Seminars in Oncology ▮ (2016) ▮▮▮–▮▮▮

Contents lists available at ScienceDirect

Seminars in Oncology

journal homepage: www.elsevier.com/locate/ysonc

Cutaneous manifestations of lung cancer

Cindy England Owen*

University of Louisville, Division of Dermatology, Louisville, KY

ARTICLE INFO

Keywords:
Lung cancer
Ectopic ACTH syndrome
Bronchial carcinoid variant syndrome
Hypertrophic osteoarthropathy
Acrokeratosis paraneoplastica

ABSTRACT

Skin findings can serve as a clue to internal disease. In this article, cutaneous manifestations of underlying lung malignancy are reviewed. Paraneoplastic dermatoses are rare, but when recognized early, can lead to early diagnosis of an underlying neoplasm. Malignancy-associated dermatoses comprise a broad group of hyperproliferative and inflammatory disorders, disorders caused by tumor production of hormonal or metabolic factors, autoimmune connective tissue diseases, among others. In this review, paraneoplastic syndromes associated with lung malignancy are discussed, including ectopic ACTH syndrome, bronchial carcinoid variant syndrome, secondary hypertrophic osteoarthropathy/digital clubbing, erythema gyratum repens, malignant acanthosis nigricans, sign of Leser-Trélat, tripe palms, hypertrichosis lanuginosa, acrokeratosis paraneoplastica, and dermatomyositis.

Skin findings may be the first sign of internal malignancy and are important to recognize. Rarely, direct extension into or metastatic infiltration of the skin by malignant cells can occur and serve as a sign of internal malignancy. Skin metastases are diagnosed prior to or at the same time as the internal malignancy in up to one third of cases. Lung cancer is the most common internal malignancy to metastasize to the skin in men over 40, and the third most common (after breast and colon cancer) in women over 40 [1]. Skin metastases may present as papules, plaques, nodules, or ulcers and often herald a poor prognosis.

Paraneoplastic dermatoses are skin disorders that occur in association with malignancy. Some paraneoplastic skin findings are the result of ectopic humoral syndromes, caused by hormone-secreting tumors. However, many paraneoplastic disorders are inflammatory or proliferative skin conditions that can also occur in the absence of associated malignancy. A dermatosis can be considered paraneoplastic if it follows a parallel course with the associated malignancy, for example [2].

1. Ectopic ACTH syndrome

Patients with adrenocorticotrophic hormone (ACTH)-secreting tumors have high levels of circulating corticotropin and cortisol levels but rarely present with the classic signs of Cushing syndrome, which is likely due to the more acute course of ectopic ACTH syndrome. One finding that is more common in paraneoplastic ectopic ACTH syndrome is dramatic hyperpigmentation of the skin. This finding is present in less than 10% of cases of Cushing syndrome and should alert the clinician to the possibility of ectopic ACTH production by a malignancy [3]. The skin hyperpigmentation is likely caused by the release of proopiomelanocortin (POMC), an ACTH precursor peptide that also includes the amino acid sequence for melanocyte-stimulating hormone (MSH) [3]. The excess cortisol can also lead to glucose intolerance, hypertension, and hypokalemic metabolic alkalosis [4]. A myasthenia gravis-like presentation with profound proximal muscle weakness may also be a presenting sign. In longstanding cases of ectopic ACTH syndrome, more typical Cushing syndrome findings can develop including central obesity, atrophic striae (stretch marks), hirsutism, and easy bruising.

The lung is the most likely site to harbor the ACTH-producing tumor. In recent studies, the most common tumor to lead to the ectopic ACTH syndrome is bronchial carcinoid, followed by small cell lung carcinoma, then adenocarcinoma [3,4].

Workup should include a dexamethasone suppression test to help identify if the source of the corticotropin is pituitary or ectopic (a $>50\%$ reduction in basal cortisol is suggestive of Cushing disease, while ectopic ACTH sources are insensitive to exogenous glucocorticoids). Identification of the tumor may be accomplished by conventional lung imaging studies, but in cases of slow growing, small tumors, functional imaging studies may be required. Where possible, tumor removal is curative. In cases where resection is not possible, pharmacologic therapy may be required to control hypercortisolemia, and ectopic ACTH syndrome often responds well to somatostatin analogues [5].

* Corresponding address. University of Louisville, Division of Dermatology, 3810 Springhurst Blvd, Louisville, KY 40241. Tel.: 502-583-1749; fax: 502-329-8184.
E-mail address: ceowen01@louisville.edu

http://dx.doi.org/10.1053/j.seminoncol.2016.02.025
0093-7754/

2. Bronchial carcinoid variant syndrome

Carcinoid tumors originate in the gastrointestinal tract in 64% of cases and in the bronchi or lung in 28%. Bronchial carcinoids comprise about 2% of primary lung tumors. These tumors can lead to ectopic ACTH syndrome but are rarely associated with the carcinoid syndrome [6]. Patients with liver metastases or bronchial carcinoid tumors of large size (>5 cm) are more likely to present with carcinoid syndrome. Classic carcinoid syndrome consists of episodic flushing of the face, neck, and chest lasting from 30 seconds up to 30 minutes, often with associated diarrhea and bronchospasm, thought to be associated with release of serotonin and 5-hydroxytryptophan from the primary tumor [7]. Long-term complications include telangiectasia and valvular heat disease. In bronchial carcinoid tumors, however, the flushing is more severe and prolonged (lasting hours to days) and may be accompanied by anxiety and confusion [7]. Measurement of urinary 5-HIAA may not be useful in bronchial carcinoid, but measurement of urinary serotonin may show elevated levels. Tumor localization can be achieved by imaging (magnetic resonance imaging, computed tomography, or somatostatin receptor scintigraphy).

3. Secondary hypertrophic osteoarthropathy

Digital clubbing and hypertrophic osteoarthropathy (HOA) can be primary or secondary. Primary forms are inherited in an autosomal dominant manner and are not associated with malignancy. Secondary HOA is more common and is associated with pulmonary malignancy or disease, heart disease, endocrine disorders, and other conditions. Lung cancer is the cause in 80% of cases of secondary HOA [8]. Clinical features of HOA include digital clubbing, periostosis of tubular bones, and synovial effusions. Digital clubbing is characterized by an increase in the angle between the nail bed and the proximal nail fold (normally 160 degrees, but increased to >180 degrees in HOA), the so-called "profile sign." Patients often have painful arthropathy as well. Clubbing and secondary HOA due to lung cancer is more common in women than men, and is more likely to be seen in patients with non-small cell lung cancer [9]. It has been shown that increased levels of platelet derived growth factor as well as vascular endothelial growth factors (VEGF) are upregulated in HOA, possibly through a hypoxemic state. Additionally, genetic mutations have been found in both hydroxyprostaglandin dehydrogenase 15-(NAD) and solute carrier organic anion transporter family member 2A1, which leads to increased prostaglandin E_2 and resultant VEGF-induced bony growth [10]. The condition may improve or resolve after resection of the tumor. Treatment with non-steroidal anti-inflammatory medication can relieve symptoms, and bisphosphonates have been reported to be effective [8].

4. Erythema gyratum repens

Erythema gyratum repens (EGR) is a rare paraneoplastic disorder with a dramatic presentation (Fig. 1). Lesions of EGR are pruritic plaques with a serpiginous, polycyclic morphology, said to resemble wood grain. The rash becomes widespread quickly with a progression rate of about 1 cm/d (hence the latin term repens, meaning "to creep"), typically starting on the trunk and spreading to the extremities. Pruritus is severe in EGR and patients often have peripheral eosinophilia. EGR is seen more commonly in men than women (2:1), with a mean age at onset of 63 in men and 56 in women [11]. Malignant neoplasms are discovered in 70% of patients with EGR [11]. Lung cancer is the most common associated malignancy (43%), followed by stomach, esophageal, and

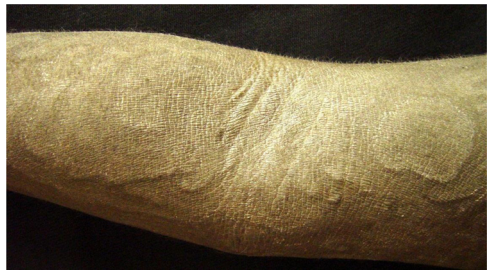

Fig. 1. Erythema gyratum repens—polycyclic annular plaques of the arm resembling wood grain.

breast cancer. EGR precedes the diagnosis of malignancy by a mean of 7 months [11]. Workup for malignancy should be undertaken in all patients with EGR. Mechanisms by which EGR develops are hypothesized to include tumor-generated antigens similar to those found on skin, deposition of immunocomplexes in the skin, and tumor-induced alteration of the skin creating antigenicity [11]. Other associated conditions include tuberculosis, pityriasis rubra pilaris, psoriasis, and connective tissue disease. The condition usually resolves with treatment of the underlying malignancy.

5. Acanthosis nigricans maligna

Acanthosis nigricans (AN) presents with velvety to verrucous, hyperkeratotic plaques in intertriginous areas. The majority of cases of AN are associated with obesity and insulin resistance but the disease can also be sign of internal malignancy. Malignancy-associated AN can be more striking in appearance with widespread or atypical sites of involvement (eg, oral cavity, hands, feet), a rapidly progressive onset, and associated pruritus (Fig. 2) [12]. These features should raise suspicion for underlying malignancy along with older age at onset, lack of underlying insulin resistance, and recent weight loss. Gastric carcinoma is the most frequently associated neoplasm, but lung cancer is also frequently reported [12]. Concurrent onset of multiple skin tags, eruptive seborrheic keratoses (sign of Leser-Trélat), and tripe palms may be noted (see below). It has been proposed that tumor-induced growth factors, such as transforming growth factor-alpha (TGF-α), insulin-like growth factor-1 (IGF-1), and fibroblast growth factor (FGF), may be involved in the development of malignancy-associated AN [13]. Malignant AN can resolve with treatment of underlying malignancy.

6. Tripe palms

Tripe palms (also known as acanthosis palmaris or pachydermatoglyphia) is characterized by velvety thickening of the skin of the palms with a ridged or rugose appearance, said to resemble

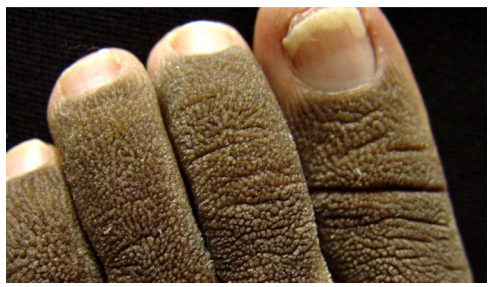

Fig. 2. Malignant acanthosis nigricans—striking hyperpigmented, velvety, filiform plaques of the feet and toes.