Protein losing enteropathy as a sole manifestation of non-Hodgkin's lymphoma

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Summary: We describe a patient who presented with oedema and hypoproteinaemia which was proved to be due to protein-losing enteropathy. Extensive gastrointestinal investigations failed to discover any definitive cause. He subsequently developed tuberculous inguinal lymphadenopathy but although treated for tuberculosis the protein-losing state persisted. Later on he developed renal failure due to obstructive nephropathy. Laparotomy was carried out and it disclosed the diagnosis of non-Hodgkin's lymphoma, treatment of which cured the protein-losing state.

Introduction

Protein-losing enteropathy should be considered as a diagnostic possibility in a patient presenting with oedema and hypoalbuminaemia, when proteinuria, liver disease and malnutrition have been excluded (Bouchier, 1982). Protein-losing enteropathy, though sometimes associated with common gastrointestinal disorders, and representing a small part of the clinical picture, can be a sole manifestation of an underlying disease and may cause a difficult diagnostic problem. We, therefore, report a case which highlights this.

Case report

In July, 1981, a 44 year old chemical plant operator presented with swelling of his legs of 10 weeks duration.

Physical examination disclosed pitting below knee oedema. The jugular venous pressure was not elevated, there was no cardiomegaly and auscultation of the heart was normal. His blood pressure was 110/80 mm Hg. Abdominal examination did not reveal any organomegaly or any ascites. The rectal examination was normal. Urinalysis did not show proteinuria.

Investigations revealed normal haemoglobin, white cell count and erythrocyte sedimentation rate (7 mm/hour). The plasma electrolytes, urea, bilirubin, and liver enzymes were also normal. Total plasma protein was 38 g/l, with albumin 19 g/l. Immunoglobulin estimation showed IgG 3.7 g/l (normal range 8–18 g/l), IgA 0.7 g/l (normal range 0.9–4.5 g/l), IgM 0.7 g/l (normal range 0.6–2.8 g/l). His chest X-ray was

normal. ⁵¹Cr-chloride study was undertaken to assess the protein loss into the gut (Waldmann, 1966). Stools were collected for 4 days after the injection of ⁵¹Cr-chloride given intravenously (Rinsler & Booth, 1985). Forty six per cent of the intravenously administered isotope was excreted in the faeces over 4 days (normally less than 4%). A diagnosis of protein-losing enteropathy was made. Subsequently, he underwent a barium meal follow-through examination which was normal apart from thickened jejunal folds and two jejunal diverticulae. An upper gastrointestinal endoscopy showed prominent mucosal folds but histologically there was no evidence of Menetrier's disease. A jejunal biopsy did not show any lymphangiectasia. Sigmoidoscopy, barium enema and colonoscopy were normal and colonic biopsies showed the lamina propria to be rather loose and oedematous but there was no inflammation, lymphangiectasis or amyloidosis.

In March, 1982, he presented with lymphadenopathy in the left groin and a lymph node biopsy showed caseating granulomata containing acid and alcohol-fast bacilli. *Mycobacterium tuberculosis* was cultured and proved to be sensitive to all standard anti-tuberculous chemotherapeutic agents. He was treated with streptomycin, isoniazid, para-aminosalicylic acid, frusemide and spironolactone. He remained symptomatically well and oedema-free on diuretics. However, his serum albumin remained low at 20 g/l, although a repeat ⁵¹Cr-chloride study after 3 months treatment suggested some improvement in the protein loss into the intestine with 19.3% faecal excretion of the isotope over 4 days. He continued on anti-tuberculous chemotherapy and diuretics and his protein-losing enteropathy was ascribed to intestinal

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tuberculosis.

In November, 1982, he presented with loin pain. Intravenous urogram showed a non-functioning right kidney, confirmed by retrograde pyelography to be a hydronephrosis, with hydroureter and stricture, strongly suspected to be tuberculous, of the right ureter. Anti-tuberculous chemotherapy was continued and he was started on prednisolone.

He was re-admitted as an emergency in April, 1983, with gross fluid retention and oliguria of one week's duration in renal failure (serum creatinine at $772 \mu\text{mol/l}$). His serum albumin was low at 20 g/l . A repeat ultrasound scan showed a left hydronephrosis and a laparotomy was performed. The right kidney was small and hydronephrotic and the left kidney was very large and oedematous. The retro-peritoneal tissue was very thickened and extended from around the ureter to the diaphragm. There were obviously enlarged retro-peritoneal lymph nodes overlying the right common iliac vessels, which were biopsied. The left ureter was not dilated but engulfed in the thick retro-peritoneal tissue. It was mobilized up to the renal pelvis and down into the true pelvis. It was not placed within the peritoneal cavity as the appearances were unlike those of retro-peritoneal fibrosis.

Post-operatively the creatinine fell to $119 \mu\text{mol/l}$. Histology of the retro-peritoneal nodes showed high grade non-Hodgkin's lymphoma (diffuse large lymphoid cell type) following which he received cyclical combination cytotoxic chemotherapy with cyclophosphamide, adriamycin, vincristine and prednisolone.

In July, 1983, he was asymptomatic and for the first time his serum albumin was in the normal range (38 g/l). His renal function remained stable with serum creatinine at $107 \mu\text{mol/l}$. In October, 1983, he completed chemotherapy and has remained in remission from non-Hodgkin's lymphoma with normal serum proteins and immunoglobulins.

Discussion

This case illustrates several points. Firstly, protein-losing enteropathy can be a diagnostic challenge when

common gastrointestinal disorders have been excluded and conditions like lymphoma should be considered.

Patients with long-standing protein-losing enteropathy – especially when due to intestinal lymphangiectasia – may have abnormalities of immunity due to continuous loss of T cells and immunoglobulins into the gut and recently it has been suggested that this defect in immunity for a long period may contribute towards the development of lymphomas (Broder *et al.*, 1981; Case Records of the Massachusetts General Hospital, 1984). In our case, however, we believe that the lymphoma was the original cause of the gastrointestinal protein loss and tuberculosis was an expression of the immuno-compromised state secondary to lymphoma. Treatment of tuberculosis did not cure the protein-losing state (Marenco *et al.*, 1969) and the serum protein levels did not reach normality even after a year's treatment. However, successful cyclical chemotherapy not only induced a remission from his non-Hodgkin's lymphoma but also cured the protein-losing enteropathy.

We present this unique case to highlight some of the practical difficulties in achieving an accurate diagnosis of underlying conditions responsible for protein-losing enteropathy. Discovery of tuberculosis led us to believe that he had been suffering from abdominal tuberculosis – which was responsible for the protein-losing state and the hydronephrosis. However, the single most suspicious biochemical finding which did not change with therapy was the serum protein level. Ultimately, the decision to proceed to laparotomy was taken in view of the unusual behaviour of the tuberculosis disease, and in spite of specific chemotherapy along with corticosteroids.

In retrospect, we believe that an abdominal computed tomographic scan would have been an appropriate investigation before laparotomy to clinch the diagnosis.

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