IMMUNOPROLIFERATIVE SMALL INTESTINAL DISEASE (IPSID) IN THAILAND

Chutima Pramoolsinsap[1], Sucha Kurathong[1], Vichai Atichartakarn[2] and Pravat Nitiyanand[3]

[1]Division of Gastroenterology and Tropical Medicine, Department of Medicine; [2]Division of Hematology, Department of Medicine; [3]Pathology Department, Ramathibodi Hospital, Mahidol University, Rama 6 Road, Bangkok 10400, Thailand

Abstract. Immunoproliferative small intestinal disease (IPSID) is prevalent in the Mediterranean region and in many Third World countries but is rare in Southeast Asia. Between 1980-1990, 4 cases of IPSID were admitted to Ramathibodi Hospital, Bangkok. Three were males and the mean age was 32 ± 20.2 years. All patients presented with chronic diarrhea of 7 months to 6 years duration, and weight loss of 15 to 31 kg. All were malnourished, three cachectic, and one patient showed growth retardation. Intestinal parasites were found in all cases: two had multiple infections and three had uncommon protozoal infections (coccidium, cryptosporidium). Barium radiographs revealed intestinal mucosal fold thickening with malabsorption pattern in all cases. Alpha chain IgA was detected in one patient. The remainder underwent exploratory laparotomy and the histological finding was of plasmalymphocytic infiltration of the small intestinal mucosa. All patients responded to oral tetracycline with complete remission occuring in one case. During the follow-up period, 3 cases had progressive retractable clinical courses but all died 2 to 5 years after the diagnosis. The causes of death in these patients were secondary bacterial infection (1 case), intestinal tuberculosis (1 case), fungal infection (1 case) and immunoblastic sarcoma in another case. The results of this study confirm the occurrence of IPSID in Thailand. IPSID responds to oral antibiotic therapy and complete remission may be achieved during the early reversible benign phase, thus an awareness of its occurrence is of clinical importance.

INTRODUCTION

Immunoproliferative small intestinal disease (IPSID), is a proliferative disorder of IgA-producing B-lymphocytes with or without detectable abnormal serum alpha-heavy chain of unknown etiology (WHO, 1976; Seligmann and Rambaud, 1978; Haghighi and Wolf, 1986; Khojasteh and Haghighi, 1990). IPSID represents a spectrum of histological changes of the enteromesenteric system ranging from benign lymphoid infiltration to malignant lymphoproliferative neoplasms. The disease is clinically manifested by chronic diarrhea, intestinal malabsorption, weight loss and abdominal pain (Lewin *et al,* 1976; WHO, 1976; Nassar *et al,* 1978, Mir-Madjlessi and Mir-Ahmadian 1979; Khojasteh and Haghighi, 1990).

IPSID is a relatively common disease in the Mediterranean and Middle Eastern regions and was originally called "Mediterranean abdominal lymphoma" or "Eastern lymphoma" (Azar, 1962; Seligmann *et al,* 1968; WHO, 1976). At first the disease seemed primarily to affect Arab populations but there now appears to be a wider spectrum of racial incidence. More cases have been recorded in Africa (Novis 1979; Rambaud, 1983), South and North America (Seligmann *et al,* 1971; Cohen *et al,* 1978) and the Indian subcontinent (Khojasteh and Haghighi, 1990). In contrast, the disease appears to be extremely rare in Western countries (Neudorf *et al,* 1983; McDonald *et al,* 1985; Matuchansky *et al,* 1988). IPSID is known to be associated with a low socioeconomic background among the rural populations of Third World countries but there have been only few reports from countries in Southeast Asia (Seligmann, 1977; Shih *et al,* 1987; Sonakul and Pacharee, 1987). In Thailand, only one case with the classical features of IPSID has been described (Atichartakarn *et al,* 1982). This study aimed evaluate the occurrence and clinical course of IPSID in Thai patients admitted to Ramathibodi Hospital during the last decade.

Correspondence to : Dr Chutima Pramoolsinsap, Division of Gastroenterology and Tropical Medicine, Department of Medicine, Ramathibodi Hospital, Mahidol University, Rama 6 Road, Bangkok, Thailand.

MATERIALS AND METHODS

Patients

All patients who were admitted to and diagnosed as IPSID at Ramathibodi Hospital during 1980-1990 were included in the study. The diagnosis of IPSID was based on clinical symptoms (chronic diarrhea, weight loss) in association with either the histopathological findings of IPSID or the presence of serum alpha-heavy chain immunoglobulin (Kharazmi *et al*, 1976). Histological findings in small intestine and other pathological specimens (mesenteric lymph nodes) were consistent with those described by Galian *et al* (1977) showing diffuse lymphoplasmacytosis and cellular infiltration (with or without malignant lymphoma). After the first hospital admission, all patients were followed up as out-patients every 1-3 months for clinical assessment and laboratory investigations. Patients were readmitted to the hospital if clinically indicated.

RESULTS

Demographic characteristic of the patients

Between 1980-1990, 4 patients with IPSID were admitted to Ramathibodi Hospital. Their mean age (SD) was 32 (20.2) years and 3/4 cases were male. Three of the patients were from the Northeast of Thailand (Table 1). All patients had been referred from provincial hospitals where the results of clinical investigations had been inconclusive and clinical responses to therapy had been unsatisfactory.

Symptoms and signs

All four patients presented with persistent chronic diarrhea ranging from 7 months to 6 years duration and weight loss of 15 - 31 kg (Table 1). The bowel frequency ranged between 2-8 times per day and a loss up to 1,000 ml per bowel movement was observed in case 2. Stool appearances were non-bloody, non-mucoid and of semi-solid to watery consistency. All patients were undernourished and 3 were in cachectic conditions. The 15 year old patient had growth retardation with the absence of secondary sexual characteristics. Other associated symptoms and physical signs are shown in Table 1. None of the cases had splenomegaly or clubbing of fingers.

Laboratory findings

Laboratory evidence of malabsorption was noted in 3/4 cases; anemia (hematocrit $< 30\%$), hypoalbuminemia (< 2.8 mg%) and hypocalcemia (corrected calcium < 8.0 gm%). D-xylose absorption test results were abnormal in all cases, confirming intestinal malabsorption. The mean (SD) 2 hour serum D-xylose was 6.75 (6.51) mg% (normal > 30 mg%) and 5 hour urine D-xylose was 0.48 (0.25) gm% (normal > 1 gm%). All cases had low serum cholesterol levels [mean (SD) = 81.8 (13.0) mg%]. Liver function test results were unremarkable with the exception of a two-fold elevation in alkaline phosphatase activity in cases 2 and 4.

Table 1

Clinical features at presentation.

Case No.	1	2	3	4
Age	61	29	23	15
Sex	Male	Male	Female	Male
Province of origin	Mahasarakam	Bangkok	Ubon	Loei
Occupation	Farmer	Laborer	Teacher	Farmer
Duration of diarrhea	2 years	1 year	7 months	6 years
Weight loss (kg)	18	31	15	Growth retardation
Abdominal pain	No	Yes	No	No
Nausea	Yes	No	Yes	No
Fever	No	Yes	No	No
Abdominal mass	No	Yes	No	No
Hepatomegaly	No	No	Yes	Yes

Repeated stool examinations revealed intestinal parasites in all patients. Multiple intestinal parasites were found in two and uncommon protozoan infections in three cases (Table 2). Stool culture from three patients grew Gram-negative enteric organisms. Urine examination indicated proteinuria (1 + to 3+) with oxalate crystals and granular cast in cases 1 and 2 and numerous red cells and white cells in case 4 who also had a concomitant urinary tract infection with *Escherichia coli*. Bone marrow biopsy and histological analysis revealed hypercellular marrow with mild plasmacytosis in all cases.

Analysis of serum (by protein and immunoelectrophoresis, and immunoquantitation) revealed variable abnormal findings but a high level of serum IgA was consistently found in all cases (Table 3). Immunoelectrophoresis from case 1 revealed the presence of alpha-heavy chain of IgA in serum, duodenal fluid and urine.

Radiological findings

Barium radiographs of small bowel revealed intestinal mucosal fold thickening consistent with a radiological pattern of malabsorption in all cases.

Table 2

Results of stool examinations.

	Case numbers			
	1	2	3	4
Parasite	*S. stercoralis* *G. lamblia* *O. viverrini* Hook worm Tape worm	*Coccidium**	*Coccidium** *G. lamblia* *E. vermicularis*	*Cryptosporidium*
Culture	*E. coli* *P. aeroginosa*	-	*E. coli* *Klebsiella*	*E. coli* *S. enteritidis* *Citrobacter*

* = unidentified species

Table 3

Results of serum immunoglobulin levels.

Parameters	Normal value	Case number			
		1	2	3	4
Albumin (mg%)	35-55	20.0	52.4	40.8	23.9
Globulin (mg%)					
Alpha 1	2-4	5.0	2.6	4.7	4.9
Alpha 2	5-9	23.0	11.2	22.8	9.4
Beta	6-11	11.0	13.6	10.7	10.1
Gamma	7-17	9.0	20.1	21.1	51.7
IgG (mg/ml)	7.7-11.3	3.6	2.6	16.2	30.8
IgM (mg/ml)	0.9-1.7	0.2	0.8	1.1	2.4
IgA (mg/ml)	0.8-2.0	87.5	10.8	5.2	26.0
Immunoelectrophoresis		abnormal	normal	abnormal	normal

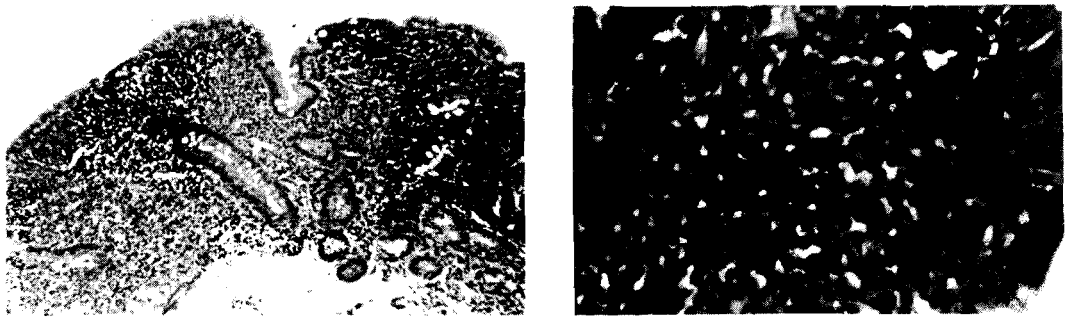

Fig 1—Photomicrograph of small intestine showing diffuse lymphoplasmacytic infiltration with villous atrophy (hematoxylin eosin stain; left × 40; right × 275).

Other associated abnormalities were submucosal nodular infiltration (cases 2 and 3) and multiple duodenal ulcers (case 2).

IVP studies done in 3 cases showed abnormal findings; a right staghorn calculus with chronic pyelonephritis (case 1), a partial obstruction of left proximal ureter by an extrinsic mass (case 2) and left hydronephrosis with a renal calculus (case 4). Lymphangiograms performed in cases 1 and 3 were unremarkable. Ultrasonographic studies performed in cases 3 and 4 revealed mild hepatosplenomegaly. Computerized tomography in case 4 revealed right hypertrophic and left hydronephrotic kidneys without abdominal lymphadenopathy.

Pathological studies

Multiple duodenal and jejunal biopsies from all cases showed diffuse lymphoplasmacytic cellular infiltration in the lamina propria. Cases 3 and 4 were also associated with chronic inflammation of intestinal mucosa with clubbing of villi and the presence of protozoa in jejunal crypts (coccidia in cases 3 and 4; cryptosporidium in case 4). Liver biopsy showed fatty changes (case 2), reactive hepatitis (case 3), reactive sinus histiocytosis with lymphocytic infiltration of portal tract (case 4). With the exception of one patient (case 1) who had circulating alpha chain immunoglobulin, 3 other cases underwent exploratory laparotomy which was carried out on first admission in 2 patients (cases 2 and 4). Case 3 was readmitted 2 months later with a relapse when abdominal exploratory laparotomy was performed. Histological findings in small bowel resections from all the three showed diffuse lymphocytoid plasma cell infiltration of the intestinal mucosa (Fig 1).

Treatment and clinical course

During hospital stay, all cases were given specific antihelmintics and nutritional supportive therapy. An initial 5-7 day course of an antibiotic (metronidazole or tetracycline) was given to all patients for intestinal bacterial overgrowth. In addition, one patient (case 4) received a 10 day course of gentamicin for the urinary tract infection.

Following the diagnosis of IPSID during the first hospital admission, tetracycline was given to all patients and their initial clinical responses were satisfactory. During the first 6-8 weeks of follow-up, all cases showed clinical improvement with cessation of diarrhea and weight gain of 5-7 kg.

None of the patients attended subsequent follow-ups regularly and tetracycline was taken only intermittently. All patients were subsequently readmitted to hospital for 4 or 5 times with bacterial infections or exacerbation of clinical conditions. The first case was readmitted 9 months after the first admission for right pyelonephrolithotomy. He was well with a complete clinical remission for 1 year, then lost to follow-up for 4 years before returning to the hospital because of pulmonary infection. This patient died of respiratory failure on the third admission, 5 years after the diagnosis. The second case progressed to malignant lymphoma (immunoblastic sarcoma stage IVB), from which he died 3.5 years after the initial diagnosis. The third case had a relapse after two months of tetracycline treatment. On exploratory laparotomy, she was found to have concurrent intestinal tuberculosis of ileum. Despite being given appropriate

antituberculous therapy and the continuation of tetracycline, the patient died 2 years after the diagnosis. The fourth case had persistent cryptosporidiosis despite taking several courses of antibiotics (spiramycin, erythromycin, sulfamethoxazol-pyrimethamine). He took tetracycline intermittently and had repeated relapses with urinary tract infections resulting in 4 further hospital admissions. On the fifth admission, he underwent nephrostomy for pus drainage and removal of pelvic and multiple muddy renal calculi. Twenty days after the operation or about 2 years after the diagnosis, the patient died from disseminated candidiasis.

DISCUSSION

This study documents the occurrence of IPSID in Thailand which is comparatively much less common than other diseases associated with poverty in the Third World. During the last decade, there have been only 4 cases with a confirmed diagnosis of IPSID referred to an 800-bed reference and teaching hospital. Nevertheless, the demographic characteristics of these Thai patients were similar to those previously reported from Arab countries (Rambaud, 1983; Khojasteh and Haghighi, 1990) *ie* young males from low socio-economic backgrounds (in the Northeastern part of Thailand). All our patients presented with the classical features of IPSID *ie* persistent chronic diarrhea, malnourishment and a progressive weight loss (Lewin *et al,* 1976; WHO, 1976; Nassar *et al,* 1978; Mir-Madjlessi and Mir-Ahmadian, 1979). These clinical features are attributed primarily to the presence of diffuse lymphoplasmacytic infiltration in the lamina propria, particularly in the proximal intestine (Nassar *et al,* 1978). Clubbing of the fingers and toes, another clinical hallmark of IPSID which has been previously reported from the Mediterranean region, was not seen in any of our patients.

The presence of anomalous serum alpha-heavy chain protein is the most specific serologic marker of IPSID and is detected in 20% to 87% of the patients (Seligmann, 1975; Lewin, 1976; Rambaud, 1983). It has been postulated that an unknown chronic antigenic stimulus results in proliferation of IgA producing cells in the lamina propria which leads to a monoclonal proliferation of plasma cells producing the abnormal protein (Novis, 1979; Seligmann, 1975). The concomitant intestinal parasitic and/or bacterial infections which usually accompany IPSID may provide such an antigenic stimulus (Rambaud and Seligmann 1976). Conversely, these concurrent infections may result from immuno-compromise caused by IPSID itself. (Zlotnick and Evy, 1971; Kharazmi *et al,* 1978). In accordance with previous reports, all our patients had intestinal parasitic infestation, some with uncommon protozoa *(Coccidium* or *Cryptosporidium)* and three patients also had bowel infections with *Escherichia coli* and other Gram negative enteric organisms.

IPSID may also be associated with other diseases. Hypokalemic nephropathy in IPSID is rare but is associated with poor prognosis (Manousos *et al,* 1974; Economidou *et al,* 1976). Factors responsible for this renal dysfunction are not known but it is not related to the duration of malabsorption or the level of serum potassium (Economidou *et al,* 1976). In this study, one patient had associated hypokalemic nephropathy and two had renal calculi. The other patient had a coinfection with tuberculosis, consistent with reports in Arab patients (Bucker *et al,* 1978). Further evaluations are needed to clarify possible significance of these clinical associations in IPSID, as both renal tubular acidosis with renal calculi and tuberculosis are common in the Northeast of Thailand (Pramoolsinsap *et al,* 1984).

Radiological examinations of the small bowel in IPSID is almost always revealed an extensive bowel disease (Ramos *et al,* 1978). All patients in this study had intestinal mucosal fold thickening with radiologic patterns of malabsorption. However, these findings are not readily distinguishable from Western lymphoma, tropical sprue or any other common causes of chronic diarrhea with intestinal malabsorption in the tropics (*eg* capillariasis, giardiasis, strongyloidiasis, etc). In areas where facilities for alpha-heavy chain determination are not available, routine quantity and quality determination of immunoglobulin may be supportive of the diagnosis. In accordance with other reports, all patients had abnormal globulin profiles together with elevated levels of serum IgA (Kharazmi *et al,* 1976).

IPSID manifests itself as a spectrum of abnormal immunocytic proliferation, ranging from a

possibly benign and reversible early stage to a late neoplastic disease of a malignant lymphoma (Galian *et al,* 1977; Khojasteh and Haghighi, 1990). All three patients who underwent abdominal surgery had diffuse mature lymphoplasmacytic proliferation of the ileum mucosa and one patient subsequently progressed to immunoblastic sarcoma. For diagnosis and staging of IPSID, multiple per oral biopsy samples via endoscopy and/or multiple resections from various segments of the small intestine are required (WHO, 1976; Salem *et al,* 1977).

In the early stages of IPSID, a dramatic and protracted clinical remission, with or without disappearance of lymphoid infiltration, may be induced by oral antibiotics alone (Galian, 1977; Nassar, 1978; Khojasteh and Haghighi, 1990). Tetracycline is the drug of choice and should be continued for at least 6 months (WHO, 1976; Seligmann and Rambaud, 1978; Khojasteh and Haghighi, 1990). All our patients responded satisfactorily to initial treatment with tetracycline. One patient achieved complete clinical, histological and immunological remission for 5 years. If relapse occurs during therapy, further investigation to look for any concurrent infections is essential. This phenomenon was observed in one patient who had a relapse after 2 months of the treatment because of co-infection with intestinal tuberculosis.

IPSID requires long-term treatment, frequent follow-ups and is associated with a poor prognosis. The reported survival rates vary from weeks to more than a decade (Gilinsky *et al,* 1987; Bowie and Hill, 1988). In this study, none of the patients attended follow-up regularly nor received regular medical attention. Following initiation of oral tetracycline, their survival times ranged from 2 to 5 years. The causes of death were similar to those reported previously, *ie* severe cachexia, concurrent infections or uncontrolled malignancy (WHO, 1976; Salem *et al,* 1977)

The present study confirms the occurrence of IPSID in Southeast Asia. A high index of clinical suspicious in patients with the classical clinical features and routine use of immunoselection may lead to the detection of more cases. In areas where the facility for alpha heavy chain detection is not possible, immunological investigation and histological analysis of pathological specimens are of diagnostic value. Our own experience and that of others (Seligmann and Rambaud, 1978) indicates that administration of tetracycline in the early stage of IPSID results in full clinical remission. Therefore an awareness of the incidence and increased efforts to detect the disease before the neoplastic phase are of clinical importance.

REFERENCES

Atichartakarn V, Kurathong S, Nitiyanand P, *et al.* Alpha chain disease in a Thai man. *Southeast Asian J Trop Med Public Health* 1982; 13 : 120-6.

Azar HA. Cancer in Lebanon and the Near East. *Cancer* 1962; 15 : 66-78.

Bowie MD, Hill ID. Alpha-chain disease in children. *J Pediatr* 1988; 122 : 46-9.

Bucker CD, Clift RA, Sanders JE, *et al.* Protective environment for marrow transplant recipients. A prospective study. *Ann Intern Med* 1978; 89 : 893-901.

Cohen HJ, Gonzalvo A, Krook J, Thompson TT, Kremer WB. New presentation of alpha heavy chain disease: North American polypoid gastrointestinal lymphoma: Clinical and cellular studies. *Cancer* 1978; 41 : 1161-9.

Economidou JC, Manousos ON, Katsaros D. Alpha-chain disease causing kaliopenic nephropathy and fatal intestinal perforations. *Am J Dig Dis* 1976; 21 : 577-85.

Galian A, Lecestre MJ, Scotto J, *et al.* Pathological study of alpha-chain disease, with special emphasis on evolution. *Cancer* 1977; 39 : 2081-101.

Gilinsky NH, Novis BH, Wright JP, Dent DM, King H, Marks IN. Immunoproliferative small-intestinal disease: clinical features and outcome in 30 cases. *Medicine* 1987; 66 : 438-46.

Haghighi P, Wolf PL. Alpha-heavy chain disease. *Clin Lab Med* 1986; 6 : 477-89.

Kharazmi A, Haghighi P, Haghshenas M, Nasr K, Abadi P, Rezai HR. Alpha-chain disease and its association with intestinal lymphoma. *Clin Exp Immunol* 1976; 26 : 124.

Kharazmi A, Rezai MH, Abadi P, Nasr K, Haghighi P, Haghshenas M. T and B lymphocytes in alpha-chain disease. *Br J Cancer* 1978; 37 : 48-54.

Khojasteh A, Haghighi P. Immunoproliferative small intestinal disease: Portrait of a potentially preventable cancer from the Third World. *Am J Med* 1990; 89 : 483-90.

Lewin KJ, Kahn LB, Path MM, Novis BH. Primary intestinal lymphoma of "Western" and "Mediterranean" type, alpha chain disease and massive plasma cell infiltration : a comparative study of 37 cases. *Cancer* 1976; 38 : 2511-28.

Manousos ON, Mountokalakis TH, Katsaros D, Economidou J, Merikas G. Reversible kaliopenic nephropathy in two cases of Mediterranean lymphoma (alpha-chain disease). In: Papadimitriou TM, ed. Proc Balkan Meeting on Renal Diseases. 1974, pp 123-9.

Matuchansky C, Touchard G, Babin P, Lemaire M, Cogne M, Preud'homme JL. Diffuse small intestinal lymphoid infiltration in nonimmunodeficient adults from Western Europe. *Gastroenterology* 1988; 95 : 470-7.

McDonald GB, Schuffler MD, Kadin ME, Tytgat GNJ. Intestinal pseudoobstruction caused by diffuse lymphoid infiltration of the small intestine. *Gastroenterology* 1985; 89 : 882-9.

Mir-Madjlessi SH, Mir-Ahmadian M. Alpha-chain disease. A report of eleven patients from Iran. *J Trop Med Hyg* 1979; 11 : 229-36.

Nassar VH, Salem PA, Shahid MJ, *et al.* "Mediterranean abdominal lymphoma" or immunoproliferative small intestinal disease. Part I: Clinical aspects. *Cancer* 1978; 41 : 2941-7.

Nassar VH, Salem PA, Shahid MJ, *et al.* "Mediterranean abdominal lymphoma" or immunoproliferative small intestinal disease: Part II: Pathological aspects. *Cancer* 1978; 41 : 1340-54.

Neudorf S, Snover D, Filipovich A. Immunoproliferative small intestinal disease (Letter). *N Engl J Med* 1983; 309 : 1126.

Novis BH. Primary intestinal lymphoma in South Africa. *Isr J Med Sci* 1979; 15 : 386-9.

Pramoolsinsap C, Kurathong S, Lerdverasirikul P. Abdominal tuberculosis: An analysis of 37 patients. *Ramathibodi Med J* 1984; 7 : 249-62.

Rambaud JC. Small intestinal lymphomas and alpha-chain disease. *Clin Gastroenterol* 1983; 12 : 743-66.

Rambaud JC, Seligmann M. Alpha-chain disease. *Clin Gastroenterol* 1976; 5 : 341-58.

Ramos L, Marcos J, Illanas M, *et al.* Radiological characteristics of primary intestinal lymphoma of the "Mediterranean" type: observations on twelve cases. *Radiology* 1978; 126 : 379-85.

Salem PA, Nassar VH, Shahid MJ, *et al.* "Mediterranean abdominal lymphoma" or immunoproliferative small intestinal disease. Clinical aspects. *Cancer* 1977; 40 : 2941-7.

Seligmann M, Danon F, Hurez D, Mihaesco E, Preud' homme JL. Alpha-chain disease: a new immunoglobulin abnormality. *Science* 1968; 162 : 1369-97.

Seligmann M, Mihaesco E, Frangione B. Studies on alpha chain disease. *Ann NY Acad Sci* 1971; 190 : 487-500.

Seligmann M. Alpha-chain disease: Immunoglobulin abnormalities, pathogenesis and current concepts. *Br J Cancer* 1975; 31 (Suppl II) : 356-61.

Seligmann M. Immunobiology and pathogenesis of alpha-chain disease. In: Immunology of the Gut. Ciba Foundation Symposium, no. 46. Amsterdam: Elsevier, Excerpta Medica, 1977; p 263.

Seligmann M, Rambaud JC. Alpha-chain disease: a possible model for the pathogenesis of human lymphoma. In: Twomey JJ, Good RA, eds. Comprehensive immunology, the immunopathology of lymphoreticular neoplasms. New York: Plenum Medical Books, 1978; 425-47.

Shih LY, Liaw SJ, Hsueh S, Kuo TT. Alpha-chain disease. Report of a case from Taiwan. *Cancer* 1987; 59 : 545-8.

Sonakul D, Pacharee P. Immunoperoxidase study on paraffin sections of gastrointestinal lymphoreticular lesions. *Southeast Asian J Trop Med Public Health* 1987; 188 : 467-78.

World Health Organisation. Memorandum on alpha chain disease and related small-intestinal lymphoma. *Bull WHO* 1976; 54 : 615-24.

Zlotnick A, Evy M. Alpha chain disease: a variant of Mediterranean lymphoma. *Arch Intern Med* 1971; 128 : 432-6.