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Immunoproliferative small intestinal disease: a report of 6 cases

Introduction

Immunoproliferative small intestinal disease (IPSID) is a rare low-grade B-cell lymphoma arising from mucosa associated lymphoid tissue (MALT), representing approximately one-third of intestinal lymphoma. Histopathologically it is characterized by infiltration of small bowel wall with lymphocytes and plasma cells. The infiltrates produces an aberrant immunoglobulin (IgA), a truncated alpha heavy chain without the light chain component.[1,2] Galian et al[3] described the disease in three stages depending upon type of cellular infiltrate and mesenteric nodal involvement (**Table 1**). Presentation may mimic that of celiac disease, tropical sprue or parasitic infestation and patients are being treated on the line of celiac disease and other causes of malabsorption for prolonged duration before being diagnosed as IPSID/NHL.[4,5] Emaciation and diarrhoea is due to malabsorption syndrome and protein losing enteropathy secondary to lymphoma infiltration of intestine. Most patients present during early stages and are curable with oral antimicrobials.[6] Few may progress to high-grade lymphoma requiring systemic chemotherapy. We present here the clinico-pathological characteristics, treatment and outcome of six patients treated at our institute during the last 10 years, along with a review of literature.

Table 1: The Galian staging system[3]

Stage	Small intestine	Lymph nodes
A	Lymphoplasmacytic or plasmacytic infiltration of the lamina propria, variable villous atrophy	Plasmacytic infiltration, nodal architecture generally preserved
B	Atypical lymphoplasmacytes or plasmacytes with immunoblast-like cells with extension to at least submucosa, subtotal or total villous atrophy	Atypical plasmacytic infiltrate with immunoblast- like cells, subtotal or total effacement of nodal architecture
C	Frankly malignant invasion through entire intestinal wall	Malignant effacement of entire lymph node

Case reports

A total of six patients with median age of 27 years (range: 15-35) were identified and treated. Median duration of symptom was 13.5 months (range: 6-26). All patients presented with history of recurrent watery loose motion with decreased appetite, weight loss and low grade fever. The median time from diagnosis of malabsorption to diagnosis of IPSID was 10 months (range: 1–20). Test for alpha heavy chain protein (AHCP) in serum was not done.

Barium meal follow through showed ileo-ileal intussusception in case number 4 and 6 (**Table 2**). All patients showed evidence of oedematous mucosal thickening in small bowel and enlarged mesenteric lymph nodes on CT scan. Endoscopic biopsy of mucosal lesions showed diffuse infiltrate of small atypical lymphoid cells or lymphoplasmacytic cells (**Figure 1A**) which were $CD20^{+}CD3^{-}$ with partial or total villous atrophy. Repeat biopsy during progression showed features of high grade B-cell lymphoma in case number 3 (**Figures 1B & 1C**).

Galian stage, treatment details and outcome are summarised in **Table 3**. Case number 1 received 6 cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) and achieved complete response (CR) lasting for 10 months and then was lost to follow-up. Case 2 also received 6 cycles of CHOP with tetracycline (1g/day) and was in stable condition for 1 year after which the disease progressed, and the patient succumbed 45 months after initial

Table 2: Radiology and histopathology features

Investigation	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Upper GI endoscopy	thick, edematous folds in stomach and duodenum	Nodular infiltrated folds in duodenum	Nodular mucosa in entire duodenum	Edematous and nodular mucosa in duodenum	Ulcerated, edematous, infiltrated mucosa in duodenum with a large polyp+	Edematous mucosal folds in duodenum
Colonoscopy	Not done	Not done	Not done	Edematous mucosa with superficial ulcers in whole segment of colon	Normal	Not done
Site of involvement	Stomach, duodenum and jejunum	2nd part of duodenum, jejunum, ileum	Duodenum, jejunum, ileum	Duodenum, ileum, colon	Duodenum, jejunum, colon	Duodenum, ileum
Barium meal follow-through	Not done	Loss of mucosal fold pattern in duodenum and thickening of jejuna mucosal folds	Normal	Ileo-ileal intussusceptions	Normal	Ileo-ileal intussusceptions
CT scan	Thickening of small bowel with dilatation, multiple para-aortic and mesenteric lymph nodes enlarged	Diffuse jejunal wall thickening with polypoidal mass related to ileum and mesenteric lymph node enlargement	Circumferential long segment thickening of distal jejunal and ileal loops	Long segment mucosal thickening involving ileum and colon with ileo-ileal intussusceptions and mesenteric lyphadenopathy	Non-specific dilated bowel loops with mesenteric lymphadenopathy	Ileo-ileal intussusception with mesenteric lymphadenopathy
Systemic staging	Negative	Negative	Negative	Negative	Negative	Negative
Histopathology (hematoxylin and eosin)	Diffuse infiltration by small lymphoid cells	Dense infiltrate of lymphocyte and plasma cells	Diffuse lymphoplasmacytic infiltrate in lamina propria	Lymphoplasmacytic infiltrate, focal crypt architectural distortion with increased intraepithelial lymphocyte	Diffuse cellular infiltrate comprising mature B cells admixed with plasma cells and occasional lymphoepithelial lesions with villous atrophy	Dense infiltration of plasma cells and few mononuclear lymphoid cells in lamina propria with villous atrophy and intraepithelial lymphocytes
Infiltrate	Small lymphoid	Lymphocyte and plasma cells	Lymphoplasmacytic	Lymphoplasmacytic	Lymphocyte and plasma cells	Plasma cells and lymphomononuclear cells
Granuloma	No	No	No	No	No	No
CD20	+ve	+ve	+ve	Not done	+ve	Not done
CD3	-ve	-ve	-ve	Not done	-ve	-ve
Ig stain	Not done	Kappa chain	Not done	Kappa chain	Not done	IgA

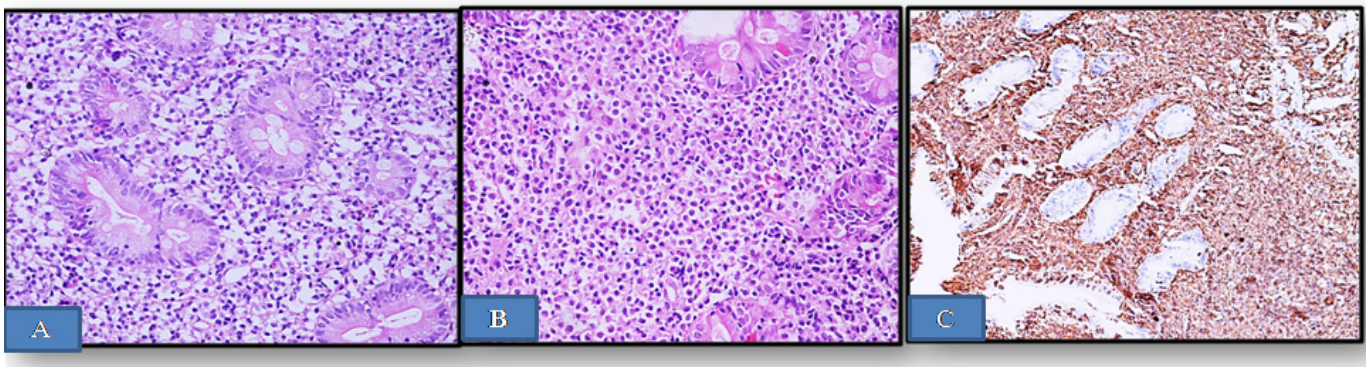

Figure 1: A) Jejunal biopsy showing dense lymphoplasmacytic infiltration of the lamina propria with normal epithelium. Some of the crypts show epithelial lymphocyte infiltration indicative of lymphoepithelial lesion (hematoxylin and eosin, x20); B) photomicrograph showing diffuse infiltration of large atypical lymphocytes in the lamina propria (hematoxylin and eosin, x20); C) the large atypical lymphocytes are CD20 positive, indicating a diffuse large B-cell lymphoma (IHC, DACO, x20).

Table 3: Treatment and outcome

Treatment parameters	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Galian stage	A	A	B	A	A	B
First-line therapy	CHOP	CHOP + antibiotics	COP + antibiotics	Antibiotics	Antibiotics	Antibiotics
Antibiotics	Nil	Tetracycline	Tetracycline + metronidazole	Doxycycline + metronidazole	Doxycycline	Metronidazol + doxycyclin
Duration of first-line Therapy	5 months	1 year	5 months	7 months	34 months	6 months
Response to first-line therapy	Complete response	Stable disease	Stable disease	Complete response	Partial response	Partial response
Recurrence/ progression	Y	Y	Y	Y	N	N
High-grade transformation	N	N	Y	N	N	N
Second-line treatment	None	PEPC	CHOP	None	NA	NA
Response to second-linetreatment	NA	Progressive disease	Progressive disease	NA	NA	NA
Final outcome	Lost to follow-up	Died in progressive disease	Died in progressive disease	Alive with disease	Alive with disease	Alive with disease
Progression-free survival (months)	10	37	6	18	64	8
Overall survival (months)	17	45	120	22	64	8

diagnosis of IPSID. Case 3 initially received CVP (cyclophosphamide, vincristine, and prednisolone) along with oral metronidazole and tetracycline (MT) without any response. Repeat biopsy revealed a high-grade B- non-Hodgkin's lymphoma (NHL). He was given 6 cycles of CHOP but his disease continued to progress. He eventually succumbed 120 months after diagnosis of IPSID. Case 4 achieved CR after MT lasting for 14 months. Currently she is asymptomatic and on regular follow-up. Case 5 achieved partial remission after oral doxycycline and is continuing on regular follow-up with same treatment. The last patient was diagnosed recently and is on doxycycline and metronidazole. Though the sample size is too small for survival analysis, we calculated a median progression-free survival of 18 months and overall survival of 64 months after a median follow-up of 22 months.

Discussion

The infectious aetiology of IPSID has been supported by the demonstration of H. pylori and C. jejuni in tumor samples of IPSID.[7,8] Al-Saleem et al[9] reported the largest series comprising of 89 IPSID patients out of a total 145 cases of small intestinal lymphoma. There are few published reports from India as well.[4,5,10] Presentation of our cases was similar to published literature; including chronic diarrhoea, abdominal pain, weight loss, low-grade fever and clubbing.[9,11–13] Very few patients in literature with a diagnosis of chronic malabsorption syndrome have been reported as IPSID.[14–16] The exact pathogenesis of IPSID is unknown. Pathologically it shows a spectrum of disease with alpha-HCD (with AHCP production), with Mediterranean lymphoma on one hand and frank high-grade malignant lymphoma on the other. AHCP is present in approximately 87% of patients with IPSID.[17] If left untreated the disease may progress to high-grade malignant lymphoma. Clinical staging depends on type of cellular infiltrate, severity of involvement and lymph node histopathology. Galian staging is most commonly used and classifies the disease into three stages (A, B and C).

The clinical course is indolent in IPSID. Though very responsive to antibiotics in early stages, the disease can progress to high-grade lymphoma if left untreated. It can cause severe morbidity secondary to malabsorption and protein losing enteropathy. Early treatment is important to control the disease and malabsorption and prevent its progression.[13] In a retrospective study of 21 Tunisian patients with IPSID, 6 had early stage disease and responded well to antibiotics. 15 patients with high/intermediate grade disease were treated with an anthracycline containing combination chemotherapy

(CHOP/or CHOP-like). The overall remission rate was 90±12% at 2 years and 67±25% at 3 years.[18] In first 2 patients we employed anthracycline-based chemotherapy given our lack of experience. Another large Turkish study also reported similar results[19] Rambaud et al[13] recommended antibiotic treatment for early stage and CHOP for those with inadequate response to oral antibiotics and for advanced stage disease. The optimum duration for antibiotics is not known, and perhaps might be required lifelong. The role of surgery is limited and is used only for symptom palliation and rarely for salvage. The usual cause of death is disease progression or transformation to high-grade lymphoma and complications of malnutrition. In our study, all six patients showed early response to antibiotics but ultimately three patients suffered disease progression. Two patients died of progressive disease; one underwent transformation to high-grade B-cell lymphoma, while remaining three patients are doing well on treatment.

BIVAS BISWAS[1]
ATUL SHARMA[1]
GOVIND K MAKHARIA[2]
SANJAY THULKAR[3]
SUDHEER ARAVA[4]
ANKUR BAHL[1]
SURENDRA CHAUDHARY[1]

Correspondence: Dr. Atul Sharma
Departments of Medical Oncology[1], Gastroenterology [2], Radiodiagnosis[3] and Pathology,[4]
Dr. B. R. A. Institute Rotary Cancer Hospital, All India Institute of Medical Sciences
Ansari Nagar, New Delhi - 110029, India
Email: atul1@hotmail.com

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