Acquired immunodeficiency, malabsorption and lymphoma

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Summary: A 66 year old female with a long history of recurrent pulmonary infection presented with a full-blown malabsorption syndrome. She was found to be suffering from acquired immunodeficiency. She later developed non-Hodgkin's lymphoma of the cervical lymph nodes. The possible relationships between immunodeficiency, malabsorption and lymphoma are discussed.

Introduction

Common variable immunodeficiency usually presents in late adolescence or early adult life. It is usually characterized by recurrent pyogenic infections, especially of the sino-respiratory tract, and frequently complicated by a sprue-like syndrome. Serum immunoglobulin levels are invariably depressed, and there is frequently an impairment of cell-mediated immunity. A further, later complication is the development of lymphoreticular malignancy.^{1,2}

This report describes a 66 year old female with a 46-year history of recurrent pulmonary infection who later developed chronic diarrhoea with marked malabsorption. She subsequently developed non-Hodgkin's lymphoma.

Case report

A 66 year old caucasian women who developed recurrent pulmonary infection at age 20, presented with anorexia, increasing weakness, weight loss and episodic swelling of the ankles. Three months prior to admission, she began to suffer from postprandial abdominal discomfort, diarrhoea 4 times daily with large yellow, frothy, fatty, odorous faeces. Two weeks before admission she developed paraesthesiae and muscle twitching.

On examination she appeared pale and in a poor nutritional state, with a blood pressure of 90/65 mmHg. Chvostek's and Trousseau's signs were elicited. The tongue was red and the papillae were atrophic. Moist râles were heard over the right lung

base. Muscle wasting was conspicuous and leg oedema prominent.

Investigations showed haemoglobin 91 g/l; haematocrit 33%; leucocytes $10 \times 10^9/l$; platelets $160 \times 10^9/l$; blood film revealed anaemia with anisocytosis, macrocytosis and hypochromia. Blood glucose 3.4 mmol/l; urea 2.7 mmol/l; uric acid 190 $\mu\text{mol/l}$; cholesterol 3.86 mmol/l; sodium 152 mmol/l; potassium 2.9 mmol/l; calcium 1.9 mmol/l; phosphorus 1.16 mmol/l; prothrombin time 23 seconds; serum carotene 21 mg/dl (normal 60–120 mg/dl); serum vitamin A 63 IU/dl (normal 100–150 IU/dl); serum iron 8.0 $\mu\text{mol/l}$; iron binding capacity 35.3 $\mu\text{mol/l}$; albumin 24 g/l; globulin 10 g/l; folic acid 4.1 ng/dl; serum B₁₂ 130 pg/ml (normal >300 pg/ml); protein electrophoresis revealed albumin 64%, alpha₂-globulin 15.4%, beta-globulin 10.8%, gamma-globulin 1.1%; quantitative determination of immunoglobulins showed: IgG 1.1 g/l (normal 12 ± 3 g/l), IgA 0.12 g/l (normal 2.5 ± 1 g/l), IgM nil (normal 880 ± 220 mg/l). Blood group was O Rh positive; serum isohaemagglutinins were absent. Lymphocyte subsets revealed total T cells 62% and B cells 9%. *In vitro* mitogenic stimulation showed impaired responses with concanavalin A (Con A) and pokeweed mitogen (PWM), but not with phytohaemagglutinin (PHA). Duodenal aspirate was negative for parasites. Stool examination revealed many leucocytes and a few erythrocytes but no organisms were isolated.

Electrocardiogram showed sinus rhythm with S-T depression, flat T-waves and a prolonged Q-T interval. The chest X-rays demonstrated a normal heart, thickening of the right interlobar fissure and a speckled opacity of the right lung base. Vertebral X-rays were suggestive of osteoporosis. There was a thoracic kyphosis. Small bowel radiography revealed an irregular mucosa with swollen,

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thickened, mucosal folds, with barium flocculation in some sites. Radiographs of skull and lung bones, barium meal and enema, intravenous pyelography, lower limb lymphography and hepato-splenic isotopic scan were all normal. Per oral suction small intestinal biopsy demonstrated partial villous atrophy. Liver biopsy was normal. Bone marrow displayed a megaloblastoid erythropoiesis with micronormoblasts and Howell-Jolly bodies. Megakaryocytes were present; there were no foreign cells.

Absorption studies were as follows: *d*-xylose absorption test 2.2 g/5 h (normal > 4.5 g/5 h), Schilling test – excretion of B₁₂ 0.6% at 24 h, 0% at 48 h (normal > 8%/24 h, 0%/48 h), polyvinyl pyrrolidone (PVP) ¹³¹I excretion 0.4%/4 days (normal > 1%), fecal fat 20 g/24 h (normal < 5 g/24 h), fecal nitrogen 5.6 g/24 h (normal < 1 g/24 h).

The patient was treated with biweekly injections of gamma-globulin, supplemented by fresh plasma. She was given intravenous calcium, intramuscular vitamins D, A and B₁₂, oral iron, potassium and folic acid. The haemoglobin, serum albumin, calcium and potassium rose to normal values. The muscle twitching ceased, the oedema subsided and the patient's condition steadily improved. The diarrhoea persisted and a trial gluten-free diet was instituted for 2 months without change in bowel frequency.

Eight months later she was readmitted for a swelling below the right jaw. A cluster of enlarged non-tender lymph nodes were palpated in the right submandibular region and several small nodes were felt along the right sternomastoid muscle. A biopsy was carried out and demonstrated complete obliteration of lymph node architecture and replacement by proliferating lymphocytes of the small- and large-cleft and non-cleft varieties. In many areas these were aggregated in follicle-like structures, each rounded partially or completely by several layers of condensed reticular fibres. There was invasion of the lymph node capsule by the abnormal lymphocytes. The histological diagnosis was non-Hodgkin's lymphoma of the follicular (B cell) variety (see Figure 1a, b). The patient was treated by excision followed by local irradiation.

During the next 4 years she continued to receive gamma-globulin replacement therapy. She felt well and no further lymphadenopathy or hepato-splenomegaly were noted. She was subsequently treated for generalized paratyphoid C infection. Despite the gamma-globulin replacement therapy the patient died one year later of septicaemia in another hospital. Autopsy was not carried out.

Discussion

Our patient suffered from recurrent pulmonary infections for over 4 decades before developing a

Figure 1 (a) Overview of lymph node architecture, demonstrating follicle-like structures within an area of complete nodal disorganization; these 'follicles' are surrounded partly or completely by dense reticular fibres. Reticulin stain, $\times 33$. (b) Proliferating lymphocytes of the small-, large- and non-cleft varieties, completely obliterating lymph node architecture. Haematoxylin and eosin, $\times 110$.

full-blown malabsorption syndrome. Throughout her illness she exhibited extremely low serum immunoglobulin levels. She had in addition a defect in cellular immunity. The malabsorption is presumably due to a primary defect in mucosal absorption associated with hypogammaglobulinaemia.

Common variable immunodeficiency occurs in both sexes and generally presents at about 15–35 years of age. It is characterized by recurrent pyogenic infections, especially sinusitis and pneumonia, and is frequently complicated by gastrointestinal disorders. Immunoglobulin levels and isohaemagglutinins are markedly reduced and cellular immunity is frequently impaired. Although no clear-cut genetic transmission can be demonstrated, several authors have described a high familial incidence of immunodeficiency^{3,4} and autoimmunity.^{5,6} However, the possibility of infection (e.g. viral) cannot be discarded.

A variety of gastrointestinal disorders have been described in acquired hypogammaglobulinaemia: disaccharidase deficiency,⁷ pernicious anaemia-like syndrome,⁸ protein-losing enteropathy which results in hypoalbuminaemia,⁹ diarrhoea and malabsorption, which may or may not be associated with infective agents,⁸ including *Giardia lamblia*,¹⁰ coccidium and *Cryptosporidium*.⁸ Intestinal biopsy may reveal villus flattening⁷ (as in the present case), nodular lymphoid hyperplasia¹¹ or even normal mucosa.¹²

Our patient subsequently developed non-Hodgkin's B-cell lymphoma. An increased tendency to neoplasia, especially lymphoreticular and gastrointestinal, has been noted in congenital and acquired immunodeficiency, both humoral and cellular.^{1,2,8,13-15} A recent prospective study has demonstrated a 30-fold increase in the incidence of lymphoma in patients with common variable immunodeficiency.¹⁶ The enhanced susceptibility to malignancy may be due to a failure of the immune surveillance mechanism associated with an impaired defence against neoplasia.¹⁷ Impaired immunoregulation may result in an enhanced proliferation of neoplastic lymphocytes.¹ Lym-

phoma is more frequent in patients with congenital immunodeficiency disease, autoimmune disease and in recipients of renal allografts.¹ Infection with a potentially oncogenic virus such as Epstein-Barr may produce polyclonal B-cell proliferation which could ultimately lead to B-cell lymphoma via conversion to monoclonality and oncogene activation.¹⁸ An increased incidence of immunological abnormalities has been demonstrated in siblings of families with multiple cases of lymphoreticular neoplasia.^{19,20} The conditions of immunodeficiency, autoimmunity and lymphoma may represent variations of the same basic disturbance, namely a failure of feedback mechanisms in lymphocyte regulation.²¹ Finally, increased age and malabsorption may also lead to nutritional deficiency and an impairment of the immune system, and these can further increase the tendency to lymphoma.

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