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Malignant Acanthosis Nigricans, Florid Cutaneous Papillomatosis and Tripe Palms Syndrome Associated with Gastric Adenocarcinoma - a Case Report

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Abstract

Malignant acanthosis nigricans is a rare obligate paraneoplastic dermatosis which accounts for 20% of all acanthosis nigricans cases. The clinical features of the disease are the same as in the benign forms: symmetrical, hyperpigmented, velvety papillomatous lesions mostly involving the axillae, neck, groins, periumbilical cubital and popliteal areas, mammary areolae and less often mucous membranes. However, unlike other forms, it is characterized by sudden onset and rapid spread, commonly (80%) after the age of 40, which may be a marker of malignancy and a key to early diagnosis, indicating the need for a detailed examination. It is a disorder that has no gender differences. Most cases are detected at the moment of cancer diagnosis (61.3%), in fewer cases (about 20%) prior to cancer diagnosis, and in 21% at a later stage of malignant disease. Acanthosis nigricans is usually associated with one of the three or all three forms of paraneoplastic lesions: florid cutaneous papillomatosis, acanthosis palmaris (tripe palms, pachydermatoglyphia) involving the palms and soles, as well as multiple seborrheic keratosis (sign of Leser-Trélat).

We report on a female patient with clinically established three paraneoplastic syndromes: malignant acanthosis nigricans, florid cutaneous papillomatosis, and acanthosis palmaris, which appeared before the diagnosis of advanced gastric adenocarcinoma, leading to fatal outcome.

Key words

Acanthosis Nigricans; Paraneoplastic Syndromes; Comorbidity; Adenocarcinoma; Stomach Neoplasms; Case Reports

Acanthosis nigricans (AN) is a symmetric cutaneous eruption characterized by the presence of a hyperpigmented, velvety skin thickening, that can develop on any part of the body, but mostly affects the axillae, back of the head region, sides of the neck, groins, cubital, popliteal and umbilical areas (1 - 6); less often it affects eyelids, palms, soles, nipples and phalanges (1, 7, 8). Histological analysis of skin biopsy specimens shows predominantly papillomatosis and hyperkeratosis (5). Acanthosis nigricans rarely affects the oral, laryngeal, conjunctival and anal mucosa (3).

The term acanthosis nigricans was introduced by Unna from the Greek "acanthus" meaning "thorn" and "nigricans" from the Latin, meaning "becoming black". The first cases of patients with AN were described by Politzer (9) and Janowski (10) in 1890.

The simplest classification of AN was given by Brown (11): malignant AN is associated with malignant internal neoplasms, and benign AN, which may be idiopathic, hereditary, drug-induced, and associated with endocrine abnormalities.

Curth (12) classified AN into malignant, benign, and syndromic or pseudo-acanthosis nigricans (identical to the benign form, but associated with diabetes).

Schwartz (2) has clinically classified AN into 8 types: 1. Benign AN, 2. obesity-associated AN, 3. Syndromic AN, 4. Malignant AN, 5. Acral AN, 6. Unilateral AN, 7. Drug-induced AN, and 8. Mixed

AN (coexistence of two types of AN). The benign type can be acquired or inherited (1, 13), but there are discussions about autoimmune AN (14, 15).

Diseases and drugs that may be associated with benign type AN (1) include: 1. endocrine diseases (acromegaly, Addison's disease, Cushing's syndrome, type 2 diabetes, insulin resistance syndrome type A, B, C, obesity, polycystic ovary syndrome); 2. congenital syndromes (ataxia telangiectasia, Bloom syndrome, Prader-Willi syndrome, total lipodystrophy); 3. drugs (estrogens, glucocorticoids, fusidic acid, nicotinic acid). There are many other drugs that may induce AN: insulin injections (16), oral contraceptives, preparations containing melanocyte-stimulating hormone, triazine, methyltestosterone (17).

DiseasesassociatedwithmalignantAN:squamouscell carcinoma (lungs, cervix, subglottis); 2. adenocarcinoma (stomach, intestines, hepatic ducts, pancreas, ovaries, urinary bladder, lungs, testicles, mammary gland);. lymphomas (Hodgkin's and non-Hodgkin's disease; other (mycosis fungoides, osteosarcoma).

AN may be present at birth or appear during puberty and adolescence, although it can also be registered at a later age. Malignant AN develops in adult life usually in late middle age or old age, but it was also reported in young patients associated with gastric cancer (12).

In obese and diabetic patients the prevalence varies from 7% to 75%, according to age, race, frequency of type, degree of obesity and concomitant endocrinopathy (5). Malignant AN is less common, although the exact incidence has never been established (18). It has been reported that 2 of 12.000 patients with cancer had signs of AN (19, 20), and 1 out of 35 patients with intra-abdominal or intrathoracic malignancy (21).

Here we present a female patient with paraneoplastic skin lesions.

Case Report

A female patient, 54 years of age, a laboratory technician by profession, sought consultation due to changes in skin color and skin thickening in folds of large joints, and simultaneous appearance of warty and papillomatous lesions. Personal history showed that after the previous summer she noticed somewhat darker skin patches, which she attributed to extensive sun exposure. Since December of the same year, wart-like lesions started appearing in the thickened skin folds of her hands and feet, with numerous small tumorous lesions. She had an impression that it all started suddenly, after one night with severe itching all over the body. Since then she noticed hair and eyebrow loss. Occasionally she experienced itching or burning of the skin, especially in the armpits after excessive sweating. In general, she felt healthy, went to work regularly, and her appetite was normal. In recent months she lost a few kilos, in her opinion due to family problems. She felt weak when going up the stairs and had difficulty breathing. She denied epigastric pain and digestive problems.

Patient history. The patient history showed that she underwent ovarian cyst surgery 25 years ago, and stomach ulcer surgery 3 years ago (detected and treated for 2 - 3 years before); she entered menopause 8 years ago. She was smoking 40 cigarettes a day and did not consume alcohol.

Family history. The patient denied serious diseases or surgeries within the family, as well as skin diseases, especially skin lesions similar to her own.

Physical examination. The initial examination showed a patient of medium height in a good general condition. Skin examination revealed general hyperpigmentation which was especially pronounced on the back of the head and both sides of the neck, with velvety skin thickening and pronounced dermatogliphics. The thickening of the skin was much more pronounced in the axilla (Figure 1), groins, the inner thighs, perigenital area and the corners of the mouth, where the skin was very rough, thick, wrinkled, particularly in the central parts of the axillae and groins, resembling the fissured bark of *Quercus cerris*, dark brown or black in color. A great number of papillomatous skin tags were found in these areas, some without hyperpigmentation. These papillomatous lesions also involved the lower right eyelid.

Also, multiple verrucous pea to hazelnut sized lesions were found on the dorsal aspects of hands (Figure 2), forearms, lower legs and some on the face. The skin on the palms and to a lesser degree on the soles was hyperkeratotic; hyperkeratosis was also present on the sides of the fingers and the lateral part of the fifth toe on both feet. Pronounced, thickened, velvety pachydermatoglyphia was affecting the palms

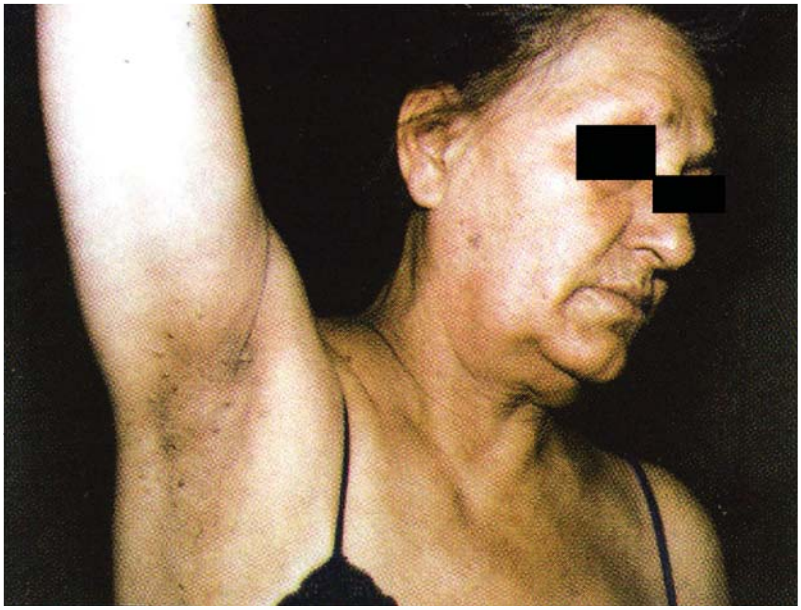

Figure 1. Pigmentation and velvety thickening of the skin, mainly in the axillae

(Figure 3). The nails were unaffected.

The lips and the mucous membranes of the soft and hard palate presented with a clearly limited thickening, with uneven surfaces, yellowish pink in color. Two transverse erosions appeared on the tongue, that did not previously exist.

Laboratory and other test results

All tests were performed to detect the presence of any visceral organs neoplasms.

Laboratory test revealed the following abnormal results: fibrinogen 5.2 g/L (normal range 2.0 - 4.0), total protein serum level 92.9 g/l (normal range 63 - 80.0), T4: 179 nmol/l (normal range 55.0 – 165.0), IgE 144 IU/ml (normal range – less than 100), IgA 2,99 g/l (normal range 0.74 - 4.0), IgM 1.52 (normal range 0.30 – 2.93), IgG 23.0 g/l ((normal range 8.8 – 18.0), soluble immune complexes 206 IU/ml (normal range 24 - 116).

Chest X-ray – normal.

Skull x-ray: normal.

Eye fundus examination: Fundus arterio-scleroticus.

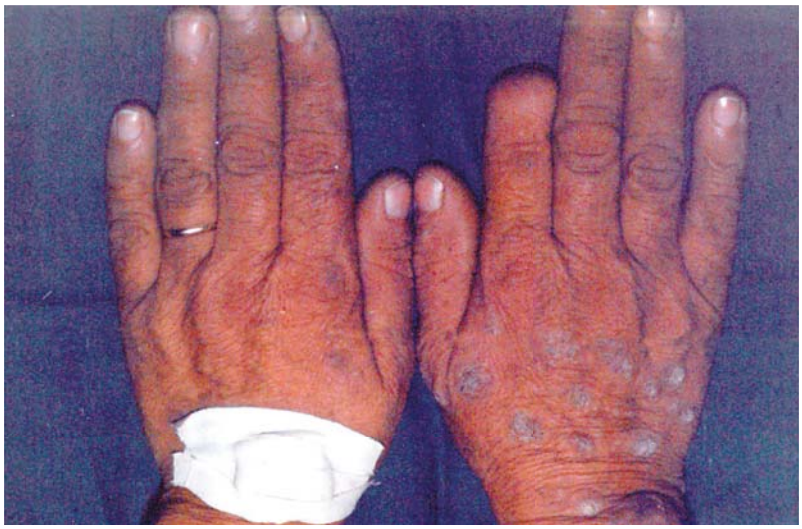

Figure 2. Multiple verrucous papules on dorsal sides of hands

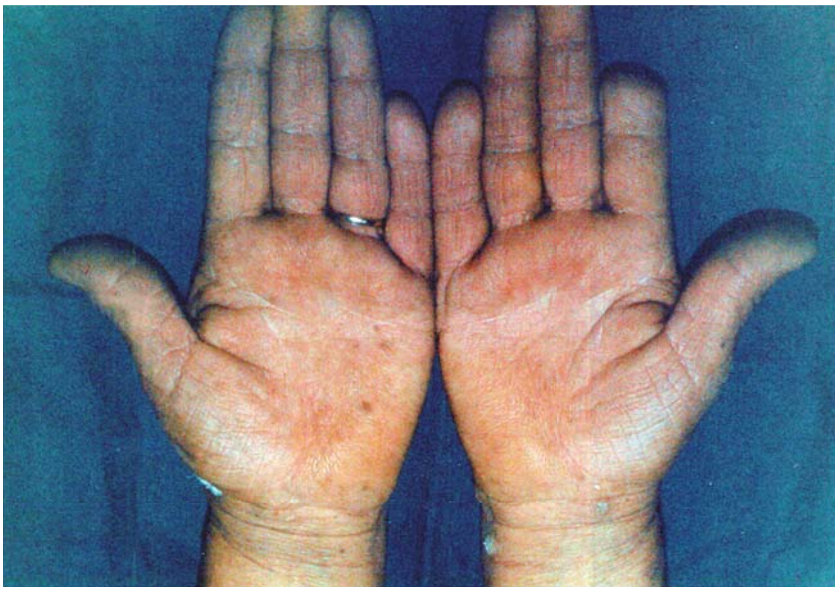

Figure 3. Prominent pachydermatoglyphia

Stomach X-ray, gastroscopy, histopathological examination of the stomach biopsy sample: gastric adenocarcinoma.

Treatment, further course: Since gastric adenocarcinoma was diagnosed at an advanced stage, the course of the disease was progressive, with rapid fatal outcome.

Discussion

Malignant acanthosis nigricans (MAN) is a rare obligate paraneoplastic dermatosis (22) which accounts for 20% of all acanthosis nigricans cases (18, 23). The term MAN is recognized and accepted, but as such it is not malignant, it only co-occurs with cancer (1, 24). A more accurate term would be paraneoplastic AN.

The clinical features of the disease are the same as in the benign AN: symmetrical, hyperpigmented, velvety papillomatous lesions mostly involving the axillae, neck, groins, periumbilical cubital and popliteal areas, mammary areolae and less often the mucous membranes, although according to some data 30 to 50% of patients with MAN have oral lesions, mostly on the tongue and lips (25 – 28). However, unlike other forms, MAN is characterized by sudden onset and rapid spread, commonly (80%) after the age of 40 (21), which may be a marker of malignancy and a key to early diagnosis (29), indicating the need for a detailed examination (4). It is a disorder that has no gender differences. Most cases are detected at the moment of cancer diagnosis (61.3%), in fewer cases (about 20%) prior to cancer diagnosis, and in 21% at an advanced stage of malignant disease (30).

In our patient, changes typical of AN appeared at the age of 53, without symptoms of malignant disease, which was diagnosed a few months later, but at an advanced stage, which does not exclude the possibility that the malignancy preceded it, or appeared simultaneously with the skin changes.

The most common malignancy associated with malignant acanthosis nigricans is abdominal adenocarcinoma, especially of the stomach. In an early study (12) of 191 patients with MAN, 177 (92%) had an underlying abdominal cancer, of which 69% were gastric. The remaining 31% had carcinoma of the uterus, liver, intestine, colon, rectum or ovaries, and only 14 had extra-abdominal malignancies (breast, lung and mediastinum). In another study (31), of 94 cases with MAN, 58 (61%) persons were diagnosed with gastric cancer. According to other authors (11, 18, 32), the most common malignancies are adenocarcinomas of the digestive tract and uterus, while carcinomas of the lung, breast, prostate, and ovary are less frequent. Recently, more papers have been published on the association between MAN and gastric adenocarcinoma (18, 29, 30, 33, 34),

ovarian cancer (35), hepatocellular carcinoma (36), adenocarcinoma of the bladder (4) and metastatic laryngopharyngeal carcinoma (37). Our patient with AN was also diagnosed with gastric adenocarcinoma. The malignancy was diagnosed several months after the onset of skin lesions, but unfortunately at an advanced stage without prospect of cure.

MAN was first described by Clarke (38); it may be associated with other cutaneous markers of internal malignancies: AN commonly occurs with some of the three or all three forms of paraneoplastic lesions, florid cutaneous papillomatosis (FCP), lesions on the palms and soles (tripe palms; pachydermatogliphia), and multiple seborrheic keratoses (sign of Leser-Trélat). These paraneoplastic syndromes are considered abortive forms of MAN (19), especially as they have similar epidemiological, morphological and histological characteristics (38). However, these are special type of paraneoplastic dermatoses (39) which can occur individually (13, 40, 41).

Florid cutaneous papillomatosis (Schwartz-Burgess syndrome) is characterized by numerous warty papules on the trunk, extremities and face that are similar to viral warts, but show different clinical and histological features (18). This condition was described and named by Schwartz and Burges in 1978 (42). It is commonly associated with gastric adenocarcinoma and MAN. The lesions regress after cancer surgery or chemotherapy, but reappear with tumor recurrence and metastasis (43, 44).

Tripe palms (acanthosis palmaris, pachy-dermatoglyphia) is an acquired palmoplantar kerato-derma (19, 45 - 48) which clinically manifests with thick and pronounced velvety-white folds in the lines of the hands (so the skin resembles boiled tripe); in 90% of cases it is associated with malignancy of the internal organs (46, 49, 50); histologically it is characterized by hyperkeratosis, papillomatosis and acanthosis (50); MAN was first described by Clarke (51); it may be the only paraneoplasia in 30-40% of cases, or it is associated with AN or Leser-Trélat (52). It mainly occurs in male patients with lung cancer. In most cases, tripe palms is associated with lung and stomach cancer (53), but also with urogenital tract carcinoma. Nail changes are common in lung cancer, whereas gastric cancer is associated with AN. The condition resolves once the underlying cancer is treated (52).

Leser-Trélat sign is characterized by the abrupt appearance of multiple seborrheic keratoses, with or without itching. It may be a cutaneous indicator of internal malignancy, most commonly digestive tract adenocarcinoma (13) when it is associated with MAN, breast or lung cancer (54); it is rarely reported in malignant hemangiopericytoma, malignant melanoma or kidney carcinoma. In lymphoproliferative diseases it occurs more often than MAN, and this comorbidity is found in about 20% of cases (52). It may occur in HIV (Human Immunodeficiency Virus) infection, acromegaly, and resolution phase of exfoliative dermatitis (49). Multiple seborrheic keratoses are common in elderly people, pruritic or eruptive, but if there is a sudden appearance of seborrheic warts with severe itching, measures should be taken in order to prove or exclude malignancy. Comorbidity between seborrheic warts and benign AN has not been reported so far.

Our patient presented with three paraneoplastic dermatoses: malignant acanthosis nigricans, florid cutaneous papillomatosis and tripe palms as a manifestation of gastric adenocarcinoma.

The pathogenesis of AN has not been fully elucidated (13, 55). In the case of insulin resistance, which is extremely rare or remains undiagnosed (56), insulin acts through a classical insulin receptor or other insulin-like receptors: high levels of insulin may activate the insulin-like growth factor 1 receptor (IGF-1R) and mediate cell proliferation (2, 57). Perspiration and/or friction may be necessary cofactors (5).

The pathogenic mechanism involved in the development of MAN is still obscure (55). A current hypothetical mechanism is the secretion of large amounts of transforming growth factor alpha (TGF-a) by the tumor into the circulation that is thought to stimulate keratinocyte growth via an endocrine route (58). There is a positive correlation between the stages of tumor progression and expression of this factor. TGF- alpha is a primary mediator of benign and malignant keratinocyte hyperproliferation in vivo (58). Some authors speculate that activation of fibroblast growth factor receptor 3 (FGFR3) might have some relevance to the formation of MAN (59). Simultaneous activation of epidermal growth factor receptor 3 (EGFR3), insulin-like growth factor-α-1 (IGF-1) and melanocyte stimulating hormone α (MSH-α) stimulates the development of MAN (55,

59); a systemic immunologic response to the primary tumor as a cause cannot be discarded (13).

There is no specific therapy for AN. Phenytoin and metformin are used in insulin resistance (56); in benign and malignant forms topical therapy is used with varying success: retinoids, ammonium lactate, trichloroacetic acid, salicylic acid, podophyllin, urea, calcipotriol, dermabrasion, laser therapy; systemic therapy includes retinoids and PUVA, and cyproheptadine in MAN (5, 60-62). It is well known that paraneoplastic syndromes regress after cancer surgery, chemotherapy or radiotherapy, but may reappear with tumor recurrence or metastasis.

Conclusion

We report on a female patient with clinically established three paraneoplastic syndromes: malignant acanthosis nigricans, florid cutaneous papillomatosis, and acanthosis palmaris, which appeared before the diagnosis of advanced gastric adenocarcinoma was made, leading to fatal outcome.

Abbreviations

AN - acanthosis nigricans
T4 - thyroxine
Ig - immunoglobulin
MAN - malignant acanthosis nigricans
FCP - florid cutaneous papillomatosis
HIV - human immunodeficiency virus
IGF-1R - insulin-like growth factor-1 receptor
TGF- α - transforming growth factor-alpha
FGFR3 - fibroblast growth factor receptor 3
EGFR3 - epidermal growth factor receptor 3
IGF-1 - insulin-like growth factor-1
αMSH - alpha melanocyte stimulating hormone
PUVA - psoralen plus ultraviolet A

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Maligna acanthosis nigricans, floridna kutana papilomatoza i acanthosis palmaris udruženi sa adenokarcinomom želuca – prikaz slučaja

Sažetak

Uvod. Maligna acanthosis nigricans obligantna je paraneoplazijska dermatoza, koja se retko javlja i čini 20% od svih slučajeva acanthosis nigricans. Kliničke osobine bolesti su iste kao kod benigne forme bolesti, međutim, za razliku od drugih formi, karakteriše je iznenadno naglo i brzo širenje, najčešće (u 80%) pojavom posle 40. godine života, što kao marker maligniteta ili ključ za ranu dijagnostiku može da ukaže na potrebu za detaljnim ispitivanjem u tom smislu. Najveći broj slučajeva se detektuje u momentu dijagnostike maligniteta (61,3%), manje pre dijagnostike (oko 20%) i 21% u kasnom stadijumu maligne bolesti. Obično se uz acanthosis nigricans javlja i jedan od tri ili sva tri oblika paraneoplazija: floridna kutana papilomatoza, acanthosis palmaris (tripe palms, pachydermatoglyphy) sa promenama na dlanovima i tabanima i multiple seboroične keratoze (Leser Trelatov znak). Bolesti udružene sa malignom). Bolesti udružene sa malignom acanthosis nigricans: skvamocelularni karcinom (pluća, cervix. subglotis); adenokarcinom (ezofagus, želudac, interstinum, hepatični duktusi, pankreas, ovarijumi, mokraćna bešika, pluća, testisi, mlečne žlezde); limfomi (Hočkinova i nehočkinska bolest; 4 ostalo (mycosis fungoides, osteosarcoma).

Cilj rada. U radu je prikazana bolesnica kod koje je klinički registrovana kombinacija tri paraneoplazijska sindroma: maligna acanthosis nigricans; floridna kutana papilomatoza i acanthosis palmaris, koje su se pojavile pre dijagnostikovanja adenokarcinoma želuca koji je otkriven u odmakloj fazi, što je rezultovalo smrtnim ishod.

Prikaz slučaja. Bolesnica stara, 54 godine, javila se na pregled zbog promene boje kože i zadebljanja na pregibima velikih zglobova i istovremene pojave bradavičastih i papilomatoznih tvorevina. Iz anamneznih podataka se saznalo da je od prethodnog leta primetila zaostatak nešto tamnije boje kože, što je ona pripisivala dugom sunčanju. Od decembra meseca iste godine, počele su da joj se javljaju bradavice po rukama i nogama, a u pregibima zadebljanje kože sa mnoštvom sitnih tumoroznih promena. Njen utisak je bio da je sve počelo odjednom, posle jedne noći kada je imala intenzivan svrab po čitavoj koži. Od tada je počela da joj opada kosa i proređuju obrve. Povremeno se javljao svrab ili pečenje kože, naročito u pazuhama i to posle jačeg znojenja. U celini se sve vreme osećala zdravom, redovno je odlazila na posao, nije gubila apetit. Poslednjih meseci je izgubila neoliko kilograma u telesnoj težini, što je objašnjavala porodičnim problemima. Jedino je primetila da se zamara kada ide uz stepenice, i tada ima otežano disanje. Bolove u epigastrijumu i smetnje pri varenju nije imala. U ličnoj anamnezi je dala podatke da je pre 25 godina imala operaciju ciste na jajniku, a pre 3 godine čira na želucu, koji je pre operacije otkriven i lečen tokom 2-3 godine; menopauza je nastupila pre 8 godina. Sve vreme, bez prestanka, pušila je po 40 cigareta dnevno ; nije konzumirala alkohol. U porodičnoj anamnezi izjavila je da kod ostalih članova porodice nije bilo težih oboljenja niti operacija i da niko nije imao oboljenja kože, naročito ne promene na koži slične njenim. Prilikom prvog pregleda, bolesnica srednjeg rasta, nalazila se u dobrom opštem stanju. Prilikom pregleda kože i vidljivih

sluznica, uočena je jača pigmentacija kože u celini; hiperpigmentacija je naročito bila izražena u potiljačnoj regiji i na bočnim stranama vrata, sa zadebljalom kožom somotaste površine i naglašenim kožnim crtežom. Mnogo izrazitije zadebljanje kože bilo je u aksilama (Slika 1), preponama, na unutrašnjim stranama butina i perigenitalno i na uglovima usana, gde je koža bila izrazito gruba, deblja, naborana, naročito u centralnim delovima aksila i prepona, sa izgledom cerove kore, mrko do sasvim crno prebojena. Na ovim površinama nalaze se u velikom broju papilomi na peteljci, a bilo ih je i na neizmenjenoj koži. Papilomatozne promene su se nalazile na ivici donjeg desnog očnog kapka. Takođe je na koži bilo prisutno mnoštvo verukoidnih promena od veličine zrna graška do veličine lešnika, uglavnom na dorzumima šaka (Slika 2), podlakticama i potkolenicama i po koja na licu. Na dlanovima i manje na tabanima koža je bila hiperkeratotična, kao i na bočnim stranama prstiju ruku i spoljašnjoj strani petog prsta na oba stopala. Na dlanovima je bila izražena pachydermatogliphia – zadebljanje kože neravne, somotaste površine (Slika 3). Nokti nisu bili promenjeni. Na usnama, na sluzokoži mekog i tvrdog nepca takođe se uočavalo zadebljanje, dosta jasno ograničeno, gde je sluzokoža bila neravne površine, žućkasto ružičaste boje. Na jeziku su bile prisutne dve poprečne plike, kojih ranije nije bilo.

Izvršena ispitivanja bila su usmerena u pravcu otkrivanja neoplazme visceralnih organa. Rezultati laboratorijskih analiza koji su odstupali od fizioloških: fibrinogen 5,2 g/l (referalna vrednost 2–4), ukupni proteini u serumu 92,9 g/l (referalna vrednost 63–80), T4: 179 nmol/l (referalna vrednost 55–165), IgE 144 IU/ml (referalna vrednost – manje od 100), IgA 2,99 g/l (referalna vrednost 0,74–4), IgM 1,52 (referalna vrednost 0,30–2,93), IgG 23 g/l (referalna vrednost 8,8–18), rastvorljivi imunokompleksi 206 IU/ml (referalna vrednost 24–116). RTG želuca, gastroskopija, PH analiza isečka sluznice želuca: adenokarcinom želuca. S obzirom da je adenokarcinom želuca dijagnostikovan u odmakloj fazi, tok bolesti je bio progresivan sa rapidnim smrtnim ishodom.

Diskusija. Najjednostavniju klasifikaciju acanthosis nigricans dao je Braun (Brown): maligna forma koja je udružena sa malignim tumorima unutrašnjih organa i benigna forma, koja može biti idiopatska, nasledna, indukovana lekovima i udružena sa endokrinim abnormalnostima. Prema Kertu (Curth), AN se može manifestovati u 4 tipa, kao: maligna, benigna, sindromska i pseudoacanthosis nigricans (identična sa benignom formom, ali je udružena sa dijabetesom). Švarc (Schwarz) je klinički klasifikovao acanthosis nigricans u 8 tipova: 1. benigna acanthosis nigricans, 2. acanthosis nigricans udružena sa gojaznošću, 3. sindromska acanthosis nigricans, 4. maligna acanthosis nigricans, 5. akralna acanthosis nigricans, 6. unilateralna acanthosis nigricans, 7. lekovima indukovana acanthosis nigricans, i 8. mešoviti tip acanthosis nigricans (kada su prisutna dva tipa acanthosis nigricans): benigna forma može biti stečena i nasledna, a u poslednje vereme govori se i o autoimunskoj acanthosis nigricans.

Kod gojaznih i dijabetičara prevalencija acanthosis nigricans varira od 7% do 75%, zavisno od godina, rase, učestalosti tipa, stepena gojaznosti i prisutne endokrinopatije. Kod maligne acanthosis nigricans učestalost je znatno manja, mada tačna učestalost nikad nije utvrđena (18). Saopšteno je da 2 od 12 000 pacijenata sa kancerom ima acanthosis nigricans, a 1 od 35 pacijenata sa intratorakalnim ili intraabdominalnim malignitetom. Najčešće se radi o adenokarcinomu i to u abdomenu, prevashodno o adenokarcinomu želuca.

Kod naše bolesnice promene tipične za acanthosis nigricans su počele da se javljaju u 53. godini, bez simptoma malignog oboljenja, koje je dijagnostikovano nekoliko meseci kasnije, ali već u odmaklom stadijumu, što ne isključuje mogućnost da je malignitet prethodio ili se javio istovremeno sa pojavom promena na koži. Maligni proces je dijagnostikovan nekoliko meseci posle pojave promena na koži, ali nažalost, u fazi kada više nije bilo pomoći.

Maligna acanthosis nigricans može biti udružena sa drugim kutanim markerima internog maligniteta: najčešće se uz acanthosis nigricans javlja i neki od tri ili sva tri oblika paraneoplazija, floridna kutana papilomatoza promene na dlanovima i tabanima (tripe palms; pachydermatogliphia) i multiple seboroične keratoze (Leser Trelatov znak). Ovi paraneoplazijski sindromi se smatraju abortivnim formama maligne acanthosis nigricans, tim pre što imaju slične epidemiološke, morfološke i histološke karakteristike. Ipak, radi se o posebnim tipovima paraneoplazijskih dermatoza, koje se mogu javiti izolovano.

Floridnu kutanu papilomatozu – Švarc–Berdžesov sindrom (Schwartz–Burgess syndrom) karakteriše pojava brojnih papuloznih lezija na trupu, udovima i licu koje su slične virusnim bradavicama, ali se od njh razlikuju klinički i histološki. Ime ove neoplazije potiče od Švarca i Berdžesa iz 1978. Najčešće se javlja kod bolesnika sa gastričnim

adenokarcinomom zajedno sa malignom acanthosis nigricans. Lezije regrediraju posle hirurške ili hemoterapije karcinoma, a recidiviraju kod pojave metastaza.

Tripe palms (acanthosis palmaris, pachydermatoglyphia), stečena je palmoplantarna akantoza; manifestuje se klinički kao somotasto, naborano zadebljanje dlanova slično škembetu (somotastoj unutrašnjoj površini želuca preživara), sa pojačanim epidermalnim linijama; udružena sa malignitetom unutrašnjih organa u 90% slučajeva. Može biti jedina paraneoplazija u 30–40% slučajeva ili je udružena sa acanthosis nigricans ili sa Leser–Trelatov znakom). Javlja se naročito kod muškaraca sa karcinomom pluća. U najvećem broju slučajeva tripe palms udružena je sa karcinomoma pluća i želuca, ali i sa karcinomom genitourinarnog trakta. Kod karcinoma pluća javljaju se i promene na noktima, a kod karcinoma želuca udružena je sa acanthosis nigricans. Rezolucija promena nastaje posle resekcije tumora.

Leser–Trelatov znak karkteriše eruptivna pojava mnogobrojnih seboroičnih keratoza, sa svrabom ili bez njega. Može biti indikator za maligno oboljenje unutrašnjih organa, najčešće za adenokarcinom digestivnog trakta, kada može biti udružen sa malignom acanthosis nigricans, potom za karcinom dojke ili pluća; retko je registrovan kod malignog hemangiopericitoma, malignog melanoma ili karcinoma bubrega. Kod limfoproliferativnih bolesti se javlja češće nego maligna acanthosis nigricans i zabeležena je udruženost u oko 20% slučajeva. Može se pojaviti kod HIV-a (eng. human immunodeficiency virus) infekcije, akromegalije i rezolutivne faze eksfolijativnog dermatitisa. Multiple seboroične keratoze su česte kod starih ljudi, kada mogu biti pruritične i eruptivne, međutim, ako dođe do nagle pojave seboroičnih veruka i uvećanja postojećih sa izraženim svrabom, treba preduzeti mere da se dokaže ili isključi malignitet. U literaturi do sada nije objavljen nijedan sltćaj udružene pojave seboroičnih veruka i benigne acanthosis nigricans.

Kod naše bolesnice registrovan je trijas paraneoplazijskih dermatoza: maligna acanthosis nigricans, floridna kutana papilomatoza i tripe palms kao manifestacija adenokarcinoma želuca.

Patogeneza acanthosis nigricans još uvek nije potpuno razjašnjena. Kada se radi o insulinskoj rezistenciji, koja je ekstremno retka ili ostaje nedijagnostikovana, insulin deluje preko klasičnog receptora i drugih receptora nalik na insulinski: visoke koncentracije insulina mogu da aktiviraju receptor za insulin – sličan faktoru rasta 1 (eng. insulin growth factor-1 receptor, IGF-1R) i budu medijatori ćelijske proliferacije. Znojenje i/ ili trenje mogu biti neophodan kofaktor.

Patogenetski mehanizam koji dovodi do maligna acanthosis nigricans nije potpuno jasan. Važeći hipotetički mehanizam podrazumeva sekreciju iz tumora u cirkulaciju velike količine TGF-alfa (eng. transforming growth factor-alpha), za koji se smatra da stimuliše rast keratinocita preko endokrinog puta. Utvrđena je pozitivna korelacija između faze progresije tumora i ekspresije ovog faktora; TGF-alfa predstavlja primarni medijator kako benigne tako i maligne hiperproliferacije keratinocita in vivo. Neki autori sugerišu da aktivacija receptora 3 za fibroblastni faktor rasta (eng. fibroblast growth factor receptor 3 - FGFR3) ima uticaja u formiranju maligne acanthosis nigricans. Istovremena aktivacija EGFR3 (eng. epidermal growth factor receptor 3), IGF-1 i MSH-α (melanocitni stimulišuući hormon alfa), stimuliše razvoj maligne acanthosis nigricans; sistemski imunski odgovor usmeren na primarni tumor kao uzrok poremećaja, ne može se odbaciti. Nema specifičnog tretmana acanthosis nigricans. Kod insulinske rezistencije koriste se fenitoin i metformin; kod benignih i maligne forme sa različitim uspehom primenjuje se lokalna terapija: retinoidi, amonijum-laktat, trihlorsirćetna kiselina, salicilna kiselina, podofilin, urea, kalcipotriol, dermoabrazija, laser, a u sistemskoj terapiji, retinoidi PUVA i kod maligne acanthosis nigricans cyproheptadin.

Zaključak. U radu je prikazan slučaj osobe ženskog pola kod koje je klinički registrovana kombinacija tri paraneoplazijska sindroma: maligna acanthosis nigricans, floridna kutana papilomatoza i acanthosis palmaris, koje su se pojavile pre dijagnostike adenokarcinoma želuca, koji je otkriven u odmakloj fazi, te je bolest rezultovala smrtnim ishodom.

Ključne reči

Acanthosis nigricans; Paraneoplazijski sindromi; Komorbiditet; Adenokarcinom; Neoplazme Želuca; Prikazi slučajeva