CASE REPORT

Linear IgA dermatosis, coeliac disease, and extraintestinal B cell lymphoma

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Abstract
Linear IgA dermatosis is a malignancy associated rare bullous disorder similar to dermatitis herpetiformis. Linear IgA dermatosis differs from dermatitis herpetiformis in that the IgA deposits in the epidermal basement membrane are linear rather than granular. A patient is presented with coeliac disease who presented with linear IgA dermatosis and anaemia caused by chronic low grade B cell lymphoma.

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The itchy vesicular eruption of dermatitis herpetiformis has a frequent association with coeliac disease. A similar vesicular eruption can sometimes be seen with linear IgA dermatosis in which the pattern of basement membrane IgA deposit is linear rather than the granular deposition in dermal papillae as seen in dermatitis herpetiformis. Linear IgA dermatosis has a strong association with internal malignancies^{1 2} and we here make the first report of linear IgA dermatosis occurring in association with B cell lymphoma developing in a patient with coeliac disease.

Case report
A 71 year old white woman presented with an extensive, symmetrical, and pruritic bullous

eruption especially on extensor surfaces of the limbs, which had intermittently troubled her for one year. It had been partially responsive to a corticosteroid cream. Twelve years previously she had presented with abdominal pain, diarrhoea, and oral aphthae but only barium enema and sigmoidoscopy has been carried out with inconclusive result.

She now had a normocytic normochromic anaemia (Table I). A biopsy of uninvolved skin showed some epithelial blisters with intradermal abscesses in the dermal papillae containing fibrin and perivascular neutrophils. Homogeneous linear deposits of IgA along the basement membrane zone together with granular deposits of complement were detected in a skin biopsy using immunofluorescence technique (Fig 1). A duodenal biopsy showed features characteristic of untreated coeliac disease (Fig 2).

A diagnosis of dermatitis herpetiformis and coeliac disease was made and the patient was advised to take a gluten free diet and dapsone 100 mg daily.

Within two months the blisters were controlled but she developed a normochromic normocytic anaemia with Heinz bodies. A Coombs test was negative. The anaemia was attributed to dapsone treatment but reduction of the dose or replacement of the drug with sulphamethoxy pyridazine caused relapse of the rash and she resumed taking dapsone.

After one year of gluten free diet a duodenal biopsy showed return of normal villi (Fig 3) but the anaemia persisted (haemoglobin 8 g/dl) with target cells, Howell-Jolly bodies, and a platelet count of $714 \times 10^9/l$. These changes

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TABLE I Haematological data

Index (reference range)	Initial	After four years of gluten free diet	After one month of chlorambucil
Hb (11.5-18 g/dl)	11.1	5.2	6.1
PCV (38-54%)	35.5	18.2	19.8
MCV (79-97 fl)	95	87	86
MCH (27-32 pg)	29.5	28	26.7
Platelet count ($150-400 \times 10^9/l$)	461	424	22
WBC ($4-11 \times 10^9/l$)	7.1	12.5	0.1
Polymorphs ($2-7.5 \times 10^9/l$)	3.1	3.5	
Lymphocytes ($1.5-4.0 \times 10^9/l$)	2.4	6.3	
Eosinophils ($0.04-0.4 \times 10^9/l$)	0.21	1.5	
Monocytes ($0.2-0.8 \times 10^9/l$)	0.85	1.1	
Basophils ($0.0-0.1 \times 10^9/l$)	0.04	0.13	
Reticulin (0.5-1.5%)	5.7	2.6	
ESR (10-25 mm in first hour)	NA	148	

Hb=haemoglobin; PCV=packed cell volume; MCV=mean cell volume; MCH=mean corpuscular haemoglobin; WBC=white blood cell count; ESR=erythrocyte sedimentation rate.

Figure 1: Biopsy specimen of clinically uninvolved skin showing dense linear deposit of IgA at the dermoepidermal junction (immunoperoxidase technique $\times 450$).

Figure 2: A duodenal biopsy specimen obtained when the patient presented. It shows typical features of untreated coeliac disease with loss of villous height, crypt hypertrophy, and a dense inflammatory infiltrate including numerous intraepithelial lymphocytes (haematoxylin and eosin $\times 155$).

were compatible with coeliac disease associated splenic atrophy, which was confirmed by ultrasonography.

At two years after presentation she was still anaemic with a normal duodenal biopsy. The bone marrow was hypercellular with all series represented. Serum B12, red cell folate and reticulocyte count were normal. The erythrocyte sedimentation rate (Westergren) was 150 mm in the first hour (10–25 for this age group). The serum ferritin was 800 $\mu\text{g/l}$ (10–300) and iron 8.8 $\mu\text{mol/l}$ (8–32). The patient had therefore shown no response to iron treatment, and indeed was iron overloaded as reflected by the raised ferritin. A plasma IgM kappa monoclonal immunoglobulin was detectable at high concentration (15.9 g/l) in the absence of Bence Jones proteinuria.

Dapsone was withdrawn and the rash continued at a low intensity. Antibodies to gluten and reticulins were not detectable in the plasma. The original skin biopsy specimen was reviewed and the initial diagnosis of dermatitis herpetiformis was changed to that of linear IgA dermatosis on recognising the linear pattern of IgA deposition.

Three years from the onset she had a normal villous pattern on duodenal biopsy (Fig 3) but was still moderately anaemic.

After four years of gluten free diet a kappa Bence Jones proteinuria was detectable although the peripheral blood paraprotein concentration was unchanged (16.5 g/l). Small

Figure 3: Duodenal biopsy specimen after two years of gluten avoidance showing normal villous architecture (haematoxylin and eosin $\times 180$).

TABLE II Peripheral blood mononuclear cell surface marker expression

Marker	Positive cells $\times 10^3/\text{l}$	Reference range
CD2	0.44	1–4.0
CD5	0.29	1–4.0
CD3	0.40	0.97–3.4
CD4	0.25	0.43–2.36
CD8	0.13	0.28–1.92
CD19	0.32	0.11–0.92
HLA DR	0.26	0.1–1.0
κ/λ Chain	28:1	1.5–2.5:1

A white cell suspension was prepared after red cell lysis (Coulter Q preparation system) and incubated with directly conjugated monoclonal antibodies. The labelled cells were analysed in a flow cytometer (Coulter Epics Profile). Mononuclear cells were washed before κ/λ analysis. The λ T cell population (marked by CD2, 5, 3, 4 expression) is normal. Although the number of total B cells (CD19, HLA DR) is normal, this population is mainly monoclonal as shown by an abnormal κ/λ ratio.

lymphocytes accounted for 95% of the nucleated cells in the bone marrow at this time, mast cells were prominent, megakaryocytes were reduced, and erythroblasts formed 1% of the nucleated cells.

Immunological studies on the patient's peripheral blood white cells showed (Table II) clear evidence of an expanded population of B lymphocytes, which were expressing monoclonal surface immunoglobulin (kappa light chain). The surface immunoglobulin staining was strong and thereby typical of lymphoma. Although double staining was not carried out, the percentage of CD5 positive cells compared with the other T cell markers makes it unlikely that CD5 positive B cells (characteristic of chronic lymphocytic leukaemia) are present. A radiological search for lymphoma by small intestinal barium series, double contrast barium enema, and abdominal computed tomography was negative.

After a red cell transfusion she started oral chlorambucil 10 mg/d for two weeks each month. The patient took chlorambucil for only eight days and on the 18th day was found to have severe pancytopenia (Table I). Sulphamethoxypyridazine and chlorambucil were stopped and the patient was given a transfusion of packed cells and platelets. She developed fever of 38.6°C that responded to intravenous ciprofloxacin, fluconazole, and filgrastim (recombinant human granulocyte colony stimulating factor, Neupogen, Roche). Two weeks later she was readmitted with epistaxis. Her haemoglobin concentration was 10.6 g/dl, white cell count $0.3 \times 10^9/\text{l}$, and platelet count of $10 \times 10^9/\text{l}$. Bleeding subsided with nasal packing and platelet transfusions. The patient died in hospital two weeks later of Gram negative pneumonia, septicaemia, and shock.

At necropsy extensive bronchopneumonic consolidation was seen in both lungs with areas of haemorrhage. The bone marrow was loaded with small lymphocytes. No evidence of cerebral haemorrhage was seen. The small and large intestine and abdominal lymph nodes showed no macroscopic abnormality.

In summary this patient with linear IgA dermatosis and clinical picture identical to dermatitis herpetiformis had confirmed coeliac

disease and developed monoclonal B cell extraintestinal lymphoma.

Discussion

This patient, like many older patients with coeliac disease^{3,4} had tolerated chronic symptoms for many years. Serial biopsies showed clear improvement of the intestinal mucosa after gluten restriction thus confirming coeliac disease. The first appearance of the rash, initially misdiagnosed as linear IgA dermatosis probably marked the onset of a lymphoma.

Lymphoma is a well recognised⁵⁻⁷ complication of coeliac disease. The tumour is usually located in the intestine,^{6,7} and has a histiocytic morphology^{7,8} and of T cell origin.⁸⁻¹¹ In our patient longstanding coeliac disease was complicated by a lymphoma of B cell type as evidenced by the resistant anaemia without haematinic deficiencies, the bone marrow lymphocyte infiltration, the monoclonal IgM, and the abnormal B cell population in the blood.

Occasionally patients presenting with lymphoma are subsequently found to have coeliac disease^{12,13} but flat mucosa unresponsive to gluten free diet has also been reported in some lymphoma patients.^{7,14} In our patient the flat mucosa is coeliac disease related because the mucosa clearly healed during gluten free diet even though the lymphoma worsened.

A B cell lymphoma is unusual in coeliac disease and it could be that this lymphoma was not directly related to the intestinal disease and reflects the increased propensity of the coeliac disease patient to malignancies generally. B cell lymphoma has been suspected in some coeliac patients but full immunohistochemical proof is lacking.¹⁰ Interestingly, both linear IgA dermatosis and dermatitis herpetiformis have been linked directly with lymphoma¹⁵ and Sigurgeirsson *et al*¹⁶ have reported that male patients with dermatitis herpetiformis, but without coeliac disease have lymphoma 5.5-times more frequently than the general population. These lymphomas are usually of extraintestinal location and of B cell origin. Dermatitis herpetiformis can therefore be a marker of lymphoma as well as an associate of coeliac disease.

There is clinical and immunopathological overlap of linear IgA dermatosis and dermatitis herpetiformis. Linear IgA dermatosis is associated with malignancy especially lymphoma.¹⁷⁻¹⁹ Linear IgA dermatosis differs from dermatitis herpetiformis in that it may be bullous rather than simply vesicular or papular and affects the lower trunk, groins, lower limbs, and circumoral skin. It responds poorly to dapsone^{1,2} or to gluten free diet.^{2,19} Typically linear IgA dermatosis patients have

both circulating IgA ant basement membrane zone antibodies (not sought in our patient) and linear IgA deposits in the dermoepidermal junction. 'Overlap' cases are reported that have both the circulating ant basement membrane zone IgA antibodies typical of linear IgA dermatosis and the IgA antiendomysial IgA antibody typical of coeliac disease associated dermatitis herpetiformis.¹

Dermatitis herpetiformis remains best known for its strong association with coeliac disease. In those patients with dermatitis herpetiformis and coeliac disease treated by gluten free diet, the skin clears in parallel to, or in advance of the improvement in flat mucosa during gluten free diet.^{3,4}

In our patient there was clearly a failure of the skin to respond and other features such as the anaemia worsened, presumably because of the underlying lymphoma. We believe that linear IgA dermatosis was the first indicator of a B cell lymphoma in this coeliac disease patient.

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