GI Complications After Lung Transplantation in Patients With Cystic Fibrosis*

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Study objective: Lung transplantation is now available for patients with cystic fibrosis (CF) and end-stage lung disease. While pulmonary graft function is often considered the major priority following transplantation, the nonpulmonary complications of this systemic disease also continue. We examined the GI complications in a cohort of patients who underwent transplantation.

Design: This was a retrospective study of all patients with CF who underwent transplantation between March 1988 and December 1998 in Toronto. Medical records were reviewed, and a short questionnaire was mailed to patients who were alive as of December 1998.

Results: There were 80 bilateral lung transplants performed in 75 patients. The questionnaire was distributed to 43 patients, of whom 27 patients (63%) responded. Pancreatic insufficiency requiring enzyme intake was evident in 72 of 75 patients (96%) at the time of surgery. Of three pancreatic-sufficient patients (4%), pancreatic insufficiency was diagnosed in two patients later. Biliary cirrhosis was diagnosed in three patients prior to transplantation. Distal intestinal obstruction syndrome (DIOS) was recorded for 15 patients (20%). Ten patients had a single episode, of which eight episodes occurred early in the postoperative period. Five patients had recurrent episodes. All were medically treated, except for two patients who underwent surgery. Other complications included cholecystitis (n = 3), mucocele of the appendix (n = 1), peptic ulcer disease (n = 3), and colonic carcinoma (n = 1).

Conclusion: GI complications after lung transplantation are common in patients with CF, and attention should be paid to the risk for DIOS in the early postoperative period. Prevention and early medical treatment are important in order to avoid acute surgery. Close collaboration with the CF clinic, in order to diagnose and treat CF-related complications, is recommended.

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Key words: cystic fibrosis; GI disease; intestinal obstruction; lung transplantation; pancreatic insufficiency

Abbreviations: BOS = bronchiolitis obliterans syndrome; CF = cystic fibrosis; DIOS = distal intestinal obstruction syndrome; EGILS = electrolytes GI lavage solution; GERD = gastroesophageal reflux disease

Although the survival for patients with cystic fibrosis (CF) has steadily improved, the majority of patients eventually acquire severe pulmonary disease and respiratory insufficiency. During the last decade, lung transplantation has become an option for these patients to the extent that CF now is the main indication for bilateral lung transplantation.1 After surgery, follow-up of pulmonary graft function assumes priority, and in our experience patients tend to be mainly followed up at the transplant program. CF is, however, a multiorgan disease with GI manifestations being common. More than 85% of patients with CF are, or acquire, pancreatic insufficiency. Examples of other GI complications in patients with CF are gastroesophageal reflux disease (GERD), distal intestinal obstruction syndrome (DIOS), cholelithiasis, biliary cirrhosis, and complications related to previous surgery due to meconium from the Canadian Cystic Fibrosis Foundation and the Sewdish Heart and Lung Foundation.

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ileus in infancy.\textsuperscript{2} In the general transplant population, GI complications such as intestinal obstruction and peptic ulcers have been described.\textsuperscript{3–5} We reviewed GI complications after lung transplantation for patients with CF.

**Materials and Methods**

**Design**

A retrospective study of medical records at the Toronto General Hospital was conducted for all patients with CF who received a bilateral lung transplant between March 1988—the first successful lung transplant for CF\textsuperscript{6}—and December 1998. For patients referred from the Adult CF Program in Toronto, charts from the CF clinic were also reviewed. Type of complication, time after transplantation, and treatment were recorded. GI problems prior to transplantation were recorded when available. A short questionnaire was sent to all patients who were still alive in December 1998. Questions regarding posttransplant history of DIOS, gallstones, kidney stones, liver disease, and surgery of the abdomen were asked.

**Follow-up and Immunosuppression**

Triple therapy with cyclosporine, azathioprine, and prednisone was standard for maintenance immunosuppression. Before 1993, induction cytolytic therapy was administered to all subjects. Between 1993 and 1995, patients were randomized to cytolytic therapy or placebo in a double-blind study, after which induction therapy with antilymphocytic products was abandoned. After discharge from hospital, patients were followed up weekly in the clinic during the first 3 months. During this time, patients participated in a structured rehabilitation program at the hospital three times weekly. Surveillance bronchoscopies were done at weeks 2 and 6; at months 3, 6, 9, 18, and 24; and then yearly. A more detailed description of the immunosuppression protocol and follow-up procedures was published recently.\textsuperscript{7}

**Results**

Between March 1988 and December 1998, 80 bilateral lung transplant procedures were performed in 75 patients with CF (26 females). The mean ± SD age at the time of transplant was 29 ± 7 years, and the median follow-up time was 2 years (range, 0.2 to 10.7 years). Five patients (two females) underwent retransplantation after 9 months to 8 years due to chronic rejection. By December 31, 1998, there were 43 patients alive. A questionnaire concerning GI complications was sent to the survivors, of whom 27 of 43 patients (61\%) responded in a response time of 30 days.

**GI Manifestations and Complications**

GI complications are summarized in Table 1. Pancreatic insufficiency requiring enzyme intake was evident in 72 of 75 patients (96\%), while only 3 patients (4\%) were pancreatic sufficient at the time of surgery; 1 of them acquired pancreatic insufficiency 4 years later, and 1 was started on enzymes in the early postoperative period because of difficulties in achieving adequate cyclosporine levels. The other patient was considered to have pancreatic insufficiency, but no diagnostic investigation was done. The third patient died in the early postoperative period from *Burkholderia cepacia* sepsis.

Biliary cirrhosis was diagnosed before transplantation in three patients; two were biopsy verified—both treated with ursodeoxycholic acid before and after transplant—and one was diagnosed based on changes on ultrasound of the liver and elevated liver enzymes. Triple immunosuppression was started with cyclosporine/azathioprine/prednisone in two patients. Azathioprine had to be discontinued for both due to elevated liver enzymes; chronic rejection developed in one patient within the first year, while the other patient has had a stable pulmonary function. One patient was initially administered cyclosporine/mycophenolate/prednisone, but due to adverse effects with seizures, cyclosporine was soon changed to tacrolimus. Mycophenolate was discontinued after 6 months due to posttransplant lymphoproliferative disease. The patient is stable two years later with no signs of posttransplant lymphoproliferative disease.

DIOS was common: 15 patients (20\%) had at least one episode of DIOS. In eight patients, there was a single episode early in the postoperative period, while two patients had a single late episode. Five patients had recurrent problems. The treatment administered was electrolytes GI lavage solution (EGILS), a balanced electrolyte solution, orally, through a nasogastric tube, or through a gastrostomy. Three patients were unable to tolerate EGILS and had signs of total obstruction or had repeated episodes of DIOS. They were treated with a contrast media enema, a hyperosmolar, diatrizoate sodium containing contrast solution, followed by EGILS.

**Table 1—GI Complications After Double-Lung Transplantation in 75 Patients With CF**

<table>
<thead>
<tr>
<th>Complications</th>
<th>No.</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic insufficiency</td>
<td>2</td>
<td>0 yr and 4 yr after transplantation</td>
</tr>
<tr>
<td>DIOS</td>
<td>15</td>
<td>Surgical treatment for two patients; one patient with previous surgery for meconeumileus</td>
</tr>
<tr>
<td>Mucocele of appendix</td>
<td>1</td>
<td>Hemicolectomy</td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td>3</td>
<td>Medical treatment</td>
</tr>
<tr>
<td>Cholecystitis</td>
<td>3</td>
<td>Cholecystectomy for one patient after 4 yr</td>
</tr>
<tr>
<td>Colon carcinoma</td>
<td>1</td>
<td>3 yr after transplantation</td>
</tr>
</tbody>
</table>
Surgery was required in two patients, one of whom had had bowel resection performed in infancy due to meconium ileus.

Three patients had episodes of cholecystitis; one of them underwent cholecystectomy 4 years after transplantation, and four others had asymptomatic gallstones. Peptic ulcer disease was reported in three patients, while heartburn or dyspeptic symptoms occurred in four patients. All were medically treated. Finally, one man underwent surgery for a mucocele of the appendix 8 years after lung transplantation, and one 50-year-old woman died 3 years after transplantation from carcinoma of the colon.

Case Reports

A 29-year-old man, who received a diagnosis of CF at 11 years of age, underwent bilateral lung transplantation. The postoperative recovery was slow, and total parenteral nutrition was started. On the ninth postoperative day, total parenteral nutrition was changed to enteral feeding, partly because of slow-moving bowels. Signs of small bowel obstruction did, however, gradually develop, and a laparotomy was performed 12 days after lung transplantation. Hard plugs of inspissated fecal material were found in the terminal ileum and appendix. The plugs were liquefied by injection of a contrast media and milked to the caecum and then treatment with N-acetylcysteine and agarol enemas was administered. Ten days later, the patient was able to tolerate enteral feeds and gradually recovered. Since then, he has had no major pulmonary or GI complications, although he underwent a successful kidney transplant 4 years ago due to renal failure. He is still alive and well, 13 years after the lung transplant.

A woman with meconium ileus in infancy, and multiple surgeries for DIOS underwent bilateral lung transplantation at 38 years of age and hysterectomy 2 years later. Repeated episodes of DIOS were conservatively managed. More severe episodes of abdominal pain began 6 years after the transplant and were interpreted as DIOS with pseudo-obstruction due to adhesions from the previous surgery. She was evaluated for surgery but considered high risk due to bronchiolitis obliterans syndrome (BOS) and pulmonary infection and therefore treated medically with EGILS. When the abdominal problems continued, laparotomy was performed. The surgery was complicated by major adhesions. It was difficult to identify a loop of bowel proximal to the obstruction, so multiple enterotomies were performed before an ileostomy could be performed proximal to the obstruction. The postoperative course was uneventful, although 1 year later she acquired cholecystitis and a duodenal ulcer, both of which were medically treated.

A 36-year-old man, 8 years after bilateral lung transplantation, presented with a lump in the right lower quadrant and intermittent, gradually worsening abdominal pain over 6 months. Abdominal ultrasound showed a thick-walled and collapsed caecum. Further evaluation with a CT scan demonstrated a larger heterogeneous mass in the right lower quadrant consisting of thick-walled bowel, dilated bowel-loops but no evidence of obstruction. EGILS treatment failed to clear the mass, as did the contrast media enema treatment. The patient had had an episode of DIOS at the age of 15 years, and chronic DIOS was the presumed diagnosis, although there was some concern of a chronic ileocolic intussusception or neoplasm. Colonic stricture was unlikely since he received ordinary doses of enzymes. During surgery, a giant mucocele of the appendix with a large intracecal portion causing intermittent obstruction of the ileocecal valve was found and a hemicolectomy was performed. The abdominal symptoms have disappeared after surgery, and the pulmonary function is unchanged.

Discussion

This study focuses on CF-related GI complications. As a retrospective study, it has several limitations. Toronto was the first lung transplant center in Canada, and many patients live far away and are only seen on yearly visits. Consequently, complications not related to the transplant may have been treated at a local hospital and not recorded at the transplant center. The importance of certain symptoms tends to be neglected by patients over time. In the immediate postoperative period, mild-to-moderate GI problems may not have been documented or defined as expected posttransplant problems. CF patients often have nausea and poor appetite before transplantation and disc may therefore not perceive posttransplant abdominal discomfort as a problem.

DIOS was the most common complication found, with an incidence of 20%, which is comparable to the reported lifetime incidence in the adult CF population. DIOS is presumably due to impaction of mucofeculent material in the distal ileum and almost exclusively affects pancreatic-insufficient patients. Other possible predisposing factors are adhesions due to previous surgery, transient postoperative adynamic ileus, dehydration, and adverse effects from drugs. In a study by Minkes et al.,7 7 of 70 of pediatric patients with CF required laparotomy because of bowel obstruction after lung transplantation. They concluded that previous major abdominal surgery
was the most important risk factor.9 Laparotomy was required in the early postoperative period for the first patient to acquire DIOS in our study. A routine has since been adopted for patients with CF, including early enteral feeding, immediate introduction of pancreatic enzymes, and, if the patient has been unable to eat within 24 h, EGILS is administered continuously at a rate of 50 to 100 mL/h through a gastrostomy or nasogastric tube. Not all patients were able to tolerate this preventive medication, and DIOS did still occur. These patients were, however, given medical treatment with EGILS according to the protocol by Koletzko et al,10 and in a few cases sodium diatrizoate enema, successfully. EGILS is not absorbed and should be excluded from calculations of fluid balance, while diatrizoate enemas may cause considerable fluid shift from the circulation to the bowel. No major early DIOS events have been seen in the last few years using this protocol. Recurrence, failure to improve after two medical treatments, or late DIOS should be investigated by radiography of the colon, (hypaque enema) and intestinal passage. Abdominal ultrasound and CT of the abdomen can help to rule out colonic stricture due to excessive enzyme intake,11 intussusception, GI malignancy,1,12 and other causes of nonnecessarily CF-related GI complications.

Pancreatic insufficiency is a marker for severe disease,13 explaining the low number of pancreatic-sufficient patients in this population. Pancreatic-sufficient patients are screened by yearly measurements of serum trypsinogen14 in the regular CF clinic follow-up, in order to detect early onset of pancreatic insufficiency.

Patients with severe lung and liver disease and hepatocellular dysfunction should be considered for liver-lung transplantation, while patients with mild-to-moderate liver disease often do well after lung transplantation alone.15–17 Adjustment of immunosuppression may be necessary, and there is a concern of risk for BOS if triple immunosuppression therapy is not tolerated. One patient with biliary cirrhosis in our population acquired BOS 1 year after discontinuation of azathioprine. It is, however, impossible to determine whether the modified immunosuppression or repeated infections with B cepacia were the main cause of BOS.

GERD is common in patients with CF, and we had suspected this complication to be common after transplantation, but only a few patients reported dyspeptic symptoms and nausea related to drug intake, and no patient had symptoms suggestive of gastroparesis. A prospective study would be able to address these questions more thoroughly. It may be difficult to distinguish side effects from drugs and transient bowel hypomotility after surgery with GERD and gastroparesis. Severe gastroparesis, even requiring gastric bypass surgery, has been described after lung and heart-lung transplantation.18,19 Gastroesophageal reflux may cause significant, but potentially reversible, graft dysfunction and should be treated.20

Cholecystitis in three patients is comparable to previous studies in heart and heart-lung transplant recipients.3–5 Gupta et al21 reported a higher incidence and suggested that biliary calculi should be eradicated when possible since cholecystitis is a severe complication, specifically early in the postoperative period.21 Asymptomatic gallstones and sludge in the gallbladder are common findings in patients with CF.22 We had no case of early cholecystitis or complication after cholecystectomy and do not find preventive surgery indicated. Maurer23 found diverticulitis to be the most common colonic complication after lung transplantation; however, all patients in this report did have COPD and were older than the majority of patients with CF undergoing lung transplantation.23

In conclusion, we found GI complications to be common in lung transplant recipients with CF. DIOS was common in the early posttransplant period. Special attention should be paid to patients with previous major abdominal surgery, meconium ileus in infancy, or previous DIOS. Preventive measures and early treatment are important since severe complications may occur. PS patients may be at risk for development of pancreatic insufficiency. We suggest close collaboration with and regular follow-up at the CF center at the time of and following transplantation for diagnosis and treatment of CF-related GI complications.

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REFERENCES
7. Chaparro C, Maurer J, Gutierrez C, et al. Infection with...


