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VITILIGO AND NEOPLASMS

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Abstract. Eleven patients with vitiligo and a malignant disease are reported. In eight of the cases vitiligo manifested itself after the age of 40. Five patients had carcinomas of the gastrointestinal tract, two had skin tumours, two had intracranial tumours, and one patient had mammary and one had uterine carcinoma. A thorough examination seems to be warranted in patients with vitiligo appearing in old age.

A variety of cutaneous manifestations are known to precede or accompany malignancies (19). Some of these signs are of common origin with the malignant process while others may reflect immunological alterations induced by the malignancy, e.g. cases of bullous pemphigoid (7, 20), dermatomyositis (2), generalized herpes zoster (22).

Hyperpigmentation of the skin of the Addisonian type has been found in association with malignant tumours of the adrenal glands (8) while diffuse or irregular hyperpigmentation has been found in connection with other internal malignancies (8). Depigmentation, on the other hand, has not been included in the list of skin markers of malignancy (4, 8, 10, 19, 21).

We began to suspect a possible connection between vitiligo and neoplasms in 1969 when we saw a patient with a treated gastric carcinoma, detected a few years after she had developed vitiligo. In addition to that case, we have examined 10 other patients with neoplastic disease and vitiligo. Four of the patients (cases 1, 2, 5, and 7) were hospitalized at a geriatric hospital while the remaining 7 patients had attended a dermatologic clinic during the period 1969–1971. These patients will be reported briefly.

CASE REPORTS

When the patients attended either the geriatric or dermatologic clinic, the diagnosis of vitiligo was made by a dermatologist (K. B., U. K., or A. L.). The type of neoplasm was in all cases histologically analysed at the Department of Pathology, University Central Hospital, or at the Department of Pathology, Kivelä Municipal Hospital, Helsinki.

Case 1. An 80-year-old woman who had started to develop vitiligo at the age of 72. Six years later she had epigastric pains with vomiting. She began to lose weight. A gastric carcinoma was diagnosed and a resection (Billroth I) performed. Two years later, with her vitiligo still increasing, a colon carcinoma was diagnosed. Three months later she died of metastases.

Case 2. A 81-year-old woman began to have diffuse abdominal pains one-and-a-half years previously. Six months later she rapidly lost pigmentation from large areas of her face and legs. Within 1 year of the onset of abdominal symptoms, a caecum carcinoma was diagnosed and a hemicolectomia performed. Thereafter, her vitiligo has remained stationary.

Case 3. A 60-year-old female patient noticed the first spots of depigmentation on her wrists and genitoinguinal region 3 years previously. Two years later she was admitted to hospital because of severe anaemia and melaena. A colon carcinoma was diagnosed and removed. Diabetes mellitus was also diagnosed. During the follow-up period of 1 year she has presented no signs of metastases, and her vitiligo has undergone partial repigmentation.

Case 4. This male patient, 73 years old, had alopecia areata in 1947 with a recurrence 4 years later. In 1967 he became aware of depigmented areas on his scrotal skin; these areas extended to penile skin and genitofemoral folds. Three months later, a colon carcinoma was diagnosed and a colectomy made. Since the operation his vitiligo has not changed, but in 1968 diabetes was diagnosed.

Case 5. A 71-year-old woman had for the first time noticed her vitiligo when she was 10 years old. Depigmented areas extended for a few years, but had thereafter remained stationary. In 1954 she had acute cholecystitis and soon thereafter a few attacks of epigastric pain and

Table I. *Clinical data of 11 patients with vitiligo and malignant neoplasms*

Case	Sex	Age of patient	Age at onset of vitiligo	Age when neoplasm was confirmed	Type of vitiligo[a]	Site of neoplasm	Histologic type	Other disease
1	♀	80	72	78	Widespread	Stomach, colon	Adenocarcinoma	—
2	♀	81	80	80	Localized	Caecum	Adenocarcinoma	—
3	♀	60	57	59	Localized	Colon	Adenocarcinoma	Diabetes mellitus
4	♂	73	70	70	Localized	Colon	Adenocarcinoma	Diabetes mellitus
5	♀	71	10	71	Widespread	Gall bladder	Adenocarcinoma	—
6	♀	54	54	54	Localized	Breast	Adenocarcinoma	—
7	♀	62	58	61	Localized	Uterus	Squamous cell carcinoma	—
8	♂	51	49	51	Widespread	Skin	Squamous cell carcinoma	Thyroid disease
9	♂	68	66	68	Widespread	Skin	Basal cell carcinoma	—
10	♂	45	38	44	Widespread	Brain	Oligodendroglioma	—
11	♂	25	16	18	Widespread	Brain	Glioblastoma multiforme	—

[a] According to Lerner (16).

vomiting. In 1970 the pains and vomiting recurred and became regular, she began to lose weight rapidly and her vitiligo began to re-extend. Laparotomy revealed tumour infiltration in the gall bladder with direct extension to the liver and metastases in the regional lymph nodes. Histopathologically, the tumour was a gall-bladder carcinoma. She died 3 weeks after the operation.

Case 6. This 54-year-old woman observed vitiligo on her eye-lids and left cheek early in 1970. Three months later she was referred to the ward because of pyodermia. In a routine examination a tumour was detected in her right breast; a ductal carcinoma was verified from a biopsy. The surgery revealed no metastases. No changes have been registered in her vitiligo for 6 months.

Case 7. This woman developed vitiligo on her legs and arms in 1965 at the age of 58. Three years later a diagnosis of uterine carcinoma was made. She died of metastases in 1969. Her vitiligo had remained localized.

Case 8. This 51-year-old male patient became aware of his vitiligo in 1968. One year later a small crusted ulcer appeared on his nose. The ulcer was removed; a squamous cell carcinoma was diagnosed. Two months later he developed a thyreotoxicosis, but had no thyreoglobulin antibodies in his serum. His vitiligo has extended rapidly during the past 2 years, but no signs of tumour relapse or metastases have appeared.

Case 9. This 68-year-old man developed vitiligo in 1968. A few months later he became aware of a small crusted area on his back. During the next 2 years both vitiligo and the crusted area increased in size. He attended the dermatologic clinic. His vitiligo was widespread; the erythematous, partially ulcerated area of 5 cm in diameter was diagnosed as a basal cell carcinoma.

Case 10. In 1956 this male patient had a gastric ulcer. Seven years later, at the age of 38, he noticed for the first time vitiligous spots. Two years later he began to have epileptic convulsions. Four years later, in 1969, a brain tumour was found in the right frontal lobe. From the resection of the lobe, an oligodendroglioma with malignant features was found. By this time his vitiligo had become widespread, but showed no further extension after the operation.

Case 11. This 25-year-old male patient has had vitiligo since the age of 16. One year later he began to suffer from headaches. Gradually his headaches became more severe with attacks of dizziness and vomiting. At the age of 18, in 1963, he attended a neurologic clinic. An examination revealed a tumour at the bottom of the fourth ventricle. This solitary tumour was removed and identified as a glioblastoma. His vitiligo continued to extend for 2 years after the operation; thereafter it has remained unchanged. During the intervening 7 years since the operation, no signs of a tumour relapse have appeared.

Clinical data of the 11 patients are summarized in Table I. In 3 of the cases (2, 4, 6) there was a close temporal relationship between the appearance of vitiligo and the diagnosis of malignancy; in 5 cases there was a relatively close temporal connection, with both diseases having been confirmed within 3 years; in the remaining 3 cases vitiligo had occurred several years earlier, but even in one of these cases (case 5) there was a rapid extension of vitiligo at the time of tumour identification.

Fasting blood sugar, protein-bound iodine, and serum cholesterol were determined in all cases. In cases 3 and 4, diabetes mellitus had been detected, as also thyreotoxicosis in case 8, before the pres-

ent study. All the other patients had normal values. The Schilling test had been performed in all cases except 1, 2, 5, and 7; the result was within normal limits in all cases.

In order to gain some insight into the relative frequency of vitiligo and malignant disease in a Finnish geriatric hospital, a total of 650 non-selected geriatric patients of the Koskela Hospital were examined. Vitiligo was found in 2% (12 cases) and a malignant disease in 7% (46 cases). On the other hand, 4 of the 12 patients with vitiligo had a malignant disease (33%).

DISCUSSION

Recent evidence seems to indicate that vitiligo might belong to the auto-immune class of diseases. A high proportion of vitiligo patients have serum antibodies against gastric parietal cells and against thyroglobulin (6, 9, 12). In addition, patients with vitiligo have been found to have serum antibodies against melanin (15).

The present report draws attention to the coexistence of vitiligo and neoplasms. Various neoplasms, especially of the intestine, are known to be frequently connected with auto-immune alterations of the skin, e.g. bullous pemphigoid and dermatomyositis. One could therefore speculate about an eventual connection between neoplasms and vitiligo on an auto-immune basis. Some indirect evidence supports this possibility: vitiligo may develop during the course of a malignant melanoma (3, 13) which, on the other hand, may stimulate production of antimelanocyte antibodies (17).

Although vitiligo might have occurred in our cases merely by chance, it is interesting that in 8 out of our 11 cases vitiligo had become manifest after the age of 40, and only in 2 before the age of 20. In general, the onset of vitiligo in old age is relatively rare; according to Lerner (16), vitiligo is manifested after the age of 40 in only 5% of cases. However, since malignant disease is common in old age, no definite conclusions can yet be drawn from our results. Because old patients with vitiligo in a geriatric hospital had a neoplastic disease five times more often than geriatric patients without vitiligo, it is suggested that this is not merely an association by chance. In addition, in 3 patients there was a very close temporal relationship between the appearance of vitiligo and malignant tumour.

The 2 patients with brain tumours and vitiligo are also of special interest. Recently Nellhaus (18) reported a patient who developed vitiligo in connection with a subacute virus encephalitis. The author suggested that both the vitiligo and the encephalitic processes may be due to a virus interfering with an enzyme system, common to both melanocytes and neurons. Our two cases suggest that loss of pigmentation might be associated with intracranial tumours without evidence of a virus infection. Koplon & Shapiro (14) described a patient with a peripheral nerve tumour and loss of pigmentation, but were unable to offer any suggestion as to the pathogenesis of the depigmentation process in their patient.

The only report we found in the literature describing the association of vitiligo and an internal malignancy was a case report of Wright et al. (23). The authors described a patient with vitiligo and gastric carcinoma. The link between the two diseases might in this case have been a verified pernicious anaemia which frequently occurs separately in connection with both these diseases. Their patient also had an auto-immune thyroid disease known to be associated with vitiligo.

Vitiligo starting later in life is known to be associated with pernicious anaemia, thyroid disease, and diabetes mellitus (1, 5, 6, 9, 11, 12). In addition, a thorough search after a malignancy seems to be warranted in patients with vitiligo appearing in old age.

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