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MALIGNANT DISEASE IN DERMATITIS HERPETIFORMIS

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Abstract. In a group of nine patients with dermatitis herpetiformis examined for gastrointestinal abnormalities five developed malignant growths during an observation period of three years. The malignant deterioration could not be due solely to celiac disease. Dermatitis herpetiformis as such, or sulfone treatment, may perhaps involve increased risk of malignant disease.

In most cases of coexisting dermatitis herpetiformis and carcinoma on record both conditions have been recognized at roughly the same time (1, 20). Successful treatment of the carcinoma has sometimes been followed by regression of the patient's skin symptoms (1, 4). But there is no evidence of an increased risk for the patient with dermatitis herpetiformis to develop a malignant disease later on.

This paper concerns the appearance of carcinoma in 5 out of 9 patients with dermatitis herpetiformis during an observation period of 3 years. An investigation as to gastrointestinal function in these 9 patients has been published previously (2). All 9 patients were sulfone-dependent and in other respects too they belonged to Smith's smaller group with uniform symptoms, signs and course of illness (22). They had been selected for gastrointestinal study because of anemia or their need of unduly large doses of sulfone.

CASE REPORTS

For details concerning laboratory studies, see Table I. The results given in the table refer to the earlier investigation of the patients in 1968 (2). For the sake of lucidity the table includes only one disaccharidase (saccharase) and one dipeptidase (L-alanyl-L-proline-dipeptidase) of the jejunal mucosa.

Case I

A man, born in 1895, with a long history of recurrent duodenal and gastric ulcer was subjected to gastric resection (B I) in 1948. In 1950 (he was then 55) he developed dermatitis herpetiformis. From 1951 to 1955 he was successfully treated with sulfapyridine. But sulfone therapy, started in 1957, had a much better effect, especially on exacerbations. During remissions the patient could almost skip medication. From 1964 the disease was more continuously active and in some periods the patient took more than 100 mg diamonodiphenylsulfone per day. In 1968 the man was admitted to hospital because of anemia (Table I). He then had hemolysis, and the serum iron bordered the lower limit of the normal range, but the serum folate and B_{12} were normal and the sternal bone marrow showed nothing remarkable. The roentgen appearance of the residual stomach and of the small intestine was normal. The colon had no demonstrable stenosing process. There was no malabsorption, and peroral mucosal biopsy of the small intestine showed normal morphology and normal enzymes of the mucosa. Iron therapy had but little effect on the anemia. In April 1969 a tumour of the right testicle was noticed. It proved to be a metastasis from an adenocarcinoma of the cecum. The ileocecum was resected, but metastases were found in mesenteric lymph nodes.

Case II

A man, born in 1912, was operated upon in 1959 with gastric resection (B II) because of recurrent duodenal ulcer. One year after the operation dermatitis herpetiformis appeared. The skin disease responded well to diaminodiphenylsulfone, but the patient often required more than 100 mg per day. In 1968 the patient had moderate anemia and was admitted to hospital for investigation (Table I). Examination revealed hemolysis and a sternal marrow dominated by cells of the erythropoetic system. There was also moderate hypogammaglobulinema (0.46 g/100 ml). There were no signs of malabsorption and the jejunal mucosa appeared normal. In 1970 the right cervical lymph nodes were enlarged. Biopsy and cytology confirmed the diagnosis of Hodgkin's disease. The appearance of the lymphadenopathy was accompanied by such regression of the skin disease that the patient could almost manage without sulfone therapy.

Case III

A man, born in 1909, developed dermatitis herpetiformis in 1940. His brother suffers from celiac disease. The

Table I. *Clinical and laboratory findings in the patients in 1968*

Pat. no.	Sex	Age (y.)	DH-duration (y.)	Sulphone treatment (y.)	Haemoglobin (g per 100 ml)	Haptoglobin (mg per 100 ml)	Sternal marrow	Serum iron (μg per 100 ml)
1	♂	73	18	8	9.9	30	Normal	75
2	♂	56	8	7	11.6	17	Increased erythropoesis	200
3	♂	59	28	6	12.8	12	Normal	130
4	♂	65	20	9	7.6	143	Increased erythropoesis	25
5	♂	45	8	5	12.0	13	Normal	65
Normal values					13.2–16.6	25–180		75–175

[a] – = not analysed. [b] Units per gram protein. [c] Units per mg nitrogen.

patient smoked, on the average, 100 cigarettes a week. In 1946 he had a long spell of diarrhea. In 1957 tuberculous lesions apically in the right lung were detected. They were conceived as inactive and they remained unchanged during observation up to 1966.

In about 1942 the patient had been treated with arsenic because of his dermatitis herpetiformis. For long periods he received no treatment, but from 1962 he was successfully treated with diaminodiphenylsulfone, though he sometimes required more than 100 mg a day. In 1968 he was admitted to hospital for investigation. He then had a rather well compensated hemolysis. The jejunal mucosa was abnormal, but there was no malabsorption (Table I).

In 1969 his general condition deteriorated with anorexia and loss of weight. Chest X-ray revealed a right-sided parenchymal process basally in the upper lobe and bronchoscopy showed a poorly differentiated squamous cell carcinoma in the right main bronchus. The tumour was inoperable and was treated with radiation. The patient died some months later. During the last few months before death the skin lesions were much less troublesome and did not require such a large dose of sulfone.

Case IV

A man, born in 1903, developed dermatitis herpetiformis in 1949. At 4 years he had had poliomyelitis and since then he had had paresis of the left arm and right lower leg. Until 1956 he was treated with sulfapyridine because of his skin disease. From that year on, the sulfapyridine was successfully replaced by diaminodiphenylsulfone but with a dosage of 200 mg a day. From 1960 the patient had anemia refractory to iron therapy. He was therefore admitted to hospital in 1968. Examination there revealed hemolysis and iron deficiency. The intestinal mucosa appeared normal, but the patient had steatorrhea (Table I). Chest X-ray showed nothing remarkable. In 1970 the patient complained of increasing respiratory symptoms and cachexia. Shortly before the patient died roentgen examination revealed bronchial cancer. Autopsy showed a moderately differentiated adenocarcinoma originating from a bronchus in the upper lobe of the right lung.

Case V

A man, born in 1923, developed dermatitis herpetiformis in 1960. He was successfully treated from the very beginning with diaminodiphenylsulfone but required 150 mg a day to control the disease. In 1968 the patient was hospitalized because of anemia. Examination revealed hemolysis, steatorrhoea and abnormal intestinal mucosa (Table I). For some months the patient was on a gluten-free diet. The intestinal mucosa improved and the patient gained 5 kg in weight. After half a year the patient found it difficult to observe the diet and then he lost the 5 kg. In 1970 he complained of pain over the right ductus deferens. The proximal part of the prostate was found to contain pea-sized diffuse nodules and urethro-cystography showed that the mucosal relief in the pars prostatica urethrae was irregular. Fine-needle aspiration biopsy of the prostate produced cells of moderately to poorly differentiated cancer. The patient is now being treated with estrogen, and prostatectomy is contemplated.

DISCUSSION

The finding of malignant diseases in these 5 patients of an admittedly selected group of 9 is remarkable. More or less severe enteropathy was diagnosed in 7 of the 9, including 3 who afterwards developed cancer. The remaining 2 patients were subjected to gastric resection and both now have a malignant disease.

A relationship between dermatitis herpetiformis and the development of malignant disease has recently been discussed. Gjone & Nordöy reported a patient with dermatitis herpetiformis, steatorrhoea and probably reticulum cell sarcoma in the abdomen and one with dermatitis herpetiformis, gluten enteropathy and renal carcinoma (8). Horgan reported a patient with dermatitis herpetiformis and carcinoma of the lung (13).

TIBC (μg per 100 ml)	Serum folate (ng per ml)	Serum B_{12} (pg per ml)	Schilling test %	5 h urinary xylose (g)	Faecal-fat excret. (g/day)	Small intestinal mucosa		
						Appearance	Saccharase[b]	L-alanyl-L-proline-dipeptidase[c]
450	1.4	190	17	1.9	2.7	Villous	67	17
420	—[a]	330	13	1.9	1.8	Villous	51	8.2
340	3.3	155	16	1.9	3.3	Convoluted	—	—
475	2.3	200	13	1.1	6.5	Villous	41	5.0
410	1.7	290	24	2.2	10.3	Flat	15	1.2
260–400	2.8–3.5	150–900	> 10	> 1.3	< 5.0		33–148	8.0–16

Like the rest of the population, patients with dermatitis herpetiformis naturally have a risk of developing cancer. The question is whether the risk in such persons is greater or not. An answer to this question requires prospective studies.

In previous investigations of the prognosis of dermatitis herpetiformis no increased risk of cancer has been shown. But many of the patients were not followed up. Eyster & Kierland studied 381 patients 10–30 years after their visit to the Mayo Clinic (7). 105 patients could not be after-examined at all and in 46 the course was only partly known. Of 51 who died, 2 had died from arsenical epitheliomas. Otherwise nothing is known about the causes of death or their possible relation to the skin disease. Only 42 of Grant Peterkin's 105 patients answered a questionnaire (10). Two had died of other diseases, which are not reported, and 61 failed to reply. Björnberg & Hellgren examined only 53 of their 92 patients. Ten had succumbed and were not included in the study (3). Evans & Fraser followed up all their 43 patients, but for at most 9 years (6). Smith could not trace 53 (35%) of his 149 patients (22). As for the 96 patients reviewed, no information about cancer is reported. It is possible that for natural reasons malignant diseases might have developed in the very groups of patients who were not traced. The development of malignant diseases in dermatitis herpetiformis may therefore have previously passed unnoticed.

In idiopathic steatorrhoea or celiac disease there is an increased risk of lymphoma or cancer of the gastrointestinal canal (9, 11). In about two-thirds of all patients with dermatitis herpetiformis the small bowel has lesions of the same type as that seen in celiac disease (21). Gjone & Nordöy (8) claim that also the enteropathy in dermatitis herpetiformis might increase the risk of malignancy. Both of their patients had enteropathy. The observations made in our 5 patients do not strengthen the assumption that enteropathy is a decisive factor in the development of cancer in dermatitis herpetiformis. Only 3 of our patients had signs of enteropathy and none of them developed lymphoma or malignant gastrointestinal lesions. Opinions differ as to whether a malignant disease in or outside the gastrointestinal tract causes disturbances of the function of the small intestine (5, 16). Our 2 patients with Hodgkin's sarcoma and cancer of the colon, respectively, had no enteropathy, but both had been subjected to gastrectomy. It is possible that gastrectomy increases the risk of malignant disease (18).

The fact that the development of malignant diseases late in the course of dermatitis herpetiformis has hitherto passed unnoticed may be due to its being a new phenomenon. If so, one must consider whether modern methods of treatment entail risks. Arsenic is known to be cancerogenic (19), but only one of our patients had received such treatment. Gjone & Nordöy's two patients (8), like our five, had been treated with diaminodiphenylsulfone for several years. The metabolism of this drug is not properly understood. Animal experiments have shown that aromatic amines are oxidized *in vivo* by microsomal enzymes to hydroxylamino-compounds. These react with haemoglobin and oxygen with the formation of met-haemoglobin and nitroso-metabolites (14). After injection of aromatic amines into laboratory animals the corresponding nitroso-derivatives ap-

pear in the blood (15). Experiments *in vitro* indicate that it is likely that diaminodiphenylsulfone in man is metabolized in a similar way (12).

Several aromatic amino- and nitroso-compounds produce atypical epithelial proliferations and malignant growths (17). It is therefore quite conceivable that cancer may be induced by diaminodiphenylsulfone or some of its metabolites with greater affinity for DNA.

Development of malignant growths in 5 out of 9 patients within an observation period of three years calls for further investigation of the risk of complicating malignant disease in dermatitis herpetiformis.

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REFERENCES

1. Balabanov, K. & Andreev, V. C.: Dermatitis herpetiformis Duhring in a patient with carcinoma of the prostate. (With further references.) Dermatologica (Basel) *129:* 461, 1964.
2. Berg, N. O., Dahlqvist, A., Lindberg, T., Månsson, T., Nordén, Å. & Rorsman, H.: Gastrointestinal dysfunction in dermatitis herpetiformis. Acta Dermatovener (Stockholm) *50:* 42, 1970.
3. Björnberg, A. & Hellgren, L.: Dermatitis herpetiformis. A laboratory and clinical investigation based on a numerical study of 53 patients and matched controls. Dermatologica (Basel) *125:* 205, 1962.
4. Bogrow, S. L.: Zur Kasuistik der Dermatitis herpetiformis Duhringi. Arch Derm Syph (Berlin) *98:* 327, 1909.
5. Dymock, I. W., MacKay, N., Miller, V., Thomson, T. J., Gray, B., Kennedy, E. H. & Adams, J. F.: Small intestinal function in neoplastic disease. Brit J Cancer *21:* 505, 1967.
6. Evans, C. D. & Fraser, I. D.: The natural history of dermatitis herpetiformis. Trans St John's Hosp Derm Soc *49:* 108, 1963.
7. Eyster, W. H. & Kierland, R. R.: Prognosis of dermatitis herpetiformis, treated and untreated. Arch Derm (Chicago) *64:* 1, 1951.
8. Gjone, E. & Nordöy, A.: Dermatitis herpetiformis, steatorrhea and malignancy. Brit Med J *1:* 610, 1970.
9. Gough, K. R., Read, A. E. & Naish, J. M.: Intestinal reticulosis as a complication of idiopathic steatorrhea. Gut *3:* 232, 1962.
10. Grant Peterkin, G. A.: Dermatitis herpetiformis: A follow-up and survey of treatment. Brit J Derm *63:* 1, 1951.
11. Harris, O. D., Cooke, W. T., Thompson, H. & Waterhouse, J. A. M.: Malignancy in adult coeliac disease and idiopathic steatorrhea. Amer J Med *42:* 899, 1967.
12. Hjelm, M. & de Verdier, C. H.: Biochemical effects of aromatic amines. — I. Methaemoglobinaemia, haemolysis and Heinz-body formation induced by 4,4'-diaminodiphenylsulphone. Biochem Pharmacol *14:* 1119, 1965.
13. Horgan, J. H.: Malignancy and dermatitis. Brit Med J *4:* 55, 1970.
14. Kampffmeyer, H. & Kiese, M.: Einige Eigenschaften der Anilin-hydroxylierenden Enzyme in Mikrosomen. Naunyn-Schmiedeberg's Arch exp Path Pharmak *244:* 375, 1963.
15. Kiese, M.: The effect of certain substituents upon the N-oxidation of aniline in vivo. Naunyn-Schmiedeberg's Arch exp Path Pharmak *244:* 387, 1963.
16. Klipstein, F. A. & Smarth, G.: Intestinal structure and function in neoplastic disease. Amer J Dig Dis *14:* 887, 1969.
17. Mayer, R. L.: Group-sensitization to compounds of quinone structure and its biochemical basis; role of these substances in cancer. Progr Allergy *4:* 79, 1954.
18. Mörl, H.: Spättodesursachen bei Magenresezierten nach Billroth II. Med Klin *62:* 1904, 1967.
19. Neubauer, O.: Arsenical cancer; a review. Brit J Cancer *1:* 192, 1947.
20. Schultze-Frentzel, U.: Die Dermatitis herpetiformis (Duhring) als morphologisches Syndrom. Derm. Wschr *132:* 1105, 1955.
21. Shuster, S., Watson, A. J. & Marks, J.: Coeliac syndrome in dermatitis herpetiformis. Lancet *1:* 1101, 1969.
22. Smith, E. L.: The diagnosis of dermatitis herpetiformis. Trans St John's Hosp Derm Soc *52:* 176, 1966.

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