study noted 67% of retained food in the stomach at 4 hours (normal <10%). Despite metoclopramide and Botox injections to the pylorus, symptoms persisted. A

small bowel follow-through showed dilated loops suggestive of ileus with reduced peristalsis throughout the small bowel.

Throughout his hospitalization, the patient's lactate levels remained elevated ranging from 2.5 to 6.8 mmol/L without a clear cause. A persistently elevated lactate and gastric and small bowel dysmotility raised concern for MNGIE. Thymidine and deoxyuridine levels were found to be elevated to 15.83 and 25.92 $\mu\text{mol/L}$, respectively, which was consistent with MNGIE. The patient was readmitted for increased vomiting and was found to be hypotensive requiring vasopressors. The etiology was felt to be sepsis from an infected peripherally inserted central catheter line and mycoplasma pneumonia. His hospital course was complicated by respiratory failure requiring tracheostomy with recurrent pneumonia and bacteremia. He was discharged to home hospice.

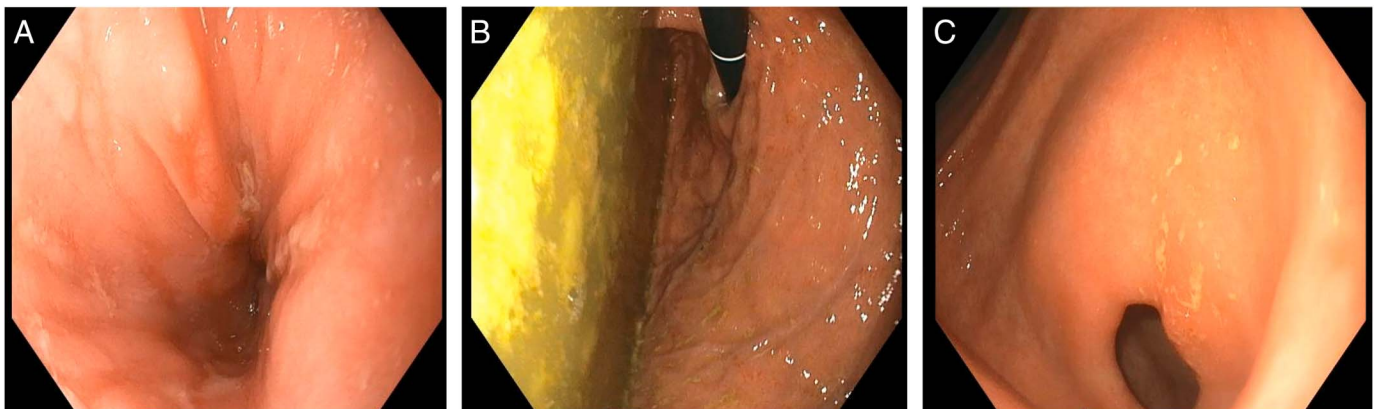


Figure 2. Esophagogastroduodenoscopy showing (A) the gastroesophageal junction with mild erythema, (B) the stomach fundus with retained semisolid food content, and (C) the antrum with mild erythema.

DISCUSSION

In MNGIE, mutations in the thymidine phosphorylase (*TYMP*) gene lead to a deficiency in TYMP activity. This enzyme catalyzes thymidine to thymine and uracil, which plays a pivotal role in DNA synthesis. This particularly affects mitochondria, which are continuously replicating. *TYMP* gene mutations lead to a disruption in the deoxyribonucleoside pool balance, leading to an accumulation of mutations in the mitochondrial DNA and failure of the mitochondria to perform oxidative phosphorylation.¹

Clinical manifestations involve multiple organ systems. Major clinical features include GI dysmotility, cachexia, peripheral neuropathy, ocular symptoms, and diffuse leukoencephalopathy. As the disease progresses, GI symptoms are exacerbated with patients succumbing to malnutrition and complications.¹ Although it has been suggested that the primary cause of GI dysmotility is a loss of interstitial cells of Cajal rich with mitochondria, a 2006 study, histologically examining the small bowel of a patient with MNGIE, found a primary myopathic pathogenesis through mitochondrial DNA depletion with subsequent atrophy and fibrosis of the muscularis propria.^{3,4}

Laboratory abnormalities include an elevated lactate level, which is indicative of an oxidative phosphorylation defect. Elevations in serum uric acid, lactate dehydrogenase, and creatine kinase are observed as well. Magnetic resonance imaging may show findings of white matter abnormalities consistent with diffuse leukoencephalopathy. Electromyography typically shows a decrease in motor and sensory nerve conduction velocities. Diagnosis can be made through thymidine or deoxyuridine levels, thymidine phosphorylase activity, or *TYMP* gene sequencing. Plasma thymidine and deoxyuridine levels are increased to >3 and >5 $\mu\text{mol/L}$, respectively, compared with undetectable levels in healthy controls. TYMP activity is severely reduced, showing little (<10% of healthy unaffected controls) to no activity. There are no specific therapies for this progressive disease with a mean age mortality of 37.6 years. Experimental therapies toward reducing pathologic concentrations of thymidine and deoxyuridine are under investigation. Hemodialysis and platelet transfusions have led to a reduction in thymidine and deoxyuridine levels in 2 cases.¹ Five patients have received enzyme replacement therapy under

compassionate use. Preclinical investigations of gene therapy have also been performed in murine models.¹

MNGIE should be suspected in cases in which GI and neurological involvement coexist, particularly in which there is leukoencephalopathy on magnetic resonance imaging or abnormalities of ocular motility. Our case of chronic GI dysmotility leading to cachexia with a persistently elevated lactate level in a young individual illustrates the clinical presentation and complications of this rare disease.

DISCLOSURES

Author contributions: SA Manski wrote the manuscript and approved the final manuscript. C. Adkins revised the manuscript for intellectual content, approved the final manuscript, and is the article guarantor. C. Smith and B. Blair edited the manuscript.

Financial disclosure: None to report.

Informed consent was obtained for this case report.

Received July 20, 2021; Accepted December 8, 2021

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