Extensive alimentary and genital ulceration, mesenteric cysts, malabsorption, T-lymphocyte depletion and subsequent anaplastic bladder carcinoma

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Summary

The occurrence of several unusual disorders in a single patient prompted the question as to whether these may all have been part of a single syndrome, and the possible differential diagnosis is discussed in detail.

The case was thought to be an instance of acquired T-lymphocyte depletion leading to the development of premature malignant disease.

Case report

A male printer born in 1937 was first seen in January 1971 complaining of dyspepsia. A barium meal examination was negative and he was treated symptomatically. In March 1973 he complained of loss of appetite, difficulty in swallowing with food appearing to stick at various levels, and a weight loss from about 66 to 60 kg over the previous few months. A month later he developed severe mouth ulcers which were noted to be extensive, confluent and yellowish in colour. At the same time he developed ulcers on the glans and shaft of the penis. A repeat barium meal was normal and subsequently a barium swallow was also normal. Oesophagoscopy showed multiple superficial ulcers at all levels, and the appearance was unlike peptic oesophagitis.

Two months later he was referred to a dermatology clinic with scaly discrete skin lesions on his trunk. A skin biopsy showed hyperplasia, dyskeratosis, spongiosis, and microvesiculation with endothelial swelling, with neutrophil and lymphocyte infiltration similar to pityriasis lichenoides et varioliformis. It was considered that he had the minor mucocutaneous variety of Behçet's disease.

In August 1973 he complained of diarrhoea for the first time, with frequent pale offensive stools which were difficult to flush away, and his weight had fallen again. His dysphagia and dyspepsia were controlled with oral hydrocortisone pellets and an antacid containing local anaesthetic. By February 1974 he felt considerably better with improved appetite and his weight was increasing. The improvement led to loss from follow-up.

He was referred to a general medical clinic 2 years later complaining again of dyspepsia. He also had diarrhoea with the character of steatorrhoea and further weight loss to 57 kg. On examination there was a vague inconstant left-sided abdominal swelling. Oral ulcers persisted but there were no genital ulcers. As his weight fell to 51 kg over the next 3 months he was admitted to hospital for full evaluation.

Investigations carried out at this time included the following: sigmoidoscopy showed pale stool with only a mild mucosal erythema; histology confirmed a mild non-specific proctitis; barium enema was normal, but barium meal and follow-through demonstrated abnormality throughout the entire small intestine and also in the right colon, with extensive loss of mucosal pattern; upper digestive endoscopy revealed severe oesophagitis with oesophageal ulcers, duodenal ulcers and evidence of a chronic gastritis; the peak acid output was normal at 33.2 mmol/hr; alimentary histology showed a severe inflammatory infiltrate in the oesophagus and chronic gastritis; jejunal biopsy histology showed subtotal villous atrophy with superficial erosions and a heavy plasma cell infiltrate into the submucosa.

The blood film showed evidence of hyposplenism; serum folate was less than one $\mu\text{g/l}$. B_{12} was normal at 442 ng/l, although a Schilling test without intrinsic factor showed only 2.4% excretion (normal >10%); faecal fat excretion was 118 mmol/day (upper limit of normal 17 mmol/day); prothrombin ratio was 25/13 sec, corrected to 13.5/12 after vitamin K_1 i.m.; a glucose tolerance test produced a flat curve, with all values between 4.8 and 5.2 mmol/l; there was a marginally raised IgG (21.7 g/l), but normal IgA (3.7 g/l) and IgM (1.1 g/l) levels; stimulated pancreatic exocrine function was normal (volume, trypsin and bicarbonate outputs).

The ulcerative jejuno-ileitis was felt to be the major component at this stage of the illness. Since this may be a variant of adult coeliac disease, he was started on a gluten-free diet in July 1976, together with oral iron therapy. After one month his weight rose to 57 kg and there was no diarrhoea. His oral ulcers cleared rapidly and completely. A repeat jejunal biopsy showed partial recovery. However, he then complained of tingling and cramps in his hands and his serum calcium fell to 1.54 mmol/l. He was given i.m. vitamin D 300 000 u. Two weeks later his symptoms of paraesthesiae were gone and his serum calcium was 2.27 mmol/l.

Although he continued to improve, in September 1976 abdominal examination revealed a hard fixed mass 6 cm in diameter in the left upper quadrant. It was feared that he had developed a lymphoma. A lymphangiogram was negative and a laparotomy was performed.

It was found that there were multiple lymph-filled mesenteric cysts matted to the mid-jejunum. No dilatation of the lymphatic vessels was noted and the cysts were drained. Fluid from cysts showed chylomicra and lymphocytes, consistent with chyle. The cyst wall histology showed no evidence of lymphoma but a heavy infiltrate of plasma cells, lymphocytes and foamy macrophages.

Blood lymphocyte studies showed 50% T-cells and 50% B-cells, with a reduced absolute T-cell count at this time.

He made an uninterrupted recovery and had no diarrhoea again. His weight rose to 70 kg in March 1977, which he felt was his normal weight. This has been maintained for 18 months. A jejunal biopsy after 8 months on diet showed further recovery. In July 1977 his lymphocyte distribution was 45% T-cells and 50% B-cells.

He remained in good health until September 1977 when he developed terminal haematuria. Cystoscopy demonstrated a 3 cm oedematous inflamed patch round the right urethral orifice and on the right side of the trigone. Histology of this was consistent with an anaplastic carcinoma.

At this time faecal fat excretion was 36 mmol/day

(markedly reduced from previous value but still twice normal). The Schilling test demonstrated normal excretion (>10%) of B_{12} , both with and without intrinsic factor. Serum folate was now 3.5 $\mu\text{g/l}$. Tissue typing showed the presence of HLA A_1 , A_3 , B_7 and B_8 . Lymphocyte studies now showed a more severe depletion of T-cells (14%) with normal B-cells (65%).

He subsequently received a course of supervoltage radiotherapy to his bladder tumour. Although he remained well in himself a check cystoscopy showed a focus of tumour 6 months later, and he has now undergone partial cystectomy.

Discussion

The initial diagnosis made in this patient was Behçet's syndrome, of which only 98 cases have been reported in Britain and 18 in the U.S.A. (Lehner, 1977). Although severe oral ulceration occurs in at least 90% of such patients (Oshima *et al.*, 1963; Lehner, 1977), and is the usual first manifestation, this in itself is a non-specific disorder. Behçet's original description was of iridocyclitis with oral and genital ulceration (Behçet, 1937), but modern practice has recognized minor forms without eye disease. The present patient had orogenital ulceration, with other skin lesions, but there were never any ocular or neurological disorders.

He also had marked gastrointestinal disease. Both ulceration of the small bowel and necrotizing oesophagitis have been recorded in Behçet's syndrome (Bøe, Dalgaard and Scott, 1958; Baba *et al.*, 1976). But more typical changes are ulcerative colitis (Bøe *et al.*, 1958; Empey, 1972; Smith, Kime and Pitcher, 1973; Baba *et al.*, 1976) and lymphangiectasia (Asakura *et al.*, 1973; Tsuchiya *et al.*, 1976). Atrophic villi were thought not to be a feature of the disease (Asakura *et al.*, 1973).

Histocompatibility antigens in the patient did not show either HLA B_5 , present in 75% with Behçet's syndrome (Ohno *et al.*, 1975; Sugiura, Sanefuji and Ohno, 1976); nor HLA A_2/B_{12} , present in 21% (Lehner, 1977).

The presence of ulcerative jejuno-ileitis in their patient led the authors to suspect that this might be Crohn's disease (Goldstein *et al.*, 1976), in which genital involvement has recently been described (Atherton *et al.*, 1978). Although this may be protean in its manifestation, the absence of characteristic pain, typical radiology, and any of the significant complications such as perineal sepsis were features against the diagnosis. The numerous biopsy samples taken never showed any evidence of granuloma formation, nor of lymphoma (Isaacson and Hodges, 1978).

Ulcerative jejunoileitis may also be a feature of coeliac disease (Bayless *et al.*, 1967; Davidson, 1969;

Shiner, 1974), and ulceration of the small intestine may occur even when on gluten exclusion (Bayless *et al.*, 1976). Study of patients with mouth ulcers suggested that 25% had jejunal villous atrophy; and that both disorders were healed by gluten exclusion (Ferguson *et al.*, 1976), although clinical response is not proportional to the mucosal lesion's severity (Stewart, 1974). The presence of subtotal villous atrophy and severe malabsorption in the present patient justified a trial of gluten exclusion, subsequent to which his weight increased by 19 kg, his steatorrhea was much reduced, although not cured, and hypocalcaemia, hypoalbuminaemia, low serum folate and deficient B₁₂ absorption were corrected. The improvement in his jejunal mucosa was in parallel with this response. The clinical course of the patient has made a trial of gluten challenge unethical to date: it would probably take a prolonged period of normal feeding to show clinical and histological relapse.

Supportive evidence for a diagnosis of gluten sensitivity was the presence of HLA A₁/B₈, which are very strongly associated (Falchuk, Roentine and Strober, 1972; Oliver, 1977). Hyposplenism was found in 10–15% of patients with adult coeliac disease (Marsh and Stewart, 1970), but this may also occur in inflammatory bowel disease. The serum immunoglobulin pattern was not that typical of coeliac disease (usually raised IgA) (Asquith, 1974) but this is often normal. Genital ulceration and mesenteric cysts were not features previously described in adult coeliac disease.

The presence of mesenteric cysts in the present case may well have been related to the ulcerative jejuno-ileitis, although there was no evidence of lymphatic duct obstruction or lymphangiectasia. There is an extensive literature of case reports on mesenteric cysts, but their aetiology remains obscure (Behrs, Judd and Dockerty, 1950).

The deficiency of circulating thymus-dependent lymphocytes was of great interest. Abnormalities of cellular immunity have been documented in Behçet's syndrome (Sugiura *et al.*, 1976), and these may include lymphopenia (Tsuchiya *et al.*, 1976) and thymic lymphoid follicular development (Tameoki *et al.*, 1972).

Deficiency of T-lymphocytes has also been noted in other conditions. In coeliac disease it occurs and reverts to normal after diet treatment (O'Donoghue, Lancaster-Smith and Kumar, 1975), and is associated also with deficient antibody production (Baker *et al.*, 1974). In Crohn's disease (but not ulcerative colitis) there is a deficiency of T-lymphocytes, unrelated to activity (Strickland *et al.*, 1968). Increase in epithelial lymphocytes is particularly marked in coeliac disease (Ferguson, 1977), although it is not specific to this condition. This may represent

increased migration into the lumen, which is known to occur in coeliac disease, and possibly other intestinal diseases (Wheatman, Hagith and Douglas, 1974).

In general, T-lymphocyte and other immune deficiencies predispose to both infections and malignant disease (Di George, 1968; Kersey, Spector and Good, 1975). It was therefore not surprising when this patient developed an undifferentiated bladder tumour. The association was probably causative in view of the lack of exposure to known carcinogens such as β -naphthylamine, and the unusual histology of the lesion.

It seems likely that the patient had severe complicated adult coeliac disease with various unusual but related manifestations. The initial presentation simulating a minor Behçet's syndrome raises the question of whether this disease, coeliac disease and possibly also Crohn's disease are related disorders representing different parts of a spectrum. It could be that patients considered to have Behçet's disease may benefit from a trial of gluten exclusion. This certainly appears to help some patients with problems other than chronic coeliac disease, such as aphthous stomatitis (Ferguson *et al.*, 1976) and granulomatous disease of bowel and liver (Bjørnkleit *et al.*, 1978). There is as yet no therapy for T-lymphopenia, and management must consist of treatment of complications as they arise.

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Addendum

The patient developed a triplegia in September 1978, considered to be a carcinomatous neuropathy, and died with widespread metastases in February 1979.