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13. ABSTRACT (Maximum 200 words)

Antemortem diagnosis of gastrointestinal involvement by non-Hodgkin's lymphoma occurs in approximately 10% of cases. Malabsorption secondary to small bowel involvement by lymphoma is distinctly uncommon and iron deficiency is rarely the sole manifestation of malabsorption. We report a patient with the unusual feature of iron deficiency anemia compounded by selective malabsorption of iron because of occult lymphomatous (diffuse large cell) involvement of the small intestine. Both upper gastrointestinal series with small bowel follow-through and CT scan demonstrated lymphomatous involvement of the duodenum and proximal jejunum by a retroperitoneal mass. An oral iron loading absorption test was consistent with malabsorption of iron. After two cycles of systemic chemotherapy, the retroperitoneal mass had resolved and the iron loading test normalized.

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Iron Malabsorption in a Patient with Large Cell Lymphoma Involving the Duodenum

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Iron malabsorption compounded the anemia in a patient with diffuse large cell lymphoma involving the small intestine. Both upper gastrointestinal series with small bowel follow-through and computerized tomographic scan demonstrated lymphomatous involvement of the duodenum and proximal jejunum by a retroperitoneal mass. An oral iron-loading absorption test was consistent with malabsorption of iron. After two cycles of systemic chemotherapy, the retroperitoneal mass resolved and the iron loading test normalized.

INTRODUCTION

Antemortem diagnosis of gastrointestinal involvement by non-Hodgkin's lymphoma occurs in approximately 10% of cases (1). The gastrointestinal tract is the most commonly involved extranodal organ. Gastrointestinal tract involvement occurs most often with diffuse large cell (DLCL) histology. Sites of involvement in decreasing order of frequency include: the stomach, small intestine, ileocecal area, and large intestine. Presenting complaints include abdominal pain, anorexia, weight loss malaise, nausea, vomiting, and weakness. Up to 15% of patients may have evidence of gastrointestinal hemorrhage. The incidence of anemia, usually attributable to gastrointestinal blood loss, is approximately 30% (2-4).

Malabsorption secondary to small bowel involvement by lymphoma is distinctly uncommon, but has been described in both Hodgkin's and non-Hodgkin's lymphomas (5-7). The presenting symptoms mimic those of celiac disease and include weight loss, usually with steatorrhea and variable peripheral edema. The diagnosis of malabsorption is made by the demonstration of increased fecal fat excretion and impaired D-xylose absorption.

Iron deficiency is rarely the sole manifestation of malabsorption. Documented cases of iron malabsorp-

tion in celiac disease were reversible by the institution of a gluten-free diet (8, 9). To our knowledge, malabsorption of iron due to lymphomatous involvement of the small bowel has not been previously reported. We report a case with the unusual feature of iron deficiency anemia due in part to selective malabsorption of iron because of occult lymphomatous involvement of the small intestine. Iron malabsorption and the normalization of iron absorption were documented before and after systemic chemotherapy, respectively.

CASE REPORT

In February 1989, a healthy 19-yr-old white male, with no previous medical problems, complained of weakness and several days of progressive dyspnea on exertion, at another hospital. One month later, a CBC showed a Hb of 5.3 g/dl; Hct, 18.3%; MCV, 61 fl; MCH, 24.1 pg; and reticulocyte count, 2.1%. The WBC and platelet count were normal. Iron studies revealed a serum iron of 1 µg/dl; TIBC, 71 µg/dl; saturation, 1%; and serum ferritin, 5 ng/ml. Stools were heme occult negative on several tests. He was placed on supplemental FeSO₄, 325 mg po qd. The following week, a CBC revealed a Hb of 6.1 g/dl; Hct, 21.3%; MCV, 63 fl; MCH, 24.7 pg; and reticulocyte count, 6.4%. A chest radiograph in March showed questionable left hilar adenopathy. In April, he received an RBC transfusion with the Hb improving to 7.9 g/dl; HCT, 27.4%; MCV, 79 fl; MCH, 29.1 pg; and reticulocyte count, 4%. There was no further improvement in the hemoglobin. The chest radiograph in May demonstrated an anterior mediastinal mass, and a computerized tomographic (CT) scan showed a 5 × 5 cm superior mediastinal mass with extension to the left hilum. Bronchoscopy was normal. The patient had a median sternotomy where the mass appeared to arise from the thymus, infiltrating the left lung and adherent to the chest wall. The entire mass and the thymus were removed. The histologic diagnosis was diffuse large cell lymphoma.

The patient was referred to Walter Reed in June 1989. He denied fevers, sweats, weight loss, melena,

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hematochezia, nausea, vomiting, diarrhea, symptoms of steatorrhea, or abdominal pain. Physical examination was remarkable only for conjunctival and mucosal pallor and a well-healed median sternotomy scar. The abdominal examination was normal. The testes revealed no masses. There was no adenopathy, and the stools were heme-occult negative on multiple examinations. The chest radiograph showed no residual mass. The WBC, differential, and platelet count were normal; the Hb was 6.4 g/dl; Hct, 21%; MCV, 60 fl; MCH 24.3 pg; and reticulocyte count, 0.7%. Erythrocytes were hypochromic and microcytic.

The serum iron was 37 $\mu\text{g}/\text{dl}$; TIBC, 311 $\mu\text{g}/\text{dl}$; saturation, 10%; and serum ferritin, 4 ng/ml—all unchanged in 2 months. Despite continued supplementation with 195 mg elemental iron per day (325 mg FeSO₄ tablets po tid), the anemia and reticulocyte counts failed to improve. The serum total protein and albumin were 6.7 and 4.0 g/dl, respectively. Serum electrolytes, BUN, creatinine, LDH, alkaline phosphatase, ALT, AST, bilirubin, calcium, and phosphate were normal. The Coombs test was negative. A bone marrow biopsy was normal except for absent iron stores; there was no evidence of lymphomatous involvement of the bone marrow. Esophagogastroduodenoscopy revealed mild esophagitis without evidence of bleeding. Biopsies showed normal villous architecture in the duodenum without evidence of submucosal infiltrates. Mild fibrosis with edema was noted in the gastric antrum. A small bowel follow-through (Fig. 1) showed a dilated fixed loop of duodenum and proximal jejunum with thickened irregular folds and displacement of adjacent bowel loops. A D-xylose absorption test was normal. A CT scan of the abdomen and pelvis revealed a large retroperitoneal mass (Fig. 2).

Because of the poor response to prolonged (4 months)



FIG. 1. Barium study of the small bowel. The small bowel is displaced inferiorly. The arrows indicate involvement of the duodenum and proximal jejunum.

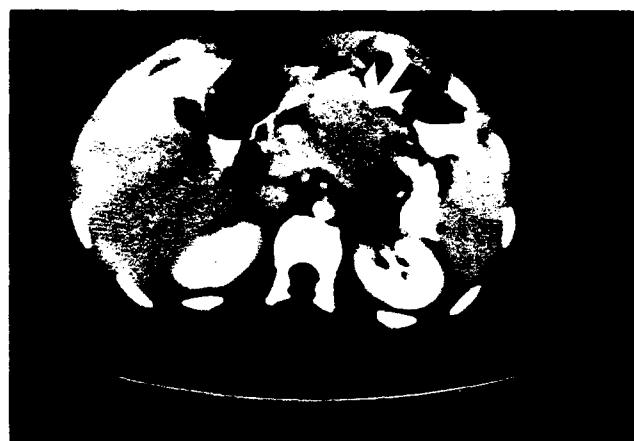


FIG. 2. CT scan of the abdomen. The retroperitoneal mass involving the small bowel is indicated by the arrow.

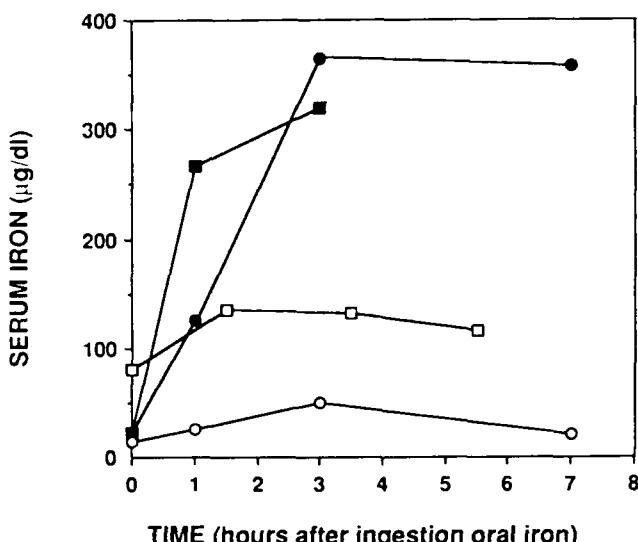


FIG. 3. Results of iron-loading test. Serum iron levels are plotted as a function of time after ingestion of 200 mg elemental iron. Two controls (unfilled squares, normal volunteer; filled squares, iron deficiency from chronic blood loss), and a patient with large cell lymphoma involving the small bowel before (unfilled circles) and after (filled circles) chemotherapy are included.

oral iron therapy, an iron-loading test was performed on this patient, a patient with iron deficiency from chronic menstrual blood loss, and a normal control (Fig. 3). The method is a modification of that previously reported (10–12). The patient and two control subjects were fasted for 12 h. At time zero, a CBC, reticulocyte count, serum iron, TIBC, and ferritin were drawn. Two hundred milligrams of elemental iron were then ingested as 8 ml of a 125 mg/ml FeSO₄ solution containing 25 mg/ml elemental iron. (HI-TECH Pharmacal Co., Inc., Amityville, NY). At one, 3 and 7 h after ingestion of oral iron, blood was drawn for serum iron. The patient and control subjects resumed eating after the 3-h sample was obtained. Informed consent was obtained from the patient and both control subjects before initiation of the iron-loading test. A greater than

120 µg/dl rise in the serum iron within the peak period (usually 2–3 h) is expected in patients who are iron deficient and have normal bowel function (11). Malabsorption is associated with little or no increase in serum iron. Patients who are iron replete and have normal bowel function demonstrate a mild increase in the serum iron.

The patient with iron deficiency from menses had a dramatic response to oral iron loading, with a 300 µg/dl rise in serum iron at 3 h. In contrast, the patient with iron deficiency and lymphomatous involvement of the duodenum failed to respond to oral iron loading. The expected mild increase in the normal control was observed. After two cycles of cytoxan, adriamycin, vin-cristine, and prednisone chemotherapy (13), the CT scan showed almost complete resolution of the retroperitoneal mass. The iron-loading test was repeated and demonstrated resolution of iron malabsorption with a response equal to that of the patient with iron deficiency from chronic blood loss (Fig. 3).

DISCUSSION

The vast majority of hypochromic anemias associated with the non-Hodgkin's lymphomas usually result from gastrointestinal hemorrhage (14). Defects in the utilization of absorbed iron, as demonstrated by the failure of parenteral iron to improve the hemoglobin concentration, may also complicate anemia associated with lymphoma (15).

This case demonstrates the unusual feature of iron malabsorption. The failure of the patient's anemia to correct on a prolonged course (4 months) of oral iron supplementation prior to chemotherapy suggested malabsorption as a component of iron deficiency. Figure 3 demonstrates markedly diminished iron absorption in our patient prior to chemotherapy, in contrast to the avid uptake in the patient with iron deficiency due to blood loss. It was estimated that our patient had at least a 2-g iron deficit (16) and, most probably, suffered from a chronic hemorrhage due to gastrointestinal involvement with lymphoma. This was subsequently compounded by malabsorption secondary to proximal small bowel involvement with lymphoma, as demonstrated by a failure to respond to enteral iron supplementation.

Iron is maximally absorbed in the duodenum and proximal jejunum (17). Although the duodenal biopsy in our patient was normal, this may reflect a sampling error with regard to lymphomatous involvement, because both the small bowel follow-through and the CT scan clearly identified involvement of the duodenum and the proximal jejunum. The absence of a history of malabsorption and the presence of normal villi suggest that celiac disease was not a precursor to the development of the lymphoma in this patient.

Iron deficiency anemia is a component of generalized

malabsorption (18–20) from several potential etiologies (e.g., celiac disease, pancreatic insufficiency); however, the utilization of iron once incorporated is normal. Celiac disease has uncommonly been associated with the selective malabsorption of iron (19). In these cases, iron malabsorption was the sole indicator of celiac disease and reversed with a gluten-free diet (8, 9) or prednisone (21). Steatorrhea may be a manifestation of small bowel lymphoma (22), and has occasionally responded to a gluten-free diet (2) after an initial jejunal mucosal biopsy consistent with celiac disease, only to return in the presence of lymphoma, suggesting a relationship of celiac disease and the subsequent non-Hodgkin's lymphoma involving the gastrointestinal tract. Iron deficiency can impair iron absorption through an unknown mechanism (23), however, the malabsorption is generally not refractory to enteral iron supplementation (23, 24), and occurs in children rather than adults. Patient noncompliance is a consideration in the lack of response to iron therapy; however, this cannot explain the inability to absorb iron during an iron-loading test.

Selective malabsorption states likely reflect severe focal abnormalities in the mucosa normally responsible for the absorption. Generalized malabsorption is a consequence of diffuse mucosal involvement (25, 26). The enhanced response to iron loading in our patient after two courses of systemic chemotherapy strongly suggests that the initial malabsorption of iron was indeed a consequence of local or focal lymphomatous involvement of the gastrointestinal tract (Fig. 3), not secondary to iron deficiency. The association of near complete resolution of the retroperitoneal mass as documented by CT scan with improved iron absorption by an oral loading test supports this conclusion. If iron deficiency was the primary cause of the malabsorption, then the observed response to oral iron loading after chemotherapy would not be expected.

The case we report demonstrates iron deficiency anemia compounded by selective malabsorption from local proximal small bowel involvement of lymphoma. The observed malabsorption corrected after systemic chemotherapy. We suggest that in patients with iron deficiency anemia and malignancy who fail to respond to enteral iron supplementation, involvement of the duodenum and proximal jejunum should be suspected.

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