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Chapter 7
Pancreatic Fistulas in Pancreatic Transplantation

W.-D. Illner, H. Schneeberger, D. Abendroth, R. Landgraf, M. Gokel, and W. Land

Introduction

First reports on a pancreatic transplantation by Minkowski [1], who performed an autologous pancreatic transplantation to the abdominal walls of a dog, date back to the year 1891. In 1966, Kelly [2] succeeded in performing the first vascular pancreatic transplantation in human. This transplantation was preceded by experimental islet cell transplantations attempting to influence diabetes mellitus either in a curative or a preventive way. In the 1970s, clinical pancreatic transplantation became common in a variety of different surgical techniques, all having the same difficulty, namely, managing the exocrine part of the gland. In spite of new surgical techniques, this problem, which can cause both early and long-term complications, has still not been adequately solved. To eliminate the exocrine part of the gland, duct occlusion, as well as enteric drainage and bladder drainage, is used at present.

The main topic of this report is our experience gained with prolamine in duct occlusion in segmental pancreatic transplantation and what is probably its most frequent surgical complication: the pancreatic fistula. In addition, the occurrence of pancreatic fistulas when using bladder drainage or enteric diversion is described here.

Effects of Prolamine

The properties of the quick-hardening, alcoholic amino acid solution (Ethibloc), are described in experimental studies by Gebhardt and Stolte [3, 4]. The injection of this solution into the pancreatic duct leads to necrosis and in the further course to atrophy of the excretory parenchyma and the formation of an interstitial fibrosis, which starts on the 11th day after injection and is completed between the 50th and 60th day with a total extinction of the exocrine part of the parenchyma. The islet cell apparatus remains unimpaired by the structural alterations. Experiences gained with this substance in clinical pancreatic transplantation are somewhat different [5]. In contrast to animal experimental findings, in this case a clearly retarded atrophy and destruction of the excretory parenchyma can be observed. The result is a temporary remaining function of the excretory apparatus with variable duration, which
is, according to our observations, a minimum of 2 months and a maximum of 18 months.

As a result of this temporary remaining function the two following major complications occur:

1. Transcutaneous pancreatic fistula
2. Peripancreatic fluid collection, which manifests itself as pseudocyst

Patients and Methods

Between 1979 and 1989 a total of 102 pancreatic transplantations with duct occlusion using Ethibloc were performed at our center. In 90 patients simultaneous pancreatic and kidney transplantation was performed. Five patients received a pancreatic regraft and seven patients a pancreas alone.

The technique of duct occlusion ex vivo has been described elsewhere [6]. In every case duct occlusion with Ethibloc was performed in a segmental pancreatic allograft consisting of body and tail. There were several modifications in surgical technique and postoperative management during the period mentioned. Only the modifications concerning surgical technique are described here [7, 8].

Group I (n = 29).
Duct occlusion was with prolamine in a segmental pancreatic allograft. Placement of the pancreatic graft was partially extra-, partially intraperitoneal, orginally described by Dubernard [9].

Group II (n = 7).
Duct occlusion was with prolamine. Placement of the graft was intraperitoneal along the colon ascendens. Drainage of the abdominal cavity was for 2 days only.

Group III (n = 28).
Duct occlusion was with prolamine. Placement of the graft was strictly intraperitoneal with continuous intraabdominal lavage for a short period (2–3 days).

Group IV (n = 38).
Duct occlusion was with prolamine. Placement of the pancreatic graft was strictly intraperitoneal. Continuous lavage plus tissue adhesive was performed.

Occurrence of Pancreatic Fistulas and Peripancreatic Pseudocysts

In total we observed a pancreatic fistula in 33 (32%) out of 102 duct-occluded pancreatic grafts. Five (5%) out of 102 duct-occluded pancreatic allografts developed a peripancreatic fluid collection like a pseudocyst. The pancreatic fistula manifests itself in the 2 or 3 week after transplantation. The formation of pseudocysts, however, occurs 1 or 2 months posttransplant.
Table 1. Incidence of pancreatic fistulas according to different surgical technique

<table>
<thead>
<tr>
<th>Surgical technique: positioning of the graft</th>
<th>Fistulas</th>
<th>Pseudo-cysts</th>
<th>Graft loss following fistula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extra-/intraperitoneally (n = 29)</td>
<td>n - 10</td>
<td>n = 3</td>
<td>n - 6</td>
</tr>
<tr>
<td></td>
<td>(34%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraperitoneally (n = 7)</td>
<td>n - 3</td>
<td></td>
<td>n = 2</td>
</tr>
<tr>
<td></td>
<td>(42%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraperitoneally plus continuous lavage (n = 28)</td>
<td>n = 9</td>
<td>n = 1</td>
<td>n = 3</td>
</tr>
<tr>
<td></td>
<td>(32%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraperitoneally lavage plus tissue adhesive (n = 38)</td>
<td>n = 11</td>
<td>n = 1</td>
<td>n = 5</td>
</tr>
<tr>
<td></td>
<td>(29%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Occurrence of Pancreatic Fistula with Different Surgical Techniques

In the early phase of the method with partially extra-, partially intraperitoneal placement of the allograft, almost every second patient developed a pancreatic fistula. And even modifying the surgical technique to strictly intraperitoneal placement of the graft and temporary peritoneal lavage, the incidence of pancreatic fistulas was not significantly reduced [10]. The application of a fibrin adhesive, the properties of which are known from general surgery, to the surface of the parenchyma, at first showed promising results concerning a reduction in pancreatic fistulas. However, considering all the clinical cases in which the duct occlusion technique has been performed, no statistical difference in fistula incidence rate is observed, whatever surgical technique was applied (Table 1). Of note is a group of patients (n = 7), in whom the graft was placed intraperitoneally but who did not receive short-term lavage and instead had the peritoneal cavity drained for only 2 days. In these patients the remaining exocrine segregation of the gland caused serious complications (adhesive ileus); therefore, we abandoned this technique.

Pathogenesis of a Pancreatic Fistula When Using Prolamine

The pathogenesis of a pancreatic fistula is not uniform and furthermore has not been completely clarified. However, the procreation of an edema which allows the enzymes to be secreted directly from the parenchyma has to be ascribed mainly to prolamine, since the duct system is more or less filled with occlusion substance. The structural alterations in the gland caused by prolamines, which finally cause the destruction of the exocrine apparatus, also allow the enzymes to be secreted from the parenchyma. Since these processes, in contrast to animal experimental data gathered by Gebhardt and Stolte, proceed with delay and lead to retarded
destruction of the exocrine apparatus, a temporary excretory active gland results. The coincidence of incomplete wound healing and remaining excretory function cause the secretions to form a pancreatic fistula on the skin surface. If, however, the wound healing is complete, the remaining secretion manifests itself as a pancreatic pseudocyst. It is unclear why the prolamine technique does not result in the gland retaining some function in every case. Therefore, other factors which can cause pancreatic edema have to be considered: traumatic pancreatitis, ischemia, perfusion injury, reperfusion injury, and immunological processes. This is the only explanation for the fact that for drainage technique peripancreatic fluid collections also need to be considered [11], although in this case the enzymes are led into the intestines or the bladder.

Is Prevention of Pancreatic Fistulas Possible?

The surgical modifications described and the introduction of fibrin adhesive were intended to prevent or reduce the formation of a pancreatic fistula. With the intraperitoneal placement of the pancreatic graft and short-term peritoneal lavage we hoped on the one hand to take advantage of the resorption capacity of the peritoneum; on the other hand, we aimed to eliminate the enzymes which are, especially in the early postoperative phase, detectable in the abdominal cavity [12]. By these means we aimed to achieve undisturbed wound healing. Furthermore we achieved suppression of the exocrine apparatus with routine administration of somatostatin over a period of 10 days. At present it can be stated that none of the modifications applied in recent years have significantly reduced the incidence of pancreatic fistula.

Surgical Complications Following Pancreatic Fistula

Table 2 shows the complications following pancreatic fistula, the main one being secondary infection, which we refer to below as complicated pancreatic fistula. In the majority of cases (53%), an infection with *Staphylococcus aureus* was demonstrable. In the remaining infection, *Pseudomonas, Escherichia coli*, and *Candida* organisms were identified.

Table 2. Surgical complications following pancreatic fistula

| 1. Secondary infection with peripancreatic abscess | n = 31 |
| 2. Adhesive ileus | n = 5 |
| 3. Small bowel fistula | n = 1 |
| 4. Pericholecystic abscess | n = 2 |
| 5. Burst abdomen | n = 1 |
| 6. Erosion bleeding | n = 9 |
| 7. Patient’s death | n = 3 |
Strategies of Treatment of Pancreatic Fistulas

Conservative Treatment

In contrast to reports by the Oslo group, we observed no spontaneous fistula healing [13]. Suppression of exocrine secretion with somatostatin and its analogue SMS or with other drugs is helpful [14, 15]. In our experience complete interruption of fistulation with conservative treatment could not be achieved.

Surgical-Conservative Treatment (Table 3)

Almost all transcutaneous pancreatic fistulas developed a secondary infection and a peripancreatic abscess at the same time. It should also be mentioned that the secretions of the pancreas represent an ideal nutritive medium for bacteria and fungi. The primary aim of the treatment has to be the application of sanitary measures to the infection in connection with a reduction of pancreatic secretion in the wound area. In addition, local or systematic antibiosis and suppression of the excretory gland with somatostatin is helpful. Because of the different placements of the pancreatic graft we used both extraperitoneal placement drainage and open wound treatment, the latter being more successful. When the pancreas was placed intraperitoneally, peritoneal lavage was applied for 1-3 weeks until sterility was achieved. If necessary, this procedure had to be repeated two or three times.

If the peritoneal lavage is not successful, either programmed or open wound treatment has to be applied. Our experience has shown that peritoneal lavage is connected with the lowest rate of graft loss, although this treatment is more time-consuming than other methods of treatment. Treatment of a pseudocyst with repeated puncture causes no problems. In 16 patients (48%) who had developed a complicated fistula these therapeutic measures failed, resulting in removal of the graft.

Two examples of complicated pancreatic fistulas are described:

Case 1. This patient had an extremely long lasting pancreatic secretion, which led to the formation of a pseudocyst. After repeated puncture 18 months posttransplant he developed an acute abdomen with tentative diagnosis of a peripancreatic abscess. This necessitated surgical intervention, whereby two small holes in the

Table 3. Success rate of surgical treatment following pancreatic fistulas

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Success rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drainage</td>
<td></td>
</tr>
<tr>
<td>Peritoneal lavage</td>
<td></td>
</tr>
<tr>
<td>Programmed peritoneal lavage</td>
<td></td>
</tr>
<tr>
<td>Open wound treatment</td>
<td></td>
</tr>
</tbody>
</table>
pancreatic parenchyma were detected, which maintained the secretions. To what extent these minor injuries were caused by the repeated puncture could not be clarified. The holes or defects in the pancreatic parenchyma closed only by open wound treatment in combination with granulation processes.

**Case 2.** In this patient a complicated pancreatic fistula with *Candida* organisms led to arterial erosion bleeding. First the rupture on the arterial donor patch was sutured. Ligation of the arteria iliaca externa proved lifesaving when there was recurrent bleeding. Thereafter, the patient developed thrombosis of the arteria poplitea, which could not be treated successfully either by thrombectomy or by local lysis. Gangrene of the lower leg developed, which necessitated amputation of the upper leg.

**Current Function Rate Following Pancreatic Fistula**

At present 13 pancreatic grafts (40%) out of 33 occluded organs, which had developed a pancreatic fistula, are functional. The pancreatic fistula does not influence endocrine function of the graft in a negative way, either in the early or in the late phase. All 13 patients, who had a pancreatic fistula are free of insulin and have a normal HbA1 level.

**Occurrence of Pancreatic Fistulas Using Neoprene for Duct Occlusion**

In his first series with extraperitoneal placement of the gland, Dubernard observed perigraft collections and local wound infections. He introduced “intraextraperitoneal” placement of the graft, performing a 4-cm peritoneal incision and an omentoplasty for drainage of perigraft leakages [16]. Brekke reported a fistula incidence of 30%–40% in a series in which the graft was placed partly intraperitoneally but the vessel anastomoses were carried out extraperitoneally (13). When using this technique, the pancreatic fistulas healed spontaneously in most cases.

**Occurrence of Pancreatic Fistulas Using Enteric Exocrine Drainage**

The most physiological approach for treatment of the exocrine secretion of the gland is a pancreaticenterostomy to a jejunal Roux-loop, originally described by Groth [17], or pancreaticoduodenal enterostomy in a jejunal Roux-loop, originally described by Liilehei [18]. However, the contamination of the graft with the intestinal contents and the digestive forces of pancreatic juice are associated with a high incidence of leakages and pancreatic fistulation. With some modifications of this technique, the Stockholm group reduced the incidence of
pancreatic fistulas. These modifications included intraperitoneal placement of the pancreatic graft and pancreatic duct drainage with a catheter to the exterior for a short period [19]. Sutherland and Hesse report intraabdominal fluid collections after pancreatic transplantation [20]. They agree with our observation that the fluid produced by the pancreatic graft provides a good medium for infection. These intraabdominal infections are associated with a high rate of mortality and morbidity.

**Occurrence of Pancreatic Fistulas Using the Bladder Drainage Technique**

Sollinger and Corry performed organ procurement without traumatizing the pancreas and careful ligation of the peripancreatic lymphatics to prevent traumatic pancreatitis and subsequent lymphatic fistula in the recipient. Sollinger noted a causal connection between wound infection incidence and the type of wound incision during surgery. He changed from an oblique incision to a midline incision and concluded that the incision should be as distant from the pancreatic graft as possible to avoid dissection of lymphatics and exocrine pancreatic fluid penetration through the wound [21]. Corry placed the pancreatic graft extraperitoneally but opened the peritoneum widely to permit any surface drainage from the pancreas to be absorbed intraperitoneally. When using this procedure no pancreatic fistulas were observed in a series of 24 patients [22].

**Conclusions**

Pancreatic fistula after duct occlusion with prolamine in 32% of patients represents a high complication rate. Our data are comparable with data reported by Brekke in the early phase of the use of neoprene for duct obliteration. Nevertheless, 40% of fistulas can be successfully cured with surgical treatment in our experience. In contrast to the data reported by the Oslo group we did not observe spontaneous fistula healing. Using our technique, the pancreatic fistula is associated with a high rate of morbidity but it does not lead to deterioration of the graft. In spite of various surgical modifications, incidence of pancreatic fistulas could not be prevented or reduced. Our observations differ from the observations of other groups, who also modified their surgical technique. They report possible reduction of fistulation by intraperitoneal placement of the pancreas and by drainage of pancreatic enzymes through an incision of the peritoneum when placing the pancreas extraperitoneally. Although different surgical techniques were applied, all groups confirm the risk of fluid collection produced by the pancreatic graft, even when the bladder or intestine is used for exocrine diversion. The surgical treatment of a complicated pancreatic fistula, however, is difficult, is time-consuming and can provoke further complications. The additional treatment with somatostatin, SMS, and other drugs is helpful, but surely not sufficient alone. Because of the simplicity of the duct
occlusion technique in pancreatic transplantation our group will undertake further studies to develop a more potent occlusion substance with a lower complication rate.

References