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SUMMARY

Severe necrotising haemorrhagic pancreatitis is a challenging clinical condition that carries a high mortality especially in resource-limited settings. The management requires a multidisciplinary approach in a well-equipped critical care unit. The decision for operative versus conservative management is a close call and one that continues to challenge clinicians. In this case report, we present a 36 years old HIV-infected African male who presented at a tertiary care teaching and referral hospital in Kenya with worsening intra-abdominal bleeding. We highlight the management challenges faced by clinicians and review the literature on this subject.

INTRODUCTION

Acute pancreatitis usually arises from early activation of digestive enzymes found inside the acinar cells and leads to compromise of the gland itself, nearby tissues and other organs. It is classified into two groups as per the revised Atlanta classification: interstitial pancreatitis accounting for 80% of the cases and necrotising pancreatitis accounting for the remainder (1).

The annual incidence of acute pancreatitis ranges between 14.6 and 40 per 100,000 of the population in various reports (2,3,4). The overall mortality in all hospitalised patients is about 10%. However, among patients with severe acute pancreatitis, mortality may be as high as 30% and approaches 50% for those with multisystem organ failure (5,6,7). Mortality is usually due to multi-organ failure and sepsis.

There is paucity of data regarding the management and outcomes of severe acute pancreatitis in Kenya, as well as from other resource-limited settings. In this case report, we highlight the challenges facing clinicians in such settings.

CASE PRESENTATION

A 36 years old HIV-infected African man presented at a teaching and referral hospital in Kenya with a three week history of abdominal pain and distention; two weeks history of diarrhoea and vomiting and a three day history of dizziness. He had been diagnosed with HIV infection two years earlier and initiated on standard first-line anti-retroviral therapy (ART) comprising tenofovir, lamivudine and efavirenz with co-trimoxazoleprophylaxis. The abdominal pain and distention were of gradual onset. The pain was initially mild in intensity, was diffuse and worse after meals, but subsequently persisted. Initially the abdominal distention was generalised, with no changes in bowel habits. These symptoms worsened over the next two weeks. This was followed, a week later, by diarrhoea and vomiting. He had two to three episodes of watery, non-bloody diarrhoea per day with post prandial, non-projectile and non-bilious vomiting. Three days prior to admission he developed dizziness but was able to ambulate with support. There was no history of palpitations, orthopnea or paroxysmal nocturnal dyspnea. He did not have leg swelling or facial puffiness and reported normal urine frequency and amount. There was no history of jaundice, pruritus or pupura. He had a mild productive cough but did not report fever or weight loss. After the onset of the illness, he confided to using herbal medications without much relief.

In his past medical history, he had successfully completed treatment for smear negative pulmonary tuberculosis a year earlier. Apart from this, he had not suffered other opportunistic infections, did not have other chronic illnesses and had generally been in good health. His last available CD4+ cell count

done at the baseline of initiating ART was 201/mm^3. He reported good adherence to his medication and clinic visits.

In his social history, it was noted that he consumed large amounts of illicit liquor on a daily basis. He admitted to cigarette smoking in the past (~3.5 pack years) but had quit two years earlier when he was diagnosed with HIV infection. He worked as a driver of a public transport van. He was separated from his wife and children who were reportedly alive and well.

Initial examination revealed a young man in good nutritional status. He was acutely sick-looking, tachypneic and moderately pale. He was mildly dehydrated. He did not have cyanosis, scleral icterus, peripheral edema, petechiae or lymphadenopathy. His blood pressure was 110/60mmHg, pulse 103/min, respiratory rate 24/min, temperature 36.7^{0}C and oxygen saturation while breathing ambient air was 95%. The abdomen was uniformly distended, moving with respiration, with generalised moderate tenderness but no guarding or rigidity. Moderate ascites was present with no palpable masses. The bowel sounds were normal and a digital rectal examination was normal. In the respiratory system, he was tachypneic but the chest was clear to auscultation bilaterally. Cardiovascular examination was essentially normal except for tachycardia. Examination of the central nervous system was normal. A bedside paracentesis revealed a sanguinous aspirate with the appearance of frank blood. An abdominal ultrasound showed massive ascites with septations but the liver, spleen, pancreas, kidney gall bladder and ducts were all reported normal.

In the diagnostic formulation, we considered that the patient was HIV infected, presented with an acute diarrhoeal illness, had anaemia and haemorrhagic ascites in the background of chronic alcoholism. Our initial differential diagnoses at this point included infectious conditions such as tuberculous peritonitis; malignancies such as haepatocellular carcinoma, peritoneal carcinomatosis or Kaposi's sarcoma; severe pancreatitis or acute liver failure. The results of investigations done are summarised in Table 1.

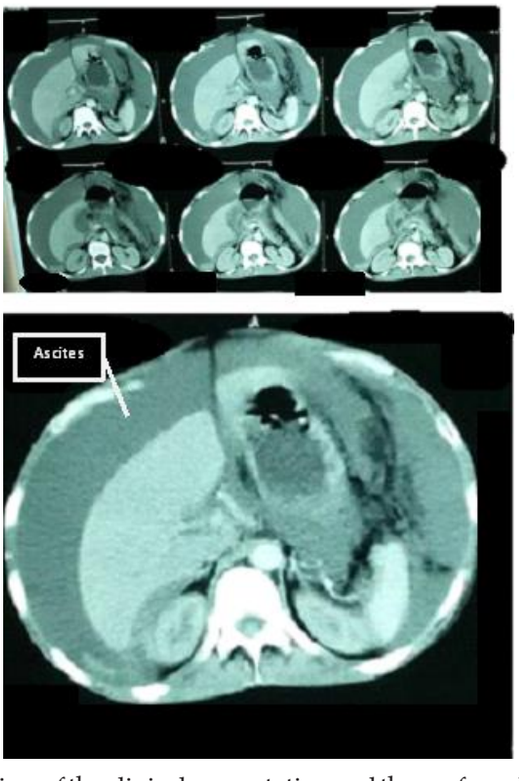
Table 1
Laboratory parameters for the patient

Parameter	Baseline	Day 3	Week 1	Week 2	Reference ranges
White Cell Count*10^9/L (%neutrophils)	16.2 (82%)	11.7 (74%)	9.7 (72%)	20.11 (91%)	5.2-10.4 *10^9 (40-74%)
Haemoglobin g/dl (haematocrit)	4.6 (18.8)	6.7 (17.8)	9.2	8.7 (30)	14-18
Platelet count *10^9/L /L)	683	336	349	629	130-400
Serum Urea (mmol/L)	3.5	15.3	2.1	7.4	0-8.3
Serum Creat (umol/l)	55	315	55	29	44-80
Serum K+ (mmol/l)	4.8	4.3	4.7	3.3	3.5-5.1
Serum Na+ (mmol/l)	118.2	114	127	137	136-145
Serum Cl- (mmol/l)	88.2	78.3	100	93	98-107
Serum Ca++	1.64				2.5-2.55
Serum PO4- (mmol/L)	1.92				
Serum Albumin g/l	22	23			35-50
Total Protein	45	52			64-83
Alkaline phosphate U/L	103	153			35-104
Aspartate Transaminase U/L	23	34			<31
Alanine Transaminase U/L	13	13			<32
Bilirubin Total (direct) umol/L	1.8 (1)	5.6(3.3)			<17.1
Ascitic Albumin g/L	13				
APTT seconds	25.4				24-36
PTI %	112.9				
INR	0.9				
Pancreatic Lipase (U/L)	940	1439	350	257	13-60

Pancreatic amylase (U/L)	1012	944	344	316	28-100
Total cholesterol (mmol/L)	2.08				<5.2
LDL cholesterol (mmol/L)	0.48				< 2.6
HDL cholesterol (mmol/L)	0.52				> 0.9
Triglycerides (mmol/L)	0.34				< 2.3
Lactate dehydrogenase U/L	360				105-333
Random Blood Sugar (mmol/L)	5.6	7.8	3.7		4-7.8

The patient was initiated on empiric anti-tuberculous therapy for possible tuberculous peritonitis, pending the results. Other investigations included a peripheral blood film which showed features of iron deficiency anaemia. Serum albumin ascitic gradient (SAAG) was 8 g/L reflecting a transudate. Ascitic fluid gram stain, acid alcohol fast (AAFB) stain and culture did not reveal any micro-organisms. Sputum analysis by Mtb/Rif geneXpert© was negative for Mycobacteria tuberculosis. Abdominal CT scan showed massive ascites but all intra-abdominal organs, including the pancreas appeared normal (Figure 1). The chest radiograph showed mild bilateral basal infiltrates, not typical of TB. Of note, both the pancreatic amylase and lipase were elevated more than ten-fold the upper limit of normal.

Figure 1
Abdominal CT scan showing massive ascites



In view of the clinical presentation and the profoundly elevated pancreatic amylase and lipase, we made a clinical diagnosis of acute kidney injury and anaemia secondary to acute severe necrotising-haemorrhagic pancreatitis with probable sepsis in a HIV infected patient. With a score of 8 on the APACHE II criteria (indicating severe pancreatitis with an increased risk of mortality), he was transferred to High Dependency Unit (HDU). His supportive treatment included nil by mouth and nasogastric tube drainage, intravenous fluids, total parenteral nutrition, multiple blood transfusions, broad spectrum antibiotics, proton pump inhibitors, somatostatin and morphine. In addition, his ART, anti-tuberculous therapy and septrin prophylaxis were withdrawn. Surgical intervention was ruled out due to the co-morbidities, which would increase the surgical mortality risk. While in HDU, the patient remained in critical condition; ascites became very tense and repeated percutaneous decompression continued to yield frank blood suggesting ongoing intra-peritoneal haemorrhage and probable intra-abdominal hypertension. He developed respiratory failure and was admitted into the intensive care unit (ICU) for ventilatory support, but succumbed after one week in ICU.

Gross autopsy findings included haemoperitoneum estimated at 1.5 litres with a further 200 mls of clotted blood in the pouch of Douglas. Other findings were necroticomentum; fatty liver and the pancreas had an area of haemorrhage towards the tail with blurred anatomy. There were two pancreatic cysts measuring 2 cm each with no abdominal tumour. Histology revealed haemorrhage into the pancreas with infiltration by chronic inflammatory cells (Figure 2). The peritoneal soft tissue and omentum exhibited marked fat necrosis, with the lungs showed pulmonary oedema. Lung, liver and peritoneal smears were negative for AAFB. The cause of death was attributed to severe necrotising haemorrhagic pancreatitis.

DISCUSSION

This case report highlights the diagnostic and management challenges of acute severe necrotising pancreatitis in a resource-limited setting. This is

a serious medical emergency that carries a high mortality and morbidity rate (8). Early diagnosis and initiation of appropriate care in a critical care unit is paramount in averting mortality. In the initial evaluation, our patient was thought to have tuberculous peritonitis and was indeed initiated on empiric anti-tuberculous therapy based on the presence of abdominal pain, ascites with septations without other evident organ pathology on imaging. Loculated ascites is a well-recognised presentation of TB peritonitis especially in high HIV prevalence settings such as ours (9,10). Although abdominal CT scan has long been used to confirm the diagnosis of acute pancreatitis, both the abdominal ultrasound and CT scan did not reveal any pancreatic abnormalities in our case, reiterating the diagnostic challenges on imaging modalities(11). Recently, diffusion weighted magnetic resonance imaging (DWMRI) is being advocated as a superior imaging modality to replace abdominal CT scan (12,13). However, this is unlikely to be available in many resource constrained settings in the near future and thus clinicians in such areas must continue to make difficult decisions without the aid of cutting edge tools.

The identified risk factors for acute pancreatitis in our patient included heavy alcohol consumption, HIV infection and exposure to drugs. Limited data from Kenya indicate that alcohol is responsible for an estimated 30 % of cases of acute pancreatitis (14). Alcohol causes sensitisation of acinar cells to cholecystokinin-induced premature activation of zymogens, generation of toxic metabolites such as acetaldehyde and fatty acid ethyl esters which are responsible for development of pancreatitis (15,16). Chronic alcohol consumption is also a major risk factor for pancreatic necrosis among patients with acute pancreatitis, as seen in our patient (17).

HIV infection per se, as well as opportunistic infections, are recognised risk factors for acute pancreatitis(18). In addition, many of the drugs used in the setting of HIV have been implicated in causing pancreatitis. The major risk has been attributed to nucleoside reverse transcriptase inhibitors (NRTI) like didanosine, stavudine and zidovudine. Non-nucleoside reverse transcriptase inhibitors like efavirenz, and protease inhibitors have also been implicated, usually through causing hyperlipidaemia(19). Co-trimoxazole used for prophylaxis of pneumocystis jirovecii pneumonia has also been implicated. Our patient was on tenofovir, lamivudine and efavirenz as well as co-trimoxazoleprophylaxis which could have contributed to development of pancreatitis in the background of chronic alcoholism.

Complications and management

Our patient experienced several complications including acute kidney injury; intra-abdominal soft tissue necrosis; severe anaemia with probable intra-abdominal hypertension and abdominal compartment syndrome secondary to uncontrolled intra-abdominal haemorrhage; sepsis and eventual respiratory failure. Despite early transfer to HDU and eventually to ICU and the aggressive supportive care, the patient succumbed. One of the most challenging aspects of his management was the ongoing intra-abdominal haemorrhage. Haemorrhagic complications occur in an estimated 6% of patients with acute pancreatitis(20). Treatment for haemorrhage ranges from multiple transfusions, laparoscopic intervention, angiographic embolisation to surgery. Angiographic embolisation is emerging as an effective treatment for life-threatening bleeding that occurs secondary to pancreatitis (21,22). In our case, the source of the bleeding could not be identified ante-mortem due to unavailability of angiography in our setting. Open laparotomy was ruled out due to the patient's poor condition. This meant that ongoing haemorrhage was managed conservatively with multiple transfusions and percutaneous decompressions to relieve intra-abdominal hypertension. The intra-abdominal haematoma likely provided a rich culture media for bacterial growth for trans-located gut bacteria which caused sepsis.

Enteral nutrition is generally preferred to parenteral nutrition in patients with acute pancreatitis (23,24). Enteral feeding helps maintain the intestinal barrier and prevent bacterial translocation from the gut. Total parenteral nutrition is associated with catheter sepsis, vein thrombosis and thrombophlebitis. Though there are no absolute contraindications for enteral feeding, our patient could not tolerate enteral feeds due to associated severe abdominal pain.

Although blood cultures revealed no growth of pathogens (likely due to on-going antibiotic use), the rise in white cell count in week two (predominantly neutrophilia) suggest that a bacterial infection had set in. The resultant sepsis likely contributed to mortality despite treatment with broad- spectrum antibiotics.

In conclusion, this case report highlights the challenges facing clinicians in resource-limited settings in the management of acute necrotising pancreatitis. Early diagnosis, multidisciplinary approach and aggressive supportive care continue to be pillars of care. Improvement in management of intra-abdominal haemorrhage, embracing angiographic embolisation,

is urgently needed to improve outcomes. Where there is high risk of pancreatitis from medical condition and/or drugs, complete alcohol abstinence must be advocated.

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