Immunoproliferative small intestinal disease (IPSID) is a special variant of extranodal marginal zone B-cell lymphoma, which affects the small intestine. In early to mid 1960s it was referred to as ‘Mediterranean lymphomas’, during the late 1960s the term $\alpha$-heavy chain disease was also used for patients with similar clinico-pathological presentations. Later it was realized that both Mediterranean lymphomas and $\alpha$-heavy chain disease represented a spectrum of the same disease which presented in different stages i.e., benign (A), intermediate (B) and overtly malignant (C) and the disease was named IPSID.1 IPSID is predominantly found in patients of Mediterranean origin, however, a few cases of IPSID are also diagnosed in the sub-continent. IPSID involves the production of truncated alpha heavy chains which may appear in the serum and other body fluids. It can be treated with broad spectrum antibiotics at its early stage.1

This study was carried out with the objective to review the cases of this rather rare and easy-to-miss entity particularly at its early stages with clinical presentations, endoscopic findings, histopathological features, management and outcome in various stages of disease. Computerized archives of the Aga Khan University Hospital contained a total of 27 cases of IPSID diagnosed and treated over an 18-year period. A M: F ratio of 2.4:1 was seen with a mean and median ages of 28.7 and 25 years. Most patients (68.8%) presented with abdominal pain and diarrhoea. In the majority (62.5%), duodenum was the primary site of involvement. Endoscopy showed polypoidal, raised or flat lesions. Biopsy findings included blunting or flattening of villi with dense plasma cell infiltrate and lymphoepithelial lesions. Twenty-four cases were categorized as stage A and B (benign and intermediate) and three were categorized as stage C (malignant, diffuse large B-cell lymphoma with plasmacytoid features). Stage A and B patients responded well to antibiotic treatment (tetracycline) with regression of the lesions while for stage C patients standard CHOP chemotherapy was administered.

**Key words:** IPSID. Lymphoma. Small intestine. Antibiotic. CHOP. Chemotherapy.

Immunoproliferative small intestinal disease (IPSID) is a special variant of, extranodal marginal zone B-cell lymphoma, which affects the small intestine. In early to mid 1960s it was referred to as ‘Mediterranean lymphomas’, during the late 1960s the term $\alpha$-heavy chain disease was also used for patients with similar clinico-pathological presentations. Later it was realized that both Mediterranean lymphomas and $\alpha$-heavy chain disease represented a spectrum of the same disease which presented in different stages i.e., benign (A), intermediate (B) and overtly malignant (C) and the disease was named IPSID.1 IPSID is predominantly found in patients of Mediterranean origin, however, a few cases of IPSID are also diagnosed in the sub-continent. IPSID involves the production of truncated alpha heavy chains which may appear in the serum and other body fluids. It can be treated with broad spectrum antibiotics at its early stage.1 The disease is said to be associated with *Campylobacter jejuni.*2

This study was carried out with the objective to review the cases of this rather rare and easy-to-miss entity particularly at its early stages with clinical presentations, endoscopic findings, histopathological features, management and outcome in various stages of disease. Computerized archives of the Aga Khan University Hospital contained a total of 27 cases of IPSID over a period of 18 years (1991-2008). Records of all these patients were reviewed along with original slides. Further immunohistochemistry (IHC) workup was done where necessary. Cases were stained with a panel of antibodies including LCA, CD20, CD79a, CD138, CD3, IgG, IgM, IgA, Kappa, Lambda and Cytokeratin CAM 5.2.

There was a male to female ratio of 2.4:1. The mean age of the patients was 28.7±10.2 years. Most patients (n=59.3%) presented in the third decade of life. Data pertaining to sign and symptoms of 16 out of 27 patients was available. Most patients (n=68.8%) presented with abdominal pain and/or diarrhoea/malabsorption followed by weight loss and vomiting. Other less common presenting complaints included nausea, abdominal mass etc. Most common site of lesion in 15 out of 24 patients (62.5%) was duodenum, followed by jejunum in 4 out of 24 patients (16.7%), 2 cases (8.33%) occurred in the ileum, while the other 2 (8.33%) were at the duodeno-jejunal junction and in one (4.17%) of the cases both jejunum and ileum were involved. In 3 patients, precise site of involvement was not available.

Two-third of the patients on endoscopy showed polypoidal or nodular lesions while others presented with hyperemic raised or flat edematous lesions. Microscopy revealed blunting and shortening of villous architecture (Figure 1a) along with flattening of mucosal folds. In most cases along with broadening of villi (Figure 1a) dense and diffuse plasma cell infiltrates was seen in the lamina propria (Figure 1b). Other histological features like lympho-epithelial lesions were similar to ‘mucosa associated lymphoid tissue’ (MALT) lymphoma except for the marked plasmacytic differentiation.

The stage A (benign) shows overwhelming plasmacytic infiltrate with only few CD20 positive marginal zone B cells. Stage B (intermediate) is characterized by lymphoid aggregates and variable villous atrophy and atypical large immunoblast like cells. The infiltrate usually extend beyond mucosa. In stage C (malignant)
high grade lymphomas of large B-cell type with prominent plasmacytoid differentiation (Figure 1c) originate in a background of low stage IPSID, which are strongly positive for CD20 (Figure 1d). In our archives all but 3 belonged to stage A or B. All patients with stage A and B IPSID were treated with broad spectrum antibiotics like tetracycline, while stage C patients were treated with 6-8 cycles of standard CHOP chemotherapy.

On IHC, lymphoid cells were positive for LCA and CD20 while plasma cells were positive for CD79a, CD138 (Figure 1b), IgA and sometimes for IgG and IgM. Serum IgA levels were also raised in most cases. All patients initially responded either completely or partially to antibiotic treatment (Tetracycline at least for a month) with follow-up biopsies showing complete or partial regression of the lesions. Three of the cases were complicated by transformation into 'Diffuse large B-cell lymphoma (DLBCL)' with plasmacytoid features (Figure 1c).

It is postulated that IPSID occurs in patients with repeated intestinal infections. Recent studies suggest association with Campylobacter jejuni. It is postulated that this results in continuous chronic antigenic stimulation of IgA secreting lymphoid tissue common in small intestine with a resultant clonal proliferation of IgA secreting lymphoid cells. Subsequently most cases lose the ability to synthesize light chain. In early stages it may be very difficult to differentiate IPSID, from chronic inflammatory process by the reporting pathologists. In such circumstances it may be impossible to diagnose without the help of clonal studies for IgH chain gene rearrangement. The other close mimicry include celiac disease as both IPSID and celiac disease are characterized by lymphoplasmacytic infiltrate and villous atrophy. In these cases demographics are important; also gluten free diet will lead to improvement of celiac disease cases. Intraepithelial lymphocytosis with surface epithelial damage shall also favour celiac disease. As some cases of IPSID particularly if untreated may transform into aggressive lymphomas like DLBCL, recognition of subtle features and follow-up is of paramount importance, particularly in endemic regions.

REFERENCES