Macroamylasemia: A Simple Stepwise Approach To Diagnosis

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Abstract: **Typically, macroamylasemia is a condition of elevated serum amylase in the absence of symptomatic disease. However, in the presence of symptoms, especially of abdominal origin, it is important that this condition be identified accurately in order to avoid unnecessary treatment for pancreatitis or other related diseases. This report offers a review of the literature, a case example, and an algorithm for systematically considering the diagnosis of macroamylasemia. (J Am Bd Fam Pract 1989; 2:279-82.)**

The typical presentation of acute pancreatitis includes an elevated serum amylase level and steady, severe upper abdominal pain radiating to the back. It is often accompanied by nausea and vomiting. Abdominal radiographs can show an enlarged duodenum, a sentinel loop, or pancreatic calcification. Hospitalization is almost always required, and the patient is fed intravenously with or without nasogastric suctioning. Successful therapy is determined by decreased clinical symptoms and a decrease in the amylase level. Few other diseases rely so heavily on a single laboratory value for diagnosis and assessment of therapy. It is essential, therefore, that the family physician be familiar with some of the other common nonpancreatic causes of an elevated level of serum amylase, in particular, macroamylasemia (Tables 1, 2) in order to avoid diagnostic confusion, needless hospitalization, and delayed or inappropriate treatment.

We present a case example and discussion of macroamylasemia, one of the common nonpancreatic causes of an elevated level of serum amylase. Macroamylasemia is not a disease in itself but a condition associated with hyperamylasemia. We also include an algorithm to assist in a stepwise approach to diagnosis of this condition and to avoid its misdiagnosis as pancreatic disease.

Case Report

A 58-year-old black man was evaluated in the emergency department because of right flank pain thought originally to be from pancreatitis. His medical history and review of systems were pertinent for alcoholism. The patient admitted to heavy drinking and had attended Alcoholics Anonymous meetings while living in another area of the country. He stated that he had to stop drinking because of recurrent blackouts and gastrointestinal bleeding, which were believed to be from esophageal varices. The patient was not working and lived with a woman friend. One daughter had sickle cell anemia, but there was no family history of alcoholism. According to the patient and to reliable, though estranged, family members, he had not drunk alcohol for almost 2 years prior to the presenting illness.

On examination, the patient was well developed, slim, and in no acute distress. He had mild right costovertebral angle tenderness, but his abdomen was soft and nontender. Initial laboratory tests showed that the amylase level was 573 U/L (310 somogyi units/dL) (normal range 30 to 110 U/L). Liver function tests were normal, and blood urea nitrogen and creatinine were 11 mg/dL (3.9 mmol/L) (normal range 7 to 18 mg/dL) and 0.9 mg/dL (79.6 μmol/L) (normal range 0.5 to 1.2 mg/dL), respectively. To confirm the provisional diagnosis of alcoholic pancreatitis, his test for serum lipase was 47 U/L (0.17 μ/mL) (normal range 22 to 208 U/L). Computed tomography scan of the abdomen showed no pseudocyst and a normal-appearing pancreas, spleen, and liver; however, there were stones in the gall bladder without dilated ducts.

Because the chest radiograph showed a large cavitary lesion (pneumatocele) in the right lung, the patient was hospitalized. The pneumatocele was believed to be caused by regurgitation and aspiration, the result of an esophageal stricture

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Table 1. Nonpancreatic Causes of Hyperamylasemia.

1.	Inflammation or trauma to the salivary glands
2.	Mesenteric infarction and perforated peptic ulcer
3.	Ruptured ectopic pregnancy and ovarian cysts
4.	Pulmonary disease
5.	Metastatic tumors originating in the lung, reproductive tract, or pancreas
6.	Uncomplicated renal failure
7.	Abdominal trauma without pancreatic injury
8.	Pelvic inflammatory disease
9.	Mumps
10.	Macroamylasemia

produced by alcoholism and esophageal varices. Treatment included dilatation of the stricture, chest tube drainage of the cavitary lesion, and intravenous antibiotics. Eventually, it resolved with the patient's recovery. The patient's flank pain remitted soon after hospitalization, but the hyperamylasemia persisted even after resolution of the pneumatocele.

Because the finding of an elevated level of serum amylase in association with normal lipase was not entirely consistent with pancreatitis, a urine amylase test was obtained. It was 232 U/L (125 somogyi units/dL) (normal range less than 32 U/L). To determine whether this value was appropriate for a concurrently obtained value for serum amylase (541 U/L [293 somogyi units/dL]), an amylase-creatinine clearance ratio (Cam:Ccr) was calculated using the urine creatinine and serum creatinine values, which were 55 mg/dL (19.6 mmol/L) and 1.2 mg/dL (106.1 μmol/L), respectively.

This ratio was determined to be less than 1 percent, indicating a poor clearance of amylase by the kidney and suggesting the presence of a large unfilterable molecule, i.e., macroamylase. Macroamylasemia was confirmed by an amylase electrophoresis. Since that occasion, the patient has been rehospitalized for esophageal stricture and aspiration. His hyperamylasemia has persisted.

Discussion

Globulin-bound amylase causing persistent elevated levels in the serum was first described in 1964.[1] This globulin-bound macromolecular complex is greater than four times the molecular weight of normal amylase (45,000). Furthermore, unlike normal amylase, of which 20 to 25 percent is filtered through renal glomeruli, this macromolecule is too large to be filtered and thus remains in the serum, giving persistently elevated amylase levels.

Amylase, including macroamylase, may be derived from multiple origins, each with its own specific characteristics. Amylase from a single origin is known as an isoamylase, and amylase from the pancreas is known as pancreatic isoamylase or P-type.

Our case illustrates how a patient with an elevated level of amylase could be misdiagnosed for a pancreatic disorder if a stepwise diagnostic approach were not followed. The patient had a history of alcoholism and flank pain that could have easily been attributed to pancreatitis, especially with an elevated amylase value. Our first real clue was a normal serum lipase value, which is inconsistent with pancreatitis. Our recommended stepwise approach (Figure 1) helps make the diagnosis of macroamylasemia with greater confidence.

Serum Lipase and Pancreatic Isoamylase

When faced with hyperamylasemia, and the possibility of macroamylasemia, the first step is to determine whether the amylase is pancreatic in origin. This can be accomplished by measuring the serum lipase level, because pancreatitis is associated with elevated serum lipase. Determinations of pancreatic isoamylase and lipase are roughly interchangeable as markers of pancreatic enzymes in the blood and often remain elevated after total amylase has returned to normal.[2] Pancreatic isoamylase may be the most sensitive marker of pancreatic inflammation. It is currently determined by electrophoretic methods or the use of newly developed selective isoenzyme inhibitors. Monoclonal antibodies to isoamylase can make rapid routine clinical assays possible in the near future.[3] Lipase declines rapidly in pancreatitis and reaches levels of activity similar to the total amylase by day 4, whereas the pancreatic isoamylase level typically remains elevated

Table 2. Types of Macroamylasemia.

Type 1 (classic)—Amylase is bound to serum proteins. (Urine amylase level is not elevated.)
Type 2—Cam:Ccr is not as low as Type 1 because of decreased serum activities.
Type 3—Urine and serum amylase levels are normal.

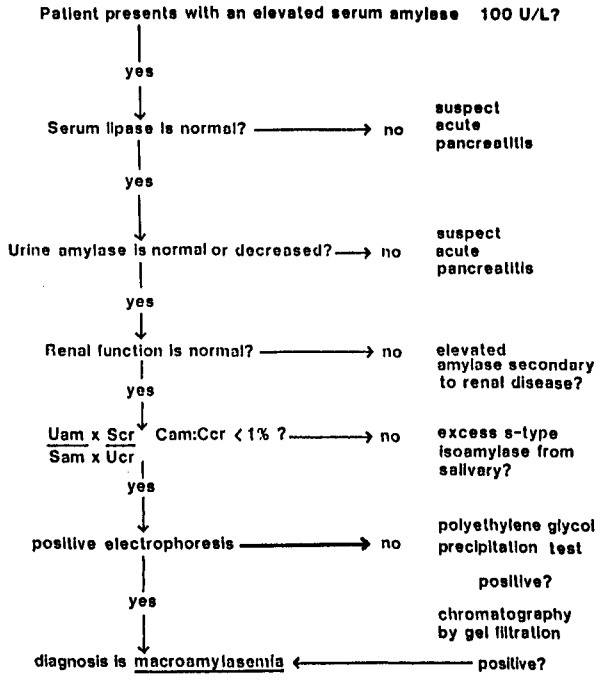

Figure 1. Diagnostic algorhythm for macroamylasemia.

longer.[4] In the search for macroamylasemia, however, the lipase assay is an even more important diagnostic tool; in macroamylasemia, the amylase and the pancreatic isoamylase levels are often elevated, but the lipase is typically normal.[2,5]

Urinary Amylase and the Cam:Ccr Ratio

The second important step in diagnosing macroamylasemia is measuring the urine amylase. Amylase is readily filtered through the kidney, and although a large amount is reabsorbed in the tubules, a proportional amount is excreted in the urine. In acute pancreatitis, urinary excretion becomes even more pronounced, not only because of the increased level of serum amylase, but because amylase reabsorption is inhibited in the tubules, thereby increasing urinary excretion. Urinary amylase can even remain elevated despite normal serum levels. In macroamylasemia, however, the 200,000-molecular-weight macromolecule is too large to be filtered by the kidney, and, although the serum activity is high, the urinary amylase level will be low.

An even more precise way of measuring the glomerular filtration rate of amylase, and the next step in proving macroamylasemia if renal function is normal, is to calculate the renal clearance of amylase relative to the creatinine clearance. This is done using the following formula:

$$\text{Urine amylase/Serum amylase} \times \text{Serum creatinine/Urine creatinine} \times 100 = \text{Amylase} - \text{Creatinine/Clearance Ratio}$$

Normal ratios are 3 percent to 5 percent.[6] A level less than 1 percent is highly suggestive of macroamylasemia, whereas normal or increased levels virtually exclude the diagnosis. It is important to note that the Cam:Ccr (amylase-creatinine clearance ratio) is seldom reduced to the extent expected, given the fraction of amylase bound to the macroamylase complex as determined by gel filtration. This is due to the fact that when the temperature of the macroamylase complex is elevated to body temperature, there is a decreased macromolecular binding and, thus, the increased Cam:Ccr ratio found in vivo. It is possible that febrile patients with macroamylasemia normalize their Cam:Ccr.[7] The Cam:Ccr ratio is still an effective tool, providing the patient's renal function is not impaired. If the patient's glomerular function is decreased, urine amylase levels will be universally low for all disease states.

Macroamylasemia is confirmed when an elevated serum amylase level is found with normal levels of serum lipase, urine amylase, and renal function and a Cam:Ccr less than 1 percent.

Amylase Electrophoresis

Amylase electrophoresis is an adequate test, providing the serum amylase activity is greater than 100 U/L.[8] A smeared band indicates macroamylasemia.[9] Isoenzymes measured by selective inhibition will not be helpful, and an electrophoresis will be necessary. This is because selective inhibition isoenzymes only give S values (salivary type) and P values (pancreatic type), not specific bands. A negative electrophoretic study, however, is inconclusive and requires the more difficult, but more often diagnostic, gel filtration chromatography for confirmation.[8-10] If serum amylase is less than 100 U/L, electrophoresis is not reliable, and a simple polyethylene precipitation test can exclude macroamylasemia.[8-12] A positive finding requires confirmation with filtration chromatography.[8-10]

Conclusion

Macroamylasemia is a fairly common cause of hyperamylasemia, involving nearly 1:50 persons in the general population,[11-13] and nearly 1:10 persons with hyperamylasemia.[8] Although rare in children, cases have been reported.[16] It is usually a benign finding in an asymptomatic patient, although it is hypothesized that there is a distinct disease entity consisting of recurrent abdominal pain and macroamylasemia.[17,18] When hyperamylasemia is found, a careful stepwise approach can confirm the proper diagnosis early in the patient's management, thereby eliminating diagnostic confusion, decreasing morbidity, and providing more cost-effective care.

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