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Short communication

Juvenile myelomonocytic leukemia in a child with Crohn disease

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Abstract Intestinal adenocarcinoma is a well-known complication of inflammatory bowel disease. Hematologic malignancies, most commonly lymphoma or acute myeloid leukemia, represent a much less well-recognized complication of these disorders; these typically occur in adults with ulcerative colitis. We report a fatal case of juvenile myelomonocytic leukemia associated with monosomy 7 in a young child with a clinical history of Crohn disease. Neither the leukemia nor the cytogenetic aberration has been previously reported in a patient with inflammatory bowel disease. The aggressive disease course emphasizes the need for proper recognition and further study of this unusual complication.

1. Introduction

Hematologic malignancies are an unusual complication of inflammatory bowel disease (IBD). We report a very unusual case of juvenile myelomonocytic leukemia (JMML) in a young child with a history of Crohn disease and discuss the poorly understood etiology of the association between leukemia and inflammatory bowel disease.

2. Case report

A 6-month-old boy was admitted due to poor weight gain since birth and diarrhea with frequent bloody stools. A complete blood count was done upon admission (Table 1). A reticulocyte count was normal. C-reactive protein was elevated at 2.0 mg/dL (reference range 0.70–1.00 mg/dL). Urinalysis was essentially normal. Bacterial cultures of blood, urine, and stool were negative, as was an assay for *Clostridium difficile* toxin.

Esophagogastric duodenoscopy and flexible sigmoidoscopy were performed the following day. Upper endoscopy showed nothing remarkable. Gastric biopsy showed no evidence of pathology, and duodenal biopsy showed blunting of villi with minimal chronic inflammation. Sigmoidoscopy showed an abnormal mucosa that was nodular, edematous, and erythematous. Colonic biopsy revealed chronic colitis.

Peripheral smear examination a few days later revealed leukoerythroblastosis, monocytosis, granulocytic reactive changes including toxic granulation and cytoplasmic vacuolization, normochromic–normocytic anemia, and thrombocytopenia. Splenomegaly was also noted on abdominal ultrasound. The white blood cell (WBC) count remained elevated, but decreased to 28.6 $\times 10^3/\mu L$, and the child was discharged.

Approximately one month later, the boy was readmitted for vomiting and continuing bloody stools. He had abdominal distention and splenomegaly, now palpable 6 cm below the costal margin. The complete blood count results were essentially the same as at the previous admission, with a WBC count of 57.3 $\times 10^3/\mu L$. A smear for fecal leukocytes was positive; blood cultures were negative. The child was started on intravenous corticosteroids. He again underwent sigmoidoscopy, which showed diffuse erythema of the rectal and sigmoid colonic mucosa. Biopsy revealed severe acute and chronic colitis with plasma cells at the crypt bases (Fig. 1), and empiric antibiotics were initiated.

The patient was readmitted several times over the following 6 months for various complaints including continuing bloody stools, oral mucosal ulcers, erythema nodosum of bilateral legs, and perirectal fistula. A gastric biopsy revealed active gastritis with pit abscesses (Fig. 2), whereupon the clinical diagnosis of Crohn disease was made. During this time, the WBC count rose significantly, with increasing monocytosis and left shift (Table 1; Fig. 3). Repeat bone marrow examination at this time revealed bone marrow hypercellularity of approximately 100%, with 6% blasts. Flow cytometric analysis now revealed a population of large mononuclear cells that were positive for CD13, CD14, CD34, CD38, CD64, myeloperoxidase, and HLA-DR,

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Table 1
Complete blood count findings

Test	At age = 6 mo	At age = 14 mo	Reference range
White blood cell count, $\times 10^3/\mu L$	55.5	81.7	6.0–17.0
Red blood cell count, $\times 10^3/\mu L$	3.72	3.65	3.70–5.30
Hemoglobin, g/dL	8.8	9.4	10.5–13.5
Hematocrit, %	27.9	31.2	33.0–39.0
Mean corpuscular volume, fL	74.9	85.2	70.0–86.0
Mean corpuscular hemoglobin, pg	23.9	25.8	23.0–31.0
Mean corpuscular hemoglobin concentration, g/dL	31.4	30.3	30.0–36.0
Platelet count, $\times 10^3/\mu L$	159	107	140–400
Absolute segmented neutrophil count, $\times 10^3/\mu L$	21.09	11.42	1.20–7.00
Absolute lymphocyte count, $\times 10^3/\mu L$	13.20	3.27	2.70–12.30
Absolute monocyte count, $\times 10^3/\mu L$	11.10	24.50	0.00–1.60
Absolute basophil count, $\times 10^3/\mu L$	0.56	0.00	0.00–0.35
Absolute band count, $\times 10^3/\mu L$	3.89	12.25	0.00–1.20
Absolute metamyelocyte count, $\times 10^3/\mu L$	0.56	9.80	0.00
Absolute myelocyte count, $\times 10^3/\mu L$	2.22	8.17	0.00
Absolute promyelocyte count, $\times 10^3/\mu L$	0.56	2.45	0.00
Absolute myeloblast count, $\times 10^3/\mu L$	2.22	8.17	0.00

consistent with a mixture of myeloblasts and monocytes. Cytogenetic analysis of the bone marrow aspirate revealed a karyotype of 45,XY,−7 (Fig. 4). Hemoglobin electrophoresis demonstrated 8.4% hemoglobin F, which is increased for the patient's age. A diagnosis of juvenile myelomonocytic leukemia was rendered, considering criteria established in 2001 by the World Health Organization (Appendix) [1].

Splenectomy was performed several months later, and the spleen was found to be positive for JMML. High-dose chemotherapy was initiated, followed by allogeneic peripheral blood stem cell transplantation. The post-transplant course was complicated by graft-vs.-host disease, but the patient ultimately died of leukemia at the age of two.

3. Discussion

Although the association of colorectal adenocarcinoma with inflammatory bowel disease has been recognized for decades, more recent attention has also been paid to an increased risk of extraintestinal malignant neoplasms in patients with IBD. Following the gastrointestinal tract, the most frequent cancers associated with IBD include hematologic, skin, breast, and genitourinary [2]. Among the hematologic malignancies, Hodgkin lymphoma and non-Hodgkin lymphoma seem to be the most numerous in patients with IBD, and these may be intestinal or extraintestinal [3].

Several studies have shown increased incidence of acute myeloid leukemias (AML) in patients with IBD [4,5]. Particular subtypes of AML most closely associated with IBD include acute promyelocytic leukemia, acute myelomonocytic leukemia, and acute monoblastic or monocytic leukemia, although in many series the subtype of AML is not specified [4–10]. Several authors have attempted to calculate the relative risk of AML in patients with ulcerative colitis and have consistently found that the risk is higher for ulcerative colitis than for Crohn disease. The relative risk for AML in ulcerative colitis has ranged from 2.0 to 8.7 in various studies, but the relative risk in Crohn disease is still uncertain, because of the relatively low numbers of

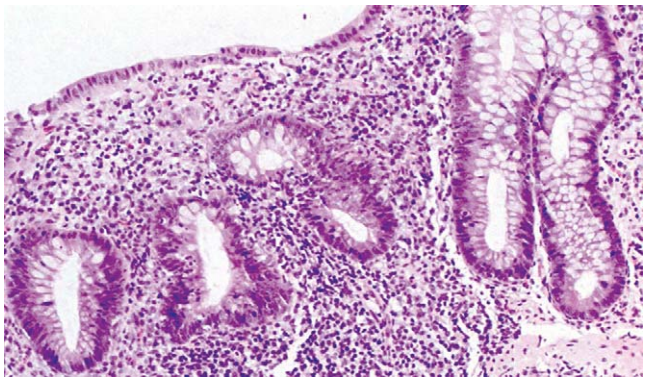

Fig. 1. Biopsy of descending colon demonstrating chronic colitis with branching crypts indicative of regenerative change (hematoxylin–eosin stain; 100×).

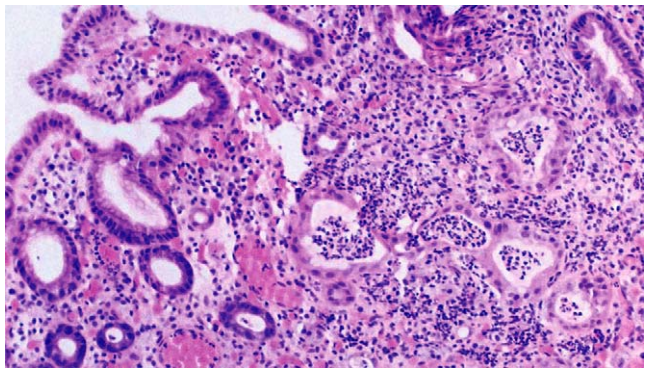

Fig. 2. Biopsy of stomach demonstrating acute gastritis with pit abscesses (hematoxylin–eosin stain; 100×).