Immunoproliferative small intestinal disease (IPS~D) is a prevalent, debilitating illness in many developing countries particularly Middle East and the Mediterranean areas. IPS1D typically presents in an adolescent or young male with chronic 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 proximal jejunum. Immunologically, it is characterized by monoclonal proliferation of lymphocytes with or without excess of alpha-heavy chains in the intestinal fluid or serum. It can be of both secretory or non-secretory type.

Management of IPSID is dependent upon stage of the disease at the time of diagnosis. Patients with stage A disease are often initially treated with antibiotics. Although many 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 management 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 necessary for the management of complications of disease and its 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 from Iran, Iraq, Israel, Tunisia, Algeria, South Africa, Lebanon and other areas in the region. More recently, we reported a series from Pakistan. 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 malabsorption syndrome. The associated findings include frequent growth retardation, clubbing of fingers 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. Although equal sex distribution has been suggested, a male preponderance and no racial predilection are quite characteristic. 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 malabsorption are usually due to alteration and loss of the absorptive surface, disordered intestinal mortality and intestinal bacterial over-growth. Lactose intolerance may also develop. 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. 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 a tumor marker. Hypogammaglobulinemia may also be present. Lactate dehydrogenase (LDH) may also be high in some patients, particularly those with frank lymphoma. Diagnostic hallmark of IPSID is elevation of alpha-heavy chain immunoglobulins in the serum. This is observed in up to 70% of patients with IPSID, which, for this reason, was previously called alpha-heavy chain disease. This abnormal protein is produced by lymphoplasmacytic cells that infiltrate the intestinal mucosa and acts as a laboratory marker for IPSID. The protein comprises heavy chain immunoglobulins and lacks conjoint light chains. Partial or complete deletion of the variable (VH) and first constant (CH-I) 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 abnormal lymphoplasmacytic cells. A variant of IPSID without detectable alpha-heavy chain immunoglobulins in the serum or on the infiltrating cells is called non-secretory IPSID. Patients with non-secretory IPSID are clinically indistinguishable from those with alpha-heavy chain disease. Barium studies of the upper gastrointestinal 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. The presence of postage stamp like mucosal folds strongly suggests IPSID related small intestinal lymphoma. Diagnostically, the most rewarding investigation, however, is intestinal endoscopy. This can be carried out in vast majority of the patients. Five primary endoscopic patterns can be defined occurring either alone or 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 nonsensitive or non-specific. Endoscopy is diagnostic in 85% of patients with IPSID related lymphoma. It is important to realize that pathologic appearance of the biopsy specimen varies with the depth; the most abnormal cells being farthest from the mucosa. Occasionally, when diagnosis cannot be established on endoscopic biopsy, diagnostic and staging laparotomy may be indicated. It has been suggested that when laparotomy is planned, following procedures should be carried out:
1. A 10cm long resection of the first jejunal loop with adjacent mesentery and mesenteric 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 abnormal.
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. The disease usually affects the duodenum and proximal jejunum but ileal and pan-intestinal involvement may also occur. 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 propria (Figure 1).
Stage B has increasingly dysplastic plasma cells and 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 circumscribed tumors (Figure 2).

Figure 1. Duodenal mucosa showing shortening and broadening of the villi with diffuse and dense infiltrate of small and large lymphoid cells (H&E x40).
In the developing countries, small intestine is a common site of GI involvement in patients with non-Hodgkin’s lymphoma. Primary small intestinal lymphoma in the endemic countries is commonly associated with IPSID and hence has been called Mediterranean lymphoma.\textsuperscript{32-36} Even in the early pre-lymphomatous stages, monoclonal heavy and light chain gene rearrangements have been observed which reflect an already established neoplastic process.\textsuperscript{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 in the 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.\textsuperscript{12} However, once cells have undergone malignant transformation, process is essentially irreversible and results in a low grade lymphoma which due to the inherent genetic instability of the transformed cells degenerates into a high-grade immunoblastic lymphoma. The more malignant cells usually evolve from the same previously established clone.\textsuperscript{37}

Management of IPSID

Patients with stage A disease often respond to antibiotic therapy with up to 50% of patients undergoing complete remission.\textsuperscript{4,38} Tetracycline and Flagyl are usually utilized for a prolonged 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 or undergo relapse of their symptoms. Patients with stage B IPSID benefit from chemotherapy. Their disease appears to behave like low-grade non-Hodgkin’s lymphoma. Low-grade NHL is essentially an incurable disease, however, prolonged remissions are possible with less aggressive chemotherapy such as meiphalan or cyclophosphamid, vincristine and prednisone (CVP) combination therapy. High-dose aggressive combination chemotherapy has been demonstrated to offer no advantage.

Presence of immunoblasts in stage B disease is an interesting finding. Behaviour of mixed variety NHL is dependent upon the extent of more aggressive diffuse component. It is unclear if immunoblasts in stage B disease have any prognostic significance. Prospective trials are necessary to further elucidate the significance of this finding. Stage C IPSU is an aggressive NHL 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. Our experience with stage C disease confirms these observations. An algorithm is presented for the convenience of the clinicians (Table).

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 European descent living in the countries where IPSID is prevalent immune 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.

References