Pleural effusion in a patient with previous alcohol excess

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Shareable abstract (@ERSpublications)
Pleural amylase and/or lipase should be analysed in cases of pleural effusion in patients with pancreatic disease or a history of excess alcohol consumption. https://bit.ly/3Rk5UfO

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A woman in her fifties presented to our emergency department with a 2-week history of left-sided pleuritic chest pain and shortness of breath. Her past medical history consisted of recurrent admissions for alcohol-related pancreatitis, cholecystectomy, chronic kidney disease (stage 3A), impaired left ventricular function with an ejection fraction of 40–45%, hiatus hernia, and diverticular disease. She was also under pulmonary nodule surveillance for a 6 mm right upper lobe ground-glass lesion, which was found 5 years earlier. She was an ex-smoker with a 25-pack-years smoking history, with occasional alcohol intake, having previously drank 98 units of alcohol per week. She had no preceding respiratory illness and no recent symptoms to suggest any underlying malignant features.

Initial observations revealed a pulse rate of 71 beats per min, blood pressure 106/70 mmHg and a respiratory rate of 16 breaths per min. She was afebrile and pulse oximetry showed oxygen saturations of 97% on room air. Physical examination showed that she was significantly underweight at 37 kg with a body mass index of 16.36 $kg \cdot m^{-2}$. Auscultation of the chest revealed left basal crepitations. Abdominal examination revealed a soft and non-tender abdomen and systemic examination showed a normal jugular venous pressure and no peripheral oedema.

Laboratory tests showed haemoglobin of 92 $g \cdot L^{-1}$, a white blood cell count of 8.6×10^9 $cells \cdot L^{-1}$ with the differential showing lymphocytes at 1.2×10^9 $cells \cdot L^{-1}$, neutrophils 3.7×10^9 $cells \cdot L^{-1}$, monocytes 0.5×10^9 $cells \cdot L^{-1}$ and eosinophils 2.8×10^9 $cells \cdot L^{-1}$ (expected range: 0.1–0.4$\times 10^9$ $cells \cdot L^{-1}$). Platelets were 598×10^9 per L, C-reactive protein was 6.0 $mg \cdot L^{-1}$, and high-sensitivity troponin-I was <3 $ng \cdot L^{-1}$. Biochemical tests revealed an estimated glomerular filtration rate at baseline for the patient of 45 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$, with serum creatinine 110 $\mu mol \cdot L^{-1}$, urea 8.3 $mmol \cdot L^{-1}$, serum potassium 4.3 $mmol \cdot L^{-1}$ and serum sodium 136 $mmol \cdot L^{-1}$. Liver function tests were unremarkable, and serum protein and albumin were 63 $g \cdot L^{-1}$ and 30 $g \cdot L^{-1}$, respectively. N-terminal pro-B-type natriuretic peptide (NT-proBNP) was >5000 $pg \cdot mL^{-1}$ (expected range: <250 $pg \cdot mL^{-1}$).

Task 1

Describe the findings on the chest radiograph (figure 1).

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Task 2

What diagnoses need to be considered for a patient with a pleural effusion and peripheral eosinophilia?

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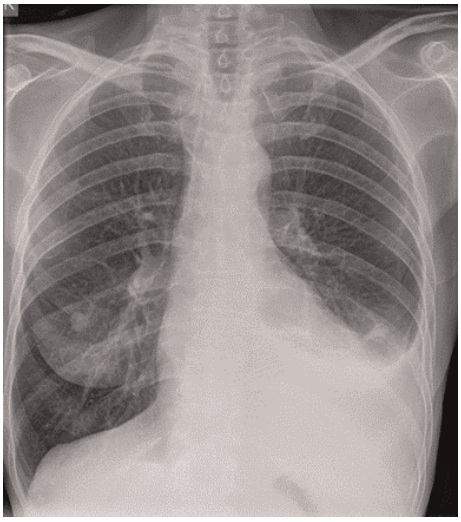

FIGURE 1 Chest radiograph at the time of admission.

Thoracic ultrasound showed a moderate unilocular, anechoic left-sided effusion. Ultrasound of the right hemithorax revealed no effusion. The patient underwent thoracocentesis and ~1 L of slightly opaque dark brown fluid was removed (figure 2). Fluid analysis demonstrated total protein of 36 $g \cdot L^{-1}$, albumin 20 $g \cdot L^{-1}$, glucose 4.2 $mmol \cdot L^{-1}$, lactate dehydrogenase 538 $U \cdot L^{-1}$, white cell count one plus, and red cell count three plus, with no organisms on microscopy and no growth on fluid culture. Pleural–serum protein ratio was calculated as 0.57 and serum–pleural albumin gradient was calculated as 1.0 $g \cdot dL^{-1}$. Cytology showed no neoplastic cells, but mainly neutrophils and macrophages. Tuberculosis culture was negative. Overall, pleural fluid analysis was consistent with an exudative effusion.

FIGURE 2 Macroscopic appearance of the pleural fluid which is notably dark.

Task 3

What are the differential diagnoses given the above results?

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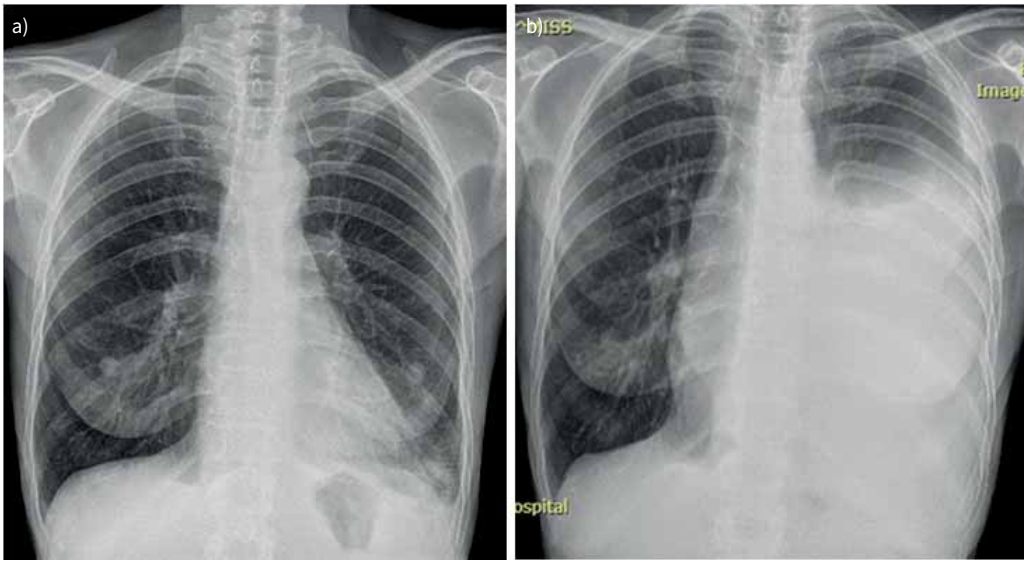

FIGURE 3 Chest radiographs: a) immediately following thoracocentesis and b) 11 days following thoracocentesis.

Due to the history of pancreatitis and pancreatic cysts, pleural fluid was additionally sent for lipase and amylase levels. Pleural lipase was >3500 $U \cdot L^{-1}$ and amylase was >4500 $U \cdot L^{-1}$ (expected range: 30–110 $U \cdot L^{-1}$). At this stage, we felt that the pleural effusion was related to chronic pancreatitis, although the mechanism by which this could occur was not apparent. Our differential diagnoses included acute pancreatitis and malignancy. The patient had normal serum pancreatic enzyme levels and no abdominal tenderness, although cross-sectional imaging of the abdomen was not undertaken at this time. Whilst cytology was negative for neoplastic cells, the patient was an ex-smoker and had a known ground glass lung nodule, so it seemed reasonable to consider malignancy. Therefore, a CT scan of the chest was performed which showed a large volume left-sided effusion and no suspicious lung lesion. We felt that the raised NT-proBNP was not significant to the presentation, and likely due to a combination of baseline left ventricular dysfunction, chronic kidney disease, and anaemia.

A good therapeutic response was achieved following thoracocentesis and the patient was discharged home. Unfortunately, the effusion reaccumulated three times after 11, 17, and 10 days respectively, each requiring pleural aspiration for symptomatic relief (figure 3 and table 1). On each occasion, the pleural fluid was dark brown in appearance, and analysis revealed an exudate with raised pancreatic enzyme levels.

Due to the elevated pleural amylase and lipase results from the first thoracocentesis, the patient's previous abdominal imaging was reviewed. During an admission for acute pancreatitis a month prior to her presentation with a pleural effusion, an ultrasound of the abdomen showed a heterogenous pancreas with a complex cystic area at the pancreatic tail measuring 12.1×2.8×4.8 cm and a second cystic area surrounding the pancreatic head measuring 4.2×2.3×4.2 cm. During that admission, she also had a CT scan of her abdomen and pelvis which demonstrated multiple pancreatic pseudocysts (figure 4), including one that appeared to communicate with the retroperitoneal space through a tract. This finding had not been noted by the surgical team at the time. She went on to have an outpatient magnetic-resonance cholangiopancreatography (MRCP) 44 days after her initial presentation with a pleural effusion (figure 5).

TABLE 1 Rate of accumulation of pleural fluid

Pleural aspiration	Days following initial admission	Volume drained (mL)
1	1	1000
2	12	1500
3	29	1200
4	39	1000

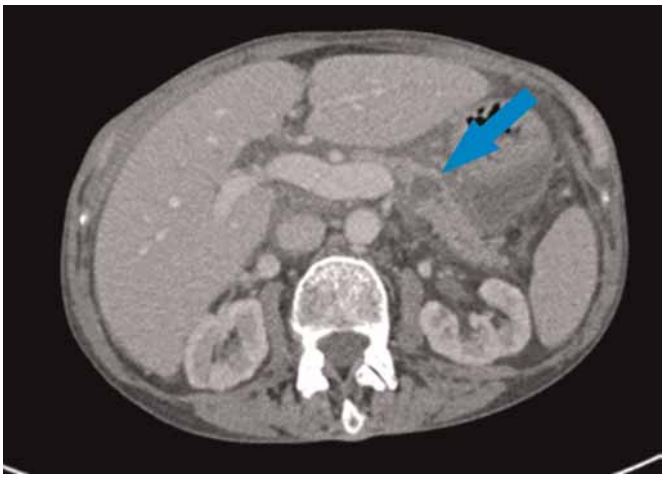

FIGURE 4 Computed tomography of the abdomen and pelvis demonstrating complex pancreatic anatomy with cyst formation (blue arrow).

This confirmed the diagnosis of a pancreaticopleural fistula (PPF) extending from the tail of the pancreas to the pleural space.

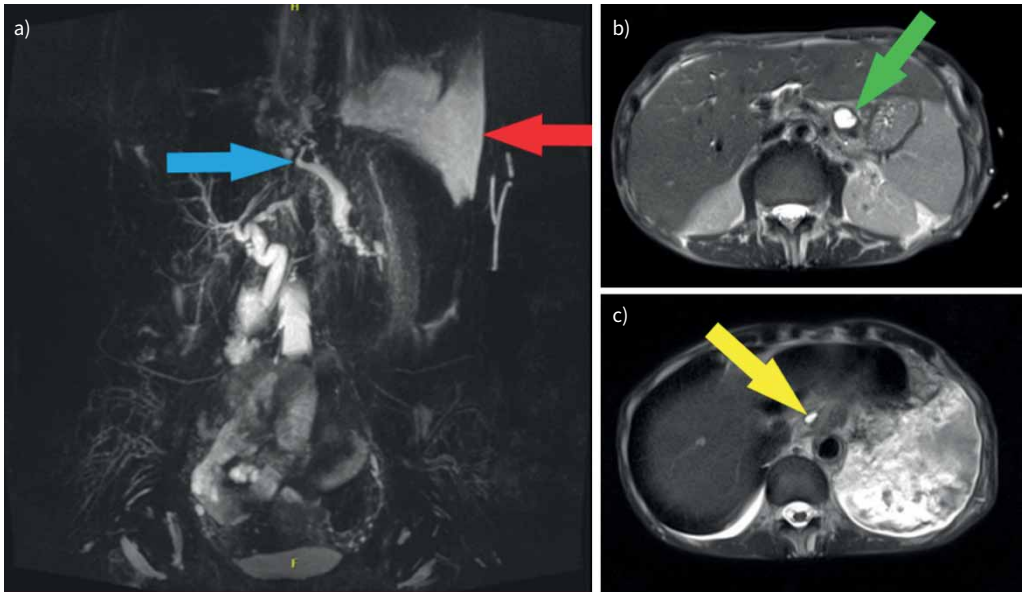

FIGURE 5 a) Magnetic-resonance cholangiopancreatography (MRCP) confirming diagnosis of pancreaticopleural fistula (blue arrow) and contrast in the pleural space (red arrow). b) MRCP image showing contrast in the pseudocyst (green arrow) and c) the fistula then runs medially and cranially before crossing the diaphragm (yellow arrow).

Task 4

What is the best treatment option for this patient?

a) Repeated pleural aspiration or indwelling pleural catheter (IPC)
b) Somatostatin analogue (*e.g.* octreotide)
c) Endoscopic retrograde cholangiopancreatography (ERCP) and stenting
d) Pancreatic-enteric anastamosis

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Our centre is small and does not perform complex hepatobiliary surgery or ERCP. In view of this, the patient was referred to a tertiary centre for definitive management. As an interim measure, we inserted a left-sided IPC because of rapid reaccumulation of the pleural fluid. 3 months after initial presentation, she underwent pancreatic duct stenting *via* ERCP, which successfully blocked the entrance to the fistula and diverted pancreatic fluid into the duodenum (figure 6). Her IPC was removed 2 weeks following the procedure. A repeat chest radiograph 3 months following treatment showed no recurrence of the pleural fluid and she remained well at a 9-month follow-up appointment.

Discussion

Pleural effusion caused by PPF is a rare complication of chronic pancreatitis, occurring in ∼0.4% of cases of chronic pancreatitis, and accounting for <1% of all patients with pleural effusion [1–3]. The risk increases to 4.5% in patients with a pancreatic pseudocyst, a localised collection containing high levels of pancreatic enzymes. A PPF forms following a pancreatic duct disruption or rupture of a pseudocyst posteriorly into the retroperitoneum, which allows pancreatic fluid to spread into the pleural cavity *via* the aortic or oesophageal hiatus. Occasionally, pancreatic fluid spreads into the mediastinum, forming a mediastinal pseudocyst, which eventually ruptures to create a PPF. Anterior rupture of a pseudocyst leaks pancreatic fluid into the peritoneum, leading to ascites [4,5].

Typically, dyspnoea is the predominant presenting symptom. Other common presenting complaints are abdominal pain (29%), cough (27%) and chest pain (23%) [1]. The characteristic pleural effusion resulting from PPF is large, rapidly accumulating, and usually left sided, with patients often requiring repeated thoracocentesis for symptomatic relief [6, 7]. Macroscopically, pleural fluid is dark brown or even black, and fluid analysis is usually exudative, with significantly raised amylase (usually >10 000 $U \cdot L^{-1}$ and can be >50 000 $U \cdot L^{-1}$) [5, 8]. Mortality risks in PPF stem mainly from sepsis, empyema and malabsorption [9].

Mildly raised pancreatic enzyme levels can be seen in other pleural effusions up to ∼200 $U \cdot L^{-1}$[10, 11]. In malignant effusions, this may be due to ectopic secretion of amylase by the tumour, or *via* tumour obstruction of pleural lymphatics [12, 13]. Salivary amylase is found in effusions secondary to

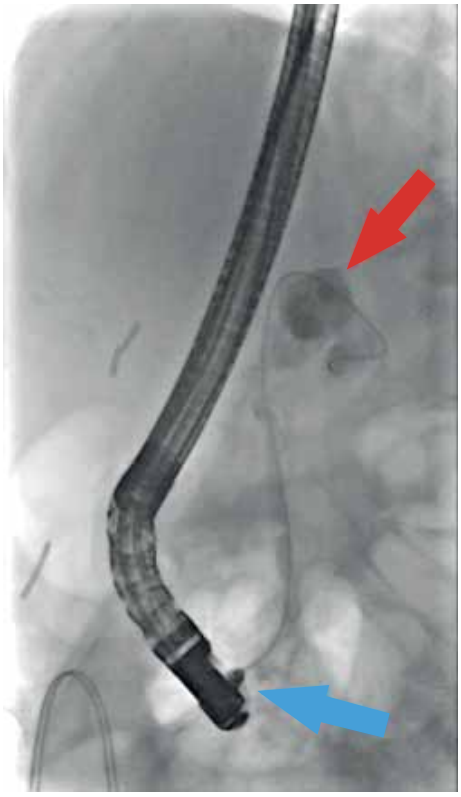

FIGURE 6 Endoscopic retrograde cholangiopancreatography image demonstrating catheterisation of the pancreatic duct (blue arrow) and contrast leak at the fistula site (red arrow).

oesophageal rupture, as gastric contents move upwards into the pleural space with the negative intrathoracic pressure of inspiration. These patients usually appear unwell, with haemodynamic instability [10]. Additionally, the inflammatory effusion associated with acute pancreatitis can show mildly raised levels of pleural fluid amylase [5, 14] and this is thought to be secondary to local fluid movement across the diaphragm from the tail of the pancreas [10]. This is a relatively common complication of acute pancreatitis, and is seen in up to 50% of patients who have undergone a CT scan [15]. It can be differentiated from PPF as it usually resolves as the inflammation alleviates, whereas effusions secondary to PPF persist [1]. While the pleural fluid analysis from our patient demonstrated amylase levels of >4500 $U \cdot L^{-1}$, this was the upper threshold of our laboratory testing capability, so we can assume that given the presence of a PPF the actual pleural amylase levels were much greater.

The diagnostic modality of choice is MRCP rather than CT scanning due to its high sensitivity [1]. However, diagnosis is often delayed as clinicians may not correlate the pleural effusion with the history of pancreatitis [3,4, 7]; therefore, a high index of clinical suspicion is required in patients with risk factors.

Management of PPF can be conservative, endoscopic or surgical, and should be based on the underlying pancreatic duct anatomy [5]. Complex pancreatic anatomy reduces the likelihood of the fistula healing with conservative management alone, so this is reserved for patients with normal pancreatic ducts and no strictures [4]. It consists of total parenteral nutrition for pancreatic rest and somatostatin analogues, such as octreotide, to decrease the volume of the fistula output and allow healing. Octreotide is a long-acting analogue of somatostatin and is administered subcutaneously. It inhibits pancreatic exocrine secretions, decreases gut motility, and reduces splanchnic blood flow [3]. However, this fails to close the fistula in 59–69% cases and is now rarely used, as the majority of patients with PPF have complex pancreatic anatomy [2, 16].

ERCP may be used following failure of conservative management, or as first-line treatment in the majority of cases. Pancreatic stents can be placed endoscopically to bridge the site of a ductal disruption and thus close the fistula by decreasing ductal pressure and blocking the fistula lumen. Sphincterotomy is also used to direct flow of pancreatic fluid away from the fistula [3]. Endoscopic management can be complicated by proximal strictures or gallstones preventing stent insertion, or disruptions too distal to reach [5, 17]. Jagielski *et al.* [18] conducted a prospective study of 22 patients undergoing endoscopic management of PPF and successful closure of the fistula was observed in 21 out of 22 patients (95.45%). One patient had significant pancreatic duct disruption leading to ongoing endoscopic drainage, and the PPF reoccurred in two patients during the short follow-up period of 1 year. Roberts *et al.* [9] conducted a smaller study of nine patients, in whom there was no recurrence of the fistula over a median follow-up of 50 months. Current evidence for longer term success rates in larger populations and follow-up strategy is lacking.

Surgical management is reserved for fit patients with complete pancreatic ductal obstruction or distal fistulas and usually involves pancreatic resection or pancreatic-enteric anastomosis [4].

Of note, is the raised level of eosinophils (2.8×10^9 cells$\cdot L^{-1}$). The patient had never previously been eosinophilic, and levels returned to within normal parameters following pancreatic duct stenting. Peripheral eosinophilia was first linked with chronic pancreatitis by Juniper [19] in 1955 and has been shown to be strongly associated with pancreatic pseudocysts and severe tissue damage to neighbouring organs, including pleural effusion and ascites [20]. Additionally, eosinophilic pancreatitis is a distinct pathology which often presents as an inflammatory mass-like pancreatic lesion due to accumulation of eosinophils in the pancreas, and these patients can have peripheral eosinophilia [21]. Suggested mechanisms for peripheral eosinophilia in chronic pancreatitis include local pancreatic inflammation and hypersensitivity reaction [20]. Respiratory physicians may be more likely to think about pulmonary eosinophilic diseases in the first instance, rather than making a connection with a pancreatic disorder. This case demonstrates the need to consider the extrapulmonary causes of peripheral eosinophilia and pleural effusion.

In summary, we present a case of PPF resulting in recurrent pleural effusion. Although a rare cause of pleural effusion, it is an important differential in patients with alcoholism and/or chronic pancreatitis.

Answer 1

The chest radiograph is posterior to anterior view. It shows a unilateral moderate-sized pleural effusion. The remaining lung fields are clear and there is no pneumothorax, consolidation, bony injury, wedge-shaped opacity (Hampton's hump) or enlarged pulmonary artery (Fleischner sign) to account for her symptoms.

<< Go to Task 1

Answer 2

Eosinophilia and pleural effusion are rare in combination, but differential diagnoses include lung malignancy, haemothorax, chronic eosinophilic pneumonia, eosinophilic granulomatosis with polyangiitis, hypereosinophilic syndrome, parasitic infection, trauma, and pancreatitis-associated effusions. Additionally, it is also plausible that the patient has dual pathology resulting in both eosinophilia and pleural effusion.

<< Go to Task 2

Answer 3

The pleural fluid analysis demonstrated an exudative effusion for which the differential diagnoses include infection, tuberculosis, malignancy, chylothorax, haemothorax, autoimmune disease and pancreatitis-associated effusions. Infection is a common cause of exudative effusions, encompassing parapneumonic effusions, tuberculosis and empyema. We felt that this was relatively unlikely as the patient was systemically well and had normal inflammatory markers. Another common cause is either lung or metastatic malignancy. There were no neoplastic cells in the pleural fluid samples, but this does not exclude malignancy, and the patient had a significant risk factor for lung malignancy as an ex-smoker. Therefore, this remained a differential diagnosis and further investigation with a computed-tomography (CT) scan would be warranted. The effusion was dark brown in colour, which does not support a diagnosis of chylothorax, where the macroscopic appearance is often milky white. Unfortunately, pleural fluid was not sent for triglyceride levels to exclude chylothorax completely. There was no history of chest trauma to support a diagnosis of haemothorax. There were no joint, skin or ophthalmic symptoms to suggest autoimmune disease, and there was no relevant family history. Finally, there was a history of heart failure with reduced ejection fraction and NT-proBNP was extremely high. Very occasionally, heart failure can cause exudative effusions, but they are much more commonly transudative and bilateral. This, coupled with the euvolaemic status of the patient, made this diagnosis less likely.

<< Go to Task 3

Answer 4

c. Conservative treatment with repeated pleural aspiration and a somatostatin analogue was considered for this patient. However, it was deemed not a definitive option due to her relatively complex and distorted pancreatic anatomy, as the fistula was unlikely to heal with a somatostatin analogue alone. Surgical treatment can be considered in some cases, but the majority of patients are treated endoscopically, and the surgeons felt that she would be high risk due to her low body weight. Therefore, she underwent successful pancreatic duct stenting *via* ERCP. Unfortunately, there were delays in the referral to the tertiary centre, so while awaiting endoscopic treatment an IPC was inserted to alleviate the need for repeated hospital admissions for thoracocentesis due to the rapid reaccumulation of pleural effusion.

<< Go to Task 4

Conflict of interest: The authors have nothing to disclose.

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