Colon Perforation After Kidney Transplantation

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Between 1962 and 1977 approximately 2% of Denver kidney transplant patients developed colon perforation. The single commonest cause was diverticulitis of the left colon (6/13 cases). In spite of drastic reduction or discontinuation of immunosuppression, only 5/13 patients survived for more than 90 days after operation. Analysis of this experience suggests that the high mortality rate associated with this complication can be reduced by early operation which removes the perforation from the peritoneal cavity (either exteriorization or resection) without primary intestinal reanastomosis. We believe that candidates for kidney transplantation with a history of previously symptomatic diverticulosis coli should have elective colon resection prior to transplantation. Any kidney transplant patient with lower abdominal signs should be investigated and treated aggressively.

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COLON PERFORATION HAS BEEN associated with a mortality rate of less than 45% in adults whose immune defenses have not been weakened by immunosuppression, whether treated by staged operations or by primary resection.[4] Patients receiving immunosuppressive medications after kidney transplantation have usually not survived colon perforation.[2-12] In this report 13 patients who developed non-traumatic colon perforation after kidney transplantation are analyzed, and recommendations are made for the management of this complication.

Clinical Material

Approximately 800 kidney transplants have been done at the University of Colorado Medical Center and the Denver Veterans Administration Hospital between 1962–1977. Table 1 outlines the age and sex of the 13 patients with colon perforation, their renal disease, the kidney donors, the locations of the transplants and colon perforations, the operations performed, the time intervals between transplantation and perforation, the patient survival, and the causes of death. The cases are listed in chronological order, according to date of perforation, spanning a ten year time period from 1967 until 1977.

The average patient age was 36 years at the time of perforation; there were four males and nine females. Four patients had related grafts and nine had cadaver kidneys. There was no correlation between the location of the transplant and the location of the perforation, which was sigmoid colon in 9/13 patients. The mean interval between transplantation and perforation was 167 days, but 9/13 perforations occurred within three months of transplantation. The preoperative diagnosis was perforated hollow viscus in most cases, although small bowel obstruction and active colitis were each diagnosed in one patient preoperatively.

The single leading cause of colon perforation was diverticulitis coli, in 6/13 patients, all of whom had their perforations in the left colon. In four patients with left colon perforation, gross or microscopic examination of the site of perforation did not reveal a cause. Disruption of appendiceal stump closure, focal colitis, and multiple colonic ulcerations each caused perforation in one patient.

The symptoms of colon perforation in these thirteen immunosuppressed patients were not markedly different from those encountered in nonimmunosuppressed patients: all of the patients had abdominal pain and some had additional gastrointestinal complaints (Table 2). Only 8/12 patients had fever (one patient's hospital

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TABLE 1. *Clinical Characteristics and Survival in Thirteen Kidney Transplant Patients with Colon Perforation*

Case	Age & Sex	Renal Disease	Donor	Side of XP	Location of Colon Perforation	Cause of Perforation	Operation	Interval Between XP & Perforation	Patient Survival Cause of Death
1	46 M	CGN	Cad.	Left	Sigmoid	Diverticulitis	Proximal colostomy	26 days*	Died 25 days Sepsis
2	46 F	Unknown	Rel.	Unk.	Sigmoid	Diverticulitis	Proximal colostomy, 1° closure	200 days	Died 10 days Sepsis
3	20 F	CGN	Rel.	Rt.	Transverse	Focal colitis	Resection, 1° anastomosis	89 days	Died 20 days Sepsis
4	39 F	Polycystic	Rel.	Rt.	Sigmoid	Diverticulitis	Colostomy, exteriorization	63 days	Died 23 days Sepsis
5	51 M	CGN	Cad.	Left	Sigmoid	Diverticulitis	Resection, end colostomy	66 days*	Died 9 days Sepsis
6	46 M	↑BP	Cad.	Rt.	Cecum	Disrupted appendiceal stump	1° Closure, drainage	47 days	Survived 2 y. 9 m. Myocardial Infarct.
7	40 F	CGN	Cad.	Rt.	Descending	Diverticulitis	Resection, 1° anastomosis	281 days	Died 23 days Sepsis
8	55 F	Polycystic	Cad.	Rt.	Sigmoid	Idiopathic	Exteriorization	21 days	Surviving 4½ yrs.
9	43 F	CGN	Cad.	Rt.	Sigmoid	Idiopathic	Proximal colostomy	24 days*	Died 12 days Sepsis
10	40 F	CGN	Cad.	Rt.	Sigmoid	Idiopathic	Proximal colostomy	411 days	Survived 118 days Pneumocystis
11	24 M	Pyelo.	Cad.	Left	Sigmoid	Idiopathic	Resection, end colostomy	900 days	Survived 92 days Pulmonary embolus
12	28 F	SLE	Rel.	Rt.	Sigmoid	Diverticulitis	Resection, end colostomy	15 days	Surviving 7 mos.
13	18 F	CGN	Cad.	Rt.	Splenic flexure	Multiple colonic ulcers	Subtotal colectomy 1° anastomosis	28 days†	Died 49 days Sepsis

* Second transplant.
† Multiple previous transplants.

chart, from 1968, could not be found); 9/12 patients had leukocytosis (WBC > 10,000 cu mm); eight patients had signs of an acute abdomen; four patients had pneumoperitoneum preoperatively.

TABLE 2. *Symptoms and Signs of Colon Perforation after Kidney Transplantation*

Symptoms	
Abdominal pain	13/13
Constipation	4/12
Nausea/Vomiting	4/12
Anorexia	6/12
Signs	
Fever	8/12
Leukocytosis	9/12
Acute Abdomen	8/13
Direct Tenderness only	3/12
Nontender Abdomen	2/13
Pneumoperitoneum	4/12
Hematochezia	1/12

Operative intraperitoneal cultures were obtained in all patients; in most cases the material was cultured under anerobic as well as aerobic conditions. These cultures revealed a variety of large intestinal bacteria, chiefly *E. coli* (11 cases) and bacteriodes (nine cases). Antibiotic therapy was given to every patient, usually a combination of a penicillin or a cephalosporin plus an aminoglycoside. All 13 patients received antibiotics by the time of operation, and in some cases the antibiotics were started preoperatively.

Results

Five of the 13 patients survived for at least 90 days after perforation; two patients are still alive, seven and 52 months after perforation (Table 1). The duration of symptoms prior to operation appeared to have a strong influence on the outcome in the 12 patients for whom this information was available: 4/6 patients with pre-

TABLE 3. *Preperforation Immunosuppression in Survivors (>90 days) and Nonsurvivors*

Patient	Prednisone		Azathioprine		Cyclophosphamide	
	mg/day	mg/kg/day	mg/day	mg/kg/day	mg/day	mg/kg/day
			Nonsurvivors			
1	30	0.60	25	0.5	—	—
2	Unknown	Unknown	Unknown	Unknown	—	—
3	40	0.77	125	2.41	—	—
4	100	2.20	—	—	50	1.1
5	30	0.33	25	0.27	—	—
7	20	0.35	37.5	0.65	—	—
9	50	0.66	75	1.0	—	—
13	15	0.60	0	—	—	—
Mean ± SE	40.7 ± 10.82		47.9 ± 18.37		50	
			Survivors			
6	30	0.36	87.5	1.1	—	—
8	80	1.34	—	—	50	0.84
10	20	0.44	—	—	30	0.66
11	20	0.38	12.5	0.24	—	—
12	70	1.35	125	2.4	—	—
Mean ± SE	44.0 ± 12.88		75.0 ± 33.07		40 ± 10.0	

operative symptoms of less than 24 hours duration survived for more than 90 days; only 1/6 patients with symptoms of greater than 24 hours duration survived for an equivalent time.

All patients (except one anephric nonsurvivor, Case #13) were taking prednisone and azathioprine or cyclophosphamide at the time of perforation. In all 12 patients immunosuppression was drastically reduced or discontinued at the time of perforation, except for a transient increase in corticosteroid to protect against acute adrenal insufficiency during and immediately after operation. There was no significant difference in the amount of preperforation prednisone received by the survivors compared to the nonsurvivors; mean azathioprine dose was actually higher in survivors than nonsurvivors (Table 3).

There was a marked difference in survival according to the quality of kidney graft function during the first week after perforation: 4/6 patients with good postoperative renal function (serum creatinine <2.5 mg%) survived, compared to 1/7 survivors with postoperative serum creatinine >2.5 mg%.

The operative procedures carried out and the results are listed in Table 4. Four patients with left colon perforation had drainage of the site of perforation and proximal loop colostomy: 1/4 of these patients survived. Three patients had resection of the site of perforation (and in one case additional ulcerated colon) with primary intestinal anastomosis: 0/3 survived. Three patients had resection of the site of perforation and end-colostomy: 2/3 survived. Two patients had exteriorization of the perforation: 1/2 survived. The single patient with disrupted appendiceal stump closure survived following reclosure. Of the eight nonsurvivors, six had operations which either did not remove the site of perforation from the peritoneal cavity or which included primary intestinal anastomosis. Of the four survivors of left colon perforation (excluding the fifth survivor following appendiceal stump reclosure), 3/4 had exteriorization or resection of the site of perforation without primary intestinal anastomosis.

The reason for death in the eight patients who died within 50 days of perforation was sepsis in every case. Two patients died 90–120 days after perforation, of pneumocystis carinii pneumonia and pulmonary embolus; one patient died two years nine months after perforation, of myocardial infarction (Table 1); all three patients died with good graft function. Two patients are still alive, seven months and four and one-half years after perforation, with good graft function.

Discussion

Although nontraumatic colon perforation is an infrequent complication following kidney transplantation,

TABLE 4. *Operation for Colon Perforation and Patient Survival (>90 days)*

Operation	# Performed	# Survived
Proximal loop colostomy, drainage	4	1
Resection, colo-colostomy	2	0
Resection, ileosigmoidostomy	1	0
Resection, end colostomy	3	2
Exteriorization of perforation	2	1
Closure of appendiceal stump, drainage	1	1

occurring in approximately 2% of Denver patients and 4% of Duke University patients,[12] the lethality of this complication indicates that its management needs improvement.

The relationship of corticosteroid therapy to gastroduodenal ulceration is well-known; in addition colonic ulceration has been associated with corticosteroid administration,[13-16] and it is likely that prednisone contributed to the colon perforations described in this report. It is not clear whether the frequency of colon perforation is increased in patients receiving corticosteroids compared to patients not receiving such medications;[14] however, a high mortality rate has been observed in so many reports of patients who have developed colon perforations while receiving corticosteroids,[3,5,7-11,14,15] including this report of 13 cases, that corticosteroid therapy must be strongly implicated, even though there was no significant difference in the amount of pre-perforation prednisone taken by survivors compared to nonsurvivors in Denver (Table 3). In a recent report of 13 acute colonic perforation associated with corticosteroid therapy in Boston (only two of which were in kidney transplant patients), 9/11 patients in whom the intraperitoneal findings were available for analysis had failed to wall off the perforation.[16]

Early diagnosis of colon perforation is more difficult in the presence of corticosteroid therapy.[14] In some patients the presence of the iliac graft has caused a misdiagnosis of graft rejection. It has been suggested that all kidney transplant patients over the age of 40 have barium enema examination before transplantation, to identify the presence of diverticulosis coli;[7] it has also been suggested that water soluble contrast enemas be used in immunosuppressed patients with lower abdominal signs, to identify occult perforations earlier.[12] We agree with both of these recommendations.

The single leading cause of perforation in Denver was diverticulitis of the left colon, in 6/13 cases. Five of the six patients with perforated diverticulitis were at least 40 years of age at the time of perforation; the sixth patient was a 28-year-old woman with systemic lupus erythematosis (Case #12, Table 1) who was thought to have a diverticulum in the area of perforation but might have had a focal area of lupus vasculitis which was responsible for the perforation. This patient recovered from the colon perforation, which was treated by resection with proximal and distal colostomies; however, approximately two months later, while at home, she perforated a gastric ulcer into the retroperitoneum and had an additional long and difficult hospitalization before returning home again.

Possible reasons for colon ulceration in the patients without diverticulosis coli, in addition to corticosteroids and vasculitis, include uremic enterocolitis, fecal impaction associated with antacid administration, and graft irradiation administered for rejection episodes. None of these three factors seemed important etiologically in the Denver patients.

In all 13 patients immunosuppression was drastically reduced or discontinued as soon as the diagnosis of colon perforation was made. The longest surviving patient (Case #8, Table 1), now 4½ years after idiopathic perforation of the sigmoid colon, had no immunosuppression for one month after perforation and needed regular hemodialysis during this period; approximately four weeks after the perforation graft function began to return, immunosuppression was gradually restarted, and the graft has been functioning very well since then. The reason for her postperforation renal failure was almost certainly nonimmunologic acute renal failure.

There is a clear relationship between the type of operation done and patient survival (Table 4). Four patients had proximal colostomy with drainage (Cases #1,2,9,10), two patients had resection of the perforation and colo-colostomy (Cases #3,7), one patient had subtotal colectomy and ileosigmoidostomy (Case #13); of these seven patients in whom either the site of perforation was not removed from the peritoneal cavity or primary intestinal reanastomosis was done, only one patient survived for more than 90 days (14%). The six patients who died all died of sepsis. Two of the three patients with primary intestinal reanastomosis had definite anastomotic leaks contributing to ongoing sepsis and requiring reoperation (Cases #3,7); the third patient with primary intestinal reanastomosis died of sepsis due to intra-abdominal abscesses which could have been related to the intestinal reanastomosis (Case #13). Of the five patients who had resection of the perforation and end colostomy (Cases #5,11,12) or exteriorization of the perforation (Cases #4,8)—in whom the site of perforation was removed from the peritoneal cavity and immediate intestinal reanastomosis was not done—there were three survivors (60%).

The infrequency of perforated sigmoid diverticulitis following kidney transplantation, approximately 1% in Denver, does not appear to warrant prophylactic elective colon resection in patients with asymptomatic diverticulosis coli, although the exact frequency of asymptomatic diverticulosis coli in kidney transplant patients is not known. However, the lethality of colon perforation after transplantation in our opinion does warrant elective colon resection prior to transplantation if there is a history of previously symptomatic diverticulosis coli. Early diagnosis and treatment of lower abdominal signs in any patient who has a kidney transplant is clearly very important.

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