IMMUNOPROLIFERATIVE DISEASE OF THE GASTROINTESTINAL TRACT : A REPORT OF FIVE CASES

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INTRODUCTION

The term immunoproliferative small intestinal disease (IPSID) has been adopted by WHO (1975) to designate an entity characterised by diffuse dense infiltration of the mucosa of proximal small intestine with plasma cells as the main component. Alpha heavy chain disease has been identified in some of these patients. Nassar *et al.*, (1978) described 25 cases of IPSID with concomitant malignant lymphoma in the small intestine and/or mesenteric lymph nodes in Lebanon. Similar cases have been reported from many other places including Algeria (Irunberry *et al.*, 1970), Israel (Edelman *et al.*, 1966; Rappaport *et al.*, 1972), Iraq (Al-Saleem and Al-Bahrani, 1973), Iran (Nasr *et al.*, 1970), Italy (Bonomo *et al.*, 1972), Nigeria (Whicher *et al.*, 1977), South Africa in the non-white population (Kahn *et al.*, 1972), and England in patients of Mediterranean and Asian origins (Doe, 1975). The distribution of the cases, the histological picture of immunological disorder, and the fact that the concomitant lymphoma occurs in younger patients than in Western Europe or North America, suggest an ethnogeographical or environmental factor in the pathogenesis.

We present here 5 cases of immunoproliferative disease (IPD) of the gastrointestinal tract, 3 involving the proximal small intestine and 2 involving the stomach; concomitant malignant lymphoma was present in 4 of the 5 patients. One case of IPD and one case of IPD with lymphoma will be described in detail, while the main clinical data and pathological findings in the remaining cases are represented in Tables 1 and 2.

REPORT OF CASES

Case I, YT: The oldest patient in the series, this 69-year-old Buddhist monk of Chinese extraction had a history of abdominal pain relieved by antacids for many years with occasional melaena. Ten days before admission the pain became more severe, accompanied by anorexia, nausea, and a palpable mass in the epigastrium. On admission he was afebrile with pulse rate 84/min and blood pressure 140/80 mm. Hg. There was no superficial lymphadenopathy. A mass, 4 cm. in diameter, was palpable in the epigastrium, tender, soft to firm in consistency, with guarding. Investigations showed Hct 34%, WBC 10,700 cells/cmm., 90%N, 10% L.; blood chemistries were non-contributory; serum proteins were not examined. Chest x-rays showed calcified nodules in both upper lobes consistent with old tuberculosis. Plain x-rays of the abdomen showed free air under the diaphragm compatible with gut perforation, and an emergency laparotomy was performed.

At operation he was found to have a gastric ulcer with 1 cm. perforation on the anterior wall of the antrum near the lesser curvature, and a penetrating ulcer on the posterior wall, fixed to the pancreas. Regional lymph nodes were enlarged. No nodules were palpable in the liver. Subtotal gastrectomy with gastrojejunostomy and cauterisation of the ulcer bed on the pancreas

Table 1

Clinical data of 5 cases with IPD.

Case No.	Age Sex	Chief Complaints	Duration	X-ray findings
1. Y.T.	69/M	1. Abdominal pain with occasional melaena. 2. Palpable mass in epigastrium, nausea, ↑ pain	Many years 10+days.	Free air under diaphragm. (plain film only)
2. B.S.	56/M	Severe intermittent epigastric pain	1+mos.	Polypoid mass in stomach.
3. E.C.	38/M	1. LUQ mass 2. Melaena	2 mos. 3 wks.	Mass at LUQ ; multifocal involvement of duodenum & jejunum.
4. O.B.	5/F	Mobile RUQ mass	3 wks.	not obtained
5. P.M.	19/M	Abdominal pain & vomiting	3-4 mos.	Obstruction of 3rd part of jejunum.

Table 2

Pathological findings in 5 cases with immunoproliferative disease of the gastrointestinal tract.

Case No.	Organ involved	Macroscopic appearance	IPD	IBS	LN involved
1. Y.T.	Stomach	Diffuse thickening	mucosal & submucosal, focal transmural	0	focal IPD
2. B.S.	Stomach	Diffuse thickening mucosal + ulcers.	mucosal & submucosal	mucosal & submucosal	0
3. E.C.	Duodenum + jejunum	Diffuse thickening + multiple masses + mass in mesentery.	transmural + mesentery	transmural + mesentery	0
4. O.B.	Jejunum	Diffuse thickening	transmural	transmural	0
5. P.M.	Jejunum	Diffuse thickening with stricture + 2 mucosal ulcers.	mucosal & submucosal, focal transmural	mucosal & submucosal, focal transmural	0

IPD = immunoproliferative disease. IBS = immunoblastic sarcoma.

were performed. Pathological findings will be described below.

The post-operative course was uneventful. On follow-up visits the patient appeared quite well apart from occasional flatulence, 6 months after the operation.

Case 3, E.C. : This 38-year-old Thai man was admitted with a two-month history of a palpable mass in the left upper quadrant of the abdomen, extending as far as the umbilicus; this was followed by diarrhoea and melaena 2 weeks before admission; no haematemesis, epigastric pain or jaundice. Three years previously he had been investigated for intermittent pitting oedema of the legs and anaemia. There was no history of diarrhoea. *Trichomonas hominis* was found in the faeces; other laboratory findings were inconclusive. He received symptomatic treatment and did not return till the present time.

Physical examination on this admission showed moderate anaemia; there was no superficial lymphadenopathy. Pitting oedema was not noted on this occasion. An ill-defined mass was palpable in the left upper quadrant of the abdomen, firm in consistency, fixed, non-tender. The liver was just palpable.

Investigations showed Hb 8.6 gm/100 ml., WBC 13,750 cells/c.mm., 60%N, 2% eos., 30% L, 2%M. No ova or parasites were found in the faeces, and benzidine test was negative. Serum albumin was 3.7 gm/100 ml., globulin 3.6 gm/100 ml. There was slight impairment of upper small intestinal absorption, with 13% of the administered dose of D-xylose recovered in the urine. Radiological examination revealed a mass in the left upper quadrant with multifocal involvement of the duodenum and jejunum, suggestive of lymphoma. Liver scan showed hepatomegaly with no evidence of hepatocellular impairment or space-occupying lesion. On duodenoscopy there was diffuse nodular infiltration of the second and third parts of the duodenum with distortion of normal mucosal pattern, and early obstruction at the duodeno-jejunal junction. Jejunal biopsy was too superficial and non-diagnostic. A bone marrow aspirate was similarly non-diagnostic.

An exploratory laparotomy was performed. A hard irregular mass 8 × 6 × 6 cm was found encircled by and stretching the duodenum. Smaller tumour masses were found in the walls of the duodenum and proximal jejunum. Regional lymph nodes were enlarged. The liver, gall bladder, stomach and colon were not involved. The tumour masses and parts of the duodenum and jejunum were resected. Pathological findings will be described below.

The patient was started on cyclophosphamide 6 weeks after the operation. On his 4th visit, 2 months after the operation, he complained of nausea on taking cyclophosphamide, which was discontinued; an appointment was made for radiotherapy, which he failed to keep; the patient was lost to further follow-up.

PATHOLOGICAL FINDINGS

Immunoproliferative disease (IPD).

On gross examination, the subtotal gastrectomy specimen of the stomach in Case I, Y.T. showed 2 peptic ulcers one on the anterior wall of the antrum, 2.5 cm in diameter with a 1.5 cm perforation, and one on the posterior wall, also of the antrum, 5.5 × 2.5 cm with a 2 cm perforation. There was diffuse thickening of the stomach wall up to 1.5-2 cm with oedematous and hypertrophic rugae (Fig. 1). The serosa was thickened and opaque. Enlarged lymph nodes, 0.8-1.5 cm in size, were present on the greater and lesser curvatures.

Microscopically the main feature was a dense, diffuse, mixed infiltrate composed predominantly of plasma cells with smaller number of lymphoid cells (Fig. 2). Inter-

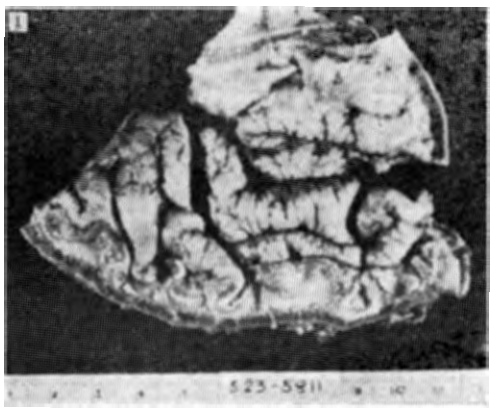

Fig. 1—Case 1 : Stomach showing hypertrophic and oedematous rugae.

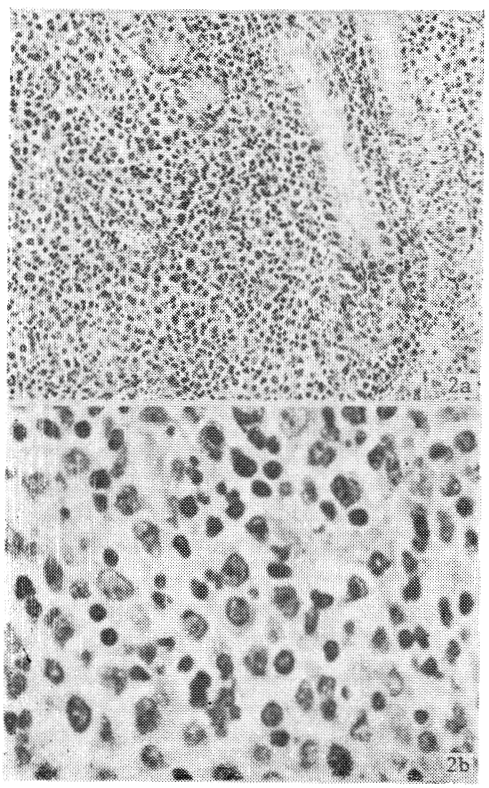

Fig. 2—Case 1 : (a) Dense diffuse infiltrate in the gastric mucosa with disruption of the glands (H & E × 100). (b) Higher magnification showing the infiltrate to be composed of plasma cells and lymphoid cells (H & E × 450).

spersed among these were large cells, 15-25 micra in size, with irregular cell borders, large, pale, oval nuclei which were often eccentrically placed, prominent nucleoli, and amphophilic cytoplasm containing fine pyronin-positive granules, consistent with immunoblasts (Fig. 3). There were also intermediate cells showing plasmacytoid differentiation. The infiltrate extended diffusely in the mucosa and submucosa, with focal transmural involvement, causing marked thickening of the stomach wall. Cells in the upper layers showed better differentiation, with mature plasma cells and lymphocytes near the surface epithelium, and immunoblasts, some binucleated (Fig. 3), a few atypical, in the deeper submucosa. The cellular infiltrate was accompanied by proliferation of newly formed capillaries. Foci of typical chronic inflammation were noted, with fibrosis, often consisting of hyalinised collagen fibres, and infiltration of small lymphocytes, some plasma cells, and variable number of eosinophils. Apart from the 2 peptic ulcers, the surface epithelium was relatively preserved although the mucosal folds were flattened and the glands disrupted and separated by the dense cellular infiltrate (Fig. 2). There was no monomorphous cellular proliferation.

Parts of the stomach near the margins of resection which were not involved by IPD showed slight to moderate infiltration of chronic inflammatory cells with lymphoid nodules and aggregates of variable size in the mucosa and submucosa. Near the peptic ulcers there was fibrosis of the submucosa and muscular layers. There was acute and chronic serositis with marked thickening and fibrosis.

Regional lymph nodes showed marked reactive hyperplasia with focal lymphoplasmacytic and immunoblastic infiltration, together with proliferation of newly formed capillaries, similar to that in the stomach. Again, there was no monomorphous cellular infiltration.

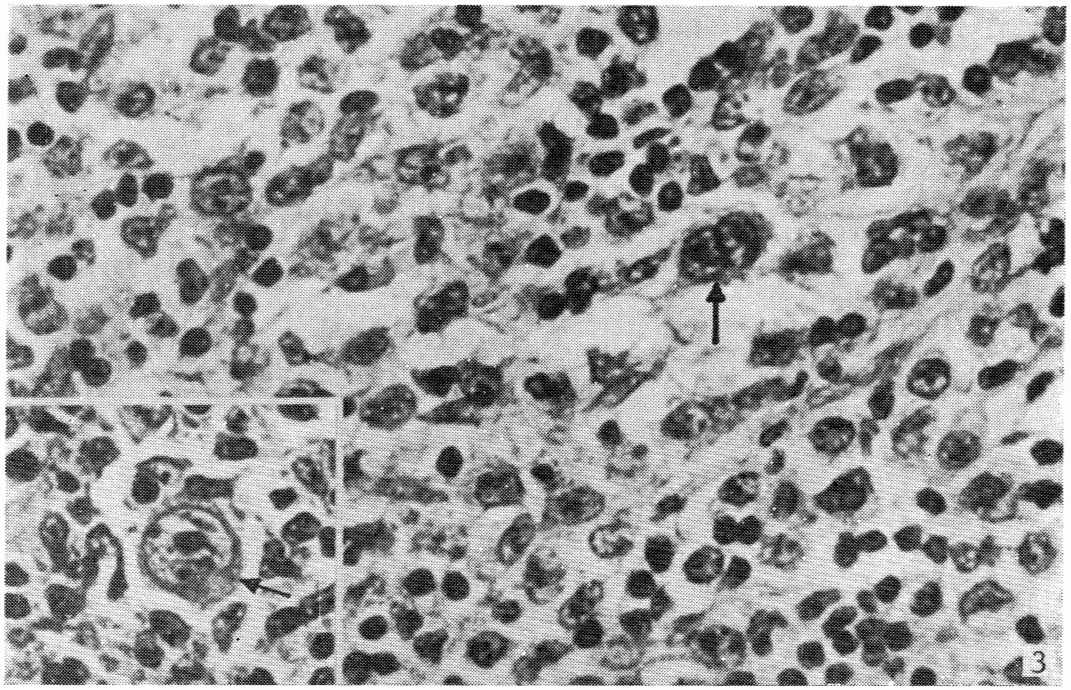

Fig. 3—Case 1 : "Classical" immunoblast (inset, with arrow) and binucleated immunoblast (arrow) scattered in the lymphoplasmacytic infiltrate (H & E × 450).

IPD with immunoblastic sarcoma (IBS).

The stomach in Case 2, BS, showed marked diffuse thickening, grey-white on the cut surface, with a central large shallow ulcer, 6 × 2 × 0.5 cm. The surrounding rugae were hypertrophic and oedematous (Fig. 4). In the remaining 3 cases, with small bowel lesions, the walls were diffusely thickened and similarly infiltrated by grey-white tissue. In case 3, E.C., this tissue also formed irregular nodular masses of variable size; one such mass measured 10 × 8 × 8 cm., extensively infiltrating the mesentery, with focal necrosis and haemorrhage (Fig. 5). In case 5, PM, a 2 cm. long stricture was also present; in this area there were 2 mucosal ulcers 0.5 cm. in size. In all cases regional lymph nodes were enlarged, 0.8-2.5 cm. in size.

Microscopic examination showed features of IPD similar to Case 1, with dense diffuse infiltrate composed of plasma cells, lymphocytes, immunoblasts and intermediate cells showing plasmacytoid differentiation. In these cases however, the immunoblasts were often atypical and some were cytologically malignant. The infiltrate caused marked thickening of the mucosa and submucosa; in the stomach the mucosal folds were flattened; in the small bowel the villi were shortened and deformed and the crypts disrupted and sparse. There were mucosal ulcers in Cases 2 and 5, but generally the surface epithelium was relatively preserved (Fig. 6). In Cases 2 and 5, IPD was predominantly mucosal and submucosal; in Cases 3 and 4 there was extensive transmural involvement Again there were foci of typical chronic inflammation, with fibrosis, often showing marked hyalinization of collagen fibres, and infiltration of small lymphocytes, plasma cells, and variable number of eosinophils.

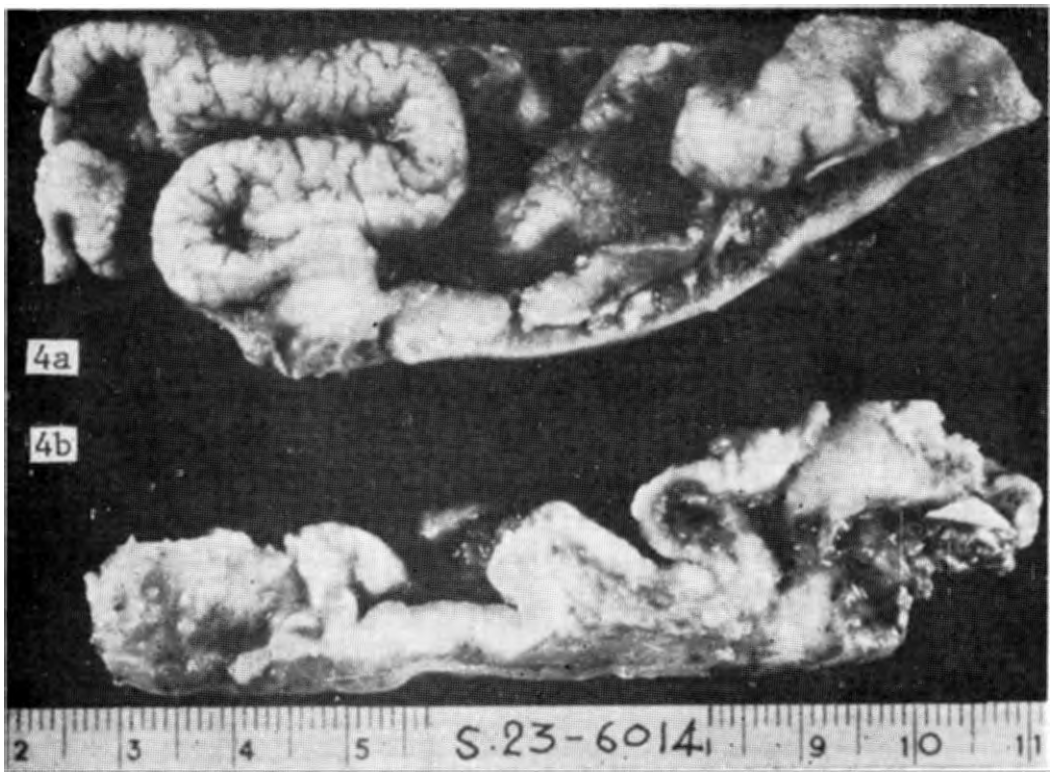

Fig. 4—Case 2 : Stomach, (a) Showing diffuse thickening, mucosal ulcer, hypertrophy and oedema of surrounding rugae; (b) Cut surface showing diffuse grey-white infiltrate.

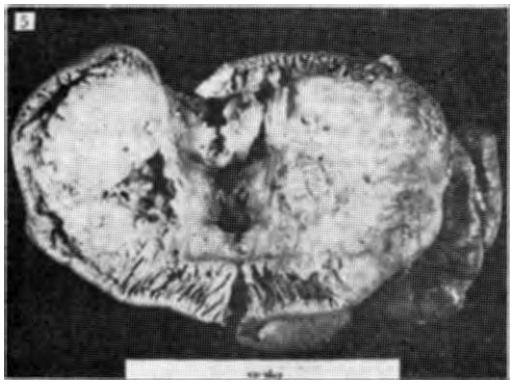

Fig. 5—Case 3 : Cut surface showing diffuse thickening of the wall of the small bowel with multiple nodular masses including one extensively involving the mesentery.

In these 4 patients there were large and small foci of monomorphous proliferation of immunoblasts. Some of these cells resembled the non-neoplastic immunoblasts previously described, while others were obviously atypical or cytologically malignant, with hyperchromatic nuclei, huge and often multiple nucleoli, thick and irregular nuclear membrane, and increased nuclear-cytoplasmic ratio (Fig. 7). The cytoplasm of most of these cells contained pyronin-positive material, even including markedly atypical cells with scanty cytoplasm, where a band of intense pyroninophilia hugged the nuclear membrane. Some foci showed a rather mixed appearance because of cells with plasmacytoid features or abnormal plasma cells. In Case 2, BS, there were many large binucleated or multinucleated cells resembling Reed-Sternberg cells (Fig. 8); in this patient some of the mature plasma cells and intermediate cells in the

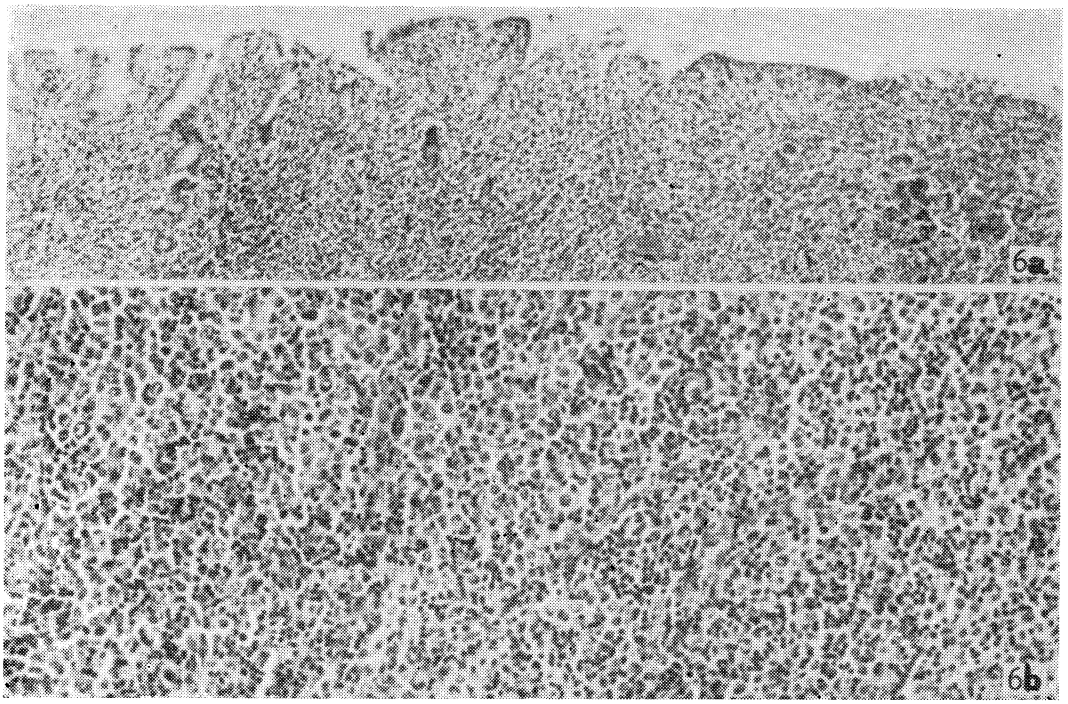

Fig. 6—Case 2 : (a) Flattening of mucosal folds with preserved surface epithelium (H & E × 35). (b) Dense diffuse infiltrate with focal monomorphous proliferation of immunoblasts (H & E × 100).

non-neoplastic IPD areas were similarly binucleated. Reticulin fibres were sparse within the neoplastic foci (Fig. 9). In Cases 2 and 5, the neoplastic process was mainly in the mucosa and submucosa, following the pattern of IPD in these patients. In Case 4, IBS extended laterally in the submucosa, beneath areas of mucosa not involved by IPD (Fig. 10), and focally through the muscular wall into the serosa and mesentery. In Case 3 there was massive tumour involvement of the mesentery.

As noted in Case 1, uninvolved parts the stomach in Case 2, mainly near the margins of resection, showed increased plasma cells and lymphocytes in the lamina propria, with lymphoid aggregates and nodules in the mucosa and submucosa. In Case 4, OB, the 5-year old girl, jejunal villi in uninvolved areas were mostly filiform but infiltreated by lymphoid and plasma cells, and there were numerous large lymphoid follicles with hyperactive germinal centres in the mucosa (Fig. 10). In Case 5, PM, who was 19 years old, filiform villi were still present but most were deformed, branching or blunted, while in Case 3, EC, who was 38 years old, most villi were flattened. In both patients there was moderate to marked lymphoplasmacytic infiltration of the lamina propria, and lymphoid follicles were increased in number and size though less strikingly so than in Case 4.

Regional lymph nodes were frequently enlarged. Microscopic examination showed enormous lymphoid follicles and dilated lymphatic sinuses with prominent sinus histiocytes; variable number of immunoblasts were found scattered throughout. None of the lymph nodes showed monomorphous immunoblastic proliferation; in fact, in 1 patient, Case 3, EC, lymph nodes appeared as

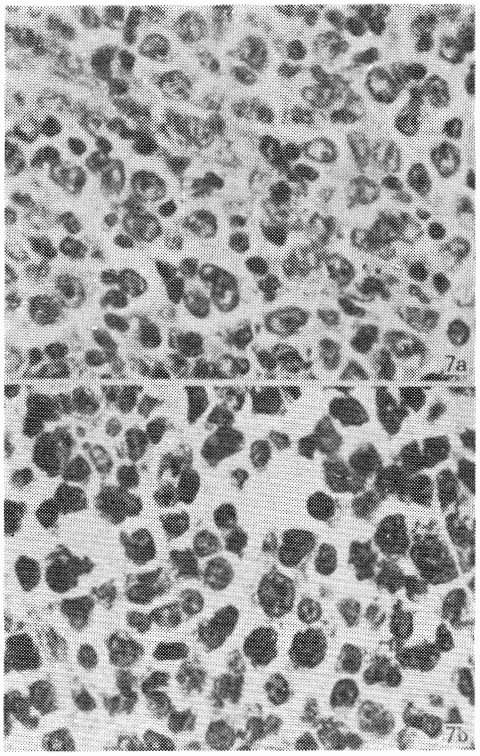

Fig. 7—Monomorphous proliferation of immunoblasts, in some cases resembling non-neoplastic immunoblasts (a), in others markedly atypical with hyperchromatic nuclei and scanty cytoplasm (b). (H & E × 450).

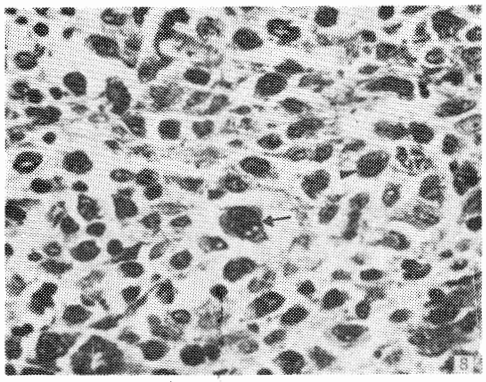

Fig. 8—Immunoblastic sarcoma with multinucleated immunoblast resembling Reed-Sternberg cell (long arrow) and cell with plasmacytoid differentiation (short arrow). (H & E × 450).

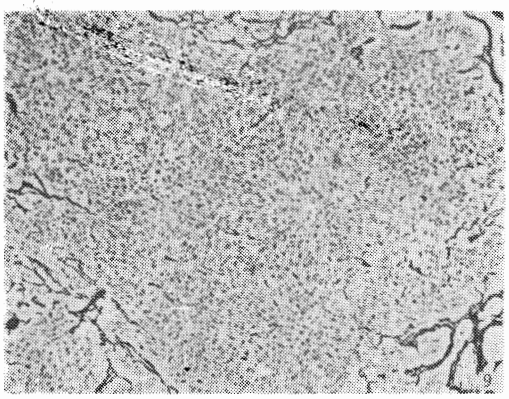

Fig. 9—Sparse reticulin fibres within neoplastic foci (Reticulin stain × 100).

islands of relative normality in a sea of neoplastic cells.

DISCUSSION

The characteristic histopathology in the five patients of this series was diffuse involvement of the stomach or small bowel by an immunoproliferative process, the infiltrate consisting predominantly of cells belonging to the plasma cell series including immunoblasts. In four of the patients frank malignant lymphoma, in the form of immunoblastic sarcoma, was present. In Case 1, although there was no monomorphous proliferation, the process could probably be regarded as premalignant because of transmural infiltration and focal involvement of a regional lymph node. On the other hand, this patient had 2 chronic peptic ulcers, one penetrating into the pancreas and one perforated, and the integrity of the separate layers of the stomach wall had been breached; thus the pattern of the immunoproliferative disorder could equally have been the result of "leakage", or merely followed the chronic inflammatory process through the gastric wall.

This histological pattern is similar to the condition known as "Mediterranean abdominal lymphoma" which occurs predominantly

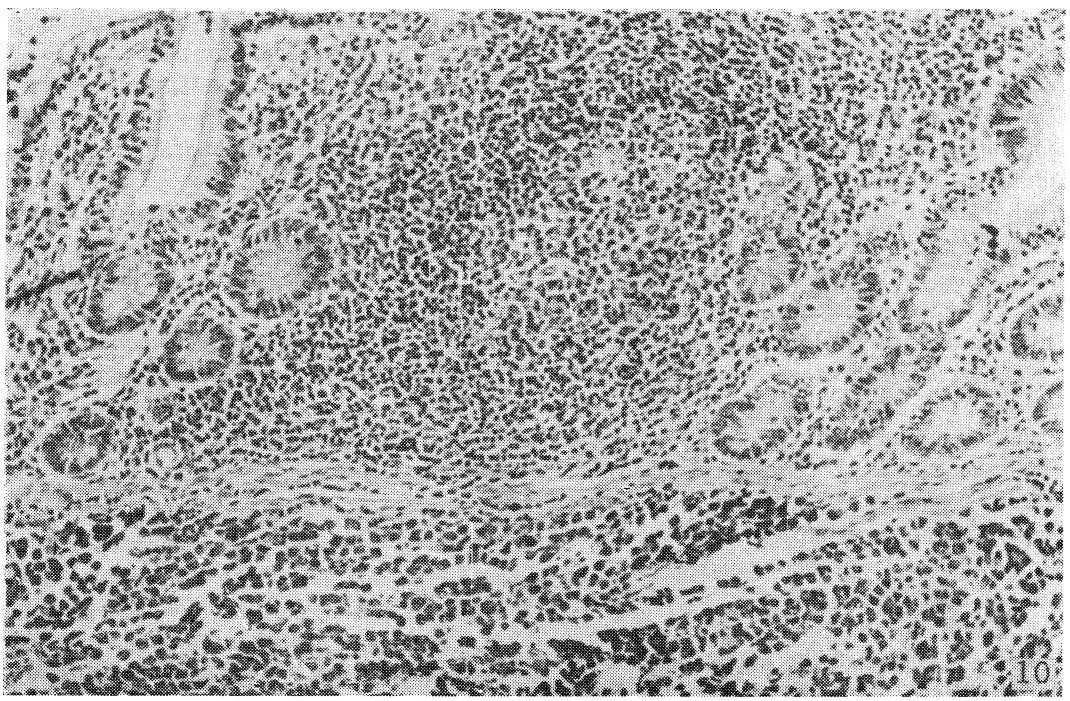

Fig. 10—Case 4 : Immunoblastic sarcoma extending in the submucosa of the jejunum, beneath uninvolved part of the mucosa with preserved villi and large lymphoid follicle with active germinal centre (H & E × 100).

in young patients, with malabsorption as the main presenting symptom, often preceding the lymphoma by many months or even years, accompanied by clubbing and peripheral oedema (Edelman, 1966; Nasr *et al.*, 1970; Rappaport *et al.*, 1972; Doe, 1975; Shahid *et al.*, 1975; Salem *et al.*, 1977; Nassar *et al.*, 1978). This is in contrast to primary gastrointestinal lymphoma in Western Europe or North America which affects older age groups and generally presents with abdominal pain, mass, or obstruction (Rappaport, 1966, 1972). Most of our patients presented as emergencies: Case 1 with perforated peptic ulcers, Case 3 with a mass and severe melaena necessitating blood transfusion, and Case 5 with intestinal obstruction. Case 2 had a short history of severe epigastric pain, and carcinoma of the stomach was suspected. The small intestine in Case 4 was received from a provincial hospital with no clinical data other than "mobile RUQ mass for 3 weeks". No history of chronic diarrhoea, let alone malabsorption syndrome, was elicited in any of the patients. A test for jejunal absorption in Case 3 showed only slight impairment. This patient had been investigated 3 years previously for peripheral oedema, but no cause was elucidated, and no oedema was present on this admission. None of the patients had clubbing.

Alpha heavy chain protein has been found in many patients with plasmacytic or lymphoplasmacytic infiltration of the small bowel mucosa (Seligmann, 1968, 1975: Irunberry, 1970; Bonomo *et al.*, 1972; Rambaud and Matuchansky, 1973; Ramot and Hulu, 1975; Whicher, 1977), and alpha chain disease is regarded as synonymous with Mediterranean abdominal lymphoma by some authors. In Poland, monoclonal IgG_3K was

found in the serum of a patient with diffuse lymphoid and plasmacytic proliferation in the gastrointestinal tract (Kopec *et al.*, 1974). In Nassar's series, alpha heavy chain protein was found in all 5 patients with pure plasma cell infiltration, but in only 3 of 8 patients with lymphoplasmacytic infiltration, a histological pattern similar to that found in our series. Unfortunately no preoperative serum electrophoresis or immunoelectrophoresis was performed in our cases as four patients presented as emergencies with no preoperative diagnosis, and one patient was in a provincial hospital. In Cases 2 and 3 serum proteins had been estimated preoperatively which showed high normal levels of globulin. Serum protein electrophoresis and immunoelectrophoresis were performed 7-10 days after the operation in Cases 1, 2 and 5, and were within normal limits. This may have reflected the fact that the main area of production of the abnormal protein had been removed; on the other hand, in some cases of IPSID the abnormal protein is not detectable in the serum and must be searched for in the jejunal fluid or at cellular level (Rambaud and Matuchansky, 1973; Salem *et al.*, 1975).

Nassar (1978) suggested that the natural history of the disease goes through 2 stages; a cellular immunoproliferative phase and a subsequent development of malignant lymphoma. Tumours of immunoblasts have been described in patients with angioimmunoblastic lymphadenopathy (Lukes and Tindle, 1975), severe rheumatoid arthritis, Hashimoto's disease, Sjogren's syndrome and systemic lupus erythematosus (Lukes and Collins, 1974; Pierce *et al.*, 1979), among diseases that can be termed "chronic abnormal immune disorders". Mediterranean abdominal lymphoma, alpha chain disease or immunoproliferative small intestinal disease have been reported mainly from countries or populations with frequent diarrhoea and intestinal infection, and local and sustained antigenic stimulation may play a part in the pathogenesis, with subsequent development of an abnormal clone in some patients. Antibiotics alone have reportedly cured a small number of patients with alpha chain disease (Ramot and Hulu, 1975; Rhodes *et al.*, 1980). Overgrowth of bacteria, intestinal parasites and oncogenic viruses have all been suggested as the causative organism, but the evidence has so far been inconclusive. In our series, Case 3 had a past history of *Trichomonas hominis* infection though none was present on this admission; stool examinations were negative for pathogenic bacteria, ova or parasite in Cases 1, 2 and 5.

Examination of the uninvolved parts of the intestinal mucosa showed normal filiform villi only in Case 4, the 5-year-old girl. In Cases 3 and 5, the villi were generally deformed shortened, branching, fused or flattened, and increased plasma cells and lymphocytes were present in the lamina propria. These findings were similar to the histological picture in small bowel biopsies of 54 subjectively normal Thais in a study by Sprinz *et al.*, (1962) who felt that the pattern resembled lesions described in some North American patients with malabsorption syndrome. D-xylose absorption was also impaired in 9 of 20 patients tested in their study. Sprinz postulated that such changes were related to irritants, such as highly spiced food, enteric pathogens and parasites, or toxic products, acting on intestinal mucosa already predisposed to inflammatory response by nutritional factors. This hypothesis would appear consistent with the fact that this disorder occurs primarily in "underprivileged" populations.

Although there have been many reports of immunoproliferative disease of the gastrointestinal tract, the majority were from the Mediterranean region, and we feel that physicians outside this belt should be alerted to the existence of this disease in less usual places, in the hope that there may be fuller investiga-

tions and more effective treatment in the future.

SUMMARY

Five patients with immunoproliferative disease of the gastrointestinal tract are presented. The main pathological feature was dense diffuse lymphoplasmacytic and immunoblastic infiltration of the mucosa and submucosa, of the proximal small bowel in 3 cases and the stomach in 2. Four of the five patients had concomitant immunoblastic sarcoma. The clinical presentation and pathological findings are compared and contrasted with those of "Mediterranean abdominal lymphoma" and alpha chain disease, and the possible role of ethnogeographical and environmental factors in the pathogenesis are discussed.

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