

CASE REPORT

Very late onset small intestinal B cell lymphoma associated with primary intestinal lymphangiectasia and diffuse cutaneous warts

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Abstract

As only a handful of lymphoma cases have been reported in conjunction with primary intestinal lymphangiectasia, it is not yet clear if this association is merely fortuitous or related to primary intestinal lymphangiectasia induced immune deficiency. We report on two female patients, 50 and 58 years old, who developed small intestinal high grade B cell lymphoma a long time (45 and 40 years, respectively) after the initial clinical manifestations of primary intestinal lymphangiectasia. They presented with a longstanding history of fluctuating protein losing enteropathy, multiple cutaneous plane warts, and markedly dilated mucosal and submucosal lymphatic channels in duodenal biopsies. One had a large ulcerated tumour of the proximal ileum and the other diffuse ileal infiltration. In both, histological examination showed centroblastic high grade B cell lymphoma associated with duodenojejuno-ileal mucosal and submucosal lymphangiectasia. They were subsequently successfully treated with surgery and postoperative chemotherapy (AVmCP: adriamycin, cyclophosphamide, Vm26, and prednisolone), and chemotherapy alone (PACOB: adriamycin, cyclophosphamide, vincristine, bleomycin, and prednisolone), respectively. A three year follow up in both cases showed persistent diffuse lymphangiectasia without evidence of lymphoma. The present findings support the hypothesis that primary intestinal lymphangiectasia is associated with lymphoma development.

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Keywords: protein losing enteropathy; immune deficiency; intestinal lymphangiectasia; malignant lymphoma; Waldmann disease

Primary intestinal lymphangiectasia (PIL) is a rare disease characterised by abnormally dilated lymphatics in the small intestinal wall and/or the mesentery. It is associated with either a systemic disorder of the lymphatic system¹ or with a process specifically located in the gastrointestinal tract.² This results in

extreme leakage of lymph into the gastrointestinal tract causing loss of proteins, immunoglobulins, and lymphocytes which in turn leads to depression of both the humoral and cellular immune systems.³ Given the rare nature of PIL, it is not clear if the occurrence of malignancy, especially lymphoma, is fortuitous or related to PIL induced immune deficiency, as in primary immunodeficiency syndromes.^{4 5} Indeed, only a handful of PIL related lymphoma cases have been reported^{4 6–11}; six of these were located in the gastrointestinal tract. We report on two further patients with longstanding PIL who developed very late onset small intestinal B cell lymphoma (several decades after the initial clinical manifestations of protein losing enteropathy).

Case reports

PATIENT NO 1

A 50 year old woman was admitted in August 1995 for assessment and management of König syndrome and leg oedema. Her past medical records dated back to 1950 when she was five years old and suffered chronic diarrhoea, steatorrhoea, and abdominal distension. In 1956, at the age of 11, a chylous ascites was discovered in association with severe hypoproteinaemia and lymphopenia. On exploratory laparotomy there was a voluminous, hard, diffuse mesenteric mass containing an opalescent fluid, small amounts of chylous ascites, and an inflammatory appendix; a diagnosis of diffuse lymphangioma was suspected on macroscopic examination but the whole intestinal wall was diffusely thickened, and dilated small intestinal lymphatics extending from the duodenum to the ileum were observed as a fatty meal had been administered 12 hours before surgery. No radical surgical treatment was considered and the patient was managed conservatively. Examination of mesenteric biopsy specimens showed marked dilatation of the lymphatics with fat filled macrophages. PIL was diagnosed; compliance with dietary fat intake and supplementation with medium chain triglycerides was low. The subsequent

Abbreviations used in this paper: PIL, primary intestinal lymphangiectasia; HTLV-1, human T cell lymphotropic virus type 1.

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evolution varied; four years later, at the age of 15, recurrent chylous ascites associated with severe hypoproteinaemia necessitated a second laparotomy. Findings were similar to the previous ones, confirming massive and even aggravated infiltration of the total small intestine and mesentery. But follow up showed that compliance to lipid dietary restrictions had improved: the clinical outcome proved satisfactory, except for short episodes of leg oedema and cutaneous plane warts. Growth and puberty proved normal; at the age of 25 a first pregnancy was uneventful.

On August 1995—that is, 45 years after the initial clinical manifestations of protein losing enteropathy and 39 years after the first diagnosis of PIL—the patient was admitted to our hospital with abdominal pain. Physical examination showed oedema of the legs and multiple warts on the dorsal of her hands, forearms, back, and legs. There was no abdominal mass, ascites, lymphadenopathy, or hepatosplenomegaly. Her weight was 63 kg and height 161 cm. The family history was not contributory. Erythrocyte and blood cell counts were normal except for lymphopenia (400–600 per μ l). Peripheral CD4 cell count was low (57 per μ l), as were the CD8 count (342 per μ l) and CD4/CD8 ratio. There was severe hypoproteinaemia (42 g/l) and hypoalbuminaemia (24 g/l), and markedly decreased levels of immunoglobulins, mainly IgG (2.2 g/l; normal >6.9 g/l), and also IgA (0.38 g/l; normal >0.8 g/l) and IgM (0.2 g/l; normal >0.4 g/l) classes. There was no proteinuria on repeated examination. Liver and renal function proved normal. Serological tests for human immunodeficiency virus type 1 and 2 and for human T cell lymphotropic virus type 1 (HTLV-1) proved negative.

Upper gastrointestinal endoscopy showed multiple whitish pseudo polyps, suggesting lymphangiectasia, extending from the proximal duodenum to Treitz's ligament. Ileocolonoscopy proved normal. Duodeno-jejunal and ileal biopsies showed markedly dilated mucosal and submucosal lymphatic channels, with polyclonal normal plasma cells. An x ray of the small bowel follow through showed an ulcerated stenosis of the proximal ileum located approximately 200 cm beyond Treitz's ligament. Computerised abdominal tomography showed a tumour-like thickened proximal ileum with no evidence of mesenteric lymphadenopathy. An x ray and CT scan of the chest were normal, as were hepatic and medullar biopsies.

At laparotomy, a large ulcerated small intestinal tumour (90×45 mm) located in the proximal ileum was found but there was no evidence of mesenteric or hepatic metastases. The whole tumour was removed with macroscopically healthy small intestinal margins. The specimens were fixed in 10% formalin. Histological examination revealed numerous diffuse lymphangiectasias in the mucosa and submucosa (fig 1). The tumour was ulcerated and associated with the whole intestinal wall. It consisted of diffuse proliferation of typical large centroblastic lymphoid cells with one or two nucleoli (fig 2). In paraffin embedded sections,

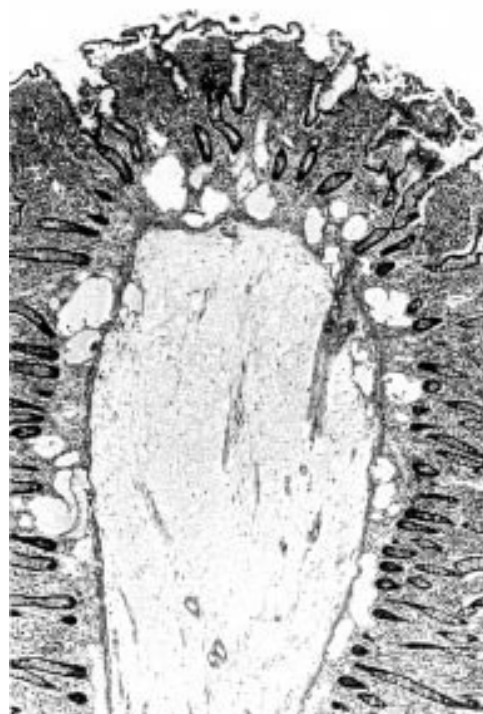


Figure 1 Patient No 1. Ileal resection piece: note the numerous lymphangiectasias in the mucosa and submucosa (haematein-erythrosin, G×100).

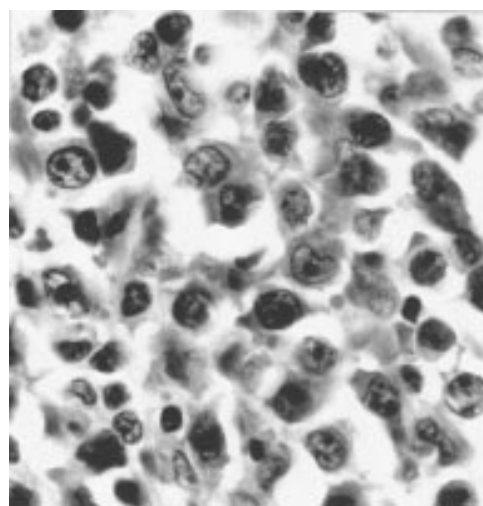


Figure 2 Patient No 1. Ileal resection piece: tumour cells are large lymphoid cells with one or two nucleoli (haematein-erythrosin, G×3000).

the tumour cells were diffusely positive for CD45 and CD20 (L26) and negative for CD3; no immunoglobulins were detected. There was neither a low grade component nor lymphoepithelial lesion. Plasma cells were normal. A diagnosis of centroblastic high grade B cell lymphoma, according to the Kiel classification, was made. In situ hybridisation and polymerase chain reaction for HTLV-1 and Epstein-Barr virus on intestinal tissue proved negative.

Postoperatively, four, 5-day cycles of chemotherapy using AVmCP (adriamycin 80 mg intravenously on day 1, cyclophosphamide 1 g intravenously on day 1, Vm26 100 mg intravenously on day 1, and prednisolone 100 mg/day orally for five days) were delivered. There were

no serum anti-IgA antibodies and the patient received polyvalent immunoglobulins intravenously at three week intervals.

In 1996, 1997, and 1998, duodenal perendoscopic biopsies showed persistent lymphatic channel dilatations with normal plasma cell density, with no evidence of lymphoma. Computerised abdominal tomography proved normal. Serum albumin was 27 g/l with decreased levels of IgG (3.35 g/l), IgA (0.38 g/l), and IgM (0.25 g/l). Polyvalent immunoglobulins were administered monthly for three years. To date, the patient has remained well except for episodes of leg oedema but with no evidence of lymphoma relapse.

PATIENT NO 2

A 58 year old woman was admitted in 1996 for evaluation of severe hypoalbuminaemia as a result of protein losing enteropathy. She had complained of leg oedema for 40 years since the age of 18, of diarrhoea for seven years, and of abdominal pain for several months. Her past medical history included post partum phlebitis at the age of 25, bilateral pleural effusion, chronic bronchitis, and arterial hypertension. On admission, physical examination showed symmetric leg oedema, moderate right pleural effusion, and plane warts on the back of the fingers and hands. There was an abdominal mass, ascites, lymphadenopathy, and hepatosplenomegaly. The familial history was not contributory.

Laboratory investigations showed severe hypoalbuminaemia (20 g/l), normal leucocyte counts, but lymphopenia (500–700 per μ l). Peripheral T cell counts showed 748 natural killers, 88 CD4, and 132 CD8 lymphocytes per μ l, with a decreased CD4/CD8 ratio (0.67; normal >1). Liver and renal function tests were normal. There was no proteinuria. An x ray of the small bowel follow through showed a diffusely thickened ileal wall with small nodular lesions, and abdominal CT scan showed a diffusely thickened small intestinal wall. Upper enteroscopy and ileocolonoscopy showed multiple whitish pseudo polyps, suggesting lymphangiectasia, involving the duodenum, the upper 50 cm of the jejunum, and the lower 80 cm of the ileum.

On duodenojejunal and ileal perendoscopic biopsies, diffusely dilated mucosal and submucosal lymphatic channels were observed (fig 3). Ileal specimens also showed diffuse proliferation of large lymphoid cells of the centroblastic type, with round nuclei and one or two nucleoli. They were mixed with normal small round lymphoid cells. There were no lymphoepithelial lesions. Immunohistochemical analysis of paraffin embedded specimens revealed that the large lymphoid cells were CD20, whereas the small lymphoid cells were CD3+ T cells of the reactive type. Plasma cells were normal. Most expressed IgA, with two thirds for the κ chain and one third for the λ chain. A diagnosis of centroblastic high grade B cell lymphoma was made, according to the Kiel classification.

Osteomedullary biopsy and CT scans of the chest and cavum proved normal. Abdominal

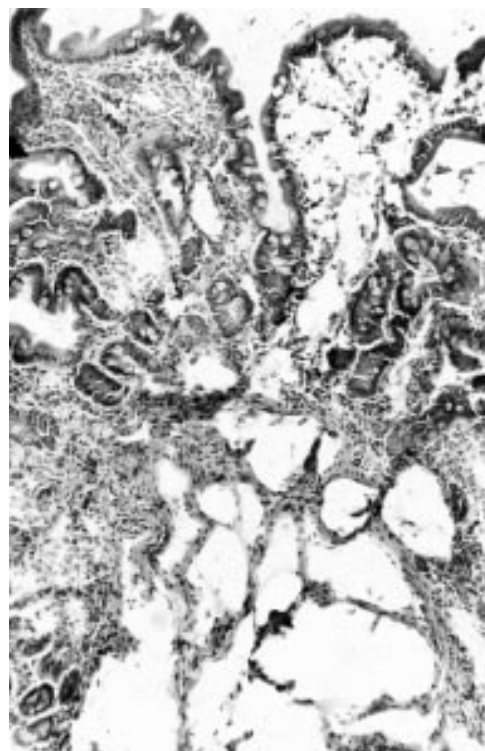


Figure 3 Patient No 2. Perendoscopic jejunal biopsy (frozen sample): numerous mucosal and submucosal lymphangiectasias (haematein-erythrosin, Gx300).

CT scan revealed no evidence of mesenteric or hepatic metastases. Three, 3-week cycles of chemotherapy using PACOB (adriamycin 50 mg on days 1–5, cyclophosphamide 600 mg on days 1–15, vincristine 2 mg on days 8–22, bleomycin 8 mg on days 8–22, and prednisolone 60 mg on days 1–5 and 15–19) were delivered.

At control ileocolonoscopy in September 1996 there was no evidence of lymphoma but persistent lymphatic dilatations on duodenal and ileal biopsy specimens were noted. To date, the patient has remained in a satisfactory clinical condition, except for bilateral leg oedema and hypoalbuminaemia, with no evidence of lymphoma.

Discussion

In our two patients, small intestinal high grade B cell lymphoma was diagnosed 45 and 40 years after the initial clinical manifestations of protein losing enteropathy caused by PIL. A diagnosis of PIL was clearly suggested by several observations: (a) early onset, in childhood and adolescence, respectively, of symptoms directly related to protein losing enteropathy—that is, peripheral hypoalbuminaemic oedema (due to intestinal lymph loss), chylous peritoneal, and pleural effusions¹²—or to marked depression of cell mediated immunity (longstanding cutaneous warts of presumably viral origin). Indeed, such cutaneous viral warts have already been reported as a clinical presentation of PIL^{6 11}; (b) anatomical demonstration in patient No 1 of enteromesenteric (pseudo lymphangiomatic) lymphangiectasia at the age of 11—that is, nearly 40 years before

Table 1 Characteristics of reported 11 patients with primitive intestinal lymphangiectasia (PIL) and lymphoma

Reference	Sex	Age at first symptoms of PIL (y)	Lymphocyte counts (μl)	Cutaneous warts	Time from PIL to lymphoma onset (y)	Lymphoma		Treatment	Outcome		
						Location	Type		Lymphoma	Enteropathy	
Waldman 1972 ¹ (3 cases)	NS	NS	NS	NS	3, 22 and 25	Breast, small bowel, stomach	NS NS NS	NS NS NS	? ? ?	? ? ?	
Ward 1977 ⁶	M	12	1000	+	27	Jejunum	NS (lymphocytic)	Surgery, radiotherapy	Complete remission	Death	Improved
Broder 1981 ^{7 a}	F	24	600	NS	15	Breast	B cell (small cells)	CVP ^b	Complete remission	Death	Improved
Case record 1984 ⁸	F	57	798	NS	13	GI tract	B cell (immunoblasts)	VCP ^c	Complete remission	Death	Unchanged
Herait 1985 ⁹	F	3	860	NS	15	Retroperitoneum, mediastinum	NS (large cells)	AVmCP ^d	Complete remission	Unchanged	Unchanged
Shpilberg 1993 ¹⁰	F	6	640	NS	13	Bone	B cell (large cells)	CHOP ^e , radiotherapy	Complete remission	Unchanged	Improved
Guma 1998 ¹¹	F	34	NS	+	20	Jejunum	B cell (centoblastic)	Surgery, CHOP	Complete remission	Unchanged	Unchanged
Present case 1	F	11	700	+	39	Midgut	B cell (centoblastic)	Surgery, AVmCP	Complete remission	Unchanged	Unchanged
Present case 2	F	18	990	+	40	Ileum	B cell (centoblastic)	PACOB ^f	Complete remission	Unchanged	Unchanged

^aThere is some evidence that this case is one of the initial three cases quoted by Waldman and colleagues¹; ^bcyclophosphamide, vincristine, prednisone; ^cvincristine, chlorambucil, prednisone; ^dadriamycin, teniposide, cyclophosphamide, prednisone; ^ecyclophosphamide, adriamycin, vincristine, prednisone; ^fprednisolone, adriamycin, cyclophosphamide, vincristine, bleomycin. +, present; NS, not stated; M, male; F, female.

the onset of lymphoma; and (c) persistent small intestinal diffuse lymphangiectasia in both patients after successful treatment of the lymphoma.

The association of primitive gastrointestinal protein loss with systemic lymphatic abnormalities has led to the suggestion that PIL may be part of a congenital disorder of the lymphatic system as a whole.¹³ But there is now evidence that the clinical spectrum of PIL is proving more protean than had been suspected originally, and that in addition to cases of systemic lymphatic abnormalities, primary lymphangiectasia confined to the intestine does exist.² None of our patients showed clinical evidence of peripheral lymphatic abnormalities (for example, asymmetric peripheral lymphoedema of the limbs) while both had recurrent symmetrical leg oedema caused by hypoalbuminaemia per se. Spontaneous fluctuations in the clinical severity of PIL, as observed in our patients and probably accounting for prolonged high clinical tolerance, have been reported previously.^{2 12}

To our knowledge, supervening lymphoma has been reported in only nine patients with PIL, 3–27 years after the clinical onset of PIL manifestations. A further patient who developed B cell lymphoblastic leukaemia has been reported.⁵ The characteristics of these patients are summarised in table 1.

Rather than being merely fortuitous, lymphoma may well be related to intestinal lymphangiectasia as a consequence of several mechanisms: (a) lymphoma may cause secondary intestinal lymphangiectasia by means of lymphatic channel blockade, an unlikely hypothesis in our patients for whom anatomical and/or clinical evidence of diffuse duodenojejuno-ileal PIL preceded the onset of lymphoma by several decades; (b) longstanding protein losing enteropathy may be resolved after combining chemotherapy and/or irradiation, as previously reported in two patients with lymphoma^{7 10}; in one, evidence was provided of the disappearance of lymphatic abnormalities on per oral duodenal biopsies five years after the end of lymphoma treatment. The hypothesis has been raised of an as yet undefined inflammatory process in these patients causing impairment of lymphatic flow which may have been coincidentally cured by a combination of chemotherapy, irradiation, and/or steroids¹⁴; (c) much more likely is the fact that lymphoma in PIL patients could well be related to immune deficiency. Several arguments support this. Firstly, the lag time between the onset of PIL and lymphoma may be very long, as in patients with primary immune deficiency and lymphoma⁴; in our patients, this lag time was more than four decades, to our knowledge the longest time reported. Secondly, a primary deficiency of B cell and/or helper T cell function has been suggested in PIL¹⁵ in association with the secondary immune deficiency induced by loss of immunoglobulins and lymphocytes^{16 17}; this hypothesis is supported by the reported persistence of immune disorders even after normalisation of Ig levels and by proteinaemia with dietary treatment^{18 19} and by

the presentation of multiple viral warts in our patients as in two other patients with lymphoma and PIL.^{6, 11} However, unlike patients with primary immunodeficiency syndromes, PIL patients do not exhibit clear evidence of depressed intestinal immunity: plasma cell number in duodenojejunal lamina propria was normal in both of our patients as in most of those reported previously. This finding is in accordance with the absence of an association in PIL of overt gut infection such as giardiasis compared with primary immune deficiency patients.^{20, 21}

Continuous loss of T cells and immunoglobulins into the gut may indeed be the decisive event in the onset of intestinal lymphoma in PIL. The role of Epstein-Barr virus²² and HTLV-1 infection cannot be considered for our patients (in particular for patient No 1 in whom it was sought), as in the single published case in which evidence for these infections was sought.⁹ Finally, the precise pathogenesis of lymphoma in these immunodepressed PIL patients has yet to be established. It may imply a defect in immunosurveillance, more specifically impairment in early detection and destruction of neoplastic cells which give rise to the lymphoma,²³ or increased loss of suppressor T cells having favoured growth of an autonomous B cell clone.²⁴ Cases of Waldenström's disease have been reported in association with acquired intestinal lymphangiectasia in the elderly but no significant correlation between such a secondary protein losing enteropathy and the occurrence of lymphoma has been reported; the rather shorter duration of protein losing enteropathy induced immunodeficiency in these patients may be an explanation.²⁵

In conclusion, our two cases of high grade B cell lymphoma associated with PIL support the hypothesis that PIL predisposes to lymphoma.

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