A 32-year-old man presented to the emergency department with a 6-hour history of intense epigastric pain. He was in his usual state of health when he experienced the abrupt onset of severe, sharp abdominal pain radiating to the back and lower abdomen which was worsened while lying supine. Nausea was associated with the pain and symptoms did not improve with 1 cup of milk and a 20-mg omeprazole capsule. He denied any fevers, melena, hematochezia or recent nonsteroidal anti-inflammatory use. During the 3 months before presentation, he reported polyphagia and a 20-pound unintentional weight loss.

His medical history was significant for gastroesophageal reflux disease and obesity. His home medications included omeprazole, ranitidine, and as-needed acetaminophen. Social history included prior nicotine use and rare alcohol use with no formal physical activity regimen. On examination, the patient appeared in moderate distress due to abdominal pain. Initial vital signs were as follows: body mass index 37 kg/m², heart rate 104 beats/min, blood pressure 150/112 mm Hg, oxygen saturation 95% (on room air), respiratory rate 16 breaths/min, and temperature of 37.1°C. Physical examination revealed dry mucous membranes, tachycardia, and clear lung fields. Abdominal examination showed a distended abdomen, tenderness to palpation over the epigastrium, no hepatosplenomegaly, and a negative Murphy sign. There was no jaundice or rash.

Laboratory studies yielded the following results (reference ranges provided parenthetically): white blood cell count, 14.5 × 10⁹/L (3.5-10.5 × 10⁹/L); hemoglobin, 15.5 g/dL (13.5-17.5 g/dL); platelets, 370 × 10⁹/L (150-450 × 10⁹/μL); sodium, 123 mEq/L (135-145 mEq/L); creatinine, 0.56 mg/dL (0.84-1.21 mg/dL); blood urea nitrogen 9 mg/dL (7-20 mg/dL); glucose, 343 mg/dL (70-140 mg/dL); aspartate aminotransferase, 45 U/L (8-48 U/L); alanine aminotransferase, 84 U/L (7-55 U/L); total bilirubin, 0.4 mg/dL (<1.2 mg/dL); and lipase, 895 U/L (10-73 U/L). Abdominal ultrasound revealed no gallstones, gallbladder wall thickening, pericholecystic fluid, or bile duct dilatation. There was diffuse hyperechogenicity of the liver parenchyma consistent with hepatic steatosis.

1. Which one of the following laboratory tests is most appropriate for determining the etiology of his current presentation?
   a. Endoscopic retrograde cholangiopancreatography (ERCP)
   b. Abdominal computed tomography
   c. Total calcium level
   d. Triglyceride level
   e. Helicobacter pylori testing

Based on our patient’s characteristic abdominal pain and lipase greater than three times the upper limit of normal, he fulfills the diagnosis of acute pancreatitis. The annual incidence of acute pancreatitis ranges from 13 to 45 per 100,000 persons. ERCP is recommended within 24 hours of presentation for patients with ascending cholangitis. Ultrasound did not reveal sonographic features concerning for a gallstone etiology and our patient was not jaundiced or icteric. If choledocholithiasis is highly suspected in the absence of jaundice or cholangitis, magnetic resonance cholangiopancreatography should be considered rather than ERCP given the noninvasive nature of this test. Abdominal computed tomography scan is not required as the diagnosis of acute pancreatitis is established by lipase levels.
pancreatitis has already been established. Radiographic evaluation of the pancreas is reserved for patients who fail to improve in 2 to 3 days after their acute presentation or in patients whom the diagnosis is unclear.

Hypercalcemia is a rare cause of acute pancreatitis, although less likely in our patient with hyperglycemia and obesity. If strong suspicion for hypercalcemia is present, obtaining a serum calcium level after the resolution of the acute episode may be beneficial, as serum calcium may be falsely low in the acute setting. Hypertriglyceridemia should strongly be considered as a cause of acute pancreatitis in patients without gallstones or significant alcohol use and in patients with uncontrolled diabetes. Although not previously diagnosed, our patient meets criteria for newly established diabetes mellitus in the setting of his symptoms (polyphagia and polyuria) and random glucose greater than 200 mg/dL. Hypertriglyceridemia can lead to pseudohyponatremia, seen in our patient, by reducing the water content in a given amount of plasma. If triglyceride testing was unrevealing, hereditary causes of acute pancreatitis could be considered given the age of the patient. Testing for Helicobacter pylori via stool antigen or breath test would be helpful if peptic ulcer disease was suspected.

A triglyceride level was obtained and found to be 5,486 mg/dL.

2. Which one of the following is the most common secondary factor causing hypertriglyceridemia?
   a. Hypothyroidism
   b. Diabetes mellitus
   c. Estrogen use
   d. Alcohol use
   e. Lipoprotein lipase deficiency

   Deficiency in thyroid hormone is associated with an increase in low-density lipoprotein (LDL) and triglyceride levels. In patients with severe hypertriglyceridemia, thyroid function should be evaluated, although this is not the most common cause of triglyceride elevation. Diabetes is the most common secondary factor causing hypertriglyceridemia and occurs more frequently in type 2 than type 1 diabetes mellitus. In a series of 272 patients with hypertriglyceridemic pancreatitis, the prevalence of diabetes mellitus was found to be 72%. Insulin resistance leads to increased free fatty acid return to the liver, increased very low-density lipoprotein (VLDL) production and decreased activity of hepatic and lipoprotein lipase which promotes development of hypertriglyceridemia.

   Exogenous (medication) and endogenous (pregnancy) production of estrogen may lead to triglyceride elevation, although this is not as common. Transdermal estrogens bypass hepatic metabolism and do not increase triglyceride levels. Chronic heavy alcohol consumption can cause hypertriglyceridemia, although light-to-moderate alcohol use does not seem to affect triglyceride levels. Genetic etiologies of triglyceride elevation are due to an overproduction of triglycerides, reduced clearance of triglycerides due to decreased lipoprotein lipase activity, or decreased VLDL and chylomicron remnant clearance by the liver. Lipoprotein lipase deficiency is a heritable etiology causing hypertriglyceridemia, but not the most common etiology.

   Intravenous volume resuscitation, antihypertensives, and analgesia were provided to the patient.

3. Which one of the following interventions should be performed next in the management on this patient’s condition?
   a. Intravenous insulin
   b. High-intensity statin
   c. Nasojejunal tube placement
   d. Apheresis
   e. Prophylactic cholecystectomy

   Intravenous insulin is most appropriate in the acute management of this patient and is also helpful in patients with uncontrolled diabetes by reducing triglyceride and glucose levels. Triglyceride levels should be checked every 12 hours and insulin should be stopped when triglyceride levels are less than 500 mg/dL. Typically, this will occur within 3 to 4 days. Insulin infusion may cause hypoglycemia, and may require concomitant intravenous
dextrose. Statin therapy is highly efficacious in reducing LDL cholesterol but has a modest effect on triglyceride level. Statins have a synergistic effect on triglyceride levels when used with fibrate medications. Monotherapy with a statin medication in the acute setting would not be recommended. Oral or enteric feeding in pancreatitis preserves gut wall integrity and is preferred if the patient can tolerate feeding. Caution must be used not to further elevate triglycerides in patients with hypertriglyceridemia and a low-fat diet is recommended. For patients with continued nausea and abdominal pain, nasojejunal and nasogastric feeding are equally efficacious, but would not assist in reducing triglyceride level.

Apheresis involves plasma removal and replacement with colloid solution and is a therapeutic option for patients with hypertriglyceridemic pancreatitis. It should be reserved for select cases of patients with severe hypertriglyceridemic pancreatitis because it has not been validated in randomized trials, has considerable side effects (bleeding, hypercoagulable state, and infection), and is costly. Patients with severe pancreatitis and persistent triglyceride elevation greater than 1000 mg/dL after 48 to 72 hours can be considered for apheresis. Cholecystectomy would be warranted in gallstone pancreatitis to prevent further episodes of acute pancreatitis, given high recurrence rates. Typically, this is performed weeks after the acute presentation to allow for resolution of pancreatic inflammation.

Our patient was started on intravenous insulin and received aggressive volume resuscitation. He responded well to crystalloid infusion, with a reduction in his blood urea nitrogen level and resolution of systemic inflammatory response syndrome.

4. Which one of the following medications would be best for prevention of further episodes?
   a. Atorvastatin
   b. Simvastatin
   c. Fenofibrate
   d. Niacin
   e. Gemfibrozil + atorvastatin

   Statin therapy (both atorvastatin and simvastatin) has modest effects on triglyceride levels. They should not be used as monotherapy for treatment or prevention of severe hypertriglyceridemia. Fibrate medications are most efficacious in reducing triglyceride levels and were prescribed to our patient. They work by activating peroxisome proliferator-activated receptors which modulate fat and carbohydrate metabolism. Older fibrate medications (gemfibrozil) have been associated with increased risk of myopathy, myalgia, and rhabdomyolysis when used with statins, so this combination should be avoided. Newer fibrates (fenofibric acid derivatives) are better tolerated when used in conjunction with statin medications. Niacin is used as a second-line agent, although its use is limited by side effects of facial flushing, elevated liver chemistries, and gastrointestinal upset. It may be used in cases where triglyceride levels are not well-controlled with fibrate medications.

After 3 days on intravenous insulin treatment, he was tolerating a low-fat diet and his triglycerides decreased to less than 500 mg/dL; therefore, he was transitioned to a subcutaneous insulin regimen and started on fenofibrate. On dismissal from the hospital, he inquired about management options for the hepatic steatosis identified on admission abdominal ultrasound.

5. Which one of the following statements is most appropriate regarding therapy for his hepatic steatosis?
   a. Statin therapy should be avoided
   b. Vitamin E has been shown to reverse the disease
   c. Weight loss is the most effective therapy
   d. Hepatitis vaccines should be avoided
   e. Metformin is an effective therapy

   Our patient’s ultrasound findings are suggestive of nonalcoholic fatty liver disease (NAFLD), which is associated with obesity, diabetes mellitus, and hypertension, and typically presents in middle age. Pharmacologic agents have shown only modest benefit in this disease. Although statin therapy has
been associated with abnormal liver function tests in a minority of patients taking the medication, it is safe to use in patients with NAFLD. As patients with NAFLD are at higher cardiovascular risk, lipid derangement should be aggressively treated. Observational studies have suggested that vitamin E improves aminotransferase levels, although meta-analysis showed no histologic benefits. Of the therapies tested, weight loss and exercise are the most beneficial strategy for improvement of NAFLD. They should be prescribed to all patients and if lifestyle and dietary modifications are not successful, then bariatric surgery should be considered. Hepatitis vaccinations (A and B) should be provided to patients without evidence of immunity and are not contraindicated in patients with NAFLD. Although metformin is of benefit in patients with diabetes mellitus, it has not shown efficacy for treatment of NAFLD. It has not been found to improve liver enzymes, histology, or alter body mass index.

Ultimately, our patient was discharged from the hospital on insulin and fibrate therapy. He was extensively counseled on lifestyle modification measures and has had no evidence of recurrent acute pancreatitis on 3-month follow-up.

DISCUSSION

Hypertriglyceridemia is a rare but well-established cause of acute pancreatitis. The most common causes of acute pancreatitis in the United States include gallstones and alcohol, although clinical suspicion for pancreatitis secondary to hypertriglyceridemia should occur in the appropriate context, as hypertriglyceridemia was found as the etiology of acute pancreatitis in 1.3% to 3.8% of all cases. Physical examination findings suggestive of elevated triglycerides include eruptive xanthomas and lipemia retinalis.

Diagnosis of acute pancreatitis is established when the patient meets two of the three following criteria: characteristic abdominal pain, amylase or lipase greater than three times upper limit of normal, and imaging findings concordant with acute pancreatitis. To be considered as a causative etiology of acute pancreatitis, triglycerides should typically be greater than 1000 mg/dL. Endocrine society guidelines define elevation of triglyceride levels based on fasting triglyceride levels: less than 150 mg/dL (normal), 150 to 199 mg/dL (mild), 200 to 999 mg/dL (moderate), 1000 to 1999 mg/dL (severe) and greater than 2000 mg/dL (very severe). Risk of acute pancreatitis generally follows a linear trend with elevation in triglyceride level above 177 mg/dL.

Approximately 17% of US adults have triglyceride levels greater than 150 mg/dL based on data from the National Health and Nutrition Examination Survey (2001–2006). Significant elevations in triglycerides can occur in conditions that result in overproduction or decreased clearance. Acquired disorders included type 2 diabetes (poorly controlled), obesity, hypothyroidism, nephrotic syndrome, alcoholism, and pregnancy. Medications known to increase triglyceride levels include estrogen-containing products, beta blockers, glucocorticoids, retinoids, and tamoxifen. There are multiple hereditable etiologies including familial hypertriglyceridemia, familial combined hyperlipidemia, familial dysbetalipoproteinemia, and chylomicronemia.

Initial treatment of acute pancreatitis focuses on aggressive hydration, pain management, and correction of contributing etiologies. To acutely lower the triglyceride level, intravenous insulin is used. Insulin leads to increased activity of peripheral lipoprotein lipase which hydrolyzes triglycerides in lipoproteins. This also is helpful in poorly controlled diabetic patients with concomitant hyperglycemia. Careful monitoring of glucose levels is necessary to prevent hypoglycemia, which should be corrected with intravenous glucose therapy. As insulin may cause large transcellular electrolyte shifts (potassium, phosphorous), serial monitoring should be undertaken to prevent derangement. As an alternative to intravenous insulin, apheresis may be used for reduction of triglyceride level. However, evidence supporting its use is limited to case reports/studies and this treatment modality is limited due to availability and cost.
Factors to prevent recurrence of acute pancreatitis include lifestyle modification and medical therapy. Offending medications should be discontinued and potential secondary causes should be addressed. For instance, avoidance of alcohol, weight loss strategies, and diabetic control are effective therapies for prevention of recurrence. As in our patient, limiting carbohydrate and fat intake in conjunction with weight reduction strategies should be prescribed.

There are typically three classes of drugs used in management of hypertriglyceridemia: fibrates, statins, and omega-3 fatty acids. Fibrates are first-line therapy for treating hypertriglyceridemic pancreatitis. Statins may be used in patients with moderate hypertriglyceridemia or in conjunction with fibrate therapy for severe hypertriglyceridemia, but not as monotherapy for severe hypertriglyceridemia. Caution is advised when using combination statin and fibrates due to a small risk of rhabdomyolysis and myopathy. Omega-3 fatty acid supplementation may be used as an adjunctive therapy, with 3 to 5 g/d reducing triglyceride levels by 30% to 50%.9

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REFERENCES

CORRECT ANSWERS: 1. d. 2. b. 3. a. 4. c. 5. c