Immunoproliferative Small Intestinal Disease and Primary Small Intestinal Lymphoma: Review of Literature

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Immunoproliferative small intestinal disease (IPS~D) is a prevalent, debilitating illness in many developing countries particularly Middle East and the Mediten'anean areas. JPS1D typically presents in an adolescent oryoung male with chrome diarrhoea, malabsorption syndrome, weight loss, clubbing, abdominal pain and occasionally abdominal mass. Pathologic hallmark is diffuse and extensive lymphoplasmacytic infiltration in small intestinal mucosa particularly duodenum and proxinialjejunum. Immunologically, itis characterized by monoclonal proliferation of lymphocytes with or without excess of alpha-heavy chains in the intestinal fluid or senim. It canbeofbothsecretoiy ornon-secretozy type. Managementof IPSID is dependent upon stage of the disease at the time of diagnosis. Patients with stage A disease are often initially treated with antibiotics. Althoughmany patients may respond, they need to be followed closely for relapse of symptoms or evolution into a higher stage of disease. Patients with stage B disease require chemotherapy. Treatment guidelines for the managementss of these patients are similar to those for low grade non-Hodgkin's lymphoma. Patients with stage III disease require aggressive combination chemotherapy with a curative intent. Long term follow-up is necessaiy for the management of complications of disease and it's therapy.

Immunoproliferative small intestinal disease (IPSID) is an uncommon disorder in the developed countries. It is, however, a frequently encountered condition in certain developing countries particularly Middle East and the Mediterranean areas. IPSID has been reported fmm Iran, Iraq, Israel, Tunisia, Algeria, SouthAfrica, Lebanon and other areas in the region[1-12]. More recently, we reported a series from Pakistan[3].

Clinical characteristics of the patients

IPSID predominantly afflicts adolescents and young adults of low socio-economic background. Most common presentation is chronic diarrhoea, weight loss and other manifestations of malabsoiption syndrome. The associated findings include frequent gmwth retardation, clubbing of fmgers and toes, abdominal pain and occasionally abdominal. The clinical features of the disease are primarily attributable to the presence of diffuse and intense infiltration of the small intestinal mucosa and mesenteric lymph nodes with lymphoplasmacytic cells[14-18]. Although equal sex distribution has been suggested, a male prepoaderance and no racial predilection are quite characteristic[12] . It is important to appreciate that although diarrhoea is chronic, in the early phase of IPSID, there can spontaneously be periods of complete improvement. This may at times be responsible for the delay in diagnosis. Diarrhoea and nialabsorption are usually due to alteration and loss of the absorptive surface, dis-ordered intestinal mortality and intestinal bacterial over-growth[19]. Lactose intolerance may also develop[20]. It has been frequently observed that patients have a prolonged duration of. symptoms before the diagnosis is finally established. In our experience, the mean duration of symptoms was 23.5 months[13]. Patients are often treated empirically for several presumptive diagnoses which vary from amebiasis to intestinal tuberculosis. All of our patients had previously received multiple antibiotics, in some cases even anti-tuberculous therapy, before the final diagnosis of IPSID was made.

Pathologic features and diagnosis of IPSID

Early diagnosis of IPSID requires clinical awareness of the existence of this entity particularly in young and adolescent males with chronic diarrhoea. Laboratory investigations often reveal anaemia, hypokalemia, hypocalcemia and hypoalbuminemia. Occasionally, intestinal isozyme of alkaline

phosphatase may be elevated and can be used as atumor marker[21]. Hypogammaglobulinemia may also be present. Lactate dehydrogenase (LDH) may also be high in some patients pailicularly those with frank lymphoma'[23]. Diagnostic hallmark of IPSID is elevation of alpha-heavy chain immunoglobulins in the serum[22,23]. This is observed in upto 70% of patients with IPSID which, for this reason, was previously called alpha-heavy chain disease. This abnormal protein is produced by the lymphoplasmacytic cells that infiltrate the intestinal mucosa and acts as a laboratory marker for IPSID pmtein compnses theas heavy chain immunoglobulins and lacks conjoint light chains. Partial or complete deletion of the variable (VH) and first constant (CH-l) regions accounts for aberrancy of the amino terminal structure. This correlates with an abnormally short alpha-chain messenger RNA produced in these patients. In some patients abnormal heavy chains are not detectable in the serum, however, they can still be demonstrated on the abnonnal lymphoplasmacytic cells. A variant of IPSID without detectable alpha-heavy chain immunoglobulins inthe serum oron the infiltrating cells is called non-secretory IPSID. Patients with non-secmtoiy IPSID are clinically indistingnishable from those with alpha-heavy chain disease[24-27]. Barium studies of the uppergastrointestinal tract and small bowel enema are the most important radiologic studies carried out in patients suspected to have IPSID. Most often, these studies will suggest malabsorption syndrome[28,29]. The presence of postage stamp like mucosal folds strongly suggests IPSID related small intestinal lymphoma. Diagnostically, the most rewarding investigation, however, is intestinal endoscopy30. This can be carried out in vast majority of the patients. Five primaiy endoscopic patterns can be defined occurring either alone on in various combinations. The infiltrated pattern is most sensitive and specific finding followed by a nodular pattern. Other lesions such as ulceration, mosaic pattern and mucosal folds alone are either non-sensitive or non-specific. Endoscopy is diagnostic in 85% of patients with IPSJD related lymphoma. It is important to realize that pathologic appearance of the biopsy specimenvaries with the depth; the most abnormal cells being farthest from the mucosa. Occasionally, when diagnosis cannot be established on endoscopic biopsy, diagnostic and staging lapamtomy may be indicated[31]. It has been suggested that when laparotomy is planned, following procedures should be carried out:

1. A 10cm long resection ofthe firstjejunal loop with adjacent mesentery and mesentenc lymph nodes.
2. Two wedge biopsy specimens from the ends of the duodenum and ilium respectively.
3. Two wedge biopsy specimens from the right and left hepatic lobes.
4. Biopsy of several mesenteric, para-aortic lymph nodes, particularly if they appear abnonnal.
5. Biopsy of any other visible abnormality.

Pathologic hallmark of IPSID is presence of diffuse and intense infiltration of the small intestinal mucosa and mesenteric lymph nodes with lymphoplasmacytic cells[12-18]. The disease usually effects the duodenum and proximal jejunum but ileal and pan- intestinal involvement may also occur[12]. Stomach and large intestinal involvement is rare. Proper pathologic analysis is important for further management of the disease. It also allows the patient to be placed in one of three well defined stages. Stage A is characterized by a diffuse thickening of the intestinal folds, histologically made of mature and occasionally slightly dystrophic plasma cells and lymphocytes densely infiltrating the lamina propna (Figure 1).

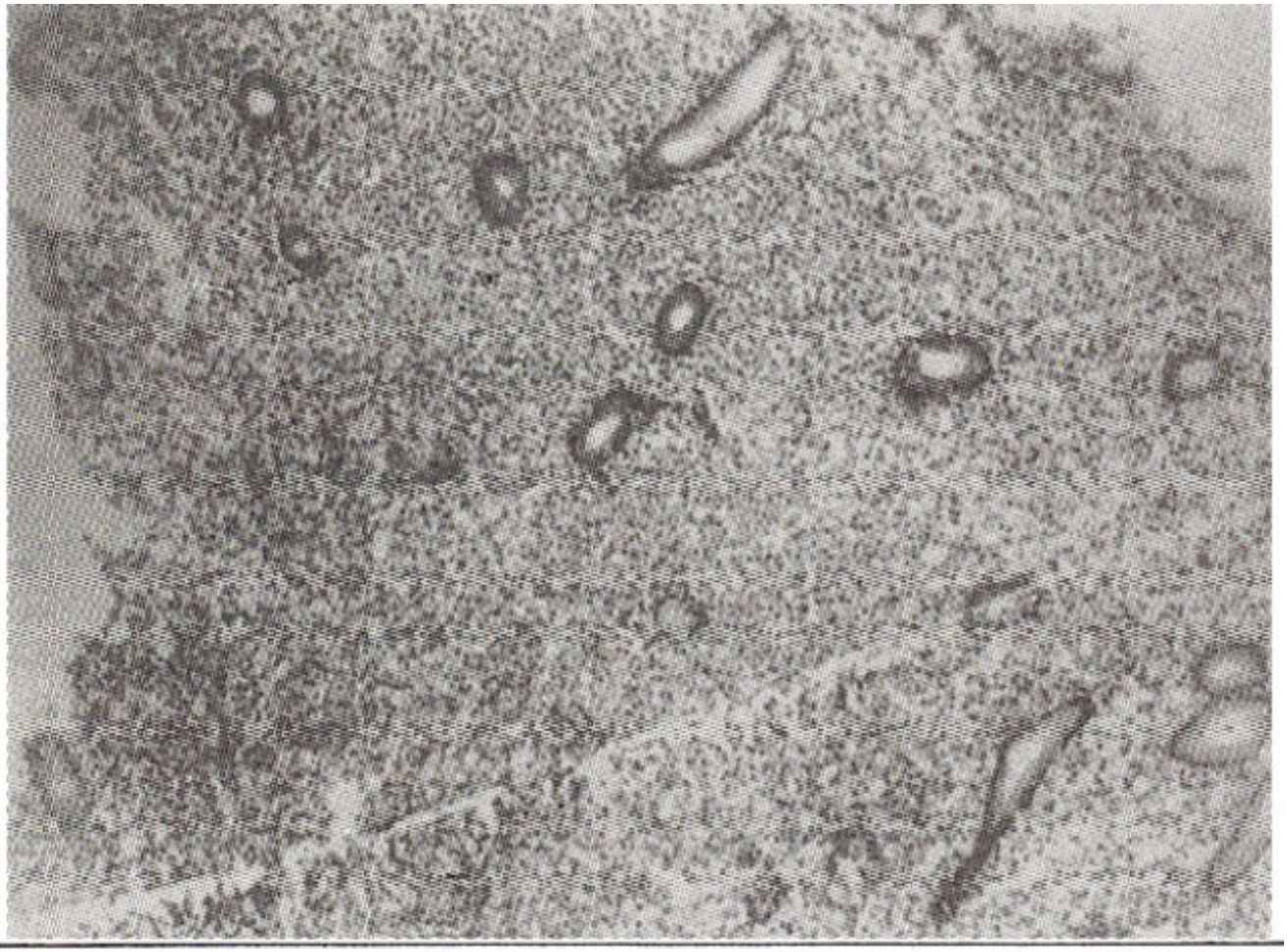


Figure 1. Duodenal mucosa showing shortening and broadening of the villi with diffuse and dense infiltrate of small and large lymphoid cells (H&Ex40).

Stage B has increasingly dysplastic plasma ceilsand lymphocytes with occasional large immunoblasts. More dysplastic cells are usually present farthest away from the surface mucosa. Stage C is characterized by immunoblastic lymphoma, infiltrating the small bowel, at places forming cimumscribed tumors (Figure 2).

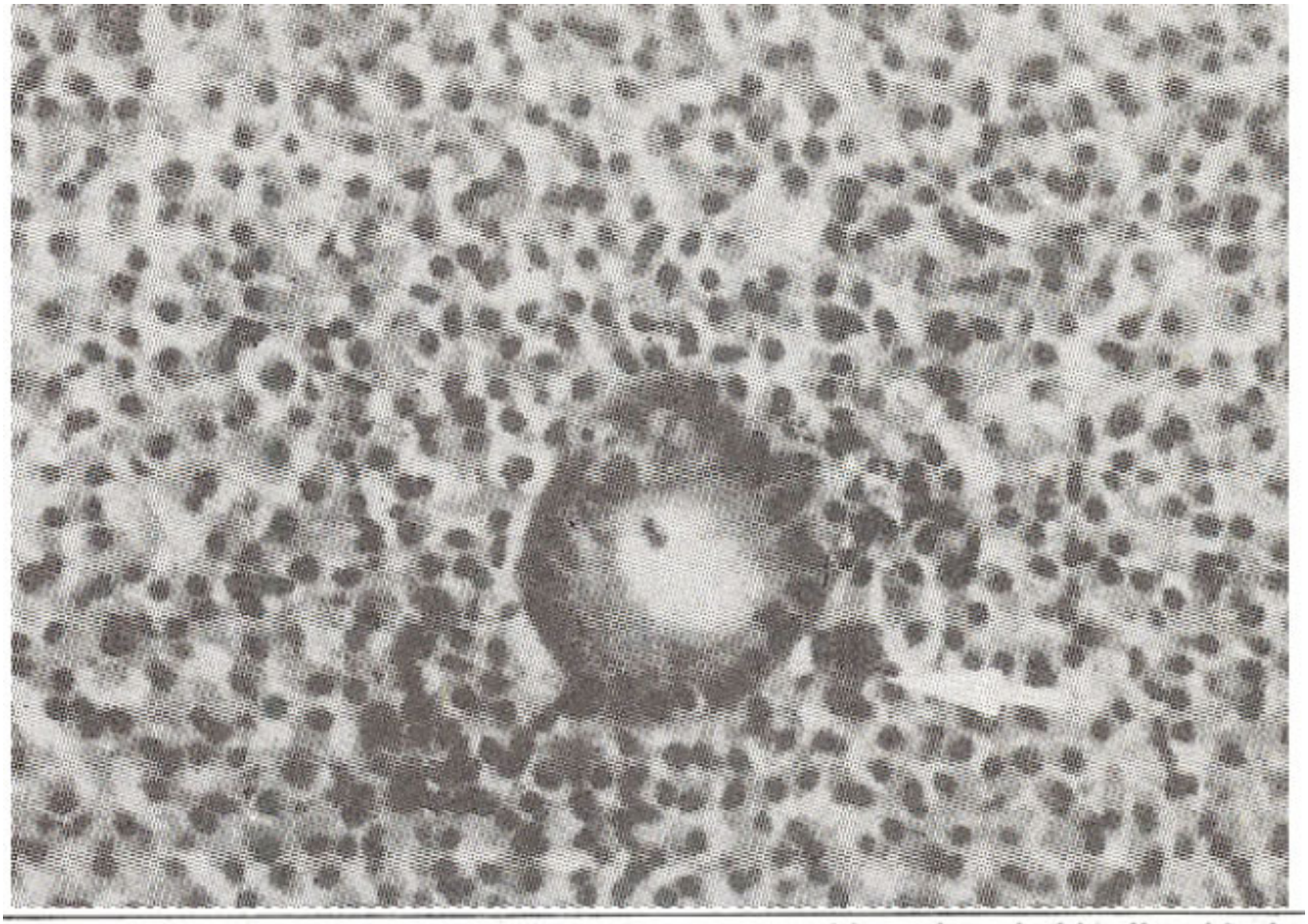


Figure 2. Duodenal lamina propria showing crypts and large lymphoid cells with abnormal mitosis (H&E x100).

In the developing countries, small intestine is a common site of GI involvement in patients with non-Hodgkin's lymphoma. Primaiy small intestinal lymphoma in the endemic countries is commonly associated with IPSID and hence has been called Mediterranean lymphoma[32-36]. Even in the early pre-lymphomatous stages, mononoclonal heavy and light chain gene rearrangements have been observed which reflect an already established neoplastic process[37]. Hence, it appears that IPSID passes progressively through phases of pre-malignant lymphomatous change to low grade malignancy to highly malignant immunoblastic lymphoma. It has been hypothesized that recurrent intestinal infections in patients living in the endemic areas are carcinogenic. The diffuse immunoproliferation inthe intestinal wall, in response to bacterial and parasitic antigens, increases the chances of random malignant transformation of rapidly proliferating cells by DNA-reactive agents such as carcinogens in food or other environmental factors. During the early phase, the process is potentially reversible if antigenic stimulus can be removed as reflected by prolonged remission induced by the antibiotic therapy[12]. However, once cells have undergone malignant transformation, process is essentially irreversible and results in a low grade lymphoma whichdue to the inherent genetic instability of the transfonned cells degenerates into a high- grade immunoblastic lymphoma. The more malignant cells usually evolve from the same previously established clone[37].

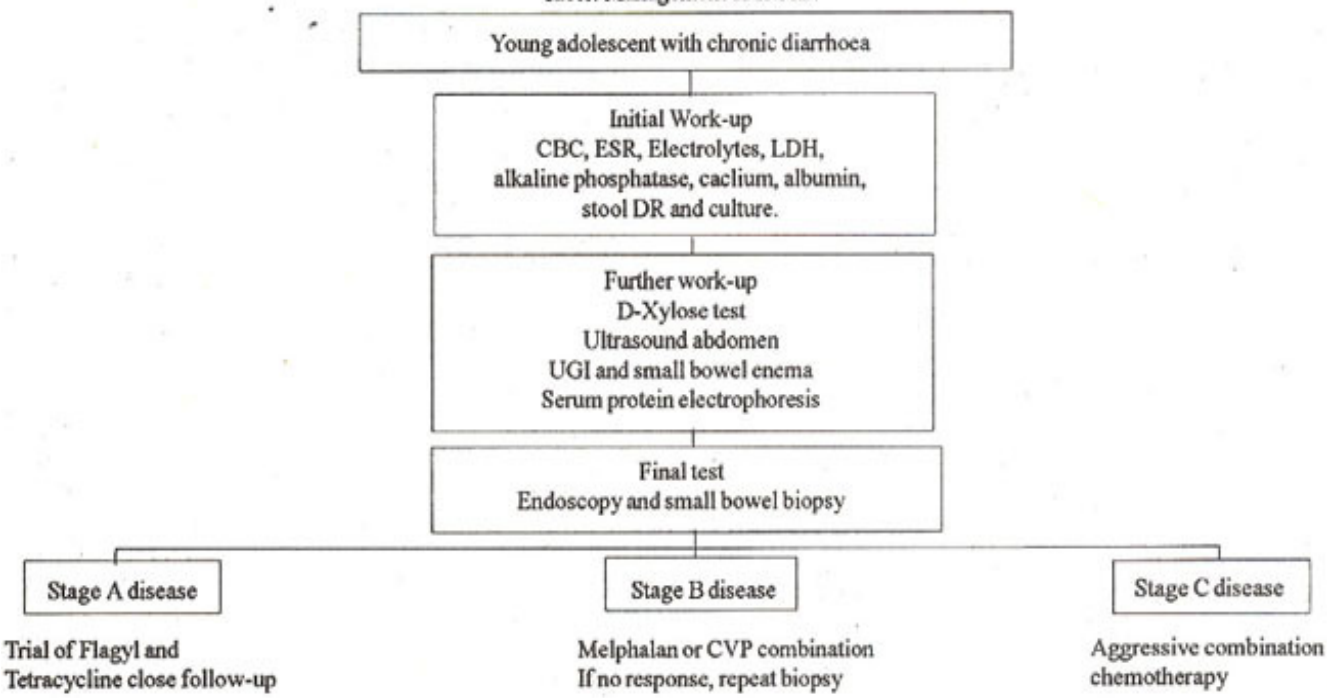
Management of IPSID

Patients with stage A disease often respond to antibiotic therapy with upto 50% of patients undergoing complete remission[4,38]. Tetracycline and Flagyl are usually utilized for a pmlonged duration. Responses, however, are usually transient. Most patients fail and develop disease progression.

Although use of antibiotics may be beneficial in patients with stage A disease, repeat biopsies are indicated in those who fail to respond orundergo relapse oftheirsymptoms. Patients with stage B IPSID benefit from chemotherapy. Their disease appears to behave like low-grade non-Hodgkin's lymphoma[39]. Low-grade NEIL is essentially an incurable disease, however, prolonged remissions are possible with less aggressive chemotherapy such as meiphalan or cyclophosphamide, vincristine and - prednisone (CVP) combination therapy. High-dose aggressive combination chemotherapy has been demonstrated to offer no advantage[40].

Presence of immunoblasts in stage B disease is an interesting fmding. Behaviour of mixed variety NHIL is dependent upon the extent of more aggressive diffuse component[39]. It is unclear if immunoblasts in stage B disease have any prognostic significance. Prospective trials are necessaiy to further elucidate the significance of this fmding. Stage C IPSU is an aggressive NEIL that requires an attempt at cure with high-dose multi-agent aggressive chemotherapy. It has been reported to induce complete remission of the disease in 50% of the patients[32]. Our expenence with stage C disease confirms these observations[13]. An algorithm is presented for the convenience of the clinicians (Table).

Table. Management of IPSID.



Several issues related to IPSID require to be elucidated further. Does IPSID develop in the individuals with pre-existing immunologic defects who are unable to control lymphoid proliferation in the gut in response to bacterial and parasitic antigens? Is early stage IPSID truly reversible particularly in those who already have immunoglobulin gene rearrangement? Is it an ethnic disorder? Are individuals of American or Eumpean descent living in the countries where IPSID is prevalent inunune from the disease? To resolve these issues, it appears necessary for the clinicians in the developing countries to collaborate with each other and their counterparts in the developed world.

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