Acute Colitis in the Renal Allograft Recipient

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Four renal allograft recipients with evidence of ischemic damage to the colon are presented and compared with 11 cases from 5 major series. Similarities in the patients included: deterioration of renal function, multiple immunosuppressive and antibiotic regimens, the use of cadaver renal allografts, and diagnostic and therapeutic measures requiring frequent enemas with barium and ion-exchange resins. Two of our patients underwent surgery for the removal of segments of necrotic colon after several weeks of fever and abdominal pain initially attributed to either acute rejection, viral infection, or pancreatitis. One patient had three days of melena and responded to non-operative therapy. The fourth patient developed ischemic colonic changes 10 weeks after allograft nephrectomy and was receiving no immunosuppression at the time. Broad spectrum antibiotics were used at various times in all patients. Early aggressive evaluation of gastrointestinal complaints—including barium enema, upper gastrointestinal series with small bowel follow-through, proctosigmoidoscopy or colonoscopy, and arteriography—is indicated, in view of the lethality of the complication of colonic ulceration. The clinical pictures presented emphasize the fact that recipients of renal allografts are commonly heir to many complications which may be considered rare in the normal population.

ISCHEMIC COLITIS is a self-limited phenomenon characterized by compromise of the circulation to the colon in patients with atherosclerotic narrowing of the superior and inferior mesenteric arteries and their branches. The patients are usually in the sixth or seventh decades and their clinical courses include one or more of three transitional patterns as originally described by Boley et al.[7] and expanded by Marston and co-workers[21] i.e.: 1) abdominal angina; 2) reversible ischemic colitis; and 3) in extreme cases, gangrenous enterocolitis.

Pathologic findings vary from the mucosal pallor often seen in patients with intestinal angina to the full-thickness loss of mucosa with ulceration, hemorrhage and stricture seen in ischemic colitis. In addition, some patients develop frank colonic infarction and gangrene. The most commonly described areas of involvement have been the left transverse colon, splenic flexure and descending colon with sparing of the rectum; however, more recent reports describe involvement of the rectum, especially in cases occurring after surgery on the abdominal aorta.[5,15,16,26]

The radiologic features include five characteristic signs on barium enema and plane films of the abdomen. These are: 1) "thumb-printing," thought to be indicative of reversible smooth muscle defects due to hemorrhage into the bowel wall; 2) "saw-tooth" irregularity of the mucosa, characteristic of mucosal ulceration; 3) tubular narrowing; 4) sacculation of the involved segment of the colon, indicative of stricture formation; and 5) pseudopolypoid filling defects, which are attributed to remaining areas of normal mucosa following partial slough of necrotic mucosa.[21]

This report reviews the clinical courses of four recipients of cadaver renal allografts, all of whom demonstrate diagnostic and pathologic features similar to those of ischemic colitis. The roles of immunosuppression, opportunistic infection, and retroperitoneal surgery, as contributing factors in the development of the colonic lesions, will be considered and a review of 11 cases in the literature follows the case reports.

Case Reports

Case 1. H. H., a 45-year-old Caucasian man, underwent bilateral nephrectomy and cadaver renal allotransplantation on 7/21/72. The kidney was placed in the right iliac fossa with an end-to-end anastomosis of the renal to hypogastric artery and an end-to-end side anastomosis of the renal to external iliac vein. In the first eighteen hours postoperatively 3800 ml of urine were produced. On the sixth, seventh and

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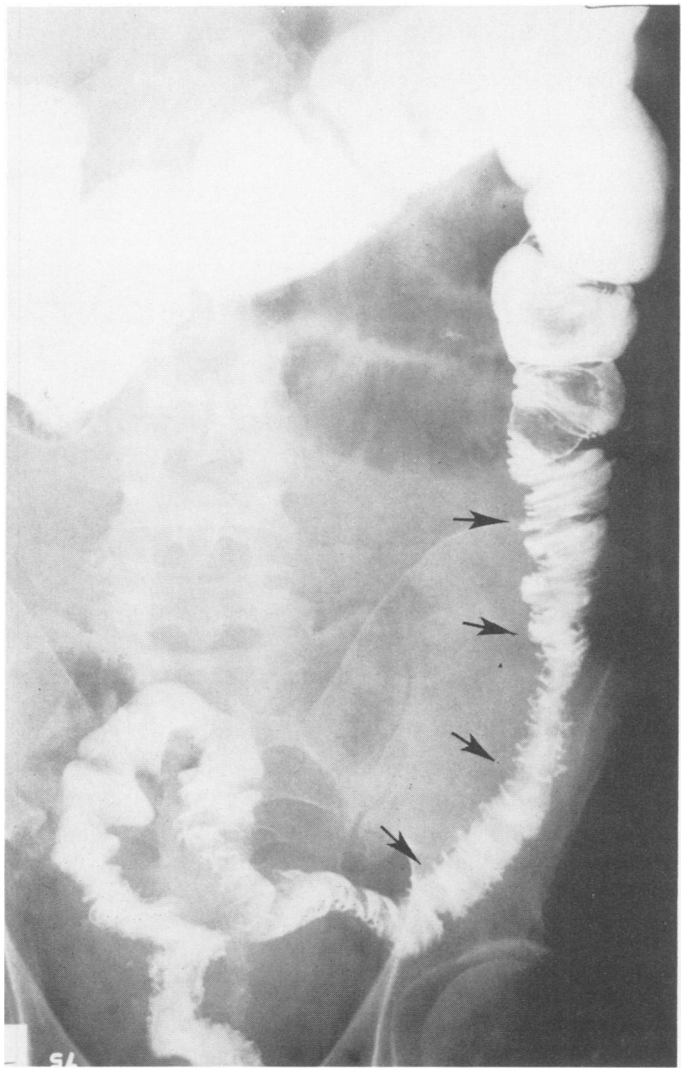

FIG. 1. Barium enema examination, Patient 1. There is edema and marked irritability of the descending colon and sigmoid colon (arrows).

eighth postoperative days, he received, in addition to the routine immunosuppression with oral prednisone and azathioprine, one gram per day of intravenous methylprednisolone for acute rejection and began oral oxacillin for a staphylococcal wound infection. During the third week post-transplantation he developed left lower quadrant pain and vomiting, and serum amylase was 516 units (N = 40 – 180). Intravenous fluid and electrolyte support were instituted, and renal function remained stable with serum creatinine 1.5 mg%. A reduction in the azathioprine dose from 150 mg to 50 mg daily was necessitated by leukopenia (2,500–3,000/mm^3). Abdominal symptoms continued, and during the fifth postoperative week, a barium enema showed spasticity and narrowing of the descending colon to the rectum (Fig. 1). Proctosigmoidoscopy revealed pale mucosa with a bluish cast. During this period nasogastric suction and intravenous hyperalimentation were maintained and the patient continued to pass small amounts of liquid stool. On 9/17, 8 weeks following the transplant operation, a tender left lower quadrant mass was first noted. It increased in size over the next six days, and exploratory laporatomy revealed acute pancreatitis, a purulent exudate over the mesentery of the small bowel and colon, and necrosis of the descending and sigmoid colon, which were resected. Peritoneal fluid cultures grew *Escherichia coli* and *Pseudomonas aeruginosa*. Intravenous cephalothin and garramycin were started on 9/27. Because of continued fever and cyanosis of the colostomy, the patient was returned to the operating room, where resection of the distal transverse colon and proximal rectum were performed. The serum creatinine at this time was 2.5 mg% and prednisone and azathioprine doses were 60 mg and 37.5 mg respectively. On 10/1 gram negative anaerobic rods were cultured from the abdominal drains, and chloramphenicol was added to the antibiotic coverage. The patient had a respiratory arrest with aspiration on 10/3 and, although immediate resuscitation was accomplished, he remained unresponsive and was declared dead on 10/6. Pathologic specimens revealed acute pancreatitis, massive fat necrosis and acute inflammatory reaction in the mesentery, and thrombosis of the veins and arteries of the mesentery. The colonic mucosa was pale, edematous, with no discrete ulceration or hemorrhage, indicative of a potentially reversible ischemic change. It was concluded that acute pancreatitis with severe peritoneal inflammation could account for the pathologic findings in the mesentery. No episodes of hypotension or intestinal obstruction were noted during the post-transplant period and the ischemic colonic changes appeared to be related to hemoconcentration and subsequent occlusion of the colonic vasculature.

Case 2. J. A., a 21-year-old Negro male, engineering student received a cadaver renal allograft on 1/9/73. The anastomoses were performed in an end-to-end manner with the renal and right hypogastric arteries and end-to-side with the renal and right common iliac veins. The patient had a very stormy postoperative course including re-exploration for retroperitoneal hemorrhage on the first postoperative day and three courses of intravenous methylprednisolone (3 gms per course) during the first three months. In addition, the patient received 1350 rads to the allograft in right iliac fossa and was treated with carbenicillin and cephalothin for a wound infection with *Pseudomonas aeruginosa* and *Staphylococcus aureus*. At the time of discharge, 4/3/73, a serum creatinine was 2.3 mg% and prednisone and azathioprine doses were 27.5 mg and 75 mg respectively. The patient did well until 6/22/73 when he was readmitted with abdominal pain, diffuse abdominal tenderness, and fever. Exploratory laporatomy revealed perforation of the gall bladder, and a cholecystectomy was performed. Postoperatively a right lower lobe pneumonia developed. Sputum cultures yielded *Escherichia coli* and cephalothin therapy was again started. Immunosuppression included azathioprine 37.5 mg and prednisone 25 mg. Between 7/1 and 7/23/73, renal function deteriorated despite two more intravenous boluses of 1 gm methylprednisolone and hemodialysis was reinstituted on 7/12/73. A pseudomonas urinary tract infection was treated with intravenous carbenicillin and by mid-August, with the exception of intermittent low grade fever, the patient was ready for discharge. At that time he was receiving only oral oxacillin for a staphylococci infection of his arteriovenous shunt site.

The patient was discharged on 8/28/73, taking a number of antihypertensive agents and 25 gm of an ion exchange resin daily. Continued low grade fever as an outpatient eventuated in readmission for removal of the cadaver allograft on 10/31/73 and the patient became afebrile on no antibiotics or immunosuppressive agents.

On 1/9/74 the patient developed crampy abdominal pain, fever, diarrhea, nausea and vomiting, at first attributed to a viral gastroenteritis. An upper gastrointestinal series was normal; however, barium enema revealed edematous thickening of the left transverse colon. Continued low grade fever, intermittent abdominal pain on hemodialysis, and occasional diarrhea led to repeat barium enema revealing an irregular edematous descending colon, asymmetric haustration of the sigmoid colon and sacculation in the region of the splenic flexture (Fig. 2). Proctoscopic examination was normal.

A clear liquid diet and intermittent intravenous fluid support was required for approximately three weeks following the second barium

enema, after which the patient became asymptomatic. He has returned to graduate school and is doing well on hemodialysis. Repeat barium enemas have been normal.

Other than the intermittent use of an ion exchange resin for control of serum potassium, no medications were being used at the time of the colonic ulceration. The specific etiology of the colonic lesion is unclear.

Case 3. D. I., a 34-year-old Negro man, received a cadaver renal allograft placed in the right iliac fossa on 6/6/74. (End-to-end: Renal to hypogastric artery, end-to-side: renal to iliac vein). The first rejection occurred during the fourth postoperative week, prior to which the patient had had no complications. Three grams of methylprednisolone, (one gram intravenously per day on three successive days) were administered during the fourth, fifth and seventh postoperative weeks, in addition to a second and third course of 450 rads directed at the kidney. During the week between the second and the third "pulses" of methylprednisolone, the hematocrit dropped from 19 to 12%, associated with the passage of several bright red to mahogany-colored stools. The leukocyte count at this time was 1200, platelet count 104,000 and the prothrombin time 17.0 seconds, compared to a control value of 12.0 seconds. The partial thromboplastin time was 69 seconds (N = 28– 35 sec). A barium enema revealed "irritability" in the distal descending colon. Stool culture was positive for Salmonella, type B. Three units of leukocyte poor, washed, packed erythocytes were administered, and ampicillin (2 grams, p.o., q.i.d.) was started. Sigmoidoscopic examination revealed a rosette of external hemorrhoids, however, no mucosal lesions were noted. Cytomegalovirus titer was 1:32.

Within one week of the rectal bleeding, the hematocrit returned to a stable level of 21%, coagulation parameters had become normal and stool cultures grew normal flora. A renal biopsy performed during the fifth post-transplant week revealed acute and chronic rejection, and the oral prednisone which had been tapered to 60 mg. daily was increased to 300 mg daily. Azathioprine dosages had been lowered because of the leukopenia. Continued renal functional deterioration necessitated return to hemodialysis during the ninth postoperative week, and allograft nephrectomy was required because of local tenderness and fever at three months. It was thought that a salmonella enteritis was superimposed upon a coagulation abnormality, producing a picture indistinguishable from transient ischemic colitis. There were no periods of hypotension other than that which occurred during the acute hemorrhage, and no evidence of intestinal obstruction was noted. Thepatient received a second cadaver renal allograft on 2/7/75. Because of the presence of a polar artery, the patient's left hypogastric artery and one of its branches were used for anastomosis to the renal vessels. Although the second kidney underwent acute rejection within three weeks and was removed no untoward effects on the colon secondary to ischemic changes were noted.

Case 4. C. J., a 22-year-old Negro woman, received her first cadaver renal allograft, placed in the right iliac fossa in February, 1972. Anastomoses were end-to-end: right hypogastric to renal artery and end-to-side: renal vein to external iliac vein. Early acute rejection necessitated return to dialysis and ultimately the kidney was removed. Transplantation of a second cadaver renal allograft was performed. Anastomoses were identical to the first kidney except for placement in the left iliac fossa. On 1/23/75, however, a biopsy of the kidney taken one hour after re-establishment of blood flow revealed many fibrin thrombi "consistent with hyperacute rejection or perfusion injury," despite a negative crossmatch preoperatively. Although 4000 ml of urine were produced in the first 12 hours, the patient suddenly became anuric, a technetium 99m DTPA flow scan revealed minimal flow, and the patient was returned to the operating room. Inspection of the kidney revealed essentially total infarction despite a strong pulse in the renal artery and its primary branches, and it was removed on the first postoperative day. Immunosuppression (which had consisted of 3 gms of intravenous methylprednisolone and 500 mg of azathioprine) was terminated. On the fourth day after allograft nephrectomy, the patient began to complain of left lower quadrant pain and the rectal temperature was 101.4°. Bacteriodes fragilis was cultured from the blood stream and ampicillin (6 gms/day) was started. Because of continued low-grade fever and abdominal pain, proctoscopy was performed, revealing pale mucosa. A barium enema showed areas of fine, saw-tooth irregularity and pseudopolypoid filling defects in the descending colon on 2/11 (Fig. 3). An upper gastrointestinal series with a small bowel follow-through was normal. Fever persisted on ampicillin, and chloramphenicol was substituted. Guaiac-positive diarrhea began on 2/20, and a repeat proctosigmoidoscopic examination revealed pale rectal mucosa and small discrete mucosal ulcer at 12 cm. A second barium enema showed an area of narrowing in the descending colon and "thumb printing" of the proximal descending colon consistent with ischemic colitis (Fig. 4a). Stool culture grew normal flora and a CMV titer was 1.4. The pain in the left lower quadrant worsened and began to radiate to the left upper quadrant in association with a temperature elevation to 102.8°. A third barium enema revealed numerous fine ulcerations in the descending and sigmoid colon and rectum. Because of increasing pain and continuous temeprature elevation, the patient underwent an exploratory laparotomy on 3/15/75. The colon was found to be severely ischemic with multiple areas of infarction from the splenic flexure to the rectum. A left colectomy was performed, leaving the patient with a left transverse colostomy and a sigmoid mucous fistula. Pathologic

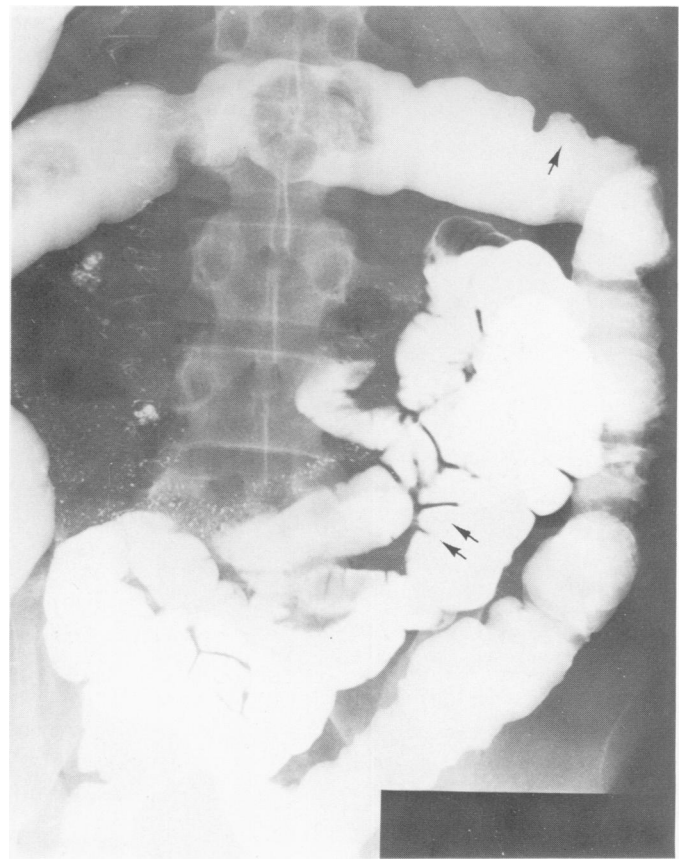

FIG. 2. Barium enema examination, Patient 2. Note edematous mucosa of the proximal descending colon, sacculation of the region of the splenic flexure (single arrow) and asymmetric haustration of the sigmoid colon (double arrows).

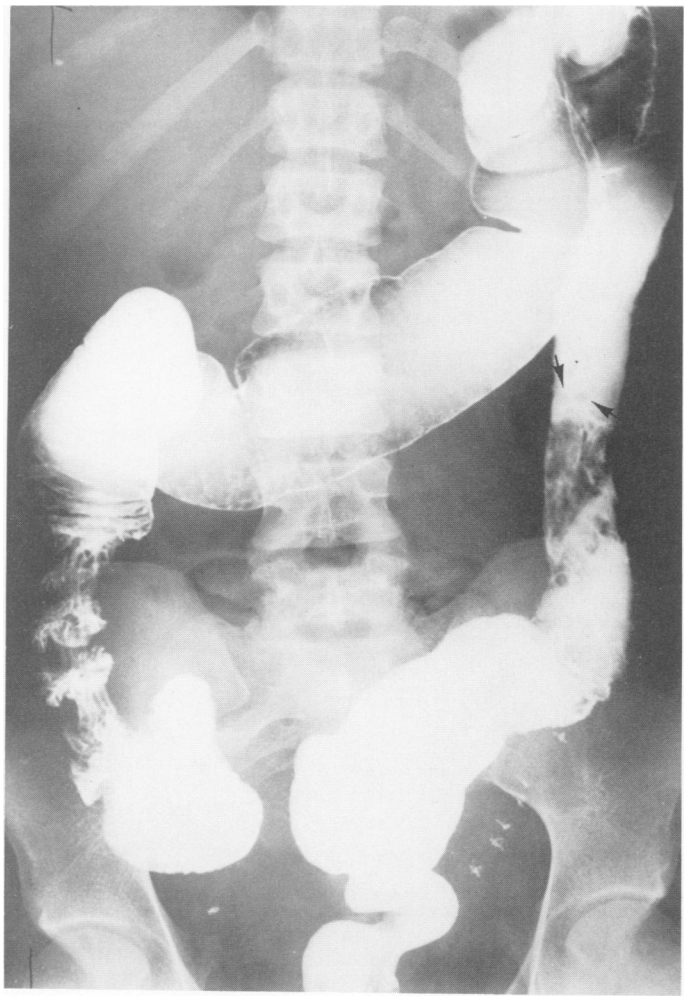

FIG. 3. Barium enema examination, Patient 4, 2-11-75. Note fine "saw-tooth" irregularity along the upper descending colon with pseudopolypoid filling defects in the lower descending colon (arrows).

diagnosis revealed a necrotic colon with an extensive mucosal loss and prominent edema of all layers. A diffuse, acute inflammatory infiltrate was noted, and the external muscle layers showed degenerative changes (Fig. 4b). In addition to the three barium enemas, the patient received ion exchange resin by rectum and by mouth during the two weeks following the allograft removal. The patient left the hospital four weeks following the colectomy and is presently awaiting colostomy closure and retransplantation.

Discussion

The etiologic mechanisms involved in the development of the colonic lesions in the four cases presented above are multifactorial and concomitant. They have been categorized clearly by Bernstein et al.[4] into five groups: 1) uremia; 2) blood volume redistribution; 3) immunosuppressive therapy and its complications; 4) antibiotic therapy and its complications; and 5) irradiation. To these may be added one more category: 6) retroperitoneal surgery with ligation of the collateral arterial supply to the colon. These mechanisms will be considered in reference to our patients.

1. Uremia

As noted by Bailey et al.,[2] the uremic patient is prone to many colonic complications including a 9% incidence of ulceration and perforation. Bleeding from small ulcers may occur anywhere in the gastrointestinal tract and bloody diarrhea is not uncommon, especially in patients undergoing chronic hemodialysis with systemic heparinization. The exact causes of the bleeding tendency of uremic patients is not known. Capillary fragility may be increased and platelet function and absolute number may be decreased, especially in those uremic patients with hypersplenism. Stewart et al.,[28] have noted, however, that some of the coagulation defects may be partially reversed by adequate dialysis. Three of four patients developed their colonic lesions at a time when renal functional deterioration was marked; two of the patients having already returned to hemodialysis. Case 1, H. H. had a serum creatinine of 1.5–2 mg% at the time of his exploratory laparotomy.

2. Blood volume redistribution and retroperitoneal surgery.

The recipient of a renal allograft, despite the usually young age, frequently has peripheral vascular changes which are indistinguishable from those seen in the non-uremic patient with generalized peripheral vascular disease. The accelerated atherosclerosis and hyperlipidemia, important potential risk factors in the etiology of cardiovascular disease in patients on chronic hemodialysis[8,20] may often result in occlusion or severe stenosis of the very vessels which are used for anastomosis to the renal artery of the allograft, i.e. the common iliac artery and its major branches, the external and internal iliac arteries. These vessels occasionally require endarterectomy before use, and their condition is likely to reflect that of the mesenteric circulation as well. The trauma of a retroperitoneal dissection added to the contracted intravascular volume of the transplant recipient may produce a situation in which less than optimal flow is carried by the pelvic and mesenteric vessels. This situation, if prolonged, can easily be seen to produce a low flow state in the major arterial and collateral supply to the colon *i.e.* the superior and inferior mesenteric, hemorrhoidal, and right, middle and left colic arteries, resulting in occlusive or non-occlusive ischemic damage to the colon. Further, a patient who has rejected a previous renal allograft and receives another placed in the contralateral iliac fossa, may be at increased risk in that the colonic arterial collaterals via the hypogastric arteries are destroyed bilaterally as in Patients 3 and 4. The importance of these collaterals is noted in a number of reports of colonic ischemia following infrarenal aortic surgery.[5,15,16,26]

In addition to the direct compromise of the mesenteric circulation, indirect embarrassment of the circulation

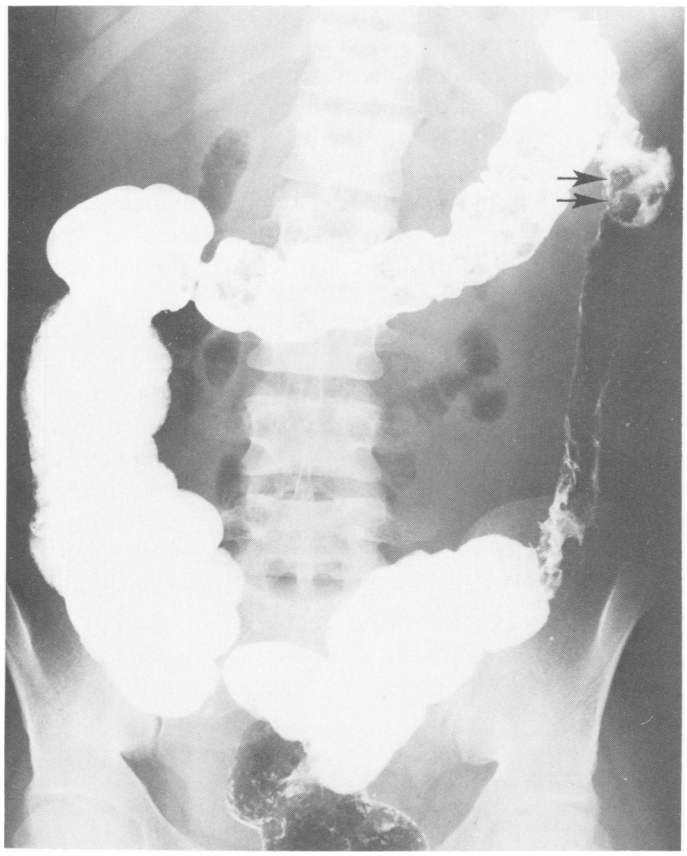

FIG. 4a. Barium enema examination, Patient 4, 20-20-75. Note persistent irregularity and slight narrowing of the descending colon. "Thumb-printing" (arrows) can be seen in the proximal descending colon.

to the colon may follow colonic distention of significant degree. This phenomenon is not uncommon in the uremic patient who has received multiple doses of an ion exchange resin, which alone or in combination with routine antacid therapy usually used in steroid-treated patients, may produce an "obturator" obstruction of the colon as the material becomes dehydrated and inspissated.[3] Furthermore many uremic patients have a form of autonomic insufficiency[18] which, if the gastrointestinal tract is involved, may allow for atony and distention of the colon. Finally, the combination of a massive diuresis in the immediate post-transplant period, the hemorrhagic tendency of the uremic patient, the stress of surgery on a myocardium possibly compromised by long standing hypertension, chronic congestive heart failure, or pericarditis calls for skillful manipulation of the fluid balance in the 24–48 hours following transplantation, attempting to avoid hypotension and hemoconcentration at all times.

3. Immunosuppressive therapy

Most organ transplantation centers use adrenocorticosteroids and azathioprine or cyclophosphamide, to which may be added other agents such as antilymphocyte serum (ALS), actinomycin D, antihistamines, and local irradiation to the allograft. Since their introduction, steroids have been associated with unusual gastrointestinal complications, including gastric, duodenal, and cecal perforation, acute pancreatitis, and peripancreatic fat necrosis. There is some controversy regarding the incidence of duodenal ulcer in steroid-treated patients compared to incidence in the general population, however there is the general clinical impression that these agents aggravate but do not initiate ulcer formation because of their generalized effect on the healing process. Tissue culture studies by Dougherty and White[10] have shown that corticosteroids inhibit cellular proliferation, decrease collagen deposition, and reduce polysaccharide deposition. The living fibroblast cells are immobile, appear swollen and demonstrate no pinocytosis.

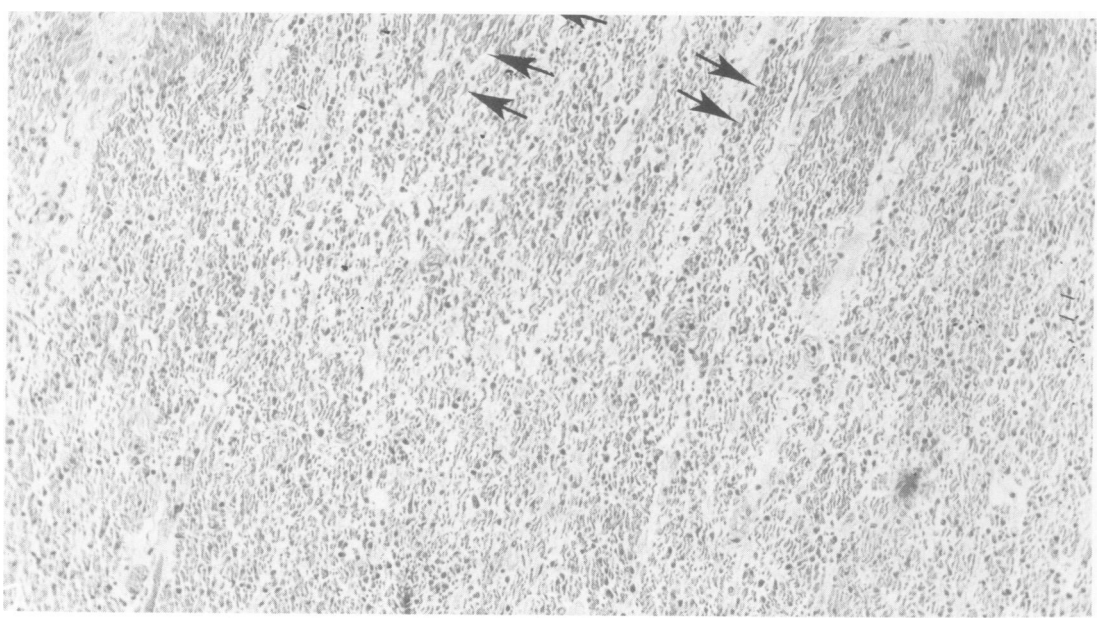

FIG. 4b. Photomicrograph of section of necrotic colon removed from Patient 4. The external muscle layers show marked degenerative changes (arrows) and there is a diffuse actue inflammatory reaction.

Indirect evidence for the deleterious effect of steroids on the gastrointestinal tract is the finding of a decreased incidence of colonic complications in patients on lower doses of steroids because of alternate day administration or the use of adjunctive immunosuppressive drugs such as ALS.[4] Experience in ulcerative colitis also does not suggest an increased evidence of colonic perforation as a result of prolonged steroid therapy. Thus Goldgraber et al.[12] found, in their own series of 400 patients, an incidence of perforation of the colon of 2.5% before the introduction of steroids and 0.8% in 240 steroid-treated patients. However, azathioprine, another major immunosuppressant, has been implicated, along with the corticosteroids, in the depletion of the lymphoid tissue of the intestine. This might result in a decreased mucosal cell turnover and subsequent slowing of the healing and regeneration which may be required following ulceration secondary to vascular compromise.

Another effect of steroid therapy which may be of etiologic significance in the development of colonic ischemia is the phenomenon of steroid induced pancreatitis, which occurs in about 2% of transplant recipients,[19] and may result in dehydration, hemoconcentration, mesenteric fat necrosis and a decrease in mesenteric and colonic blood flow as seen in Patient 1.

Finally, because of the immunosuppressed state of the transplant recipient, a number of opportunistic pathogens may be allowed to flourish. One specifically implicated in colonic ulceration is the cytomegalovirus. Viruses have been associated with ulcers from the mouth to the rectum and have even been implicated as a causative factor in ulcerative colitis especially when intranuclear inclusion bodies are seen within the ulcer craters.[14]

Thus, the non-specific effects of immunosuppression are sufficiently damaging as to provide fertile ground for the destructive influence of ischemia and infection, resulting in the production of colonic ulceration.

4. Antibiotic therapy

Although discussed in this report as a separate category, the frequent use of antibiotics in renal allograft recipients follows directly from those conditions which predispose to frequent infections in these patients, i.e. uremia and immunosuppression. A wide spectrum of antimicrobial agents is in use in all transplant centers, and there are many reports of the lethal effects of the overgrowth of pathogens related to the supression of normal gastrointestinal flora. Pseudomembranous enterocolitis is an entity whose pathophysiology may be indistinguishable from that of ischemic colitis and the two have been discussed interchangeably in some cases.[17] Histologic changes seen in postoperative pseudomembranous enterocolitis include epithelial necrosis with erosion of the tips of the intestinal villi, necrosis of glandular epithelium, and congestion or occlusion of small venules and capillaries in the mucosa. The submucosa is found to be edematous and there is a network of fibrin and acute and chronic inflammatory cells in both the mucosa and submucosa.[6] Although staphylococci were originally considered to be the primary pathogen in the development of postoperative pseudomembranous enterocolitis, there are also reports of systemic fungal infections, particularly candida sepsis, related to enterocolitis.[17]

Antibiotic agents which have been directly implicated in hemorrhagic ulceration of the colon, and which may produce radiologic and pathologic changes identical to those seen in "classical" ischemic colitis are clindamycin,[27] lincomycin,[22] tetracycline,[25] chloramphenicol,[25] and ampicillin.[17] All of the patients in our report were exposed to at least one of these drugs before the development of the colonic lesions, and, in fact the symptoms of diarrhea and colitis have been observed up to several weeks following cessation of therapy with clindamycin. In addition, antiperistaltic agents such as diphenoxylate and opiates may aggravate or prolong the condition.

5. Irradiation

Another immunosuppressive modality is local irradiation to the allograft, which is thought to destroy those sensitized cells trapped within the graft and responsible for active rejection. Because of the high susceptibility of lymphoid cells to the effects of irradiation, relatively low doses may be given to the allograft without fear of irradiation damage to the gastrointestinal tract or kidney itself. The total dose of irradiation should be kept under 1350 rads. Although total body irradiation of doses greater than 900 rads will produce denudation of the gastrointestinal tract with hemorrhage and death in one to two weeks, in order to produce significant changes in the colonic mucosa by local irradiation, doses of 4500–5000 rads are required.[9] The lowest dose which has been associated with gastrointestinal injury is 2250 rads noted in a review by Gillies and Skyring,[11] Three of our four patients received three courses of 450 rads each during the post transplant period and the fourth received 150 rads once. There is little likelihood of irradiation induced colitis in these patients, although the threshold for injury may be reduced in the presence of other complicating factors such as renal failure, ischemia, or infections.

Review of Literature

In five large series of patients totalling 1156 allografts (3 hepatic)[1,4,13,23,24] 106 gastrointestinal complications occurred, an incidence of 9%. Eleven (10.4%) of

these complications were considered to be colitis, colonic ulceration, or pseudomembranous enterocolitis. Duodenal ulcer, perforated diverticulitis, and hepatitis comprised the majority of the remaining complications. The age range was 8–60 years, but 8 patients were under 50 and 5 were under 40 years old. Five of the patients had rejections severe enough to require hemodialysis before the development of the colonic ulceration and at least 4 of the 11 patients were recipients of cadaver kidneys. Two additional patients required reoperation for repair of anastomotic urinary tract leaks.

The time of onset of the colitis ranged from one month to 18 months and the mortality rate for the 11 patients was 90%. Treatment included only fluid and blood replacement in 10 of the 11 patients including the one survivor. Two patients underwent infusions of pitressin into the superior mesenteric artery without success. One patient underwent exploratory laparatomy and died shortly thereafter of septic complications of the surgery.

Although there was no obvious relationship to immunosuppressive medication dosage, all of the patients reported in the literature were noted to have deteriorating renal function and probably high dose immunosuppression at the time of development of their colon abnormality. Although three of our 4 patients survived, one following colectomy, none has a functioning kidney at the time of this report.

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