Celiac disease presenting as iron-deficiency anemia in northern India

S VARMA, P MALHOTRA, R KOCHHAR,* N VARMA,** S KUMARI, S JAIN

Departments of Internal Medicine, *Gastroenterology and **Hematology, Post Graduate Institute of Medical Education and Research, Chandigarh 160 012

Background: Adult celiac disease is infrequent in India. Iron-deficiency anemia as its presenting manifestation is still rarer. Methods: We investigated patients with refractory iron-deficiency anemia attending the hematology clinic of a tertiary-care hospital for celiac disease. The diagnosis of celiac disease was based on histology, serology and response to treatment. Results: Of 19 patients with refractory iron-deficiency anemia seen from April 1998 to March 2000, 11 were diagnosed to have celiac disease. Four of these had abnormal D-xylene test and 3 had fat malabsorption. All 11 patients responded to gluten-free diet with improvement in hematological parameters. Conclusion: Patients with refractory iron-deficiency anemia of unknown cause should be investigated for subclinical celiac disease. [Indian J Gastroenterol 2001;20:234-236]

Key words: Malabsorption syndrome

The most common causes of nutritional anemia due to iron deficiency in India are inadequate intake, low bioavailability of dietary iron and parasitic infestation. Iron-deficiency anemia (IDA) is the most common extraintestinal manifestation of celiac disease (CD). Extraintestinal manifestations are now increasingly recognized as the mode of presentation of subclinical adult CD. Iron deficiency in CD may result from impaired iron absorption, occult intestinal blood loss from damaged mucosa, and/or iron loss because of rapid turnover of epithelial cells.

CD is not uncommon among children in northern India, constituting approximately 25% of all cases of malabsorption syndrome in this age group. There is paucity of data on adult CD in India. One such study from Delhi reported 7 adult patients with malabsorption who had celiac disease. However, in five of these the disease had started in childhood. As the sole manifestation of CD has only recently been reported in a case report. We present here our preliminary results among patients who presented with refractory IDA and who were found to have CD.

Methods

Patients presenting with refractory IDA (hemoglobin <11 g/dL) to the Adult Hematology Clinic of our institute were screened for CD. IDA was diagnosed by the presence of microcytosis and hypochromia on peripheral blood film and low serum ferritin or low bone marrow iron stores, low serum iron and high total iron-binding capacity. IDA was considered refractory if the hemoglobin did not normalize after adequate oral iron supplementation for 2 months and if other causes of IDA like paroxysmal nocturnal hemoglobinuria, worm infestation and gastrointestinal tumors had been excluded.

All patients were screened for gastrointestinal bleeding by stool occult blood examination. Stool was also examined for presence of ova and cysts. Proctosigmoidoscopy was done to look for the presence of hemorrhoids. The patients were questioned about bleeding from other sites (e.g., epistaxis, gum bleed, hematuria, menorrhagia). Upper gastrointestinal endoscopy was done to look for any obvious cause of chronic or recurrent bleeding. Hemoglobin electrophoresis and tests for paroxysmal nocturnal hemoglobinuria were carried out wherever indicated.

The diagnosis of CD was based on histological examination of duodenal biopsy obtained at endoscopic examination, serology (presence of anti-gliadin and/or anti-endomysial antibodies) and clinical response to gluten-free diet, with at least two of these three parameters required for diagnosis. Anti-gliadin antibody (IgA and IgG) and anti-endomysial antibody were estimated by ELISA and immunofluorescence technique, respectively. Seventy-two-hour fecal fat estimation after challenge with 75 g/day of fat and measurement of urinary excretion of D-xylene after 5 grams of oral dose were done in patients suspected to have malabsorption.

Results

Of 62 new patients with anemia referred between April 1998 and March 2000, 35 had IDA. Of these, 19 did not have any identifiable cause for IDA and did not respond to oral iron therapy. These 19 patients were investigated for CD and 11 (aged 15-52 years; 7 women) were diagnosed to have CD. The mean hemoglobin level at presentation was 6.9 g/dL and serum ferritin was low in all patients (Table). Duration of symptoms ranged from 2 months to 10 years (median 4 years). Patients were not interrogated for history of wheat intolerance.

Ten of 11 patients with CD had positive serology.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD) [range]</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ferritin (ng/mL)</td>
<td>3.8 (1.4) [2.5-5.0]</td>
<td>10-400</td>
</tr>
<tr>
<td>TIBC (mg/dL)</td>
<td>413.6 (111.8) [229-572]</td>
<td>150-400</td>
</tr>
<tr>
<td>Serum iron (µg/dL)</td>
<td>39.7 (20.8) [13-74]</td>
<td>60-150</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>6.98 (1.96) [4.5-10.7]</td>
<td>Women ≥12</td>
</tr>
<tr>
<td>Baseline</td>
<td>6.98 (1.96) [4.5-10.7]</td>
<td>Men ≥13</td>
</tr>
<tr>
<td>Anti-gliadin antibody (mg/L)</td>
<td>218.6 (225) [15.6-490]</td>
<td>&lt;14.0</td>
</tr>
</tbody>
</table>

TIBC = total iron-binding capacity

One patient with negative serology had total villous atrophy and abnormally low D-xylose excretion. Her hemoglobin was 6.0 g/dL and her hemoglobin increased after gluten withdrawal. Duodenal histology in six patients showed total villous atrophy whereas 4 had subtotal villous atrophy along with crypt hyperplasia and lymphocytic infiltration of lamina propria. One patient refused endoscopy. Response to gluten-free diet was documented in all the 11 cases, with improvement in hematological parameters on follow up of 8 to 12 weeks.

Of the six patients in whom malabsorption was suspected because of weight loss or failure to gain weight, 2 patients had simultaneous abnormality in D-xylose urinary excretion (urinary excretion of <20% of oral dose in 5 hours) and 72 hours' fecal fat excretion (>7 g fat/day), 2 patients had only abnormal D-xylose excretion, 1 patient had abnormality in 72 hours' fecal fat excretion, and in one patient both tests were normal. Steatorrhea (>7 g/day) was seen in three patients. None of these six patients had diarrhea (≥3 stools per day). The four patients with abnormal tests gained weight on gluten withdrawal within 8-12 weeks.

Two of 11 patients with CD had associated autoimmune disease. The first, a 20-year man, had insulin-dependent diabetes mellitus and cirrhosis of liver. The second, a 35-year-old woman, developed hypothyroidism on follow up. One man (reported previously) had an esophageal web in the post-cricoid region.

Discussion

The number of patients diagnosed to have adult CD has increased in recent years because of increased awareness of the various manifestations of this disease. The classical symptoms of malabsorption (chronic diarrhea, abdominal distension and weight loss) are now considered to be much less frequent than presentation with occult manifestations of the disease. In a case-finding epidemiological study in England, the prevalence of CD was found to be 0.3% in a high-risk population. The commonest mode of presentation (50% of cases) was IDA. Similarly, in a study carried out in patients with IDA in Turkey, 6.3% had celiac disease.

In the present study, 11 of 19 patients with refractory IDA of undetermined etiology had CD. IDA as a presenting manifestation of CD has been reported only recently from India. Two of the 10 patients with adult CD reported from Delhi had long-standing IDA.

Classic malabsorption syndrome is a readily recognized manifestation of adult CD. More common, however, are the other ways in which CD presents. Among these are deficiencies of single nutrients, including IDA. Our experience suggests that patients with refractory IDA should be investigated for CD.

Two of our patients had associated hypothyroidism and insulin-dependent diabetes mellitus. These associations may be related to both CD and autoimmune diseases being associated with the same HLA haplotype, i.e., B8 and DR3, although the relation between these diseases is perhaps more complex. The presence of such conditions in patients with IDA may be a pointer towards presence of CD.

We conclude that patients with refractory IDA should be investigated for CD especially if they have one or more associated autoimmune diseases.

References

12. Yenerol MN, Kalayoglu-Besikci S. Iron deficiency anemia


Correspondence to: Prof. S Varma, Head, Fax: (172) 44 4401, 74 3976. E-mail: svarma@iat.ernet.in