

Clinical Communications

A case of acquired hereditary angioedema

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Clinical Implications

- We present a case of type 1 hereditary angioedema suspected to have been acquired through a liver transplant.

TO THE EDITOR:

Angioedema related to C1 inhibitor (C1-INH) deficiency is a debilitating disorder characterized by recurrent episodes of tissue swelling within the skin, upper respiratory tract, and gastrointestinal tract without the presence of pruritus or urticaria. The most serious manifestations include bouts of severe abdominal pain with vomiting lasting 2 to 5 days as well as laryngeal edema that can lead to fatal asphyxiation. We describe a patient who we believe acquired angioedema after liver transplantation from a donor with hereditary angioedema due to C1-INH deficiency.

This 53-year-old white man with type 2 diabetes and obesity underwent uncomplicated liver transplantation on April 6, 2010, for hepatitis C and alcohol-induced cirrhosis. Three months after transplantation he was seen initially at another facility with enteritis. Computed tomography of the abdomen/pelvis showed small-bowel edema and some pelvic fluid with a possibility of portal vein stenosis. Portal venography and dilation of a mild portal vein stenosis was performed, but the patient continued to have recurrent bouts of abdominal pain, vomiting, and diarrhea. The infectious workup was unrevealing with the exception of a positive stool *Clostridium difficile* antigen, which was later cleared following antibiotics.

His presentation evolved over the ensuing 12 months, when episodes of tongue swelling with difficulty swallowing began to follow the attacks of abdominal pain. Abdominal pain episodes typically lasted 2 to 4 days and resulted in several hospitalizations. The patient also experienced scrotal and hand swelling in addition to 1 episode of severe laryngeal edema requiring intubation. Urticaria was consistently absent. Patient denied ever experiencing any of these symptoms before liver transplantation, and he had no history of anaphylaxis, severe allergic reactions, and drug or environmental allergies. The patient had never been on an angiotensin-converting enzyme-inhibitor or angiotensin-receptor blocker. He denied any illicit substance use and had no family members with angioedema.

Diagnostic evaluation included measurement of C1-INH: 6 mg/dL (normal range, 21-39 mg/dL), C1q: 17.2 mg/dL (normal range, 11.8-23.8 mg/dL), complement factor 4: undetectable, and complement factor 3: 124 mg/dL (normal range, 88-165 mg/dL). Repeat laboratory evaluation approximately 1 month later confirmed the complement cascade findings as well as the diagnosis of C1-INH deficiency as the cause of his recurrent angioedema.

Given his age and immunosuppressed state, we suspected acquired angioedema even though C1q was normal. There were no examination finding nor radiographic evidence to support lymphoma and the patient's serologic studies of serum protein electrophoresis and kappa and lambda light chains were all within normal limits. It was later found that the donor had also experienced periodic angioedema and abdominal pain leading to the diagnosis of hereditary angioedema treated with icatibant although angioedema was not related to the cause of the donor's death. No laboratory data were available to confirm the diagnosis of C1-INH deficiency in the donor.

We treated our patient with subcutaneous injections of icatibant (30 mg) when abdominal attacks and/or angioedema occurred, which provided complete relief of symptoms. Later in his course, because of increasing frequency of abdominal attacks, we started prophylactic infusions of C1-INH plasma concentrate. Since initiating prophylactic infusions, his attack frequency has averaged once every 2 months with resolution within 2 hours of self-administering icatibant.

We have followed him for 24 months since diagnosis. He has continued to show no clinical or laboratory findings concerning for the development of lymphatic malignancy.

On review of the literature, we found that reported cases of type 1 hereditary angioedema acquired through a liver transplant are quite rare.¹ Parenchymal cells of the liver are the major source of C1-INH production (other cells such as monocytes and endothelium also contribute), which serves to regulate proteases of the complement, coagulation, and endothelial contact system. A deficiency of hepatic-derived C1-INH through either genetic or acquired means (as in our transplanted patient) results in the dysregulated creation of bradykinin from high-molecular-weight kininogen, a process normally conducted under periods of inflammation or other physiologic stress.² Variations in the *SERPINE1* gene have been traditionally viewed as a genetic cause for HAE; however, more recent data suggest that some alleles may create problems with secretion of normal C1-INH due to the creation of large intracellular aggregates within the endoplasmic reticulum.³ Regardless of the cause, there develops an increase in vascular permeability and the symptoms of angioedema through the binding of bradykinin to endothelial B2 receptors.² With administration of plasma-derived C1-INH, the interaction of the kallikrein precursor prekallikrein with high-molecular-weight kininogen is stabilized and control of this inflammatory system is restored.⁴ Correction of HAE has also been seen as a secondary effect in allogeneic stem cell transplantation.⁵

Other examples of hepatic synthesis defects that have been subsequently acquired from donor livers are rare. Transplanted hemostatic factor deficiencies leading to hemophilias have been published in case reports.⁶ Carriers of the MZ allele for alpha-1 antitrypsin have a 10 times greater incidence of cryptogenic cirrhosis than do carriers of the wild-type MM phenotypes and have a greater development of end-stage liver disease in patients infected with hepatitis C virus.⁷ Because most carriers of the MZ alleles do not go on to develop liver disease, donor organs containing the potentially harmful variant may be used for transplantation. This was illustrated in a study of 789 liver transplantation patients in which 6 patients (0.8%) showed

mutated alpha-1 antitrypsin accumulation in the transplanted liver.⁸

The theme among these situations is that deficiencies in many hepatic-derived synthetic proteins and enzymes may have very subtle symptoms or laboratory findings and may even be completely asymptomatic. Currently, donor screening questionnaires do not ask about episodes consistent with angioedema. Our case further underscores the importance of thorough donor screening practices and the need for awareness of potential hereditary conditions that may be overlooked.

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