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Inflammatory Bowel Disease and Leukemia

A Report of Seven Cases of Leukemia in Ulcerative Colitis and Crohn's Disease and Review of the Literature

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In a review of a large number of patients with inflammatory bowel disease, leukemia was observed in five patients with chronic ulcerative colitis and in two patients with Crohn's disease. In ulcerative colitis patients, there were three cases of acute myelocytic leukemia and one case each of acute lymphoblastic leukemia and chronic granulocytic leukemia. In Crohn's disease patients, there was one case each of chronic granulocytic leukemia and chronic lymphocytic leukemia associated with thrombocythemia. Sixteen other cases of leukemia have been reported to date in inflammatory bowel disease. All types of leukemia, but particularly acute myelocytic leukemia, have been described. There has been no single common feature as to type (whether ulcerative colitis or Crohn's disease), extent and course, or medical and surgical treatment of the bowel disease. The relative risk of leukemia in patients with ulcerative colitis was 5.3 [95% confidence interval 1.7 to 12.3 (P < 0.01)] and of acute myelocytic leukemia 11.4 [95% confidence interval 2.3 to 24.9 (P < 0.01)]. Our data on patients with Crohn's disease were not sufficient to assess the statistical significance of leukemia in this disease. This study suggests that there may be an increased risk of leukemia, particularly acute myelocytic leukemia, in ulcerative colitis. The causal relationship, if any, remains undetermined.

Although the association of intestinal carcinoma with inflammatory bowel disease is a well-recognized phenomenon (1–5), not much is known regarding the incidence of other malignancies in this disorder. The few studies devoted to this subject have generally concluded that the risk of extraintestinal neoplasms is not increased in inflammatory bowel disease (3–5), with the possible exception of carcinoma of the bile ducts (5, 6). Single cases of Kaposi's sarcoma (7), hepatoma (8), basal nevus syndrome (9), and thymoma (10) reported in ulcerative colitis probably represent nothing more than pure coincidence. Several cases of non-Hodgkin's and Hodgkin's lymphoma have been also reported with both ulcerative colitis and Crohn's disease, but the causal relationship is unknown (11–14).

In recent years, attention has been drawn to the possible increased incidence of leukemia in inflammatory bowel disease. In 1980, Fabry et al reported on five cases of acute myelocytic leukemia in ulcerative colitis (15). Cuttner, from the same hospital, in 1982 reported on six patients (including three previously reported by Fabry et al) with acute promyelocytic leukemia in ulcerative colitis (16). In the same year, Hanauer et al described two patients,

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one with ulcerative colitis and another with Crohn's ileocolitis, who developed acute myelocytic leukemia and acute myelomonocytic leukemia, respectively (17). In 1984, Cohn and Pearlstein reported on five cases, four of acute myelocytic leukemia (three in Crohn's disease and one in ulcerative colitis) and one of acute lymphoblastic leukemia in ulcerative colitis (18). Finally in 1985, Giron et al reported on a patient with Crohn's ileocolitis, treated with metronidazole, who developed acute lymphoblastic leukemia (19). The increased occurrence of leukemia in patients with inflammatory bowel disease raises the possibility of a causal relationship between the two conditions. Factors proposed to be influential are either bowel disease itself, perhaps through immunologic abnormalities, or drugs and repeated exposure to diagnostic radiation (15–19). However, the small number of cases reported so far does not permit such conclusion.

In a review of a large number of patients with inflammatory bowel disease, seen at the Cleveland Clinic between 1948 and 1984, we found seven patients who developed leukemia during the course of their bowel disease. Our aim in this paper is to report these cases and to review the literature of leukemia associated with ulcerative colitis and Crohn's disease.

MATERIALS AND METHODS

Medical records of 1204 cases of ulcerative colitis seen at the Cleveland Clinic between 1948 and 1984 and 3500 cases of Crohn's disease seen between 1950 and 1984 were reviewed. Five cases of leukemia in ulcerative colitis and two cases in Crohn's disease were identified.

To estimate the relative risk of leukemia in patients with ulcerative colitis, the number of person-years follow-up were calculated by five-year age groups of each sex. Length of the follow-up was determined from the date of onset of colitis up to the time of leukemia, death, or end of follow-up, whichever came first. Expected incidence rates were based upon the age- and sex-specific white rates from the Third National Cancer Survey (20). Applying these rates to the observed person-years of follow-up gave the expected number of leukemia; the ratio of observed to expected cases (or relative risk) was calculated and its statistical significance as well as a 95% confidence interval were determined by assuming that the observed number of cases had a Poisson distribution. A relative risk of 1 would indicate that the number of observed cases was the same as the number expected. Data regarding patient-years of follow-up was not available in Crohn's disease patients.

Leukemia in Ulcerative Colitis

Patient 1. A 42-year-old white man, with past history of discoid lupus of the skin, developed ulcerative proctosigmoiditis, which was treated with salicylazosulfapyridine (SAS) with marked improvement. Bowel disease was moderately active for 11 years and quiescent for the subsequent 20 years. At 73, during an annual check-up, he was found to be leukopenic. A preliminary bone marrow aspiration was nondiagnostic, but repeat aspiration two months later revealed acute myelocytic leukemia. No chemotherapy was given, and he died eight months later. No autopsy was performed.

Patient 2. A 66-year-old white man with a history of childhood eczema developed extensive ulcerative colitis which was treated with SAS and prednisone. The disease was moderately active for six years and relatively quiescent thereafter. At 80 years of age, acute myelocytic leukemia was diagnosed. No chromosomal abnormality was found. He was treated with cytosine arabinoside, 6-thioguanine, daunomycin, vincristine, and prednisone. The course was complicated by disseminated intravascular coagulation, upper gastrointestinal bleeding, and sepsis which resulted in his death. No autopsy was performed.

Patient 3. A 54-year-old white man presented with left-sided ulcerative colitis which was treated with SAS and prednisone. Medical treatment was unsatisfactory, and at 56 he underwent total proctocolectomy and ileostomy. He did well for six years, but at 62, acute myelocytic leukemia was diagnosed, and he died shortly thereafter. The latter information was obtained from his family physician.

Patient 4. A 9-year-old girl was seen at the Cleveland Clinic where a diagnosis of total colitis was confirmed. She had suffered from a protracted fungal skin infection at the age of 2, and at 5 years of age, total ulcerative colitis had developed which was treated with ACTH and prednisone. The bowel disease remained active and, when she was seen at the Cleveland Clinic, SAS was added to her therapeutic regimen. She also received a course of Diodoquin and carbarsone, but was subsequently lost to follow-up. She died of acute lymphocytic leukemia at the age of 17. This information was obtained from her family physician.

Patient 5. A 21-year-old white man, with past history of duodenal ulcer, developed total ulcerative colitis, which was treated with SAS and prednisone. His disease was protracted and complicated by polyarthritis, spondylitis, thrombophlebitis, nephrolithiasis, and sclerosing cholangitis and was never completely controlled by medical treatment. The patient underwent subtotal colectomy and ileorectal anastomosis at 36 years of age. At age 37, Graves' disease was discovered and treated with radioactive iodine (15 mCi) which resulted in hypothyroidism. At 47, chronic granulocytic leukemia was diagnosed and treated with busulfan which resulted in total remission. At 49, the patient died in respiratory failure and septic shock. At autopsy, no evidence of leukemia was found. Significant findings included bilateral *Pneumocystis carinii* and cytomegalovirus pneumonitis, diffuse fibrosing alveolitis (probably busulfan-induced), sclerosing cholangitis, liver abscess, and extensive pancreatic necrosis.

Leukemia in Crohn's Disease

Patient 6. A 71-year-old white female with a history of Crohn's disease since 1954; right hemicolectomy, resection of the terminal ileum and ileotransverse colostomy in 1967; and recurrent ileitis since 1969, had been controlled on SAS until June 1976. The family history was significant because a brother and a sister had died of gastric carcinoma and another sister of breast carcinoma. A third sister was alive with a rectal carcinoma. She was admitted to the Cleveland Clinic Hospital because of bone pain, fever, melena, hemoptysis, and a markedly elevated white blood cell count. At the examination, no hepatosplenomegaly was present. The hematocrit 38%, platelet count 350,000, and white cell count 147,000 with many blasts. (WBC was normal in 1972 and 13,300 with rare metamyelocyte in 1974.) The leukocyte alkaline phosphatase was low, and a bone marrow aspiration showed changes of chronic granulocytic leukemia. Investigation of the gastrointestinal tract showed hiatus hernia and Crohn's disease of the ileum. The patient received treatment with SAS, isoniazid, and busulfan which resulted in partial improvement of the blood picture. Bleeding duodenal ulcer occurred in October 1977, when the WBC was 43,000 and the platelet count 1,018,000. A blast crisis was diagnosed in December 1977 and was treated with vincristine, hydroxyurea, 6-mercaptopurine, and prednisone. The subsequent course was one of progressive deterioration, ending in the patient's death in September 1978. No autopsy was performed.

Patient 7. A 48-year-old white male with Crohn's disease of the colon and the anus, since May 1965, underwent total proctocolectomy and ileostomy elsewhere in March 1966, because of persistent perianal disease following hemorrhoidectomy and rectal fistulotomy. Postoperatively, he did well except for two episodes of small bowel obstruction in 1972 and 1975 which were treated conservatively. A routine blood count, during the last episode, showed an increased number of WBC between 18,000 and 23,800 with an absolute lymphocytosis and occasional atypical lymphocytes. Other laboratory tests included: hematocrit 42%, platelet count 460,000, uric acid 10.5 mg/100 ml, IgG 900 mg/100 ml (normal 1380 ± 255), B-cell 86% (normal 21.8 ± 6.1%), T-cell 9.4% (normal 75.2 ± 5.3%) and SIg 18.2% (normal 14.7 ± 4.3%).

The patient was discharged with a diagnosis of chronic lymphocytic leukemia and no treatment. He did well until June 1983, when a platelet count of 1,000,000 was found. He denied any bleeding, bruisability, or gastrointestinal symptoms. The spleen was felt 2 cm below the costal border. Other findings included: hematocrit 34%; WBC 28,800 (55% lymphocyts); platelet count 1,740,000; serum acid phosphatase 1.9 ng/ml (normal up to 1.7); CEA < 2.3; negative Coomb's test; normal clotting, partial thromboplastin, thrombin, prothrombin, and bleeding times, and normal plasma fibrinogen. The platelet function tests revealed normal clot retraction, platelet adhesiveness of 55% (normal 80–100%), biphasic platelet aggregation with ADP, adrenalin, and arachidonic acid, and normal aggregation with collagen. The platelet factor 3 was at the lower limit of normal, 26 sec (normal 25–35). The bone marrow aspirate showed L–E ratio of 3.9:1, hypercellularity, and moderate increase in megakaryocytes with giant atypical forms and platelet clumps. The lymphocytes did not appear to be increased, and the picture was interpreted as to show a myeloproliferative disorder. However, the bone marrow biopsy showed a mixed pattern of myeloid hyperplasia with numerous atypical megakaryocytes, and a low level of diffuse infiltration by the small lymphocytes with several lymphoid nodules composed of the same lymphocytes. Because of marked thrombocytosis, the patient was treated with, and partially responded to, hydroxyurea. The platelet count was 974,000 and WBC 19,600 when last done in December 1983. The patient is being followed by his family physician and when last contacted in July 1984, he was doing well and continuing his medication.

DISCUSSION

Including our 7 patients, we have information regarding 23 patients with inflammatory bowel disease who developed leukemia during the course of their bowel disease (Table 1 and 2). Of these 23 patients, 17 developed acute nonlymphocytic leukemia (including five cases of acute promyelocytic and one of acute myelomonocytic leukemia), three acute lymphoblastic leukemia, two chronic granulocytic leukemia, and one chronic lymphocytic leukemia and thrombocythemia. The incidence of leukemia in our patients with ulcerative colitis is 0.40% (0.25% if considering acute leukemia only). In the series of Fabry and colleagues (15), five of 400 patients with ulcerative colitis developed leukemia, for an incidence of 1.25%.

Based on 18,883 person-years of follow-up (Table 3), we would have expected 0.95 cases of leukemia in our ulcerative colitis patients. However, we observed five patients with leukemia in our series. Therefore, there is a fivefold increase risk (the relative risk, 5.3) of developing leukemia in ulcerative colitis patients as compared to the general population. The 95% confidence interval on the relative risk of leukemia was 1.7 to 12.3, and this increased risk was statistically significant ($P < 0.01$). Furthermore, for acute myelocytic leukemia, there was also an increased risk in our colitis patients, the relative risk being 11.4 with 95% confidence interval of 2.3 to 24.9, also statistically significant ($P < 0.01$). It should be noted that the expected incidence rates of leukemia that were used were based upon U.S. data of 1969–1971 (20), whereas our patients were observed from 1948 to 1982. Therefore, the expected rates used were at about the midpoint of the observed follow-up period. However, these rates may not accurately

TABLE 1. CLINICAL DATA OF 16 PATIENTS WITH CHRONIC ULCERATIVE COLITIS WHO DEVELOPED LEUKEMIA

Reference	*Pt.*	*Sex*	*Colitis (age)*	*Onset of leukemia (age)*	*Diagnosis of CUC to leukemia (yr)*	*Quiescent period CUC (yr)*	*Extent of bowel disease*	*SAS**	*Steroid*	*Type of leukemia*
Fabry et al, 1980 (15)	1	M	19	22	3	3	Left-sided	+	+	Acute promyelocytic leukemia, M_3†
	2	F	14	51	37	25	Total (subtotal colectomy 29 yr and AP resection 25 yr before leukemia)	−	+	Acute promyelocytic leukemia, M_3†
	3	F	49	50	1	?1	To hepatic flexure	−	+	Acute myelocytic leukemia, M_1†
	4	F	37	57	20	?20	Left-sided	+	+	Acute myelocytic leukemia
	5	M	37	47	10	(2 yr postop)	Total (ileoproctostomy for cancer of colon 2 yr before leukemia)	−	−	Acute promyelocytic leukemia, M_3†
Cuttner, 1982 (16)	6	M	64	74	10	?	Ulcerative colitis	+	−	Acute promyelocytic leukemia, M_3†
	7	M	15	20	5	?	Ulcerative colitis (proctocolectomy and ileostomy)	−	−	Acute promyelocytic leukemia, M_3†
	8	M	33	43	10	?	Ulcerative colitis (proctocolectomy and ileostomy)	−	−	Acute promyelocytic leukemia, M_3†
Hanauer et al, 1982 (17)	9	F	29	53	24	10	Ulcerative colitis; diffuse (later ulcerative proctitis)	+	+	Acute myelocytic leukemia, M_5†
Cohn and Pearlstein, 1984 (18)	10	F	19	20	1	1/2	Proctosigmoiditis	+	−	Acute lymphoblastic leukemia
	11	M	9	24	15	1	Ulcerative colitis (subtotal colectomy, 7 yr before leukemia)	+	+	Acute myelocytic leukemia
Mir Madjlessi et al, present series, 1985	12	M	42	73	31	20	Left-sided	+	−	Acute myelocytic leukemia
	13	M	66	79	13	6	Total	+	+	Acute myelocytic leukemia, M_4†
	14	M	54	62	8	(6 yr postop)	Left-sided (proctocolectomy and ileostomy 6 yr before leukemia) Totals	+	+	Acute myelocytic leukemia
	15	F	5	17	12	?		+	+	Acute lymphocytic leukemia
	16	M	21	46	25	Active	Total (subtotal colectomy and ileorectal anastomosis 10 yr before leukemia)	+	+	Chronic granulocytic leukemia: ph+

*SAS = Salicylazasulfapyridine.
†M = French–American–British classification.

reflect the incidence rates over the colitis patients' follow-up period. Unfortunately, we had no similar data in patients with Crohn's disease to assess the statistical significance of leukemia in this disease.

Leukemia appeared with both ulcerative colitis and Crohn's disease, although the ratio is 16:7 in favor of ulcerative colitis. Of the 16 patients with ulcerative colitis, 10 had total or extensive colitis and six proctosigmoiditis or left-sided colitis. Of the seven patients with Crohn's disease, two had ileocolitis, and three had terminal ileitis, and two colitis.

There were 13 males and 10 females. The mean age of onset of bowel disease was 30.7 years (range 5–66 years). The duration of bowel disease prior to the diagnosis of leukemia averaged 13.8 years, with a range of 1–44 years. The mean age at time of diagnosis of leukemia was 46.3 years (range 19–82

TABLE 2. CLINICAL DATA OF 7 PATIENTS WITH CROHN'S DISEASE WHO DEVELOPED LEUKEMIA

Reference	*Pt.*	*Sex*	*Crohn's disease (age)*	*Onset of leukemia (age)*	*Diagnosis of Crohn's disease to leukemia (yr)*	*Quiescent period of Crohn's (yr)*	*Extent of bowel disease*	*SAS**	*Steroid*	*Type of leukemia*
Hanauer et al, 1982 (17)	1	F	4	54	7	3	Terminal ileum (right hemicolectomy 6 yr and 6 cm ileal resection at recurrence 2 yr before leukemia)	+	−	Acute myelomonocytic leukemia, M_4†
Cohn et al, 1984 (18)	2	M	15	19	4	?4	Ileum, colon	−	+	Acute myelocytic leukemia
	3	F	?38	?82	44	6	Regional enteritis (ileotransverse colonostomy 44 yr before leukemia)	−	+	Acute myelocytic leukemia
	4	M	18	19	1	1	Terminal ileum	−	+	Acute myelocytic leukemia
Giron et al, 1985 (19)	5	F	20	23	3½	2/12	Terminal ileum colon	−	−	Acute lymphoblastic leukemia
Mir Madjlessi et al, present series, 1985	6	F	49	71	22	(Recurrent postop)	Terminal ileum, sigmoid colon (resection of ileum, right hemicolectomy and ileocolic anastomosis 9 years before leukemia)	+	−	Chronic granulocytic leukemia
	7	M	48	58	10	(Postcolectomy)	Colon, rectum, anus (total proctocolectomy and ileostomy 9 years before leukemia)	−	−	Chronic lymphocytic leukemia; thrombocythemia

*SAS = Salicylazasulfapyridine.
†M = French–American–British classification.

years). However, the three patients with acute lymphocytic leukemia were much younger (17, 19, and 23 years, respectively). The course of bowel disease prior to the development of leukemia varied. In the majority, the disease was relatively mild or totally inactive from one year to as long as 20 years prior to the diagnosis of leukemia. However, an occasional patient had continuously active bowel disease. In 11 patients, leukemia appeared after variable periods of time following total or subtotal colectomy or bypass surgery.

As to the treatment of bowel disease, most patients had received either prednisone and/or salicylazosulfapyridine, but a few received neither drug. No patient received immunosuppressives. Although cases of acute leukemia have been described in patients receiving immunosuppressives with or without corticosteroids, no instance of acute leukemia as an effect of SAS or prednisone alone has been documented (21). The carcinogenic effects of metronidazole have been questioned (19). The majority of patients had been exposed to variable amounts of radiation for diagnostic purposes, but a few had received minimal or no radiation exposure.

TABLE 3. OBSERVED PERSON-YEARS OF FOLLOW UP IN 1204 PATIENTS WITH ULCERATIVE COLITIS BY AGE AND SEX

Age	*Males*	*Females*	*M + F*
<5	29	10	39
5–9	80	81	161
10–14	269	264	533
15–19	703	594	1297
20–24	1106	954	2060
25–29	1283	1119	2402
30–34	1250	1097	2347
35–39	1113	1012	2125
40–44	989	837	1826
45–49	903	695	1598
50–54	772	598	1370
55–59	639	481	1120
60–64	531	371	902
65–69	361	265	626
70–74	155	138	293
75–79	54	59	113
80–84	22	28	50
85+	7	14	21
Total	10,266	8,617	18,883

In two patients, skin dose was estimated at 98.7 and 94 rads, and the bone marrow dose at 30 and 28 rads, respectively (17). The patients of Fabry and colleagues received an estimated 1800–3000 g-rads (15). In our series, the estimated bone marrow dose was 10, 5, 1.5, and 1 rads for patients 1, 5, 2, and 3, respectively.

In man, the role of radiation in producing leukemia has been demonstrated beyond doubt in atomic bomb survivors (22) and in patients undergoing radiotherapy (23–25). However, the leukemogenic effect of diagnostic exposure is controversial. Although several authors have expressed concern about the leukemogenic effects of diagnostic exposure (23, 24, 26), Linos et al (27) found no increased relative risk of leukemia in the diagnostic bone marrow range of 0–300 rads. Furthermore, women receiving radiotherapy for cervical cancer do not develop an excess leukemia despite large radiation exposure (28). Given the chronicity and often complicated course of inflammatory bowel disease, it is likely that most patients had been exposed to an excessive amount of radiation. Thus, the relationship between radiation exposure and leukemia in inflammatory bowel disease requires further investigation.

In three of our patients with ulcerative colitis, there was a history of diseases which are linked to disturbed immunity (discoid lupus, eczema, and Graves' disease), and one patient with Crohn's disease (case 6) had strong family history for malignancies. In addition, our case 4 suffered a prolonged fungal skin lesion at 2 years of age which may indicate the presence of some cellular immune defect. There is no information as to immune abnormalities in other series. One of the patients described by Fabry et al (15) (No. 5 of their table) had cancer of the colon as a complication of ulcerative colitis which was resected; leukemia developed two years later. Although we found no reports of increased incidence of leukemia with other bowel diseases, including colon cancer, cases of acute myelogenous leukemia in familial polyposis coli and colon carcinoma have been reported (29), indicating the possible influence of genetic factors. Since leukemia may result from the interaction of several factors including host susceptibility, chemical or physical injury to chromosomes, and presumably incorporation of genetic material of viral origin into the susceptible host (30), inflammatory bowel disease either directly through its putative defects of immunity (31, 32) or indirectly through the effects of diagnostic radiation may provide the injuring factor. However, the exact role of these factors cannot be determined with the available information.

The development of chronic lymphocytic leukemia in our case 7 may have been coincidental. Of interest was the late superimposition of thrombocytosis in this patient. Although, thrombocytosis has been described in inflammatory bowel disease (33, 34), and highest platelet count recorded was 1,300,000 and the duration of thrombocytosis less than three months (33). Thrombocytosis is more frequent with Crohn's disease of the colon and is regarded as a sign of activity of the bowel disease. In our patient, the bowel disease was relatively inactive and, although no thrombohemorrhagic complications were observed, the findings in bone marrow biopsy, the high values of platelet count, and the long duration of thrombocytosis raise the possibility of a primary thrombocythemia. Thrombocythemia is considered as a member of myeloproliferative disorders along with chronic granulocytic leukemia, polycythemia vera, and myeloid metaplasia. Although chronic lymphocytic leukemia may be associated with a second neoplasia (35), to our knowledge the association of chronic lymphocytic leukemia with thrombocythemia has not been previously reported.

The prognosis of leukemia in inflammatory bowel disease is poor. Despite the use of various chemotherapeutic regimens, only exceptionally has a patient with acute leukemia survived for more than one year from the time of diagnosis (19).

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