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Alpha heavy chain disease (report of 18 cases from Iraq)

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SUMMARY The clinical and pathological features of 18 new patients with alpha heavy chain disease seen at two referral centres in Baghdad, Iraq, are described. The series included 14 males and four females ranging in age from 14 to 47 years. Almost all patients presented because of long-standing abdominal pain and diarrhoea. The tissue diagnosis and extent of the disease were established at laparotomy in most patients. Peroral jejunal biopsy was used in a number of patients, mainly for follow-up. The serological abnormality was confirmed by immunoselection technique. Most of the patients had extensive thickening of the bowel wall and/or tumour masses of the small intestine and mesenteric nodes. Histopathological sections showed lymphoplasmacytic proliferation involving the mucosa and extending to the submucosa and muscularis. Preliminary results of the treatment, including two long remissions, are reported. In general, our observations agree with those made by other authors, mostly from the Middle East and Africa. We believe that a high index of clinical suspicion, routine use of the immunoselection, and recognition of the early pathological changes may hopefully lead to the detection of more cases before the frank neoplastic phase of the disease.

Alpha heavy chain disease (AHCD) is a lymphoproliferative process involving the IgA secretory system and producing immunoglobulin molecules consisting mainly of incomplete alpha chains (Seligmann *et al.*, 1971; Rambaud and Seligmann, 1976). So far, over 100 cases of the intestinal form of AHCD have been reported, mainly from the Middle East and Mediterranean area. Most of the patients had primary intestinal lymphoma, an observation that raised the question of the relationship between AHCD and this type of lymphoma (Rambaud and Matuchansky, 1973; Lewin *et al.*, 1976). This paper reports the clinicopathological features of 18 new patients with AHCD in Iraq, the largest series of patients published from the area.

Methods

This report includes 16 patients diagnosed and treated at the Medical City Teaching Hospital (15 patients), and the Rashid Military Hospital (one patient) during the years 1975 and 1976. During these two years 64 817 patients were admitted to the Medical City Hospital. Two additional patients seen earlier were investigated by us but the immunochemical diagnosis was established elsewhere. The pathological material includes 12 peroral jejunal biopsies, 16 gastrointestinal tumours and/or mesenteric lymph nodes obtained at laparotomy, and one axillary node.

All specimens were routinely processed and stained with eosin-haematoxylin, periodic acid schiff, Snook's reticulin, methyl green pyronin, and Giemsa stains.

SERUM PROTEIN STUDIES

Serum protein electrophoresis was done on cellulose acetate strips, stained and percentage determined by scanning, using a Jayce Loeble Co. chromoscan. Serum immunoglobulins were estimated by single radial immunodiffusion method using Tripartigen plates (Behring, W. Germany). Free alpha heavy chains in the serum (and ascitic fluid in one case) were detected by immunoelectrophoresis against rabbit antihuman IgA (alpha chain specific; Hoechst Lab, W. Germany). Electrophoresis was performed using 2% agarose in 0·06 M barbitone buffer pH 8·6 for two to three hours at 150 V, after which the serum was loaded and allowed to diffuse for 16

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hours. The non-precipitated proteins were washed off with 0·9% NaCl and the dry plates were stained for protein with Panceaus.

IMMUNOSELECTION

After the mono-specific immunoelectrophoresis, immunoselection was done in all cases (Doe *et al.*, 1972). It was performed in a 1% agarose gel (Meath, England), incorporated with 30% anti-l and anti-k light chain protein (Hoechst Lab) respectively in a 0·06 M barbitone buffer, pH 8·6. After two to three hours electrophoresis at 150 V, anti-IgA (alpha specific) was loaded and allowed to diffuse overnight. The unprecipitated proteins were washed and protein stained as above. The free alpha chains appeared as a fast moving arc, either continuous with, or distinct from the normal IgA (Figure). Control studies were done, including healthy individuals and patients with various gastrointestinal diseases and other types of lymphomas (160 patients). In addition, three patients' families were similarly investigated.

Results

There were 14 males and four females with an age range of 14 to 47 years (mean 24·1 years). Fifteen patients were Arabs, two Kurds, and one Assyrian.

The clinical findings are summarised in Table 1. The main laboratory and radiological data are shown in Table 2. Pain, which was the main presenting symptom in all patients, was generally described as diffuse, and initially intermittent. In late stages, however, it was described as colicky and more persistent. The diarrhoea was mostly watery, but bulky and offensive in three, and contained blood and mucus in one patient only. The duration of diarrhoea varied from a few months to 17 years with a mean duration of 40 months. Gross steatorrhea was not observed. Stool examination was performed in all cases; most patients showed few pus cells. Two of them had ova of ascaris. *Giardia lamblia* was not found in the stool or biopsy specimens.

Table 1 *Clinical findings in 18 patients with AHCD*

Clinical findings	*Patients*	
	(*no.*)	(%)
Abdominal pain	18	100
Weight loss	18	100
Diarrhoea	16	89
Clubbing	11	61
Abdominal masses	9	50
Ascites	5	31
Fever	4	22
Vomiting	3	17
Hepatomegaly	3	17*
Peripheral lymphadenopathy	1	6†
Splenomegaly	1	6†

*One patient with thalassaemia.
†An additional patient developed splenomegaly and generalised lymphadenopathy while under therapy.

Table 2 *Results of laboratory and radiological investigations (number of patients tested) in AHCD*

Test		*Patients*
Haemoglobin (18)	< 10 g/dl	3*
	10-12 g/dl	5
	> 12 g/dl	10
ESR (18)	> 30 mm/h	9
Alkaline phosphatase (14)	> 13 KAU/100 ml	6
Serum albumin (17)	< 30 g/l	12
IgA (16)	< 200 IU/ml (3·31 g/l)	3
	200-300 IU/ml	5
	> 300 IU/ml (5·04 g/l)	8
Impaired D-xylose absorption (7)		6
Radiological pattern (17)		
Diffuse 'malabsorption pattern' only		9
Diffuse malabsorption pattern + irregular filling defects		7
Gross filling defects only		1

*One patient with thalassaemia and two with gastrointestinal haemorrhage.

OPERATIVE FINDINGS

Fourteen patients underwent laparotomy for diag-

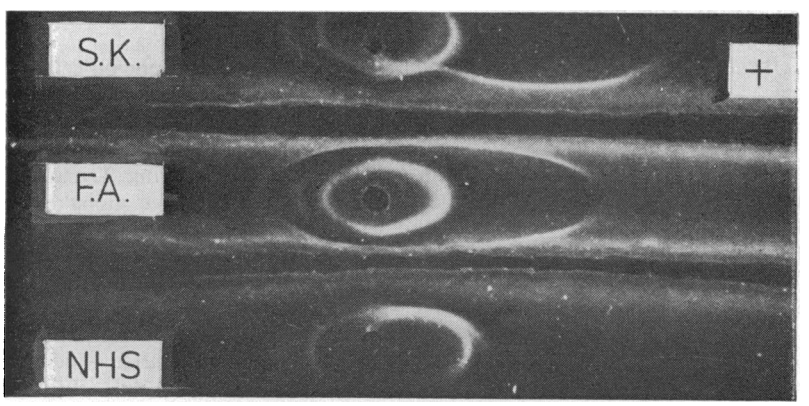

Figure *Immunoselection plate showing a normal control (NHS), and two patients, F.A. and S.K., with a separate heavy chain are in the first, and one which is continuous with the normal IgA in the second patient.*

nostic and/or palliative purposes. The localisations and extent of tumours are summarised in Table 3. At laparotomy, the small intestine and mesenteric lymph nodes were inspected and biopsies obtained. Corrective and palliative procedures were performed in six patients.

Table 3 *Operative findings (14 cases)*

Slight thickening with oedema of small intestine	4*
Marked thickening with strictures of small intestine	2†
Gross tumour formation (1 gastric, 5 jejunal and 2 extensive small intestinal)	8†
with peritoneal seedlings	2

*Slight-moderate enlargement of mesenteric lymph nodes.
†Marked enlargement of mesenteric lymph nodes particularly at root.

PATHOLOGY

In all patients, the jejunal mucosa showed villar atrophy of variable severity, from slight to total. However, the enterocytes were generally intact and the crypts were sparse. In addition, there was a plasma cell proliferation involving the mucosa and, in most cases, extending to the submucosa and muscularis. In four cases, the plasma cell infiltrate was mature and non-dystrophic. Two of these, however, had highly pleomorphic lymphoplasmacytic lymphoma in the mesenteric lymph nodes in one and axillary nodes in another. In the remaining 14 cases there was a frank neoplastic proliferation of pleomorphic lymphoreticular cells showing various degrees of plasmacytic differentiation. A similar infiltrate involved the regional mesenteric lymph nodes. In three cases, extracellular and intracytoplasmic PAS positive inclusions were observed, presumably immunoglobulins. In two, they appeared to be intranuclear on light microscopy. Immunofluorescent studies, however, were not done.

SERUM PROTEIN STUDIES

On serum protein electrophoresis a distinct diffuse band in the β region was detected in three cases only. Immunoglobulin levels were slightly raised in five patients and moderately to markedly increased in eight patients only (the normal IgA level in a control group of Iraqi population is 139 ± 68·2 IU/ml). IgG and IgM levels were significantly lower than the controls ($P < 0{\cdot}1\%$ for both). Immunoelectrophoresis against monospecific anti-human IgA, yielded an abnormal precipitin line, usually prolonged or with a spur in 15 cases. However, in all 16 cases, the free AHCs were clearly demonstrable on immunoselection (Figure). This method resulted in the demonstration of AHCs in 16 out of 42 patients with lymphoplasmacytic lymphoma and/or heavy lymphoplasmacytic infiltrate of the small intestinal mucosa (38%). None of the controls or other lymphomas had demonstrable AHCs in the serum. All members of three patients' families had normal immunoglobulins profiles.

ASSOCIATED DISEASES

One patient had thalassaemia. Another had extensive colonic ulceration clinically diagnosed as ulcerative colitis, though it was pathologically hard to distinguish from extensive lymphomatous involvement. A third patient had bilharziasis of the urinary bladder diagnosed at necropsy.

CORRELATION OF SYMPTOMS WITH PATHOLOGY, TREATMENT AND OUTCOME

In general, it was noted that patients with extensive bowel disease, as shown by radiological examination and/or laparotomy, had severe symptoms of long duration. Microscopically, dystrophic plasma cell proliferation in the bowel wall and penetration beneath the mucosa was associated with advanced disease, gross tumour formation, and clinical symptoms of severe colicky abdominal pain, weight loss, and the presence of abdominal mass(es).

Five patients, all with extensive involvement of the small intestine, died within one to 30 days postoperatively. The cause of death was related to sepsis and the poor general condition in all instances. The remaining 13 patients were initially treated with the oral administration of a combination of cyclophosphamide, 2-3 mg/kg/day, prednisolone, 0·5 mg/kg/day, and tetracycline, 0·75-1 g/day. Treatment was continued indefinitely with reduced dose as maintenance. One patient received total abdominal irradiation before chemotherapy.

All patients obtained full or partial remission. After initial improvement, six developed recurrence with a relentless downhill course in spite of increasing the dose of steroids and the use of large intermittent doses of cyclophosphamide (20-30 mg/kg, intravenously, every two to three weeks), and the addition of vincristine, 0·04 mg/kg, intravenously, weekly. These six patients died with extensive abdominal disease and related complications four to 14 months after diagnosis. The remaining seven patients are still alive nine to 59 months after diagnosis. Of these, three are in full clinical and immunological remission (documented by disappearance of the alpha heavy chain on immunoselection). In two of these patients, repeat peroral jejunal biopsies showed histological remission as well. It is interesting to note that the longest survivor had total abdominal irradiation in addition to chemotherapy. Pathologically, all the longest survivors had lesions limited to the mucosa only with no deeper penetration. The cellular proliferation consisted of mature non-dystrophic, closely packed plasma cells. One of these, however, had

cervical and axillary lymphoadenopathy with the histological picture of lymphoplasmacytic lymphoma. In short, the prognosis correlated with the extent and pathology of the bowel disease at the time of presentation. Disappearance of the AHC accompanied the clinical and pathological remission, but lowering of the IgA levels with the persistence of the AHC was observed on several occasions in patients with deteriorating clinical conditions and extensive recurrence. In fact, two patients, while still in clinical remission, had a gradual progression of the neoplastic process as demonstrated by sequential peroral jejunal biopsies. In these two patients, there was a persistence of the AHC and, as expected, a clinical relapse and a rapidly growing tumour immediately followed; it was accompanied by malignant ascites in one and general extra-abdominal dissemination and death in the second.

Discussion

The observations collected on our 18 patients are in general agreement with previously published reports about this rather rare disease (Doe *et al.*, 1972; Manousos *et al.*, 1974; Shahid *et al.*, 1974; Doe, 1975; Ramot and Hulu, 1975; Guardia *et al.*, 1976; Kharazmi *et al.*, 1976; Tabbane *et al.*, 1976). However, certain aspects not emphasised in previous publications deserve comment. The demonstration of AHC in the sera of 38% of patients with intestinal lymphoplasmacytic lymphoma and/or heavy lymphoplasmacytic proliferation is a higher percentage than the 20-30% reported earlier (Kharazmi *et al.*, 1976). We believe that the routine use of immunoselection and proper pathological analysis of the biopsy material are responsible for these positive results.

Diarrhoea, reported previously in 100% of patients (Rambaud and Seligmann, 1976), was not observed in two of our cases with extensive tumour.

The rarity of hepatic, splenic, and peripheral lymph node involvement in AHCD was again confirmed in this series. It is interesting to note that one of our patients presented with generalised lymphoadenopathy and abdominal masses. Another patient developed generalised lymphoadenopathy and splenomegaly while under therapy.

Our observations are also in agreement with those of the Tunisian workers (Tabbane *et al.*, 1976) who had recently proposed that AHCD may be divided into a 'gastrointestinal phase' and a 'tumour phase'. Pathological studies in our patients indicate that the first phase presents as a diffuse plasmacytic proliferation of mature cells limited to the mucosa, while the tumour phase showed multicentric neoplastic proliferation of dystrophic lymphoreticular cells with plasmacytoid features. This progression was observed on multiple peroral jejunal biopsies obtained during the course of the disease in two patients. Such progression has also been recently reported by others in patients in clinical remission (Guardia *et al.*, 1976; Skinner *et al.*, 1976).

The appearance of extensive mucosal ulceration in the colon in one patient might have been due to a diffuse tumour involvement. Pathologically, there was marked ulceration and plasma cell infiltration, a lesion hard to distinguish from ulcerative colitis.

The association of AHCD and thalassaemia caused some clinical confusion in one patient, as splenomegaly and severe anaemia are rare in AHCD. Though most probably it is coincidental, such an association should be further investigated for a possible genetic predisposition.

Individuals with blood group B and O have high levels of alkaline phosphatase intestinal isoenzyme as compared to others. The observation that some of the patients had high alkaline phosphatase (44% in our series) raised some speculations regarding the relationship of AHCD to blood groups (Rambaud and Matuchansky, 1973). Though the number is small, in this study we observed no excess of patients with blood group B or O and no correlation of the serum alkaline phosphatase level with the duration or severity of the disease.

The role of parasitic infestations in the pathogenesis of AHCD has been discussed extensively (Rambaud and Seligmann, 1976). Two of our patients had ascariasis and one suffered from extensive bilharziasis of the urinary bladder. This might have been a coincidental association, as parasitic infestation is common in Iraq.

Combination chemotherapy as used in our patients seems to be reasonably effective in early cases without tumour formation. In the more advanced stages, particularly with gross tumour formation, our limited experience indicates that the triple combination of cyclophosphamide, tetracycline, and corticosteroids is ineffective. The addition of vincristine and adriamycin in two patients with advanced, disseminated disease brought no improvement. Further clinical trials should be pursued for a more effective therapeutic regimen.

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