CASE REPORT

Acanthosis nigricans as a paraneoplastic syndrome

Case reports and review of literature

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KEY WORDS

acanthosis nigricans malignant (ANM), gastric cancer, paraneoplastic syndrome

ABSTRACT

Acanthosis nigricans (AN) is a skin disorder characterized by focal or diffuse hyperkeratosis symmetric hyperpigmentation of the skin and oral cavity mucosa. Various neoplasms, especially gastrointestinal adenocarcinomas are associated with acanthosis nigricans (AN malignant). Chemotherapy may cause regression of skin lesions. The etiology of AN is not clear. A role of growth factors such as melanocyte stimulating hormone α, transforming growth factor α, and insulin-like growth factor 1 has been discussed. Two cases of AN have been reported in this paper. Both have been associated with gastric adenocarcinoma. In the first case skin lesions were sensitive to chemotherapy (until cancer progression), while in the second case treatment had to be discontinued because of cardiotoxity without regression of skin lesions.

INTRODUCTION Acanthosis nigricans (AN) is defined as focal, hyperkeratotic symmetric discoloration and verrucous lesions rarely involving the oral mucosa. Lesions are most often located on the face, axilla, elbows, knees, intermammary area, navel and around the anus.[1] Infrequently, during cachexia AN is generalized with symmetric lesions and provokes mild pruritus of the skin. The alterations can be accompanied by nail dystrophy, thinning hair and veruccous lesions on the palpebral conjunctiva.

The 2 forms are distinguished:

1 benign:

A congenital – manifested in children

B acquired in adulthood accompanied by endocrinopathies (insulin resistance, hypophyseal tumors), obesity, erythema nodosum, or produced by medications (sex hormones, nicotinic acid)[1,2]

2 malignant associated with cancer of various organs (*acanthosis nigricans maligna* – ANM).

The term "malignant" is not justified as the dermatosis alone has a mild course and only coexists with cancers, which means that it is included in paraneoplastic syndromes. Among skin lesions that harbor an occult malignancy and always are a symptom of the existing malignant internal tumors, the following are: AN and its clinical abortive forms with the Leser-Trélat symptom, paraneoplastic pemphigus, necrolytic migratory erythema. ANM most often occurs in the course of adenocarcinomas of the abdominal organs (70–90%), particularly gastric cancer (55–61% ANM),[2-4] then adenocarcinoma of the pancreas, the ovary, kidneys, the bladder, bronchi, the thyroid, the bile duct, the breast, the esophagus and others. It rarely coexists non-epithelial tumors such as sarcomas or lymphomas.[3,5] On histopathologic evaluation of skin lesions developed in the ANM course, the proliferation of keranocytes with hyperkeratosis dominates, there is papillary hyperplasia, however, the hyperpigmentation of lesions is minimal.[5] Histological alterations are similar in all forms of AN and, therefore, establishing the cause of skin lesions on the basis of histopathologic examination is not feasible.[3]

With regard to the time of the paraneoplastic syndrome occurrence, about 61.3% of cases are detected simultaneously with the cancer manifestation, in about 17.6% it predates the diagnosis of malignancy, sometimes even by years,

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however in 21% of cases it appears after the detection of the malignant nature of a tumor.[4]

Since several years there is debate about a role of substances produced by cancer in the pathogenesis of ANM. Growth factors such as transforming growth factor α (TGF-α), insulin-like growth factor 1 (IGF-1), fibroblast growth factor (FGF), melanocyte stimulating hormone α (MSH-α) can play an important role in the pathogenesis of hyperplasia and hyperpigmentation observed in ANM. A cytokine TGF-α produced by cancer, which is structurally similar to epidermal growth factor α (EGF-α), interacts with the same receptor on the cell surface, although they probably bind with it in different sites.[5] The receptor for EGF is found on the normal epidermal cells, particularly on the actively proliferating cells of the basal layer where it is involved in the growth and differentiation of normal keranocytes and wound healing.[5,6] TGF-α and its receptor participates in tumor progression through auto-and paracrine secretion leading to autostimulation.[6] Koyama et al. showed the presence of TGF-α and EGF in gastric adenocarcinoma cells and EGF receptor expression in skin cells within lesions typical of AN.[5] Ellis et al. presented a case of AN with serum and urine increased levels of TGF-α and the presence of EGF receptors in skin lesions in the course of melanoma.[7] In both cases, the increased TGF-α levels in serum or urine decreased to undetectable values following surgery on the primary malignant lesion. Simultaneously, regression of skin lesions could be observed.[5] Activation of IGF-1, FGF and EGF receptors may also lead to excessive skin proliferation.[3,8] Another etiological factor can be MSH-α which regulates melanocyte pigmentation and stimulates the growth of keranocytes.[3] A few cases of increased levels of MSH-α in patients with intestinal and gastric adenocarcinoma with accompanying ANM have been described.[3]

The aim of the work was to present 2 cases of ANM as the first symptom preceding the diagnosis of gastric cancer.

CASE REPORTS **Case 1** A 44-year-old patient was admitted to the Department of Internal Diseases and Oncological Chemotherapy Medical University of Silesia, Katowice, in January 2005. In the patient's history, a papular rash with excessive keratosis, skin discoloration and pruritus appeared on the trunk especially in the axilla area since November 2004. At the same time, the patient noticed an enlarged lymph gland in the right supraclavicular area which was excised in January 2005. Metastatic adenocarcinoma was diagnosed with histopathologic evaluation and the patient was referred to the local Department in order to establish the primary focus of the cancer and initiate the treatment.

On admission, the patient complained of pruritus of the skin mainly in the region of the axilla. Micropapular rash on the trunk with excessive keratosis and discoloration especially in the axilla were diagnosed on physical examination. The consulting dermatologist linked the symptoms of AN with neoplastic disease, and local symptomatic treatment was started. To further evaluated the patient, gastroscopy was performed and revealed a cauliflower infiltration about 3 × 5 cm in the prepyloric region. Histopathological examination of tissue specimen showed mucocellular carcinoma. Moreover, carcinoembryonic antigen (CEA) levels were increased to 12 ng/ml. Blood cell count and biochemical tests were normal. After diagnostic procedures had been finished, a stage of the cancer was defined as clinical staging IV. Based on the oncology guidelines the tumor was declared inoperable and the patient was scheduled for palliative chemotherapy according to PELF protocol algorithm involving cisplatin, epirubicin, leucovorin, and 5-fluorouracil in appropriate doses.

The patient was given 4 cycles of chemotherapy from January to May 2005 with an acceptable tolerance of treatment and regression of skin lesions after the 2nd cycle. After the 4th cycle, the patient complained of abdominal pain, flatulence and troublesome pruritus that recurred. Softened mucosa encompassing the entire circumference of the stomach was diagnosed on the follow-up gastroscopy. A larger infiltration encompassing a half of the stomach and within the lesion, there were numerous erosions. Compared to the initial examination, a cancer progression was observed. Computed tomography of the abdomen showed progression of the cancerous infiltration and enlarged lymph nodes in the abdominal cavity, which caused the small intestine obstruction. Together with the diagnosed progession of gastric cancer, enhanced skin lesions like excessive keratosis, skin discoloration of the trunk, upper limbs, knees, mucosa of the tongue and increased pruritus were detected on clinical examination. Laboratory investigations showed normal CEA values (3.7 ng/ml), normal blood cell counts and biochemical tests. Due to the disease progression, the chemotherapy was completed and the medical treatment was used, then, the patient was discharged home for further palliative treatment. The patient died of symptoms of cancer progression (increasing ascites, cachexia) 2 months after completion of chemotherapy.

Case 2 A 75-year-old patient was admitted to the Department of Internal Diseases and Oncological Chemotherapy Medical University of Silesia, Katowice, in September 2005 in order to start cytostatic treatment for gastric cancer with lung metastases and the left adrenal gland. He was diagnosed for the skin lesions similar to AN since June 2005 in the medical unit of the municipal hospital. Two focal lesions in the left lung were shown. The patient was referred to the pulmonology unit where bronchoscopy was made, however, specimen taken for the histopathologic evaluation did not confirm the presence of cancer. Moreover, the abdominal ultrasound showed a tumor

in the left adrenal gland and the patient was referred to further diagnostic evaluation in the division of endocrinology at the local department. The adrenocorticotropic hormone level, cortisol in the serum and the determination of free cortisol level, aldosterone, vanillyl mandelic acid, urinary metanephrine urine were determined in order to exclude the endocrine causes of AN and the hormonal diagnostic evaluation of the left adrenal gland tumor. There were no abnormalities in electrolyte and hormone levels. The imaging examinations confirmed cancer disseminated to the lungs and the left adrenal gland. Gastroscopy showed a cauliflower infiltration in the body of the stomach encompassing almost its entire circumference; the lesion was partly ulcerated and softened. Specimens were taken and histopathologic features of adenocarcinoma were confirmed. On admission, the patient was in a good general condition, with increased generalized pruritus. Physical examination showed hyperpigmented, dry, cornifying skin in the axillary area, groins and the scrotum, together with warts around the mouth and on the hand skin. Following dermatologist consult, AN was diagnosed. Symptomatic and antipruritic treatments were ordered.

After the clinical data analysis, stage IV gastric adenocarcinoma was diagnosed; the patient was scheduled for palliative chemotherapy according to the PELF program. He was given 4 cycles. Imaging examinations (abdominal ultrasound, chest X-ray, gastroscopy) showed no further progression of cancer. However, due to reduced exercise tolerance, and anxiety about cardiotoxicity of treatment – paroxysmal atrial fibrillation which occurred during the treatment – the chemotherapy based on the hitherto algorithm was terminated. Regression was not observed in the skin lesion presentation during the chemotherapy. The patient was directed to further symptomatic treatment and the palliative care. The patient died 4 months after the treatment completion.

DISCUSSION Hyperkeratotic symmetric hyperpigmentations and verrucous skin lesions on the face, in the anatomical region of the axilla, elbows, knees, intermammary and navel area, and around the anus constitute an infrequent problem with which patients present to a family doctor. There are 2 forms of AN which should be such as benign and malignant forms. It is always necessary to exclude the presence of malignant diseases. A sudden occurrence of AN in patients, particularly those aged >40 years, who did not report previous endocrine disorder or any genetically determined disease, should incline to perform meticulous diagnostic evaluation in order to exclude coexisting malignant disease. The digestive tract requires special attention (AN accompanies 70–90% of adenocarcinomas located in the abdomen, most often in the stomach 55–61% of ANM).[2-4] In terms of the prevalence, gastric cancer is the 5th most common cancer among men and the 9th amongst women. The prognosis in gastric cancer is poor, which mainly results from the late diagnosis and initiating the treatment when the neoplastic disease is markedly advanced. Early diagnosis of cancer is important as the optimal way of gastrointestinal cancer treatment is surgery. From laboratory tests, blood cell count, feces occult blood test, tumor marker levels (CEA, carcinoma antigen CA19-9) are useful, however, it should be noted that endoscopic examinations (gastroscopy, colonoscopy) – during which there is a possibility of taking specimens for histopathological evaluation – are characterized by the highest sensitivity in diagnosing cancer of the digestive tract. An oncologist should establish a spectrum of imaging examinations after confirming the malignant nature of the lesions (abdominal ultrasound, computed tomography). The patients described in the current paper were initially diagnosed based on skin lesions and treated this way, which delayed the detection of cancer by about 2 months.

Treatment of AN is most often unsatisfactory. In rare cases, the treatment of primary disease, which is cancer, lead to regression of skin lesions. Retinoids, cyproheptadine, etretinate, PUVA (psoralen + UVA treatment) are used in the treatment of paraneoplastic syndrome.[6,7] Some cases of irradiation administration are described in a 26-year-old patient with ANM involving on the lips, gums, the anus area, together with persistent pruritus.[6] Despite unsatisfactory results, some therapeutic options are undertaken as the skin lesions are not only a cosmetic defect, but it also leads to discomfort during food intake; the pruritus of the altered areas is also a troublesome symptom.

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