CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 13-2014: A 41-Year-Old Man with Fever and Abdominal Pain after Stem-Cell Transplantation

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PRESENTATION OF CASE

Dr. Ricardo J. Cigarroa (Medicine): A 41-year-old man with B-cell acute lymphoblastic leukemia (ALL) underwent allogeneic peripheral-blood stem-cell transplantation, and afterward, fever and abdominal pain developed.

The patient had been well until approximately 7 months before admission, when low-grade fevers and fatigue occurred; the fevers were associated with an unintentional weight loss of approximately 10 kg. Five months before admission, pain in his right arm and leg developed. Imaging performed at another hospital revealed deep venous thromboses, and analysis of a peripheral-blood smear revealed a white-cell count of 33,000 per cubic millimeter, with 53% blasts. Pathological examination of a bone marrow–biopsy specimen reportedly revealed 74% lymphoid blasts. A diagnosis of B-cell ALL was made, and cytogenetic analysis revealed the presence of the Philadelphia chromosome (BCR-ABL translocation). Induction chemotherapy with a standard multidrug regimen, including cyclophosphamide, daunorubicin, vincristine, prednisone, L-asparaginase, and dasatinib, was administered.

Six weeks after the diagnosis was made, follow-up examination of another bone marrow–biopsy specimen revealed morphologically complete remission. Two weeks later, the patient was seen in the cancer center at this hospital for a consultation about allogeneic hematopoietic stem-cell transplantation. He underwent consolidation chemotherapy while an HLA-matched unrelated donor was identified through the National Marrow Donor Program. Plans were then made to proceed with HLA-matched unrelated-donor peripheral-blood stem-cell transplantation after myeloablative conditioning. Five months after the diagnosis of ALL and 3 days before the patient's admission for the transplantation, pathological examination of another bone marrow–biopsy specimen revealed continued complete remission. One day before admission, a triple-lumen tunneled catheter was placed. The next day, he was admitted to this hospital.

The fevers and fatigue that had occurred before the diagnosis of ALL had resolved. The patient had a history of low-back pain and intravenous opiate use. Maintenance

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chemotherapy, including 6-mercaptopurine and dasatinib, was stopped 2 weeks before admission; medications on admission included enoxaparin and oxycodone. Palifermin was administered 3 days before admission, for prevention of mucositis. The patient had no known allergies. He had smoked cigarettes for more than 25 years (and continued to do so), drank alcohol rarely, and stopped opiate use after receiving the diagnosis of cancer. He lived alone in New England, had one child, and was disabled because of this illness. He was of Native American ancestry. His mother and maternal grandmother had died; both had had lung cancer. The patient's maternal aunt had breast cancer, and his father had multiple sclerosis.

On examination, the vital signs were normal and the weight was 98 kg. The Eastern Cooperative Oncology Group performance score was 1 (on a scale of 0 to 5, with 0 indicating that the patient has no symptoms, 1 indicating that the patient is ambulatory but restricted in terms of physically strenuous activity, and 5 indicating death); the score on the Karnofsky performance scale was 90 (on a scale of 0 to 100, with 100 indicating that the patient has no symptoms, 90 indicating that the patient is able to perform normal activities with minor signs or symptoms of disease, and 0 indicating death). The abdomen was soft, without tenderness, distention, or organomegaly. The skin of the right arm had numerous scars and chronic superficial thromboses, features that were consistent with previous intravenous drug use. The remainder of the examination was normal. Results of renal-function tests were normal, as were blood levels of electrolytes, glucose, calcium, phosphorus, magnesium, and total and direct bilirubin; other test results are shown in Table 1. The administration of allopurinol, famciclovir, ursodiol, and trimethoprim–sulfamethoxazole was begun, and narcotic analgesic agents were continued. During the first week, the patient underwent total-body irradiation and the administration of high-dose intravenous cyclophosphamide. He also agreed to participate in a phase 3, randomized, placebo-controlled clinical trial of antithymocyte globulin (ATG), administered 3 days before stem-cell transplantation, for the prevention of chronic graft-versus-host disease (GVHD) (ClinicalTrials.gov number, NCT01295710). The administration of fluconazole and ciprofloxacin as infectious disease prophylaxis was begun on the day before transplantation, as was tacrolimus for the prevention of GVHD; trimethoprim–sulfamethoxazole was stopped.

On hospital day 9, HLA-matched unrelated-donor peripheral-blood stem cells were infused. As expected, pancytopenia occurred and persisted for many days thereafter; test results are shown in Table 1. Severe mucositis and diarrhea developed, and total parenteral nutrition was initiated for nutritional support. On hospital day 13 (day 4 after transplantation) and intermittently thereafter as needed, packed red cells and platelets were transfused. On hospital day 15 (day 6 after transplantation), the temperature rose to 38.4°C. Fluconazole was continued, ciprofloxacin and famciclovir were stopped, and intravenous cefepime, vancomycin, and acyclovir were begun; the fever resolved within 32 hours. Loperamide was administered for diarrhea. Episodes of epistaxis and melena occurred on hospital day 18 (day 9 after transplantation) and intermittently thereafter; aminocaproic acid was administered for the prevention of bleeding due to refractory thrombocytopenia, despite multiple platelet transfusions.

On hospital day 21 (day 12 after transplantation), the temperature rose to 38.4°C, and fevers with associated episodes of confusion and hallucinations persisted daily thereafter. Fluconazole was stopped, and micafungin was started. The weight was 106 kg, and there was swelling of the face, erythema and ulceration of the throat and mouth, and edema of the arms and legs. A chest radiograph showed mild pulmonary edema and small pleural effusions. Test results are shown in Table 1. Blood cultures were sterile. Furosemide was administered, without improvement. Four days later, abdominal distention and pain that was localized to the right lower quadrant occurred and was associated with guarding and rebound.

Dr. Mahan Mathur: Computed tomography (CT) of the chest revealed patchy ground-glass opacity in the upper lungs, opacity in the right lower lobe (suggestive of atelectasis), apparent esophageal-wall thickening, mild pulmonary edema, and trace bilateral pleural effusions. CT of the abdomen, performed after the administration of contrast material, revealed changes consistent with acute retrocecal appendicitis and inflammation of the cecum, as well as hepatomegaly, splenomegaly, periportal edema, free fluid, and innumerable subcentimeter retroperitoneal lymph nodes (Fig. 1).

Table 1. Laboratory Data.

Variable	Reference Range, Adults*	On Admission	Hospital Day 9 (before Transplantation)	Hospital Day 21 (Day 12 after Transplantation)	Hospital Day 25 (Day 16 after Transplantation)	Hospital Day 27 (Day 18 after Transplantation)
Hematocrit (%)	41.0–53.0 (men)	32.6	27.5	23.4	25.7	26.0
Hemoglobin (g/dl)	13.5–17.5 (men)	10.6	9.1	8.1	8.7	8.7
White-cell count (per mm^3)	4500–11,000	4700	200	100	2000	4900
White-cell differential count						
Method of differential count		Automatic	Manual	Manual	Manual	Manual
Total no. of cells counted			15	10	100	100
Neutrophils (%)	40–70	18.9	86.7	20.0	36.0	51.0
Band forms (%)	0–10				8.0	5.0
Lymphocytes (%)	22–44	63.9	13.3	50.0	13.0	15.0
Atypical lymphocytes (%)	0					2.0
Monocytes (%)	4–11	15.9	0	30.0	38.0	21.0
Eosinophils (%)	0–8	0.2	0	0	0	0
Basophils (%)	0–3	1.1	0	0	1.0	0
Myelocytes (%)	0	0	0	0	1.0	4.0
Metamyelocytes (%)	0	0	0	0	3.0	2.0
Nucleated red cells (per 100 white cells)	0	0	0	0	2	1
Platelet count (per mm^3)	150,000–400,000	291,000	73,000	5000	5000	7000
Activated partial-thromboplastin time (sec)	22.0–35.0	28.6		33.4	35.3	37.7
Prothrombin time (sec)	11.0–14.0	13.6		14.8	16.2	17.6
International normalized ratio		1.1		1.2	1.3	1.5
Protein (g/dl)						
Total	6.0–8.3	5.8	4.8	5.1	5.5	5.2
Albumin	3.3–5.0	3.8	3.2	2.7	3.1	2.8
Globulin	2.3–4.1	2.0	1.6	2.4	2.4	2.4
Alkaline phosphatase (U/liter)	45–115	55	43	70	170	243
Alanine aminotransferase (U/liter)	10–55	20	14	9	14	64
Aspartate aminotransferase (U/liter)	10–40	31	18	11	21	151
Lactate dehydrogenase (U/liter)	110–210	192	175	165	296	468
Fibrinogen (mg/dl)	150–400			638		603
Immunoglobulins (mg/dl)						
IgA	69–309	72		85		
IgG	614–1295	594		544		
IgM	53–334	90		86		
Aspergillus galactomannan assay (OD ratio)†	<0.5			0.971	0.828	
1,3-β-D-glucan assay (pg/ml)	<60			<31	45	

* Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

† OD denotes optical density.

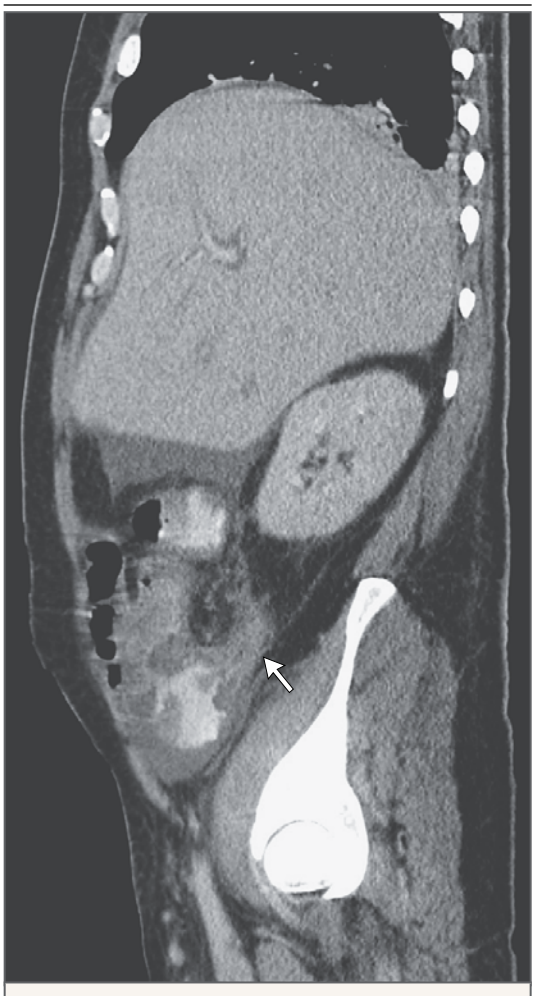

Figure 1. Image of the Abdomen.
A sagittal reconstruction of a CT scan of the abdomen and pelvis, performed after the administration of intravenous and oral contrast material on day 16 after stem-cell transplantation, shows cecal-wall thickening, a thickened retrocecal appendix, and periappendiceal inflammatory changes (arrow). A small amount of free fluid is present.

Dr. Cigarroa: Surgical consultants evaluated the patient and determined that he had a very high operative risk, and conservative therapy was recommended. All oral intake was stopped. Metronidazole was administered; however, pain and signs of peritonitis worsened and fevers persisted. Blood cultures remained sterile, and testing of the stool for *Clostridium difficile* toxin was negative. The next day, the patient was transferred to the medical intensive care unit (ICU).

On examination in the ICU, the temperature was 38.8°C, the blood pressure 126/70 mm Hg, the pulse 109 beats per minute, the respiratory rate 32 breaths per minute, the oxygen saturation 90% while the patient was breathing ambient air, and the weight 108 kg. He appeared uncomfortable and inattentive. The oral mucosa was erythematous, and there were ulcerations of the lips, oral cavity, and throat. The jugular vein was distended above the right atrium, and the jugular venous pressure was 10 to 12 cm of water. Breath sounds were decreased at the right lung base. Bowel sounds were normal, and the abdomen was distended and slightly firm to palpation, with tenderness to percussion throughout, rebound and guarding in the right lower quadrant, and tenderness to palpation in the left lower quadrant. There was 3+ pitting edema to the sacrum. The rest of the examination was normal. The plasma lactic acid concentration was normal. Chest radiography revealed diffuse interstitial pulmonary edema. Supplemental oxygen and additional furosemide were administered; infusion of total parenteral nutrition was stopped.

On hospital day 27 (day 18 after transplantation), the temperature rose to 40.6°C. The blood pressure was 139/94 mm Hg, the pulse 112 beats per minute, the respiratory rate 26 breaths per minute, and the oxygen saturation 88% while the patient was breathing ambient air. A repeat CT examination of the abdomen and pelvis revealed no substantial change. Because of the patient's worsening clinical status, a diagnostic procedure was performed.

DIFFERENTIAL DIAGNOSIS

Dr. Dimitrios P. Kontoyiannis: This 41-year-old man with ALL underwent HLA-matched unrelated-donor peripheral-blood stem-cell transplantation, after which severe mucositis and pancytopenia developed and fever occurred (on days 6 and 12 after transplantation). During the second febrile episode, the temperature remained elevated and was accompanied by intermittent melena, right-sided abdominal pain, and abdominal distention. All blood cultures were negative. Findings on abdominal imaging were consistent with acute retrocecal appendicitis and neutropenic enterocolitis, and I suspect that the patient has the syndrome of chemotherapy-associated right-sided colitis.

CAUSES OF CHEMOTHERAPY-ASSOCIATED COLITIS

There is a short list of entities that can cause chemotherapy-associated colitis (Table 2). Several

diseases on the list, including cytomegalovirus (CMV), early GVHD, intestinal obstruction, leukemic infiltration, ileus, and intramural hemorrhage, are rare causes of right-sided enterocolitis, and they are unlikely to be the cause in this case because of a lack of clinical, laboratory, and radiologic evidence. Pseudomembranous colitis due to *C. difficile* warrants some consideration because it causes clinical signs and symptoms similar to those of neutropenic enterocolitis[1-3] and associated appendicitis; however, testing of the stool for *C. difficile* toxin was negative and involvement of the cecum is atypical.

Neutropenic enterocolitis (sometimes referred to as "typhlitis") has been reported to occur with 5.3% of neutropenic episodes,[4] although its frequency is probably underestimated. It is not uncommon for neutropenic enterocolitis to occur after the administration of high-dose cytotoxic chemotherapy, which disrupts the integrity of the gastrointestinal mucosa, thereby resulting in mucosal or transmural gastrointestinal inflammation, hemorrhagic necrosis, and bacterial translocation, with or without septicemia.[1,2] Neutropenic enterocolitis typically involves the cecum because of the limited blood supply to and increased distensibility of that part of the colon.[1,2] Agents that promote colonic stasis, such as narcotics or the antidiarrheal medications that this patient had received, could increase wall tension and transmural ischemia and thus aggravate neutropenic enterocolitis.

There are several clinical manifestations of neutropenic enterocolitis.[1-3] In its early stages, fever, abdominal pain, and impaired bowel function (constipation or diarrhea) — a series of symptoms known as the chemotherapy-associated bowel syndrome — are seen.[5] In more severe cases of neutropenic enterocolitis, fever, pain in the right lower quadrant, nausea, vomiting, abdominal cramping, diarrhea, lower gastrointestinal bleeding, and septicemia (even without abdominal symptoms) may occur.[2] In particular, the presence of lower gastrointestinal bleeding after chemotherapy for acute leukemia strongly supports a diagnosis of neutropenic enterocolitis.[1] Because cecal inflammation can be masked by the absence of neutrophils, a mass in the right lower quadrant or abdominal fullness and distention could be the clinical signs on presentation.[1,2] Major and minor diagnostic criteria have been proposed that incorporate abdominal CT findings, specifically the degree of bowel-wall thickening,[5] but these criteria have not been prospectively validated.

Table 2. Differential Diagnosis of Chemotherapy-Associated Colitis.

Neutropenic enterocolitis (typhlitis)
Clostridium difficile infection
Cytomegalovirus infection
Leukemic infiltration
Early graft-versus-host disease (in patients who have undergone stem-cell transplantation)
Intramural hemorrhage
Paralytic ileus, with or without pseudo-obstruction
Ischemia
Diverticulitis

This patient appears to have full-fledged neutropenic enterocolitis and evidence of appendicitis. Clinical differentiation between neutropenic enterocolitis and appendicitis is difficult because the two entities can occur simultaneously.[6] In fact, appendiceal thickening has been seen in children with neutropenic enterocolitis.[6] Acute appendicitis is not an uncommon complication of chemotherapy-associated neutropenia among children with acute leukemia[7] and has been reported in 27% of that patient population at autopsy.[2] Appendicitis is less common in adults with acute leukemia.[8]

CAUSES OF NEUTROPENIC ENTEROCOLITIS AND APPENDICITIS

This patient is in the preengraftment period after stem-cell transplantation. During this period, neutropenia and mucositis are the major immune defects that predispose patients to infections, typically those arising from disrupted anatomical barriers.[9] Bacterial infections are very common during this period and can occur in association with neutropenic enterocolitis; in fact, bacterial bloodstream infections, which are typically caused by anaerobic gram-negative rods, have been described in 84% of patients with neutropenic enterocolitis.[2] Many of these infections are polymicrobial.[3] However, this patient had negative blood cultures and his condition did not improve after empirical broad-spectrum antibacterial therapy. Furthermore, atypical pathogens, such as *Mycobacterium tuberculosis* or parasites, seem to be very unlikely causes in this case.

This patient may have received an infusion of ATG, a lympholytic agent associated with reactivation of Epstein–Barr virus (EBV) infection and EBV-associated lymphoproliferative disease.[10] However, nothing in the presentation suggests that EBV or an EBV-associated disease is the cause of the cecal disease.

Fungi can cause neutropenic enterocolitis (although less commonly than bacteria), and candida accounts for up to 94% of such cases.[4,11] Culture-negative sepsis caused by fluconazole-resistant candida species is a possibility. However, candida species typically do not cause this clinical syndrome; they have been described as the cause of perforation and necrotizing enterocolitis only in premature low-weight neonates.[12] Gastrointestinal involvement by invasive fungi is probably underestimated,[13,14] and appendicitis due to aspergillus is rare, but it does occur.[15] The pathogenesis of gastrointestinal aspergillosis is undefined but can involve preexisting gastrointestinal colonization. Consumption of food tainted by molds is a possible source, even for patients in a hematology unit.[16]

An angioinvasive mold could be the cause of neutropenic enterocolitis and appendicitis in this patient. He had received a stem-cell transplant from an HLA-matched unrelated donor; recipients of such transplants are at a high risk for invasive fungal disease (up to 7.7% of recipients are infected).[17] One of the most common invasive fungal infections is aspergillosis. Symptoms developed in this patient during the second week of neutropenia, the time during which the risk for aspergillosis begins to rise.[18] The administration of ATG, with the subsequent rapid depletion of T cells,[10] could also be a risk factor for aspergillosis; although invasive fungal infections occur sporadically as a complication of ATG-based therapy, fatal mycoses have been reported in up to 38% of recipients of stem-cell transplants who received an infusion of ATG for GVHD prevention in addition to fluconazole prophylaxis.[19] Furthermore, he is at risk for breakthrough aspergillosis because he was receiving fluconazole, an azole that has no activity against aspergillus.[20]

The patient had two consecutive positive aspergillus galactomannan assays. The aspergillus galactomannan assay frequently produces false positive results[21] in patients who have mucositis, have received antibiotic agents or blood products, or have consumed certain foods. However, this patient had several major risk factors for aspergillosis, including profound neutropenia, acute leukemia, and use of fluconazole for antifungal prophylaxis,[22] and in the presence of these risk factors, the sensitivity, specificity, and positive predictive value of the aspergillus galactomannan assay are highest. It is important to note that a positive aspergillus galactomannan assay is not diagnostic of invasive aspergillosis, because this test cross-reacts with other fungi, such as fusarium and histoplasma.[23]

This patient also had an indeterminate 1,3-β-D-glucan assay result (positive result, >80 pg per milliliter).[24] Similar to the aspergillus galactomannan assay, the 1,3-β-D-glucan assay is likely to yield false positive results in patients who have bacterial infections or mucositis, have consumed certain foods, or have received antibiotics or filtered blood products or in patients in whom dialysis catheters have been placed. Also, its performance is yet to be validated in persons with cytopenia and the chemotherapy-associated bowel syndrome who have received a stem-cell transplant.[24] However, the combination of a positive aspergillus galactomannan assay and a positive 1,3-β-D-glucan assay is reported to be 100% specific.[25]

Finally, this patient could have a mixed infection with aspergillus and mucorales, a particularly aggressive, tissue-destructive opportunistic mold. Neutropenic enterocolitis, with associated appendicitis, bowel infarction, and acute abdomen, has been reported as a consequence of invasive mucorales infection.[26] However, a mixed infection with aspergillus and mucorales is extremely unlikely.

In conclusion, I believe that this patient had acute appendicitis and concurrent neutropenic enterocolitis with probable cecal perforation caused by infection with an angioinvasive mold, most likely an aspergillus species. Because he had no clinical evidence of disseminated or sinopulmonary aspergillosis, I suspect that he had a primary aspergillus infection of the cecum and appendix, and I would administer an agent that covers molds broadly, such as intravenous voriconazole or liposomal amphotericin B. Because the neutropenic enterocolitis has worsened and the patient is no longer cytopenic, I would proceed with an open laparotomy,

which would serve both diagnostic and therapeutic purposes.

Dr. Eric S. Rosenberg (Pathology): May we have the third-year medical students' diagnosis?

Harvard Medical School students: We focused our differential diagnosis on opportunistic infections that cause appendicitis in recipients of allogeneic stem-cell transplants. We thought that CMV, fluconazole-resistant candida species, and aspergillus species were the pathogens that were most likely to be causing appendicitis in this patient.

Dr. Rosenberg: Dr. Chen, what was your impression when you initially evaluated this patient?

Dr. Yi-Bin Chen: Given the location of the tenderness on examination and the clinical context, we thought the clinical presentation was most consistent with neutropenic enterocolitis and appendicitis. We noted the positive aspergillus galactomannan assays; however, we interpreted these as possible false positive results, because there was a lack of other evidence to support an invasive fungal infection, the patient had received several days of micafungin therapy, and there was ongoing mucositis and mucosal gastrointestinal inflammation. Thus, our clinical diagnosis was acute neutropenic enterocolitis with extension to acute appendicitis. We did not believe that early acute GVHD was a contributing cause in this case. We asked our surgical colleagues to assist in the evaluation and treatment of this patient.

CLINICAL DIAGNOSIS

Neutropenic enterocolitis and acute appendicitis.

DR. DIMITRIOS P. KONTOYIANNIS'S DIAGNOSIS

Acute appendicitis and neutropenic enterocolitis caused by a primary infection with an angioinvasive mold, most likely aspergillus species.

MANAGEMENT

Dr. Paul C. Shellito: At the time of this patient's presentation, I was thinking less about the cause of his abdominal process and more about his being a very poor candidate for surgery. He had peritonitis on examination, and I was hoping that his condition would improve with medical treatment alone; most of the time, surgery can be avoided in patients with neutropenic enterocolitis. Despite supportive care and antimicrobial therapy, he had persistent fever and peritonitis over the ensuing 48 to 72 hours.

Because of the lack of improvement, we decided to intervene with surgery, and our initial plan was to perform an appendectomy. During the surgery, we found the appendix to be very indurated and inflamed. It was in a retrocecal position and difficult to access. In the process of mobilizing and retracting the cecum, the appendix became detached from its base because it was so inflamed and necrotic. The base of the cecum was also very indurated and inflamed, and so a satisfactory stump closure was impossible, especially in an infected field in an immunosuppressed patient. Therefore, I decided to perform an ileocecal resection instead of an appendectomy alone.

The next surgical decision was whether to perform an anastomosis after resecting the ileocecum. I thought it would be safest to perform an end ileostomy and close the ascending colon. Fortunately, the surgery was performed without major complications.

PATHOLOGICAL DISCUSSION

Dr. Julie Y. Tse: The resected ileocecum consisted of a 5-cm segment of ileum, an 8-cm segment of ascending colon, and the attached mesentery. A tannish-yellow fibrinopurulent exudate was present on the cecum, at the presumed base of the appendix and on the mesenteric fat. On microscopic examination, the bowel wall was architecturally intact, with submucosal edema. There was a mixed inflammatory infiltrate in the lamina propria, and neutrophils were infiltrating the crypt epithelium, causing cryptitis, crypt injury, and scattered apoptosis. These findings are nonspecific and can be caused by medications, CMV infection, or acute GVHD. In other areas, there was evidence of epithelial regeneration, with prominent crypt branching and crypt-cell hyperplasia. In summary, examination of the resected ileocecum revealed moderately active enterocolitis, with crypt injury and epithelial regeneration. There was not enough evidence of infection or severe neutropenic enterocolitis to fully account for the severe abdominal pain.

The appendix was grossly enlarged (measuring 7 cm in length, with a maximum diameter of 1 cm). The serosal surface was diffusely hyperemic, focally hemorrhagic, and covered with a tannish-brown fibrinopurulent exudate. No perforation was seen. A cross section of the appendix showed a thickened, necrotic wall, with a largely denuded mucosa and a lumen filled with abundant necrotic material (Fig. 2A). There was a paucity of inflammatory infiltrate, a finding indicative of the profound neutropenia. Examination of the luminal contents revealed the presence of hyphal forms with acute-angle branching (Fig. 2B). Grocott methenamine–silver nitrate staining highlighted the septated hyphal forms, which were of a uniform width and had true dichotomous branching with regular acute angles; these features are consistent with aspergillus (Fig. 2C). The fungal organisms had invaded the full thickness of the appendiceal wall, including the serosal surface. Examination of submucosal vessels in the appendiceal wall revealed fungal angioinvasion, with vessels occluded by hyphal forms (Fig. 2D); the thrombosis of these vessels probably contributed to the widespread infarction of the appendix. Although there was transmural involvement by the fungus, most of the organisms were in the lumen of the appendix, a finding that suggests that the infection arose from the gastrointestinal tract rather than being disseminated from another site. Therefore, our diagnosis was invasive aspergillosis of

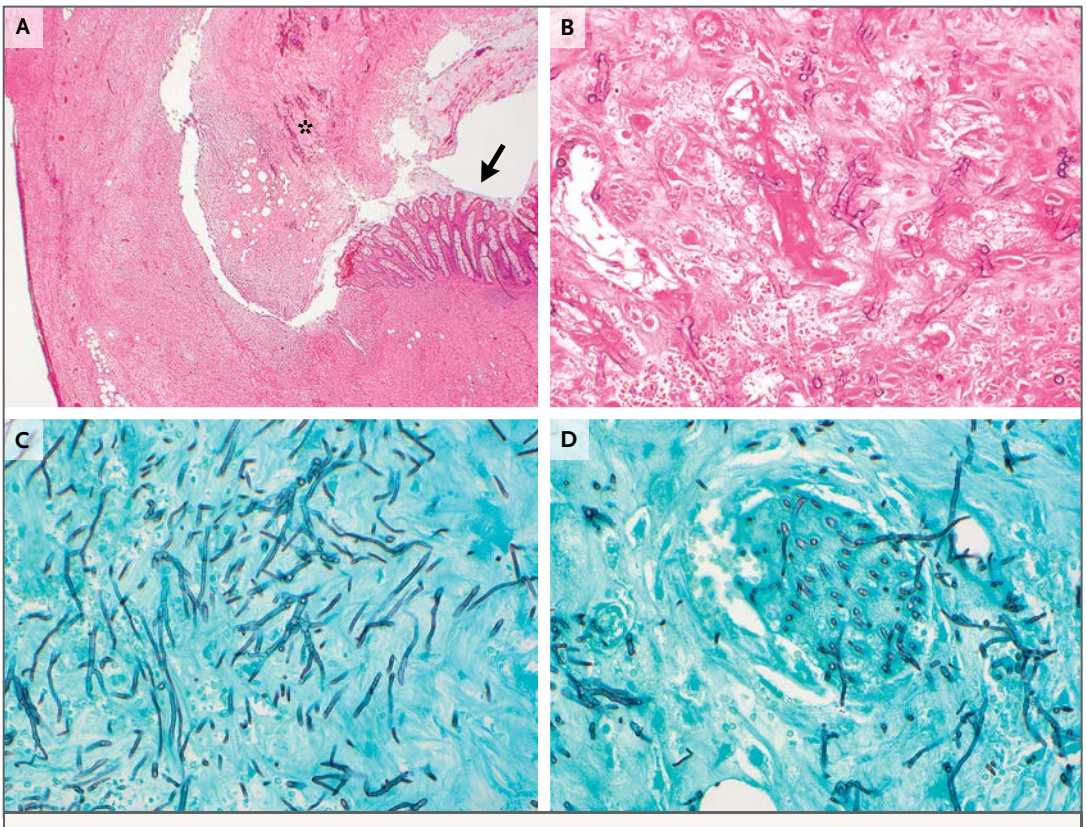

Figure 2. Appendectomy Specimen.

A cross section of the appendix shows a thickened and necrotic wall with loss of the normal architecture. Hematoxylin and eosin staining shows that the mucosa (Panel A, arrow) is mostly denuded and there is abundant necrotic material in the lumen (asterisk). At a higher magnification, the luminal contents consist of fungal hyphal forms with acute-angle branching admixed with fibrin (Panel B, hematoxylin and eosin). Grocott methenamine–silver nitrate staining of the luminal contents highlights the septated hyphal forms, which are of a uniform width and have true dichotomous branching with regular acute angles; these features are consistent with aspergillus (Panel C). Submucosal vessels show evidence of angioinvasion by fungal forms (Panel D, Grocott methenamine–silver nitrate).

the appendix. It is important to note that there was no evidence of leukemic infiltration or bacterial infection.

FOLLOW-UP

Dr. Tiffany Y. Lu (Medicine): Liposomal amphotericin B was administered as induction therapy (in addition to micafungin), but it was discontinued on the third day of therapy, when acute kidney injury developed; voriconazole was started. The patient received voriconazole and micafungin throughout the rest of his hospitalization.

At approximately the time of the surgery, hepatic veno-occlusive disease developed, which probably explains the hepatosplenomegaly that was evident on imaging, as well as the accumulation of ascites. Fortunately, the disease resolved spontaneously with supportive care. The patient's hospital course was further complicated by reactivation of CMV (the patient and the donor were both seropositive for CMV). He was discharged home on day 73 after transplantation, with a well-functioning end-ileostomy stoma and a plan to continue voriconazole therapy for 2 to 3 months.

Dr. Chen: Approximately 3 months after transplantation, examination of a bone marrow–biopsy specimen revealed morphologic and molecular remission and full donor chimerism. At 12 months after transplantation, the patient is now living at home and recovering from his complicated hospital course. He remains in complete remission. He has not had acute GVHD, but moderate chronic GVHD of the eyes, mouth, esophagus, and liver has developed. The symptoms have responded to low-dose glucocorticoid therapy, and he is preparing to undergo operative reanastomosis of his bowel. He has not had any further complications of the aspergillus infection.

ANATOMICAL DIAGNOSIS

Invasive aspergillosis of the appendix.

This case was presented at the Medical Case Conference.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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