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Original Scientific Paper

CAN SKIN BE A MARKER FOR INTERNAL MALIGNANCY? EVIDENCE FROM CLINICAL CASES

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SUMMARY – Although there are many single case reports on paraneoplastic dermatoses in the literature, there are very rare articles containing multiple cases. A retrospective study was performed to examine paraneoplastic dermatoses and accompanying malignancies based on skin manifestations and appropriate diagnostic evaluations. We recorded outcomes, current conditions, and surgical/oncologic treatments. Analysis revealed paraneoplastic dermatoses in 17 patients with various skin lesions, i.e. eczematous dermatitis, vasculitis, subacute cutaneous lupus erythematosus, pruritus, chronic urticaria/angioedema, alopecia areata, flushing, bullous pemphigoid, dermatomyositis, and localized scleroderma (morphea). They were associated with different solid and hematologic malignancies (3 gastric, 2 prostate, 2 bladder, 2 thyroid, and 2 lymphoma), along with 1 case each of the following: lung, hepatocellular, esophageal, endometrial, kidney, and multiple myeloma. The majority of skin lesions gradually regressed after malignancy treatment. To our knowledge, our three cases of paraneoplastic eczematous dermatitis are the first to be associated with gastric, prostate and endometrial cancer. Additionally, we report a case of a patient with alopecia areata of the beard associated with thyroid cancer. Early malignancy detection based on skin markers makes early introduction of surgical/oncologic therapy possible and usually leads to skin lesion regression while reducing revolving door visits to specialists and the (financial) burden on the healthcare system.

Key words: *Cutaneous paraneoplastic disorders; Malignancy; Cancer; Skin; Eczema; Vasculitis; Cutaneous lupus erythematosus; Pruritus; Urticaria; Angioedema; Alopecia; Pemphigoid; Dermatomyositis; Scleroderma*

Introduction

When deciding on diagnostic tests in patients with various skin lesions, questions of the scope, extent of diagnostic procedures and workup on the possible malignancies often arise. The cases of paraneoplastic disorders, including paraneoplastic dermatoses (PDs), found in the literature indicate that diagnostic tests are sometimes essential for the outcome of treatment. However, currently there are no specific guidelines instructing when expanded diagnostics should be performed, and some recommendations for dermatoses actually require limited diagnostics. An additional problem is that various skin lesions in the context of PDs can belong to either obligate PDs (underlying malignancy in >95%) or facultative PDs (in 5%-15%)[1-5]. Obligate PDs comprise acanthosis nigricans, the Leser-Trélat sign, tripe palms, acrokeratosis Bazex, erythema gyratum repens, necrolytic migratory ery-

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thema, hypertrichosis lanuginosa acquisita, and paraneoplastic pemphigus. Facultative PDs comprise a number of diseases that can sometimes be paraneoplastic, i.e. bullous pemphigoid (BP), pyoderma gangrenosum, dermatomyositis (DM), Sweet syndrome, erythroderma, scleromyxedema, and filiform follicular hyperkeratoses[1-5]. Currently, more than 50 dermatoses have been reported as potential markers of malignancy, which is something dermatologists should keep in mind to catch underlying malignancies early on[2-8]. Although there are many single case reports, the literature lacks clinically based evidence/cases of patients with different clinical pictures of PDs. To our knowledge, this is the first study that monitored dermatology patients with diagnostic indicators of PDs over a long time period and confirmed the related malignancies.

Materials and Methods

A retrospective study was performed at the Department of Dermatovenereology, Sestre milosrdnice University Hospital Center, Zagreb, Croatia. We examined the prevalence of confirmed malignancy-related dermatoses (PDs) and their characteristics by collecting medical records spanning 9 years of hospitalized patients and outpatients (from January 2009 to November 2017). Only patients with medical records containing evidence required for the diagnosis of dermatosis and accompanying internal malignancy were taken into account, meaning evidence for malignancy, simultaneous development and skin lesions with unusual resistance to therapy. All patients signed written informed consent, and the study was conducted according to the Helsinki Declaration guidelines.

The diagnoses of PD and accompanying malignancy were based on clinical manifestations, histologic findings of skin samples (except for pruritus and alopecia), and appropriate diagnostic evaluations carried out in each patient, including basic laboratory and other tests [tumor markers, endoscopic methods, computed tomography (CT), etc.]. We excluded patients with chronic dermatoses treated for more than 4 years and those with skin cancers. After detecting a malignoma, patients were not regularly examined by dermatologists but were informed that they could contact us as needed in the case of a dermatosis relapse or adverse skin reactions. We recorded the outcome by contacting each patient and asking about their current condition, and recorded whether surgical/oncologic treatments were performed, although precise data on the type of therapy were not collected. Finally, we compared our data with recent literature findings. Logistic and linear regression were used on statistical analysis to explore predictors of the time elapsed from the first dermatologic assessment to detection of malignancy. The period until malignoma detection was used as a continuous variable (in months) in linear regression and as a dichotomous variable (0 = up to 6 months and 1 = longer than 6 months) in the logistic regression model. Logistic regression was also used to detect predictors of mortality. Due to the small number of patients, other statistical analyses were not possible. The commercial statistical software IBM SPSS 21 (IBM Corp, Armonk, USA) was used.

Results

Our analysis revealed PDs in 17 patients (9 males and 8 females), mean age 63.17 (range: 32-89 years) and various skin diseases (Table 1), as follows: eczematous dermatitis (Fig. 1a, b, c), vasculitis (Fig. 1d, e), subacute cutaneous lupus erythematosus (SCLE) (Fig. 1e, f, g), pruritus, chronic urticaria (CU) or angioedema, alopecia areata (AA) (Fig. 2a, b), flushing, BP, DM (Fig. 2c, d), and localized scleroderma. All evidenced PDs were facultative; obligate PDs were not found. We also detected different solid and hematologic malignancies (3 gastric, 2 prostate, 2 bladder, 2 thyroid, 2 lymphoma), along with 1 case each of the following: lung, hepatocellular, esophageal, endometrial, kidney, and multiple myeloma.

Most of our patients had visited different specialists over a mean period of 6.65 months before their first dermatology appointment, and were often being misdiagnosed and received unnecessary therapies many times, such as corticosteroids. Internal malignancy was detected at a mean of 22.06 months after the patient's first visit to a dermatologist (Table 1). In 12 patients, the outcome was gradual dermatosis regression after surgical and/or oncologic treatment of the underlying malignancy, while another five patients succumbed to their illnesses and clinical outcome could not be observed or recorded.

Logistic and linear regression did not detect any significant predictors of the time elapsed from the first dermatologic examination to malignancy detection.

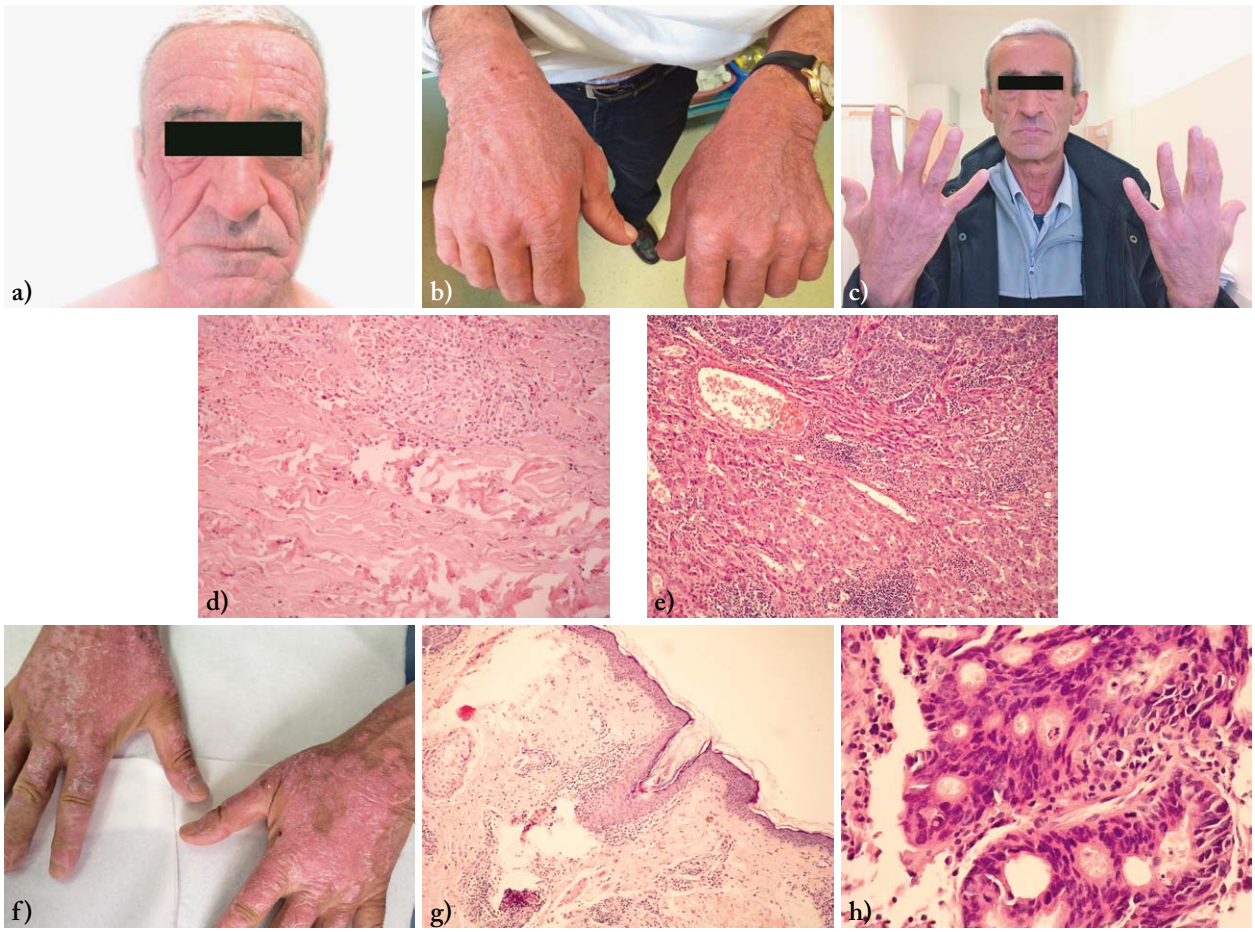

Fig. 1. (a, b) Clinical picture in the patient with eczematous dermatitis with lesions on the hands and face secondary to gastric cancer; (c) regression of dermatosis after surgical and oncologic treatment; (d) neutrophilic inflammation with fibrinoid necrosis and fragmented nuclei (leukocytoclasis (H&E, x200); (e) tumor cells with hyperchromatic nuclei in a compact growth pattern (hepatocellular carcinoma (H&E, x100); (f) clinical picture in the patient with subacute cutaneous lupus erythematosus secondary to gastric cancer; (g) liquefactive degeneration and atrophy of the epidermis, small hemorrhages, and mild infiltrate of lymphocytes in the upper dermis (lupus (H&E, x100); (h) irregularly shaped and fused neoplastic glands (adenocarcinoma (H&E, x400).

Gender, age, and duration of lesions prior to dermatologic examination or the presence of tumor markers were not predictors of the period until malignoma detection. None of the factors was a significant predictor of mortality.

Data on each patient are categorized and presented by diagnosis (Table 1).

1) Eczematous dermatitis

In a patient with persistent eczematous lesions on the hands and face (Figs. 1a, b) who was repeatedly treated with topical and parenteral corticosteroids for several years with quick relapses after drug discontinuation, we performed extended diagnostics to screen for the possible underlying malignancy. After the results showed elevated tumor markers [carcinoembryonic antigen (CEA), lactate dehydrogenase (LDH), cytokeratin fragment (CYFRA)[21-1]], esophagogastroduodenoscopy (EGD) with biopsy verified gastric cancer. After the introduction of oncology treatment, a relapse of dermatosis occurred and dermatologic therapy was administered, but after completing oncologic therapy, both diseases went into remission (Fig. 1c). Our female patient with persistent eczematous lesions on the trunk and extremities was examined by a gynecologist, among others, who finally diagnosed endometrial cancer. Our

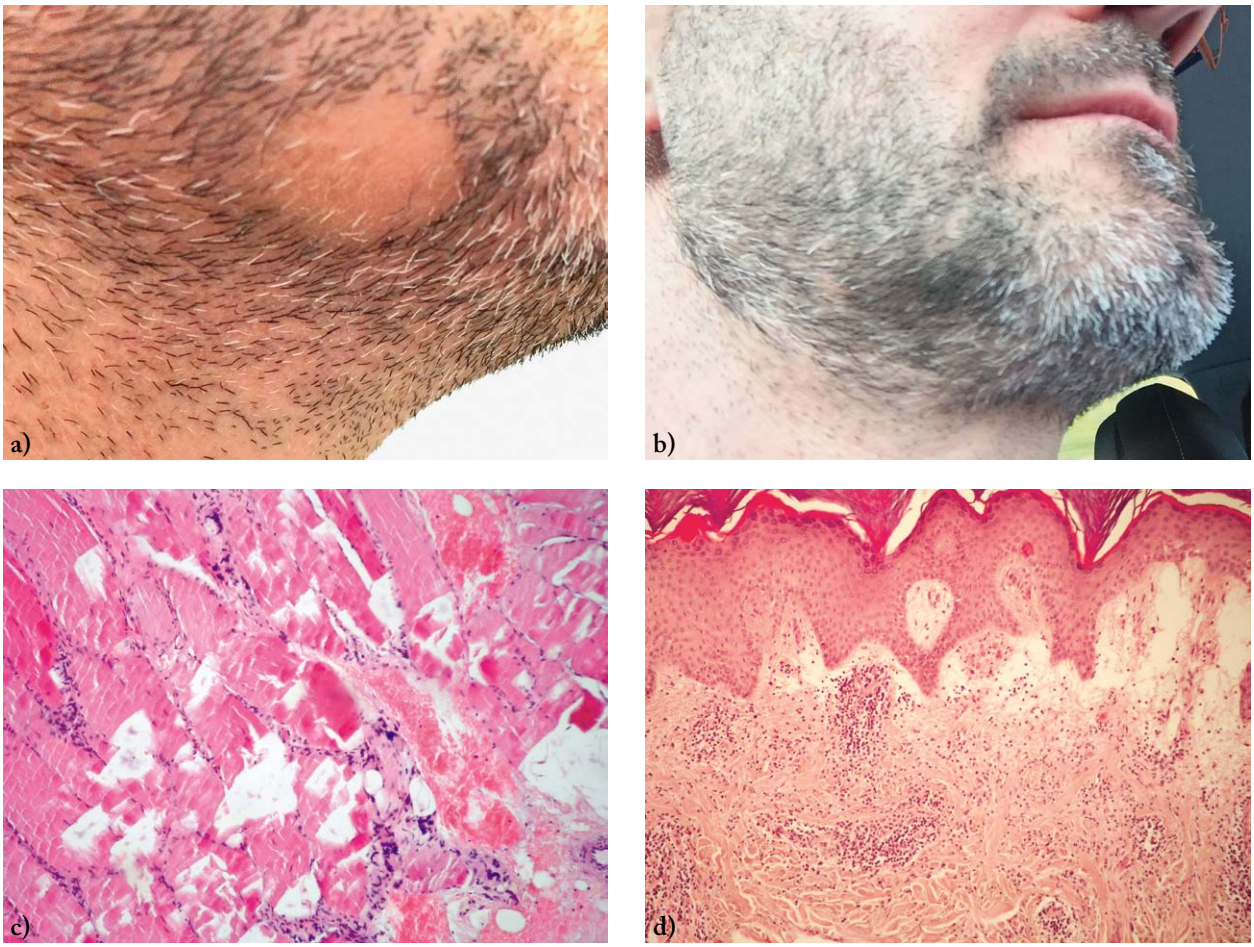

Fig. 2. (a) Clinical picture in the patient with alopecia areata of the beard secondary to thyroid cancer (b); alopecia areata resolution after surgical and oncologic treatment (c); muscles show edema, mild fibrosis and rare lymphocytes (H&E, x100); (d) chronic nonspecific dermatitis and edema in the upper dermis (H&E, x100).

third eczematoid dermatitis patient had lesions (trunk and extremities) that lasted for more than a year despite topical therapy, so expanded diagnostics were performed and revealed elevated prostate-specific antigen (PSA), followed by prostate biopsy that did not confirm cancer. Although the urologist did not see any need for further testing, at our insistence, prostate biopsy was repeated and revealed prostate cancer. In each of our three eczematoid dermatitis patients, allergy tests were positive, which initially led us to incorrect diagnoses, and in all of them, skin lesions gradually resolved after surgical/oncologic treatment.

2) Vasculitis

In a patient who presented with palpable purpura of lower extremities, skin biopsy verified leukocytoclastic vasculitis (Fig. 1d), screening for malignancies revealed elevated alpha fetoprotein (AFP) levels, and gastroenterologic diagnostics [abdominal ultrasonography (US) and CT, biopsy] detected hepatocellular cancer (Fig. 1e). Concerning another patient with recurrent leukocytoclastic vasculitis treated for several years, elevated CYFRA and AFP levels were found; thoracic CT revealed a large mass on the right pulmonary lobe, and further pulmonary diagnostics (bronchoscopy, biopsy) confirmed lung cancer. In our female patient with purpura lesions on lower extremities and significant sideropenic anemia, gastroenterologic diagnostics (EGD with biopsy) finally revealed gastric cancer. Treatment of the aforementioned malignancies led to resolution of skin lesions in two patients, while the patient with hepatocellular cancer died soon after diagnosis.

Table 1. Characteristics of patients with malignancy-related dermatoses (paraneoplastic dermatoses)

Paraneoplastic dermatosis	Sex	Age at disease onset	Duration of skin lesions before seeing a dermatologist	Time from first dermatologic examination to malignancy detection	Positive tumor markers	Other useful diagnostic tools	Malignancy	Outcome
1 Eczematous dermatitis	M (Fig. 1a, b, c)	52 years	4 months	66 months	CEA, CYFRA	EGD	Gastric cancer	In remission
	F	54 years	2 months	9 months	Normal	US	Endometrial cancer	In remission
	M	64 years	3 months	24 months	PSA	Prostate biopsy	Prostate cancer	In remission
2 Vasculitis	M (Fig. 1d, e)	66 years	1 month	1 month	AFP	US, CT	Hepatocellular cancer	Died
	M	56 years	1 month	72 months	CYFRA, AFP	CT, bronchoscopy	Lung cancer	In remission
	F	70 years	3 months	6 months	Normal	EGD	Gastric cancer	In remission
3 Subacute cutaneous lupus erythematosus	M (Fig. 1f, g, h)	64 years	3 months	18 months	CA 19-9, CEA	EGD	Gastric cancer	Died
	F	79 years	1 month	40 months	Normal	Cystoscopy	Bladder cancer	In remission
4 Pruritus	F	54 years	24 months	24 months	LDH	CT, lymph node cytopunction, bone marrow biopsy	Lymphoma (HL)	Died
	M	75 years	12 months	48 months	Normal	Bone marrow aspiration	Multiple myeloma	In remission
5 Chronic urticaria and angioedema	F	89 years	1 month	2 months	Normal	US, lymph node cytopunction	Lymphoma (non-HL)	Died
	M	67 years	3 months	36 months	PSA	Prostate biopsy	Prostate cancer	In remission
6 Alopecia areata	M (Fig. 2a, b)	49 years	4 months	3 months	Normal	Thyroid hormones, antibodies, US	Thyroid cancer	In remission
7 Dermatomyositis	M (Fig. 2c, d)	62 years	2 months	1 month	LDH	EGD	Esophageal cancer	Died
	F	32 years	36 months	18 months	Normal	Thyroid hormones, antibodies, US	Thyroid cancer	In remission
8 Flushing	F	32 years	36 months	18 months	Normal	Thyroid hormones, antibodies, US	Thyroid cancer	In remission
9 Bullous pemphigoid	F	70 years	1 month	1 month	Normal	US, CT	Kidney cancer	In remission
10 Localized scleroderma	F	71 years	12 months	6 months	Normal	Cystoscopy	Bladder cancer	In remission
Mean age /duration		63.17 years	6.65 months	22.06 months				

M = male; F = female; CEA = carcinoembryonic antigen; LDH = lactate dehydrogenase; CYFRA = cytokeratin fragment; EGD = esophagogastroduodenoscopy; PSA = prostate-specific antigen; AFP = alpha fetoprotein; CA 19-9 = cancer antigen 19-9; LDH = lactate dehydrogenase; US = ultrasonography; CT = computed tomography

3) Lupus erythematosus

In our male patient with erythematous lesions on photosensitive areas (face and hands) (Fig. 1f), SCLE was confirmed histologically (Fig. 1g), by direct immunofluorescence (DIF) [immunoglobulin (Ig) IgG and IgM deposits within basal membrane] and by highly positive antinuclear antibodies (1:5120), SS-A/Ro-52 and SS-B antibodies. Since lesions were resistant to chloroquine therapy, we insisted on expanded diagnostics including tumor markers [elevated cancer antigen 19-9 and CEA levels] and gastroscopy with biopsy, which finally led to gastric cancer detection (Fig. 1h). Unfortunately, the patient succumbed to the malignant disease. In our elderly female patient with erythematous macules and papules on photosensitive areas, analysis showed SCLE histologically and by positive antinuclear antibodies (1:640). As she reported disuric problems, we analyzed urine and found microhematuria. We did urine cytology and cystoscopy, followed by transurethral resection (TUR), and finally detected bladder cancer. The patient showed improvement of skin lesions after surgery and chemotherapy.

4) Pruritus

Our female patient with constant pruritus of unknown etiology lasting for two years, followed by cervical lymphadenopathy development, underwent diagnostics (LDH, cervical, thoracic and abdominal CT, enlarged lymph node cytopuncture, bone marrow biopsy, etc.) that revealed Hodgkin's lymphoma (HL), but she died soon after. Another patient struggled with itching (persisting despite oral antihistamines) without skin lesions for five years before diagnosis of multiple myeloma (MM). Since diagnostics showed abnormal blood and urine test results (M proteins), bone marrow aspiration and oncologic treatment for MM was performed, and pruritus was resolved.

5) Chronic urticaria/angioedema

In our 89-year-old patient with angioedema (face and throat) and difficulty breathing, cervical US revealed an enlarged cervical lymph node. Cytopuncture was performed, and the results revealed non-Hodgkin lymphoma (non-HL). Unfortunately, her outcome was fatal. Before arriving at our department, another CU patient had been treated with short-course systemic corticosteroids and antihistamines for many years. The results of expanded diagnostics showed elevated PSA levels; prostate biopsy verified prostate cancer. After surgical removal of the cancer and radiotherapy, he was symptom-free.

6) Alopecia areata

A patient who presented with AA of the beard (Fig. 2a) was, following our suggestion, tested for associated diseases, including thyroid hormones and thyroid antibodies. Since diagnostics revealed a thyroid disturbance, thyroid US and fine needle aspiration biopsy were performed revealing thyroid cancer. After surgery and radioiodine therapy, the AA slowly improved (Fig. 2b).

7) Dermatomyositis

In our 62-year-old male patient with typical DM signs (heliotrope rash, Gottron papules and poikiloderma on photosensitive skin), diagnostic procedures revealed elevated muscle enzyme levels (creatine kinase, LDH). Electromyography showed myopathic findings (proximal muscles of upper and lower limbs), and muscle biopsy verified mild inflammation consistent with early stage DM. Skin biopsy of hand lesions verified chronic nonspecific dermatitis (Fig. 2c). EGD with biopsy suggested esophageal cancer (Fig. 2d). After surgical and oncologic treatment, skin lesions slowly regressed, with recurrence after three years concomitantly with metastasis detection.

8) Flushing

In our young patient with recurrent facial nonspecific redness and history of autoimmune thyroid disorder, thyroid US followed by fine needle aspiration biopsy revealed thyroid cancer. The patient underwent surgery and radioiodine therapy, leading to gradual skin lesion regression.

9) Bullous pemphigoid

In our patient who initially presented with nonspecific erythematous trunk lesions and concomitant pruritus, skin biopsy verified eczematous dermatitis. After several weeks, she developed tense blisters, so diagnostics for BP were performed. Direct immunofluorescence verified complement C3 and C1q deposits within the dermoepidermal junction, and indirect immunofluorescence revealed circulating IgG antibodies.

After expanded diagnostics (abdominal US and CT) and right kidney tumor detection, the patient underwent surgery and the lesions then slowly resolved.

10) Localized scleroderma (morphea)

In our patient who presented with a handful of hard and shiny skin areas on the trunk, localized scleroderma was verified histologically (thickening and homogenization of collagen bundles). Since the patient reported disuric problems, basic laboratory tests were performed, and microhematuria was found. Further testing (urine cytology, cystoscopy and TUR) revealed bladder cancer. After appropriate surgical and oncologic treatment, skin lesions slowly disappeared.

Finally, concerning data on the possible association between targeted anticancer therapies and development of adverse skin effects, only the patient with eczematous dermatitis with gastric cancer came to us because of a relapse of dermatosis, so dermatologic therapy/support was administered.

Discussion

Skin paraneoplasia itself refers to all complex, tumor-induced lesions, primarily due to immune and endocrinological mechanisms such as autoimmune reactions (paraneoplastic pemphigus, DM), granulocytic inflammations (Sweet syndrome, pyoderma gangrenosum), hormone influences (necrolytic migratory erythema – glucagon from glucagonoma, Cushing syndrome – ACTH secreting tumors), metabolic changes (glucagonoma-induced reduction in zinc and amino acids), and growth factors (acanthosis nigricans – epidermal growth factor (EGF), transforming growth factor α (TGF-α), insulin-derived growth factor)[1-8]. Although obligate PDs were not confirmed in work with our patients during this period, they were initially suspected (acanthosis nigricans, the Leser-Trélat sign, acrokeratosis Bazex, etc.) and tested for PDs. A few of our patients presented with velvety to verrucous hyperpigmented lesions in the intertriginous areas, so acanthosis nigricans was suspected (a benign disease mostly associated with obesity and insulin resistance that can sometimes herald the onset of malignancy). Aditionally, a few of our patients presented with explosive onset of multiple pruritic seborrheic keratoses; thus, we suspected Leser-Trélat (a possible sign of internal malignancy). We also had a few patients who presented with erythematous psoriasiform plaques predominantly on acral areas, indicating possible acrokeratosis Bazex, a rare disease associated with malignoma (upper aerodigestive tract, head and neck, lung, gastrointestinal, genitourinary, lymphomas). Therefore, when analyzing skin lesions, it is necessary to know the characteristics of obligate PDs and consider them when we have to establish the diagnosis. To diagnose PD, several criteria should be fulfilled, i.e. evidence for malignancy, unusual resistance of skin lesions to therapy, and simultaneous development of malignancy and PD[1]. However, common dermatoses may also be PDs even without meeting these criteria, especially if they behave in an atypical or aggressive manner, or are recalcitrant to standard therapies. Furthermore, as internal malignancies are sometimes asymptomatic, skin markers could be possible indicators.

Several studies have evaluated the potential associations between skin allergies and malignancies, e.g., HL, lung, pancreas, which could be explained by their complex relationship (chronic inflammation, immunosurveillance, prophylaxis, inappropriate T-helper cell immune skewing)[9-14]. Sometimes, in eczematoid dermatitis patients, allergy is confirmed by tests, which may lead to incorrect diagnoses and treatment courses, as was the case in our patients. Since eczematoid lesions and pruritus are the most common cutaneous HL manifestations, eczematoid dermatitis onset in adults should be considered a possible warning sign deserving further investigation for HL (full lymph-node examination, complete blood count with differential, chest x-ray, etc.)[14]. Our three paraneoplastic eczematoid dermatitis cases that resulted in resolution after surgical/oncologic treatment are, to our knowledge, the first eczematous dermatitis patients associated with gastric, prostate and endometrial cancer in the English literature. As our eczematoid dermatitis patients denied malignancy symptoms, only the skin manifestations indicated malignancy.

Chronic urticaria and angioedema can also be paraneoplastic signs (lymphomas, prostate, breast), as confirmed in our patients with non-HL and prostate cancer[15-20]. Since 80% of CU cases are of unknown etiology, malignancy association remains controversial. Chen *et al.* noticed a higher malignancy risk in CU patients, especially of hematologic malignancies, which is commonly detected within the first year of disease onset[15]. Our patient who had suffered from CU

for a number of years felt symptom relief after we detected prostate cancer and its appropriate treatment.

Malignancy-associated vasculitis is rare and seen with hematologic or sometimes solid malignancies (bronchi, kidneys, bladder, prostate)[21-26]. Other vasculitis types may also be associated with solid tumors, e.g., polyarteritis nodosa, Henoch-Schönlein purpura (IgA vasculitis), and small-vessel vasculitis[27-29]. Chronologically, vasculitis can occur years before malignancy is diagnosed, as in our patient with lung cancer, almost concurrently, or after diagnosis, as in our patients with gastric and hepatocellular cancer[22]. Therefore, search for a malignancy should be based on detailed personal and family histories, physical check-up, and basic laboratory tests. Successful malignancy treatment can also resolve concurrent vasculitis, as our vasculitis cases confirm. Rarely, other vascular skin disorders have also been markers of internal malignancies, e.g., 'flushing' as a manifestation of a carcinoid syndrome possibly associated with malignancies of the small intestine and colon, bronchi, stomach, pancreas, and thyroid[23,24,30,31]. However, in our patient with thyroid cancer, subsequent surgical/oncologic treatment induced gradual skin lesion regression.

As for generalized pruritus in patients without jaundice, search for a systemic disease (e.g., thyroid, liver, kidney) and potential malignancy is crucial, particularly in generalized refractory pruritus without skin lesions and in elderly persons[32]. Paraneoplastic pruritus can be the result of a malignancy local effect on tissue or a systemic reaction to a malignancy[33]. This type of pruritus usually occurs together with lymphoproliferative malignancies (i.e., HL and non-HL, leukemia, MM), as in our two cases, but also with solid tumors (e.g., gastrointestinal, lung, prostate, breast, central nervous system)[32-34]. Itch severity correlates with HL disease stage[33]. Chronologically, this type of pruritus can precede a malignancy or occur later in its advanced stages[33-35], as in our patient with MM. It has been established that paraneoplastic pruritus can be improved if the underlying malignancy is treated simultaneously[35], which is also supported by our case.

Paraneoplastic diseases and collagen vascular diseases may manifest similarly and/or simultaneously, often with many skin (acral) findings (LE, localized scleroderma, DM, rheumatoid arthritis). Therefore, dermatologists could be the patient's first physician to suspect a malignancy or collagen vascular disease[35]. On occasion, LE can be a paraneoplastic manifestation, especially in newly-diagnosed cases with a nontypical picture, as in our SCLE patient with gastric tumor[34]. Similarly, Koritala *et al.* report atypical SCLE in an elderly man with underlying esophageal cancer who responded to cytotoxic chemotherapy[38]. Regarding paraneoplastic DM, it often manifests with a fulminant course, as in our patient with esophageal cancer. In adults, up to 20% of DM cases are paraneoplastic, particularly in elderly patients (approximately 15%-30%), and in women for whom the risk doubles[1,39]. In women with DM, common cancers are uterine, ovarian and breast; in men with DM, testicular cancer and, in advanced age, colon, bronchi, gastric, pancreas and prostate cancers are common[5,7,39]. Its pathophysiological mechanism most likely includes malignancy-stimulated production of antibodies and a T-cell-mediated immune response that damages the skin and muscles. The abovementioned cancers are usually detected within one to three years[40,41]. As DM skin manifestations can completely disappear after tumor removal, a timely diagnosis is crucial for the outcome of both the malignancy and the skin[1].

Cancer and localized scleroderma (paraneoplastic scleroderma) usually develop independently, but sometimes they do occur together[42-45]. To date, paraneoplastic scleroderma has been associated with various malignancies (lung, carcinoid, plasma cell, ovary, cervix, breast, esophagus, gastric, nasopharynx, melanoma, sarcoma)[42,43]. Skin manifestations may be induced by substances secreted by the tumor cells (hormones, cytokines, etc.), which further induce cytotoxic and antibody responses[38-41].

Elderly patients with localized scleroderma may also have a short cancer-scleroderma interval, as recorded in our localized scleroderma patient with bladder cancer.

Associations between BP and internal malignancies have previously been observed, e.g., association with hematologic malignancies, and less frequently with other cancers (colon, gastric, kidney, lung, cholangiocarcinoma, tongue)[46-50]. Pathogenetically, it is likely that antibodies are directed against tumor-specific antigens and cross-react with antigens in the basement membrane zone, leading to blister formation. As dra-

matic skin improvement was observed after appropriate malignancy treatment, oncologic screening is suggested in early-onset BP, in patients with oncologic history, in those with signs/symptoms possibly related to a malignancy, and in BP refractory to common immunosuppressive therapy.

An association between AA and hematologic malignancies (e.g., HL) and digestive tumors has also been presented in the literature[51,52]. Thus, Gong and Lim report a case of a man who was diagnosed with AA several months prior to HL onset and in whom, after HL treatment, complete AA resolution was observed[52], as in our AA patient with thyroid cancer. To our knowledge, our patient's AA-thyroid cancer connection is the first such case presented in the literature.

In cases of atypical or persistent lesions, expanded diagnostics can be crucial, as confirmed by our results (tumor markers, endoscopic tests, x-rays, CT scans, US, tissue biopsies, etc.). Consequently, the role of dermatologic examination may be crucial, making this a justification for laboratory tests and sophisticated diagnostic imaging techniques for malignancy detection[53]. Timely detection of a malignancy stops widespread malignoma, as observed in our patients with vasculitis and lung cancer, flushing and AA with thyroid cancer, SCLE with bladder cancer, eczematous dermatitis and CU with prostate and gastric cancers. In PD cases, therefore, there is the need for involvement and active role of other specialists (e.g., internal medicine, oncology) and further testing according to their suggestions, even though they often do not see the need to do it because general recommendations do not require it. Aditionally, we emphasize the need for more teamwork and multidisciplinary approach involving radiologists, surgeons, pathologists, geneticists, and other specialists.

In conclusion, only exact knowledge about malignancy-related skin changes (PDs) can lead to successful treatment of both. Since dermatoses and malignancies mostly develop simultaneously, curing the malignancy usually causes dermatosis to regress; recurrence of the latter can indicate a cancer relapse or metastases. Early malignancy detection makes early introduction of surgical/oncologic therapy and metastasis prevention possible. In this way, we can avoid expensive oncologic therapies in advanced stages, revolving door visits to specialists and reduce the (financial) burden on the healthcare system.

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Sažetak

MOGU LI SE NA KOŽI ODRAZITI MALIGNOMI UNUTARNJIH ORGANA? DOKAZI IZ KLINIČKIH SLUČAJEVA

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Iako postoje mnogi pojedinačni prikazi slučajeva paraneoplastičnih dermatoza u literaturi, vrlo je malo radova koji prikazuju mnogobrojne slučajeve. Provedena je retrospektivna studija kojom smo istražili kožne promjene i provedenu dijagnostiku radi dokaza paraneoplastičnih dermatoza i s njima povezanih zloćudnih bolesti. Pritom smo uzeli u obzir dijagnostičko-terapijske rezultate, postojeće manifestacije i provođenje kirurško-onkološke terapije. Analizom smo paraneoplastične dermatoze utvrdili kod 17 bolesnika s različitim kožnim promjenama: ekcematoidnim dermatitisom, vaskulitisom, subakutnim kožnim eritematoznim lupusom, pruritusom, kroničnom urtikarijom/angioedemom, alopecijom areatom, crvenilom, buloznim pemfigoidom, dermatomiozitisom i lokaliziranom sklerodermijom (morfeom). One su bile povezane s različitim malignomima unutarnjih organa i hematološkim malignomima (zabilježena su 3 karcinoma želuca, 2 karcinoma prostate, 2 karcinoma mokraćnog mjehura, 2 karcinoma štitnjače i 2 limfoma te po jedan slučaj karcinoma pluća, jetre, endometrija, bubrega i multipli mijelom). Većina kožnih promjena se postupno povukla nakon odgovarajućeg liječenja zloćudne bolesti. Prema našim saznanjima, naša tri slučaja paraneoplastičnog ekcematoidnog dermatitisa su prvi slučajevi te bolesti povezane s karcinomima želuca, prostate i endometrija. Također smo prikazali i slučaj bolesnika s alopecijom areatom brade koji je bio povezan s karcinomom štitne žlijezde. Rano otkrivanje malignih bolesti pomoću praćenja kožnih promjena vodi do pravodobne kirurško/onkološke terapije i moguće regresije kožnih promjena. Time se ujedno smanjuje lutanje bolesnika kod raznih specijalista i sveukupni trošak zdravstvenog sustava.

Ključne riječi: *Paraneoplastični poremećaji kože; Malignitet; Karcinom; Koža; Ekcem; Vaskulitis; Eritemski lupus; Svrbež; Urtikarija; Angioedem; Alopecija; Pemfigoid; Dermatomiozitis; Skleroderma*