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Case Report

Acute Necrotic-Hemorrhagic Pancreatitis in a 2 Year Old Girl at Kampala International University Teaching Hospital (Uganda): Case Report

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Abstract: Acute necrotic-hemorrhagic pancreatitis is one of the most rare and less remembered causes of acute abdomen in children despite its fatal outcome. We report the case of a 2 year-old girl admitted through accident and emergence department with reported anorexia for 2 weeks, associated with over crying after meals, abdominal distention, vomiting and chills for 2 days. The patient had a temperature of 37.9^0C, rebound tenderness of the abdomen and absent bowel sounds. Abdominal ultrasonography revealed fluid collection at the pancreatic bed. No focal pancreatic masses or gallstones were reported. Gram staining of peri-pancreatic collection revealed Gram negative rods, whereas its culture revealed *Escherichia coli* sensitive to gentamycin and ceftriaxone. Other laboratory findings were; hypocalcaemia of 2.0mmol/L, total serum amylase of 350 U/L, Hb of 8.0g/dl and raised ESR of 40mm/hr. Liver and renal function tests were within normal ranges. Enhanced CT scan and serum lipase were unavailable in our settings. We subjected the patient to an emergence exploratory laparotomy. Intraoperative findings were: hemorrhagic ascites, retroperitoneal haematoma, edematous pancreatic body with areas of grey-white necrosis; and steato-necrosis in the omentum and mesentery leading to a diagnosis of acute necrotic-hemorrhagic pancreatitis. We compare the characteristics of our patient with the available data on literature review. Informed consent was sought from the patient's mother in writing, for the surgery and case documentation.
Keywords: Acute-abdomen, Children, Laparotomy, Necrotic-pancreatitis.

INTRODUCTION

Acute necrotic-hemorrhagic pancreatitis is a severe form of acute inflammation of the pancreas clinically presenting with acute abdomen that is associated with macroscopic hemorrhage and fat necrosis in and around the pancreas [1]. There is paucity of data on prevalence of this condition in Uganda, however its epidemiology differ by country [2]. According to National Digestive Diseases Information Clearinghouse; overall, annual incidence of 210,000 people is reported in the United States; with Caucasians being more affected than African Americans [3]. This severe form of acute pancreatitis occurs in 20% of cases [4] and is associated with increased risk of multiple organ failure with subsequent high mortality rates of up to 70% [5], especially in presence of infected necrosis [6]. The condition is assumed to affect males than females, predominantly affecting adults of 40 to 70 years [1, 2]. We present a case of a 2 year old African girl who was successfully managed surgically at Kampala International University Teaching Hospital, Ishaka, Uganda.

CASE REPORT

This 2 year old female was admitted through accident and emergence department for reported constant abdominal discomfort and anorexia that had lasted 2 weeks prior to admission. The pain was reportedly associated with over crying after meals, abdominal distention, vomiting and chills for 2 days. There was no preceding history of accidental alcohol intoxication. The patient had no known chronic illnesses and reportedly had not been on any medication 4 months prior to admission. There was no history of trauma or diagnostic procedures before onset of symptoms. The patient's immunization schedule was up-to-date. On general examination, the patient had a temperature of 37.9^0C. There was moderate pallor of conjunctiva but no jaundice. There was dehydration, tachycardia of 120 beats per minute. Other vital signs were normal.

There was generalized abdominal tenderness more marked in the epigastrium and left renal angle, rebound tenderness and absent bowel sounds. The liver and spleen were not palpable. The rectum was empty

with normal anal tone.Abdominal ultrasonography revealed bowel ileus, fluid collection at the pancreatic bed. No focal pancreatic masses or gall stones were reported.Other intra-abdominal organs were reported normal. Gram staining of sonographically obtained peri-pancreatic collection revealed Gram negative rods and its culture revealed *Escherichia coli* sensitive to gentamycin and ceftriaxone. Other laboratory findings were; hypocalcaemia of 2.0mmol/L, elevated serum amylase of 350 U/L, normochromic normocytic anaemia of 8.0g/dl with no anisocytosis, raised erythrocyte sedimentation rate (ESR) of 40mm/hr. Liver function tests (ALT,AST, and serum protein levels); renal functions tests (serum creatinine, blood urea and nitrogen levels), fasting blood glucose level and serumelectrolytes (K^+, Na^+) were all within normal ranges.

We administered pre-operative intravenous metronidazole and ceftriaxone and subjected the patient to an emergency exploratory laparotomy; upon informed consent. Intraoperative findings were: hemorrhagic ascites of 100mls, retroperitoneal haematoma, edematous body of the pancreas with areas of grey-white necrosis; and steato-necrosis appearing as white flecks of fat necrosis in the omentum, mesentery and adjacent transverse colon.A walled-off necrosis (WON) containing a mixture of fluid and necrotic material that was fully encapsulated was also noted on surgery conforming to the category 4 of the (2012) revised Atlanta Classification of peri-pancreatic collections in acute pancreatitis [7], leading to the diagnosis of acute necrotic-hemorrhagic pancreatitis. A purse string suture of vicryl 2/0 was secured to burry a weak necrotized area of transverse colon. Neither pseudocysts nor erosion into major splenic and mesocolonic vessels was observed. We did surgical necrosectomy of pancreatic and peri-pancreatic necrotic tissue and copiously lavaged the peritoneum and pancreatic bed with 5 litres of warm normal saline.

One sump drain was instituted at the pancreatic bed and another in the pouch of Douglas. The abdomen was primarily closed in layers with exception of the peritoneum. The rectus sheath was repaired with interrupted nylon 2/0. A vented drainage tube was sandwiched between the rectus sheath and skin before closure of skin with interrupted vertical mattress sutures of nylon 2/0. The sandwiched tubular drain was then connected to an infusion set calibrated for a drop factor of 15gtts/ml; through which continuous post-operative peritoneal irrigation with 4800mls of warm normal saline was administered daily (over 24hrs) at a rate of 50gtts/minutes. Daily charting of fluid collection in the two sump drains was conducted to ensure balance between irrigation and drainage. Negative pressure was maintained in the two sump drainage suction collection reservoirs and these were emptied whenever full. Postoperatively, the patient was managed in intensive care unit on intravenous fluids (Ringer's Lactate and 10% dextrose), ceftriaxone and gentamycin appropriate for her weight. Peritoneal irrigation was stopped after 96 hours. The sump drains were removed120 hours after surgery when sample drainage fluid was microscopically negative for: red blood cells, pus cells and the patient had blood culture negative for micro-organisms. Nasogastric tube decompression was maintained for 48 hours post-surgery after which early oral intake was initiated; well as antibiotics were stopped after 10 days. The abdominal stitches were removed in 14 days when the wound had healed completely and the patient was discharged. Follow up blood biochemistry was performed 2 weeks later after discharge (Table 1).

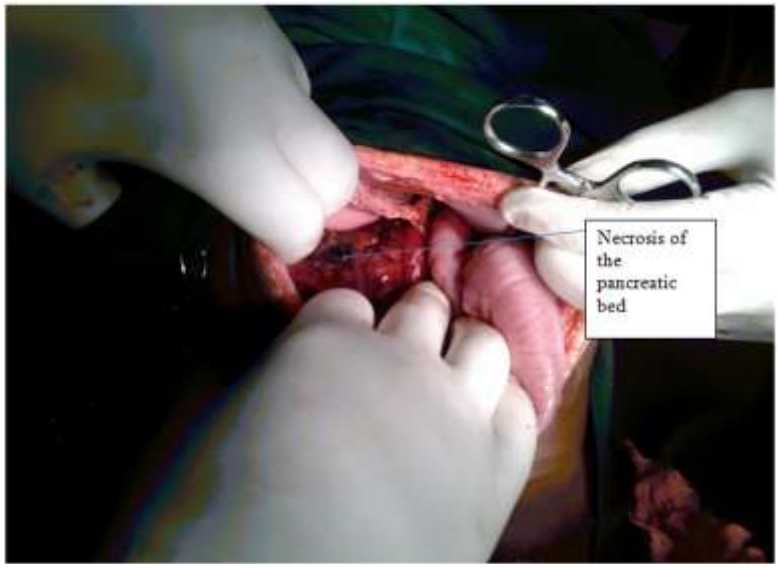

Fig. 1: Necrotic appearance of the pancreatic bed on inspection just after opening the abdomen

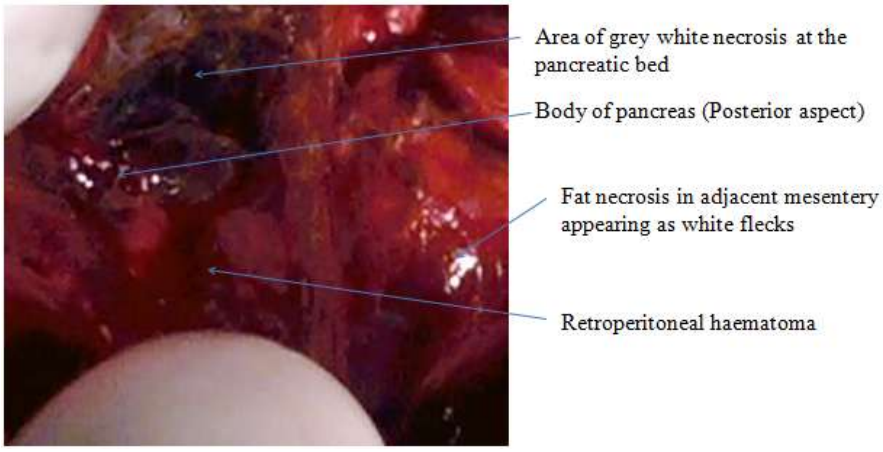

Fig. 2: Showing edematous pancreas with grey white necrosis, retroperitoneal haematoma and fat necrosis

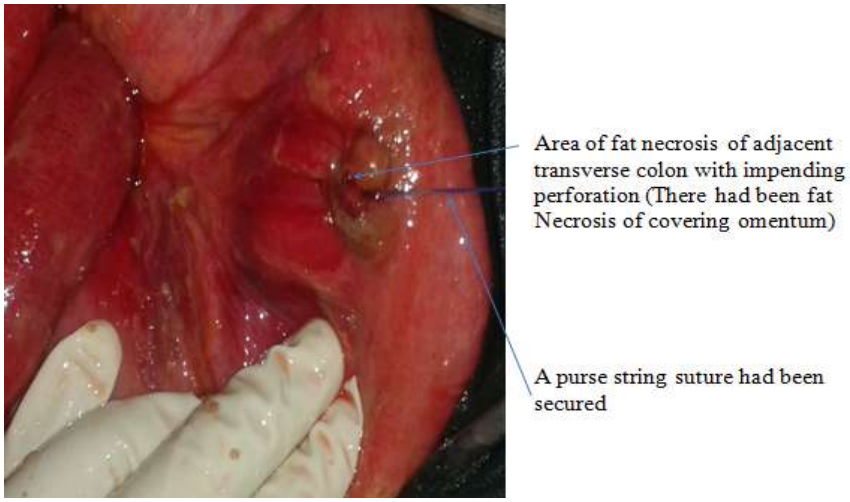

Fig. 3: Showing fat necrosis of adjacent transverse colon and its covering omentum. A purse string suture had been secured at site of impending perforation

Table 1: The Biochemical, hematological and clinical chemistry results for the patient

Laboratory Characteristics	Patient's Value at admission	Value at 4 weeks post-surgery	Normal Ranges
Hb	8.0g/dl	12g/dl	14-16g/dl
Hct	28.40%	37.4%	37-47%
ESR	40mm/hr (Westergren)	8mm/hr	0-10mm/hr
Fasting blood sugar	104mg/dl	100mg/dl	80-120mg/dl
Serum Amylase	350U/L	80U/L	25-125U/L
AST	24.0U/L	14.2U/L	12-39U/L
ALT	21.9U/L	7.2U/L	5-40.0U/L
Platelet Count	$180x10^9$ cells/L	$200x10^9$ cells/L	$150-400x10^9$ cells/L
WBC	$4.7x10^9$ cells/L	$4.5x10^9$ cells/L	$4.0-11x10^9$ cells/L
Granulocytes	$3.4x10^9$ cells/L(70%)	$3.0x10^9$ cells/L	(45%-77%)
Lymphocytes	$1.4x10^9$ cells/L(30%)	$1.38x10^9$ cells/L	$1.50-4.00x10^9$cells/L(25%-45%)
Monocytes	<1%	<1%	0%-5%
Na+	132mmol/L	130mmol/L	130-135mmol/L
K+	3.7mmol/L	3.9mmol/L	3.5-4.5mmol/L
Ca^{2+}	2.00mmol/L	2.20mmol/L	2.15-2.65mmol/L
Serum Creatinine	0.9mg/dl	0.7mg/dl	0.7-1.5mg/dl
Blood Urea Nitrogen	12.0mg/dl	8.0mg/dl	7.0-18mg/dl
Thin blood film report RBCs Platelets	Normochromic Normocytic; No evidence of Leukemic process	Normochromic Normocytic; No evidence of Leukemic process	

DISCUSSION

Clinical presentation and diagnosis of acute necrotic haemorrhagic pancreatitis

The present case presented with 2 weeks history of abdominal discomfort and anorexia which are the commonest symptoms. Although in this particular case there was no obvious predisposing factor, the onset of acute necrotic-hemorrhagic pancreatitis is sudden often occurring after a bout of alcohol or a heavy meal and can present with diversity of symptoms with varying severity. Presence of acute abdomen, elevated serum pancreatic lipase tripling normal levels and consistent sonographic and computerized tomographic findings are diagnostic [7].There appears to be two types of acute pancreatitis refractory to conventional supportive therapy, which differ in the extent of surgery required and in mortality. The mild form with persistent life-threatening acute biliary tract disease (biliary type), and a more severe form (pancreatic type) presenting early in the course of the disease [8], but the classification of these is often impossible until surgery. Patients may also present with vomiting and collapse and the condition may be misdiagnosed for other causes of acute abdomen. Presence of fever signals systemic inflammatory response or existence of superimposed infections. Characteristically there is often but not always elevation of serum amylase level within the first 24 hours and elevation of serum lipase level after 3 to 4 days; the latter being more specific for the pancreas although may not be feasible in developing countries. In such settings, thorough clinical judgment and use of intravenous contrast associated to the use of abdominal ultrasound is a comparable alternative to abdominal CT although the latter is superior in evaluating the extent of pancreatic necrosis [9]. Absence of radiation exposure and convenience in children has made magnetic resonance imaging (MRI) replace endoscopic retrograde cholangiopancreatography (ERCP) in elective patients.

Epidemiology and etiology

According to Fagenholz *et al.* [10], the incidence of childhood acute pancreatitis between1998 to 2003 was reported to be 0.1 new cases per 1000 inhabitants in the Unites States though poor case definition is reported particularly for children. Only 279 childhood cases of acute pancreatitis were reported in an Australian study between 1993 and 2002 with median age of 10 years [11]. Authors [10] and [11] however report an increasing incidence of this condition in children attributable to increasing availability of diagnostic methods.

The two common etiological factors associated with acute necrotic-hemorrhagic pancreatitis in adults are alcoholism and cholelithiasis both of which contribute to more than 80% of cases [1, 4].Excessive drinking of alcohol coupled with poor feeding and malnutrition especially in males is a common cause and can be associated with high mortality especially if misdiagnosed or presenting at a later stage with organ failure [12]. In childhood, up to 75% of cases are attributable to mainly trauma, metabolic and systemic diseases, and drugs [11]. In order of importance, the five leading causes of acute pancreatitis in childhood population are biliary lithiasis and tumors; drugs; idiopathic causes; systemic diseases and trauma [13]. Other causes include but not limited to surgical procedures like duodenal surgery, endoscopic retrograde cholangiopancreatography, metabolic, familial, bacteremia, viraemia, ischemic shock, intestinal worms, insect or animal bites with subsequent glomerulonephritis and extension of inflammation to adjacent tissue. Even after thorough investigations 10 to 35% of childhood pancreatitis has been reported to be idiopathic [14-16], although some of the seemingly idiopathic causes have been attributed to genetic mutations [14, 17-21] and still remain of diagnostic challenge in the developing world [15]. Although trauma accounts up to 10 to 40% of childhood acute pancreatitis [22], the retroperitoneal location of the pancreas poses diagnostic challenges particularly in resource limited settings where CT scans are not readily available, a fact that contributes to high morbidity in this age group [23].

Upon review of cases documented, drugs particularly L-asparaginse used in management of acute lymphocytic leukemia, sodium valproate as an anticonvulsant and steroid therapy especially for renal diseases remain one of the commonest causes of childhood drug induced haemorrhagic necrotic pancreatitis [24-31].

Disseminated adenoviral infection [32] and hemolytic uremic syndrome [33] are also known causes of childhood pancreatitis and its association with viral hepatitis has been probed [34]. Pregnancy in its own right has been documented to be a significant cause of acute pancreatitis often presenting 3rd and 4th trimester; but also a risk factor to newly born child through bacteremia [35], although spontaneous abortions often occur for such mothers in early trimesters [36]. The etiology remains idiopathic in a proportion of cases amongst which the one under description seems to follow. Although a positive bacterial culture of peri pancreatic aspirate could have been a cause, it remains equivocal as Gram negative isolates and less commonly polymicrobial isolates can occur as a complication of pancreatic necrosis due to gut flora translocation [37-40]. It is important to note that normal values of serum and urine amylases are not uncommon for this category of patients and should not be the basis for exclusion of the diagnosis. In absence of obvious etiology and CT scan services in remote settings, ultrasound guided fine needle aspiration and bacteriology has to be performed to exclude infected pancreatic necrosis and need for urgent appropriate surgical intervention without which the condition is fatal.

Pathophysiology

It is assumed that severe acute pancreatitis manifests in two phases [41, 42]. The first two weeks are characterized by sterile systemic inflammatory response that may lead to multiple organ failure. The later anti-inflammatory stage after 2 weeks is the most feared, associated with translocation of intestinal flora leading to infected pancreatic necrosis, sepsis and multiple organ failure [41, 42]. The pancreatic Proteases like trypsin and chymotrypsin are the most important in proteolysis. Trypsin activates the kinin system by converting prekallikrein to kallikrein thus activating the clotting and complement systems, resulting in inflammation, tissue damage, thrombosis and hemorrhages found in this condition [1]. The Lipases and phospholipases degrade lipids and membrane phospholipids as Elastases destroy the elastic tissue of blood vessels. On this account, the splenic and mesocolonic vessels may be eroded, warrantying preoperative angiography [43-46]. The erosion may also result in a pancreatic fistula [45, 46]. All these enzymes are released through acinic cell destruction, blockage in exocytosis of pancreatic enzymes and or duct obstruction caused by one or more etiological factors discussed [1, 40]. The inflammation forms pancreatic and or peri-pancreatic fluid collections that can be sterile or later be infected. The microorganisms most frequently isolated in cases of infected pancreatic hemorrhagic-necrosis are gram-negative bacteria of enteric origin particularly Enterococci species [37], although gram-positive cocci are increasingly not uncommonly isolated [39, 40]. The infected fluid can later be walled off to form an encapsulated abscess [47, 48]; often seen on CT scan as heterogeneous peripancreatic collections with fluid and fatty densities in presence of air bubbles [49-51]. Once fluid collection is documented, CT or ultrasound guided fine needle aspiration and bacteriology has to be performed to differentiate infected from sterile necrosis as sterile fluid collections do not uncommonly resorb spontaneously [52].

Postmortem findigs of acute necro-hemorrhagic pancreatitis

Morphologically; an edematous pancreas with variegated appearance of grey-white necrosis subsequently, hemorrhagic ascetic fluid, and white flecks of fat necrosis in the omentum and mesentery are common findings [12]. Resolved lesions may show areas of fibrosis, calcification and ductal dilatation [53]. Microscopically, necrosis of pancreatic lobules and ducts; arteries and arterioles with areas of hemorrhage and fat necrosis surrounded by polymorphs are not uncommon [1, 53].

Management of acute necrotic-hemorrhagic pancreatitis

Although the treatment of acute pancreatitis is primarily non-surgical, an interdisciplinary approach as well as timely and aggressive intensive care has led to a significant improvement of the prognosis in severe necrotizing pancreatitis [2]. Early surgical procedures were associated with high morbidity and mortality and therefore were abandoned and replaced with forceful conservative treatment [2, 6, 54]. Medical management by peritoneal dialysis combined with other therapeutic modalities has been shown to result in early improvement of abdominal and toxemic signs such as shock and renal insufficiency [55]. However, there are still specific indications for surgery during the course of acute pancreatitis. These include cholecystectomy for biliary pancreatitis, surgical debridement of infected necrotic tissue in septic patients and emergency operations for gastrointestinal perforations or hemorrhage [56]. Open laparotomy with continuous post-operative peritoneal lavage and external drainage are the main surgical modalities [37- 39, 47, 57-59].The competing surgical and non-surgical concepts like laparoscopic or endoscopic management are still debatable, but advances in laparoscopic technology and instrumentation allow the utilization of minimally invasive techniques, that lessen the stress of surgery in the already compromised pancreatic patient and minimize duration of hospitalization [54]. However laparoscopic approaches like transluminal endoscopic drainage, laparoscopic retroperitoneal necrosectomy and percutaneous or CT guided drainage need further evaluation despite not being feasible in every tertiary health facility in many of the developing countries [46, 54, 60, 61]. Whatever the approach, the need for the cooperation of an experienced team of gastroenterologists, surgeons, radiologists and intensive care specialists, who are able to manage the potentially life-threatening complications of this disease, is justified. All patients with severe necrotizing pancreatitis should be transferred to a specialized Centre for interdisciplinary therapy [56]. Although non-surgical options remain more than ever the cornerstone of management in many of these patients [62], the role of surgery in the treatment of infected necrotic-hemorrhagic pancreatitis is overemphasized [63-65]. The goal of the surgical procedure is to remove the septic focus by debridement of the infected pancreatic and peripancreatic necrotic tissue. There is a growing body of evidence that a combination of necrosectomy and peritoneal irrigation improves surgical outcome [66, 67]. If pancreatic infection is suspected; fine needle aspiration and bacteriological analysis should always be performed [41, 42].

Complications of acute necrotic-hemorrhagic pancreatitis

Patients who survive acute necrotic-hemorrhagic pancreatitis may develop a variety of systemic and local complications ranging from chemical and bacterial peritonitis, endotoxic shock, and acute renal failure to pancreatic abscess, pancreatic pseudo-cyst and duodenal obstruction [1, 47]. Pancreatic pseudocysts occur in up to 6 to 18.5% of cases [7, 68] and these can become infected, rapture or

exert pressure effect on pancreatic duct and adjacent bowel. Hypocalcaemia occurs in upto 30% of cases [69] due to calcium binding on areas of fat necrosis often characterized by a positive Chvostek's sign (spasm of the facial muscles when the facial nerve is tapped); positive Trousseau's sign (flexion of the wrist, hyperextension of the fingers and flexion of the thumb after inflating a blood pressure cuff above the systolic BP for severalminutes) alongside Laryngeal and bronchial spasms.

Peritoneal infections and shock lung may develop in patients undergoing peritoneal dialysis and those who need assisted ventilation [55]. Although spontaneous resorption of the peri-pancreatic necrotic masses can occur [52], new necrotic masses can develop [55]. Rare complications like necrosis of the transverse colon and subsequent perforation have been reported [70], thus purse string sutures need to be secured around such impending areas of perforation. Erosion into splenic and mesocolonic vessels can occur resulting in severe hemorrhage and pancreatic fistula [45, 46].

Prognosis and factors contributing to mortality in acute necrotic-hemorrhagic pancreatitis

Mortality of acute necrotic-hemorrhagic pancreatitis is up to 20-30% [1, 62] or even higher up to 70% - 93% in presence of infected necrosis [4, 60, 71]. Review of mortality due to hemorrhagic necrotic pancreatitis in 7 childhood cases by Munhoz RP *et al.* [7] revealed that 4 out of 7 (57%) died. Hypotensive shock, infection, acute renal failure and disseminated intravascular coagulopathies are poor prognostic factors. The Ranson's score [64] and Balthazar's criteria [49]are reliable in predicting prognosis although many other predictors of severity [51, 73] have been tested to make progress in early detection of complications. On average 50% of patients operated on for pancreatitis are reported to have the mild edematous form and most of these survive the operation, whereas 50% of the severe form of pancreatitis with infected necrosis or hemorrhage die postoperatively [60, 71] and some literature reports no survivors at all, in those treated without operation [74]. This suggests the usefulness of early surgical treatment once infected pancreatic necrosis is suspected. However, the advisability of operation and the prognostic implications derived from the morphologic categorization of acute pancreatitis are applicable only retrospectively after the operation or autopsy [75]. Current studies [73] show no superiority of prognostic assessment using CT scans as opposed to clinical and biochemical evaluation in the initial phase of the disease, thus thorough clinical assessment is the single most important tool in developing countries where CT scans and MRI are not feasible. Whenever in doubt, it is important to remember that minimally invasive approaches and or laparotomy; with continuous postoperative peritoneal lavage are the main surgical interventions for infected hemorrhagic necrotic pancreatitis, with better outcome [6, 54].

CONCLUSION

Acute hemorrhagic necrotic pancreatitis is a diagnosis worth to think of in acute abdomen amongst children of 2 years and below. Infection of pancreatic necrosis and hemorrhage are still the main risk factors of morbidity and mortality in the course of necrotizing disease, for which diagnostic challenges still exist in many developing countries. Today, infected pancreatic necrosis is a well-accepted indication for surgery in which necrosectomy with postoperative continuous lavage and or closed packing, to continuously remove necrosis and debris are rewarding. Thorough clinical assessment, multidisciplinary approach, appropriate antibiotics, fluid and electrolyte balance, and early detection of need for surgery can reduce morbidity and mortality in developing countries as for the case presented.

REFERENCES

1. Harsh M; Textbook of pathology. 6th Edition, Jaypee Brothers Medical Publishers (P) Ltd, New Delhi, 2010: 646.
2. Whitcomb; Acute Pancreatitis. N Engl J Med., 2006; 354: 2142-2150
3. National Digestive Diseases Information Clearinghouse (NDDIC); Pancreatitis. Available from http://digestive.niddk.nih.gov/ddiseases/pubs/pancreatitis/index.aspx
4. Cleveland Clinic; Acute pancreatitis: Prevalence. Available from http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/gastroenterology/acute-pancreatitis/#prevalence
5. Andris A; Pancreatitis: understanding the disease and implications for care. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/20431448
6. Besselink MG, Bollen TL, Boermeester MA, Van Ramshorst B, van Leeuwen MS, Gooszen HG; Timing and choice of intervention in necrotising pancreatitis. NedTijdschr Geneeskd., 2005, 149: 501-506
7. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG *et al.*; Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. Gut, 2013; 62:102–111.
8. Isogai M, Hachisuksa K, Yamaguchi A, Nakano S; Clinical diversity in biliary pancreatitis-classification of two types. HPB Surg., 1993;6(4): 263-275.
9. Rickes S, Uhle C, Kahl S, Kolfenbach S, Monkemuller K, Effenberger O *et al.*; Echo enhanced ultrasound: a new valid initial imaging approach for severe acute pancreatitis. Gut, 2006; 55: 74-78

10. Fragenholz PJ, Castillo CF, Harris NS, Pelletier AJ, Camargo CA Jr.; Increasing United States hospital admissions for acute pancreatitis,, 1988-2003. Ann Epidemiol., 2007; 17: 491-497
11. Nydegger A, Heine RG, Ranuh R, Gegati-Levy R, Crrameri J, Oliver MR; Changing incidence of acute pancreatitis, 10-year experience at the royal children's Hospital, Melbourne. J Gastroenterol Hepatol., 2007; 22: 1313-1316
12. Hayase T, Yamamoto K, Matsumoto H; Death caused by undiagnosed acute pancreatitis. Nihon Hoigaku Zasshi, 1996; 50(2): 87-91
13. Lopez MJ; The changing incidence of acute pancreatitis in children: a single institution perspective. J Pediatr., 2002; 140: 622-624
14. Sanchez-Ramirez CA, Larrosa-Haro A, Flores-Martinez S, Sanchez-Corona J, Villa-Gomez A, Macias-Rosales R; Acute and recurrent pancreatitis in children: Etiological factors. Acta Paediatr., 2007; 96: 534-537.
15. Segal I, Yaakov Y, Adler SN, Blau H, Broides E, Santo M *et al.*; Cystic fibrosis transmembrane conductance regulatorion channel function testing in recurrent acute pancreatitis. J. Clin Gasstroenterol., 2008; 42: 810-814.
16. Lucid V, Alghisi F, Dall'Oglio L, D'apice MR Monti L, De Angelis P *et al.*; The etiology of acute recurrent pancreatitis in children: a challenging for paediatricians. Pancreas, 2011; 40: 517-521
17. Lee YJ, Kim KM, Choi JH, Lee BH, Kim GH, Yoo HW; High incidence of PRSS1 and SPINK1 mutations in Korean children with acute recurrent and chronic pancreatitis. J Pediatr Gastroentol Nutr., 2011; 52: 478-481.
18. Lal A, Lal DR; Hereditary pancreatitis. Pediatr Sur In., 2010; 26:1193-1199.
19. Comfort MW, Steinberg AG; Pedigree of family with hereditary chronic relapsing pancreatitis. Gastroentology, 1952; 21(1): 54-63.
20. Whitcomb DC, Preston RA, Aston CE, Sossenheimer MJ, Barua PS, Zhang Y *et al.*; A gene for hereditary pancreatitis maps to chromosome 7q35. Gastroentology, 1996; 110: 1975-1980.
21. Corleto VD, Gambardella S, Gullottta F, D'Apice MR, Picucchi M, Galli E *et al.*; New PRSS1 and common CFTR mutations in a child with acute recurrent pancreatitis could be considered a "Hereditary" form of pancreatitis? BMJ Gastroentol., 2010; 10:119
22. Sutherland I, Ledder O, Crrameri J, Nydegger A, Catto Smith A, Cain T *et al.*; Peadiatric trauma in children. Pediatr Surg Int., 2010; 26: 1201-1206.
23. Matttix KD, Tataria M, Holmes J, Kristoffersen K, Brown R, Groner J *et al.*; Pediatric pancreatic trauma: predictirs of nonoperative management failure and associated outcomes. J Pediatr Surg., 2007; 42; 340-344.
24. Frey C, Redo SF; Inflammatory lesions of the pancreas in infancy and childhood. Peadiatrics, 1963; 32: 93-102.
25. Akhtar M, Bhakoo DN, Chandra RK; Pancreatitis in a child woth leukemia on intensivesteroidtherapy: Report of a case. Indian J Pediat., 1964; 31: 327.
26. Reimenschneider TA, Wilson JF, Vernier RL; Glucocorticoid induced pancreatitis in children. Peadiatrics, 1968; 41: 428-437.
27. Chandra RK, Rao MN, Kapoon P; Pancreatitis in a child on intensive predinisolone therapy: report of a case. J Indian Pediat Soc., 1963; 2: 93.
28. Baar HS, Wolff OH; Pancreatic necrosis in cortisone treated children. Lancet, 1957; 1: 812-815.
29. Morinville VD, Barmada MM, Lowe ME; Increasing incidence of acute pancreatitis at an American pediatric tertiary care center: is greater awareness among physicians responsible? Pancreas, 2010; 39: 5–8.
30. Heuser E, Lieberman E, Donnell GN, Landing BH; Subcutaneous fat necrosis with acute hemorrhagic pancreatitis-a case in a child with steroid-resistant nephrosis treated with 6-mercaptopurine. Calif Med., 1967; 106(1): 58-63.
31. Mileusnic D, Donoghue ER, Lifschultz BD; Pathological case of the month: sudden death in a child as a result of pancreatitis during valproic acid therapy. Pediatr PatholMol Med., 2002; 21(5): 477-484.
32. Niemann TH, Trigg ME, Winick N, Penick GD; Disseminated adenoviral infection presenting as acute pancreatitis. Hum Pathol., 1993; 24(10):1145-1148.
33. Grodinsky S, Telmesani A, Robson WL, Fick G, Scott RB; Gastrointestinal manifestations of hemolytic uremic syndrome: recognition of pancreatitis. J Pediatr Gastroenterol Nutr., 1990; 11(4): 518-524.
34. Geokas MC, Olsen H, Swanson V, Rinderknecht H; The association of viral hepatitis and acute pancreatitis. Calif Med., 1972; 117(3): 1-7.
35. Bartelink AK, Gimibrere JS, Schoots F; Maternal survival after acute hemorrhagic pancreatitis complicating late pregnancy. Eur J Obstet Gynecol Reprod Biol., 1988; 29(1): 41-50.
36. Durea P; Pregnancy in the 4thmonth;spontaneous abortion: Acute hemorrhagic pancreatitis.Presentation of a clinical case. Med Interna(Bucur)., 1971; 23(12):1513-1516.
37. Bassi C, Vesentini S, Nifosi F, Girelli R, Falconi M, Elio A, Pederzoli P; Pancreatic abscess and other pus-harboring collections related to pancreatitis: a review of 108 cases. World J Surg., 1990; 14:505–512.
38. Beger HG; Surgical management of necrotizing pancreatitis. Surg Clin North Am., 1989; 69(3): 529-549.

39. Howard TJ, Wiebke EA, Mogavero G, Kopecky K, Baer JC, Sherman S *et al*.; Classification and treatment of local septic complications in acute pancreatitis. Am J Surg., 1995;170: 44–50.
40. Garg PK, Madan K, Pande GK, Khanna S, Sathyanarayan G, Bohidar NP *et al*.; Association of extent and infection of pancreatic necrosis with organ failure and death in acute necrotizing pancreatitis. Clin Gastroenterol Hepatol., 2005; 3:159–166.
41. Werner J, Schneider L, Uhl W, Büchler MW; Acute pancreatitis: surgical therapy. Praxis (Bern 1994), 2005; 94(20):825-30.
42. Werner J, Feuerbach S, Uhl W, Buchler MW; Management of Acute Pancreatitis: from surgery to interventional intensive care. Gut, 2005; 54:426-36
43. Lee MJ, Wittich GR, Mueller PR; Percutaneous intervention in acute pancreatitis. Radiographics, 1998; 18:711–724
44. Hughes SJ, Papachristou GI, Federle MP, Lee KK *et al*; Necrotizing pancreatitis. GastroenterolClin North Am 2007; 36(2): 313–323.
45. Connor S, Alexakis N, Raraty MGT,Ghaneh P, Evans J, Hughes M; Early and late complications after pancreatic necrosectomy. Surgery, 2005; 137: 499–505.
46. Connor S, Raraty MG, Howes N,Evans J, Ghaneh P, Sutton R *et al*.; Surgery in the treatment of acute pancreatitis—minimal access pancreatic necrosectomy. Scand J Surg., 2005; 94:135–142.
47. Bittner R, Block S, Büchler M, Beger HG; Pancreatic abscess and infected necrosis: different local septic complications in acute pancreatitis. Dig Dis Sci., 1987; 32:1082–1087.
48. Buchler MW, Gloor B, Muller CA, Friess H, Seiler CA, Uhl W; Acute necrotizing pancreatitis: treatment strategy according to the status of infection. Ann Surg., 2000; 232: 619–626.
49. Emil JB; Acute Pancreatitis: Assessment of severity with clinical and CT Evaluation. Radiology, 2002; 223: 603-613
50. Bollen TL, van Santvoort HC, Besselink MG, van Es WH, Hein GG, Maarten SL; Update on acute pancreatitis: ultrasound, computed tomography, and magnetic resonance imaging features. Semin Ultrasound CT MR, 2007; 28(5): 371-383.
51. Dipti KL, Emil JB; MDCT of Acute Mild (Nonnecrotizing) Pancreatitis: Abdominal Complications and Fate of Fluid Collections. AJR, 2008; 190: 643-649.
52. Working Group IAP/APA Acute Pancreatitis Guidelines.IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology, 2013; 13(4 suppl 2): e1–5.
53. Gillet M, Combe J, Aubert D; Echotomographic and arteriographic images in acute hemorrhagic pancreatitis: Report of a case. Chirugie, 1973; 99(10): 727-733.
54. Besselink MG, Van Santvoort H, Bollen TL, Van Leeuwen MS, Hofker S, Boermeester MA *et al*.; Minimally invasive 'step-up approach' versus maximal necrosectomy in patients with acute necrotising pancreatitis (PANTER trial): design and rationale of a randomised controlled multicenter trial (PDF). BMC Surg., 2006; 6: 6.
55. Reynaet M, Otte JB, Kestens PJ, Tremouroux J; Peritoneal dialysis treatment for acute necrotic hemorrhagic pancreatitis. Acta Chir Belg., 1981; 80(6): 363-371
56. Kleespies A, Thasler WE, Schäfer C, Meimarakis G, Eichhorn ME, Bruns CJ *et al*.; Acute Pancreatitis: Is there a Need for Surgery? Z Gastroenterol., 2008; 46(8): 790-798.
57. Obermeyer RJ, Fisher WE, Salameh JR, Jeyapalan M, Sweeney JF, Brunicardi FC; Laparoscopic pancreatic cystogastrostomy. Surg Laparosc Endosc Percutan Tech., 2003; 13: 250– 253.
58. Pappas TN, Haney JC; Necrotizing pancreatitis: Diagnosis and management. Surg Clin N Am., 2007; 87:1431-46.
59. Campos T, Parreira JG, Utiyama E, Rasslan S; Pesquisa nacional sobre condutas na pancreatite aguda. Rev Col Bras Cir. [periódicona Internet], 2008; 35(5)304-10
60. Schoenberg MH, Rau B, Beger HG; Diagnosis and therapy of primary pancreatic abscess. Chirurg., 1995; 66: 588–596
61. Freeny PC, Lewis GP, Traverso LW, Ryan JA; Infected pancreatic fluid collections: percutaneous catheter drainage. Radiology, 1998; 167:435–441
62. Dugernier T, Dewaele J, Laterre PF; Current surgical management of acute pancreatitis. ActaChir Belg. 2006; 106(2):165-171.
63. Machado MC; The role of surgery in the treatment of necro-hemorrhagic pancreatitis. Rev HospClinFac Med Sao Paulo, 1979; 34(6): 244-246.
64. Roseano M, Lovadina S, Calligaris L, Ursic I, Cuviello A, Liguori G; The multidisciplinary management of acute pancreatitis: a review of 244 cases. Ann Ital Chir., 2004; 75(4): 443-453.
65. Wullstein C, Bechstein WO; Acute pancreatitis. Chirurg., 2004; 75(6): 641-651.
66. Yang SH, Xie JY; Treatment of acute hemorrhagic necrotizing pancreatitis with necrosectomy and peritoneal irrigation. Zhonghua Wai Ke Za Zhi, 1985; 23(12): 719-20, 781.
67. Gebhardt C, Gall FP; Importance of peritoneal irrigation after surgical treatment of hemorrhagic, necrotizing pancreatitis. World J Surg., 1981; 5(3): 379-385.
68. Maringhini A, Uomo G, Patti R, Rabitti P, Termini A, Cavallera A *et al*; Pseudocysts in acute non-alcoholic pancreatitis: incidence and natural history. Dig Dis Sci., 1999; 44: 1669–1673.
69. van Veelen MJ, Visser MF, Baggen MGA, Dees A; Hypocalcaemia laryngeal spasm in emergence department. BMJ Case Reports 2011; 10.1136/bcr.11.2010.3555

70. Viglion G, Rivetti R, Lavagna F, Lisa F, Cartia Q; Necrosis of the transverse colon: a rare complication of acute necrotic hemorrhagic pancreatitis. Minerva Chir., 1990; 45(15-16):1053-1054.
71. Schmid SW, Malfertheiner P, Büchler MW; The role of infection in acute pancreatitis. Gut, 1999, 45: 311-6.
72. Munhoz RP dos Santos ML, Hernández-Fustes OJ; Fatal necro-hemorrhagic pacreatitis related to sodium valproate: Case report. Arq Neuropsiquiatr, 2001; 59(3B): 821-823.
73. Casas JD, Díaz R, Valderas G, Mariscal A, Cuadras P *et al*.; prognostic value of ct in the early assessment of patients with acute pancreatitis. AJR, 2004; 182: 569-574.
74. Jimenez H, Aldrete JS; Clinical implications derived from the morphological classification of 89 patients with acute pancreatitis. J Clin Gastroenterol., 1983; 5(2):137-142.
75. Sakorafas GH, Tsiotos GG, Sarr M G*;* Extrapancreatic necrotizing pancreatitis with viable pancreas: a previously under-appreciated entity. J Am Coll Surg., 1999; 188(6): 643-648.