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Cutaneous Manifestations of Internal Malignancy

Bruce H. Thiers, MD¹, Rachel E. Sahn, BA², Jeffrey P. Callen, MD³

Abstract

The skin often mirrors changes in the organism it envelops. Many neoplastic diseases that affect internal organs display cutaneous manifestations, which may be the presenting signs and symptoms of the underlying malignancy. These may reflect direct involvement of the skin by the tumor (ie, tumor metastasis) or indirect involvement, in which changes in the skin occur in the absence of malignant cells. This review focuses on the latter conditions, which are often referred to as paraneoplastic dermatoses. Included in the discussion are the cutaneous manifestations of inherited syndromes that are associated with an increased risk of internal malignancy, cutaneous changes in patients with hormone-secreting tumors, and the wide spectrum of proliferative and inflammatory dermatoses that have been associated with internal cancer. *CA Cancer J Clin* 2009;59:73-98. ©2009 American Cancer Society, Inc.



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Introduction

This article serves as an update of a review published in this same journal more than 20 years ago.¹ The conditions discussed here are often referred to as paraneoplastic dermatoses, which in the strictest sense describes those disorders in which there is a direct and often parallel course of the dermatosis and an underlying malignancy.² Although many of these conditions do not always follow such a course, their presence serves as an important marker of a potential associated neoplastic process. In our discussion, we adhere to Curth's postulates, which define the criteria for establishing a relation between an internal malignancy and a cutaneous disorder (Table 1).³

Involvement of the skin by visceral tumors may occur either directly or indirectly. Direct involvement implies the presence of tumor cells in the skin. This may occur either by direct extension or by tumor metastasis. Nearly any internal cancer can metastasize to the skin, a full discussion of which is beyond the scope of this article. Herein we concentrate on indirect involvement of the skin by visceral tumors, which can cause a variety of characteristic inflammatory, proliferative, metabolic, and neoplastic changes without the actual presence of tumor cells. In this diverse group of disorders, we include inherited syndromes associated with skin manifestations and an increased incidence of systemic neoplasia, cutaneous changes resulting from hormone secretion by tumors, and the wide spectrum of proliferative and inflammatory disorders that have been reported in patients with internal malignancies (Table 2). For each condition, we review the clinical manifestations, include an update on any new knowledge regarding disease pathogenesis, and provide practical advice regarding cancer prevention and detection.

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TABLE 1. Curth's Postulates

1) The malignancy and the skin disease are of concurrent onset
2) The malignancy and the skin disease run a parallel course. Successful treatment of the tumor leads to regression of the skin disease, and recurrence of the tumor leads to a return of cutaneous signs and symptoms
3) The relation between the skin disease and the malignancy is uniform. A specific tumor cell type or site is associated with a characteristic cutaneous eruption
4) Based on sound case-control studies, a statistically significant association exists between the malignancy and a specific cutaneous disease, and/or
5) A genetic association exists between the malignancy and a specific cutaneous disease

NOTE: Not all criteria must be met to postulate a relation between a skin disease and an underlying malignancy.

Inherited Syndromes

Many familial cancer syndromes have prominent dermatologic features.⁴ Often, the potential for internal malignancy is first suspected when the skin disease is recognized. The skin changes are protean and are described below.

Cowden Syndrome (Multiple Hamartoma Syndrome)

Description

Cowden syndrome is an autosomal dominant condition whose clinical manifestations are appreciated more often in women than in men. A variety of cutaneous and mucosal manifestations can occur; these are observed at any time from childhood to middle age.⁴⁻⁷ Small (1-4 mm) flesh-colored papules (trichilemmomas) are found mainly on the head and neck and may assume a wart-like appearance (Fig. 1). Similar papules on the tongue and gingiva may coalesce to produce a cobblestone appearance. Flat wart-like papules may be observed on the dorsum of the hands and feet, and punctate keratoses may be present on the soles, sides of the feet, and palms. Lipomas and hemangiomas may complete the clinical picture.

Internal manifestations are variable. Fibrocystic disease of the breast is detected in nearly all affected women, 25% to 50% of whom ultimately develop breast cancer, which may be bilateral.⁶ Thyroid tumors are frequent (62% of patients) and are usually benign, with 10% of patients being diagnosed with thyroid cancer.⁶ Endometrial cancer occurs in 5% to 10% of affected women.⁶ Cancers of the lung and

TABLE 2. Cutaneous Manifestations of Internal Malignancy

INHERITED SYNDROMES
1) Cowden syndrome
2) Gardner syndrome
3) Peutz-Jeghers syndrome
4) Muir-Torre syndrome
5) Howel-Evans syndrome
6) Birt-Hogg-Dubé syndrome
7) Hereditary leiomyomatosis/renal cell cancer syndrome
8) Melanoma/pancreatic cancer syndrome
9) Multiple mucosal neuromas syndrome
10) Neurofibromatosis type 1
11) Inherited immunodeficiency syndromes
HORMONE-SECRETING TUMORS
1) Ectopic ACTH syndrome
2) Carcinoid syndrome
3) Multiple endocrine neoplasia syndrome
4) Glucagonoma syndrome
PROLIFERATIVE AND INFLAMMATORY DERMATOSES
1) Acquired hypertrichosis lanuginosa
2) Acanthosis nigricans
3) Sign of Leser-Trelat
4) Tripe palms
5) Bazex syndrome
6) Primary systemic amyloidosis
7) Scleromyxedema
8) Sweet syndrome
9) Pyoderma gangrenosum
10) Blistering disorders
11) Dermatomyositis
12) Clubbing and related disorders
13) Cutaneous leukocytoclastic vasculitis
14) Coagulopathies
15) Figurate erythemas
16) Extramammary Paget disease
17) Infectious disorders
18) Generalized pruritus, ichthyosis, and exfoliative dermatitis
19) Pigmentary disorders
20) Miscellaneous skin, hair, and nail disorders

colon have been reported as well. Hamartomatous polyps of the gastrointestinal tract occur in approximately one-third of patients.

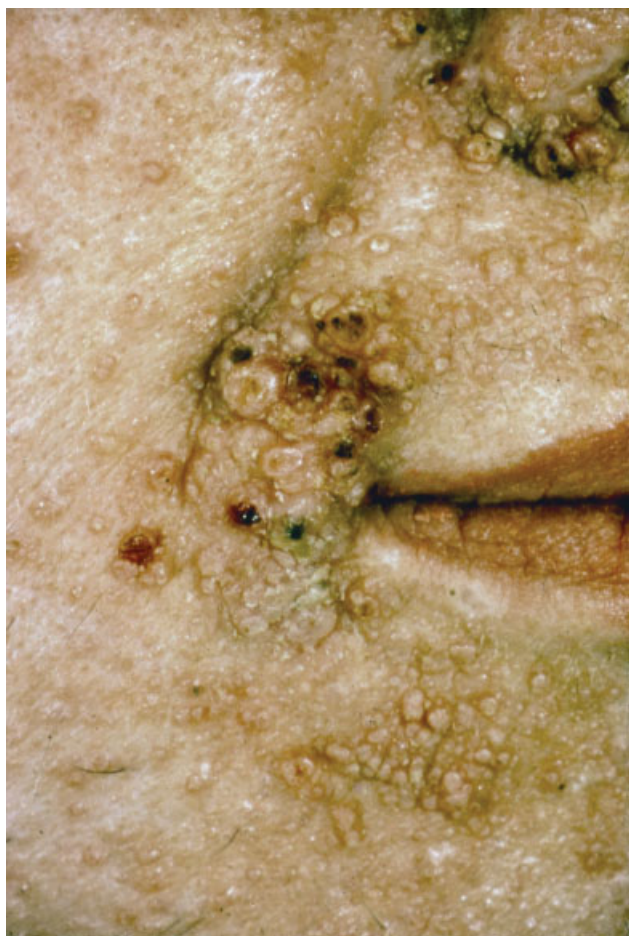


FIGURE 1. Cowden Syndrome: Trichilemmomas. Courtesy of Joseph Bikowski, MD, Sewickley, Pennsylvania. Reprinted with permission from Thiers BH. Dermatologic manifestations of internal cancer. *CA Cancer J Clin.* 1986;36:130-148.

What's new

Cowden syndrome has been linked to mutations in the *PTEN/MMAC1* tumor suppressor gene on chromosome 10q22-23, which encodes a tyrosine phosphatase protein that regulates cell proliferation.⁴⁻⁷ Human papillomavirus (HPV) DNA has been found in the trichilemmomas that characterize this condition.⁸

Patient management

The significance of Cowden syndrome lies in its value as a marker for the eventual development of breast cancer and thyroid tumors. Because fibrocystic changes occur in most affected women, routine screening for breast cancer is more difficult, and prophylactic mastectomy may be recommended. Monthly self-breast examination should begin at age 18 years with clinical breast examinations performed every 6 months beginning at age 25 years (or 5-10 years sooner than the earliest known familial breast cancer).⁹ Mammography and magnetic resonance

imaging (MRI) should be performed yearly beginning at age 30 to 35 years (or 5-10 years sooner than earliest known familial breast cancer).⁹

Thyroid ultrasound should be done yearly beginning at age 18 years. Total thyroidectomy is often recommended for those who develop thyroid cancer and even for those who develop benign thyroid tumors such as adenomas.⁹

Annual endometrial biopsies are advised for premenopausal women older than 35 to 40 years (or 5 years sooner than the earliest known familial endometrial cancer). Annual endometrial ultrasound studies should be initiated after menopause.⁹

Gardner Syndrome

Description

Gardner syndrome is an autosomal dominant disorder that is characterized by extensive adenomatous polyps of the gastrointestinal tract, especially the colon and rectum. The polyps have a very high incidence of malignant transformation, which usually occurs by age 35 to 40 years. Some extracolonic malignancies appear to occur with increased frequency, and the incidence of thyroid cancer is increased, especially in females. The skin lesions that occur in Gardner syndrome include large, deforming epidermoid cysts (Fig. 2); fibromas; lipomas; leiomyomas; trichoepitheliomas; and neurofibromas. Osteomas involving the membranous bones of the face and head are noted in approximately one-half of affected patients.¹⁰ Congenital hypertrophy of the retinal pigment epithelium also has been observed in patients with Gardner syndrome.⁸

What's new

Gardner syndrome has been associated with the adenomatous polyposis coli (*APC*) tumor suppressor gene on chromosome 5q21-q22.^{5,6} The *APC* gene product regulates β -catenin, an adherens junction protein, which in turn is involved in cell migration and cell cycle control.

Patient management

The risk of colon cancer mandates annual colonoscopy beginning at puberty for patients with Gardner syndrome and for family members who have not undergone genetic testing. Because the potential for malignant transformation of these polyps approaches 100%, prophylactic total colectomy is often recommended. The timing of such is critical and for men



FIGURE 2. Gardner Syndrome: Cysts. Reprinted with permission from Thiers BH. Dermatologic manifestations of internal cancer. *CA Cancer J Clin.* 1986;36:130-148.

the possibility of impotence after total proctocolectomy is an important consideration. Therefore, family planning services and genetic counseling should be provided. Surgery may be postponed for several years in children and adolescents.

First-degree relatives should be offered genetic testing for the identified mutation because direct sequencing for the *APC* gene can be used to detect asymptomatic individuals.¹¹ Examination of first-degree relatives for subtle skin changes is warranted.

Peutz-Jeghers Syndrome

Description

Peutz-Jeghers syndrome is an autosomal dominant disorder characterized by extensive hamartomatous polyps and carcinomas throughout the gastrointestinal tract, mainly the small intestine.¹² Intussusception with resultant bleeding and abdominal pain is the most common gastrointestinal manifestation.¹² The characteristic cutaneous features of this condition are the freckle-like

pigmented macules that occur on the lips, nose, buccal mucosa, fingertips, and under the nails (Fig. 3). The risk of gastrointestinal tumors is higher than in the general population, although most of these lesions do not evolve from the polyps, which are histologically benign. There appears to be an increased risk of pancreatic cancer, breast cancer, and reproductive neoplasms, including tumors of the cervix, ovary, and testis.¹³⁻¹⁶

What's new

Most cases of Peutz-Jeghers syndrome have been found to be related to mutations in the *STK11/LKB1* gene on chromosome 19p13.3.^{5,14,17} This tumor suppressor gene encodes a serine/threonine protein kinase that modulates cell cycle progression. Approximately 40% of cases are estimated to represent spontaneous mutations.

Patient management

In contrast to Gardner syndrome, malignant transformation of these polyps is rare, with the majority of tumors arising from coexisting adenomas.¹⁸ Upper and lower endoscopy should be performed every 2 years.¹⁹ Removal is advised for symptomatic polyps or for those measuring >1.5 cm in size.

Regular breast and gynecologic examinations are recommended for women with Peutz-Jeghers syndrome. Because they are at higher risk for malignancy than the population at large, monthly breast self-examinations should be performed, with clinical breast examinations beginning in the late teen years and mammography by age 25 years. Papanicolaou (Pap) tests are recommended no less frequently than every 3 years.²⁰



FIGURE 3. Peutz-Jeghers Syndrome: Perioral Pigmented Macules. Reprinted with permission from Thiers BH. Dermatologic manifestations of internal cancer. *CA Cancer J Clin.* 1986;36:130-148.

Muir-Torre Syndrome

Description

Muir-Torre syndrome (also known as Torre syndrome) defines the association of visceral carcinoma, usually involving the gastrointestinal tract, with numerous sebaceous gland tumors (both benign and malignant), occurring primarily on the trunk (Fig. 4). Other internal cancers have also been reported, as have other skin lesions, particularly keratoacanthomas (which often demonstrate sebaceous differentiation).²¹ In contrast, solitary sebaceous gland tumors are not genetically determined, are not associated with visceral malignancy, and occur most often on the head and neck. The diagnosis of gastrointestinal cancer usually precedes recognition of the cutaneous lesions. The cutaneous tumors do not display aggressive behavior even if histologically malignant. Similarly, the gastrointestinal cancers often behave as low-grade malignancies. Hematologic malignancies and cancers of the genitourinary tract and breast have been reported as well.

What's new

Muir-Torre syndrome is considered to be a subset of the hereditary nonpolyposis colon cancer (HNPCC) syndrome.²² It is inherited as an autosomal dominant trait and is related to mutations of the DNA mismatch repair (MMR) genes, most often the *MSH2* gene located at 2p22-p21, and less commonly the *MSH1* gene located at 3p21.3. This mutation leads to microsatellite instability, which may be responsible for the carcinomas observed in these patients. Some of the MMR gene mutations associated with HNPCC are found in Muir-Torre syndrome whereas others are not.²²



FIGURE 4. Muir-Torre Syndrome: Sebaceous Gland Tumors.

Patient management

The general propensity for cancer mandates regular screening examinations and laboratory testing. Most tumors occur at age 30 years and later, but screening at younger ages may still be worthwhile. Colonoscopy recommendations vary from intervals as long as 3 to 5 years to as frequently as every 1 to 2 years.²¹ Endometrial biopsy has been suggested every 3 to 5 years beginning at age 50 years. Some authorities recommend computed tomography (CT) scans of the abdomen and pelvis be obtained every 3 to 5 years as well. Mammograms should be performed annually.²¹ Detailed guidelines for screening individuals with HNPCC have recently been published.²³

Howel-Evans Syndrome

Description

Howel-Evans syndrome describes the association between tylosis (thickened skin of the palms and soles) (Fig. 5) and esophageal cancer. It was first reported in 2 English families. The keratoderma usually develops during childhood and is accentuated over pressure sites, although the onset of the esophageal carcinoma is delayed until middle age. There may be associated oral leukoplakia.

What's new

The genetic locus on chromosome 17q25, now referred to as the tylosis (o)esophageal cancer (*TOC*) gene, appears to be associated with this syndrome. It is frequently deleted in sporadic esophageal squamous cell carcinoma as well.²⁴

Patient management

Annual upper endoscopic screening should be performed in patients and in affected family members.

Birt-Hogg-Dubé Syndrome

Description

Birt-Hogg-Dubé syndrome is an autosomal dominant condition characterized by skin tags and benign hair follicle tumors (fibrofolliculomas and trichodiscomas) that most often occur on the head and neck (Fig. 6).²⁵⁻²⁷ The incidence of chromophobe and oncocyctic types of renal carcinoma is increased, as is the incidence of lung cysts and spontaneous pneumothorax. Although several cases of medullary carcinoma of the thyroid were noted in the original family reported with this syndrome, to our knowledge it has not been observed since. There



FIGURE 5. Howel-Evans Syndrome: Palmoplantar Hyperkeratosis. Reprinted with permission from Thiers BH. Dermatologic manifestations of internal cancer. *CA Cancer J Clin.* 1986;36:130-148.

have been some families in whom a link to colonic polyposis has been proposed.²¹

What's new

Birt-Hogg-Dubé syndrome has been mapped to a mutation in the 17p11.2 gene, which encodes folliculin.^{5,6,27}

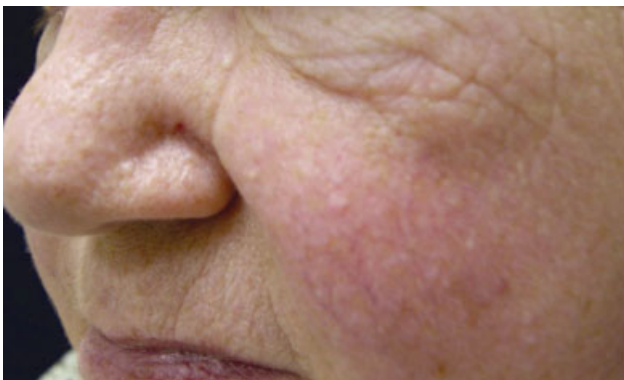


FIGURE 6. Birt-Hogg-Dubé Syndrome: Benign Hair Follicle Tumors.

Patient management

Patients suspected of having Birt-Hogg-Dubé syndrome should be questioned regarding a personal or family history of kidney cancer or lung disease, specifically spontaneous pneumothorax, bullous emphysema, or lung cysts. Dermatologic evaluation and CT examination for lung cysts and renal abnormalities are recommended for complete assessment. Family members should be offered these screening examinations as well, usually beginning at age 40 years.²⁷ It should be recognized that skin lesions may be minimal or absent in some carriers of the mutation.²⁷

Hereditary Leiomyomatosis/Renal Cell Cancer Syndrome

Description

Hereditary leiomyomatosis/renal cell cancer syndrome is an autosomal dominant condition characterized by multiple leiomyomas of the uterus and skin in conjunction with papillary renal cell carcinoma.^{25,28,29} The cutaneous leiomyomas may be segmental or band-like rather than diffuse and symmetric (Fig. 7). They are firm, flesh-colored, red or brown, and may be painful. They usually appear by age 25 years.²⁹ The renal tumors are associated with early spread to lymph nodes and a poor prognosis.³⁰

What's new

Hereditary leiomyomatosis/renal cell cancer syndrome appears to result from a mutation of the gene encoding fumarate hydratase, an enzyme of the tricarboxylic acid cycle. The disorder has been mapped to the 1q42.3-43 locus.^{6,30}



FIGURE 7. Hereditary Leiomyomatosis/Renal Cell Cancer Syndrome: Grouped Cutaneous Leiomyomas.

Patient management

The aggressive nature of the renal tumors makes early detection and surgical removal mandatory.³⁰ Radiologic evaluation of the kidneys with CT and/or MRI is recommended for individuals suspected of having the syndrome. Family members should undergo genetic counseling and testing.³¹

Melanoma/Pancreatic Cancer Syndrome

Description

Patients with the melanoma/pancreatic cancer syndrome (also known as the familial atypical multiple mole melanoma-pancreatic cancer syndrome) initially present with multiple nevi, many of which are “atypical,” (ie, large [≥ 6 mm in diameter], with pigmentation and border irregularities) (Fig. 8). The incidence of melanoma is increased, and a family history of melanoma and pancreatic cancer should be sought.³² In addition to the increased risk of pancreatic cancer (estimated to be as high as 22-fold) in affected families, reports have linked this family cancer syndrome to an increased risk of breast cancer.^{33,34}

What's new

Melanoma/pancreatic cancer syndrome appears to be related to a mutation of the gene encoding cyclin-dependent kinase inhibitor-2A (CDKN2A) on chromosome 9p21.⁶



FIGURE 8. Melanoma/Pancreatic Cancer Syndrome: Multiple Atypical Nevi With Melanoma Visible at the Top Center. Courtesy of Darrell Rigel, MD, New York, New York.

Patient management

Patients should be educated regarding self-examination of the skin for the diagnosis of melanoma, and should undergo a regular dermatologic examination at least every 6 months. Dermatoscopic examination of pigmented lesions may also be helpful, as may serial total body photography to detect new lesions or subtle changes in existing lesions. Unusual or changing lesions should be subject to biopsy.

Because of the difficulty in detecting pancreatic cancer at an early stage and the poor prognosis of the disease, management is difficult and referral to a gastroenterologist is appropriate. Endoscopic retrograde cholangiopancreatography and endoscopic ultrasound are sensitive screening tests for pancreatic cancer.³²

Genetic counseling is mandatory for patients with the melanoma/pancreatic cancer syndrome.

Multiple Mucosal Neuromas Syndrome

Description

Multiple mucosal neuromas syndrome (also referred to as multiple endocrine neoplasia [MEN], type 2B) is a rare autosomal dominant disorder that includes a constellation of abnormalities, including medullary carcinoma of the thyroid and pheochromocytoma. The medullary carcinoma is aggressive and occurs in 95% of patients.³⁵ Pheochromocytomas occur in approximately 50% of individuals with the MEN 2 gene mutation; they are usually in the adrenal bed and are often bilateral. Intestinal ganglioneuromatosis may give rise to episodes of severe constipation or diarrhea.³⁶ Hyperparathyroidism because of parathyroid hyperplasia may occur but is rare in MEN type 2B compared with MEN type 2A (Sipple syndrome). The multiple neuromas appear as whitish nodules mainly on the lips and the anterior one-third of the tongue (Fig. 9). They also may be noted on the buccal mucosa, gingivae, palate, pharynx, conjunctivae, and cornea. Affected individuals have characteristic facies, with thick, protuberant, bumpy lips. The eyelids are sometimes thickened and slightly everted. Many patients have a “marfanoid” habitus, displaying long, slender extremities; poor muscle development; sparse body fat; laxity of joints; pectus excavatum; and dorsal kyphosis. In addition to the inherited syndrome, many sporadic cases have been reported.



FIGURE 9. Multiple Mucosal Neuromas Syndrome: Neuromas. Reprinted with permission from Thiers BH. Dermatologic manifestations of internal cancer. *CA Cancer J Clin.* 1986;36:130-148.

What's new

The disease is associated with mutation of the receptor tyrosine kinase (*RET*) proto-oncogene on chromosome 10. *RET* mutations in exon 16 are found in 95% of cases.^{35,36}

Patient management

Endocrinologic evaluation and follow-up are necessary. Genetic counseling and *RET* germline testing are also recommended. Given the aggressive nature of the thyroid tumors, prophylactic thyroidectomy is advised for those patients with proven *RET* gene mutations.³⁶ Some authors advocate that the timing of the prophylactic thyroidectomy be based on the type of *RET* mutation present: in those with high-risk mutations by age 1 year, in those with moderate-risk mutations by age 5 years, and in those with low-risk mutations by age 10 years or younger.³⁵

Screening for pheochromocytoma, including serum catecholamines and 24-hour urinary catecholamines and metanephrines, should be included in the monitoring of patients with multiple mucosal neuromas syndrome. If pheochromocytoma is suspected, a CT scan will help locate the tumor.

Neurofibromatosis Type 1 (von Recklinghausen Disease)

Description

The classical features of autosomal dominant neurofibromatosis (NF) type 1 (von Recklinghausen disease) include axillary and inguinal freckling, cafe-au-lait macules, cutaneous neurofibromas, and occasionally, plexiform neuromas (Fig. 10).³⁷ Its clinical course may be complicated by multiple Schwann cell

tumors, malignant degeneration of neurofibromas, and pheochromocytomas, which may be bilateral but are usually benign. Gastrointestinal stromal tumors also have been observed, as have many other neoplasms in a variety of locations.³⁸

What's new

The characteristic genetic abnormality found in neurofibromatosis type 1 is a mutation of the *NF-1* gene at the 17q11.2 locus, whose gene product, neurofibromin, appears to be a tumor suppressor protein.³⁹ Approximately 50% of cases represent spontaneous mutations.⁵ Features of neurofibromatosis type 1 have been reported in patients with homozygous MMR gene mutations.⁴⁰ Because both the *NF-1* gene and the *BRCA1* gene are located on chromosome 17, there may be an association between neurofibromatosis type 1 and the early development of breast and gynecologic malignancies.⁴¹ However, be-



FIGURE 10. Neurofibromatosis Type 1 (von Recklinghausen Disease): Cafe-au-Lait Macules and Neurofibromas. Reprinted with permission from Thiers BH. Dermatologic manifestations of internal cancer. *CA Cancer J Clin.* 1986;36:130-148.

cause many patients with NF and breast cancer do not have the *BRCA* mutation, the molecular mechanism underlying this relation remains undefined.

Patient management

Other types of neurofibromatosis must be ruled out. Patients should undergo genetic counseling and genetic testing. Blood pressure should be monitored on a regular basis. Although to our knowledge there are no established cancer screening protocols specifically for patients with neurofibromatosis, its protean manifestations demand regular clinical evaluation.⁴²

Inherited Immunodeficiency Syndromes

Description

Several inherited immunodeficiency diseases, including Bloom syndrome, Rothmund-Thomson syndrome (poikiloderma congenitale), ataxia-telangiectasia (Louis-Bar syndrome), and Wiskott-Aldrich syndrome, are associated with an increased incidence of internal cancer. Although the clinical manifestations of these conditions vary, they have in common autosomal recessive inheritance, a predisposition to lymphoma and leukemias and, for the first 3 conditions, the presence of cutaneous telangiectasia.

Patients with Bloom syndrome manifest a photo-distributed erythema in a butterfly distribution over the central face, an appearance that has been likened to the malar rash of lupus erythematosus. Other typically sun-exposed areas may be affected as well. The incidence of neoplasia is increased, with leukemia, lymphoma, and adenocarcinoma of the gastrointestinal tract being most common.^{5,43} Rothmund-Thomson syndrome is a photosensitive disorder characterized by the development of erythema, telangiectasia, dyspigmentation, and atrophy on the face, extensor extremities, and buttocks. There may be associated alopecia and dystrophic changes of the nails.^{5,43} Osteosarcoma, fibrosarcoma, gastric carcinoma, and cutaneous squamous cell carcinoma are uncommon but have been reported. Patients with ataxia-telangiectasia develop difficult walking in the second or third year of life usually, but not always, before the cutaneous changes (which may first be noted on the bulbar conjunctiva) become apparent (Fig. 11). Other common sites for telangiectasia are the corners of the eyes, the ears, and the cheeks. Sinopulmonary infections are frequent and endocrine abnormalities and other neurologic signs may com-



FIGURE 11. Louis-Bar Syndrome (Ataxia-Telangiectasia): Conjunctival Telangiectasia. Courtesy of Joseph Bikowski, MD, Sewickley, Pennsylvania. Reprinted with permission from Thiers BH. Dermatologic manifestations of internal cancer. *CA Cancer J Clin.* 1986;36:130-148.

plicate the clinical course. The risk of malignancy in ataxia-telangiectasia patients is 37-fold higher than in the general population, with the risk of developing lymphoid tumors (100-fold higher than the general population) being the most striking. The overall risk of developing leukemia or lymphoma is 10%; in affected patients, death generally occurs by the second decade of life.^{5,43} Wiskott-Aldrich syndrome is characterized by a hemorrhagic eczema with secondary infectious complications, both cutaneous and systemic. Lymphoreticular malignancy, usually non-Hodgkin lymphoma, occurs in 20% of patients.⁵

What's new

Both Bloom syndrome and Rothmund-Thomson syndrome have been associated with defective DNA helicase genes (*RECQL3* and *RECQL4*, respectively), which may reduce chromosomal stability and DNA repair capacity. Ataxia-telangiectasia is associated with a defect in the ataxia-telangiectasia-mutated (*ATM*) gene on chromosome 11q22-23, which plays an important role in signaling DNA damage.^{5,43} Wiskott-Aldrich syndrome has been mapped to the eponymous Wiskott-Aldrich syndrome (*WAS*) gene on chromosome Xp11.^{5,44,45}

Many studies have suggested an increased risk of cancer, especially breast cancer, in carriers of the *ATM* gene, but others have produced contradictory results.^{46,47} Nevertheless, heterozygote carriers of the *ATM* gene require regular monitoring.

Patient management

The variable manifestations of the inherited immunodeficiency syndromes mandate a team approach.

Genetic counseling is a necessary part of the care of families with members affected by any of these conditions.

Hormone-Secreting Tumors

Neoplastic proliferation of cells that can secrete a variety of biologically active amines and polypeptide hormones may result in characteristic symptom complexes associated with specific cutaneous changes. These conditions have been described as ectopic humoral syndromes.

Ectopic ACTH Syndrome

Description

Patients with ectopic adrenocorticotrophic hormone (ACTH)-producing tumors frequently lack the signs and symptoms typically associated with Cushing syndrome, in part because of the acuteness of the clinical course. Hypokalemic metabolic alkalosis, hypertension, glucose intolerance or frank diabetes, and weight loss are classical clinical features. Especially noteworthy is the intense hyperpigmentation (Fig. 12). Although this is present in only 6% to 10% of patients with Cushing disease, it is especially common in association with ectopic ACTH production and should alert the clinician to the possibility of a hormone-secreting tumor.⁴⁸ The cause of the hyperpigmentation is uncertain, but may be related to



FIGURE 12. Ectopic ACTH Syndrome: Hyperpigmentation. Courtesy of Donald Lookingbill, MD, Jacksonville, Florida.

tumor production of the peptide β -lipotropin, which contains within its sequence of 91 amino acids the 22-amino acid sequence of β -melanocyte stimulating hormone (MSH). A striking clinical feature of ectopic ACTH-producing tumors may be a myasthenia gravis-like syndrome manifested as profound proximal muscle weakness. This may reflect either underlying hypokalemia or associated polymyositis. Small cell carcinoma of the lung is the tumor most often associated with ectopic ACTH production, although other malignancies, including carcinoid tumors, pancreatic islet cell tumors, and pheochromocytomas, have also been reported.

What's new

The gene for proopiomelanocortin (POMC), the precursor peptide for ACTH, is expressed in high levels in the anterior pituitary gland as well as in ACTH-producing tumors.⁴⁹

Patient management

The majority of tumors can be localized through plain film x-ray, CT, MRI, and ultrasound studies.⁴⁹ ACTH-producing tumors can cause marked hypercortisolemia with its attendant complications. Surgery is often curative, although pharmacologic therapy may assist in control of the hypercortisolemia.

Carcinoid Syndrome

Description

Carcinoid syndrome is a second example of a humoral syndrome associated with a neuroendocrine tumor.^{50,51} Carcinoid tumors can produce a variety of vasoactive substances. The most striking cutaneous manifestations are episodes of flushing, which are caused at least in part by the release of the enzyme kallikrein from tumor cells, with subsequent conversion of kininogen to vasoactive kinin peptides, including bradykinin. Serotonin may play an important role in the flushing reaction as well. Typical episodes initially last 10 to 30 minutes and involve only the upper half of the body. As the flushing resolves, gyrate and serpiginous patterns may be noted. With successive attacks, more extensive areas may be affected and the redness takes on a cyanotic quality. This eventually leads to a more permanent facial cyanotic flush with associated telangiectasia, resembling rosacea (Fig. 13). Leonine facies may result from the persistent facial edema and erythema. Some patients develop a pellagra-like picture, which may result from

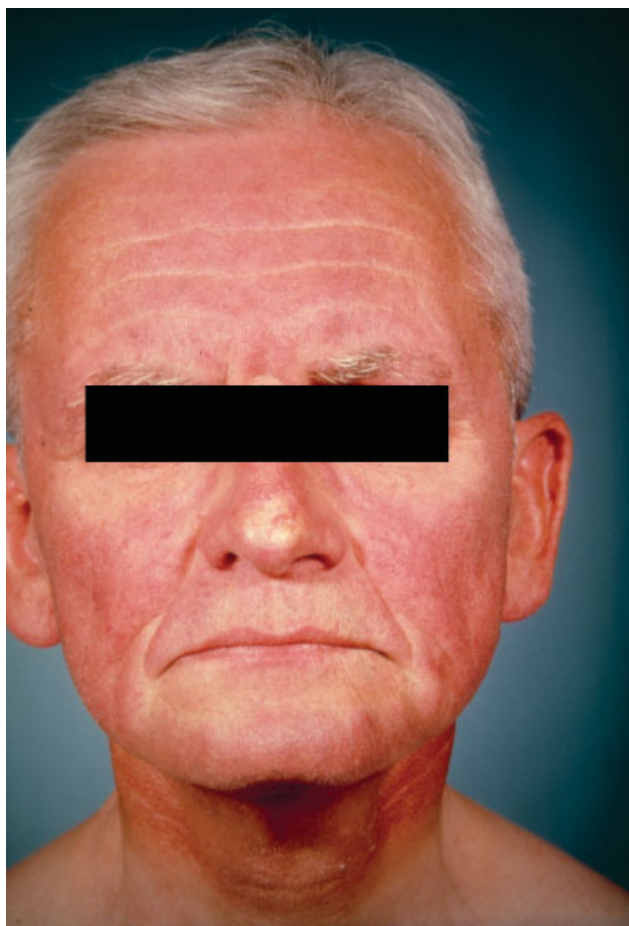


FIGURE 13. Carcinoid Syndrome: Flushing. Courtesy of Walter Lobitz, MD (deceased), Portland, Oregon.

abnormal tryptophan metabolism. Systemic symptoms associated with the episodic cutaneous flushing may include abdominal pain with explosive watery diarrhea, bronchospasm, hypotension, and tachycardia.

Carcinoid tumors are most often found in the appendix or small intestine; extraintestinal carcinoids may arise in the bile ducts, pancreas, stomach, ovaries, or bronchi. Classical carcinoid syndrome occurs primarily with intestinal carcinoids metastatic to the liver or with extraintestinal tumors. Attacks of flushing occasionally can be provoked by the palpation of hepatic or abdominal metastases or by alcohol ingestion, enemas, emotional stress, or sudden changes in body temperature. When the syndrome is associated with pulmonary carcinoid tumors, the flushing is more prolonged and is often associated with fever, marked anxiety, disorientation, sweating, salivation, and lacrimation.

What's new

Urinary excretion of 5-hydroxy-indoleacetic acid (5-HIAA), a metabolite of serotonin, is increased in

75% of cases, and its measurement has been considered the gold standard for the diagnosis of carcinoid syndrome. Several reports have suggested that measurement of circulating immunoreactive chromogranin A (CgA) also may be a valuable tool for the diagnosis of neuroendocrine neoplasia, including carcinoid tumors, and that CgA immunohistochemistry can help to confirm the neuroendocrine origin of these tumors.⁵²

Patient management

Surgery may be curative; if complete tumor resection is not possible, partial removal may be beneficial. Somatostatin analogues are often used to control symptoms and to reduce the risk of carcinoid crises.⁵³

Multiple Endocrine Neoplasia Syndrome

Description

The 3 clinical patterns of familial multiple endocrine neoplasia (MEN types 1, 2A, and 2B) are examples of polyglandular endocrine disorders involving the APUD cell system (ie, cells with a capacity for Amino Precursor Uptake and Decarboxylation).^{54,55} These cells, which may have a common origin from the neural crest, can secrete a variety of biologically active amines and polypeptide hormones. Skin lesions do not characterize MEN 1, which has been associated with pancreatic insulinomas and gastrinomas. A carcinoid-like syndrome has been described in MEN 2A (Sipple syndrome)^{56,57}; otherwise, mucocutaneous lesions occur only in MEN 2B (multiple mucosal neuromas syndrome), which has been discussed earlier (Fig. 9).⁵⁷

What's new

The genetics of the MEN syndromes have recently been elucidated. MEN 1 is associated with a germline mutation in the *menin* gene, which most likely functions as a tumor suppressor gene and is located on chromosome 11q13. Both MEN 2A and 2B are associated with germline mutations in the *RET* gene, a proto-oncogene.⁵⁷

Patient management

The management guidelines for MEN 1 and MEN 2 are significantly different. Patients with MEN 1 do not receive prophylactic treatment; therapy should be delayed in these patients until disease occurs. Family members may be tested for MEN 1 gene mutations. Those with the syndrome should be followed on a

regular basis for signs and symptoms of disease. Tumors, when they occur, are treated medically and/or surgically.⁵⁷

Because the primary cause of mortality in patients with MEN 2A and MEN 2B is medullary thyroid cancer and because nearly all of these patients eventually develop this malignancy, prophylactic thyroidectomy is recommended, the timing of which is based on the risk level of the patient's *RET* codon mutation, as described previously for MEN 2B (multiple mucosal neuromas syndrome). Once medullary thyroid carcinoma does develop, the patient should undergo total thyroidectomy with regional lymphadenectomy. Family members should be tested for *RET* mutations.⁵⁷

Glucagonoma Syndrome

Description

Glucagonoma syndrome is associated with neoplastic proliferation of the glucagon-secreting alpha cell of the pancreas.^{58,59} The characteristic cutaneous eruption, necrolytic migratory erythema, often affects the perioral region and the distal extremities, but may also occur on the abdomen, perineum, thighs, and buttocks, as well as in the groin. Patches of intense erythema with irregular outlines expand and coalesce to result in circinate or polycyclic configurations (Fig. 14). Fragile superficial vesicles on the skin surface rupture quickly to form crusts, although new vesicles may continue to develop along the active margins. The skin may be very dry and fissured. Pressure or trauma may initiate or aggravate the eruption, which appears to share features of staphylococcal scalded skin syndrome and the zinc-deficiency disorder acrodermatitis enteropathica. However, unlike the lat-

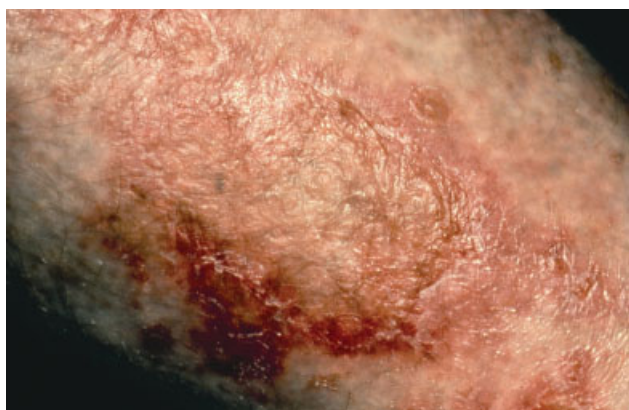


FIGURE 14. Glucagonoma Syndrome: Necrolytic Migratory Erythema.

ter disorder, patients with necrolytic migratory erythema have normal zinc levels and zinc treatment is ineffective. The cause of necrolytic migratory erythema is uncertain, and the various theories that have been advanced to explain its pathogenesis, such as zinc or fatty acid deficiency and decreased cutaneous tryptophan levels (all of which have been associated with hyperglucagonemia), remain unproven. Anemia, diabetes, weight loss, abdominal pain, diarrhea, venous thromboses, alopecia, and stomatitis may complicate the clinical picture.

What's new

A recent study found that somatostatin receptor scintigraphy is positive in 95% of glucagonomas.⁶⁰ The somatostatin analogue octreotide inhibits glucagon production and may help relieve clinical signs and symptoms in some patients. It does not, however, appear to inhibit tumor growth.

Patient management

Complete surgical resection is the only curative treatment for the tumor because chemotherapy yields only modest benefit.⁶¹ Prophylactic measures to prevent venous thromboses should be considered, especially in the postoperative period. Early tumor recognition, before metastasis occurs, is associated with enhanced survival.⁵⁹

Proliferative and Inflammatory Dermatoses

Many of the conditions to be discussed in this section are nonspecific and have been reported both in association with and in the absence of underlying malignant disease. Thus, a diagnosis of any of these conditions mandates a complete physical examination but in no way guarantees that a tumor will be found. Malignancy is most often only one of several possible provoking factors.

Acquired Hypertrichosis Lanuginosa

Definition

Acquired hypertrichosis lanuginosa (malignant down) describes the extensive growth of silky, non-pigmented lanugo hair on the face, neck, trunk, and sometimes the extremities, particularly in sites previously perceived as hairless by the patient (Fig. 15). A painful glossitis, angular cheilitis, and swollen red fungiform papillae on the anterior half of the tongue



FIGURE 15. Acquired Hypertrichosis Lanuginosa: Lanugo Hair.

may accompany the cutaneous changes. Women are affected more often than men. The hypertrichosis usually antedates discovery of the malignancy, and its association with cancer is among the most consistent of the conditions discussed in this section.^{62,63} The tumors associated with acquired hypertrichosis lanuginosa are often adenocarcinomas and frequently occur in the gastrointestinal tract; however, lung cancer appears to be especially common in males. Tumors have been reported at multiple other sites as well. No specific hormonal or biochemical abnormalities have been identified to date.

What's new

The appearance of acquired hypertrichosis lanuginosa also may be a harbinger of tumor metastasis.

Patient management

The fine, silky hair of acquired hypertrichosis lanuginosa must be differentiated from the coarse terminal hairs often noted on the face of postmenopausal and dark-skinned women. Underlying metabolic and endocrine disorders, including conditions such as porphyria cutanea tarda, and the use of certain drugs must be excluded. A complete gastrointestinal workup as well as chest evaluation and mammography are mandatory.

Acanthosis Nigricans

Description

Acanthosis nigricans is perhaps the best known of the cutaneous markers of internal malignancy.⁶⁴ The term is purely descriptive because neither melanocyte proliferation nor hyperpigmentation can be appreciated histologically. Affected skin has a hyperpig-

mented, velvety appearance and in severe cases can become quite verrucous. Flexural areas, especially the axillae, groin, and neck, are most often involved (Fig. 16). Papillomatous changes may be noted in the oral cavity, and hyperkeratosis in a wrinkled or ridged pattern may develop on the palms (tripe palms; see below) and the dorsal surfaces of large joints.^{65,66} The cutaneous changes can occur before, coincident with, or after the discovery of an underlying malignancy, which most often is an adenocarcinoma of the stomach. Tumors may be found in other organs within the abdominal cavity as well, with more than 95% being adenocarcinomas.

What's new

Epidermal growth factors related to the underlying tumor have been proposed as a pathogenetic mechanism for acanthosis nigricans associated with malignancy, although none have been definitively identified.^{67,68}

Patient management

Acanthosis nigricans commonly occurs in obese persons, especially dark-skinned teenagers, in association with insulin resistance and other endocrinopathies, and after the ingestion of certain drugs. Therefore, a detailed medical history must be included in the evaluation of all affected patients.^{69,70} The possibility of an underlying cancer should be strongly considered in any nonobese adult with rapidly developing acanthosis nigricans in the absence of a recognizable endocrinopathy. In such an individual, an extensive gastrointestinal evaluation is mandatory.



FIGURE 16. Acanthosis Nigricans: Hyperpigmentation With Velvety Surface. Courtesy of Frederic Stearns, MD, Tulsa, Oklahoma. Reprinted with permission from Thiers BH. Dermatologic manifestations of internal cancer. *CA Cancer J Clin.* 1986;36:130-148.

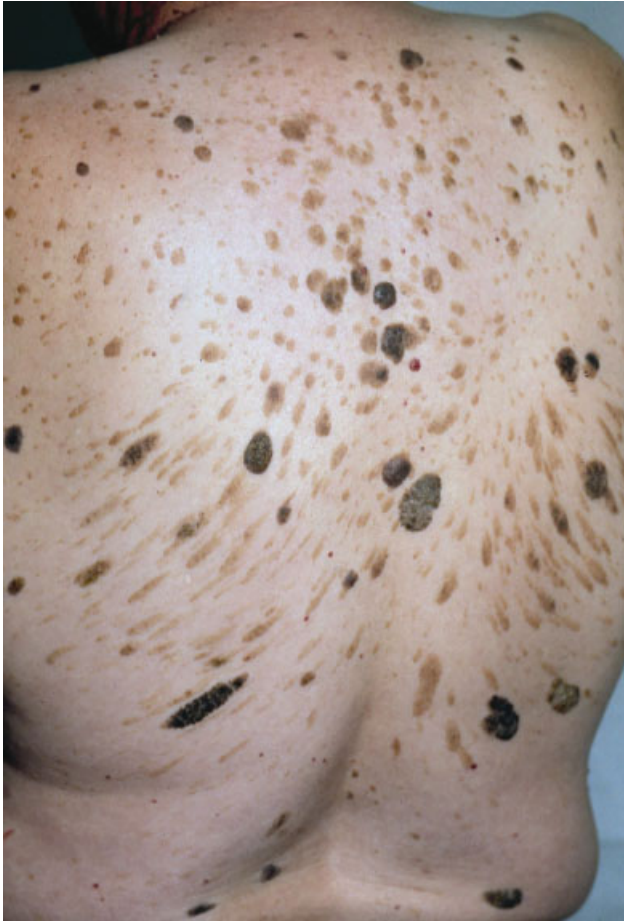


FIGURE 17. Sign of Leser-Trelat: Eruptive Seborrheic Keratoses.

Sign of Leser-Trelat

Description

The sign of Leser-Trelat describes the sudden appearance and/or rapid increase in size of multiple seborrheic keratoses, most often in association with carcinoma of the gastrointestinal tract (Fig. 17).⁷¹ Many of these patients have coexistent acanthosis nigricans, and some clinicians believe that this condition may represent a generalized variant of that disorder. Because the number of seborrheic keratoses and the incidence of malignancy increase with age, the classification of the sign of Leser-Trelat as a paraneoplastic dermatosis has been disputed.

What's new

As with acanthosis nigricans, epidermal growth factors related to the underlying tumor have been proposed as a pathogenetic mechanism.⁶⁸

Patient management

In addition to adenocarcinoma of the gastrointestinal tract, tumors of the female reproductive system and

lymphoproliferative disorders have been associated with the sign of Leser-Trelat. Affected patients should be investigated accordingly.

Tripe Palms

Definition

Tripe palms refer to a wrinkled or ridged appearance of palmar skin; the soles may occasionally be involved as well (Fig. 18). Patients often have associated acanthosis nigricans and occasionally the sign of Leser-Trelat, suggesting that the 3 conditions may be related.

What's new

As with many of the conditions discussed earlier, circulating epidermal growth factors are believed to play a role in pathogenesis.⁶⁸

Patient management

Patients with tripe palms and acanthosis nigricans should be investigated for adenocarcinoma of the gastrointestinal tract. When tripe palms occur in the absence of acanthosis nigricans, squamous cell carcinoma of the lung should be suspected.

Bazex Syndrome (Acrokeratosis Paraneoplastica)

Description

Bazex syndrome (acrokeratosis paraneoplastica) manifests as an erythematous to violaceous psoriasis-like eruption that occurs primarily on acral surfaces (Fig. 19).⁷²⁻⁷⁴ The ears, nose, cheeks, hands, feet, and knees are most often affected. With time, the palms



FIGURE 18. Tripe Palms: Rugose Changes on Palms. Image courtesy of Jonathan A. Dyer, MD, Columbia, Missouri.



FIGURE 19. Bazex Syndrome (Acrokeratosis Paraneoplastica): Acral Psoriasisiform Changes.

and soles may develop a keratoderma and the nails may become dystrophic. The disorder is associated primarily with carcinomas of the upper respiratory and digestive tracts (larynx, pharynx, trachea, bronchus, and/or upper esophagus) and the malignancy is often detected concurrent with the cutaneous findings. Metastasis to the cervical lymph nodes appears to be particularly common in patients with Bazex syndrome.

What's new

The diagnosis of Bazex syndrome does not preclude an associated tumor in an “atypical” location such as the genitourinary or lower digestive tract. The pathogenesis of the condition is unknown but, as with acanthosis nigricans, epidermal growth factors secreted by the tumor may play a pathogenetic role.⁶⁸

Patient management

There is no known effective treatment for the eruption, although topical corticosteroids and keratolytic agents may provide some relief. If the malignancy is effectively treated, the skin changes often resolve but may recur with tumor recurrence.

Primary Systemic Amyloidosis

Description

Amyloidosis historically has been classified into primary amyloidosis, which is intended to include idiopathic and myeloma-associated amyloidosis, and secondary amyloidosis, which occurs in association with underlying chronic inflammatory disorders. Although the current classification system based on the biochemical composition of the deposited amyloid

fibril protein is now more widely used, the older system appears to be better suited for understanding associated skin involvement. In primary systemic amyloidosis, involved skin may take on a generalized waxy appearance and bleed easily when traumatized (“pinch purpura”). Hemorrhagic lesions are especially common around the eyes (Fig. 20). Macroglossia is an associated finding. The disease carries a poor prognosis, with the most common causes of mortality being cardiac or renal failure.⁷⁵ Skin lesions do not occur in patients with secondary amyloidosis.

What's new

Although traditional chemotherapy including oral melphalan and systemic steroids has been used in the past, newer therapies have been proposed. These may directly target amyloid polymerization (eg, eprosi-date) or any underlying plasma cell dyscrasia (eg, bortezomib, lenalidomide). High-dose chemotherapy with hematopoietic stem cell transplantation has also been proposed.^{75,76}

Patient management

The cutaneous changes should not be confused with so-called “senile” purpura, which is observed on the arms of elderly persons, persons with severely photodamaged skin, or those receiving chronic anticoagulant or corticosteroid therapy. In patients with the typical clinical and histologic findings (demonstrat-

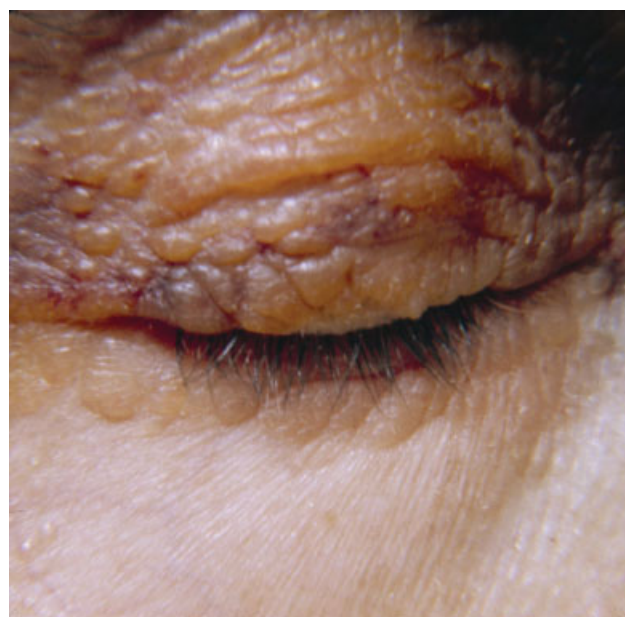


FIGURE 20. Primary Systemic Amyloidosis: Periocular Waxy Papules With Hemorrhage. Reprinted with permission from Thiers BH. Dermatologic manifestations of internal cancer. *CA Cancer J Clin.* 1986;36:130-148.



FIGURE 21. Scleromyxedema: Lichenoid Papules.

ing amyloid deposits in the papillary dermis), there is almost always an underlying plasma cell dyscrasia, which may range from a low-grade monoclonal gammopathy to overt myeloma.⁷⁷

Scleromyxedema

Description

Scleromyxedema is a cutaneous mucinosis representing the generalized variant of lichen myxedematosus. It has been associated with a peculiar serum monoclonal immunoglobulin (Ig) G paraprotein that almost always possesses light chains of the lambda type.⁷⁸⁻⁸⁰ Clinically, the lichen myxedematosus variant appears as a generalized eruption of 2-mm to 3-mm waxy lichenoid (flat-topped) papules, often in a linear arrangement; lesions are most common on the hands, elbows, forearms, upper trunk, face, and neck, but may be found anywhere (Fig. 21). In the scleromyxedema variant, the lichenoid lesions coalesce, leading to induration of the underlying tissue and a resemblance to scleroderma. Longitudinal furrowing somewhat reminiscent of leonine facies may result from involvement of forehead skin. Histologic examination of involved skin demonstrates fibroblast proliferation, fibrosis, and dermal deposition of mucin. There is no amyloid deposition as might be expected given the associated paraproteinemia. The relation between the paraprotein, the fibrosis, and the mucin deposition is unknown. No correlation appears to exist between levels of the paraprotein and the extent or progression of the skin disease. Overt myeloma or a detectable plasma cell dyscrasia develops in only a minority of patients with scleromyxedema, lichen myxedematosus, or papular mucinosis.

What's new

The use of autologous stem cell transplantation was reported to be beneficial in some published case reports and case series, but more data are needed before a definitive assessment of its utility can be made.⁸¹ Although anecdotal reports attest to the efficacy of melphalan, thalidomide, and intravenous Ig, the skin disease is characteristically quite resistant to therapy.

Patient management

Affected patients should undergo a serum protein electrophoresis, immunofixation electrophoresis, and measurement of Ig levels, with these tests repeated every 6 months.

Sweet Syndrome (Acute Febrile Neutrophilic Dermatitis)

Description

Sweet syndrome (acute febrile neutrophilic dermatosis) describes the acute onset of erythematous, tender papules, plaques, or nodules on the face, extremities, and upper trunk (Fig. 22).⁸² The surface appears vesicular and may be studded with pustules. In some patients, the lesions bear some clinical resemblance to pyoderma gangrenosum, and a link between the 2 conditions has been postulated. Fever, malaise, and neutrophilia often accompany the cutaneous eruption. Biopsy of a skin lesion demonstrates a dense dermal neutrophilic infiltrate. There is typically no vasculitis, although some vascular inflammation may be detected.

Sweet syndrome has been described in 3 clinical settings: 1) a classical or idiopathic variant, which



FIGURE 22. Sweet Syndrome (Acute Febrile Neutrophilic Dermatitis): Juicy Papules and Plaques With Central Ulceration Resembling Pyoderma Gangrenosum.



FIGURE 23. Classical Pyoderma Gangrenosum: Blue Overhanging Border With Central Ulceration.

may be associated with inflammatory bowel disease or a preceding upper respiratory tract infection; 2) in association with malignancy; and 3) after the administration of certain drugs, most notably granulocyte-colony-stimulating factor. Malignancy-associated Sweet syndrome occurs in individuals with a hematologic dyscrasia, most commonly acute myelogenous leukemia, and less often in individuals with solid tumors. The presence of moderate to severe anemia may be helpful in distinguishing Sweet syndrome that is associated with myeloproliferative disease from the idiopathic variant.

What's new

Clonality has been described in the neutrophilic infiltrate in patients with Sweet syndrome, although this does not appear to be limited to individuals with underlying myeloproliferative disease.⁸³ Indeed, clonality has been demonstrated in a variety of cutaneous inflammatory infiltrates associated with presumably benign conditions.

Patient management

The skin condition generally responds to treatment with oral corticosteroids. Other systemic agents that have been used include oral potassium iodide, colchicine, and dapsone. High-potency topical steroids or intralesional steroids may aid in the control of individual lesions.

Pyoderma Gangrenosum

Description

Pyoderma gangrenosum is a neutrophilic ulcerative dermatosis. Its classical form occurs most commonly on the extremities and is often associated with in-

flammatory bowel disease or inflammatory arthritis, although it may be idiopathic (Fig. 23).⁸⁴ Lesions appear as purulent ulcers, often with cyanotic overhanging borders. Occasionally, classical pyoderma gangrenosum has been associated with a monoclonal gammopathy (and occasionally myeloma), with several solid tumors, and with non-Hodgkin lymphoma. The gammopathy, which has been noted in up to 20% of patients with pyoderma gangrenosum, results from an IgA paraprotein. However, a parallel course is not characteristic in patients with coexistent pyoderma gangrenosum and IgA paraproteinemia or myeloma.

The superficial form of pyoderma gangrenosum, known as atypical or bullous pyoderma gangrenosum, usually occurs on the head and neck, and has been associated with hematologic malignancy (Fig. 24).^{84,85} Lesions tend to be more superficial than in the classical form of the disease. Most often, the association is with acute myelogenous leukemia, but several cases of chronic myelogenous leukemia, acute lymphoblastic leukemia, and preleukemic states such as myelofibrosis or agnogenic myeloid metaplasia have also been reported. The skin and blood disease often present concurrently and run a parallel course.

What's new

Although pyoderma gangrenosum is most often managed with oral corticosteroids, dapsone, and other immunosuppressive agents, the recent develop-



FIGURE 24. Atypical Pyoderma Gangrenosum: Superficial, Purulent, Ulcerated Plaque.

ment of anti-tumor necrosis factor- α (TNF- α) drugs has allowed for a more targeted therapeutic approach. Whether these agents are superior to traditional treatment remains uncertain.⁸⁶

Patient management

Topical or intralesional steroids may be helpful for individual lesions in patients with limited disease. Systemic corticosteroids remain the first-line treatment, often in conjunction with steroid-sparing agents such as dapsone or other immunosuppressive drugs. Meticulous wound care is necessary to minimize tissue loss. Necrotic tissue can be gently removed, but aggressive surgical debridement can cause enlargement of the ulcer and should be avoided. Antibiotics are ineffective in patients with pyoderma gangrenosum but may be useful for treating secondary infections.

Any patient with unexplained pyoderma gangrenosum needs evaluation for occult lymphoproliferative disease or blood dyscrasia.

Blistering Disorders

Description

Several blistering disorders have been reported in patients with underlying neoplasia. As suggested by its name, the association of paraneoplastic pemphigus (PNP) with cancer, especially lymphoreticular malignancy, is the most consistent.⁸⁷⁻⁹⁰ PNP is a life-threatening autoimmune skin disease characterized by severe mucosal erosions and cutaneous blisters and erosions (Fig. 25). Castleman tumor, non-Hodgkin lymphoma, thymoma, follicular dendritic cell sarcoma, and chronic



FIGURE 25. Paraneoplastic Pemphigus: Oral Erosions. Courtesy of Ross Pollack, MD, Charleston, South Carolina.

lymphocytic leukemia are commonly associated neoplasms.⁸⁷⁻⁹⁰ Autoantibodies that cross-react with epidermal proteins are believed to be evoked by antigens released by the underlying tumors. Various other forms of pemphigus also have been observed in patients with thymoma. The proposed association between bullous pemphigoid and malignancy most likely reflects the tendency of both of these conditions to occur in the elderly; whether any true correlation exists is uncertain. The antiepiligrin variant of cicatricial pemphigoid, an autoimmune disease characterized by antibodies against the epidermal basement membrane, has in particular been associated with an increased incidence of malignancy, especially adenocarcinomas.^{91,92} Dermatitis herpetiformis is a highly pruritic dermatosis that frequently is associated with a gluten-sensitive enteropathy. The cutaneous symptoms improve with gluten withdrawal. Affected individuals appear to have an increased relative risk of intestinal lymphoma, as has been observed in patients with celiac sprue.⁹³ Very rarely, epidermolysis bullosa acquisita, an autoimmune disease characterized by antibodies against type VII collagen (the major component of the anchoring fibrils that connect the basement membrane to the dermis), has been reported in patients with lymphoreticular tumors.

What's new

A gluten-free diet may have a preventative benefit on the development of intestinal lymphoma in patients with dermatitis herpetiformis.

Patient management

The treatment of patients with PNP and antiepiligrin cicatricial pemphigoid is based on early detection and removal of the tumor. Systemic corticosteroids and other immunosuppressive agents are often beneficial. Intravenous administration of rituximab and intravenous Ig may be worthwhile therapeutic adjuncts for patients with PNP.^{94,95} A gluten-free diet is advised for patients with dermatitis herpetiformis but dapsone is usually needed for adequate control.

Dermatomyositis

Description

Pathognomonic clinical manifestations of dermatomyositis include an edematous, violaceous eruption of the upper eyelids (heliotrope rash) and atrophic



FIGURE 26. Dermatomyositis: Gottron Papules, Periungual Telangiectasia. Courtesy of William James, MD, Philadelphia, Pennsylvania.

scaly papules over bony prominences (Gottron papules) (Fig. 26). Photosensitivity, malar erythema, scalp inflammation, poikiloderma, and periungual telangiectasia are significant, although less specific, findings.⁹⁶ Associated symptoms that suggest muscle involvement include proximal muscle weakness, manifested as difficulty arising from a chair, climbing stairs, or lifting, and problems with swallowing. Some patients also report muscle tenderness.

Approximately 10% to 30% of adult patients with dermatomyositis have an associated malignancy, which may occur before, during, or after the diagnosis of dermatomyositis.⁹⁷⁻¹⁰⁰ An awareness of this potential should alert the physician to carefully evaluate all dermatomyositis patients for malignancy. Raynaud phenomenon or sclerodermatous changes in an adult with dermatomyositis suggest an overlap syndrome; this variant is only rarely associated with malignant disease. Childhood dermatomyositis is not associated with malignancy.

What's new

The pathophysiologic processes that lead to dermatomyositis in patients with an underlying malignancy are uncertain. In contrast to patients with idiopathic disease, patients with tumor-associated myositis tend to require other immunosuppressive drugs in addition to glucocorticoids for control.

Patient management

Patients require close, age-appropriate monitoring to assess the possibility of an underlying malignancy. The disease is not specific to any particular site or cell type of cancer. However, compared with the general population, ovarian and breast carcinoma in women and lung and prostate carcinoma in men are highly associated with dermatomyositis and its related condition, polymyositis, which lacks cutaneous manifestations.⁹⁷⁻¹⁰⁰ Other tumors have been reported as well. The association with malignancy is stronger for dermatomyositis than for polymyositis. The risk of finding an underlying malignancy is highest within the first year after the diagnosis of either condition and then drops substantially afterward. For patients with polymyositis, the risk falls to expected rates 5 years after diagnosis, whereas the risk for patients with dermatomyositis does not return to expected population values for most cancers.⁹⁷⁻¹⁰⁰ Successful treatment of the malignancy generally improves the associated skin and muscle disease.

Clubbing and Related Disorders

Description

Several musculoskeletal disorders have been reported in patients with cancer. Clubbing can be observed in approximately 10% of individuals with lung cancer and tumors metastatic to the lung (Fig. 27).^{101,102} Hypertrophic osteoarthropathy, a manifestation of subperiosteal new bone formation in patients with clubbing, occurs most commonly along the shaft of the phalanges but may affect other bones as well.¹⁰³ Joint swelling, synovitis, periarticular swelling, hyperhidrosis, and palmar erythema may be pronounced and create a picture similar to that of early rheumatoid arthritis. Pachydermoperiostosis, which describes the association between hypertrophic osteoarthropathy and acromegaloid features, can occur either in association with lung cancer or as a genetic disease unassociated with malignancy.



FIGURE 27. Clubbing: Loss of Angle between Nail and Posterior Nail Fold.

What's new

Other causes of clubbing such as thyroid acropachy (a manifestation of autoimmune thyroid disease) should be considered in the differential diagnosis.¹⁰⁴

Patient management

Because clubbing and related conditions may have predictive value in the diagnosis of lung cancer, any patient with unexplained changes requires a complete pulmonary evaluation.¹⁰² A pituitary tumor needs to be ruled out in patients with acromegaly features.

Cutaneous Leukocytoclastic Vasculitis

Description

Cutaneous leukocytoclastic vasculitis presents as palpable purpura (Fig. 28). It is most commonly observed on the legs but can occur anywhere. To our knowledge, an association between it and cancer has never been proven, although numerous individual case reports have correlated various vasculitic syndromes with malignancy, including solid tumors and lymphoproliferative disorders.¹⁰⁵ Often, the patient with coexistent neoplastic disease has the malignancy at the time of diagnosis of the vasculitis. In such patients, cutaneous leukocytoclastic vasculitis presumably is initiated by the release of tumor antigens into the circulation, especially after radiotherapy or chemotherapy. Immune complexes are formed that lodge in the small vessels of the skin. Complement fixation and the ensuing inflammatory reaction lead to the characteristic clinical signs and symptoms.

What's new

The nature of the underlying malignancy often affects the clinical presentation. Vasculitis occurring in association with myelodysplastic syndromes tends to

be more severe and recalcitrant to therapy than vasculitis associated with other malignancies. These patients tend to be more steroid-dependent, and have a higher incidence of renal involvement and a lower rate of remission. Renal involvement is less common in patients with lymphoid malignancy. Peripheral neurologic involvement characterizes patients with solid tumors. A parallel course between the tumor and the vasculitis has been noted only rarely.

Patient management

Vasculitis as a sign of underlying malignancy is the exception rather than the rule. Although an extensive evaluation is usually not required, patients with chronic or recurrent vasculitis should undergo an age-appropriate evaluation to rule out the possibility of an associated neoplastic process.

Coagulopathies

Description

Coagulopathies may cause extensive areas of purpura, which may be figurate, linear, or diffuse, depending

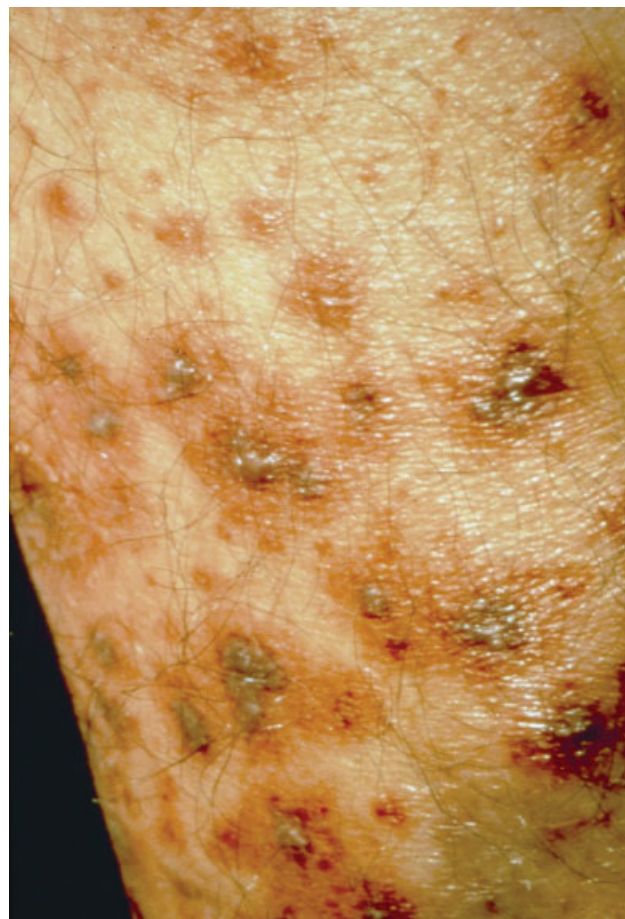


FIGURE 28. Cutaneous Leukocytoclastic Vasculitis: Palpable Purpura.



FIGURE 29. Disseminated Intravascular Coagulation: Large Areas of Cutaneous Hemorrhage. Reprinted with permission from Thiers BH. Dermatologic manifestations of internal cancer. *CA Cancer J Clin.* 1986;36:130-148.

on the underlying hematologic disorder (Fig. 29). In contrast to vasculitis, which results in palpable purpura, the purpura associated with coagulopathies is typically nonpalpable. In some patients with cancer, especially those with leukemia, coagulopathies may represent a paraneoplastic expression of disseminated intravascular coagulation (DIC). Migratory superficial thrombophlebitis and multiple deep venous (and rarely arterial) thromboses (Trousseau syndrome¹⁰⁶) also have been noted in cancer patients, especially those with tumors arising in the pancreas, lung, stomach, prostate, or hematopoietic system.¹⁰⁷ The neck, chest, abdominal wall, pelvis, and limbs are affected most frequently.

What's new

Multiple pathophysiologic mechanisms may play a role, including prothrombotic agents secreted by the tumor, excess thrombin and/or fibrin production, or a microangiopathy (most often in patients with mucin-producing carcinomas).

Patient management

The treatment and elimination of the underlying cause of the coagulopathy is the key to long-term control. Other causes of hypercoagulability must be ruled out, including septicemia, an obstetrical crisis, or a connective tissue disease with associated antiphospholipid antibodies. The short-term management of DIC involves a delicate balance between the replacement of blood clotting factors to control hemorrhage and the administration of heparin to prevent thrombosis. For patients with Trousseau syndrome, heparin administration appears to be the treatment of choice, although warfarin is ineffective.¹⁰⁶

Figurate Erythemas

Description

The figurate erythemas are characterized by annular or serpiginous erythematous papules or plaques that spread peripherally. They may be divided into at least 3 groups. Erythema chronicum migrans follows a tick bite and may be associated with Lyme disease. Erythema annulare centrifugum may be secondary to a variety of causative factors including, rarely, malignancy. Erythema gyratum repens is the figurate erythema most consistently associated with cancer.¹⁰⁸ No one tumor type or site appears to predominate. Multiple wavy urticarial bands with fine scales migrate over the cutaneous surface, leaving an appearance similar to the grain of wood (Fig. 30). The eruption typically occurs within a few months before or after the diagnosis of cancer.

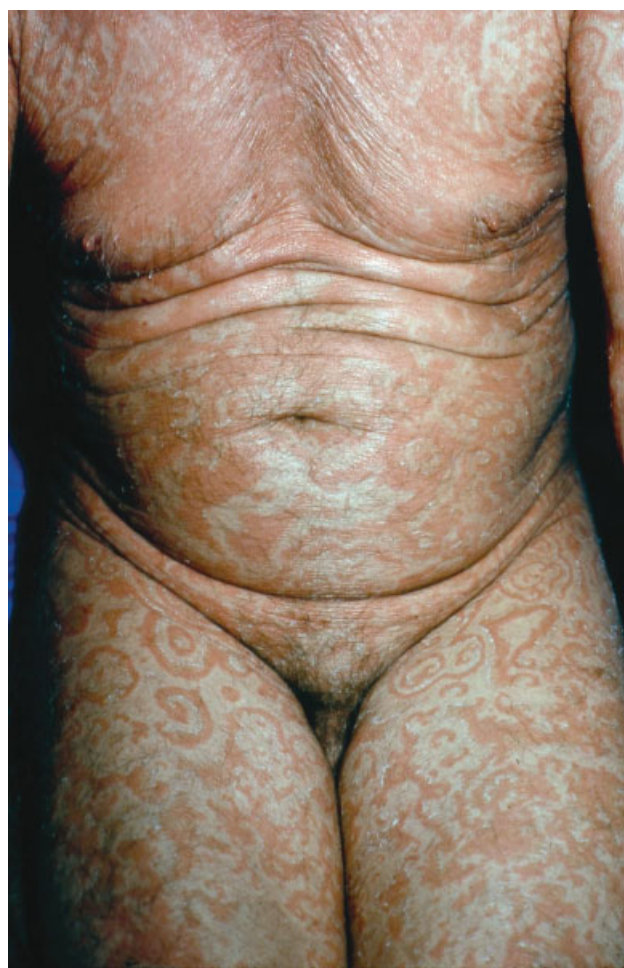


FIGURE 30. Erythema Gyratum Repens: Wavy Urticarial Bands Resembling the Grain of Wood. Courtesy of Donald Lookingbill, MD, Jacksonville, Florida.



FIGURE 31. Extramammary Paget Disease: Perianal Erosions.

What's new

An eruption resembling erythema gyratum repens can occur in patients with subacute lupus erythematosus or other non-neoplastic conditions.

Patient management

The treatment of erythema gyratum repens involves elimination of the causative tumor. Systemic steroids are sometimes useful.

Extramammary Paget disease

Description

Extramammary Paget disease manifests as an erythematous plaque in locations other than the breast, most often on the inguinal fold, vulva, or scrotum (Fig. 31). Underlying malignancy, often near the cutaneous lesion but not necessarily contiguous with it, is more common in these patients than in age-matched controls.

What's new

Sentinel lymph node biopsy has been used safely and reliably to identify occult lymph node metastasis in patients with clinically negative lymph nodes.¹⁰⁹

However, more data are needed to determine its role in improving prognosis.

Patient management

Patients with extramammary Paget disease should be evaluated for possible tumors in the lower gastrointestinal tract (colon and rectum) and in the lower portion of the genitourinary tract (bladder and prostate). A carefully performed complete skin examination, mammography, colonoscopy, cystoscopy, and abdominal CT examination are recommended.¹¹⁰

Infectious Disorders

Description

Infectious disorders are frequent in cancer patients and may either be directly related to depressed immunity associated with the neoplasm or secondary to pharmacologic immunosuppression. Candidiasis, especially the oral variant, may be an early sign of depressed cell-mediated immunity associated with lymphoproliferative disease, human immunodeficiency virus infection, or diabetes mellitus (Fig. 32). The increased incidence of herpes zoster, either localized or disseminated, in patients with leukemia and lymphoma has been appreciated for years, although such infection usually develops during the course of the illness rather than as a presenting sign (Fig. 33).¹¹¹ Rarely, herpes zoster may be associated with an underlying carcinoma.

What's new

The consequences of infections, especially viral infections, in immunosuppressed individuals may extend beyond the short term. Specifically, the interrelation between immune dysfunction, viral



FIGURE 32. Oral Candidiasis: Cheesy Exudate on Tongue. Reprinted with permission from Thiers BH. Dermatologic manifestations of internal cancer. *CA Cancer J Clin.* 1986;36:130-148.



FIGURE 33. Herpes Zoster: Linear Eruption of Grouped Vesicles on Erythematous Base. Courtesy of Joseph Bikowski, MD, Sewickley, Pennsylvania.

infection, and carcinogenesis has been the subject of intense investigation. HPV infection may play a key role in the development of cutaneous squamous cell carcinoma in immunosuppressed patients.¹¹² A new polyomavirus has been detected that is integrated into the host cell genome in patients with the rare Merkel cell carcinoma, whose incidence is reported to be increased in the elderly and the immunosuppressed.¹¹³ Human herpesvirus-8 infection leads to the development of Kaposi sarcoma.¹¹⁴

Patient management

Transplant patients who are iatrogenically immunosuppressed should receive the least aggressive drug regimen needed to permit graft survival.

Generalized Pruritus, Ichthyosis, and Exfoliative Dermatitis

Description

Generalized pruritus, ichthyosis (noninflamed dry scaly skin), and exfoliative dermatitis (inflamed dry scaly skin) are nonspecific features of lymphoproliferative disorders (Fig. 34);¹¹⁵ their association with solid tumors is uncommon. Pityriasis rotunda may be a variant of acquired ichthyosis. The eruption consists of geometrically perfect, circular patches of scales. The disease was first reported in the Japanese, South African blacks, and West Indian blacks, in whom an associated neoplasm was occasionally described.¹¹⁶ A familial variant has been recognized in Europe that does not appear to be associated with cancer.¹¹⁷

What's new

Hypovitaminosis A (because of malabsorption), decreased dermal lipogenesis, and tumor secretion of

epidermal growth factors have all been postulated to play a pathogenetic role in these conditions.

Patient management

Although the exact status of these entities as paraneoplastic conditions remains to be delineated, it appears prudent to rule out concurrent malignancy in affected patients.

Pigmentary Disorders

Description

Hyperpigmentation or, less commonly, hypopigmentation of the skin may be a sign of internal malignancy. The pigmentary changes may be idiopathic or related to the pharmacologic activity of a substance produced by the tumor. For example, as already noted, ectopic ACTH production may stimulate cutaneous melanocytes, resulting in diffuse hyperpigmentation (Fig. 12). Diffuse hyperpigmentation may also occur in hemochromatosis, a condition that predisposes to liver cancer, and in widely metastatic



FIGURE 34. Acquired Ichthyosis: Dry Scaly Skin in a Patient with Hodgkin Disease. Courtesy of Donald Lookingbill, MD, Jacksonville, Florida.

melanoma. Interestingly, vitiliginous depigmentation can also be observed in patients with melanoma. Diffuse cutaneous and mucosal hyperpigmentation may also occur in the Cronkhite-Canada syndrome (see below).

What's new

The pathogenesis of the hyperpigmentation associated with ACTH-secreting tumors has already been discussed. The depigmentation occasionally associated with melanoma is presumed to result from an immune response directed against melanocytes.

Patient management

A complete medical history (including prior use of topical and systemic drugs) is necessary to elucidate the likely cause of the pigmentary changes. Endocrinologic and gastroenterologic consultation should be requested if diseases specific to these organ systems are suspected.

Miscellaneous Skin, Hair, and Nail Disorders

Description

Patients with Cronkhite-Canada syndrome exhibit diffuse cutaneous and, rarely, mucosal hyperpigmentation. Other cutaneous features include dystrophic nails and alopecia. Hamartomatous polyps occur throughout the stomach and intestines, and the incidence of gastrointestinal cancer is approximately 15%. The disease occurs in adults in a sporadic, nongenetic manner. The prognosis is poor because of the potential for life-threatening complications including malnutrition, gastrointestinal bleeding, and infection.¹¹⁸

An acquired form of tylosis (palmoplantar keratoderma) has been observed in patients with sporadic esophageal cancer (in addition to the Howel-Evans variant noted earlier), as well as in patients with Sezary syndrome.

What's new

Despite its classification as a nonhereditary polyposis syndrome, overlap has been proposed between Cronkhite-Canada syndrome and Peutz-Jeghers syn-

drome.¹¹⁹ The gene for the syndrome of tylosis associated with sporadic squamous cell carcinoma of the esophagus has been mapped to the *TOC* locus on chromosome 17q25, the same region associated with the familial variant of this condition.¹²⁰

Patient management

Symptoms associated with the polypoid lesions of Cronkhite-Canada syndrome occasionally can be reversed with medical treatment. Proposed approaches include systemic corticosteroids (to reduce gastrointestinal inflammation), nutritional supplementation (including fluids to correct electrolyte imbalance), transfusions (to correct anemia), antibiotics, and H₂ blockers.¹²¹ Patients with this condition and patients with acquired tylosis require close follow-up to monitor for the development of gastrointestinal malignancies.

Conclusions

A complete skin assessment should be part of every physical examination because it may provide useful information regarding the patient's overall health. The skin examination can reveal signs of a predisposition toward malignancy and can yield valuable early clues suggesting an underlying neoplastic process. Although the molecular basis of the association between the skin changes and internal cancer is often unclear, recognition of these cutaneous signs and symptoms should alert the clinician to initiate appropriate diagnostic measures. A multidisciplinary approach involving the dermatologist, oncologist, radiologist, geneticist, and other specialties will assure optimal patient care and, when indicated, the necessary counseling and screening to encourage the prompt implementation of preventive measures.

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