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Alpha-chain disease and its association with intestinal lymphoma

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SUMMARY

Twenty-seven intestinal lymphoma patients were studied. Abnormal alpha-chain immunoglobulin was detected in the sera of seven of these patients. The alpha-chain disease patients were from the rural areas of Southern Iran. They were of low socio-economic status and their age ranged from 15–44 years. Predominant clinical features were malabsorption, diarrhoea, abdominal pain, vomiting, and weight loss. Infiltration of mucosa of the small intestine with plasma cells and also distortion and flattening of the villi were common histopathologic characteristics of these patients. Involvement of mesenteric lymph nodes with infiltration of tumour cells was observed in a number of cases. Protein studies revealed no significant differences between the serum immunoglobulin levels of these patients and normal values. Immunoelectrophoresis using monospecific antiserum against H-chain of human IgA demonstrated the abnormal precipitin band of alpha-chain disease protein.

INTRODUCTION

The so-called Mediterranian Lymphoma (ML) is a disease of upper small intestine. The high incidence of this disease in South Africa, around the southern and eastern sides of Mediterrania and the Middle East is well known (Novis *et al.*, 1971; Rappaport *et al.*, 1972). The Jews of Middle Eastern and North African origin in Israel show higher incidence of ML than the Jews of European origin (Eidelman *et al.*, 1966). The higher frequency of the disease among the lower socio-economic class and lower age is peculiar to the ML and not to the intestinal lymphoma found in the Western world (Rambaud, Bognel & Prost, 1968; Dutz *et al.*, 1971).

The first case of alpha-chain disease was reported by Seligmann *et al.*, in 1968 and since then there have been many reports of the disease in the literature (Laroche, Merillon & Turpin, 1970; Seligmann, Mihaesco & Frangione, 1971; Doe *et al.*, 1972; Shahid *et al.*, 1975). The association of alpha-chain disease with the so-called Mediterranian Lymphoma has been documented conclusively (Seligmann *et al.*, 1968; Rambaud & Matuchansky, 1973; Shahid *et al.*, 1975). Recently at a WHO meeting in Geneva the disease was called Immunoproliferative Small Intestinal Disease (IPSID). Alpha-chain disease with involvement of the respiratory tract has also been reported (Stoop *et al.*, 1971).

Nasr *et al.* (1970) have reported the disease under the name of primary upper small intestinal lymphoma from Iran for the first time. We had the opportunity of studying this disease at the Pahlavi University Medical School, Shiraz, and were able to detect eight positive cases of abnormal alpha chain in the serum of twenty seven intestinal lymphoma patients studied (incidence of 30%). To our knowledge this is the highest incidence of alpha-chain disease associated with intestinal lymphoma reported so far. Case 8 has very recently been identified and therefore this case is not included in the manuscript.

MATERIALS AND METHODS

Sera were obtained from intestinal lymphoma patients admitted to Pahlavi Medical School hospitals. Immunoelectrophoresis was carried out as described by Wieme (1965). Phoroscope, Immunoelectrophoresis System, AR 311 and Immuno-Agaroslide (obtained from Millipore Corporation, Bedford, Massachusetts) were used. Each serum sample was placed into the wells of

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Immuno-Agaroslide, and then electrophorised for 35 min. After electrophoresis appropriate antisera were added to each trough and allowed to diffuse for 15 hr at room temperature. The slide was then stained with amido black (1·0 g amido black 10B in 5% v/v aqueous acetic acid in a final volume of one litre).

All antisera were obtained from Behring Institute, Hoechst AG, Frankfurt. Rabbit anti-human whole serum and rabbit anti-human IgA (specific for H-chain) were used throughout these experiments.

Quantification of serum immunoglobulins was performed by the radial diffusion technique as described by Mancini, Carbonar & Heremans (1965) using partigen immunodiffusion plates (Behring Institute, Hoechst AG, Frankfurt). Anti-IgG, anti-IgM and anti-IgA was incorporated into the agar in each plate separately.

Clinical features. The predominant clinical features of the seven patients are summarized in Table 1. The ages of the patients at the time of presentation ranged from 15–44 years and there were six males and two females (ratio of 3:1). All

TABLE 1. Clinical findings of seven cases of alpha-chain disease

Case	Age	Sex	Duration of symptoms (months)	Symptoms and signs
1 MB	38	M	9	Abdominal pain, diarrhoea, weight loss, fever, clubbing, adenopathy, splenomegaly
2 MK	23	M	4	Abdominal pain, diarrhoea, weight loss
3 TS	18	F	2	Abdominal pain, diarrhoea, vomiting, clubbing, weight loss
4 ER	25	M	24	Abdominal pain, diarrhoea, weight loss
5 MF	44	M	48	Abdominal pain, diarrhoea, weight loss
6 RP	15	F	4	Abdominal pain, diarrhoea, weight loss, clubbing
7 DK	15	M	3	Abdominal pain, diarrhoea, weight loss, clubbing, adenopathy

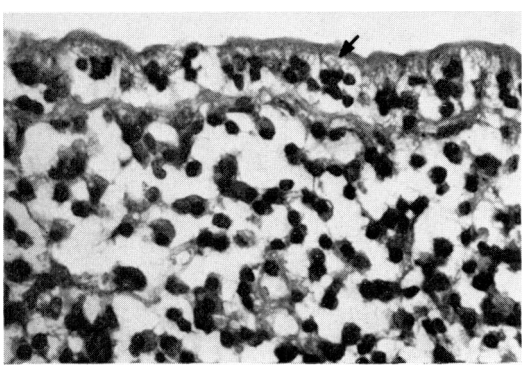

FIG. 1.

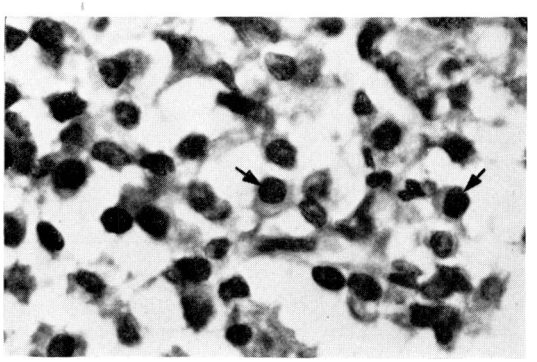

FIG. 2.

FIG. 1. Case 6. Peroral small intestinal biopsy showing: (a) cuboidal surface epithelium with loss of nuclear polarity; (b) Marked transepithelial lymphocytic migration (arrow); (c) Dense mature plasma cell infiltrate in partially-flattened villous core. (Haematoxylin-eosin stain; original magnification × 200).

FIG. 2. Case 6. Peroral small bowel biopsy. Cytological detail of the cell infiltrate in villous core and lamina propria. Note the plasmacytic appearance of cells (arrows). (Haematoxylin-eosin stain; original magnification × 400).

the patients were Iranian and from the rural areas of the Fars province except one patient (case 7) who was from Bandar Abbas (Persian Gulf Area). The patients were presented with diarrhoea, abdominal pain, vomiting, and weight loss. Finger clubbing was observed in four of them. Duration of the symptoms varied from 2–48 months. Adenopathy was observed in two of the patients. Splenomegaly was not a common feature but it was noticed only in one case. In two cases there were abdominal masses.

TABLE 2. Results of absorption studies

Case	Schilling test (%)	D-xylose excretion (g/5 hr)	Faecal fat (g/24 hr)
1 MB	6·25	9·6	7·22
2 MK	2·0	4·4	11·1
3 TS	29·0	n.d.	3·0
4 ER	9·0	n.d.	36·6
5 MF	5·0	7·0	9·1
6 RP	4·0	3·5	11·9
7 DK	n.d.	n.d.	n.d.
Normal values	10	5	5

n.d.=Not determined.

Laboratory studies. Haematological findings were as follows: haemoglobin level was within normal range in all of the cases (9·6–14·6 g/100 ml). Total white blood count ranged from $5{\cdot}1\times10^3$–$17{\cdot}0\times10^3/cm^3$. In cases 5, 6 and 7 the total white blood cell count was slightly elevated.

Biochemical studies revealed that glucose, alkaline phosphatase, SGOT/SGPT, and calcium levels of the serum were within the normal range in all of the patients.

The results of gastrointestinal findings as shown in Table 2 indicate malabsorption of fat in five cases, and D-xylose in two cases.

Radiological findings. The X-ray of the small bowel series showed abnormal pattern of jejunal loops with markedly thickened mucosa and fragmentation in six of the cases. In case 5 the lesions were extended to the second portion of duodenum.

Pathology. In five cases (3–7) the small bowel material (peroral biopsy in four cases and autopsy material in one case) revealed a dense, slightly immature to mature population of plasma cells packing and sometimes distorting (and in case 5 flattening) the villi (Figs 1 and 2). In cases 5, 6 and 7 where muscularis mucosae was available this infiltrate extended beyond the muscularis mucosae. In case 6 there were some atypical cells resembling histiocytes in the infiltrate beyond the muscularis mucosae. However, this cell type could not be evaluated further. Of note in all cases where the surface epithelium was available for examination was considerable transepithelial lymphocytic migration through the surface epithelium with a cuboidal appearance of the latter (Fig. 1). Mesenteric nodes were available for examination in five cases. In case 1 the entire node architecture was replaced by tumour cells with features of immunoblastic sarcoma. Extension of mature and slightly immature plasma cells beyond the node capsule into the adjacent fat was seen in case 5. In case 7 the entire node at autopsy was replaced by predominantly immature plasma cells. Furthermore in the latter case extraintestinal spread into the portal spaces of the liver was also seen at autopsy.

Protein studies. The results of serum protein studies are shown in Table 3. Total serum protein levels ranged from 4·4–6·5

TABLE 3. Results of serum protein studies

Case	Total serum protein (g/100 ml)	Serum albumin (g/100 ml)	Serum immunoglobulins (mg/100 ml)		
			IgG	IgM	IgA
1 MB	4·4	2·0	1400	95	275
2 MK	5·5	3·3	1050	110	560
3 TS	5·7	3·1	850	69	520
4 ER	6·5	3·7	1450	75	525
5 MF	4·9	2·5	800	22	275
6 RP	4·7	3·5	1090	22	145
7 DK	5·4	1·9	1420	150	560
Normal	6·7	3·5–5·5	500–1700	45–180	140–420

n.d. = Not determined.

g/100 ml of serum. It seems that in most cases the protein levels are slightly lower than normal value. The level of serum albumin varied from 1·9–3·7 g/100 ml indicating low levels of serum albumin in all cases except cases 4 and 6. Normal values for albumin are 3·5–5·5 g/100 ml.

Sera of the seven cases were tested for the presence of abnormal alpha chain immunoglobulin. By immunoelectrophoresis using monospecific antiserum to H-chain of IgA the abnormal alpha chain was detected in the sera of these patients. This technique readily showed the fast precipitin line of abnormal alpha chain of each individual patient. The relatively high electrophoretic mobility of the abnormal alpha-chain is compared with that of IgA from a normal individual as shown in Fig. 3. Immunoelectrophoretic results with polyvalent antisera to normal human serum are also shown in Fig. 3. Monospecific antisera to K and λ light chains were used to demonstrate the lack of free light chains in the sera of alpha-chain disease patients. As shown in Fig. 4 the precipitin lines formed with anti-K and anti-λ antisera correspond to the positions of normal IgA on the immunoagaroslide and not to the abnormal alpha-chain.

Serum immunoglobulin concentrations of all the patients under investigation are shown in Table 3. The level of the various classes of immunoglobulins in the serum seems to be within the normal range, IgG from 850–1450 mg/100 ml, IgM from 22–150 mg/100 ml, and IgA from 145–650 mg/100 ml. In cases 5 and 6 IgM level was slightly lower than normal.

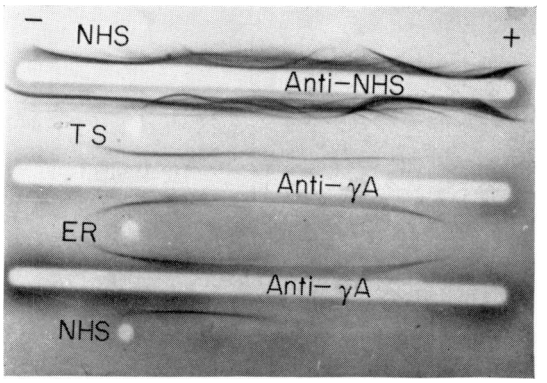

FIG. 3.

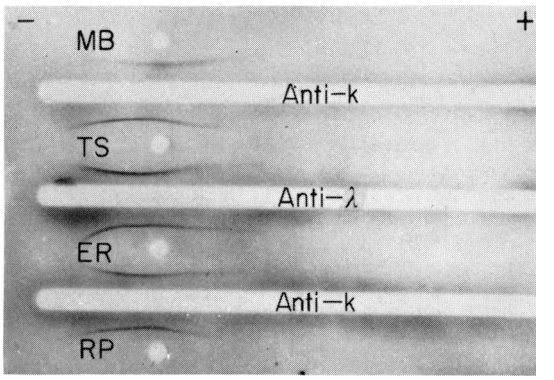

FIG. 4.

FIG. 3. Immunoelectrophoretic results of alpha-chain disease patients, sera (TS and ER) compared with normal human serum (NHS) developed with anti-γA and anti-NHS.

FIG. 4. Immunoelectrophoretic analysis of sera from four alpha-chain disease patients developed with anti-K and anti-λ.

DISCUSSION

The patients studied and presented in this report are in many respects similar to those with alpha-chain disease previously described by Seligmann, Mihaesco & Frangione (1971). The age range was 15–44 years and the clinical picture of malabsorption, diarrhoea, abdominal pain, vomiting, and weight loss was common in most of them. The patients with abnormal alpha chain were all from villages of Southern Iran and all of them were from a low socio-economic bracket. This is in agreement with reports from other parts of the world (Ramot & Hulu, 1975).

The high incidence of alpha-chain disease (30%) among the intestinal lymphomas studied at our centre is of interest. In Israel, incidence of up to 25% has been reported (Ramot, 1971). In many cases of alpha-chain disease the abnormal protein is found in much lower concentrations than normal serum IgA. Therefore, the conventional methods such as immunoelectrophoresis which are commonly used are not able to detect the small amounts of abnormal alpha chain. More sensitive assays such as radioimmunoassay might reveal incidences much higher than those presented in this report.

The histopathological findings of the small bowel material in most of the cases described here are fairly similar to those of alpha-chain disease patients reported by others elsewhere (Doe *at al.*, 1972; Rappaport *et al.*, 1972; Ramot & Hulu, 1975). Infiltration of mucosa with plasma cells was a common feature. Distortion and flattening of the villi was observed in five cases. Involvement of mesenteric lymph nodes and infiltration of these nodes with tumour cells was shown in four cases.

Protein studies of these patients revealed no significant differences between the serum immuno-

globulin levels of these patients and normal controls. However in two cases IgM level was slightly decreased. In the case of serum IgA levels because of variable degree of polymerization the radial immunodiffusion technique is not very accurate (Doe *et al.*, 1972). Thus the concentrations obtained are rough values and in our cases they seem to be within the normal range.

Immunoelectrophoretic results demonstrated the presence of abnormal alpha-chain. The use of monospecific antiserum against H-chain of IgA was essential. It was difficult to detect the abnormal precipitin band when polyvalent antiserum was used. It has been shown (Seligmann *et al.*, 1971) that the abnormal alpha-chain polymerizes in the serum and also because of varying amount of carbohydrate content of these abnormal proteins they appear to be quite heterogenic. Such electrophoretic heterogeneity as shown in Fig. 3 is in agreement with the report of Seligmann *et al.* (1971).

Further work in the area of serodiagnosis such as application of immunoselection technique, and immune deficiency studies are underway on similar patients.

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