

A Cause of Recurrent Iron Deficiency Anemia: An Atypical Presentation of Crohn's Disease: Case Report

Tekrarlayan Demir Eksikliği Anemisinin Bir Nedeni: Crohn Hastalığının Atipik Bir Prezantasyonu

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ABSTRACT A 17-year-old male patient with recurrent iron deficiency anemia for 3-4 years presented to our hospital for advanced medical evaluation. The physical examination of the patient was normal other than skin and mucosal paleness with no clinical findings suggestive of Crohn's disease, such as diarrhea, abdominal pain, and growth retardation. The cause of the iron deficiency anemia could not be explained with hematological, serological, and conventional endoscopic (upper and lower gastrointestinal endoscopy) studies. Oral and parenteral treatments with iron resulted in transient improvement. A capsule endoscopy was performed to detect a possible small bowel lesion. Endoscopic and pathologic findings were in accordance with Crohn's disease. The ulcerated area of the small bowel was resected due to a recurrent iron deficiency anemia after a year of medical treatment with Mesalamine/Pentasa and Budesonide. The patient had no complaints afterwards without a recurrent iron deficiency anemia. This case indicates that, whenever the cause of an iron deficiency anemia is not clear with hematological and serological studies and with conventional endoscopy (upper and lower gastrointestinal endoscopy), lesions of the small bowel should also be investigated.

Key Words: Anemia, iron-deficiency; Crohn's disease

ÖZET Yaklaşık 3-4 yıldan beri tekrarlayan demir eksikliği anemisi olan on yedi yaşındaki erkek hasta ileri incelemeler yapılmak üzere hastanemize başvurdu. Başta ishal, karın ağrısı ve gelişme geriliği olmak üzere Crohn hastalığını düşündürecek hiçbir klinik bulgusu olmayan hastanın cilt ve mukoza solukluğu dışında anormal fizik inceleme bulgusu yoktu. Demir eksikliği anemisinin nedeni, hematolojik, serolojik ve geleneksel endoskopik (alt ve üst barsak endoskopisi) çalışmalarla açıklanamadı. Uygulanan oral ve parenteral demir tedavilerine geçici yanıt sağlandı. Olası bir ince bağırsak lezyonunu saptamak için kapsül endoskopisi yapıldı. Endoskopik ve patolojik bulgular, Crohn hastalığı ile uyumlu bulundu. Bir yıl süre ile uygulanan tıbbi tedavi (Mesalazin/Pentasa, Budesonid)'ye rağmen tekrarlayan demir eksikliği anemisi devam eden hastanın ülserli bölgesi cerrahi olarak çıkarıldı. Hastanın, daha sonra herhangi bir şikayeti olmadı; demir eksikliği anemisi tekrarlamadı. Bu olgu, demir eksikliği anemisinin nedeni, hematolojik, serolojik, geleneksel endoskopik (üst ve alt barsak endoskopisi) çalışmalarla açıklanamayan olgularda, ince bağırsak lezyonlarının da araştırılması gerektiğine dikkat çekmektedir.

Anahtar Kelimeler: Anemi, demir eksikliği; Crohn hastalığı

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Iron deficiency is the most frequently seen nutritional deficiency in the world, as well as in Turkey, and it is an important health issue in infants, adolescents, pregnant women, and individuals of low socioeconomic status, especially in developing countries.¹⁻⁴ Etiology is variable; however, it develops most frequently due to nutritional deficiencies, absorption de-

fects, blood losses, inadequate presentation of iron to erythroid precursors (Atransferrinemia) or the abnormal intracellular transport of iron (DMT1 mutations). It presents with pallor, cardiovascular and neurological symptoms and epithelial changes such as, pica, spoon nail, glossitis and angular stomatitis in children.^{5,6}

Whenever the cause of iron deficiency anemia (IDA) is not clear with hematological and serological studies or conventional endoscopy (upper and lower gastrointestinal endoscopy), lesions of the small bowel should also be investigated. Therefore, capsule endoscopy (CE) plays a major role in the diagnosis of IDA with an unexplained cause.⁷⁻⁹ Anemia is a frequent complication of Crohn's disease (CD). The inflammatory disease process itself might also affect erythropoiesis, however, deficiencies of iron, folic acid, and vitamin B12 are accused of being the underlying causes of anemia.^{10,11}

Capsule endoscopy is a new and noninvasive method of investigating the small bowel. The indications of CE in children have not extensively been evaluated.¹² In patients with no definitive diagnosis reached by conventional methods, lesions compatible with CD can be detected by small bowel capsule endoscopy (SBCE) in almost one third of the patients with symptoms extremely compatible with CD.¹³

Herein, a case with no clinical (diarrhea, abdominal pain, or growth retardation) and laboratory (serological) findings other than IDA, which transiently responds to oral (po)/intravenous (IV) iron treatment and sometimes requires erythrocyte suspension transfusions, whose IDA was attributed to CD, is presented.

CASE REPORT

A 17-year-old male patient with recurrent anemia complaints presented to our hospital for advanced medical evaluation. In his medical history it was disclosed that he had episodes of deep pallor every 3-4 years, and he had received oral iron treatment with a clinical benefit from the study for only the first one or two months. He was told that his blood values had reached normal values; however, he de-

veloped pallor again with decreased blood values. The patient's medical history revealed that he ate an ample amount of meat and he consumed food of every kind and he did not have any known gastrointestinal disease (diarrhea and abdominal pain) and he did not use any drugs. His and his family's past medical histories were unremarkable. He had a body temperature of 36 °C, blood pressure of 120/80 mmHg, a peak heart beat of 76 beats/min, a body weight of 65 kg (75-90%), and a height of 180 cm (>97%). His physical examination was otherwise normal besides pallor in skin and mucosae.

His laboratory values were as follows: Hemoglobin (Hb): 66.8 g/L; hematocrit level (Hct): 21.6%; WBC, 7.470 x10⁹/L; platelet, 302x10⁹/L; reticulocyte: 0.474 % (Normal range: 0.5-2.5%); mean erythrocyte volume (MCV): 62.8fl (Normal range: 76-96); mean erythrocyte hemoglobin: 20.1 pg (Normal range: 27-32.2); mean erythrocyte hemoglobin concentration: 22.3 g/dL (Normal range: 32.2-36.5); red cell distribution width: 19.5% (Normal range: 11.7-14.6). red cells were hypochromic and microcytic in the peripheral smear with mild poikilocytosis and anisocytosis and no target cells. Serum iron (SI) level was 10 ug/dl; serum iron binding capacity: 454 ug/dl; transferrin saturation: 2.2%; ferritin: 2.1 ng/ml (Normal range: 22-322) (Table 1); Vitamin B12: 311 pg/mL (Normal range: 189-883); folic acid: 6.26 ng/mL (Normal range: 1.8-12.5); blood type: AB RH (+); direct Coombs (-); and the indirect Coombs test was negative. Urea breath (C-14) test for *Helicobacter pylori* was positive. He had a normal abdominal ultrasonography and a negative stool occult blood test. Parenteral iron (iron III hydroxide sucrose) was administered in a dose calculated from the formula "normal Hb-Patient's Hb/100 x blood volume (ml) x 3.4 x 1.5". This dose was administered three times a week, and no more than 100 mg, in fractions, intravenously in 100 ml of 0.9% NaCl during 30 minutes.

In addition, he was given triple therapy consisting of amoxicillin, metronidazole, and lansaprazole for *Helicobacter pylori* positivity. His gastro-duodenoscopy and colonoscopy findings were normal. There was no sign for a Meckel diverticulum

TABLE 1: The patient's hematologic response to oral and parenteral iron therapy and status after surgical treatment.

	Hb g/L (13.5-17.5)	Hct % (40-53)	MCV fl (77-87)	SI ug/dl (45-160)	SIBC ug/dl (110-370)	TS% (18-46)	Ferritin ng/ml (22-322)
Pretreatment	66.8	21.6	62.8	10	454	2.2	2.1
The end of the parenteral iron treatment	110						
Ten days after the cessation of the treatment	88.9						
30 th oral iron therapy	114						
One month after oral iron therapy	72	23.1	63.3	15	466	3.2	11.1
15 days after parenteral iron treatment	68.4	21.9	63.2	11	453	2.4	4.3
3 months after surgical therapy	12.1	37.5	76.3	36	341	10.5	4.6
6 months after surgical therapy	13.7	43.1	79.9	50	301	16.6	27

Hb: Hemoglobin; Hct: Hematocrit; Ret: Reticulocyte; MCV: Mean corpuscular volume; SI: Serum iron; SIBC: Serum iron binding capacity; TS: transferrin saturation.

in the scintigraphic scans. His Hb level at the end of the parenteral iron treatment was 110 g/L, while it was 88.9 g/L ten days after the cessation of the treatment. Oral iron preparation was started (as iron sulphate 2 x 100 mg elementary iron). Hb levels were 114 g/L on the 30th day of the iron treatment. At the same time, the breath urea test for *Helicobacter pylori* was negative. This level of Hb was assessed as inadequate, thus the diet was reorganized again (red meat). In the meantime, the stool guaiac tests were +, -, +, and - in four different times after three days of diet with no iron consumption. Colonoscopy was normal. The Hb value of 114 g/L was found to decrease to 72 g/L. SI was 15 ug/dl, SIBC was 466 ug/dl, TS was 3.2%, ferritin was 11.1 ng/ml (Normal range: 22-322), and the reticulocyte count was 0.374%. Hypochromia, anisocytosis, and poikilocytosis were identified in the peripheral smear. Parenteral iron treatment (iron III hydroxide sucrose) was administered again in the same way. After 15 days, Hb was 68.4 g/L, SD was 11 ug/dL, SIBC was 453 ug/dL, TS was 2.4%, ferritin was 4.3ng/ml, reticulocyte count was 0.472%. Hypochromia, anisocytosis, and poikilocytosis were identified in the peripheral smear. Tissue transglutaminase IgG and IgA and anti-gliadin IgA and IgG levels were negative with negative hemoglobin electrophoresis, haptoglobin, and serum zinc levels. Iron absorption test was normal.

The second colonoscopy was normal. In the second gastroduodenoscopy, the enteroscope was

advanced 5 cm in the terminal ileum and could not be advanced further due to anatomic and technical reasons. The mucosa of the ileum was found to be generally spared with a hyperemic and edematous surrounding mucosa with one aphthous ulcer in a diameter of 1 mm. Thus these findings were found to be in accordance with CD. He received medical therapy (Mesalamine/Pentasa 500 mg, 3x2 for 2 months) for two months. Since the medical therapy was not beneficial, capsule endoscopy was administered. Duodenum and proximal jejunum were normal. Many exudative ulcers, starting from the distal jejunum to distal ileum, with normal mucosa in between the ulcers, were observed. The ulcers were observed to be bigger and deeper with the advancement of the capsule to the distal parts of ileum, and they were more prone to bleeding. Thus these findings were found to be in accordance with CD. The pathological examination of the biopsy taken from the terminal ileum was found to be compatible with terminal ileitis (CD). Therefore, a drug treatment with Mesalamine/Pentasa (500 mg, 3x2 for 8 months and Budesonide 3x1 for 6 months) was administered for almost a year.

His anemia was not corrected in spite of this therapy at the end of the first year of treatment for CD. Other alternative treatments like azathioprine were not considered depending on the atypical clinical progress of the disease, recurrent deep anemia which affected the social life of the patient considerably, the family's expectations of a definite

solution, and the fact that child and adolescent cases are known to be already more resistant to medical treatment compared to adults.¹⁶ Therefore, a small bowel resection of 20 cm, at a distance of 110 cm from the Treitz ligament was performed. He had no recurrent complaints and anemia after the ulcerated small bowel was excised. He is being follow-up on without any problems by the gastroenterology department and our department. Informed consent was obtained from the patient.”

DISCUSSION

Iron deficiency is accepted as the most frequent cause of anemia in all age groups, and in babies and children, especially between 6-24 months. Since iron is extensively used in the human organism, all the systems are affected in its deficiency, resulting in many systemic symptoms and clinical findings. The clinical findings of IDA in children show differences compared to the adults with more prominent effects, other than anemia. It is more commonly observed during periods of rapid growth in children, with the type of nutrition and socioeconomic status and past infections contributing to its occurrence.

Although a significant period of time has elapsed after the definition of IDA as a social health problem, a major drop in its incidence has not been provided yet. It is estimated that over 500 million individuals have IDA around the world.⁵ According to the World Health Organization's (WHO) data, IDA is seen in 36% and 8% in the developing and developed countries, respectively.^{7,10} Iron deficiency and IDA are seen more frequently in Turkey compared to developed countries. This rate in childhood age groups has been reported to be between 15.2% and 62.5% in various studies.^{14,15}

The causes of IDA are evaluated under four main chapters. Inadequacy of iron absorption (use of antacids, fitate, tannate, and other metals), inadequacy of iron storages (gastrointestinal, vaginal, and pulmonary blood losses, inflammation/infection, and absorption defects in the bowel [TM-PRSS6]), inadequacy of presentation of iron the erythroid precursors (Atransferrinemia) and DMT1

mutations.⁶ The most important cause of IDA is an inadequacy of iron storage. Gastrointestinal blood losses (epistaxis, gastritis, ulcer, Meckel diverticulum, milk-induced enteropathy, parasitosis, varices, tumors or polyps, inflammatory bowel diseases, arteriovenous malformations, colonic diverticula, and hemorrhoids) are the most common among an inadequacy of iron storage.⁶

The possibility of occurrence of CD in children and adolescents with inflammatory bowel disease (IBD) has been reported to be much more frequent compared to ulcerative colitis (UC), and a tendency for the disease was identified to be more severe and generalized in children and adolescents compared to adults.¹⁶ Anemia is a frequent complication of CD. Iron, folic acid, and vitamin B12 deficiencies have been blamed for the underlying causes of anemia in various ways. However, iron deficiency is the most common cause of anemia in CD.^{10,11} The frequency of anemia was reported to be 70% in children, 42% in adolescents, and 40% in adults. In general, iron deficiency was found to be more frequent in children (88%) and adolescents (83%), compared to adults (55%).¹⁷ The presence of a deep IDA in our patient, with the absence of folic acid and vitamin B12 deficiencies, is compatible with the literature findings.

Chronic inflammatory bowel diseases (CIBD) are a group of diseases with a clinical picture of intermittent acute episodes and remission periods with an unknown etiology. UC, CD, and “indeterminate colitis”, which is an intermediate type of colitis, are the main diseases in this group. CIBD is seen in both genders in equal frequency. These diseases can be also seen in children, and especially in the adolescent age group. It has a peak incidence between 15 and 25 years of age.¹⁷ The mean age at diagnosis is reported to be 11.8 years in United Kingdom; children less than 10 years of age comprised 13% of those cases. Incidence of the disease varies according to the geographical region and ethnic group.¹⁸ Although the incidence of UC has been stable, the incidence of CD has increased in the last decade. The current incidence of CD is 3-4:100,000.¹⁷ CD has a clinical picture of colicky abdominal pain around the umbilicus which

increases after meals, in addition to diarrhea, fever, and weight loss. Symptoms of CD differ according to the location of the lesions. The most frequently seen type is the type with ileocolitis (52%). The ileum and small bowel are involved together in 20% of the cases. Diarrhea and weight loss are more prominent in cases with diffuse small bowel involvement. The onset of the disease is generally insidious; however, the onset occasionally might be a with clinical picture resembling appendicitis before puberty. Findings of gastrointestinal involvement might be absent in some cases.¹⁷ No clinical and laboratory findings such as diarrhea, abdominal pain and growth retardation other than a deep IDA anemia were present in our case. The patient's serum albumin level started to decrease after he began to have abdominal pain later in the course of the disease. Both abdominal pain and hypoalbuminemia resolved after bowel resection. The age of our patient (17 years, now 19 years) is compatible with the current literature findings; however, it was interesting that no findings typical for CD such as diarrhea, abdominal pain, and growth retardation were present.

Dense mononuclear cell infiltration and accompanying non-caseating granulomatous lesions can occur anywhere in the gastrointestinal system, including the mouth, esophagus, and stomach. The ileocecal region is the most common site of involvement in all age groups. In some cases, the small bowel or colon is involved diffusely. All the intestinal layers are involved in the inflammation at the location of the lesion, the bowel wall is thickened, the lumen is narrowed, and strictures may develop. Lesions are distributed asymmetrically. Healthy and diseased mucosae form a "cobblestone" appearance.¹⁷ In our patient, the capsule endoscopy demonstrated many ulcers with exudate starting from the distal jejunum until the distal ileum with completely normal mucosa in between the lesions. The ulcers at the more distal regions of the small bowel were larger, deeper, and more prone to bleeding, and these findings were found to be compatible with CD. This endoscopic diagnosis was confirmed with pathological examinations.

Fifty percent of the patients with CD become refractory to corticosteroids. They might also become refractory to other kinds of medical treatment (immunosuppressives). Surgical interventions are only recommended in CD with ulcers localized at only the colon or only the small bowel, in cases that are unresponsive to medical treatment, in bowel perforation, in partially symptomatic fibrous adhesions of the bowel, and in cases with gastrointestinal bleeding resistant to medical treatment.¹⁸ Our case was unresponsive to medical treatment for one year. Child and adolescent cases are known to be more resistant to medical treatment compared to adults.¹⁶ The surgical approach was the excision of a segment of small bowel of 20 cm length, 110 cm distal to the Treitz ligament. We selected the surgical treatment approach for our patient and were successful in this treatment.

Reticulocyte count might increase as a result of massive bleeding that might cause acute tissue hypoxia. Intermittent occult blood test positivity in our patient demonstrated that he was having intermittent gastrointestinal bleeding. However, a reticulocyte count increase was never defined. This might be related to the intensity of the gastrointestinal bleeding; the bleeding may not have been severe enough to result in tissue hypoxia, and the intermittent nature of iron deficiency might prevent reticulocyte count increase.

Our case with a normal iron absorption test had no prior inflammatory signs. However, the patient developed hypoalbuminemia during the late phases of the disease and he was diagnosed with CD after recurrent deep IDA had developed. The anemia did not recur after the surgical excision of the bleeding segment of the patient without who was partially unresponsive to medical treatment. Therefore, we believed that continuous occult bleeding occurred from this region of the lesion in this patient with IDA.

This case that had a recurrent IDA with obscure etiology unexplained by serologic, hematological and gastrointestinal system endoscopic (upper and lower gastrointestinal) studies, and was diagnosed by capsule endoscopy and biopsy with CD, which transiently responded to medical ther-

apy. The recurrent IDA resolved only after surgical treatment is reported here to point to the fact that in cases with recurrent iron deficiency, the anemia itself could be an atypical sign of CD, and in cases with recurrent IDA, CD should be thought of as a

differential diagnosis even if symptoms such as diarrhea, abdominal pain and growth retardation are absent.

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