CLINICAL REPORTS

Alpha heavy chain disease developing in an Asian resident in the United Kingdom and responding to antibiotics

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Summary

A 40-year-old man born in Bangladesh developed alpha heavy chain disease whilst a resident in the United Kingdom. An incomplete, low molecular weight alpha heavy chain protein, devoid of light chains was demonstrated in his serum. Clinical remission of his disease was achieved by antibiotics alone.

KEY WORDS: alpha chain disease, naso-pharyngeal tumour, antibiotic-induced remission.

Introduction

Alpha chain disease (α-CD) is defined as a lymphoid proliferation of the secretory IgA system in which plasma cells synthesize an incomplete, low molecular weight α heavy chain. It is the commonest form of heavy chain disease, although little more than 150 cases have been recognized (Seligmann *et al.*, 1979). Only a small number of patients have been described with respiratory α-CD and the majority of patients have involvement of the intestine. Many patients develop a fatal malignant lymphoma. The condition is thought to arise from an aberrant immune response by the secretory IgA system to sustained topical antigenic stimulation (Rambaud and Seligmann, 1976).

We describe a patient who developed the early 'pre-malignant' stage of α-CD (Seligmann *et al.*, 1979), whilst resident in England and who responded to long-term antibiotic therapy alone.

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Case report

A 40-year-old man born in Bangladesh presented with diarrhoea and abdominal cramps of 3 weeks duration having previously been well. He had lived and worked as a labourer in the United Kingdom for 12 years, but had since visited Bangladesh twice, most recently 6 months before the onset of his illness. On examination, there was evidence of weight loss, finger clubbing and a polypoidal tumour in the post-nasal space. Sigmoidoscopy showed thickened, fleshy and friable mucosal folds obliterating the lumen of the rectum.

Laboratory tests: Erythrocyte sedimentation rate (ESR) 64 mm/h, haemoglobin concentration 15·2 g/dl, mean lymphocyte count $1·82 \times 10^9$/litre. Prothrombin time, red cell folate and vitamin B_{12} normal. Bone marrow aspiration showed normal numbers of IgA fluorescing plasma cells. Serum IgA, 24·92 g/litre (normal 0·95–5·2); IgG, 4·15 g/litre (normal 6–16); IgM, 0·41 g/litre (normal 0·30–1·80); IgE, 105 ng/ml (normal <750). Salivary IgA, 0·44 g/litre (normal <0·3). Jejunal luminal fluid IgA, 0·2 ng/ml (normal <0·28), secretory component present. Urine, IgA reacting protein present in small amounts. His serum IgA was purified by column chromatography and the molecular weight of the depolymerized α heavy chain protein was measured as 37800 Daltons (normal α heavy chain 55000) by electrophoresis on 10% sodium dodecyl sulphate polyacrylamide gel. On densitometry, the ratio of heavy chain protein to light chain protein was increased from approximately 2:1 in normal IgA to 27:1 in the patient's IgA reacting protein, indicating the presence of predominantly α heavy chains. Free α heavy chain
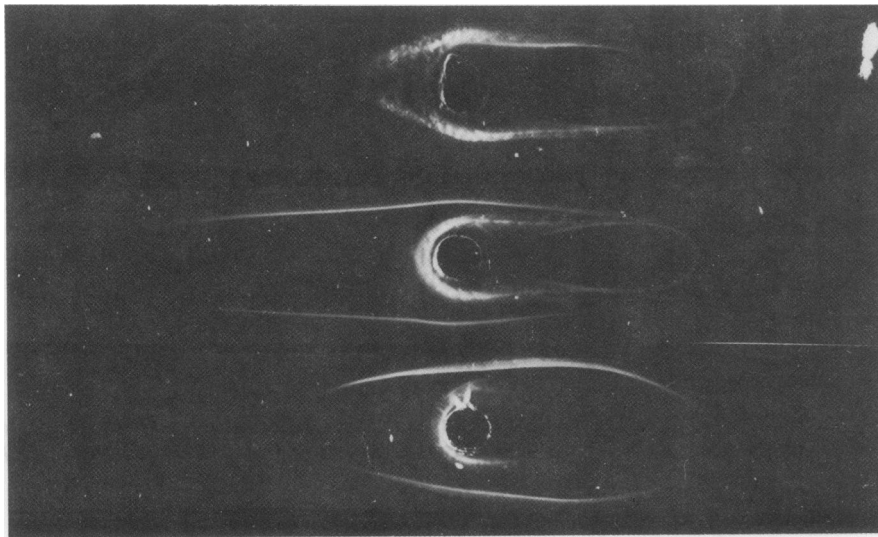
FIG. 1. Immunoselection plate with anti-light chain antisera incorporated into the agar and anti-IgA antiserum added to the troughs after electrophoresis. Top well contains normal serum, middle well contains the patient's sera and the bottom well contains IgA myeloma serum. The patient's IgA reacting protein shows rapid mobility towards the anode on the left.

in the serum was also confirmed by using an immunoselection plate (Doe, Danon and Seligmann, 1979) (Fig. 1). Karyotype 46 XY; histocompatibility typing HLA-A3/11, A10, BW 17, BW 15. Urea and electrolytes normal. Serum albumin 34 g/litre (35–52). Total alkaline phosphatase 148 IU/litre (normal <75), intestinal alkaline phosphatase 38 IU/litre (normal <18). One hour blood xylose after a 5 g dose, 0·45 mM/litre (normal >0·75). Faecal fat, 43·4 mM/24 hr (normal <17·5). Faeces contained *Giardia lamblia* cysts and *Trichuris trichura* and grew *Salmonella paratyphi B.* Jejunal luminal fluid grew *Streptococcus faecalis* and *Escherichia coli.* Barium follow-through revealed thickened mucosal folds in the jejunum and ileum. Barium enema showed coarse mucosal folds and polypoidal filling defects in the colon and rectum.

A peroral jejunal biopsy showed on light microscopy, subtotal villous atrophy and atrophy of the crypts. There was preservation of the surface epithelial cells, which were tall and columnar. The most prominent finding was a marked increase of plasma cells, containing IgA reacting protein, in the lamina propria. A rectal biopsy again showed a heavy infiltration of similar IgA-containing plasma cells (Fig. 2). Electron microscopy of these tissues revealed mainly mature plasma cells with a few forms intermediate between plasma cells and lymphocytes present. A biopsy of the post-nasal space tumour showed only a slight increase of plasma cells which did not fluoresce with anti-IgA conjugate. The main

cellular population consisted of lymphocytic cells, histiocytes and fibroblasts.

The histological and immunochemical findings confirmed a diagnosis of α-CD. Laparotomy was declined by the patient. He was treated with metronidazole 200 mg, four times daily, but he continued to deteriorate clinically and lose weight. Cotrimoxazole, 2 tablets twice daily, was started, following which he improved considerably. Eight months after the start of treatment he was feeling completely well, with no diarrhoea. His ESR was 12 mm/hr and albumin 44 g/litre. His post-nasal tumour completely regressed. However, there was still evidence of an abnormal α chain protein in his serum. The patient subsequently returned permanently to Bangladesh.

Discussion

Alpha chain disease has been classified as an immunoproliferative small intestinal disease because, in its early stages, α-CD is not truly malignant and the abnormal plasma cell proliferation is reversible (WHO Memorandum, 1976). This classification would appear to be a misnomer as the disease can involve the large bowel, as described here, and also the stomach (Guardia *et al.,* 1980). Most affected individuals come from areas of poor hygiene and have a low socio-economic status. However, the majority of patients are from North Africa and the Middle East and only 5 cases (approximately 3% of all known cases of α-CD) have previously been reported from the Indian subcontinent (Seligmann *et*
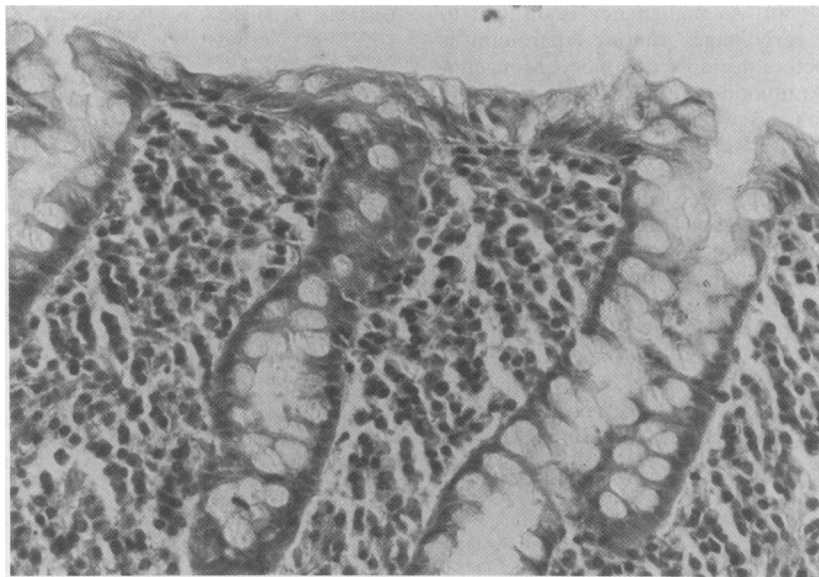
FIG. 2. Rectal biopsy × 280 showing a dense infiltrate of plasma cells which contained IgA.

al., 1979; Tandon *et al.,* 1980). The important environmental factors responsible for triggering off α-CD appear to be small intestinal pathogens. *Giardia lamblia* seems to be particularly prevalent, present in 24% of one group of patients studied (Rambaud and Seligmann, 1976). Nevertheless, the dramatic response of a small number of patients to oxytetracycline and in the patient here to cotrimoxazole, points towards bacterial antigen as the initiator of α-CD (Rambaud *et al.,* 1978). Additionally, genetic factors must play a part to account for the low incidence of α-CD in the Indian subcontinent. In southern India for example, a large number of people with a high prevalence of intestinal infection have been monitored over a long period of time for tropical sprue studies, without a single case of α-CD ever being detected (Baker and Mathan, 1971; Ross and Mathan, 1981). Further evidence of a possible genetic susceptibility is an abnormal chromosomal marker (Gafter *et al.,* 1980) and the occurrence of a Hodgkin's lymphoma some years after successful treatment of α-CD (Monges *et al.,* 1981).

The intestinal pathogens of our patient were probably acquired whilst in Bangladesh, but the delayed onset of the disease 6 months later, whilst resident in the United Kingdom, is evidenced by the abrupt appearance of symptoms and a near normal albumin and vitamin status in the face of severe malabsorption. In some patients, manifestation of α-CD may be delayed for more than 10 years after withdrawal from the initiating environmental factors (Seligmann *et al.,* 1979).

The diagnosis of α-CD relies on laboratory studies designed to demonstrate the presence of incomplete α heavy chain protein in serum and secretions, although, rarely, a patient may have a non-secretory form of α-CD (Rambaud *et al.,* 1980). Initial immunochemical diagnosis is difficult as single radial immunodiffusion measurement of IgA may give falsely normal, high or low 'IgA' values in α-CD, due to varying polymerization of the abnormal protein (Doe, 1979). Immunoselection by immunoelectrophoresis of serum into a gel containing antisera to the Fab portion of the IgA1 α heavy chain is currently the most precise diagnostic test (Doe *et al.,* 1979). Use of anti-light chain antisera instead of anti-Fab$_α$ increases the chance of mistaking IgA myeloma protein for α-CD protein. Alpha-heavy chain disease has also been diagnosed by rectal biopsy, followed by differential immunofluorescent staining of plasma cells with light chain and α heavy chain antisera (Rhodes, Jewell and Janossy, 1980). Finally, the IgA protein can be analyzed in the fashion described here to confirm the diagnosis of α-CD. Using a similar technique in other α-CD patients, the molecular weight of the α-heavy chain protein varies between 29000 and 34000, indicating a chain length between half and three-quarters that of normal α heavy chain (Rambaud and Seligmann, 1976).

Alpha chain disease is thought to evolve from a benign plasma cell infiltrate, the premalignant phase, through to a lymphoma by dedifferentiation of mature plasma cells to immature cells rather than formation of an additional malignant clone of cells

(Gafter *et al.,* 1980). As malignancy is difficult to diagnose in the early stages, routine laparotomy is recommended before deciding treatment (Mougenot *et al.,* 1981). Antibiotic-induced remission of the premalignant phase is well documented (Rambaud and Seligmann, 1976; Rambaud *et al.,* 1978; Monges *et al.,* 1980; Rhodes, Jewell and Janossy, 1980), while patients with lymphoma can be successfully treated with cytotoxic chemotherapy (Mougenot *et al.,* 1981). Our patient showed a marked clinical improvement and a fall in concentration, but not disappearance of his α heavy chain protein, after antibiotic therapy. One striking improvement was the disappearance of his naso-pharyngeal lymphoid tumour. Such a tumour has been recorded in only one other patient (Doe, 1979). Possibly these two cases might represent a combined respiratory and intestinal form of α-CD.

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