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Cutaneous paraneoplastic disorders in stomach cancer: Collaboration between oncologically active dermatologists and clinical oncologists

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ABSTRACT

To our knowledge this is the first systemic review that provides an overview of the cutaneous paraneoplastic syndromes (CPS) (i.e., clinical manifestations, pathomechanisms, and treatment modalities) occurring in stomach cancer. CPS are caused by substances produced by stomach cancer and may precede, coincide with, or follow the diagnosis of this malignancy. More than 20 possible CPS in association with stomach cancer have been identified. CPS mostly compromises the patient's quality of life by skin impairment plus discomfort and are often associated with a dismal prognosis on survival. Studies of these CPS not only in stomach cancer have partially contributed to the understanding of pathomechanism and since CPS may be the presenting sign of an occult cancer, cognizance of their features and clinical implications are of considerable importance. Patients with these syndromes should have an appropriate work-up for a possibly occult malignancy with consecutive successful early treatment.

1. Introduction

Although the incidence of stomach cancer (SC) is declining, more than 100,000 new annual cases are diagnosed in Europe (Keoghley,

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2003). It remains one of the leading causes of cancer-related death and therefore a major health problem (Comella et al., 2009). At the time of diagnosis patients mostly present in advanced stages which explains the poor survival rate. Diverse dermatologic paraneoplastic syndromes predate a diagnosis of SC and thus may aid the physician in the early identification of malignancy. If tumors are detected in earlier stage with rapid curative surgical resection, 5-year survival increases to approximately 60% (Kamangar et al., 2006).

In 1976Curth defined the term paraneoplastic syndrome due to various malignancies (Curth, 1976). CPS are non-contiguous skin and mucous membrane changes caused by processes distant from the primary and/or its metastases. The reason for the appearance of cutaneous manifestations of SC may be the production of biologically active hormones, peptides, growth factors or depletion of substances leading to direct or indirect symptoms and host responses to the malignancy (Thiers et al., 2009; Ehst et al., 2010). Successful treatment of SC often also leads to disappearance of coexistent paraneoplastic dermatoses. To our knowledge, this review is the first to give a systemic overview of published literature concerning CPS in association with SC with special emphasis on underlying pathophysiology, clinical presentation, and treatment options. Many of these CPS were found and described (only in case reports) in other tumor entities (i.e. lung, breast, prostate and ovarian cancer). Therefore, the following CPS are not only specific events in stomach cancer. By a computerized search we cannot identify the following CPS in other GI-cancers especially in colo-rectal cancer.

2. Methods

To identify papers on CPS in SC, a computerized (MEDLINE) as well as a manual search were performed and additional references were extracted from reference lists of published manuscripts. Only articles in English or with an English abstract were included, thus a slight amount of publication bias cannot be excluded. Information abstracted included cutaneous clinical presentation, clinical and/or histological verification of the diagnosis, pathomechanisms and treatment. Searches were last updated in the second quarter of the year 2015 .

3. Results

3.1. Papulosquamous disorders (see also Table 1)

3.1.1. Acanthosis nigricans

Acanthosis nigricans (AN), one of the best defined cutaneous markers of malignancies, typically shows hyperpigmented, roughened plaques of velvety consistency and infrequently verruca-like papillations usually occuring in the intertriginous zones (axillae, groin, neck, and inframammary folds) but also in areas subjected to trauma, the scalp, areolae, eyelids and oral mucosa (Fig. 1) (Thiers et al., 2009; Ehst et al., 2010). AN is a purely clinical diagnosis and can be supported by histopathologic changes (i.e., hyperkeratosis and papillomatosis). A CPS is manifest if drug-induced or familial AN and AN associated with autoimmune disease, diabetes-obesity syndromes and polycystic ovary disease are excluded. Malignancies including liver, lung, ovary, kidney, breast and SC (the most common cause of paraneoplastic AN) may be found in abdominal cavity organs with more than 95% being adenocarcinomas (Thiers et al., 2009; Ehst et al., 2010; da Costa França and Siqueira et al., 2007). A review including 227 patients with paraneoplastic AN demonstrated SC in 55% (Rigel and Jacobs, 1980). It is speculated that transforming growth factor–alpha (TGF-alpha) and melanocyte-stimulating hormone may play a role in the pathogenesis of the CPS (Ellis et al., 1987; Kleikamp et al., 2006; Moore and Devere, 2008). AN in combination with the sign of tripe palms and or Sign of Leser-Trélat (SOLT) was described as a CPS of SC in 35% of cases (Kleikamp et al., 2006; Moore and Devere, 2008; Pentenero et al., 2004). Definitive treatment of the underlying malignancy can lead to a disappearance of paraneoplastic AN (Ehst et al., 2010; Ellis et al., 1987; Kleikamp et al., 2006; Walling et al., 2003).

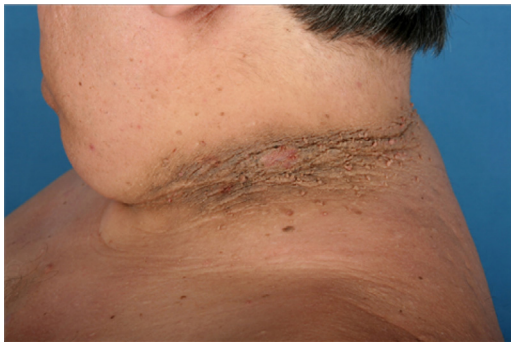

Fig. 1. Acanthosis Nigricans.[MH1].

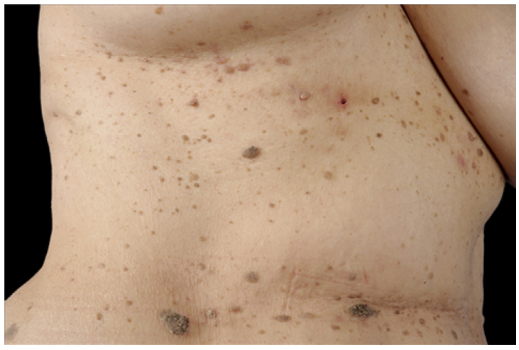

Fig. 2. Sign of Leser-Trélat.

3.1.2. Tripe palms (synonym: acanthosis palmaris, pachydermatoglyphy)

Tripe palm (TP) resembles the rugose stomach mucosa (tripe) of ruminants and is characterized by velvety thickening of the palms and soles. Receptor tyrosine kinases of subclass I, TGF-alpha, and the oncogenes *SRC* and c-*myc* may play a role in pathogenesis of TP (Ehst et al., 2010; Mullans and Cohen, 1996; Cohen et al., 1989; Chosidow et al., 1998). TP often precede cancer diagnosis in approximately 40%, 17% of lesions are seen coexistently (Cohen et al., 1989). TP is 90% associated with solid tumors, predominantly stomach or lung cancer (Cohen et al., 1989; Patel et al., 2005), and 30% of TP respond to cancer therapy (Ehst et al., 2010).

3.1.3. Sign of leser-Trélat (synonym: eruptive seborrhoic keratosis)

SOLT is defined as rapid onset, multiple seborrhoic keratoses, which can occur anywhere (76% on chest and back) and are associated with pruritus in 50% of cases (Fig. 2) (Sroa and Witman, 2010; Ratnavel and Griffiths, 1997). About 35% of these patients have coexistent AN and/or TP (Ratnavel and Griffiths, 1997). Commonly associated solid tumors are adenocarcinomas, especially of stomach, breast, lungs or rectum (Sroa and Witman, 2010; Ratnavel and Griffiths, 1997; Votion et al., 1982; Murata et al., 1998). Cytokines and epidermal growth factors produced by malignancies play a possible role in pathogenesis (Votion et al., 1982). SOLT resolves after successful cancer treatment in younger patients (Ratnavel and Griffiths, 1997). It is debatable whether SOLT should be classified