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CASE REPORT

MNGIE Syndrome: Liver Cirrhosis Should Be Ruled Out Prior to Bone Marrow Transplantation

Armin Finkenstedt • Melanie Schranz • Sylvia Bösch • Daniela Karall • Sabine Scholl Bürgi • Christian Ensinger • Mathias Drach • Johannes A. Mayr • Andreas R Janecke • Wolfgang Vogel • David Nachbaur • Heinz Zoller

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Abstract Mitochondrial neurogastrointestinal encephalopathy (MNGIE) is an autosomal recessive mitochondriopathy caused by loss-of-function mutations in the thymidine phosphorylase gene. The disease leads to premature death and is characterized by gastrointestinal dysmotility and cachexia, external ophthalmoplegia, a sensorimotor neuropathy, and leukoencephalopathy. Bone marrow transplantation (BMT) is the only potentially curative treatment that can achieve a sustained biochemical correction of the metabolic imbalances.

We report a 23-year-old male homozygous for the c.866A > C, p.Glu289Ala mutation of the TYMP gene, who presented with fatty liver and cachexia. Laboratory examinations were unremarkable except for increased transaminase activities. Grade II fibrosis and steatosis was found in an initial and a follow-up liver biopsy 4 years later. Myeloablative conditioning and BMT was performed 10 years after initial presentation due to the progressive weight loss and polyneuropathy. Pre-transplant liver staging was normal except for an elevated transient elastography of 31.6 kPa. Severe ascites developed after transplantation and liver function deteriorated progressively to liver failure. Despite engraftment on day +15, the patient died on day +18 from liver failure. Autopsy revealed micronodular liver cirrhosis, and postmortem diagnosis of acute-on-chronic liver failure was done.

This case illustrates the difficulties and importance of diagnosing liver cirrhosis in MNGIE. Before BMT, patients must be carefully evaluated by transient elastography, liver biopsy, or assessment of hepatic venous pressure gradient. In patients with liver cirrhosis, further studies should evaluate if liver transplantation may be an alternative to BMT. Considerable amounts of thymidine phosphorylase are expressed in liver tissue which may prevent accumulation of toxic metabolites.

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A. Finkenstedt · M. Schranz · W. Vogel · H. Zoller (✉)
Department of Medicine II Gastroenterology and Hepatology, Medical University of Innsbruck, Anichstrasse 35, 6020 Innsbruck, Austria
e-mail: heinz.zoller@i-med.ac.at

S. Bösch
Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria

D. Karall · S.S. Bürgi
Department of Pediatrics I, Medical University of Innsbruck, Innsbruck, Austria

C. Ensinger · M. Drach
Department of Pathology, Medical University of Innsbruck, Innsbruck, Austria

J.A. Mayr
Department of Pediatrics, Paracelsus Medical University, Salzburg, Austria

A.R. Janecke
Division of Human Genetics, Molecular and Clinical Pharmacology, Medical University of Innsbruck, Innsbruck, Austria

D. Nachbaur
University Hospital for Internal Medicine V, Hematology and Oncology, Medical University, Innsbruck, Austria

Introduction

Mitochondrial neurogastrointestinal encephalopathy (MNGIE) is an autosomal recessive mitochondriopathy caused by loss-of-function mutations in the thymidine

phosphorylase gene TYMP. Imbalances in the mitochondrial deoxynucleoside 5'-triphosphate pools result in increased uracil incorporation into the mitochondrial DNA, producing mitochondrial DNA instability and accumulation of mutations. Clinically, the disease is characterized by gastrointestinal dysmotility and cachexia, ptosis, external ophthalmoplegia, and a sensorimotor neuropathy. A leukoencephalopathy is observed in brain magnetic resonance imaging (MRI) (Hirano et al. 2004). Symptoms usually begin between the first and fifth decade of life with a progressive course leading to premature death (Nishino et al. 2000). Bone marrow transplantation (BMT) or allogeneic hematopoietic stem-cell transplantation (HSCT) is the only potentially curative treatment that can achieve genetic correction of the defect in hematopoietic cells and a sustained biochemical correction of the metabolic imbalances (Hirano et al. 2006). To date, HSCT for MNGIE has been reported in 11 patients with varying outcome (Halter et al. 2011; Filosto et al. 2012). A standardized approach to HSCT has been proposed recently to optimize the therapy for patients with MNGIE (Halter et al. 2011). We report a lethal outcome due to acute-on-chronic liver failure from myeloablative conditioning in a patient with MNGIE complicated by liver cirrhosis undiagnosed prior to BMT.

The patient was a 23-year-old male, who presented with fatty liver and cachexia (body mass index 19 kg/m^2). In his family history, two sisters had died at the age of 28 and 30 years, respectively, with a diagnosis of "anorexia nervosa with secondary leukodystrophia." Laboratory examinations were unremarkable except for increased transaminase activities. The liver biopsy showed grade II fibrosis (Metavir) and 70 % steatosis (Fig. 1a). Leukoencephalopathy was found on MRI of the brain. During the next 4 years, the patient developed diarrhea and lost further 10 % of his body weight. A follow-up liver biopsy showed stable steatosis and fibrosis (grade I-II). The patient then presented with ptosis, external ophthalmoplegia, and sensorimotor neuropathy. Based on the family history and clinical presentation, MNGIE syndrome was considered and the diagnosis confirmed by an increased urinary 2-deoxyuridine concentration and homozygosity for the pathogenic c.866A > C, p.Glu289Ala mutation of the thymidine phosphorylase gene in the index patient and an older symptomatic sister. This mutation is known to be restricted to European patients where it is associated with a clinical presentation similar to that of our patient. The prevalence of liver disease has been reported to be < 10 % in MNGIE patients, where exact data in patients homozygous for p.Glu289Ala are lacking. (Garone et al. 2011).

In the light of the progressive course of the disease and the family history, BMT was discussed and offered to the patient as a treatment option. Pre-transplant liver staging included a complete clinical-biochemical and serological evaluation of common metabolic, viral, and immune liver diseases; computed tomography; and ultrasound. Except for transaminase activities lower than twice the upper limit of normal and an elevated transient elastography of 31.6 kPa, all other liver investigations were normal. Ten years after initial presentation, a 28-year-old female 1/12 HLA-antigen-mismatched donor (HLA-C-allele) had been identified and myeloablative conditioning was performed with busulphan 3.2 mg/kg bodyweight in divided doses (day −7 to day −4; total dose 12.8 mg/kg), cyclophosphamide 60 mg/kg bodyweight once daily (day −3 and −2; total dose 120 mg/kg), and anti-thymocyte globulin 2.5 mg/kg bodyweight (day −3 to day −1; total dose 7.5 mg/kg). Standard cyclosporine and methotrexate were given for prophylaxis

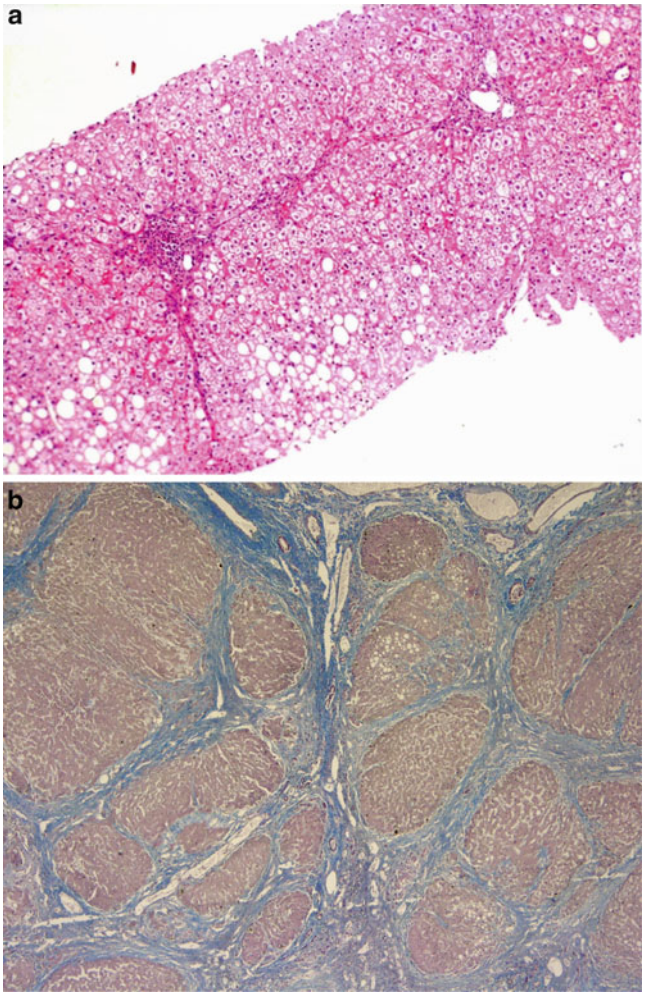

Fig. 1 **Panel a**: Liver biopsy at the time of first presentation 10 years prior to BMT shows a normal liver architecture with fibrosis grade II and 70 % steatosis (hematoxylin and eosin stain). **Panel b**: Postmortem liver histology shows bridging fibrosis and micronodular cirrhosis (chromotrop-anilinblue staining). Pictures were captured using an Olympus BH2 microscope (Olympus, Vienna, Austria) with a Jenoptik Progress C12 digital camera and Progress Capture Pro 2.5 software (Jenoptik, Jena, Germany). Panel a 100x, panel b 40x

against graft-versus-host disease according to the Seattle Protocol (Storb et al. 1989). On day 0, 2.69 x 10^8 nucleated bone marrow cells/kg bodyweight were transplanted. During the next days, the patient developed a progressive paralytic ileus and severe ascites. This was complicated by pneumonia. Despite treatment with antibiotics and steroids, the patient developed an acute respiratory distress syndrome and was mechanically ventilated from day +10 onward. Hemofiltration was started on day +11 due to renal failure. Liver function deteriorated progressively and the patient developed liver failure with intractable lactic acidosis. Despite engraftment on day +15, the patient died on day +18 from multi-organ failure secondary to acute-on-chronic liver failure. Autopsy revealed advanced micronodular liver cirrhosis macroscopically, which was confirmed by post-mortem histology (Fig. 1b). Acute deterioration of liver function after BMT could have been due to vascular liver diseases such as sinusoidal obstruction, or Budd Chiari Syndrome. Alternative causes include acute infection with hepatitis viruses and non-hepatotrophic viruses such as EBV or CMV in the immunocompromised host, all of which were excluded after liver failure was recognized. Hepatotoxic myeloablative conditioning may have been the precipitating event of acute-on-chronic liver failure, although a relation with the infectious complication cannot be excluded.

The present case illustrates the difficulties in detecting advanced-stage liver disease in MNGIE. Liver cirrhosis, which is a rare complication of MNGIE and probably caused by accumulation of toxic intermediates (Shoffner 2011), was excluded by liver biopsy 7 years prior to BMT and remained undetectable upon imaging studies immediately prior to the intervention. The only pre-transplant test suggestive of cirrhosis was an increased transient elastography, but lacking other findings compatible with cirrhosis, a liver stiffness of >30 kPa was not attributed to advanced fibrosis. The presence of cirrhosis was only identified during autopsy. This is in accord with the emerging concept that liver disease staging requires multidimensional assessment by noninvasive and invasive tests (Auberger et al. 2012). The progressive natural course advocates careful evaluation including transient elastography, liver biopsy, or assessment of hepatic venous pressure gradient.

Diagnosis of advanced-stage liver disease will determine the management of patients with MNGIE, and in particular affects the decision of whether BMT/HSCT should be carried out. Considering the hepatotoxicity of drugs required for myeloablative conditioning, the risk for severe complications or liver-related death is significantly increased in patients with liver cirrhosis. Furthermore, clinically relevant mitochondrial toxicity of myeloablative conditioning has been described. Despite the limited experience with stem cell transplantation for MNGIE, conditioning with busulphan and fludarabine seems favorable (Halter et al. 2011). In liver disease patients, even the risk of reduced intensity conditioning might be unacceptably high. Based on the experience from patients with hepatic amyloidosis where liver transplantation has been performed prior to BMT, such an approach could be adopted for MNGIE patients (Kumar et al. 2002). If such a sequential approach is considered, it should be carefully evaluated if liver transplantation alone would also prevent further accumulation of toxic metabolites as considerable amounts of thymidine phosphorylase are expressed in liver tissue (Zimmerman and Seidenberg 1964). If this were the case, subsequent BMT after liver transplantation might no longer be necessary.

In conclusion, despite significant progress in diagnosis and treatment of MNGIE syndrome, the disease remains a challenge. The presence of advanced-stage liver disease should be excluded prior to BMT/HSCT using noninvasive and invasive tests and liver transplantation should be evaluated as an alternative treatment option in selected patients.

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