Immunoproliferative Small Intestinal Disease: A Frequently Missed Diagnosis

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Abstract

Immunoproliferative small intestinal disease (IPSID) is a poorly recognized cause of malabsorption syndrome in India. Clinico-pathological features of five patients with IPSID seen over a two-year period are described. Our data suggest that IPSID is commonly misdiagnosed as intestinal tuberculosis due to lack of awareness and reluctance to obtain small bowel biopsies. Empirical institution of anti-tubercular chemotherapy not only leads to delayed diagnosis but also possibly alters the natural history of the disease, resulting in an intermediate phase of amelioration followed by a terminal phase of lymphomatous transformation. The disease is therefore usually diagnosed at an advanced stage and hence is associated with a relatively poor outcome.


Key words: Intestinal lymphoma, alpha 2 chain disease, malabsorption, pyrexia, tuberculosis.

Introduction

Immunoproliferative small intestinal disease (IPSID) represents a spectrum of histologic changes in the enteromucosal system ranging from apparently benign lymphoid infiltration to aggressive malignant lymphoproliferative neoplasms that manifest clinically with diarrhea, abdominal pain, malabsorption, weight loss, growth retardation and clubbing of fingers and toes. The disease was previously termed as Mediterranean lymphoma and alpha 2 chain disease. After its original description from the Mediterranean region, most of these from the developing countries; however, only four cases have so far been reported from India.

We present our experience of five cases diagnosed during a 2-year period (March 1991-March 1993) at a tertiary-care center, and highlight certain atypical features in the clinical presentation of IPSID, which might be of relevance to physicians working in the tropics.

Case Reports

Case 1

A 42-year-old man presented in March 1991 with a two-year history of large volume diarrhea, abdominal pain and weight loss. He had been treated elsewhere with ipecacuanha, dilucil and entramide for 18 months, with partial relief of symptoms. Symptoms recurred while he was still receiving anti-tubercular drugs. Physical examination revealed mild pallor, marked muscle wasting, pedal edema, and clubbing of fingers and toes. There was no hepatosplenomegaly, ascites or palpable mass in the abdomen.

Investigations: Fecal fat excretion (193 g/24h; normal < 30 g/24h) and urinary D-xylose (0.5 g/5 g/H; normal > 1.0) were abnormal. Serum immunoelectrophoresis (Fig 1) using polyclonal anti-human alpha 2 chain antibodies (Dako) against alpha chain, beta, gamma and mu alpha 2 chain suggested the presence of an abnormal alpha 2 chain. Small bowel biopsies showed thickening and irregular folds in the entire small intestine and areas of narrowing and small intramural nodular filling defects in the jejunum. Endoscopic duodenal biopsy showed complete loss of villi, paucity of crypts and dense infiltration of lamina propria by lymphocytes, plasma cells, immunoblasts and eosinophils. Liver biopsy and bone marrow aspiration did not show evidence of lymphomatous infiltration.

Subsequently he developed severe Campylobacter jejuni diarrhea and left-sided hemiplegia due to infarction in the right posterior and middle cerebral artery territories on the day after completion of the first cycle of chemotherapy with cyclophosphamide, Adriamycin, vincristine and prednisolone (CHOP regimen). The details of this case has been described previously. Thereafter the patient was lost to follow-up.

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Case 2

A 29-year-old woman was referred with a four-year history of large-volume diarrhea, weakness and profound weight loss. She had been treated with anti-tubercular therapy with no relief of symptoms. Physical examination showed marked reduction in muscle mass and mild anaemia.

Investigations: Hemoglobin 10.3 g/dL, TLC 4400/µL, platelets 145,000/µL, ESR 93 mm/h in first hour. Biochemical investigations were unremarkable except for marked hypoalbuminaemia (23 g/dL). Serum immunoglobulin levels: IgG 2850 mg/dL, IgA 1270 mg/dL, IgM 156 mg/dL (normal: 151±180, 322±66 and 160±45 mg/dL, respectively; turbidimetric method, Behring, Germany). Stool smear examination was normal; aerobic culture did not grow any pathogenic organism. Fecal fat excretion (15g/24h) and urine D-sytocae test (0.3 g/gCr) were abnormal. Ultrasound examination of the abdomen showed heterogeneity, increased liver echogenicity and ascites. Endoscopic biopsy of the normal appearing duodenal mucosa revealed IPSID stage C (Fig. 2).

She was treated with tetracycline; combination chemotherapy was deferred in view of marked emaciation (weight 24 Kg). She had a cardiac arrest in hospital due to hypokalemia. At limited autopsy, 30 cm of jejunum along with the mesentery and a piece of the liver were removed. On gross inspection, this segment showed marked thickening. Microscopically, the villi were broad and flatten; the lamina propria showed diffuse lymphoplasmacytic infiltrate. Numerous immature lymphoid cells were present in the lamina propria. Mesenteric lymph nodes and the liver did not show lymphomatous infiltration.

Case 3

A 52-year-old man presented with a three-year history of painless large-volume diarrhea, weight loss and emaciation. Partial symptomatic improvement had occurred after a 3-month course of anti-tubercular drugs two years ago. Thereafter he had relapse of symptoms despite continuing anti-tubercular therapy. Physical examination revealed mild edema, diminished muscle mass and clubbing of fingers and toes. Abdominal examination did not reveal free fluid or hepatosplenomegaly.

Investigations: Hemoglobin 9.0 g/dL, total leukocyte count 7000/µL, ESR 32 mm/h in first hour. Biochemical investigations were unremarkable except for marked hypoalbuminaemia (20 g/dL). Serum immunoglobulin levels were low: IgG 584 mg/dL, IgA 33 mg/dL, IgM 40 mg/dL. Urinary D-sytocae excretion was 0.1 g/gCr. Stools smear examination and aerobic culture were unremarkable. Endoscopic biopsy from the duodenal pelvic inadequate tissue. Ascaris was detected during his hospital stay (protein 0.8 g/dL, occasional lymphocytes).

Oral tetracycline (1.6 g/d) was started; he however died 3 days later following massive pulmonary aspiration. A small loop of jejunum and liver tissue were obtained during limited autopsy. Gross examination showed markedly thickened jejunal wall. Microscopic examination revealed diffuse broadening and thickening of villi with paucity of crypts. The lamina propria contained heavy lymphoplasmacytic infiltrate including immature lymphoid cells. The infiltrate was extending into the submucosa. Liver biopsy showed normal lobular architecture and widening of portal tracts due to moderate infiltration by lymphoplasmacytic cells. The final diagnosis was IPSID-associated lymphoma (stage C) with hepatic infiltration.

Case 4

A 25-year-old man presented with history of central abdominal pain of five years' duration. He had been treated with anti-tubercular drugs (isoniazid, rifampicin and ethambutol) for eight weeks without benefit. Large volume diarrhea develop later. Physical examination was unremarkable.

Investigations: Hemoglobin 13.5 g/dL, TLC 5400/µL, ESR 7 mm/h in first hour. Urinary D-sytocae excretion was 1.0 g/gCr. Stool smear examination was normal; aerobic culture did not grow any pathogenic organism. Fecal fat excretion was 7.0 g/24h. Endoscopic biopsy from the duodenum revealed IPSID (stage A). Serum immunoelectrophoresis did not show any abnormal band suggestive of a heavy chain.

He was treated with tetracycline 2 g/day. Clinical, biochemical and histological improvement was noted after eight weeks of treatment. He has been followed up for six months and is currently asymptomatic.

Case 5

A 23-year-old man presented with a two-year history of painless large-volume diarrhea, weight loss and pedal edema. He had been treated elsewhere with isoniazid, rifampicin and ethambutol for nine months. Stool frequency decreased with these drugs during the initial six months, followed by relapse despite continuation of anti-tubercular drugs. Physical examination showed mild anaemia, pedal edema, marked muscle wasting, and clubbing of fingers and toes. Abdominal examination was unremarkable except for a palpable spleen tip.

Investigations: Hemoglobin 8.5 g/dL, TLC 3000/µL, ESR 30 mm/h in the first hour. Biochemical investigations revealed marked hypoalbuminaemia (20 g/dL). Serum IgA was markedly elevated (4400 mg/dL); serum immunoelectrophoresis showed anodic expansion suggestive of an abnormal IgA chain. Stool smear examination and aerobic culture were unremarkable. Fecal fat excretion (12.0 g/24h) and urine D-sytocae test (0.5 g/gCr) were grossly abnormal. Endoscopic showed marked nodular duodenal mucosa; biopsy from these nodules showed IPSID (stage B) for which he was started on combination chemotherapy. He received two cycles of CHOP regime with significant reduction in diarrhea. Thereafter the patient was lost to follow-up.

Discussion

Each of our five patients presented with classical features of IPSID, namely, long-standing voluminous diarrhea, weight loss, abdominal pain, clubbing and malabsorption. The diagnosis in each case was based on histological features of small intestinal tissue (duodenum or jejunum) obtained at endoscopy or autopsy. A heavy chain was demonstrated in two cases.

IPSID — PURI ET AL
IPSID accounted for five of 54 (9%) adult patients with malabsorption syndrome at our center over this period. This figure may not represent the true prevalence of this disease in our region since ours is a tertiary-care referral center. However, prior to this report, only a few patients with IPSID have been described from India. The true prevalence of the disease must therefore be between these two extremes.

IPSID is expected to be more prevalent in developing countries because of protracted antigenic stimulation of enteric lymphoid tissue due to frequent gastrointestinal infections. Thus, it is difficult to explain the low frequency of this disease in the Indian subcontinent where intestinal parasitosis is common.

Each of our patients as well as those reported earlier from India had been erroneously treated for intestinal tuberculosis before the correct diagnosis was made. This practice of empirically treating all patients with prolonged diarrhea and weight loss with anti-tubercular drugs may be responsible for failure to recognize the presence of IPSID. Lack of endoscopic facilities may also be a contributory factor since all cases of IPSID in India have so far been reported from tertiary-care centers which have access to endoscopic facilities; in fact, the total number of IPSID cases reported among expatriates from the Indian subcontinent approximates those reported from India itself.

Administration of anti-tubercular drugs may also alter the natural history of IPSID. The duration of symptoms prior to diagnosis (median 30 months) in Indian patients was longer than that in South African patients (mean 11.8 mo). Patients with IPSID are known to respond clinically and biochemically to antimicrobial agents in the initial stage. Co-existing intestinal tuberculosis is unlikely to be responsible for this amelioration with anti-tubercular therapy as histological examination of viscera obtained at autopsy (cases 2,3) in our patients and at laparotomy in two patients reported previously did not show any evidence of tuberculosis.

Thus the disease as seen in India is characterized by three phases: an initial symptomatic phase, an intermediate phase of relative quiescence induced by anti-tubercular drugs (probably rifampicin), and terminal lymphomatous transformation. This pattern was observed in three of our five cases.

Given the limited availability of endoscopic and immunologic facilities, differentiation of IPSID from intestinal tuberculosis is difficult as both present with abdominal pain, diarrhea and weight loss. Clubbing of digits favors IPSID. Barium meal follow-through examination may be helpful since IPSID predominantly involves the proximal small bowel whereas tuberculosis affects the distal ileum and ileocecal region. Other features that may favor intestinal tuberculosis include presence of prolonged fever, right lower quadrant mass and a coexisting pulmonary lesion.

In conclusion, IPSID is perhaps an under-recognized disease in developing countries like India largely due to lack of awareness and diagnostic facilities. Since the outcome of this disease is not so dismal if it is diagnosed early, we recommend that duodenal or jejunal biopsies be obtained in all patients with suspected malabsorption. Indiscriminate use of anti-tubercular drugs in patients with prolonged diarrhea should be strongly discouraged.

References