

COMMENT

The results indicate that the perfume mixture in the standard patch test series is a useful fragrance screening agent. There were, however, some patch test reactions which could not be explained, or were false-positive (Table II). The combined patch test results for the 96 patients in whom positive test results could be related to fragrance allergy (Table II) indicate that a number of fragrance allergies in this group would have been overlooked had only one of the screening agents been used. For purposes of routine testing, it is therefore still necessary to employ several screening agents to detect fragrance allergy.

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Lymphoma in Dermatitis Herpetiformis: Report on Four Cases

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Abstract. Four patients suffering from protracted dermatitis herpetiformis (DH) developed lymphomas while undergoing gluten-free diet treatment. This had lasted between 6 months and 4 years. The first patient died of histiocytic lymphoma involving mesenterial lymph nodes, liver, spleen and blood marrow. The second patient died of histiocytic lymphoma disseminated in the ileum, colon, stomach and mesenterium. This patient had been operated on 14 years earlier for a solitary ulcerating lymphoma in

the ileum. The third patient had a localized histiocytic lymphoma in the colon. This was successfully removed by hemicolectomy. The fourth patient had a lymphocytic lymphoma of B-cell origin in the inguinal lymph nodes which was treated with radiotherapy. These 4 patients with lymphomas suggest that, like coeliac disease patients, DH patients also run an increased risk of developing lymphomas.

Key words: Dermatitis herpetiformis; Coeliac disease; Lymphoma

The increased risk of developing lymphomas and gastrointestinal carcinomas is well documented in coeliac disease (CD) but it is not known whether a gluten-free diet (GFD) reduces this risk (11, 18). Dermatitis herpetiformis (DH) is very closely related to CD; most patients have a gluten-sensitive enteropathy, the same genetic (HLA) pattern and moreover, a strict GFD controls the rash in patients with DH (5, 13, 15).

Recently some lymphomas have been reported in DH patients on a normal diet, showing that this malignancy can also occur in DH (1, 4, 6, 7, 8). In this report we describe 4 patients with DH in whom the lymphomas were found during GFD treatment and discuss the relationship between DH and lymphomas.

CASE REPORTS

Case 1. A 31-year-old man had had DH for 10 years. This was controlled with 100 mg of dapsone daily. He then got abdominal pain, loose stools and his weight dropped by 18 kg. SGPT (101 U/l), SGOT (58 U/l) and bilirubin (48 μ mol/l) were increased and therefore dapsone was stopped. An intense itch with many blisters developed and the diagnosis of DH was confirmed with routine histology and direct IF. Jejunal biopsy showed subtotal villous atrophy with no villi. GFD was started and after 2 months the rash was much better, although dapsone was still withdrawn.

After 6 months on a GFD he was again losing weight, had septic fever and elevated liver enzyme levels. The WBC was $1.3 \times 10^9/l$. Some atypical mononuclear cells were seen in peripheral and blood marrow smears (about 10% of all nucleated cells) and in aspiration biopsy specimens taken from the liver and spleen. A diagnosis of reticulum cell sarcoma, i.e. histiocytic diffuse type of malignant lymphoma (Rappaport) was made. The patient received two courses of cyclophosphamide, prednisone and vincristine with antibiotics. Blood marrow showed no response and he died soon after. At autopsy, malignant cells were found in the mesenterial lymph nodes, liver and spleen. The small-intestine mucosa was macroscopically normal but, due to autolysis, microscopic evaluation failed.

Case 2. A 50-year-old man had undergone an emergen-

Table 1. *Lymphoma in patients with dermatitis herpetiformis*

| Patients | Duration of DH (years) | Previous treatment | Jejunal morphology | Lymphoma | | Author |
|----------|------------------------|--------------------|--------------------|----------------------------|---------------------------|------------------------|
| | | | | Site | Type | |
| 1. m/44 | 18 | Dapsone | N | Jejunum | Malignant lymphoma | Gjone & Nordöy, 1970 |
| 2. m/58 | 10 | Dapsone | N | Cervical lymph nodes | Mb. Hodgkin | Månsson, 1971 |
| 3. f/56 | 40 | Dapsone | SVA | Mesenterium | Malignant lymphoma | Andersson et al., 1971 |
| 4. m/57 | 25 | Dapsone | Con-voluted | Jejunum | Reticulum cell sarcoma | Goodwin & Fry, 1973 |
| 5. m/52 | 10 | Dapsone | PVA | Jejunum | Reticulum cell sarcoma | Connon et al., 1975 |
| 6. m/59 | 7 | N.k. | SVA | Skin | Lymphocytic lymphoma | Fowler & Thomas, 1976 |
| 7. f/64 | 0.2 | None | SVA | Ileum | Reticulum cell sarcoma | Tönder et al., 1976 |
| 8. m/43 | 20 | Sulphapyridine | PVA | Jejunum | Reticulum cell sarcoma | Gebbers et al., 1977 |
| 9. m/60 | 19 | Dapsone + GFD | SVA | Jejunum | Reticulum cell sarcoma | Gould & Howell, 1977 |
| 10. m/51 | 12 | Dapsone | PVA | Duodenum, jejunum | Histiocytic lymphoma | Silk et al., 1977 |
| 11. m/60 | 20 | None | SVA | Stomach | Histiocytic lymphoma | Freeman et al., 1977 |
| 12. m/42 | 0.5 | Dapsone | SVA | Jejunum | Histiocytic lymphoma | Freeman et al., 1977 |
| 13. m/62 | 5 | None | N.k. | Jejunum, ileum | Undifferentiated lymphoma | Freeman et al., 1977 |
| 14. m/31 | 10 | Dapsone + GFD | SVA | Mesenterium, liver, spleen | Histiocytic lymphoma* | Present case |
| 15. m/50 | 3 | Dapsone + GFD | SVA | Ileum, colon, stomach | Histiocytic lymphoma* | Present case |
| 16. m/37 | 9 | Dapsone + GFD | PVA | Colon | Histiocytic lymphoma* | Present case |
| 17. f/42 | 7 | Dapsone + GFD | PVA | Inguinal lymph nodes | Lymphocytic lymphoma | Present case |

n.k. = not known; * = Rappaport classification; SVA = subtotal villous atrophy, PVA = partial villous atrophy, N = normal jejunal mucosa.

cy operation at the age of 36 because of ileal perforation caused by an orange-sized ulcerating tumour. This was removed and histological investigation revealed malignant cells in the tumour but not in the mesenterial lymph nodes. The diagnosis was reticulum cell sarcoma and postoperatively he received a course of abdominal X-ray irradiation. No signs of dissemination were found at the follow-up examinations over the next 10 years. He then contracted abdominal pain, diarrhoea and suffered a 10 kg weight loss. CD was diagnosed on the basis of pathological laboratory tests for malabsorption, small-intestine roentgen findings and subtotal villous atrophy (mean villous height (MVH) 80 μ m, 95 intra-epithelial lymphocytes (IEL)/100 epithelial cells). GFD was started and he responded well to GFD although he ate several pieces of bread at least once a week.

At the age of 47 a pruritic rash appeared. The histopathology was typical of DH and 100 mg of dapsone daily was started. Three years later he was still adhering partially to his GFD but managed on 50 mg dapsone daily. He then developed severe abdominal pain and melena. An

emergency laparotomy revealed several small tumours in the wall of the ileum, colon and stomach and enlarged lymph nodes in the whole mesenterium. The proximal ileum was resected. Ileal villi were atrophic and several small ulcers were seen. Malignant cells were found in the mucosa and draining lymph nodes. The histological diagnosis was histiocytic diffuse-type malignant lymphoma. One week after the operation the patient died; no autopsy was performed.

Case 3. A 37-year-old man had had DH for 9 years. The clinical picture was typical of DH and direct IF was positive. He responded well to 50 mg dapsone daily and used it for 3 years. A jejunal biopsy was then performed and partial villous atrophy (MVH 180 μ m, 52 IEL/100 cells) was found. GFD was started and 2 years later he managed without dapsone. After 4 years on a GFD he began to feel abdominal pain which worsened insidiously. He also had melena and a low haemoglobin level (101 g/l). Barium and angiographic studies suggested a tumour in the colon.

At operation a 15 cm large solitary tumour was found in the flexura hepatis and hemicolectomy was performed.

Microscopic examination showed only mucosal involvement and the histology was histiocytic type malignant lymphoma. The patient made an uneventful recovery and 2 years after the operation he adheres strictly to his GFD. is in good general health, and has no rash or signs of lymphoma.

Case 4. A 42-year-old woman contracted DH at the age of 35. Direct IF was positive and treatment with 25 mg dapsone daily was started. Three years later she developed gastrointestinal disturbance and jejunal biopsy showed partial villous atrophy (MVH 250 μ m, 68 IEL/100 cells). GFD was started and she continued with 25 mg dapsone daily. After 2 years on a GFD the rash was asymptomatic without dapsone, but a 3 cm large tumour was observed in her left groin. Histology showed an enlarged lymph node with no germinal centres. It was filled with a diffuse cellular mass which extended to the nearby subcutaneous tissue. A diagnosis of poorly differentiated, diffuse lymphocytic lymphoma was made.

Studies for the demonstration of intracellular immunoglobulins or muramidase were performed as earlier described (10). Muramidase was negative, but immunoperoxidase staining showed intracellular μ (IgM) and λ chains indicating B-lymphocyte origin. Lymphography revealed two other enlarged nodes and she received 4 400 rads of 60 cobalt radiotherapy. On a visit 6 months later she was in good general health, had no gastrointestinal or skin symptoms or signs of lymphoma and the jejunal mucosa was normal (MVH 410 μ m, 21 IEL/100 cells).

DISCUSSION

In 1970 Gjone & Nordöy (7) reported the first DH case associated with intestinal lymphoma. Since then several patients with lymphomas have been described (Table I). The patients have usually had DH for a long time. In the present cases DH also began several years before the lymphomas appeared, although one of the patients had two lymphomas, the first of which was found before DH began. The frequent occurrence of an occult CD in DH suggests that the development of lymphomas is related to the intestinal disease, i.e. to CD in patients with DH. In agreement with this, 3 of our patients had gastrointestinal symptoms and all 4 had jejunal villous atrophy compatible with CD during their disease.

The localization of lymphomas in DH also favours their relationship to the intestinal disease. Most lymphomas have occurred within the gastrointestinal tract, where they often affect mucosa and ulcerate (2, 7, 9, 16, 17). Such a pattern is also common in lymphomas found in CD (4, 12). In our first patient mesenteric lymph nodes were affected, but no malignancy was found in the mucosa. However, this cannot be ruled out, since mucosal micro-

scopy failed at autopsy. Our second patient had ileal lymphomas in two occasions and the third patient had a lymphoma in the colon. Lymphomas occurring outside the gastrointestinal tract are not unknown in DH (3, 14) and in agreement with this our fourth patient had no gastrointestinal involvement. She had a localized lymphocytic lymphoma affecting the inguinal lymph nodes. Special stainings showed that the malignant cells were positive for intracellular IgM and λ chains, indicating that they were of B-cell origin.

It is generally accepted that due to the risks of malabsorption, both children and adults with CD should adhere to GFD for the rest of their life. However, lymphomas have occurred in CD patients on a GFD and there are no statistical data to show that GFD provides protection from this malignancy (11). In agreement with this, all our DH patients and the patient reported by Gould & Howell (9) were on a GFD when lymphomas appeared. However, lymphomas often develop insidiously and it is also quite possible that they had begun before GFD was started in these 5 patients. In support of this view, our second patient had his first intestinal lymphoma 10 years before CD was diagnosed and GFD started.

According to British studies the risk of developing lymphoma in CD is statistically very high, from 25 to 100 times that expected (11, 18). If the development of lymphomas is attributed to the severity of intestinal disease, the risk may not be as high in DH, since the mucosal changes are usually milder in DH than in CD (13). However, to elucidate the exact risk of developing lymphomas in DH and the effect of GFD on it, further studies in large patient populations are required.

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Palmar Hyperlinearity in Atopic Dermatitis

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Abstract. Hyperlinearity of the palms is a common feature of atopic dermatitis, in this study present in 15 of 40 patients (or 37%). Previously it has been postulated to be a manifestation of a concomitant ichthyosis vulgaris, but according to our study it rather seems to be a trait of atopic dermatitis *per se*.

Key words: Palmar hyperlinearity; Atopic dermatitis; Ichthyosis vulgaris

Among the clinical signs of atopic dermatitis the presence of a characteristic hyperlinearity pattern of the palms and soles has attracted relatively little attention, although it is a rather common trait easily recognized at the clinical examination.

The few previous studies from Germany (1, 3) and quite recently from Japan (6) have concordantly reported a close relationship between this sign and a concomitant ichthyosis vulgaris affecting a remarkably high proportion of these materials.

The present study of a Danish material of patients suffering from atopic dermatitis has led to somewhat deviating conclusions.

MATERIALS AND METHODS

40 consecutive patients with definite atopic dermatitis attending the out-patient clinic, 14 males aged 2-27 years and 26 females aged 3-51 years, were included in the study. 20 members of the staff without any evidence of atopic dermatitis served as controls.

The palms were examined by careful inspection and the findings were substantiated by taking imprints on paper of both palms after blacking them with a small rubber cylinder. The persons were clinically examined for evidence of ichthyosis vulgaris.

According to the interpretation of the linearity pattern we have chosen to operate with only two categories: normal and palmar hyperlinearity. A more elaborate scoring system designed by Tillner (5), operating with four degrees of linearity based on quantitative differences in the number and extent of the creases, seemed too complicated for our purpose.