Clinical and pathologic characteristics of pancreatic necrosis in critically ill children

Yi-min Zhu, Fang Liu, Xiao-yu Zhou, Xi-rong Gao, Zhi-yue Xu, Yu-kai Du

Emergency Center (Zhu YM, Xu ZY), Department of General Surgery (Zhou XY) and Department of Neonatology (Gao XR), Hunan Children’s Hospital, Changsha 410007, China; Department of Maternal and Children Health Care, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China (Liu F, Du YK)

Corresponding Author: Yi-min Zhu, Email: cszhuyimin@163.com

BACKGROUND: Pancreatic damage in critically ill patients is associated with the progressive failure of multiple organs, but little is known about its clinical characteristics. At present, no guidelines are available for the diagnosis and management of pancreatic damage. This study was undertaken to analyze the clinical and pathologic characteristics of pancreatic necrosis in critically ill children, and to find some biological markers of pancreatic damage or pancreatic necrosis.

METHODS: We retrospectively reviewed the clinical data, laboratory results, and autopsy findings of 25 children, who were admitted to Hunan Children’s Hospital, China from 2003 to 2009, and died of multiple organ failure. The autopsy revealed pancreatic necrosis in 5 children, in whom sectional or gross autopsy was performed.

RESULTS: The 5 children had acute onset and a fever. Two children had abdominal pain and 2 had abdominal bulging, flatulence and gastrointestinal bleeding. Four children had abnormal liver function, characterized by decreased albumin and 3 children had elevated level of C-reactive protein (CRP). B-ultrasonography revealed abnormal acoustic image of the pancreas in all children, and autopsy confirmed pancreatic necrosis, which may be associated with the damage of the adrenal gland, liver, lung, heart, spleen, kidney, intestine, thymus, mediastinal and mesenteric lymph nodes and other organs. Children 1 and 2 died of acute hemorrhagic necrotizing pancreatitis (AHNP); children 3-5 died of multiple organ dysfunction syndrome (MODS) due to pancreatic necrosis.

CONCLUSION: Pancreatic damage or pancreatic necrosis in critically ill children is characterized by acute onset, severity, short course, multiple organ damage or failure. It may be asymptomatic in early stage, and easy to be ignored.

KEY WORDS: Autopsy; Pancreatic damage; Pancreatic necrosis; Critically ill children

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care unit (ICU) with diagnosis of diseases other than pancreatitis. The elevation of serum amylase and/or lipase levels three or less than three times the normal values was not specific, and couldn't predict significant changes of the pancreas.

Pancreatic damage also occurs in some critically ill children. The results of autopsy showed that pancreatic injury varied from edema/inflammation to hemorrhage and necrosis. In this study we investigated the clinical manifestations and pathologic characteristics of pancreatic damage in children, and detected the relationship between pancreatic damage/necrosis and other organ damage.

METHODS
Patients
We retrospectively reviewed the clinical data, laboratory results and autopsy findings of 25 children who were admitted to Hunan Children's Hospital, China from 2003 to 2009 and died because of multiple organ failure. Autopsy demonstrated pancreatic necrosis in 5 children, who were enrolled in this study.

Among the 5 children, 2 were boys, and 3 girls; their age ranged from 9 months to 7 years, with a mean age of 3.81 years. Two children were directly admitted to PICU, 2 to the department of hematology, and 1 to the department of infectious diseases. Primary diseases included severe sepsis, disseminated tuberculosis, fulminant necrotizing hepatitis, systemic juvenile rheumatoid arthritis, and malignant histiocytosis.

Routine laboratory examinations after admission included tests of blood, electrolytes, liver and kidney function, myocardial enzymes, and C-reactive protein. The 5 children received symptomatic and supportive treatments such as anti-inflammatory, antipyretic administration of fluid and electrolytes. They were also given anti-shock therapy or subjected to tracheal intubation and mechanical ventilation according to their clinical manifestations. They died from the deterioration of the illness.

Autopsy
Sectional or gross autopsy was performed in the 5 children. Tissues were taken from the brain, lung, heart, liver, spleen, and kidney. The tissues were fixed with 10% formalin, paraffin embedded, sectioned, and observed after HE staining. The autopsy study was approved by the Ethical Committee of the Hospital.

RESULTS
Clinical characteristics
The 5 children had a fever. Child 1 who had been already in shock at admission to PICU died an hour later although many rescue measures were taken. Child 2 had paroxysmal abdominal pain on the 6th day after admission. The pain was released after administration of drugs; a week later the pain recurred with vomiting till the next day. Subsequently shock appeared, and the child died 1 to 2 hours later. Children 3 and 4 had no pain at all, but abdominal bulging, abdominal distension, and gastrointestinal bleeding. They died rapidly. Child 5 had a disorder of electrolyte and internal environment characterized by low levels of kalium, sodium, chloride, metabolic alkalosis, etc.

Laboratory tests
Child 1 presented no laboratory data because she died within 2 hours after admission. The laboratory results of the other 4 children are shown in Table 1.

<table>
<thead>
<tr>
<th>Child</th>
<th>Clinical presentation</th>
<th>Severe progression</th>
<th>Laboratory tests</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Vomiting, abdominal pain, dispirited</td>
<td>Shock, cardiopulmonary arrest</td>
<td>WBC&lt;sub&gt;×10&lt;sup&gt;9&lt;/sup&gt;/L&lt;/sub&gt; HCT&lt;sub&gt;%&lt;/sub&gt; K&lt;sub&gt;mmol/L&lt;/sub&gt; Ca&lt;sup&gt;2+&lt;/sup&gt;&lt;sub&gt;mmol/L&lt;/sub&gt; BG&lt;sub&gt;mmol/L&lt;/sub&gt; TB&lt;sub&gt;μmol/L&lt;/sub&gt; ALB&lt;sub&gt;g/L&lt;/sub&gt; ALT&lt;sub&gt;IU/L&lt;/sub&gt; AST&lt;sub&gt;U/L&lt;/sub&gt; LDH&lt;sub&gt;IU/L&lt;/sub&gt; BUN&lt;sub&gt;mmol/L&lt;/sub&gt; Cr&lt;sub&gt;μmol/L&lt;/sub&gt; CRP&lt;sub&gt;mg/L&lt;/sub&gt;</td>
</tr>
<tr>
<td>2</td>
<td>Fever, systemic bone joint pain</td>
<td>Shock, cardiopulmonary arrest</td>
<td>16.06 20.27 4.47 2.09 6.30 8.16 28.90 54.00 84.00 386.00 4.16 43.00 68.80</td>
</tr>
<tr>
<td>3</td>
<td>Fever, thrombocytopenia</td>
<td>DIC, heart failure</td>
<td>15.64 25.20 4.53 2.32 162.20 44.10 823.00 847.60 583.00 4.72 44.00 15.90</td>
</tr>
<tr>
<td>4</td>
<td>Cough, fever, diarrhea</td>
<td>Alimentary tract hemorrhage</td>
<td>1.09 19.66 4.73 1.80 21.20 70.03 23.00 59.00 335.00 2264.00 5.33 47.00</td>
</tr>
<tr>
<td>5</td>
<td>Recurrent cough, fever, tachypnea</td>
<td>Type II respiratory failure</td>
<td>5.25 23.43 2.78 1.57 1.36 15.85 11.30 28.00 149.00 1737.00 5.86 65.00 127.00</td>
</tr>
</tbody>
</table>

Normal reference ranges: WBC 4-10×10<sup>9</sup>/L, HCT 35%-45%, K<sub>mmol/L</sub> 3.50-5.50 mmol/L, Ca<sup>2+</sup><sub>mmol/L</sub> 2.10-2.70 mmol/L, BG (blood glucose) 3.8-6.2 mmol/L, TB (total bilirubin) 3.40-17.10 μmol/L, ALB (albumin) 35-55 g/L, ALT 0.00-40.00 IU/L, AST 0-40 U/L, LDH 0-450 IU/L, BUN 1.80-8.20 mmol/L, Cr 20-120 μmol/L, CRP 0-8.00 mg/L.
Peripheral white blood cell count was abnormal in 3 children, and a lower level of hematocrit was found in 4 children. The level of blood calcium was decreased in 3 children, and blood glucose abnormalities were seen in 2 children. In the 4 children there was abnormal hepatic function, whereas in the 3 children the level of albumin was significantly decreased, and C-reactive protein (CRP) was elevated.

Auxiliary examinations

B-ultrasonography showed hepatomegaly and cholecystitis in child 1, and splenomegaly, abdominal lymphadenopathy, seropertioneum and liquid anechoic area in the right pelvic cavity in child 2. In child 3, flatulence appeared, and there were slightly reinforced echo in the parenchyma of the kidneys and the overfilling bladder. Child 4 demonstrated hepatosplenomegaly, tonic intensive echo in the parenchyma of the liver, edematous gallbladder wall, and mesenteric fluid. None of the 4 children had abnormal pancreas. Bone marrow stab and bone marrow biopsy revealed infected bone marrow and increased peripheral blood eosinophils in child 2; active proliferation of bone marrow, with decreased granulocyte hyperplasia, active erythroid proliferation and scattered platelet in child 3; bone marrow hypoproliferation in child 4 when granulocyte and erythroid proliferation was inhibited, but there were no megakaryocytes and platelets because 92.0% were histiocytes.

Autopsy and pathological examination

Pancreatic necrosis was confirmed in all 5 children (Figure 1). Children 1 and 2 died of acute hemorrhagic necrotizing pancreatitis (AHNP); children 3-5 died of multiple organ dysfunction syndrome (MODS) due to pancreatic necrosis. In addition to pancreatic necrosis, the 5 children had the damage of multiple organs including the adrenal gland, liver, lungs, heart, spleen, kidneys, intestine, thymus, mediastinal and mesenteric lymph nodes (Table 2).

DISCUSSION

The incidence of pancreatic diseases has been increasing in recent years. Pancreatic damage would develop after the onset of primary diseases in some critically ill patients. The clinical manifestations of the damage include abdominal pain, vomiting, intestinal obstruction or other symptoms and signs. The levels of serum amylase and lipase are elevated separately or both in this condition, as seen in acute pancreatitis. \[6,7\] Pancreatic damage may be transient; if primary diseases were cured, other clinical manifestations of pancreatic damage would have disappeared. \[8,9\] However, other studies showed that pancreatic damage does not cause
### Table 2. Pancreatic necrosis and damage of other organs in the 5 critically ill children

<table>
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<tr>
<th>Child Pathological diagnosis</th>
<th>Organ systems</th>
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Serious clinical consequences in critically ill patients, but occurrence of pancreatitis would contribute to morbidity and mortality. \[1\] Tribl et al.\[2\] found that the secretion of amylase, chymotrypsin, trypsin (P<0.01 each) and bicarbonate in duodenal fluid (P<0.05) was impaired in septic shock patients compared with healthy controls. The content of trypsin was different between sepsis patients and septic shock patients (P<0.05). Spearman’s rank-order correlation coefficient analysis showed a significant difference between amylase secretion and APACHE III and SOFA scores (P<0.01). The SOFA score was also related to the secretion of trypsin (P<0.05). In our study, the 5 children rapidly developed severe hemorrhage and necrosis after acute pancreatic damage, and this made the treatment difficult.

Acute pancreatic damage can be secondary to bacterial and viral infections in many organs. The viruses or bacteria may enter the pancreas via blood or lymphatic tissues. Sheridan et al.\[3\] reported that sepsis in burn patients could develop intraperitoneal infection such as acute cholecystitis, acute pancreatitis, and disappearance of enterokinesia. Hypotension and splanchnic hypoperfusion are the main causes of pancreatic damage. In 1978, Warshaw et al.\[4\] observed that the pancreas of patients with shock was significantly susceptible to ischemic injury. Animal studies also showed changes of microcirculatory blood flow in organs were heterogeneous, and pancreatic blood flow decreased more significantly than regional flow during early septic shock. Hiltebrand et al.\[5\] used severe septic shock models of pigs to study dynamic distribution of microcirculatory blood flow in multiple splanchnic organs during septic shock, and they found that systemic and regional flows decreased by 50% during the first 240 minutes, while microcirculatory flow significantly decreased in the pancreas, liver, colon, kidney and stomach by 56%, 49%, 47%, 44%, and 41%, respectively. Endotoxin was found to play an important role.
role in septic shock patients with pancreatic damage, activating complements and coagulation systems, generating bradykinins and cytokines, and causing shock and damage to various organs including the pancreas. Pancreatic damage is associated with systemic metabolic diseases, such as diabetic ketoacidosis, systemic lupus erythematosus, Henoch-Schönlein purpura, hemolytic uremic syndrome and others. L-asparaginase can cause pancreatic dysfunction in children with acute lymphoblastic leukemia (ALL). Pancreatic necrosis is one of the serious adverse effects, and the mortality of this type of pancreatitis is 2.5%. The effect of high doses of L-asparaginase on different tissues has been investigated, and other factors include exogenous CCK, fibroblast growth factor-7 and fibroblast growth factor-10 (FGF-7, FGF-10), keratinocyte growth factor receptor (KGFR).

In our study, children 1 and 2 were older than 3 years, and both complained of abdominal pain before death. Since it was difficult to define pancreatic damage, the levels of serum amylase, urine amylase and lipase were not determined. B-ultrasonography showed no signs of abnormal pancreas in the 5 children; suggesting difficulty in determining pancreatic damage. The 5 children died soon after the deterioration of their illness. Autopsy revealed pancreatic necrosis in all children, indicating pancreatic damage could aggravate primary diseases. Primary diseases of the 5 children included severe infectious diseases such as severe sepsis, disseminated tuberculosis, and fulminant necrotizing hepatitis, as well as underlying diseases like systemic juvenile rheumatoid arthritis, and malignant histiocytosis. The clinical symptoms varied, but all of the 5 children had a fever. Such fever in ICU is usually caused by infection or inflammation. The pathologic changes of the 5 children suggested that the following manifestations may be related to pancreatic damage: 1) acute onset, severity, or a short course of the disease before developing MODS; 2) inexplicable fever, vomiting, abdominal distension, ascites, mesenteric lymphadenopathy and abdominal fluid; 3) rapid pathologic changes, even development of shock; 4) rapid pathologic changes of respiratory failure, pulmonary edema, pulmonary hemorrhage; 5) hepatomegaly, abnormal liver function, decreased serum albumin, hemorrhage, thrombocytopenia or coagulation disorder; 6) lower level of calcium, higher level of blood glucose; and 7) higher level of CRP. CT is the "gold standard" for the diagnosis of pancreatic necrosis and peripancreatic collections, and also for the noninvasive diagnosis of pancreatic necrosis with an accuracy rate of over 90 % when there is a rate of 30 % for glandular necrosis. Thus the diagnosis of pancreatic necrosis should be based on the clinical manifestations, biochemical parameters, and radiologic imaging.

In the 5 children we observed necrosis of liver cells, infiltration of lymphocytes, monocytes or allogenic histiocytes; reduced serum albumin, increased total bilirubin and transaminase; alveolar edema and hemorrhage, infiltration of lymphocytes, neutrophils in pulmonary interstitial tissue, respiratory disorders, and respiratory failure; spleen and renal necrosis; degenerated langendorff cells in thyroid gland, lymph nodes reactive hyperplasia. Adrenal necrosis and inflammatory cells infiltration were also seen in 4 of the 5 children. Further investigation is required to confirm their relationship.

Morphological changes of pancreatic damage are not obvious in critically ill children. None of the 5 children in our study showed abnormal pancreas although all but one were subjected to B-ultrasonography after admission. Since the pancreas is often ignored in the diagnosis of primary diseases in critically ill patients, laboratory examination of pancreas-related enzymes is rare. Hence studies have focused on the sensitivity and specificity of biological markers in the diagnosis of acute pancreatitis. Serum amylase and lipase are the most common indicators for acute pancreatitis. Blood biochemical examination is also of paramount importance. WBC>20×10⁹/L, 72 h CRP>150 mg/L, calcium<2 mmol/L, glucose>11.2 mmol/L (no history of diabetes), hematocrit (Hct)>44 may indicate pancreatic necrosis. Serum lactate dehydrogenase (LDH) is widely present in various tissues as a glycolytic enzyme, and it reflects cells damage. LDH is a sensitive marker of pancreatic necrosis. In our study, the LDH levels of 3 of the 5 children were elevated. In recent years, the diagnosis of pancreatitis and pancreatic injury has been improved because of the use of many new diagnostic techniques such as tests of procalcitonin (PCT), trypsinogen (TPG), trypsinogen activation peptide (TAP), pancreatic elastase-1 (E1), and leukocyte elastase (PMN-E). Of these methods, rapid urinary TPG-2 test and TAP test are considered as the most reliable and simple ways to early diagnose acute pancreatitis because they can predict accurately the severity of acute pancreatitis in 24 hours after appearance of symptoms. Studies have shown that severe ischemia, even if ischemia for a short time, can cause pancreatic damage and that the duration of ischemia is associated with the elevated pancreatic enzymes. Therefore, if pancreatic damage is highly suspicious, the levels of pancreatic enzymes and other sensitive indicators...
should be dynamically monitored.

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**REFERENCES**


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