A 5-Year-Old Boy with Vomiting, Abdominal Pain, and Fatigue

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A 5-year-old boy presented to our hospital with complaints of vomiting and abdominal pain. We were informed that his complaints began 1 day before he presented, and he also had concurrent fatigue and subfebrile fever. There were no accompanying symptoms such as dysuria, arthralgia, rash, diarrhea, or jaundice. The patient had previously been admitted to a different hospital where it was noted he had high serum transaminases (aspartate aminotransferase was twofold normal and alanine aminotransferase was fivefold normal levels) and elevated liver function tests at 8 months and 4 months previously. His symptoms had resolved within 2 days and his liver function tests returned to normal values about 1 month after discharge. His medical history is remarkable for an episode of neutropenia secondary to viral infection at age 18 months. He had no history of travel and his family history is unremarkable.

Upon physical examination, his weight and height were in the 25th to 50th percentile and vital signs were normal for his age. There was no lymphadenomegaly and organomegaly.

Laboratory findings were as follows: hemoglobin 13.1 g/dL (11.5-12.5 g/dL), hematocrit 38.3% (34%-37%), white blood cell 6,400/mm³ (5.0 to 14.5×10³ / mm³), platelets 477,000/mm³ (150 to 400 x 10³ / mm³), ESR 30 mm/h (0-20), glucose 79 mg/dL (74-106), blood urea nitrogen 10 mg/dL (9-23 mg/dL), creatinine 0.52 mg/dL (0.6-1.1 mg/dL), sodium 138 mmol/L (132-146 mmol/L), potassium 4.4 mmol/L (3.5-4.5 mmol/L), chlorine 107 mmol/L (99-109 mmol/L), calcium 8.6 mg/dL (8.3-10.6 mg/dL), phosphorous 3.8 mg/dL (2.4-5.1 mg/dL), uric acid 2.5 mg/dL, aspartate aminotransferase 116 U/L (0-35 U/L), alanine aminotransferase 196 U/L (0-45 U/L), gamma-glutamyl transferase 14 IU/L (7-50), alkaline phosphatase 183 U/L (0-383), creatine kinase 29 U/L (33-211), lactate dehydrogenase 145 U/L (126-246), total bilirubin 0.3 mg/dL (0.3-1.2 mg/dL), direct bilirubin 0.1 mg/dL (0-0.2 mg/dL), total protein 5.2 g/L (5.7-8.2 g/L), albumin 3.5 g/L (3.2-4.8 g/L), C-reactive protein 35 mg/L (0.5 mg/L), iron 45 ng/dL (65-175 ng/dL), iron binding capacity 343 ng/dL (250-450 ng/dL), and ferritin 120 ng/dL (7-140 ng/dL). Prothrombin time (12.2 seconds, 10.7-13 seconds) and activated partial thromboplastin time (32.16 seconds, 22-36.9 seconds) were normal in the coagulation profile. Urine analysis was normal. Blood and urine cultures were unremarkable.

Other laboratory studies were conducted for etiology. Serology tests for hepatitis B and C, HIV, cytomegalovirus, Epstein-Barr virus, rubella, and toxoplasmosis were negative except for anti-HBs positivity. Serum ceruloplasmin and alpha-1 antitrypsin were normal (0.379 g/L [0.286-0.561 g/L], and 1.72 g/L [1.02-1.57 g/L], respectively). Serum immunoglobulins were normal, and autoimmune hepatitis markers (anti-nuclear antibodies, anti-smooth muscle antibodies, anti-mitochondrial antibodies, smooth muscle antibodies, and anti-liver-kidney-microsome antibodies) were negative. Thyroid function tests and celiac antibodies were normal. Abdominopelvic ultrasonography revealed no specific pathology.

The patient was given intravenous hydration and his symptoms improved within 48 hours. Serum aminotransferase levels decreased within 1 week, and after 3 weeks they returned to normal levels.

For diagnosis, see page 351

Editor’s note: Each month, this department features a discussion of an unusual diagnosis. A description and images are presented, followed by the diagnosis and an explanation of how the diagnosis was determined. As always, your comments are welcome via email at pedann@Healio.com.
Because of his recurring symptoms of vomiting, abdominal pain, and transient elevation, a genetic test for familial Mediterranean fever (FMF) was conducted. The test revealed a heterozygous M694V mutation. Family screening demonstrated that his mother had a homozygous M694V mutation. Due to positive family history, his cyclic clinical findings, and his positive genetic test, colchicine at a dose of 1 mg/day was administered. For the next 9 months he did not have any symptoms and his liver enzyme tests were within normal limits.

**DISCUSSION**

FMF is an autosomal recessive disorder characterized by recurrent attacks of fever, peritonitis, pleuritis, arthritis, and aseptic meningitis, optic neuritis, and afebrile episodes. For example, aseptic meningitis, optic neuritis, and afebrile episodes have been documented during episodes of FMF.

Fatty liver disease is associated with non-alcoholic fatty liver disease. Secondary amyloidosis in FMF may involve the liver, but the primary symptoms involve renal and gastrointestinal symptoms.

The FMF gene (MEFV) encodes a protein called pyrin. Pyrin is thought to indirectly regulate caspase-1 function, and therefore influence interleukin-1 (IL-1) processing and apoptosis. In patients with FMF, pyrin is defective; therefore, an exaggerated inflammatory response that is secondary to cytokine stimulation (including IL-6, tumor necrosis factor [TNF]-alpha, and IL-1) can be triggered by unknown stimuli. Although these cytokines cause fever and a brisk increase in the acute phase reactants by the liver during FMF attacks, no clear evidence exists regarding whether these cytokines have an effect on liver function.

Despite being commonly used diagnostic tests in liver diseases, liver function tests (LFTs) do not reveal the exact disorder of the liver. When discussing LFTs, two important parameters come to mind: alanine aminotransferase (ALT), and aspartate aminotransferase (AST). A careful history and review of laboratory data are critical for identifying a medication as the reason for elevated serum aminotransferases. Our patient had not used any herbal or chemical medicine. He had accompanying symptoms such as jaundice, arthralgias, myalgias, rash, anorexia, weight loss, pruritus, and changes in urine and stool. He had only mild abdominal pain, and fever during his attacks was mild. Acute, chronic, or transient elevation of serum aminotransferase is important in the clinical evaluation. However, simultaneous elevation of several LFTs is important as well.

Abnormal LFTs could be caused by a variety of diseases, such as infections, hereditary hemochromatosis, cholestasis, muscle disorders, thyroid disorders, celiac disease, autoimmune hepatitis, Wilson disease, and alpha-1 antitrypsin deficiency. Infectious causes such as hepatitis B and C, HIV, Epstein-Barr virus, and cytomegalovirus were excluded on the basis of multiple negative serological results. Hereditary hemochromatosis (HHC) is a common genetic disorder. Because serum iron, total iron binding capacity, and serum ferritin values of the patient were normal, HHC was not assessed for this case. Elevated serum aminotransferases may be caused by disorders that affect organs other than the liver, such as striated muscle disorder. In cases of striated muscle disorder, serum levels of creatine kinase and lactate dehydrogenase (LDH) are elevated to the same degree, but this was not observed in our patient. Thyroid disorders can cause elevated aminotransferases but the mechanism is unclear.

Because thyroid function in our patient was normal, celiac disease was noted as another diagnostic possibility. Several reports have investigated elevated serum aminotransferases in patients with undiagnosed celiac disease. For a diagnosis of celiac disease, appropriate antibody screening with serum anti-endomysial immunoglobulin A (IgA) or anti-tissue transglutaminase IgA antibodies should be positive; the negative results of our patient were not compatible with celiac disease. Similarly, autoimmune hepatitis, Wilson disease, and alpha-1 antitrypsin deficiency were excluded with normal results of tests including antinuclear antibodies, anti-smooth muscle antibodies, liver-kidney microsomal antibodies, serum ceruloplasmin, and normal serum alpha-1 antitrypsin levels. This patient had transient elevations of serum transaminases that occurred cyclically.

Abnormal liver function during episodes of FMF is rarely seen. A study by Korkmaz et al. investigated whether...
or not FMF patients display abnormal liver functions during attack periods. Forty-one consecutive FMF patients with attacks were included in this case report, and levels of liver transaminases increased in four patients with FMF during the attack. Because pyrin is defective in FMF patients, this leads to exaggerated inflammatory response secondary to cytokine stimulation, including IL-6, TNF-alpha, and IL-1. Even though these cytokines cause fever and a brisk increase in acute phase reactants by the liver during FMF attacks, no clear evidence exists regarding whether these cytokines have an effect on functions of the liver. It should also be noted that TNF-alpha and IL-6 may cause some changes in liver function during sepsis.

How can we explain the reason for elevations of serum transaminases seen during attacks in an FMF patient? Some arguments can be made regarding the effects of cytokines on the liver. Inflammation in the absence of pathogens occurs in all tissues in response to a wide range of stimuli that cause tissue stress and injury. In sterile inflammation, endogenous damage-associated molecular patterns, which are usually hidden from the extracellular environment, are released on tissue injury and activate receptors on immune cells. Activation of this pattern results in a wide range of immune responses, including production of pro-inflammatory cytokines and localization of immune cells to the site of injury.

With accumulation of a cytosolic protein complex known as the inflammasome in the cell, damage-associated molecular patterns activate the serine protease caspase-1, which results in activation and secretion of IL-1 and other cytokines. Such sterile inflammation is a key process in drug-induced liver injury, non-alcoholic steatohepatitis, and alcoholic steatohepatitis and is a major determinant of fibrosis and carcinogenesis. FMF is an inflammatory disease, and cytokines such as IL-6, TNF-alpha, and IL-1 play a role in the development of inflammation. Cytokines such as TNF-alpha and IL-6 may cause some changes in liver functions.

This patient was an unusual case presenting with FMF-associated transient elevation in LFTs. In countries where FMF is prevalent (a carrier incidence of 1 in 3 to 1 in 5) such as Turkey, FMF is an inflammatory disease, and cytokines such as IL-6, TNF-alpha, and IL-1 play a role in the development of inflammation. In the context of hepatocyte injury and hepatic failure, cytokines’ effects on liver functions. In countries where FMF is prevalent, such cyclic symptoms and laboratory findings should be considered.

REFERENCES