Abdominal pain and a raised amylase? It's not always pancreatitis…

IO Oluwatowoju, OE Abu & G Lawson

Abstract

We report the case of a 72 year old man with a history of COPD and heavy alcohol consumption who was initially diagnosed with acute pancreatitis based on a presentation with epigastric pain and elevated serum amylase. Review of his notes revealed several previous similar admissions and extensive normal investigations apart from persistently elevated amylase. Further analysis showed evidence of macroamylasaemia which accounted for the apparently high serum amylase level.

Keywords

Macroenzymes, macroamylasaemia, chronic obstructive pulmonary disease.

Key Points

- Acute physicians should be aware of macroamylasaemia as a benign explanation for an apparently elevated serum amylase level.
- Macroamylasaemia should be considered in patients with a persistently elevated serum amylase in the context of a normal lipase and low urinary amylase clearance.
- Macroamylasaemia can be confirmed by gel filtration chromatography.
- The finding of macroamylasaemia can save unnecessary and inappropriate investigation, and should lead to an alternative explanation for the patient's symptoms being sought.

Case

A 72 year old man was admitted to the Acute Medical Unit with a history of recurrent abdominal pain, chest tightness and wheeze. He was a heavy smoker, and his past medical history included chronic obstructive airways disease (COPD); he reported being more breathless in the days leading up to his presentation, without cough or increased sputum production. Examination revealed mild epigastric tenderness with normal bowel sounds; there was expiratory wheeze throughout his chest. Chest radiograph showed hyper inflated lung fields but no focal changes or consolidation. Based on a combination of heavy alcohol use (70 units per week) and a serum amylase level of 600iu/l (normal range 36-128iu/l), a diagnosis of alcohol-induced acute pancreatitis was made by the admitting medical team. He was commenced on opiate analgesia, intravenous antibiotics, intravenous fluid and nebulized salbutamol, which improved his symptoms.

Review of his notes revealed a number of previous similar admissions to hospital, dating back to March 2004. At the time of his first admission the pain was noted to be mild to moderate in intensity and localized in the epigastric area without vomiting or diarrhoea. Serum amylase was 655 iu/L and abdominal ultrasound was unremarkable. Acute pancreatitis was diagnosed and managed in accordance with UK guidelines for management of acute pancreatitis;[1] he was referred to an alcohol rehabilitation programme, but unfortunately refused to stay for further investigations and self discharged on the third day. He was re-admitted in September 2007 with a similar episode, again associated with an elevated serum amylase, and was again treated for pancreatitis and an exacerbation chronic obstructive pulmonary disease. Serum amylase was noted to be elevated on all samples sent to the laboratory during this and subsequent admissions (Figure 1).

During the current, and previous admissions, all other biochemistry tests including renal function, troponin I, bilirubin, alanine transaminase and alkaline phosphatase, remained normal. Calcium was normal and triglyceride averaged at 0.8 mmol/L. He had a mild normocytic anaemia with normal or mildly elevated white blood cell count. Blood clotting and tissue transglutaminase were also normal. In addition to two normal abdominal ultrasound examinations, he had also undergone normal upper gastrointestinal endoscopy and colonoscopy in the past 2 years for investigation of the anaemia which was deemed to be related to a poor nutritional state.

In view of the unusual finding of persistently elevated amylase which appeared to correlate poorly with his presenting symptoms, the findings were discussed further with the clinical chemistry department. Serum lipase was noted to be normal at 25 iu/L (normal range 5- 65iu/L) giving a serum lipase:amylase ratio of 0.4 (ratio greater than 2 is associated with alcohol induced pancreatitis). Further analysis of blood and urine samples was undertaken for fractional excretion of amylase which was 0.5 % (normal range 1.1 – 4.2%); polyethylene glycol (PEG) precipitated 98% of the patient's serum amylase activity (normal < 49%). The presence of macroamylase was confirmed by using Gel Filtration Chromatography, accounting for approximately 96% of total amylase activity (Figure 2).

Oluwatowoju IO
Department of Clinical Biochemistry,
University Hospital Southampton

Abu EO
Department of Clinical Biochemistry,
University Hospital Southampton

Lawson G
Department of Clinical Biochemistry,
Tunbridge Wells Hospital at Pembury,
Kent

Correspondence:
Oluwatowoju IO
Department of Clinical Biochemistry,
University Hospital Southampton
NHS Foundation Trust,
MP6,
Level D,
South Block,
Tremona Road,
Southampton
SO166YD
UK
Email: Isaac.oluwatowoju@uhs.nhs.uk

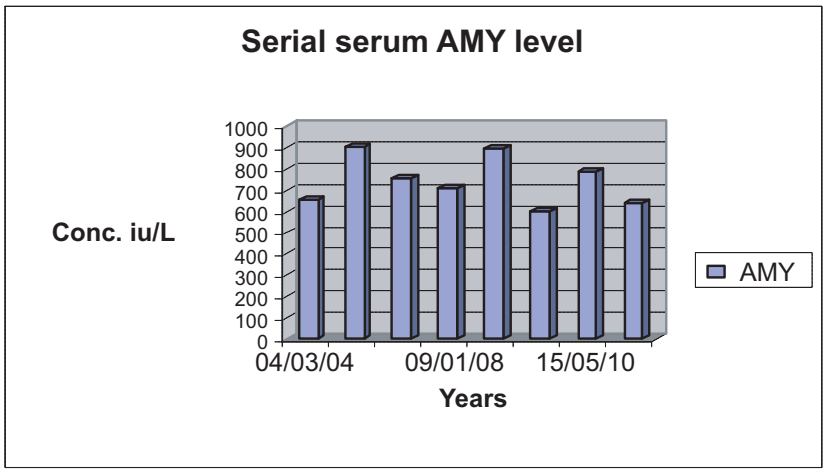

Figure 1. Serum Amylase level over time.

His abdominal symptoms settled with simple analgesia and he was treated with a combination of oral prednisolone and inhaled bronchodilators for a presumed non-infective exacerbation of his COPD. He continues to be supported by the community alcohol team and his general practitioner in an attempt to reduce his alcohol intake.

Discussion

Abdominal pain is a common reason for presentation to acute medical and surgical teams, and measurement of serum amylase is usually undertaken as part of the initial diagnostic assessment. The finding of a significantly elevated serum amylase is usually considered diagnostic of acute pancreatitis in this setting. However other explanations should also be considered; a raised serum amylase may be familial, drug-induced[2,3,4] or may result from salivary gland damage. Using gel electrophoresis, serum or urinary amylase can be fractionated into pancreatic (P) and salivary (S) isoenzymes characterized by different subunits to enhance clinical test specificity.[5]

Serum amylase clearance is mostly achieved by the reticuloendothelial system with approximately 24% of serum amylase cleared via glomerular filtration.[6] In acute pancreatitis, renal serum amylase clearance rises and some investigators have used amylase:creatinine clearance (Cam/Ccr) ratios for diagnosis of acute pancreatitis.[7, 8] Lipase/amylase ratio may be used to distinguish acute episodes of alcoholic from non-alcoholic acute pancreatitis with

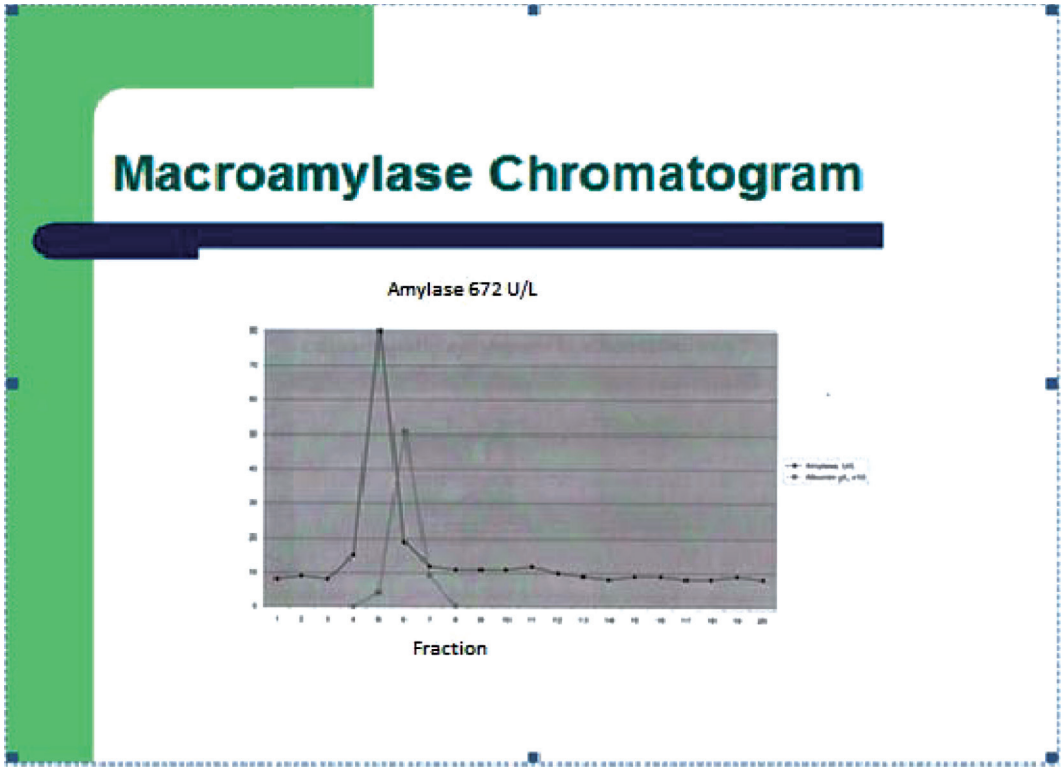

Figure 2. Macroamylase Chromatogram.

a lipase/amylase ratio greater than 2 suggesting that alcohol is the likely cause.[9]

Our patient was noted to have a persistently elevated serum amylase over repeated admissions during a number of years, and was diagnosed with recurrent acute pancreatitis. His history of heavy alcohol intake suggested a plausible explanation for the finding, although abdominal pain was often not a prominent aspect of his presentation; furthermore other investigations including ultrasound, liver function tests and lipase were normal. Polyethylene glycol precipitated 98% of the patient's amylase activity; it has been recommended that serum exhibiting more than 57% precipitation of the original amylase activity by PEG should be examined by Gel Filtration Chromatography (GFC) to confirm or exclude macroamylasaemia,[10] and this was subsequently confirmed in our case. In patients with persistent serum amylase elevation, normal urine amylase and lipase levels and abnormally low urine amylase clearance (1.1- 4.2%), the diagnosis of macroamylasaemia must be considered.[11]

Macroamylasaemia is a benign condition caused by the presence of macromolecular complex of amylase in the serum.[12] Macroamylasaemia occurs in 0.4-1% of the general population, many of whom have no other medical condition.[13] Macroamylase molecules consist of serum amylase bound to the Fab portion of immunoglobulin molecules and complexes with IgA, IgG or macromolecules have been reported in the literature.[12, 14] Macromolecular amylase complexes have a molecular weight of 150,000 – 2 million Dalton units.[15] This cannot be excreted by the kidneys and is retained in the blood, resulting in high serum and normal or low urine amylase levels.[8] Macroenzymes are composed mainly of an enzyme immunoglobulin complex; however, other forms of macromolecules containing enzymes and lipoprotein or enzyme oligomers have been reported.[16] A failure to detect macroenzymes as a cause of unexplained increase in enzyme levels can result in expensive, unnecessary and often invasive procedures in search of an alternative diagnosis.

The pathogenesis of macroenzyme formation is unknown. However, classic immunological models of auto antibody formation have been proposed as potential explanations. In the antigenic-driven theory, a self-antigen is altered or released from a sequestrated site in the body and cross reacts with an antibody, initially formed against a foreign antigen; this forms an antigen-antibody complex.[16] A second theory is the dysregulation of immune tolerance which is likely to occur in auto- immune disorders, though few reported patients with macroamylase have evidence of other autoimmune diseases.[16]

It is unclear whether this patient's macroamylasaemia could be related to his COPD. An association with COPD has not been documented previously in the literature apart from a case report in a patient with recurrent sino- pulmonary infection, selective IgA deficiency and antiphospholipid antibodies.[17] There have been reports of differential switching of innate immune response to IgG and IgA production due to adaptive cigarette smoke induced antigen directed against decorin and induction of anti-decorin IgG and IgA antibody production from lymphoid follicles in COPD patients.[18,19] This could form non specific agglutination with enzymes resulting in macro enzymes including macro amylase.

Conflict of interest

This study was funded entirely by the authors and they have no conflict of interest with any third party.

References

1. UK guidelines for the management of acute pancreatitis. *Gut* 2005; **54 (suppl.3):** 1–9.
2. Hyperamylasaemia, a drug interaction of Prograf, Acyclovir, Antibiotics, Methotrexate: Who have it and how? www.ahealthme.com/sa/3215634/hyperamylasaemia.
3. Could your drug cause hyperamylasaemia?-eHealthMe.com - www.ahealthme.com/sa/symptom/hyperamylasaemia.
4. Cuckow PM, Foo AY, Jamal A, *et al.* Familial hyperamylasaemia. *Gut* 1997; **40:** 689–690.
5. Fridhandler L, Edward B, Montgomery K. Nature of Isoamylase released by acidification from macroamylase complexes. *Clin. Chem*. 1974; **20(1):** 26–29.
6. Lewison EF. The clinical value of the serum amylase test. *Surg Gynecol Obstet*. 1941; **72:** 202.
7. Dreiling DA, Leichtling JJ, Sanowitz . The amylase – creatinine ratio; Diagnostic parameter or physiologic phenomenon? *Am J Gastroenterol*. 1974; **61:** 290.
8. Stocks P. The quantitative determination of amylase in blood, serum, and urine as an aid to diagnosis. *Q J Med*.1916; **9:** 216.
9. Gumaste VV, Dave PB, Weissman D, *et al.* Lipase/amylase ratio: A new index that distinguishes acute episodes of alcoholic from nonalcoholic acute pancreatitis. *Gastroenterology*.1991 Nov; **101(5):** 1361–6.
10. Lawson GJ. Prevalence of macroamylasaemia using polyethylene glycol precipitation as a screening method. *Ann Clin Biochem* 2001 Jan; **38:** 37–45.
11. Quilez C, Martinez J, Gomez A, *et al.* Chronic elevation of enzymes of pancreatic origin in asymptomatic patients. *Gastroenterol Hepatol.* 1998 May; **21(5):** 209–11.
12. Fujio Z, *et al.* Macro-amylasaemia: clinical and laboratory features in 7 patients. *Gasroenterologia Japonica* 1975; **10(4):** 255–260.
13. Galasso, P. J, Litin, *et al.* Macroenzymes: a clinical review. *Mayo Clin Proc* 1993; **68:** 349–54.
14. Bruns D E, Mills S E, *et al.* Amylase in fallopian tube and serous ovarian neoplasms. *Arch Pathol Lab Med.* 1982; **106:** 17–20.
15. Wilding P, Cooke WT, *et al.* G.I. Cause of persistently elevated levels in serum. *Ann. Intern. Med.* 1964; 40: 1053.
16. Turkcapar, N, Ozden A, Macroenzymes. *Guncel Gastroenterology* 2005; **9:** 161–6.
17. Could Chronic Obstructive Pulmonary Disease cause hyperamylasaemia? www.ehealthme.com/cs/chronic+obstructive+pulmonary+disease/hyperamylase.
18. Brusselle GG, Demoor T, Bracke KR, *et al.* Lymphoid follicles in (very) severe COPD: beneficial or harmful? *Eur Respir J* 2009; **34:** 219–230.
19. Brandsma CA, Kerstjens HAM, van Geffen WA, *et al.* Differential switching to IgG and IgA in active smoking COPD patients and healthy controls. Eur Respir.