Case 32-2011: A 19-Year-Old Man with Recurrent Pancreatitis

Uzma Shah, M.D., and Anuradha S. Shenoy-Bhangle, M.D.

Dr. Christopher J. Moran (Pediatric Gastroenterology): A 19-year-old man was admitted to this hospital because of recurrent pancreatitis.

The patient had been well until approximately 6 months earlier, when lethargy and epigastric pain developed, associated with a dry throat, subjective fever, and frontal headache, which were relieved by acetaminophen. He went to a clinic for evaluation. He reported that 3 days earlier he had consumed six alcoholic beverages in one sitting (0.7 to 1.0 liters of vodka and two beers). On examination, the blood pressure was reportedly 140/100 mm Hg. A rapid screening test for streptococcus was positive. Penicillin and an antacid were prescribed, without improvement in the pain. Two days after the onset of pain, the patient saw his pediatrician. On examination, the blood pressure was 142/100 to 152/100 mm Hg. A monospot test was negative. The epigastric pain decreased slightly, and pain in the flanks and back developed. He returned to his pediatrician; laboratory-test results are shown in Table 1. Computed tomography (CT) of the abdomen reportedly showed fat stranding and inflammation of the pancreas, features consistent with pancreatitis, with a normal gallbladder and no evidence of dilatation or obstruction of the biliary tree. He was transferred to this hospital.

The patient reported constant epigastric pain, which he rated at 7 on a scale of 0 to 10, with 10 indicating the most severe pain. The pain intermittently increased in intensity and changed location with positioning. The patient had had constipation, difficulty sleeping because of the pain, decreased appetite, and during the previous week, weight loss of approximately 4.5 kg, without nausea, vomiting, or hematuria. His symptoms were not relieved by the administration of antacids, acetaminophen, lansoprazole, psyllium fiber supplement, polyethylene glycol, or defecation. The temperature was 38.1°C, the blood pressure 139 to 162 mm Hg systolic and 77 to 90 mm Hg diastolic, and the pulse 96 beats per minute; the respiratory rate was normal, and the oxygen saturation was 95% while he was breathing ambient air. The weight was 142.2 kg, the height 188 cm, and the body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) 40 (>97th percentile). The posterior oropharynx was erythematous, with moist mucous membranes; there was white plaque on the tongue. The abdomen was soft, with decreased bowel sounds, tenderness to deep palpation in the epigastrium, and slight
guarding; there was no distention or rebound. There was tenderness in the midback and no tenderness at the costovertebral angle. The skin was diffusely flushed on the cheeks, extremities, and trunk. The red-cell indexes and platelet count were normal, as were tests of renal function and measurements of electrolytes, glucose, phosphorus, calcium, protein, albumin, total and direct bilirubin, alkaline phosphatase, aspartate aminotransferase, cholesterol, triglycerides, and low-density lipoprotein cholesterol; other test results are shown in Table 1. Urinalysis revealed 1+ ketones and bilirubin and trace urobilinogen.

The patient was admitted to this hospital. Intravenous fluids, narcotic analgesia, and omeprazole were administered, with improvement. Initial restriction of oral intake was followed by a gradually increasing diet. He was discharged on the fifth day on a low-fat diet and referred to the Division of Adolescent and Young Adult Medicine for primary care, blood-pressure monitoring, a weight-loss program, and a discussion about high-risk behaviors, including binge drinking. At follow-up, results of thyroid-function tests were normal and testing for hepatitis B and C viruses was negative; other test results are shown in Table 1. Urinalysis revealed 1+ ketones and bilirubin and trace urobilinogen.

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The patient abstained from alcohol for 3 months and then began to drink socially again. Two weeks later, severe abdominal pain recurred, with radiation to the back and decreased appetite. On the fifth day of symptoms, he was readmitted to this hospital. On examination, the blood pressure was 142/98 mm Hg; other vital signs were normal. There were abdominal striae, decreased bowel sounds, a palpable liver edge, and mild tenderness to deep palpation in the epigastrium; the remainder of the examination was normal. The prothrombin time was 14.4 seconds (reference range, 10.3 to 13.2); other tests of coagulation and renal function were normal, as were measurements of electrolytes, glucose, protein, albumin, globulin, bilirubin, alkaline phosphatase, and aspartate aminotransferase. Other test results are shown in Table 1. Results of an abdominal ultrasound examination were normal. Intravenous fluids and morphine were administered, with improvement. The patient was discharged on the fourth day.

At follow-up visits in the Adolescent and Young Adult Medicine Division during the next 6 weeks, the patient felt well and the blood pressure was normal; test results are shown in Table 1. During the next 5 weeks, he consumed one or two alcoholic beverages approximately twice a week. Three days before this admission, abdominal pain (rated at up to 9 on a scale of 0 to 10) recurred that was associated with nausea, decreased appetite, clamminess, and light-headedness. He was readmitted to this hospital.

The patient had received all routine immunizations and had been well. He was a college student and lived in an apartment with other students when not living with his parents and sibling. He smoked one or two cigarettes weekly and reportedly had no use of illicit drugs. His girlfriend had recently had infectious mononucleosis. His father had high cholesterol, his maternal grandfather had coronary artery disease, his maternal grandmother had throat cancer, and other maternal relatives had type 1 diabetes mellitus and gallstones; paternal and maternal family members reportedly had alcoholism.

On examination, the blood pressure was 160/93 mm Hg and the weight 133.5 kg; other vital signs and the oxygen saturation were normal. There were decreased bowel sounds, pain in the upper quadrants that radiated to the back and occurred at rest and with palpation, and no distention or rebound. The remainder of the examination was normal. Urinalysis revealed clear, amber urine with 1+ bilirubin, 2+ ketones, and trace albumin and urobilinogen; it was otherwise normal. Laboratory-test results are shown in Table 1. Ultrasonography of the abdomen revealed mild splenomegaly (14 cm). Intravenous fluids, ranitidine, and narcotic analgesics were administered, with symptomatic improvement. On the second day, tests for heterophile antibody and antibodies to Epstein–Barr virus (EBV) were negative; T-lymphocyte subsets were normal.

Magnetic resonance imaging (MRI) of the abdomen after the administration of gadolinium and magnetic resonance cholangiopancreatography (MRCP) revealed a normal pancreas and pancreatic duct. The common bile duct was normal, with no calculi.

A diagnostic test was performed.

**Differential Diagnosis**

*Dr. Uzma Shah:* When he was 19 years of age, this previously well young man began to have recurrent episodes of abdominal pain, with laboratory
Table 1. Laboratory Data.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference Range, Age-Adjusted†</th>
<th>Pediatrician’s Office</th>
<th>This Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 Days before Admission</td>
<td>Day of 1st Admission</td>
<td>Outpatient Follow-up, 15 Days after Admission</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>41.0–53.0 (men)</td>
<td>39.9</td>
<td>44.4</td>
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<tr>
<td>Hemoglobin (g/dl)</td>
<td>13.5–17.5 (men)</td>
<td>14.5</td>
<td>16.2</td>
</tr>
<tr>
<td>White-cell count (per mm³)</td>
<td>4500–13,000</td>
<td>16,200</td>
<td>18,100</td>
</tr>
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<td>Differential count (%)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Neutrophils</td>
<td>40–62</td>
<td>80</td>
<td>87</td>
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<tr>
<td>Lymphocytes</td>
<td>27–40</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Monocytes</td>
<td>4–11</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>0–8</td>
<td>1</td>
<td>3</td>
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<tr>
<td>Basophils</td>
<td>0–3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Magnesium (mmol/liter)</td>
<td>0.7–1.0</td>
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<tr>
<td>Lipase (U/liter)</td>
<td>13–60</td>
<td>74</td>
<td>47</td>
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<tr>
<td>Amylase (U/liter)</td>
<td>3–100</td>
<td>99</td>
<td>69</td>
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<tr>
<td>Alanine aminotransferase (U/liter)</td>
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<td>92</td>
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<tr>
<td>High-density lipoprotein cholesterol (mg/dl)</td>
<td>35–100</td>
<td>21</td>
<td></td>
</tr>
</tbody>
</table>

* To convert the values for magnesium to milligrams per deciliter, divide by 0.4114. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are age-adjusted for patients who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.
evidence of acute pancreatitis, that required repeated hospitalizations.

CAUSES OF RECURRENT ACUTE PANCREATITIS
When acute episodes of pancreatitis occur repeatedly, as they have in this patient, the condition is described as recurrent acute pancreatitis. Acute pancreatitis is much less common in children and adolescents than in adults, and the causes differ between the two groups. It is important to determine the cause in this patient and treat it, since recurrent acute pancreatitis may result in injury to the pancreatic duct and progressive inflammation and scarring of the duct, leading to chronic pancreatitis. Chronic pancreatitis may result in exocrine and endocrine pancreatic insufficiency and an increased risk of pancreatic cancer. In this case, I would first investigate the most common causes of acute and chronic pancreatitis (Table 2).

STRUCTURAL ABNORMALITIES
One of the most common causes of acute pancreatitis is obstruction of the pancreaticobiliary tree. It is important to rule out gallstones, structural anomalies of the duct, and cysts. Although 40% of episodes of acute pancreatitis in adults are caused by gallstones, pancreatitis developed in only 4% of 382 children with gallstones in one study. It would nonetheless be important to consider a diagnosis of gallstones in this adolescent, in view of the high BMI and family history of elevated cholesterol levels and cholelithiasis.

Other, rarer structural anomalies that should be considered include pancreas divisum, choledochal cysts, annular pancreas, and dysfunction of the sphincter of Oddi. In this case, the first imaging study was CT, performed at another facility, rather than ultrasonography, which is preferred. On the CT scan, the gallbladder appeared normal, with no evidence of biliary-duct dilatation or obstruction. MRCP or endoscopic retrograde cholangiopancreatography (ERCP) would allow better examination of the biliary tree for evidence of pancreas divisum.

May we review the imaging studies?
Dr. Anuradha S. Shenoy-Bhangle: Ultrasound examination of the abdomen was the first study performed at this hospital. In pediatric patients with pancreatitis, our initial screening tool is ultrasonography. It is a noninvasive bedside procedure, involves no radiation, and is the best imaging method for seeing gallstones. Biliary obstruction and choledochal cysts are also evident. The disadvantage is poor visualization of the pancreas and pancreatic ductal anatomy, so that congenital anomalies such as pancreas divisum or annular pancreas, which are the most common causes of pediatric pancreatitis, are not shown well. In this case, ultrasonography revealed an absence of cholelithiasis, cholecystitis, ascites, or loculated fluid collections in the abdomen. The pancreas was obscured by bowel gas and thus was poorly visualized. There was borderline splenomegaly and no imaging evidence of portal hypertension.

After recurrent episodes of pancreatitis, secretin-enhanced MRCP and MRI of the abdomen were performed. At this hospital, we find that MRCP is the best method for assessing pancreatic ductal anatomy and congenital anomalies of the pancreaticobiliary system. It is noninvasive (in contrast to ERCP), does not involve radiation, and can reveal congenital anomalies and cysts. Secretin can be administered to distend the pancreatic duct, allowing better visualization of the ductal anatomy and quantification of pancreatic exocrine function. A disadvantage of MRI in young children is that sedation or anesthesia may be required. We do not use CT as a primary diagnostic tool for acute pancreatitis; it is reserved for diagnostic mysteries or the evaluation of complications. In this case, MRCP revealed a single, normal-size pancreatic duct, with no evidence of

<table>
<thead>
<tr>
<th>Table 2. Causes of Acute and Chronic Pancreatitis in Children.*</th>
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<tbody>
<tr>
<td><strong>Cause</strong></td>
</tr>
<tr>
<td>--------------------</td>
</tr>
<tr>
<td>Biliary-duct obstruction</td>
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<tr>
<td>Idiopathic obstruction</td>
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<tr>
<td>Medication</td>
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<td>Trauma</td>
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<td>Systemic disease</td>
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<td>Viral infection</td>
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<tr>
<td>Metabolic</td>
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<td>Genetic</td>
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* Data are from Clifton et al. for chronic pancreatitis (percentages do not total 100 because of rounding) and from Park et al. for acute pancreatitis (some patients had more than one cause).
pancreas divisum or annular pancreas (Fig. 1). The duct distended normally in response to the administration of secretin and reverted back to normal size within 10 minutes after administration. The common bile duct was normal and had no calculi in it. There was no pancreatic parenchymal necrosis.

Dr. Shah: Structural and obstructive causes of the patient's pancreatitis are ruled out by these studies.

**METABOLIC CAUSES**

This patient had a high BMI and had been hypertensive on many occasions. Although hypertension may be a clinical manifestation of acute pancreatitis and pain, it was unclear whether the patient had had hypertension before these episodes. Because of his high BMI, a metabolic disease should be considered. His family history included hypercholesterolemia, diabetes mellitus, and gallstones. Metabolic causes of chronic pancreatitis include hyperlipidemias (due to lipoprotein lipase deficiency and apolipoprotein C2 deficiency) and less common causes, such as defective transport of amino acids. Hypertriglyceridemia in particular may be a risk factor for acute pancreatitis in patients who have some genetic mutations that increase the risk of pancreatitis. This patient's lipid profile, blood chemical profile, and thyroid screening were normal.

**TOXINS**

Although there is a long list of drugs that lead to pancreatitis, the most common are anticonvulsant agents, chemotherapy agents for the treatment of cancer, and diuretics. This patient received penicillin during the first episode of pancreatitis. This antibiotic has been associated with pancreatitis but would be unlikely to cause recurrent episodes. Drug-induced injury was unlikely to have been the cause of his symptoms.

**INFECTION**

The patient was febrile and had an elevated white-cell count during the episodes of pancreatitis; therefore, infectious causes should be considered. He had intermittent mild elevations in serum alamine aminotransferase levels. Although a rapid streptococcal screen was positive on his initial presentation, tests for other infectious agents associated with acute pancreatitis (e.g., EBV) and tests for infectious agents associated with recurrent inflammation (e.g., hepatitis B and C viruses and the human immunodeficiency virus) were negative. His girlfriend reportedly had had infectious mononucleosis, but repeat testing of the patient for acute EBV infection was negative. An infectious cause for his pancreatitis seemed unlikely.

**SYSTEMIC DISEASES**

On ultrasound examination, mild splenomegaly was identified. Splenomegaly is occasionally seen during episodes of pancreatitis, but it may be a clinical feature of systemic autoimmune diseases such as autoimmune pancreatitis, inflammatory bowel disease, and primary sclerosing cholangitis. Therefore, an evaluation for autoimmune pancreatitis was indicated, including measurement of serum IgG4, antinuclear antibody, and rheumatoid factor. The patient's IgG4 level was normal, and there was no evidence of beading of the biliary duct on imaging, as would be seen with sclerosing cholangitis.
GENETIC CAUSES

An alcohol binge preceded the first episode of acute pancreatitis in this patient. In adults, alcohol accounts for 35 to 40% of all cases of acute pancreatitis; in children, this would be unusual. However, alcohol is a trigger for pancreatitis in children with an underlying genetic or metabolic predisposition. Genetic mutations are an important cause of recurrent and chronic pancreatitis in pediatric patients (Table 2), and the episodes of pancreatitis are frequently triggered by hyperlipidemia or, as in this patient, alcohol consumption. Among children with chronic pancreatitis, 30% of cases are considered to be idiopathic, possibly because of mutations that have not yet been identified. Identifying a genetic mutation in this patient would have important implications for his future, since mutations are associated with an increased risk of the development of pancreatic insufficiency and pancreatic cancer.

How could a genetic abnormality cause the recurrent episodes of pancreatitis in this patient? In the pancreas, there is a delicate balance between trypsinogen and its activated form, trypsin (Fig. 2). Uncontrolled action of trypsin causes inflammation and pancreatitis. Genetic factors can influence this balance. Cationic trypsinogen (encoded by PRSS1), a high calcium level, and a low pH promote activation of trypsinogen to trypsin. Calcium levels are regulated in part by the calcium-sensing receptor (encoded by CASR) and dysregulated by ethanol. Trypsin is removed both by degradation and by excretion via the pancreatic duct. Degradation is facilitated by chymotrypsin C (encoded by CTRC), and the cystic fibrosis transmembrane conductance regulator (encoded by CFTR) functions to eliminate trypsin by flushing the pancreatic duct. If inflammation occurs, it leads to up-regulation of expression of the serine protease inhibitor Kazal type 1 (encoded by SPINK1), which blocks trypsin, prevents further activation of trypsinogen, and limits further tissue injury.

PRSS1

Gain-of-function mutations in the PRSS1 (serine protease 1) gene are the most common cause of autosomal dominant hereditary pancreatitis. These mutations lead to increased trypsin in the cells, which promotes inflammation. A diagnosis is made in adolescence in most patients. Alcohol, smoking, and dietary fat are triggers for inflammation.

SPINK1

Mutations in SPINK1, also called the pancreatic secretory trypsin inhibitor gene, confer an increased risk of pancreatitis due to an inability of the pancreatic acinar cells to inhibit intracellular trypsin. A combination of genetic and environmental factors influences the development of pancreatitis. In several series, 16 to 23% of previously “idiopathic” cases of pancreatitis were due to SPINK1 mutations. The N34S mutation, in particular, has frequently been associated with pancreatitis.

CFTR

Mutations in the CFTR gene, inherited in an autosomal recessive pattern, are an important cause of chronic pancreatitis. Several studies have shown that CFTR mutations, including uncommon or mild mutations, may be identified in patients with idiopathic chronic pancreatitis, suggesting that additional genetic or environmental disease modifiers may be present. Four subtypes of CFTR mutations have been proposed as causes of chronic pancreatitis. Type 1 is associated with two severe mutations and is the classical form of cystic fibrosis. In type 2, which has variable severity, one allele has a severe mutation and one has a mild mutation. Type 3 is characterized by CFTR mutations that are similar to those seen in type 2, but with an additional mutation in a susceptibility gene such as SPINK1; and type 4 has a heterozygous CFTR mutation with a strong environmental trigger factor, such as alcohol.

CTRC

CTRC destroys activated trypsin. CTRC mutations, in particular the R254W mutation, have been identified in pancreatitis.43

SUMMARY

The recurrent theme in this case is alcohol exposure followed by pancreatic inflammation. I think the most probable cause of recurrent pancreatitis in this adolescent, in view of his history and the absence of structural or obstructive lesions, infectious agents, or other metabolic disease, is an underlying genetic mutation. The alcohol probably triggered these episodes of pancreatitis. I would recommend testing for mutations in PRSS1, SPINK1, CFTR, and CTRC. The patient will also require aggressive management of his high-risk behavior (i.e., his alcohol and tobacco use) and will need to address his overweight status.
**Clinical Diagnosis**

Recurrent pancreatitis, due to a genetic abnormality.

**Dr. Uzma Shah’s Diagnosis**

Recurrent pancreatitis, due to a genetic abnormality.

**Diagnostic Testing**

Dr. Moran: The diagnostic test was screening for genetic mutations associated with pancreatitis. The patient was found to have two *CFTR* mutations — ΔF508 and R31C. The ΔF508 mutation carries the more severe phenotype. A sweat test was equivocal. Genetic testing of the patient’s parents showed that both parents were carriers, a finding that was consistent with a diagnosis of cystic fibrosis in the patient. In addition, the patient had a *SPINK1* mutation. The *PRSS1* gene was normal. The final diagnosis was recurrent pancreatitis due to mutations in the *CFTR* and *SPINK1* genes, triggered by alcohol consumption.

Dr. Shah: It is important to note that a patient with a *CFTR* mutation may have a normal sweat test, because the mutations that affect the pancreas affect the acinar cells, not the sweat glands. This patient has compound heterozygosity for the *CFTR* mutation, as well as a mutation in the susceptibility gene *SPINK1*, so he can be considered to have a type 3 *CFTR* mutation.

**Management and Follow-up**

Dr. Moran: The patient recovered uneventfully from this episode of acute pancreatitis and was discharged on the fourth day.

The patient was counseled on his very strong...
genetic predisposition for pancreatitis (500 times that of the general population) and the potential for the development of exocrine pancreatic insufficiency, diabetes, and pancreatic cancer. He is at particular risk for diabetes owing to pancreatic insufficiency from recurrent pancreatitis and insulin resistance due to his weight. He was counseled on weight loss and on the need to minimize all factors that could contribute to pancreatitis (e.g., alcohol consumption and smoking), which can increase his risk for pancreatic cancer.

In order to rule out a contribution of dysfunction of the sphincter of Oddi, we recommended obtaining an ERCP, despite the risk that performing ERCP could trigger another episode of pancreatitis. The ERCP showed no evidence of an anatomical abnormality that could contribute to the patient’s recurrent pancreatitis, and there were no signs of chronic pancreatitis. Nevertheless, a sphincterotomy was performed, with stent placement; this was complicated by a brief episode of pancreatitis.

The patient was referred to Dr. Mary Shannon Fracchia at the pediatric pulmonary service for evaluation for pulmonary involvement due to cystic fibrosis. He had no history of sinus or pulmonary infections or symptoms, and the results of pulmonary-function tests were normal. Dr. Fracchia recommended beginning treatment with oral pancrelipase.

The patient and his family have been carefully and repeatedly counseled about the implications of recurrent pancreatitis and the need to address the triggering factors. He and his family have heard a consistent message, that alcohol intake is going to affect his long-term health. Each episode of pancreatitis carries a risk of death, and the additive effect of recurrent pancreatitis increases his risks of diabetes and pancreatic cancer.

We offered a referral to the weight center, but the patient did not follow up with this referral. He has quit smoking tobacco. We continue to counsel him that the most important step toward avoiding future episodes of pancreatitis is alcohol abstinence. He has stopped binge drinking but has refused to stop drinking altogether and has declined referral to counseling. Two years after the diagnosis, he continues to be readmitted approximately every 6 months for acute pancreatitis.

Dr. Nancy Lee Harris (Pathology): Dr. Goldstein, you cared for this patient. Would you like to comment?

Dr. Mark A. Goldstein (Adolescent and Young Adult Medicine): I saw this patient recently for another episode of acute pancreatitis. He reported a 2-day history of right-upper-quadrant pain that radiated to his back. He reported no intake of alcohol in the preceding 24 hours. After the pain began, he modified his diet to clear liquids only and placed himself on bed rest. On examination, his weight had increased to 150.8 kg, and the BMI had increased to 43.3. There was upper abdominal tenderness. The serum amylase level was moderately elevated, at 121 U per deciliter, and the lipase level was elevated, at 131 U per liter (reference range, 13 to 60). The patient declined to be admitted to the hospital. Together with the pediatric gastroenterology service, we developed a plan to treat him as an outpatient with narcotic analgesic tablets and a clear liquid diet. Several days later at a follow-up examination, he reported no pain, and the amylase level was normal.

Dr. Harris: What is the likelihood of the development of pancreatic insufficiency if the patient doesn’t stop drinking altogether?

Dr. Shah: In hereditary pancreatitis, pancreatic insufficiency may develop in 35 to 45% of patients. The risk depends on the number of episodes of pancreatitis and is likely to be accelerated if the patient continues to drink alcohol.

A Physician: Although there is a sense of satisfaction at having determined the cause of his pancreatitis, it is very unfortunate that we have been unable to persuade this young man to accept the only measure that might help him—cessation of alcohol consumption.

**Final Diagnosis**

Recurrent pancreatitis due to CFTR and SPINK1 mutations, triggered by alcohol.

This case was discussed at Pediatric Grand Rounds.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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REFERENCES


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