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REVIEW ARTICLES

Cutaneous Paraneoplastic Syndromes

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A review of a variety of cutaneous paraneoplastic conditions is presented. Although the conditions discussed appear in only 7–15% of cancer patients, they are considered indicators of possible underlying malignancy. ***Key word: Malignancy.***

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The relationship between paraneoplastic syndromes and cancer remains obscure and controversial, although more than 100 years have lapsed since Trosseau first noted an association between gastric carcinoma and migratory thrombophlebitis (1). The meager progress made in understanding paraneoplastic syndromes stems in great part from the difficulty in classifying cutaneous phenomena as paraneoplastic.

Paraneoplastic conditions are cancer-associated phenomena which, although not a direct part of the malignancy or metastases, appear associated with cancer in a frequency that makes their presence significant. The delineation of a syndrome as paraneoplastic is fairly simple in the case of a rare dermatosis, whose rarity and frequent association with cancer make the connection apparent. These syndromes can be quite specific, e.g. necrolytic migratory erythema for a glucagon-producing tumor of the pancreas, while others are associated with a wide range of cancer types. More common skin manifestations pose significant problems in classification especially because many of them also appear without any underlying malignancy (2). Some paraneoplastic conditions antedate the appearance of the internal malignancy; others run a course parallel to or independent of the neoplasm.

Several mechanisms have been proposed for paraneoplastic syndromes, including the production of biologically active hormones (3, 4) or unidentified "humors" (3). The endocrine consequences of neoplasia involve the secretion of polypeptide or other hormones or humoral mediators that act on distant target organs, as in Cushing syndrome or the inappropriate ADH secretion in small cell carcinoma of the lung.

The capacity of cancer cells to produce and respond to their own growth factors has been extensively studied and has led to a connection between oncogenes and growth factor research (5). The activation of oncogenes or the loss of oncogene inhibitory proteins may lead to inappropriate production and expression of various cytokines such as growth factors. Recent research suggests that the interaction of an αTGF-like species may be at least partially involved in the proliferation of certain human malignant tumors such as breast cancer (3).

Ellis and co-workers (6), who reported a patient with cutaneous melanoma, acanthosis nigricans, sign of Leser-Trélat and skin tags, speculated that growth factors may play an important part in the etiology of many cutaneous paraneoplastic syndromes that are proliferative. Their findings suggest that the melanoma in their patient participated in the production of EGF or αTGF. EGF receptors were found throughout the epidermis before excision of the melanoma.

EGF binding was also found throughout the seborrheic keratoses and skin tags. This finding contrasts with the EGF binding limited to basal keratinocytes observed in slowly proliferating lesions and in normal skin (7). The αTGF level in the patient's urine declined markedly after surgery together with clinical improvement.

Tumor-induced antigen-antibody interactions have also been implicated in paraneoplastic syndromes. Recent data on bacterial superantigens, a family of related proteins that elicit potent T-cell proliferative responses, are also relevant (8). Superantigens combine with the major histocompatibility complex (MHC) class II molecules to form ligands that stimulate T cells via the V beta element of the T cell receptor (9). Superantigens have been identified encoded in the mouse genome. They are also produced by bacteria, e.g. staphylococcal enterotoxins (10). Some tumors express bacterial superantigens that may directly bind to the MHC receptors (11). There may be a connection between some paraneoplastic syndromes and superantigens through T cell proliferative responses.

Tumor-induced depletion of specific substance(s) has also been suggested to lead to paraneoplastic conditions such as the pellagra-like dermatosis in patients with a carcinoid tumor, and necrolytic migratory erythema in patients with pancreatic islet cell carcinoma (12). Least likely, but possible, is an aberrant host response to various types of cancer (2).

We review cutaneous paraneoplastic conditions that appear in only 7–15% of cancer patients (3, 12) but are considered indicators of a possible underlying malignancy. Despite their infrequency they are occasionally the earliest marker for an underlying malignancy, sometimes even before the cancer is found.

ERYTHEMA GYRATUM REPENS (EGR)

EGR is an unusual, rapidly changing and progressing scaling erythema in a "wood grain" pattern. It is strongly, almost invariably, associated with internal malignancy. The disease was first described by Gammel in 1952 in a patient with breast carcinoma (13). In most reported cases the eruption preceded the detection of malignancy by 1–21 months, and in several cases it followed or appeared concurrently (14). There is a

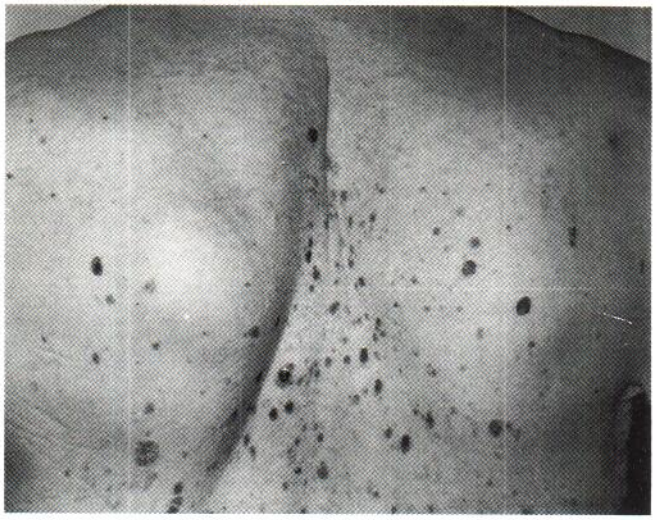


Fig. 1. The sign of Leser-Trélat in a 65-year-old man with carcinoma of the pancreas.

good correlation with treatment, and reappearance may indicate recurrence of malignancy (15). It has been associated with a variety of neoplasms, especially lung (15, 16), uterus (15), breast (13, 17) and upper gastrointestinal tract (18), and to a lesser extent bladder (19), prostate (19), cervix (20) and multiple myeloma (21).

THE SIGN OF LESER-TRÉLAT (Fig. 1)

Although many reported cases occurred in elderly patients in whom the association could have been coincidental (22), the number of reports of the simultaneous occurrence of seborrheic keratoses and malignancy, and regression of the cutaneous lesions after the cancer is treated, point to a possible direct relationship (22–24).

The two conditions usually appear more or less concurrently, but the seborrheic keratoses may appear before, during or after the malignancy has been detected.

Adenocarcinoma, primarily of the stomach, is the most common neoplasm associated with the Leser-Trélat sign (in 60% of the cases according to Holdiness (25)). The gastrointestinal tract is the most common site of the malignancy, followed by lymphoma and breast cancer, and squamous cell carcinoma of the lung. Other reports include prostate, ovary, uterus, hepatoma of the liver and pancreas, as well as mycosis fungoides, Sézary syndrome and leukemias.

HYPERTRICHOSIS LANUGINOSA ACQUISITA

Hypertrichosis lanuginosa acquisita, or malignant down, is the sudden profuse growth of soft, non-medullary, non-pigmented, downy hair in the adult. This rare paraneoplastic syndrome presents with varying intensity and has a documented association with a number of malignancies, most frequently carcinoma of the lung (26–28) and colon (29, 30), and less commonly breast (31), uterus (32, 33), ovary (34), bladder (35), gallbladder (36), pancreas (37), liver (38) and lymphoma (32).

According to the review of Jemec et al. (39), the cancer was widespread at the time of the appearance of the down in the majority of cases, although malignancy can be preceded by hypertrichosis lanuginosa acquisita by months (26, 27), or even several years (31). Most patients are women, and the reported survival time varies greatly. The malignant down was reported associated with a number of other manifestations with varying frequency; the most common are glossodynia, dry, scaly and hyperkeratotic skin and changes in pigmentation. Other paraneoplastic signs observed inconsistently with hypertrichosis lanuginosa acquisita include acanthosis nigricans, palmar and plantar hyperkeratosis and the sign of Leser-Trélat.

SUBCUTANEOUS FAT NECROSIS

These violaceous nodules are associated with acinar cell carcinoma of the pancreas (40) and are frequently accompanied by polyarthralgia, fever and eosinophilia (40, 41). The nodules may be the presenting sign. Identical lesions can be seen with pancreatitis (42). Increased serum levels of lipase, amylase or trypsin seem to play an important role in the pathogenesis.

SWEET'S SYNDROME

Acute febrile neutrophilic dermatosis, first described by Sweet in 1964, consists of fever, neutrophilia, and the abrupt appearance of erythematous, painful, raised cutaneous plaques, most commonly on the upper limbs, face and neck. A dense dermal infiltration of neutrophils is the dominant histological feature. The syndrome is associated in 10–20% of the cases with an underlying malignancy, most frequently acute myelogenous leukemia. There are also reports of other myeloproliferative disorders, lymphoproliferative disorders, myelodysplastic syndrome and carcinomas (43–46). The diagnosis of Sweet's syndrome is often the presenting sign of a new or recurrent tumor, but the dermatosis may precede detection of malignancy by a few years (47) or appear later. The etiology is unknown but is commonly suggested to be a hypersensitivity.

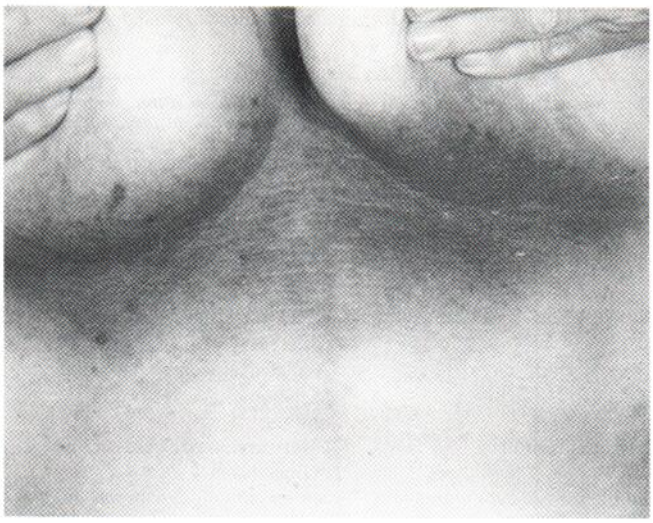
In a retrospective study (48), 6 of 18 cases of Sweet's syndrome appeared in patients who either had or later developed a lymphoproliferative or myeloproliferative disorder. An older age at onset and male sex were more frequently associated with an underlying malignancy (43, 48).

MELANOSIS

This grey-brown pigmentation of the skin, caused by abnormal deposition of melanin in the tissues, has been well documented (49–54) since Legg first described the association of pigmentation of the face and hands with melanoma in 1884. Melanosis may appear before (49, 50) or after (51, 52) detection of the primary melanoma and is often accentuated in light-exposed areas of the upper part of the body (46). Melasma-like hyperpigmentation observed by Andreev & Petkov (55) in 5 patients with brain tumors resolved in 3 after surgery.

The pathogenesis is controversial. Histopathologic findings consist mainly of melanin granules in perivascular or interstitial melanophages. Free granules of melanin may be seen in the dermis (53).

Fig. 2.
A. Acanthosis nigricans in a 63-year-old woman with carcinoma of the stomach.
B. Acanthosis nigricans with a sign of Leser-Trélat in a 61-year-old woman with carcinoma of the breast.
C. Acanthosis nigricans of the axilla with hyperkeratosis, acanthosis, papillomatosis and hyperpigmentation.



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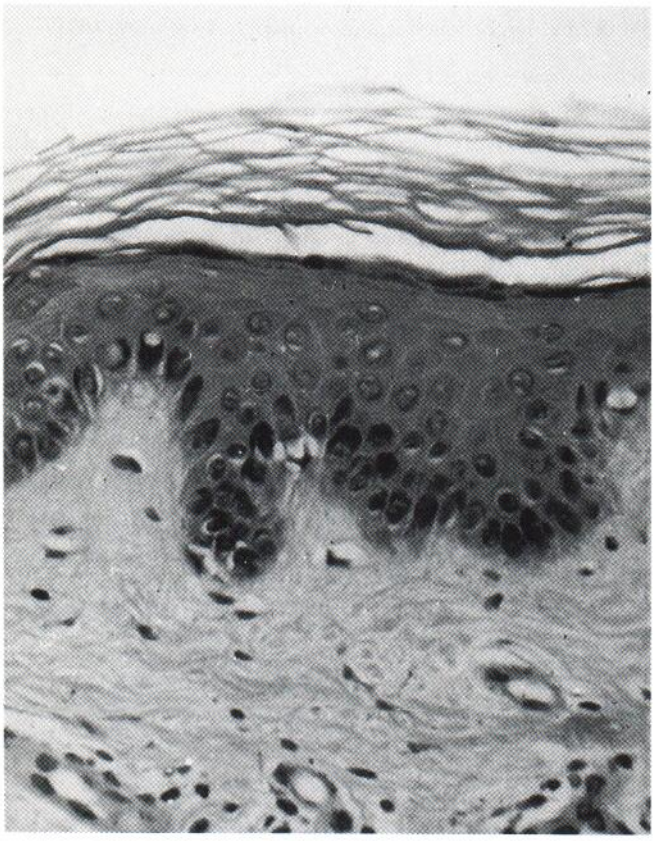

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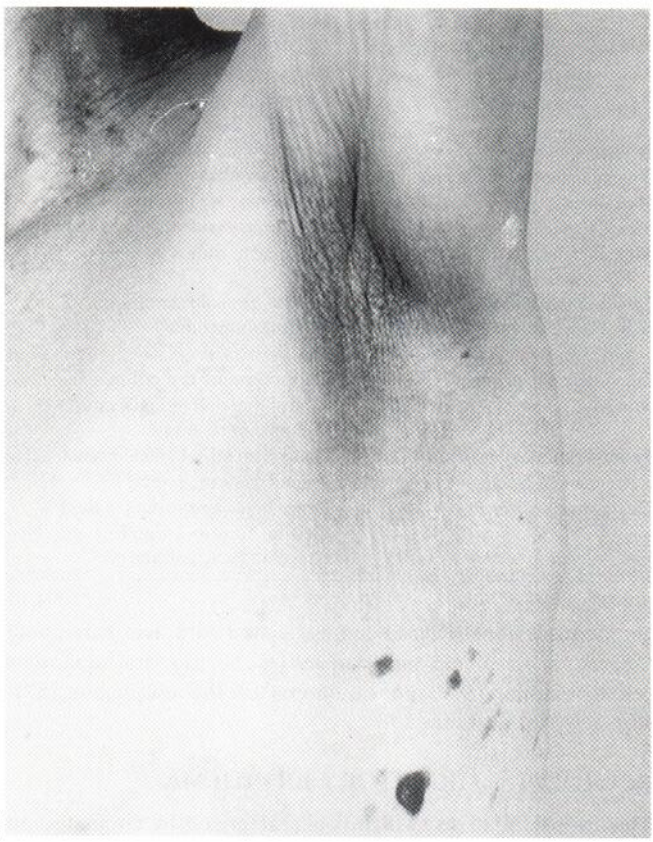

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Melanosis can also be caused by ACTH-producing tumors (54, 56) or adrenal insufficiency caused by neoplastic infiltration of the adrenal gland. Another cause of diffuse grey-brown pigmentation of the skin is hemochromatosis, an iron storage disorder; hepato-cellular carcinoma can develop in untreated patients.

PITYRIASIS ROTUNDA

Pityriasis rotunda, a unique geometric eruption, was first described in Japan in 1906 under the name pityriasis circinata. It is characterized by circular brown scaly patches, sharply demarcated from the normal skin, with no associated inflammation. The lesions appear on the trunk and extremities, are single or multiple, vary from 1–28 cm in diameter and are usually asymptomatic.

The disorder has been described in Japanese, South African blacks, and West Indian blacks and is often associated with chronic and debilitating illness or malignancy. The pathogenesis is obscure. The presence of hyperkeratosis and atrophy of the granular layer has led authors to view this disease as a variant of acquired ichthyosis (57, 58).

Some investigators like Leibowitz et al. (57) consider pityriasis rotunda a cutaneous marker of cancer and report that treatment of the neoplasia may result in resolution of the

Table I. *Cutaneous syndromes and commonly associated neoplasms*

Paraneoplastic syndrome	Commonly associated neoplasms
Erythema gyratum repens	Lungs, uterus, breast, upper gastrointestinal (GI) tract
Sign of Leser-Trélat	Adenocarcinoma of the GI tract, usually the stomach
Hypertrichosis lanuginosa acquisita	Carcinoma of lung and colon
Subcutaneous fat necrosis	Acinar cell carcinoma of the pancreas
Sweet's syndrome	Acute myelogenous leukemia
Melanosis	Melanoma, ACTH-producing tumors
Pityriasis rotunda	Liver carcinoma, hematologic malignancies
Acrokeratosis paraneoplastica (Bazex's syndrome)	Squamous cell carcinoma of upper aerodigestive tract
Acanthosis nigricans	Adenocarcinoma of GI tract, usually the stomach
Keratosis palmaris et plantaris	Gastrointestinal tract
Keratosis palmaris	Bladder, lung
Acquired ichthyosis	Lymphoproliferative neoplasms, primarily Hodgkin's disease
Erythroderma	Lymphoma, leukemia
Necrolytic migratory erythema	Glucagonoma
Vasculitis	Leukemia, lymphoma
Flushing	Carcinoid syndrome, leukemia
Migratory thrombophlebitis (Trousseau's syndrome)	Pancreatic tumor
Cowden's disease	Breast, thyroid carcinoma
Nevoid basal cell carcinoma syndrome	Medulloblastoma
Gardner's syndrome	Carcinoma of the colon
Mucosal neuroma syndrome	Medullary thyroid carcinoma, pheochromocytoma
Peutz-Jeghers syndrome	Gastrointestinal tract, breast, genital system, pancreas
Dermatomyositis	Bronchial carcinoma (males) Genital tumors (females)
Pachydermoperiostosis (PDP)	Bronchogenic carcinoma

cutaneous lesions. It has been associated with liver carcinoma (58, 59), hematologic malignancies (57, 60, 61), oral squamous cell carcinoma (57) and carcinoma of the esophagus (57), stomach (58) and lung (58).

NECROLYTIC MIGRATORY ERYTHEMA

This rare dermatosis, which is characterized by circinate and gyrate areas of blistering and erosive erythema on the limbs, abdomen and face, is a hallmark of glucagonoma. The eruption clears after resection of the tumor, sometimes within days. Clearance of the erythema after infusion of amino acids might indicate an association with low serum amino acid levels (62–66).

ERYTHEMA ANNULARE CENTRIFUGUM

Erythema annulare centrifugum has been occasionally associated with malignancy (67). However, a review of 24 cases with special reference to its association with underlying disease by Mahood (68) did not reveal any evidence of malignancy. He concluded that the association was unproven.

KERATINIZATION DISORDERS

Acrokeratosis paraneoplastica (Bazex's syndrome)

This rare symmetrical dermatosis, first described by Bazex et al. in 1965, is characterized by psoriasiform acral hyperkeratosis. It is connected with virtual certainty to cancer, most commonly an occult squamous cell carcinoma of the upper aero-digestive tract. Cervical lymph nodes are often involved (69–72), usually by a distant, poorly differentiated squamous cell carcinoma (69). The carcinomas are usually squamous in type, but rare cases of adenocarcinoma and undifferentiated carcinoma and carcinoid tumor have been reported (73). The dermatosis can precede the detection of the neoplasm by several months to a few years (69) and may parallel the malignancy with respect to growth and remission (71).

The condition should not be confused with another syndrome described by the same author that consists of genetically induced basal cell epitheliomas, follicular atrophoderma, hypotrichosis, and disorders of sweating (69).

Acanthosis nigricans (Fig. 2)

Acanthosis nigricans is a symmetrical, grey-brown, hyperpigmented, velvety plaque often affecting the axillae, neck, flexures and anogenital region. It is classified into four main groups: malignant, inherited, endocrine and idiopathic. The endocrine type is found in a variety of conditions including obesity and insulin-resistant diabetes mellitus. Most patients

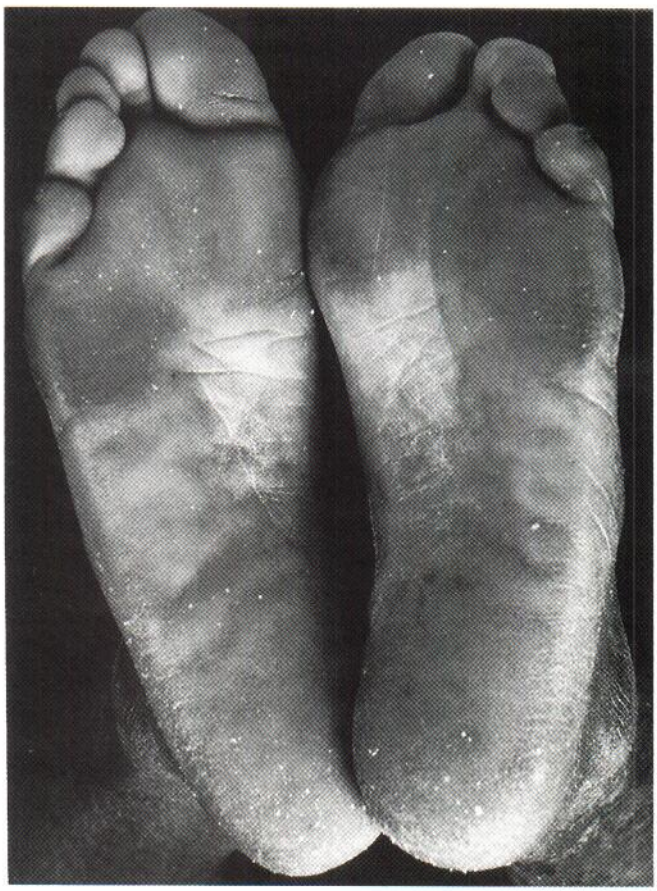

Fig. 3. Plantar hyperkeratosis in a 45-year-old man with palmoplantar keratoderma and squamous cell carcinoma of the larynx.

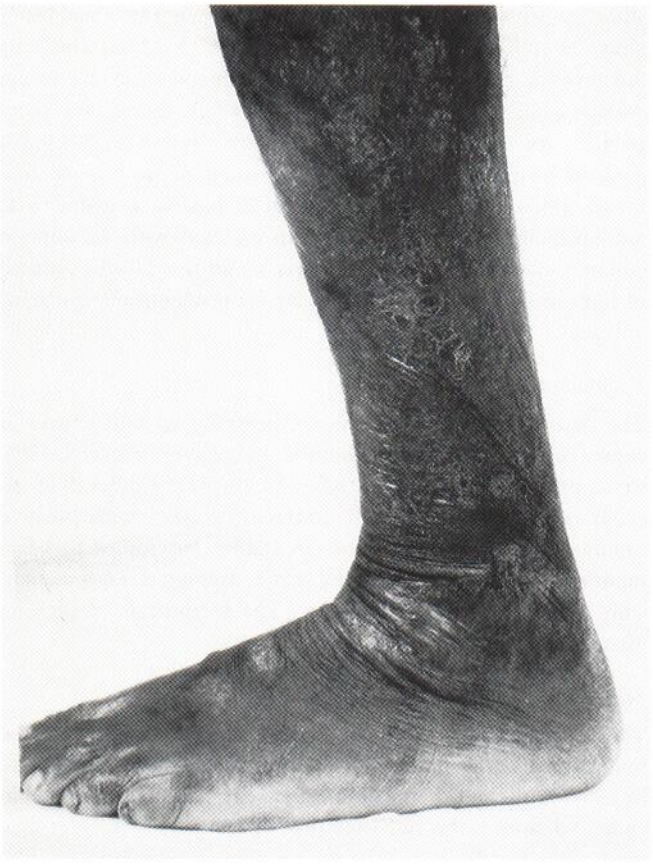

Fig. 4. Acquired ichthyosis in a 50-year-old man with carcinoma of the lung. Histology of the skin shows hyperkeratosis, acanthosis and vacuolization of the granular layer.

with the malignant form have adenocarcinoma (74, 75), especially of the gastrointestinal tract, predominantly gastric (76), and of the lung and breast. Among other reported cases are uterus (77), ovary (77), prostate (77) and hematologic malignancies (78) and sarcomas (79, 80).

The malignant form is indistinguishable from the benign forms, but it is more often of sudden onset, rapidly progressive and associated with pruritus. According to Dobson (81), it is usually associated with involvement of the face and eyes. It precedes the development of malignancy in 17% of the cases (sometimes by several years), occurs simultaneously in 61%, and follows the appearance of the tumor in 22% of the cases (75). Men and women are equally affected (74–76). There is an increased incidence after 40 years of age (74, 76, 82, 83), although a few cases have been observed in children. If a non-obese, previously healthy adult develops acanthosis nigricans, an underlying malignancy is highly likely (77–79, 83, 84).

Keratosis palmaris et plantaris

Keratosis palmaris et plantaris (Fig. 3), or tylosis, was reported by Howel-Evans et al. in 1958 (85) to be associated almost certainly with the development of esophageal carcinoma. Since that time there have been other reports of the association of carcinomas of the skin and visceral organs with acquired and hereditary tylosis. This autosomal inherited disorder consists of discrete hyperkeratotic papules on the palms and soles. Bennion et al. (86) reported a large family in which the dermatosis was associated with carcinoma of the gastrointestinal tract, mainly the colon. There have been reports of internal malignancy associated with non-familial palmoplantar keratoderma of late onset. The malignancies reported were both of the esophagus (87, 88) and other organ systems (87–88). Ten of 12 patients reviewed by Murata et al. (87) had intrathoracic carcinoma of the lung or esophagus, 8 of whom had squamous cell carcinoma. The time interval between the onset of keratoderma and carcinoma was relatively short and the prognosis was poor: patients died in about a year. The two conditions appeared to follow a parallel course.

Dobson and co-workers (89) reported in 1965 an association between palmar keratoses and cancer. The keratoses, which occurred 4–5-fold more frequently in patients with malignancies than in control subjects, ranged from one to several millimeters in diameter, and were asymptomatic. They resembled those produced by arsenic, which is associated with the development of both skin and internal cancers, mainly of the pulmonary system and the genitourinary tract (90, 91).

Cuzick et al. (92, 93) recently supported these findings, although earlier studies failed to confirm the association between nonarsenic palmar keratosis and cancer (94–96). Cuzick and co-workers found a relationship with lung cancer and a strong connection with bladder cancer, an observation also reported by Cartwright et al. (97). The keratoses were of long duration in many cases and preceded the appearance of cancer (92). This was supported in another study (93) of patients with bladder cancer and palmar keratoses, whose blood relatives and spouses had an increased risk for palmar keratoses. Palmar keratoses seem to be markers of internal malignancy, specifically of carcinoma of the bladder and lung.

ACQUIRED ICHTHYOSIS (Fig. 4)

Acquired ichthyosis has been associated most commonly with lymphoproliferative neoplasms, primarily Hodgkin's disease. As reviewed by Van Dijk, 26 of 28 patients with acquired ichthyosis associated with internal malignancy had lymphoproliferative neoplasms (98). Acquired ichthyosis has also been reported with other lymphomas, leukemia, mycosis fungoides (99) and multiple myeloma. Solid tumors have been reported less frequently, e.g. carcinoma of the lung, colon, cervix and breast (100), as well as sarcomas. Finally, an association has been described with Kaposi's sarcoma (101, 102) and AIDS-related Kaposi's sarcoma (103, 104). A close parallelism may be found between the appearance of ichthyosis and malignancy in many cases, and remission of the cancer may be accompanied by disappearance of the ichthyosis.

ERYTHRODERMA

Erythroderma (exfoliative dermatitis) is caused by a variety of underlying causes, benign and malignant. Hasan and associates (105) compared the relative incidence of malignancy in erythrodermic patients in a few series and found that it ranged from 4–21%; all studies, however, corroborate that erythroderma may be associated with malignancy, usually of the lymphoma-leukemia group. Erythroderma is characteristic of Sézary's syndrome (106).

VASCULAR DISORDERS

Vasculitis

Paraneoplastic vasculitides are predominantly cutaneous. Most involve small vessels, but some, particularly those associated with hairy cell leukemia, may involve medium sized arteries (107). They are most commonly associated with leukemias and lymphomas (107). Other reported malignancies include carcinoma of bronchus (108), lung (109), breast, colon (110), esophagus (107), prostate (111), kidney (112), cervix (113), vocal cords (107) and melanoma (114).

Vasculitis may appear as the presenting feature of malignancy, or antedate, follow or herald a recurrence. Although circulating immune complexes are common in patients with many types of cancer, most of these conditions affect patients with lymphoma, leukemia or myeloma. This implies a possible predisposition in these conditions to the deposition of immune complexes, possibly of neoplastic origin, and an interaction with the vascular endothelium (115).

Flushing

A transient reddening, especially of the face, lasting a few minutes or more, is a consistent sign of carcinoid syndrome. Other cutaneous manifestations of carcinoid syndrome include cyanosis, telangiectasis and pellagra-like dermatosis.

Other types of neoplasia have been associated with flushing, such as leukemias, pancreatic tumors (116), medullary carcinoma of the thyroid (117) and renal cell carcinoma (118). Flushing reactions, including a heightened sensitivity to alcohol, may be the first clue to an underlying malignancy, such as carcinoid (119). A number of mechanisms have been proposed to explain the flushing, including the role of prostaglandins, serotonin, bradykinin, histamine and vasoactive intestinal polypeptides (119–121). It has been postulated that bradykinin, serotonin or histamine might play a role in the production of flushing in the carcinoid syndrome.

Vasoactive intestinal polypeptides have been implicated in the flushing associated with pancreatic tumors; excess calcitonin in plasma may cause flushing in medullary carcinoma of the thyroid. Prostaglandins also appear to be involved in both these conditions.

Trousseau's syndrome

Trousseau's syndrome, or migratory thrombophlebitis, is most frequently associated with pancreatic malignancy (122), but the association exists for many other neoplasms (123). The tumor is often occult and difficult to identify. The mechanism remains unclear. The overall frequency of clinically apparent and post-mortem established thrombotic coagulopathies associated with neoplasms has been reported to be 2–58% (123).

BULLOUS DISORDERS

Pemphigus vulgaris

The association between pemphigus vulgaris and malignancies is not clear. A causal relationship has been proposed (124, 125). A variety of neoplasms have been reported, including thymoma, lymphomas, tumors of the ovary, breast, uterus, stomach, squamous cell carcinoma of the esophagus and bronchus, as well as Kaposi's sarcoma (124). A recent study by Armin et al. (126) could not find a clear association. Recently, Anhalt et al. (127) suggested the term "paraneoplastic pemphigus" for a clinically distinct entity, based on 5 cancer patients with a novel acantholytic mucocutaneous disease, featuring autoantibodies pathogenic after passive transfer. The autoantibodies from these patients reacted with an antigen complex composed of desmoplakin 1 and the 230-Kd antigen of bullous pemphigoid, and two as yet unidentified epithelial antigens.

Bullous pemphigoid

The association between bullous pemphigoid and cancer is controversial. Apart from a number of case reports (128, 129), there are few controlled studies (130–132). Lindelöf et al. (133) recently reviewed 497 consecutive cases with positive immunofluorescence tests for circulating antibodies to basement membrane and concluded that pemphigoid is not statistically associated with malignancy. The hypothesis of such an association was based on age alone.

Muir-Torre syndrome

The association of sebaceous gland neoplasms and internal malignancies was first reported by Muir in 1967 and Torre in 1968. Although the most common cutaneous lesion is sebaceous adenoma, the full spectrum of sebaceous proliferative neoplasms has been seen, ranging from hyperplasia to adenoma, epithelioma, basal cell carcinoma with sebaceous differentiation, and sebaceous carcinoma (134), including also keratoacanthomas.

The sebaceous neoplasms may precede, follow or coexist with the visceral cancer. The visceral malignancies may involve the gastrointestinal tract (most often adenocarcinoma of the colon), the genitourinary tract, or present as non-Hodgkin's lymphomas (135, 136). The associated carcinomas are usually of comparatively low grade malignancy with a good survival rate. The syndrome seems to appear as a genetic condition, probably related to the cancer family syndrome (137).

COWDEN'S DISEASE

Cowden's disease, named after one of the first reported patients (138), or multiple hamartoma syndrome, is an uncommon autosomal dominant condition characterized by many benign and malignant tumors. The main features are mucocutaneous verrucoid papules, "cobble stoning" of the tongue, acral palmoplantar keratoses, and hamartomas of multiple organ systems. Multiple facial trichilemmomas appear to be pathognomonic (139). An increased prevalence of malignancy (38%) is found more often in women: most often breast (20–28% in affected women) (140, 141) and thyroid carcinoma (3–7%) (140, 141). The breast changes reported in women with Cowden's disease range from fibrocystic disease to adenocarcinoma. A higher percentage of bilateral breast malignancy is reported in the affected women (140). In about 35% of the cases multiple polyposis or diverticulosis has been

found in the gastrointestinal tract (141), but they seem to cause negligible morbidity and mortality (142).

NEVOID BASAL CELL CARCINOMA SYNDROME

The nevoid basal cell carcinoma syndrome, first documented by Howell & Caro in 1959, is an autosomal dominant condition with a gene penetrance of 97%, variable expressivity, early onset of multiple basal cell carcinomas, and increased risk for malignancy (143). It is characterized by basal cell carcinomas, multiple jaw cysts and anomalies of the skeletal system, specifically rib abnormalities, ectopic calcification and pits of the hands and feet. The pits are a useful cutaneous marker and, according to Howell (144), pathognomonic of the syndrome, occurring in approximately two thirds of adults with the syndrome. Leiomyomas and fibromas of the ovary can occur. The most common malignant tumor is a medulloblastoma. Central nervous system tumors can be seen in early childhood. Gorlin (145) described an increased tendency to various other neoplastic lesions in his review.

GARDNER'S SYNDROME

Gardner's syndrome is an autosomal dominant inherited condition with a high malignant transformation rate. The syndrome includes multiple osteomas, fibromas, lipomas, desmoid tumors, fibrosarcomas, epidermal cysts and leiomyoma as well as dental abnormalities associated with intestinal polyposis exclusively in the colon and rectum. Apart from the large bowel adenomas that are always present, the most constant component of Gardner's syndrome is epidermoid cysts. If untreated, death occurs before the age of 50, with the development of carcinoma of the colon before the age of 30 in half the patients. Total colectomy is recommended for prevention (146–148).

PEUTZ-JEGHERS SYNDROME

This autosomal dominant hereditary syndrome, characterized by hamartomatous polyps of the gastrointestinal tract and mucocutaneous pigmentation, is commonly associated with both benign and malignant neoplasms. Patients appear to have an increased risk of developing cancer both within and outside the gastrointestinal tract. Risk of the former is estimated at 2–3% (149–151), with duodenal preference (149). Carcinomas may arise in hamartomatous polyps (149, 150, 152). Non-gastrointestinal carcinoma affects mainly the breast, genitals and pancreas (153). Fifteen of 31 patients studied by Giardiello and co-workers (153) developed cancer, gastrointestinal in only 4. Cancer developed more frequently at a younger age. There appears to be a higher incidence of multiple neoplastic growths (154). A genetic predisposition to the development of cancer has been suggested. Routine examination for cancer is recommended (153, 154), especially breast and gynecologic examination, gastrointestinal tract and maybe pancreas (153).

MUCOSAL NEUROMA SYNDROME

This rare association of mucosal neuromas, medullary thyroid carcinoma and pheochromocytoma may be viewed as a variant of multiple endocrine neoplasia (MEN III or IIB). Typical signs are enlarged lips, marfanoid habitus and frequent skeletal abnormalities like scoliosis and kyphosis. Multiple mucosal neuromas involve mainly the lips ("blueberry" lips) and tongue, although other parts of the mucosa including the conjunctiva and gastrointenstinal tract may be affected (155). The neuromas usually precede the detection of cancer. The pheochromocytoma is frequently bilateral and multiple. About 8% metastasize (155).

The combination of tumors in MEN IIB might be explained by the common origin from the neural crest of the "C cells", the adrenal medullary cells and the mucosal neuroma cells (156).

DERMATOMYOSITIS

Dermatomyositis is a rare, severe inflammatory myopathy with typical cutaneous manifestations, including erythema or telangiectases of the periorbital region, upper chest or knuckles. It is perhaps the most extensively studied paraneoplastic condition and has been linked to malignancy, especially in adults after the age of 40. The frequency of cancer in adult patients varies from less than 10% to more than 50% (157) and increases with age (157, 158).

Reports do not reveal a definite sex predilection, although some investigators found a preponderance of bronchial carcinoma in men and a high frequency of genital tumors in women (157, 159). In addition, gastrointestinal tumors and nearly every other malignant tumor have been reported with dermatomyositis (160). The malignancy can precede, follow or occur with dermatomyositis (161), and the most frequent pattern is onset of the cancer within 1 year before or after the diagnosis of dermatomyositis (162).

The value of a malignancy evaluation in patients with dermatomyositis has been discussed in two major studies. Callen (161) analyzed 57 patients who had dermatomyositis. He concluded that malignancy evaluation is indicated. The same conclusion was reached in a 5-year multicenter study of 118 cases of dermatomyositis (162), in which the tumor was identified in most cases without need for extensive diagnostic procedures. In a study of 392 patients with dermatomyositis, Sigurgeirsson et al. (163) found a definite increase in the risk of cancer, and an increase in mortality that was more pronounced in women.

PACHYDERMOPERIOSTOSIS

Pachydermoperiostosis has been associated in some cases with bronchogenic carcinoma. Elevated human growth hormone (HGH) in these cases is usually indicative of bronchogenic carcinoma, usually of ectopic origin (164). Resection of the tumor lowers the HGH levels to normal (165). The HGH j25 concentration has been demonstrated to be higher in the tumor than in the surrounding lung tissue by Cameron et al. (166).

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