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CONCURRENT DEVELOPMENT OF CROHN DISEASE AND MYELODYSPLASTIC SYNDROME IN A CHILD: Case Report and Literature Review

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□ *A small number of cases of Crohn disease associated with myelodysplastic syndromes or leukemia have been reported in adults in the last 25 years in the English-language medical literature. The authors report a case of a 9-year-old boy who developed Crohn disease and myelodysplastic syndrome concurrently. Analysis of his bone marrow showed a chromosome 20 abnormality. Although chromosome 20 abnormalities have been reported in a minority of these patients, the significance of this association remains unclear at the present time.*

Keywords Crohn diseas, leukemia, myelodysplastic syndromes, pancytopenia

An association between Crohn disease (CD) and myelodysplastic syndromes (MDS) or leukemia has been suggested on the basis of concomitant findings of these disorders in a total of 24 cases reported in the English-language medical literature [1–11]. Interestingly, all patients reported were adults (mean age of 68 years old, range 28–83). Eng et al. [1], the first to report such a condition in 4 patients, found clonal abnormalities of chromosome 20 in 3 cases. Although the association of chromosome 20 abnormalities and MDS has been described [12], whether such abnormalities account for the association between MDS and CD is unknown. Moreover, since Eng's

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publication, all subsequent reports have failed to demonstrate chromosome 20 abnormalities in patients with CD and MDS [2–11].

Herein, we report a case of concurrent development of CD and MDS in a child with a chromosome 20 abnormality.

CASE REPORT

A 9-year-old boy presented with a 1-week history of high fever (39–40°C) associated with a 1-month history of anorexia, nausea, and intermittent diffuse colicky abdominal pain. He had experienced episodes of diarrhea and a 10% weight loss over the last month. On physical examination a right lower quadrant tender mass was palpable. Laboratory data revealed normocytic anemia (hemoglobin level, 85 g/L; mean corpuscular volume, 89 u^3), leukopenia (leukocyte count, 2.6×10^9/L), and thrombocytopenia (platelet count, 110×10^9/L). Reticulocyte count was 1.6%. Erythrocyte sedimentation rate was 90 mm/h. He had negative serology for infectious diseases, negative stool cultures, and normal rheumatologic markers.

A colonoscopy was performed because of a clinical suspicion for inflammatory bowel disease and revealed segmental aphthous ulcerations and longitudinal fissures throughout the cecum and terminal ileum with typical histopathologic features of CD. Prednisolone (1 mg/kg/day) and 5-ASA (1 g/day) were started. With a worsening clinical examination and radiographic evidence of pneumatosis, he was taken to the operating room for a right colectomy. Histological examination of the specimen confirmed the diagnosis of CD. Postoperatively, the patient continued to be febrile and was pancytopenic with normal folate and vitamin B_{12} serum levels. He required blood transfusions for his anemia. Fanconi's anemia was ruled out by a negative diepoxybutane (DEB) test. Hemoglobin electrophoresis showed an increased fetal hemoglobin (5.6%). Bone marrow aspiration at 2 weeks after initiation of steroids and 5-ASA revealed trilineage dysplasia with a moderate hypocellularity, and 2% blasts. A peripheral blood smear showed no blasts at that time. Cytogenetic analysis of the bone marrow revealed chromosome 20 abnormalities (monosomy), chromosome 1 derivative duplication, and chromosome 8 trisomy in 8 of a total of 9 cells analyzed. These abnormalities were confirmed by fluorescence in situ hybridization (FISH). The patient had significant improvement of trilineage cell counts after administration of granulocyte-colony stimulating factor (G-CSF) (5 μg/kg) daily for 2 weeks and was discharged in satisfactory condition.

Over the next 2 years, G-CSF treatments were given at 6, 12, and 18 months for recurrent pancytopenia. Bone marrow biopsy prior to starting each additional G-CSF treatment showed dyshematopoietic abnormalities similar to the first bone marrow examination but with 3, 3, and 17% blasts, respectively. In addition to increased bone marrow blasts, the peripheral

blood smear showed 7% blasts, suggestive of a diagnosis of refractory anemia with excess blasts in transformation (RAEB-2). At 22 months the patient progressed to an acute myeloid leukemia, requiring treatment with chlorodeoxyadenosine and citarabine (one cycle). A bone marrow aspiration performed 2 weeks after completion of treatment showed complete remission. As of this manuscript (at 24 months follow-up), the patient's disease remains in remission.

DISCUSSION

MDS is a bone marrow stem-cell disorder characterized primarily by peripheral cytopenias and hypocellular dysplastic bone marrow, although occasionally it can be found to be associated with hypercellular or normocellular bone marrow. Based on the French–American–British (FAB) classification [13], MDS includes refractory anemia (type I), refractory anemia with ringed sideroblasts (type II), chronic myelomonocytic leukemia (type III), refractory anemia with excess blasts (type IV), and refractory anemia with excess blasts in transformation (type V). More recently, the classification of the myeloid neoplasms had been refined by the World Health Organization (WHO)[14], utilizing not only morphologic findings but also all available information, including genetic, immunophenotypic, biologic, and clinical features, to define specific disease entities. Because of the lack of specific data in the previous literature reports, we find it necessary to use the original FAB classification. We have included in Table 1, however, our suggested categorization of these case reports according to the WHO classification.

A total of 21 cases of CD associated with one of five different types of MDS described above have been reported in the indexed English-language medical literature [1–9]. In addition, 3 cases of CD in association with other leukemias apart from the FAB classification have been reported [10, 11].

A pathophysiologic link between CD and MDS has been suggested on the basis of a common immunologic impairment. It is unknown whether underlying immunologic alterations account for the development of these diseases or whether the additional immunosuppressive status caused by one disease predisposes to the development of the other. In 1992, Eng et al. [1] were the first to find chromosome 20 abnormalities in the bone marrow cells of 3 of the 4 patients with coexistent MDS and CD. Unlike the frequent occurrence of clonal chromosomal abnormalities in the bone marrow cells of patients with MDS, karyotypic abnormalities in intestinal cells have not been seen in patients with CD. The chromosome 20 abnormality is described in 5% of primary MDS in the elderly population [15]. However, since Eng's publication, all other reports of patients with coexisting CD and MSD or CD and leukemia have failed to report that abnormality (except ours) (see Table 1) [2–11].

TABLE 1 Characteristics of the 25 Cases of CD and MDS/Leukemia (Including the Present Report)

N	Ref.	Gender/ Age at diagnosis	First diagnosis	Type of MDS or leukemia FAB classification)	Suggested WHO classification	Chromosome 20 abnormality	Location of CD	Associated conditions	CD treatment	MDS specific treatment
1	Eng et al. [1]	F/83	MDS	II	RARS	Yes	Colon	None	5-ASA	Not reported
2	Eng et al. [1]	F/78	MDS	II	RARS	Yes	Ileum, colon	None	5-ASA	Not reported
3	Eng et al. [1]	M/56	MDS	I	RA	No	Colon	None	Steroids	Not reported
4	Eng et al. [1]	F/70	MDS	II	RARS	Yes	Colon	None	Steroids	Not reported
5	Yoshida et al. [2]	M/67	Simultaneous	I	RA	No	Ileum	Pyoderma gangrenous	Steroids	No specific therapy
6	Sahay et al. [3]	M/71	Simultaneous	IV	RAEB-1	Not done	Colon	Pyoderma gangrenous	Steroids/5-ASA	No specific therapy
7	Sahay et al. [3]	M/66	CD	I	RA	No	Colon	Immunocomplex glomeru-lonephritis	Steroids/5-ASA	No specific therapy
8	Castellote et al. [4]	M/82	CD	II	RARS	Not done	Colon	None	Steroids	No specific therapy
9	Boberg et al. [5]	M/70	CD	I	RA	No	Colon	None	Steroids	No specific therapy
10	Bosch et al. [6]	M/82	Simultaneous	V	RAEB-2	No	Ileum, colon	None	Steroids/5-ASA	No specific therapy
11	Bosch et al. [6]	M/68	Simultaneous	IV	RAEB-1	No	Ileum, colon	None	Steroids/5-ASA	No specific therapy
12	Bosch et al. [6]	F/73	Simultaneous	IV	RAEB-1	No	Ileum	None	Steroids/5-ASA	No specific therapy
13	Hebbar et al. [7]	M/52	Simultaneous	I	RA	No	Ileum	None	Steroids	No specific therapy
14	Hebbar et al. [7]	F/39	Simultaneous	I	RA	No	Ileum	None	Steroids/5-ASA	Danazol
15	Hebbar et al. [7]	M/62	CD	I	RA	No	Ileum	None	Steroids/5-ASA	No specific therapy
16	Hebbar et al. [7]	F/75	Simultaneous	II	RARS	Not done	Colon, anus	None	Steroids	No specific therapy
17	Hebbar et al. [7]	M/61	Simultaneous	IV	RAEB-1	Not done	Colon, rectum	None	5-ASA	Danazol
18	Hebbar et al. [7]	F/80	CD	V	RAEB-2	Not done	Colon, anus	None	Steroids	Etoposide
19	Halme et al. [7]	F/48	CD	IV	RAEB-1	No	Ileum, colon	None	Steroids/5-ASA/ surgery	Daunorubicin, cytosine arabinoside, thioguanine

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20	Halme et al. [8]	F/65	CD	IV	RAEB-1	Not done	Ileum, colon, rectum	None	Surgery, 5-ASA	Etoposide, mercaptopurine, methotrexate
21	Tani et al. [9]	M/28	Simultaneous	V	RAEB-2	No	Ileum, colon	None	5-ASA/surgery	Mercaptopurine, daunomycin, behenoyl ara C
22	Mir Madjlessi et al. [10]	F/71	CD	CGL	CML	Not done	Ileum, colon	None	Surgery, SAS	Vincristine, mercaptopurine, hydroxyurea, steroid
23	Mir Madjlessi et al. [10]	M/58	CD	CLLT	CML	Not done	Ileum, colon, rectum, anus	None	Surgery	Hydroxyurea
24	Pomeroy et al. [11]	F/76	CD	CML	CML	No	Ileum	None	Steroids/5-ASA/ surgery	Etoposide
25	Present case	M/9	Simultaneous	V	RAEB-2	Yes	Ileum, colon	None	Steroids/5-ASA/ surgery	G-CSF

Note. 5-ASA, 5-aminosalicylic acid; CGL, chronic granulocytic leukemia; CLLT, chronic lymphocytic leukemia; thrombocythemia; CML, chronic myelomonocytic leukemia.

MDS usually develop in patients over 60 years of age. CD is typically diagnosed in younger persons, with a suggested second peak after 60 years. In this case, curiously, both conditions were present in a 9-year-old boy, while all other reported cases of coexistence of both conditions involved older patients (mean age 68 years; range 28–83). Gumruk et al. [16] described one case of pyoderma gangrenosum in a 11-month-old girl with MDS who had a normal cytogenetic study of her bone marrow and did not have intestinal abnormalities.

Regarding the temporal relationship between presentation of MDS/leukemia and CD, these disorders were simultaneously diagnosed in 10 other patients in addition to ours (cases 5, 6, 10–14, 16, 17, 21, 25) [2, 3, 6, 7, 9]. CD clearly antedated (at least one year) MDS/leukemia in 10 patients (cases 7–9, 15, 18–20, 22–24) [3–5, 7, 8, 11, 17], whereas MDS antedated those of CD in the remaining 4 patients (1–4) [1]. All 24 previous cases reported had CD involvement of either colon and/or ileum. As for the treatment of CD, most patients received steroids and/or 5-ASA. Although cases of acute leukemia have been described in patients receiving immunosuppressives with or without corticosteroids, acute leukemia as a direct effect of either 5-ASA or prednisone has not been documented.

In the majority of cases, CD was clinically managed. Four patients required an operation because of failure of medical treatment (cases 19–23). Specific therapy for MDS/leukemia varied among the 20 patients for whom that kind of information was reported. Eleven patients received no specific therapy. However, 4 patients with MDS (2 with FAB type IV, and 2 with FAB type V), and 3 with non-FAB leukemia required antineoplastic medications. Two other patients received synthetic testosterone (Danazol) (Table 1).

Due to the fact that most of these disorders affect mainly the elderly, aggressive treatment is difficult in most cases, leaving only expectant therapy with supportive measures. In the present report, despite progression to myeloid leukemia, the young age of onset may have contributed to a good initial response to the chemotherapeutic agents. However, the relative short follow-up period after treatment of myeloid leukemia does not allow us to make further statements regarding outcome.

In conclusion, although the coexistence of MDS and CD has been exclusively reported in adults and elderly, the diagnosis of MDS should also be considered in children with CD and persistent peripheral cytopenia. The significance of an association between chromosome 20 abnormalities with the development of concomitant conditions (MDS and CD) remains unclear.

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