Clinical pathology of acute necrotising pancreatitis

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SUMMARY Seventy nine pancreatic specimens were obtained from patients treated with pancreatic resection for acute necrotising pancreatitis. The necroptic process had started in the periphery of the gland, so that eight of seventy nine cases contained peripancreatic (mainly fat) necrosis only without any parenchymal necrosis. Peripheral parenchymal necrosis was characterised by a severe inflammatory reaction, with multinucleated leucocytes and microabscess. In the deep parts of the pancreas coagulation necrosis was found. Vascular changes (thrombosis, vessel necrosis) correlated with postoperative haemorrhagic complications, but they did not seem to have had any important role in the necroptic process. The vascular changes seemed to be a secondary phenomenon. In clinical practice the most important aspects in reporting the histology of acute necrotising pancreatitis are the extent of parenchymal necrosis, because the surgeon may overestimate its extent, and the existence of vascular changes, because of the correlation with postoperative recovery.

In recent years pancreatic resection has become a fairly widespread treatment for acute necrotising pancreatitis, especially in Europe.1–6 The precise indications and contraindications for the procedure are, however, far from clear. The aim of pancreatic resection is to reduce the amount of necrotic tissue, to cut down the release of toxic substances, and to reduce the likelihood of infection. Whether the incidence of these sequences of pancreatitis is most effectively reduced is not yet known. For this reason and because severe forms of pancreatitis with necrosis are quite rare most of the workers concerned with this kind of treatment, including pathologists, have as yet very limited experience of the procedure. We had an opportunity to study 79 surgical pancreatic samples obtained by resection from patients with acute necrotising pancreatitis. The correlations between histology and certain clinical variables were investigated in the first 50 patients from whom clinical data were obtainable.

Material and methods

Seventy nine patients treated between 1973 and 1983 who had undergone pancreatic resection for acute necrotising pancreatitis were studied. The age range was 23–75 years (mean 46 years). The aetiology of the pancreatitis was alcohol in 55 cases (70%), gallstones in 13 cases (16%), and blunt abdominal trauma in one case. The aetiology of the remaining cases was unknown.

Laparotomy was performed in patients with pancreatitis who deteriorated despite intensive medical treatment and who had signs of peritonitis and in patients with an uncertain diagnosis who were suspected of having visceral perforation. The criterion for pancreatic resection was clear evidence of necrosis of the pancreas based on the macroscopic evaluation made by the surgeon during laparotomy. A left pancreatic resection, starting with splenectomy, was performed, extending to the level of the portal vein or the middle of the head of the pancreas. One pancreaticoduodenectomy was performed.

The specimens were immediately fixed in formalin or frozen in liquid nitrogen. Four to eight transverse sections were taken at regular intervals throughout the pancreatic specimen, the number depending on its length. This dissection was carried out after fixing in formalin, or while the specimens were still frozen; in the latter case the tissue slices were then thawed in formalin at room temperature to ensure simultaneous fixing. Routine paraffin sections were processed and stained with hematoxylin and eosin and with Herovici stain for identification of connective tissue.7

Necrosis in the specimen was evaluated in each slice as a percentage of the necrosis in the whole section in both parenchymal tissue (acin and islets) and parapancreatic tissue (fat and fibrous connective tissue, which was either peripancreatic or septal). The mean percentage of the different slices was calculated for each patient and placed on a semiquantitative scale of

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Histological assessment was carried out in all 79 cases. Data on the postoperative course and complications were obtained on the first 50 patients, in whom the clinicopathological correlations were also investigated. Twenty-nine cases had to be excluded from the clinical study because the data had not been reliably obtained at the time of investigation. Analysis was carried out using the $\chi^2$ test.

Results

On macroscopical examination black areas or a uniform black covering could be seen on the surface of the specimen. After dissection it was found that in nine cases (11%) the whole specimen was dark brown or black, while in the others the black areas were mainly concentrated in the peripheral parts of the specimen. The paler areas of the specimen seemed to be swollen.

On histological examination features of acute pancreatitis were evident in each sample. The interstitial inflammation process was characterised by accumu-

Fig. 1  Inflammatory reaction spreading through interlobular septum from peripancreas into pancreas. Peripancreatic fat is necrotic (top right). Acinar structures seem swollen with interstitial accumulation of fluid. $\times$ 500.

Fig. 2  Staging of pathological changes according to depth. Peripancreatic fat is necrotic haemorrhaged (top right). Most superficial layer of pancreatic parenchyme is necrotic with inflammatory cell reaction (top middle). Next layer contains recently necrotised parenchyme with pycnotic nuclei and disarrangement of structure (top left, bottom right and middle), whereas following layer shows oedematous acinar and ductal structures (bottom left). $\times$ 500.
Fig. 3 Microabscess with dense accumulation of inflammatory cells in liquefactive necrosis. × 80.

lation of fluid and leucocytes, of which most were polymorphonuclear. The inflammatory reaction was more severe in the interlobular spaces and septal tissue than within lobules, giving an impression of inflammation starting from the peripheral parts of the gland and protruding through the septa into the deeper parts (Fig. 1).

In each case cell necrosis was also found. The most vulnerable areas seemed to be the peripancreatic adipose tissue, from where the necrosis spread through the septa towards the pancreatic parenchyma (Fig. 1). In the parenchyma necrosis with inflammatory cells was first seen in the superficial layers of the gland; deep to this were swollen and disrupted acini, also with an accumulation of inflammatory cells; and deeper still were preserved but oedematous acini (Fig. 2). In some cases micro-abscesses were found. These were areas a few millimeters in diameter that contained a dense accumulation of inflammatory cells, exudate, and fibrinous material (Fig. 3). Bacteria could not be detected microscopically. Thus the presence of inflammatory cells was especially typical of superficial necrosis. The occurrence of vascular changes was no prerequisite for this type of necrosis. Coagulative necrosis was found in the cases in which the deeper layers of the pancreas were necrotic (Fig. 4). Acinar necrosis was not detected in 8 cases (10%), although parapancreatic necrosis had occurred. Table 1 summarises the distribution of the extent of necrosis in cases studied.

The vascular changes were numerous. Thrombosing vasculitis with segmental necrosis of the vessel wall was a common finding; the affected vessels were small arteries, arterioles, and capillaries. In contrast, thrombosis without phlebitis was noticed in the veins. Haemorrhages were almost always found, the most severe being clearly associated with disruption of the vessel wall due to necrosis (Fig. 5). Table 2 shows the incidence of these histological changes. In some of the specimens an increased amount of connective tissue was seen; necrosis was also found in these specimens.

Table 1  Extent of necrosis in pancreatic parenchymal and parapancreatic (mainly adipose) tissue in 79 patients studied

<table>
<thead>
<tr>
<th>Degree of necrosis (%)</th>
<th>No of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenchymal:</td>
<td></td>
</tr>
<tr>
<td>0–25</td>
<td>38 (48)</td>
</tr>
<tr>
<td>26–50</td>
<td>10 (13)</td>
</tr>
<tr>
<td>51–75</td>
<td>11 (14)</td>
</tr>
<tr>
<td>76–100</td>
<td>20 (25)</td>
</tr>
<tr>
<td>Parapancreatic:</td>
<td></td>
</tr>
<tr>
<td>0–25</td>
<td>5 (6)</td>
</tr>
<tr>
<td>26–50</td>
<td>9 (11)</td>
</tr>
<tr>
<td>51–75</td>
<td>19 (24)</td>
</tr>
<tr>
<td>76–100</td>
<td>46 (58)</td>
</tr>
</tbody>
</table>

Fig. 4 Coagulation necrosis in middle of pancreas with slightly increased amount of connective tissue. × 200.

Fig. 5 Necrotising vasculitis and vascular wall disruption followed by severe haemorrhage and secondary accumulation of inflammatory cells. × 200.
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Table 2  Histological findings in pancreatic specimens from 79 patients studied with acute necrotising pancreatitis

<table>
<thead>
<tr>
<th>Histological findings</th>
<th>No of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenchymal necrosis</td>
<td>71 (90)</td>
</tr>
<tr>
<td>Pancreatic necrosis</td>
<td>79 (100)</td>
</tr>
<tr>
<td>Increased amount of connective tissue</td>
<td>18 (23)</td>
</tr>
<tr>
<td>Microabscesses</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Intravascular thrombosis</td>
<td>68 (86)</td>
</tr>
<tr>
<td>Vascular wall necrosis</td>
<td>38 (48)</td>
</tr>
<tr>
<td>Haemorrhages</td>
<td>71 (90)</td>
</tr>
</tbody>
</table>

Calcium deposits, flattened epithelium, or dilated ducts were not found.

No histological difference was found between the various aetiological groups (gallstones, alcohol, unknown). Table 3 shows that the extent of extensive parenchymal necrosis was proportional to the length of time from onset of symptoms until operation. The severity of vascular necrosis increased in the early stages of pancreatitis but then decreased as the symptoms persisted.

Nineteen of the first 50 patients died (38%). Three died from cardiac arrest, one from liver necrosis, one from bone marrow depression, and one from renal failure and pneumonitis of toxic origin. The main cause of death was sepsis (seven patients), which started as an abscess in the region of the pancreas. Only one of the patients with microabscesses in the pancreas, however, developed a postoperative abscess. Of the eight cases of postoperative abscess, three occurred in glands with under 50% parenchymal necrosis and five in glands with over 50% parenchymal necrosis. Six patients died from postoperative haemorrhage. Haemorrhage was the only histological variable that correlated significantly with mortality; p < 0.001 (Table 4). Altogether, 17 patients required further surgery for postoperative haemorrhage arising in the operated area. Histological evidence of necrosis and haemorrhage seemed to predict a higher risk of postoperative haemorrhage. On the other hand, vascular thrombosis seemed to predict a significantly lower risk of postoperative haemorrhage; p < 0.02 (Table 5).

Discussion

Both the gross pathology and the microscopical

Table 3  Incidence of histological changes occurring between onset of symptoms and date of operation in 50 patients with acute necrotising pancreatitis

<table>
<thead>
<tr>
<th>Duration of symptoms</th>
<th>4-7 days (n = 9)</th>
<th>&gt; 7 days (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Over 50% parenchymal necrosis</td>
<td>1 (11)*</td>
<td>7 (64)*</td>
</tr>
<tr>
<td>Over 50% parapancreatic necrosis</td>
<td>7 (78)</td>
<td>8 (73)</td>
</tr>
<tr>
<td>Increased amount of connective tissue</td>
<td>1 (11)</td>
<td>4 (36)</td>
</tr>
<tr>
<td>Microabscesses</td>
<td>1 (11)</td>
<td>2 (18)</td>
</tr>
<tr>
<td>Intravascular thrombosis</td>
<td>8 (89)</td>
<td>9 (82)</td>
</tr>
<tr>
<td>Vascular wall necrosis</td>
<td>8 (89)†</td>
<td>5 (45)‡</td>
</tr>
<tr>
<td>Haemorrhages</td>
<td>8 (89)†</td>
<td>11 (100)</td>
</tr>
</tbody>
</table>

*Total mortality 19/50 (38%).

Table 4  Mortality in relation to histological changes in 50 patients treated with pancreatic resection for acute necrotising pancreatitis

<table>
<thead>
<tr>
<th>Mortality* (%)</th>
<th>Pancreatic parenchymal necrosis</th>
<th>Parapancreatic necrosis</th>
<th>Increased amount of connective tissue</th>
<th>Microabscesses</th>
<th>Vascular thrombosis</th>
<th>Vascular wall necrosis</th>
<th>Haemorrhages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nr3</td>
<td>11/34 (32)</td>
<td>8/16 (50)</td>
<td>5/15 (33)</td>
<td>14/35 (40)</td>
<td>16/45 (36)</td>
<td>9/24 (38)</td>
<td>19/48 (40)</td>
</tr>
</tbody>
</table>

*p < 0.001; †p < 0.01; ‡p < 0.02.

Table 5  Histological vascular changes and incidence of reoperation required for postoperative haemorrhage in 50 patients treated with pancreatic resection for acute necrotising pancreatitis

<table>
<thead>
<tr>
<th>Patients requiring reoperation for haemorrhage</th>
<th>Vascular thrombosis</th>
<th>Vascular wall necrosis</th>
<th>Haemorrhages</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>12/43 (28)</td>
<td>5/7 (71)</td>
<td>17/48 (35)</td>
</tr>
</tbody>
</table>

(p < 0.02).
appearance of acute necrotising pancreatitis have
been described in detail over the past 50 years. Most of the studies were, however, based on studies
on animals or necropsy specimens. It is well known
that rapid autolysis of the pancreas by the glands
digestive enzymes destroys the normal histology of
the organ soon after the patient's death. The tech-
niques of immediate fixation or freezing of the pan-
creas after interruption of its blood supply used in our
study have only been possible since the introduction
of pancreatic resection for treating acute necrotising
pancreatitis. Since Watt's first report in 196311 this
method has been increasingly used. Nevertheless,
only a few reports have been published on the histol-
ogy of the pancreatic specimen.

In most studies on animals the pathology of necro-
tising pancreatitis is characterised by liquefactive
necrosis with abundant leucocyte infiltration, whereas
in pancreatitis in man the necrosis is considered
rather as coagulative necrosis from pancreatic
infarction.1213 Phat et al studied 20 total pan-
createctomy specimens from patients with acute necro-
rotising pancreatitis and found both coagulative
necrosis and liquefactive necrosis with a severe
inflammatory cell reaction.14 The histology of the
necrosis was essentially similar in our study. Coagu-
lative necrosis was especially common in the inner
parts of the pancreas, while in the superficial paren-
chyma leucocyte infiltration was severe.

The material obtained for this study differs from
that used in earlier studies in its aetiological distri-
bution. Usually pancreatitis from gallstones constitutes
about two thirds and pancreatitis induced by alcohol
one quarter of the diseases.15 The distribution in our
study, however, represents typical Finnish material,
comprising principally men with heavy drinking
habits.16

The histology of the different aetiological types of
pancreatitis agreed with the findings of Phat et al.14
Boutelier found necrosis to be caudal in pancreatitis
of gallstone or unknown aetiology but diffuse or
cephalic in the remaining cases. Diffuse or patchy
necrosis was rare among our patients: we found only
one case with areas of necrotic and non-necrotic tis-

due to side by side throughout the specimen and consid-
ered this to be a diffusely necrotised organ. This might
have been, however, only the preliminary stage of
total necrosis, because the non-necrotic areas had

clearly swollen acini.

Necrosis was seen predominantly in peripancreatic
tissue or in the peripheral parts of the pancreas itself,
while the inner parts were, in most cases, not necrotic.
This poses the surgeon a difficult problem—namely,
how to make therapeutic decisions based on the
superficial appearance of the organ, which do not
seem to correlate with changes deep in the organ.

Overestimation of the extent of necrosis is not uncom-
mon.1819 This also explains the high number of cases
in this study with pancreatic parenchyma that were
not greatly necrotic. We considered the histological
biopsy technique suggested by Phat et al14 too haz-
ardous because of the possibility of pancreatic fistulae
in patients in whom no resection was performed. It is
not known whether fine needle aspiration cytology
would give useful information.

In studies that analyse necrotising pancreatitis
pathoanatomically and pathophysiological the
most interesting aspects are the early histological
changes, and the features which distinguish irre-
versible from reversible damage. In an electron micro-
scopical study Helin et al showed acinar dilatation
with accumulation of amorphous material in the
lumen of acini, disappearance of microvilli, and swell-
ing of the apical parts of the acinar cells.20 We also
found considerable swelling and even vacuolisation
of acinar cells, especially near the necrotic areas. These
changes, together with the loss of adhesion of epithe-
ilial cells from their basement membranes, are non-
specific and are to be found in cellular damage of
various origins.

The fact that the amount of necrosis increased with
the interval from the onset of symptoms suggests a
continuation of the necrotising process. Retro-
peritoneal extension of the necrosis has been docu-
mented.21 It occurs in about one third of patients,
despite pancreatic resection, causing total or partial
necrosis of the pancreas remnant.22 In two thirds of
cases, however, extension of the necrosis ceased; the
limiting factors involved are unknown.

It has been suggested that the vascular changes
(vasculitis, thrombosis) are responsible for the necro-
sis, which has hitherto been regarded as pancreatic
infarction.23 The peripheral or subcapsular onset of
parenchymal necrosis may support this vascular
hypothesis. In contrast, in this series 27 of 31 (87%)
of patients with necrosis of over 50% of parenchymal
tissue had vascular thrombosis, and no difference was
found when these were compared with cases with
under 50% parenchymal necrosis (41 of 48 (85%).
Indeed, there was one case with multiple thrombosis
but without noticeable parenchymal necrosis. More-
over, eight cases with peripancreatic but without pan-
creatic parenchymal necrosis were found. Thus the
theory of necrosis as a consequence of vascular
changes seems questionable. Thrombosing vasculitis
may equally well be a secondary phenomenon, as sug-
gested by Takada et al.24 For experimental pan-
creatitis we prefer the term "tryptic" or enzymatic
lytic necrosis, which describes the role of lipolytic and
proteolytic enzymes in the necrotising process.25 We
found early and extensive fat necrosis, suggesting an
increased function of lipoactive enzymes (lipase,
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phospholipase A₂. The superficial parenchymal necrosis with severe inflammatory reaction resembled that of tryptic necrosis found in certain animal models. It has also been suggested that the coagulative necrosis typical of pancreatitis in man found in this study, especially in the inner parts of the pancreas, might be caused by the destruction of cell membrane induced by phospholipase activity. Although we do not consider that vascular changes are the basis of the necrosis, systemic circulatory disturbances with hypotension induced by pancreatitis, together with intrapancreatic vascular changes may, however, be important cofactors in the extension of pancreatic necrosis, because the pancreas, like the kidney, is vulnerable to hypoxia.

The prevalence of vascular lesions (48% with vessel wall necrosis, 86% with thrombosis) exceeded that described earlier: the corresponding figures in the necropsy study carried out by Blenkinsopp (31 cases) were 39% and 42%, respectively, and those of the study by Phat et al (31 cases) were 28% (pancreatic fibrosis). This may be taken to indicate that vascular wall necrosis increased the danger of postoperative haemorrhage and the trend to thrombosis reduced it.

To conclude, in clinical practice the most important points to be specified on the pathology report of the histology of acute necrotising pancreatitis are the extent of pancreatic necrosis, and the presence of vascular damage. The first would be instructive for the surgeon, who may have overestimated the extent of necrosis because of the severity of superficial pancreatic damage. The second correlates with the postoperative clinical course.

References

14 Phat VN, Guerrieri MT, Alexander JH, Camilleri JP. Early histological changes in acute hemorrhagic necrotizing pancreatitis. A


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