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Postgraduate Medical Journal (July 1977) **53**, 411–415.

Co-existent eosinophilic gastroenteritis and hypothalamic-pituitary dysfunction

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Summary

A case of eosinophilic gastroenteritis in a 42-year-old man is described. The patient had diarrhoea, faecal blood loss, a protein-losing enteropathy, malabsorption of fat, xylose and vitamin B₁₂. Co-existent hypopituitarism, diabetes insipidus and hypothalamic dysfunction was demonstrated. Complete clinical recovery occurred with pituitary replacement therapy alone. The association of this endocrine abnormality with the picture of eosinophilic gastroenteritis has not previously been described.

Introduction

In 1937, Kaijser described the first three cases of eosinophilic infiltration of the stomach and small bowel, following which further reports appeared in the literature. Terminology became increasingly confusing with lesions being reported under a variety of names, until Ureles *et al.* (1961), after a review of the world literature, proposed a classification of the reported cases into diffuse and circumscribed types. The latter is the so-called eosinophilic

granuloma, a localized, submucosal, inflammatory, polypoid lesion. This variety appears to be much more common than the diffuse type, which is now generally termed eosinophilic gastroenteritis (Ureles *et al.*, 1961; Edelman and March, 1964; Klein *et al.*, 1970). Eosinophilic gastroenteritis can be readily differentiated from eosinophilic granuloma on clinical, pathological, laboratory and radiological findings (Ureles *et al.*, 1961; Edelman and March, 1964; Burhenne and Carbone, 1966).

A patient with eosinophilic gastroenteritis has recently been seen. The case appears unique in that the patient was also found to be suffering from hypopituitarism, diabetes insipidus and hypothalamic dysfunction. The features of eosinophilic gastroenteritis were completely reversed by cortisone acetate prescribed in standard dosage as pituitary replacement therapy. This raises the possibility that the pituitary-hypothalamic defect may be implicated in the pathogenesis of the gastrointestinal lesion.

Case report

A 42-year-old car assembly worker presented in April 1974 with nocturnal diarrhoea of 3 months'

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duration, associated with borborygmi, general malaise, anorexia and weight-loss. He also gave a 5-year history of gradual onset of impotence, loss of facial, pubic and axillary hair, decrease in genital size, thirst and inability to tan in sunlight. He had a 15-year-old son and the past medical history was non-contributory.

He was well nourished, 172 cm in height with a span of 163 cm. There was marked pallor, a smooth dry skin and bilateral gynaecomastia. Facial hair was minimal, there was complete absence of axillary hair and pubic hair was sparse and of female distribution. The right testis was soft, measuring 2×1 cm, while the left testis was pea-sized. Abdominal and rectal examinations and sigmoidoscopy were all normal.

Investigations

Haematology. Haemoglobin 10.3 g/dl; MCV $81 \mu^3$; WBC ranged from 5.0 to 9.0×10^9 /l; a differential count showed 12–47% eosinophils, with direct eosinophil counts ranging from 0.84 to 3.0×10^9 /l. Serum folate, vitamin B₁₂, iron and iron binding capacity were normal.

Biochemistry. Serum sodium 155–170 mmol/l; serum potassium 2.4–3.7 mmol/l; blood urea 3.83 mmol/l. Liver function tests, serum calcium and phosphate were normal, but the alkaline phosphatase level ranged between 73 and 111 i.u./l (normal 17–70 i.u./l). Serum orosomucoid normal.

Microbiology. Repeated stool microscopy showed no evidence of ova, cysts or parasites and no pathogenic organisms were cultured.

Immunology. Serum IgG 20 g/l (normal 6.0–16.0 g/l); IgA 1.56 g/l (normal 0.75–5.20 g/l); IgM 0.27 g/l (normal 0.30–1.80 g/l); IgE 200 ng/ml (normal up to 300 ng/ml). There was no Bence-Jones proteinuria. Immunochemical complement levels: C₃ 2.49 g/l (normal 0.78–1.61 g/l); C₄ 0.52 g/l (normal 0.15–0.45 g/l). Organ specific antibodies to gastric parietal cells, intrinsic factor, thyroglobulin, adrenal, parathyroid and pancreatic tissues were all negative.

Endocrine function.

Thyroid. Serum thyroxine 44 nmol/l (normal 60–135 nmol/l); thyopac 140% (normal 92–117%); free thyroxine index 36.7 nmol/l; T₃ radioimmunoassay 165 ng/100 ml (normal 85–175 ng/100 ml).

Gonadotrophins. Basal FSH 1 u./l (normal 1–7 u./l); basal LH < 1 u./l (normal 2–8 u./l). Following stimulation with 100 μ g of intravenous LHRH (luteinizing hormone releasing hormone), there was no rise in the serum levels of FSH (follicle-stimulating hormone) or LH. Total serum androgens were 14 nmol/l (normal 15.5–48.5 nmol/l).

Growth hormone. Following intravenous soluble insulin (0.1 u./kg body-weight), the blood glucose

level fell to 1.1 mmol/l, but the growth hormone level failed to rise above 1 mu./l.

Adrenal function. Mean urinary 17-oxosteroid and 17-oxogenic steroid excretions were 4.2 μ mol/24 hr and 0.9 μ mol/24 hr respectively (normal 4–24 μ mol/24 hr and 5–19 μ mol/24 hr). Diurnal plasma cortisol levels (mean of three estimations): 09.00 hours: 120 nmol/l (normal 140–700 nmol/l); 23.00 hours: 50 nmol/l (normal 80–140 nmol/l). In response to insulin-induced hypoglycaemia, a basal plasma cortisol of 100 nmol/l rose to only 160 nmol/l. There was a partial response to tetracosactrin (250 μ g, i.m.), the basal cortisol of 100 nmol/l rising to 320 nmol/l after 30 min.

Posterior pituitary. Two to four litres of urine were passed daily. Serum osmolality ranged between 300 and 350 mosmol/l, when the serum sodium level was 155–170 mmol/l and urine osmolality was 120–300 mosmol/l.

The visual fields and pituitary fossa were normal. Urine excretion of vanillyl mandelic acid and 5-hydroxyindoleacetic acid was not increased. Blood lymphocyte karyotype was 46 XY.

Intestinal function. Daily stool volumes ranged between 350 and 2700 ml/day. The motion was fluid and grey, with persistently positive occult bloods and faecal fat excretion of up to 49 mmol/day (normal < 17.5 mmol/day).

Xylose absorption. Following a 5 g dose, 19% was excreted in the total 5 hr period (normal 35% $\pm$ 7%).

Double isotope Schilling test. Recovery of ⁵⁸Co vitamin B₁₂ without intrinsic factor was 8.6% (normal 11–28%) while recovery of ⁵⁷Co vitamin B₁₂ with intrinsic factor was 6.6% (normal 12–30%).

Faecal protein loss. Five-day faecal recovery of ⁵¹Cr following intravenous injection of 100 μ Ci of ⁵¹CrCl₃ was 2.0% (normal 0–1%).

Radiology. Barium enema examination was normal. Barium follow-through examination showed fragmentation and segmentation of barium with dilatation of bowel loops, compatible with malabsorption.

Jejunal intubation. The jejunal aspirate showed no ova, cysts or parasites on microscopy. Lipase and protease activity were normal. IgG, IgM, IgA and free secretory piece were all detected in the aspirate.

Jejunal biopsy. The dissecting microscope appearance was normal. Histologically, the mucosa showed broadening of the bases of some villi, a small increase in plasma cells, and prominent eosinophils in the lamina propria (Fig. 1). A small piece of gastric mucosa was included in the biopsy specimen and this too showed eosinophilic infiltration of the mucosa. Estimation of the disaccharidase content of the jejunal biopsy showed normal values for lactase, sucrase and maltase.

FIG. 1. A jejunal biopsy showing predominant eosinophilic infiltration of the lamina propria ($\times 105$).

Progress (Fig. 2)

A diagnosis of eosinophilic gastroenteritis was made on the basis of peripheral blood and tissue eosinophilia. The patient's medical history was reviewed but there was no past history of allergic disease. Although no specific foodstuffs consistently reproduced his gastrointestinal symptoms, the patient volunteered that pork occasionally produced diarrhoea. Scratch tests to a variety of food antigens were performed, and the only significantly positive reaction was a 4-mm weal with erythema in response to pork.

In view of the endocrine defect, replacement therapy was commenced with subcutaneous pitressin tannate in oil. This resulted in normal urine volumes and a return of serum and urine osmolalities towards normal but had no effect on the intestinal abnormality. Cortisone acetate was then started in a dose of 37.5 mg/day. The diarrhoea and steatorrhoea subsided and peripheral blood eosinophil counts fell to normal within 2 weeks (Fig. 2). A repeat xylose absorption was normal, 48% of the 5 g dose being excreted within 5 hr. The serum immunoglobulin levels also improved, the IgG being 13.1 g/l, IgA 1.01 g/l, IgM 0.21 g/l and IgE 150 ng/ml. The C_3 level fell to 2.03 g/l, while C_4 remained almost unchanged at 0.56 g/l.

The patient was discharged home on cortisone acetate plus intramuscular testosterone and a lysine vasopressin nasal spray. At follow-up 3 months

FIG. 2. The clinical response to pituitary replacement therapy.

later, he was fit and well with no recurrence of diarrhoea and the direct eosinophil count was 67 cells/ μ l. A repeat jejunal biopsy showed a normal dissecting microscope appearance. Histologically, some non-specific broadening of the villi was noted but there was no infiltration of the lamina propria by eosinophils. The patient has been regularly reviewed to date and remains clinically well with no gastrointestinal symptoms and no peripheral blood eosinophilia. His endocrine defect is well controlled by replacement therapy.

Discussion

The condition of eosinophilic gastroenteritis has emerged as a distinct entity from what was initially a confusing picture. Leinbach and Rubin (1970) consider that three criteria should be used to establish the diagnosis: (1) an increase in the blood eosinophil count; (2) histological demonstration of infiltration of some part of the gastrointestinal tract by increased numbers of eosinophils, and (3) gastrointestinal symptoms and/or signs following food ingestion. The first criterion is fulfilled in the case described, with direct eosinophil counts ranging from 0.84 to 3.00×10^9 /l. Secondly, microscopy of the jejunal biopsy showed prominent eosinophilic infiltration of the lamina propria. The third criterion is the least reliable. In the larger series of eosinophilic gastroenteritis reported to date, fewer than 50% of patients have demonstrated reaction to foodstuffs (Edelman and March, 1964; Klein *et al.*, 1970). Some authors have demonstrated accentuation of mucosal eosinophilia with severe clinical symptoms when implicated food was instilled into the jejunum of a patient with this disease (Greenberger, Tannenbaum and Ruppert, 1967; Klein *et al.*, 1970). In contrast, Leinbach and Rubin (1970), in a blind review of intestinal biopsies taken during challenge with known precipitating foodstuffs, showed no significant changes either in villous architecture or in the degree of intestinal infiltration with eosinophils. The present patient volunteered that pork occasionally precipitated episodes of diarrhoea, and prick tests to a number of foods produced a positive response to pork antigen only. The significance of such skin tests in this condition, however, is debatable since Leinbach and Rubin (1970) found the results of skin tests in their patient to correlate poorly with symptomatology.

Small intestinal mucosal involvement has become increasingly recognized and at least 50% of recently reported cases have shown small bowel disease (Klein *et al.*, 1970). Although jejunal disease can occur by itself, it is less frequent than combined pathology. Only four of the twenty-four patients reviewed by Edelman and March (1964) complained of diarrhoea. The presentation of the present case

with diarrhoea, steatorrhoea and faecal blood loss is unusual and presumably reflects predominant mucosal disease. Protein-losing enteropathy and/or malabsorption have been increasingly described in cases with mucosal involvement (Bentlif *et al.*, 1966; Greenberger *et al.*, 1967; Waldmann *et al.*, 1967; Scudamore *et al.*, 1969; Kaplan *et al.*, 1970; Leinbach and Rubin, 1970; Klein *et al.*, 1970). Intestinal blood and protein loss might be explained by exudation through areas of surface epithelium compromised by massive underlying eosinophilic infiltration (Leinbach and Rubin, 1970). Abnormal vitamin B₁₂ absorptive capacity appears to be rare. The present patient showed significant impairment of vitamin B₁₂ absorption reflecting the terminal ileal involvement documented in eosinophilic gastroenteritis (Swarts and Young, 1955; Koneman, Sawyer and Lubchenko, 1959; Higgins, Lamm and Yutzy, 1966; Salmon and Paulley, 1967; Kaplan *et al.*, 1970).

Studies on serum immunoglobulin and complement levels in affected patients are fragmentary. Pre-treatment immunoglobulin levels are usually depressed. The depression may affect all three major immunoglobulin classes (Leinbach and Rubin, 1970), IgG and IgM (Scudamore *et al.*, 1969; Klein *et al.*, 1970), or IgG alone (Kaplan *et al.*, 1970). The response of the immunoglobulin pattern to treatment also varies. No alteration was found by Kaplan *et al.* (1970), while Leinbach and Rubin (1970) noted a slight elevation of previously depressed levels on a protein elimination diet, although absolute levels were still subnormal. Before therapy, the present patient demonstrated a significantly elevated IgG level, normal IgA and IgE, and a low normal IgM. In the jejunal aspirate, IgG, IgM, IgA and free secretory piece were all detected. Following steroid therapy, the serum IgG returned to a normal level. Both C₃ and C₄ complement levels were elevated before treatment and were still elevated at discharge. The clinical response to cortisone acetate was quite dramatic, the steatorrhoea and diarrhoea ceasing within 72 hr of commencing therapy. This rapid improvement on steroids is typical in eosinophilic gastroenteritis, and no case refractory to such therapy had been documented up to 1970 (Klein *et al.*, 1970). Occasionally, remissions have been obtained with elimination diets (Waldmann *et al.*, 1967; Scudamore *et al.*, 1969; Leinbach and Rubin, 1970) but have not necessarily been sustained without the addition of corticosteroids (Klein *et al.*, 1970). Attempts to treat patients with anti-histaminics have been unsuccessful (Lane, 1967).

In addition to eosinophilic gastroenteritis, the patient described shows evidence of pituitary-hypothalamic dysfunction. From the history, the endocrine disturbance antedated the gastrointestinal

features by many years, and one might speculate that the small intestinal lesion is secondary to the hormonal abnormality. The authors have been unable to find any published evidence in the English literature of such an association in man. Gelb and Gerson (1969), in reviewing the influence of endocrine glands on small intestinal absorption, noted that hypophysectomy results in intestinal atrophy which is partly reversed following growth hormone administration. Clinical and experimental observations show that gut motility is altered in thyroid disease (Middleton, 1971). In man, it is recognized that steatorrhoea and diarrhoea both occur in hyperthyroidism (Siurala, Julkunen and Lamberg, 1966; Middleton and Thompson, 1968; Hellesen *et al.*, 1969) but the mechanism is unknown, and sometimes in hypothyroidism (Siurala, Varis and Lamberg, 1968). The relationship of adrenal function to fat absorption has been known for some time. In clinical studies, McBrien, Jones and Creamer (1963) documented steatorrhoea in four patients with Addison's disease, the abnormality being readily corrected with cortisone and deoxycorticosterone. Per-oral jejunal biopsies were normal in the two patients in whom they were performed. Guarini and Macaluso (1963) confirmed the steatorrhoea in a further six patients. In contrast to the studies on most endocrine glands, there has been almost no work on the role of the gonads in intestinal disease (Gelb and Gerson, 1969).

Thus, in the present patient, the diarrhoea and steatorrhoea could be due to hypoadrenalism or hypothyroidism secondary to his pituitary-hypothalamic disease. Although the response of symptoms to cortisone is in keeping with a hypoadrenal aetiology, the protein-losing enteropathy, vitamin B₁₂ malabsorption, peripheral blood eosinophilia and eosinophilic infiltration of the jejunal biopsy are not features previously reported in cases of endocrine dysfunction. No previously reported endocrine abnormality explains the complete clinical picture in the patient described. The response to cortisone therapy in standard replacement dosage raises the interesting possibility that steroid deficiency may predispose to the development of eosinophilic gastroenteritis, although the authors have not been able to find any documentation of such an association in the literature up to the present time.

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