CASE REPORT

A multidisciplinary approach to an unusual cause of hyperamylasaemia

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SUMMARY

Clinical features together with elevation of pancreatic enzymes are the key diagnostic indicators of acute pancreatitis. We report a case of a woman in her 50s who presented with abdominal distension and serum amylase raised to more than 30 times the upper limit of normal. She was initially treated for acute pancreatitis, however, she was not symptomatic of this and the pancreas appeared to be normal on CT scan. Further investigations revealed the patient had a high-grade serous ovarian carcinoma with nodal metastatic spread. An amylase-secreting ovarian tumour was suspected, which was supported by elevated salivary-amylase isoenzymes, consistent with previous reports in the literature. The patient was treated with chemotherapy and surgery, during which her serum amylase and CA-125 initially fell significantly, but eventually both increased, reflecting disease progression. This case serves as an important reminder to consider non-pancreatic causes of raised serum amylase, to avoid misdiagnosis.

BACKGROUND

Amylase is primarily thought to be produced by the pancreas and therefore raised serum amylase is usually attributed to pancreatic disease, especially when markedly elevated. This case highlights the fact that there are different isomers of amylase, such as those excreted by ovarian tumours. In order to avoid diagnostic confusion, attention should be given to alternative causes of hyperamylasaemia, particularly when the clinical context does not support pancreatic disease.

CASE PRESENTATION

A woman in her 50s was referred with a gradual onset of abdominal distension and lower abdominal discomfort, along with an increase in weight despite a reduction in appetite and new-onset dyspnoea. On examination, she had reduced air entry at both lung bases and her abdomen was distended with ascites. She had no significant medical history other than a 3-month history of leg swelling due to a persistent right common femoral deep vein thrombosis for which she had been on low-molecular-weight heparin. She had no other regular medications and no significant family history.

At this time, it was considered that the amylase may not be of pancreatic origin and, following her full clinical work up, a provisional diagnosis of ovarian cancer was made based on imaging evidence and laboratory tests (serum markers and tissue biopsy).

During her initial admission, the patient developed several pulmonary emboli, requiring thrombolysis, following which she started neoadjuvant chemotherapy before discharge.

INVESTIGATIONS

At the time of initial presentation, she had a mild thrombophilia (platelets $444 \times 10^9/L$), and normal renal and liver function. Initial blood tests revealed amylase raised to more than 30 times the upper limit of normal (3163 U/L, reference range (RR) <100).

Analysis of urine amylase showed a very high level of 28 436 U/L, and amylase:creatinine clearance ratio (ACCR) of 4.5%, which effectively excluded macroamylase (immunoglobulin-bound amylase) as a cause of raised serum amylase. Raised serum and urine amylase supported increased production, rather than decreased clearance, of the enzyme. Serum amylase isoenzyme analysis was performed by a specialist laboratory (King's College Hospital, London), demonstrating: total amylase 3076 IU/L (RR <100), pancreatic amylase 145 IU/L (RR <50) and salivary amylase 2931 IU/L (RR <50).

X-ray showed bilateral pleural effusions and a densely calcified opacity with diffuse soft tissue opacification in the pelvis suggestive of a gynaecological mass. This was further detailed by CT scan showing a large (approximately $14 \times 12 \times 11$ cm) ovarian cystic lesion (figure 1) with evidence of peritoneal and nodal metastatic spread. There was no peripancreatic stranding or pancreatic oedema.

Figure 1 Sagittal CT of the abdomen showing a large ovarian cyst and surrounding ascites.

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on CT to confirm pancreatitis. Tumour markers were also elevated; cancer antigen-125 (CA-125) 3216 KU/L (RR 0–35) and carcinoembryonic antigen 40.7 µg/L (RR 0–5) consistent with, but not diagnostic of, malignancy.

The patient had a CT-guided biopsy of omental tissue at initial presentation, diagnosing a high-grade serous carcinoma of probable ovarian origin (serous/clear cell histopathology) with positive staining for CA-125, estrogen receptor (ER1) and Wilms' tumour (WT1) proteins. In addition, the tissue stained positive for amylase, demonstrating tumour as the likely source of the raised serum level (figure 2). Biopsy of the primary tumour also stained positive for the same tumour markers and confirmed International Federation of Gynecology and Obstetrics Stage IIIB disease.

DIFFERENTIAL DIAGNOSIS

Initial working diagnosis was of acute pancreatitis, with concurrent abdominal mass. Other potential causes of raised serum amylase with abdominal pain, including perforated peptic ulcer, small bowel obstruction, gastrointestinal infarction and diabetic ketoacidosis, were rapidly excluded by clinical findings.

Isoenzyme analysis can often help shorten the list of differential diagnoses, especially if the salivary isoenzyme is predominantly raised, as in this case. Salivary gland disorders (eg, calculi, mumps), however, appeared even less likely in the clinical context. Markedly elevated serum CA-125 strongly suggested ovarian malignancy, which raised the possibility of an amylase-secreting tumour.

TREATMENT

Three cycles of neoadjuvant carboplatin and paclitaxel chemotherapy were given, followed by a total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy and appendicectomy. Currently (6 months after initial presentation), the patient is undergoing three further cycles of chemotherapy. She also continues on dalteparin in view of her underlying prothrombotic tendency and has received a blood transfusion for anaemia.

OUTCOME AND FOLLOW-UP

The patient initially had an excellent clinical and imaging response to chemotherapy, and her CA-125 level dropped from over 9000 KU/L to 395 KU/L just prior to surgery. Similarly, there was a sequential fall in serum amylase levels with

chemotherapy-induced tumour shrinkage, until amylase was only 2.5 times the upper limit of normal (268 U/L), prior to surgery (figure 3). Following surgery, amylase and CA-125 steadily increased until the second round of chemotherapy was started. Subsequently, both markers periodically increased and decreased during the next three cycles, reflecting disease progression and responses to treatment, respectively.

Due to the pathology of the tumour, the patient was eligible for BRCA gene testing and has consented to this.

DISCUSSION

The current official UK guideline for the management of acute pancreatitis states CT scan is only indicated if biochemical and clinical features are inconclusive.¹ However, this case demonstrates the limitations of an arbitrary serum amylase limit (3 or 4 times the upper reference limit) for diagnosis, and imaging may provide a vital role in the initial work up.

The measurement of pancreatic enzymes is standard practice in investigation of suspected acute pancreatitis. Amylase is the most commonly measured enzyme in the UK, due to the availability of cheap, easily automated methods. The main drawback is the lack of specificity for the pancreas; amylase exists as two isoenzymes in the circulation from both pancreatic and non-pancreatic (mainly salivary) sources in equal amounts. Consequently, good communication between clinical and scientific staff is essential when laboratory results do not fit with the clinical picture.

Where lipase measurement is available, it is the preferred test for diagnosis of acute pancreatitis, due to its superior sensitivity, specificity and overall accuracy.¹ Despite this recommendation, lipase is not widely available in the UK, due to analytical issues and cost. Pancreatic-amylase-specific assays are available in some laboratories and can help overcome the non-specificity issue of total amylase measurement, but again, these are not widely available. It is noteworthy that in this case, the pancreatic isoenzyme was also marginally raised. This is almost certainly a feature of the small amount of cross-reactivity in the antibody-based assay used (personal communication, Prof Roy Sherwood, King's College Hospital, London).

Macroamylasaemia, due to a benign IgA or IgG-bound macromolecular complex, leads to elevated levels of serum amylase due to reduced renal clearance and, hence, extended serum half-life. Although this is a relatively well-recognised entity, it may be forgotten about, especially by non-laboratorians, potentially leading to diagnostic confusion.² This was excluded swiftly during the patient's initial admission, using paired urine and serum samples, which showed 4.5% ACCR, which did not support macroamylasaemia as a cause.

The first case of hyperamylasaemia secondary to ovarian carcinoma was reported in 1976,³ and since then several other case reports have been published.^{4–7} Despite an awareness of these tumours, the mechanism of high serum amylase in such cases remains elusive. It might be related to neoplastic transformation of cells resulting in expression of the AMY1 gene, biosynthesis of salivary amylase⁷ and ectopic production.

It has been suggested that measurement of serum amylase in conjunction with existing tumour markers may represent a more specific screening regimen for ovarian pathology,⁷ however, the evidence base for this is weak. In the present case, serum amylase activity closely mimicked CA-125 levels in terms of disease progression, response to treatment and relapse. To the best of the authors' knowledge, no other study has followed amylase together with CA-125, and their response to treatment. Previous case reports have demonstrated amylase decline with

Figure 2 Omental tissue infiltrated by adenocarcinoma. Dark staining showing amylase production by the tumour.

Figure 3 Serum amylase and cancer antigen-125 activities and response to treatment.

cytotoxic chemotherapy, radiotherapy⁸ and surgery.⁹ Increased amylase production following relapse, as in the present case, has also been described before,⁹ and suggests a potential role as marker of disease progression. It is not clear, however, if this will add additional benefit over CA-125, which is traditionally used; larger studies are required.

Learning points

- ▶ Good communication and clinical liaison among various healthcare professionals is necessary for correct interpretation of laboratory test data.
- ▶ Consider non-pancreatic causes of raised serum amylase, particularly when clinical findings are not in keeping with pancreatic disease.
- ▶ Analysis of serum amylase isoenzymes can be performed to differentiate between pancreatic and salivary amylase, to help narrow the list of potential causes, however, this test is not routinely available in all hospitals and turnaround times are relatively slow, therefore, a degree of clinical suspicion is necessary.
- ▶ Urine amylase analysis can exclude macroamylase due to immunoglobulin-bound enzyme, and its reduced renal clearance, and is important to identify simply to avoid over-investigation in such cases.

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Competing interests None declared.

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