TYPHLITIS IN ACUTE LEUKEMIA
Successful Treatment by Early Surgical Intervention

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Inflammation of the cecum ("typhlitis") has been an unusual, but generally fatal complication of severe granulocytopenia and immunosuppresion, occurring during the therapy of hematological malignancies. The diagnosis has usually been made only at autopsy, and early surgical intervention has often been withheld because of the patient's precarious hematological status. We report here a patient in whom the clinical diagnosis of typhlitis led to early operation, with intensive blood component support. The successful outcome suggests that such an approach might improve the usually grim prognosis in patients whose underlying malignancy offers a clear chance for remission.

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"TYPHLITIS," or inflammation of the cecum (Greek: "Typhlon"), occurs as a fulminant localized necrotizing colitis in the setting of granulocytopenia and immunosuppression associated with chemotherapy of leukemias and lymphomas. The outcome has been, with rare exceptions, fatal, even in those patients with an otherwise excellent prognosis with regard to their primary disease.[2,3,7,8] The majority of the reported cases have been recognized only at autopsy.[4,7,8] Medical therapy has been uniformly ineffective, and in the few cases where surgical intervention was attempted as a last resort, it did not improve the outcome.[3,5] The pathogenesis of typhlitis is not clear, but may involve a combination of factors, including chemotherapy, immunosuppression, granulocytopenia, massive steroid therapy, and malignant infiltration. We report here a patient with severe typhlitis in whom early clinical recognition and surgical intervention resulted in survival.

CASE REPORT

A 48-year-old female with acute lymphoblastic leukemia underwent induction therapy with prednisone 100 mg/day for one week, vincristine 2 mg iv weekly, and adriamycin 30 mg/m^2 iv for three days. Therapy was tolerated well, and the first week was uneventful. On day 7, she complained of headache. A spinal tap was performed and 15 mg of methotrexate was given intrathecally. Blasts were absent in a cytocentrifuge spun preparation. The headache resolved. On day 10, the patient complained of nausea, but physical examination was negative. The following morning, there was an episode of vomiting, associated with diffuse abdominal pain and a fever of 38.5 C. Physical examination revealed only slight right-sided abdominal tenderness. Cultures of blood and urine were negative. Gentamicin 1 mg/kg q. 8 hours and clindamycin 600 mg iv q. 8 hours were started. Two hours later, the pain became severe, and point tenderness developed in the right iliac fossa, with guarding and rebound. Right psoas spasm was demonstrable, suggesting a retroperitoneal process. A diagnosis of typhlitis was made (appendectomy had been done many years earlier). A plain film of the abdomen revealed no significant abnormality.

Within 30 minutes, rebound tenderness became generalized, and bowel sounds were absent. The patient was diaphoretic, anxious, and hyperventilating, with a heart rate of 130/minute. Absolute granulocyte and reticulocyte counts were zero, and the platelet count was 47,000/mm^3 following the platelet transfusion. The anion gap was 20, with a CO_2 content of 16 MEq/liter and a pH of 7.35. An exploratory laparotomy was performed. One liter of cloudy ascitic fluid was removed that was sterile on culture. The cecum appeared grossly edematous and engorged, with discoloration of the anterior wall. A right hemicolectomy and ileocolic anastomosis were carried out without event.

Pathological examination revealed a normal terminal ileum. Several areas of mucosal ulcerations were noted over the anterior and posterior walls of the cecum, with a large area of bullous edema of the submucosa extending upward into the ascending colon. The mesentery appeared congested, but showed no other abnormality. Micro-

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TABLE 1. Reported Management of Typhlitis

Ref.	Age/ Sex	Primary diagnosis*	Diagnosis made: clinically	Diagnosis made: at surgery	Diagnosis made: at autopsy	Surgery done	Interval from onset: to surgery	Interval from onset: to death	Stated cause of death
5	34/M	AML	–	–	+	—	—	3 days	Cecitis. Pseudomonas sepsis.
	57/M	HCL	–	–	+	—	—	18 hrs.	Cecitis. Peritonitis Clostridial Sepsis.
	63/F	AML	–	–	ND†	exploration only	3 wks.	4 wks.	Cecal rupture.
7	3/M	ALL	–	+	ND	right hemicolectomy	"early"	47 days	Persistent E. coli & Klebsiella sepsis.
3	47/F	Breast CA	–	+	ND	right colectomy	2–3 days	4–5 days	Cecal perforation. Septic shock.
	11/F	ALL	–	–	+	—	—	4 hrs.	Cecal perforation. Peritonitis. Necrotic cecum.
	26/F	PDL	–	–	+	—	—	24 hrs.	E. coli septicemia.
	19/M	AUL	–	+	ND	exploration	3 days	7 days	Cecal necrosis. Peritonitis.
8	51/M	"Blast Crisis"	–	+	ND	right colectomy	1 day	1 mo.	E. coli septicemia. GI bleeding.
6	3	ALL	–	–	+	—	—	21 days	Necrotic cecum
	3	ALL	–	–	+	—	—	23 days	Cecitis. Peritonitis.
	7	AUL	–	–	+	—	—	11 days	Cecitis. Sepsis.
	9	ALL	–	+	+	ileostomy	?	60 days	Cecitis with perforation.
	7	AML	–	–	+	—	—	23 days	Cecitis. Sepsis.
2		6 cases of typhlitis in children with acute leukemia. 1 patient (in remission) survived after surgery. Details of management not given.							

* AML–Acute myeloblastic leukemia; HCL–Hairy cell leukemia; ALL–Acute lymphoblastic leukemia; PDL–Poorly differentiated lymphoma; AUL–Acute undifferentiated leukemia; CGL–Chronic granulocytic leukemia.
†ND–Not done.

scopically, the ileocecal valve and the cecum revealed flattened and focally ulcerated mucosa, marked edema, and congestion of the submucosa, and stasis thrombi in the small veins. In the areas of mucosal ulceration, there was transmural necrosis of the cecal wall, with dense growth of gram-positive cocci. No acute inflammatory exudate or leukemic infiltrate was seen. Cultures revealed mixed flora.

The postoperative course was unremarkable. Granulocyte transfusions (10×10^9 cells) were given daily, and platelets were transfused to keep the platelet count greater than 50,000/mm^3. Further induction therapy utilizing vincristine, prednisone, and L-asparginase resulted in complete remission, and the patient was discharged after cranial irradiation and further injections of intrathecal methotrexate. She remained in remission for 6 months while on maintenance therapy with methotrexate and 6-mercaptopurine. A routine bone marrow at that point diagnosed relapse and successful reinduction was performed with the same regimen. She now remains in complete remission receiving maintenance therapy with oral cyclophosphamide 8 months after the surgery.

DISCUSSION

Typhlitis has been previously reported both as a distinct entity[1,3,8] and lumped together with other forms of necrotizing enteropathy[4,7] and ileocecal complications of malig-

nant disease. The diagnosis has been rarely made clinically, and surgical treatment attempted only occasionally (Table 1). Cecal perforation, peritonitis, and sepsis have been common terminal events.

The etiopathogenesis of this syndrome is not clear. Leukemic infiltration, intramural hemorrhage, and massive bacterial invasion of the cecal wall have been suggested as primary events, with granulocytopenia, and perhaps steroid and cytotoxic therapy playing a permissive role. Clinically, it has been poorly recognized, often confused with vincristine toxicity, appendicitis, and other causes of acute abdomen. X-ray findings of ileal obstruction with absence of gas shadows in the right iliac fossa have been noted in retrospect.[1,8]

The survival of our patient could be attributed to early clinical diagnosis and surgical intervention. The absence of bacteria from the peritoneal cavity in the presence of clinical signs of peritoneal irritation suggested that bacterial invasion was imminent, but was averted by immediate removal of the necrotic cecum. It has been noted previously that leukopenia does not constitute a contraindication to an otherwise essential surgical procedure.[5] The granulocyte transfusions were given emperically, and it is impossible to evaluate their contribution to the benign postoperative course.

In summary, we suggest that a high index of suspicion should result in early clinical diagnosis of this life-threatening complication of severe granulocytopenia. Since medical therapy is ineffective, surgical intervention should be strongly considered in patients in whom therapy of the underlying disease offers a chance for remission.

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