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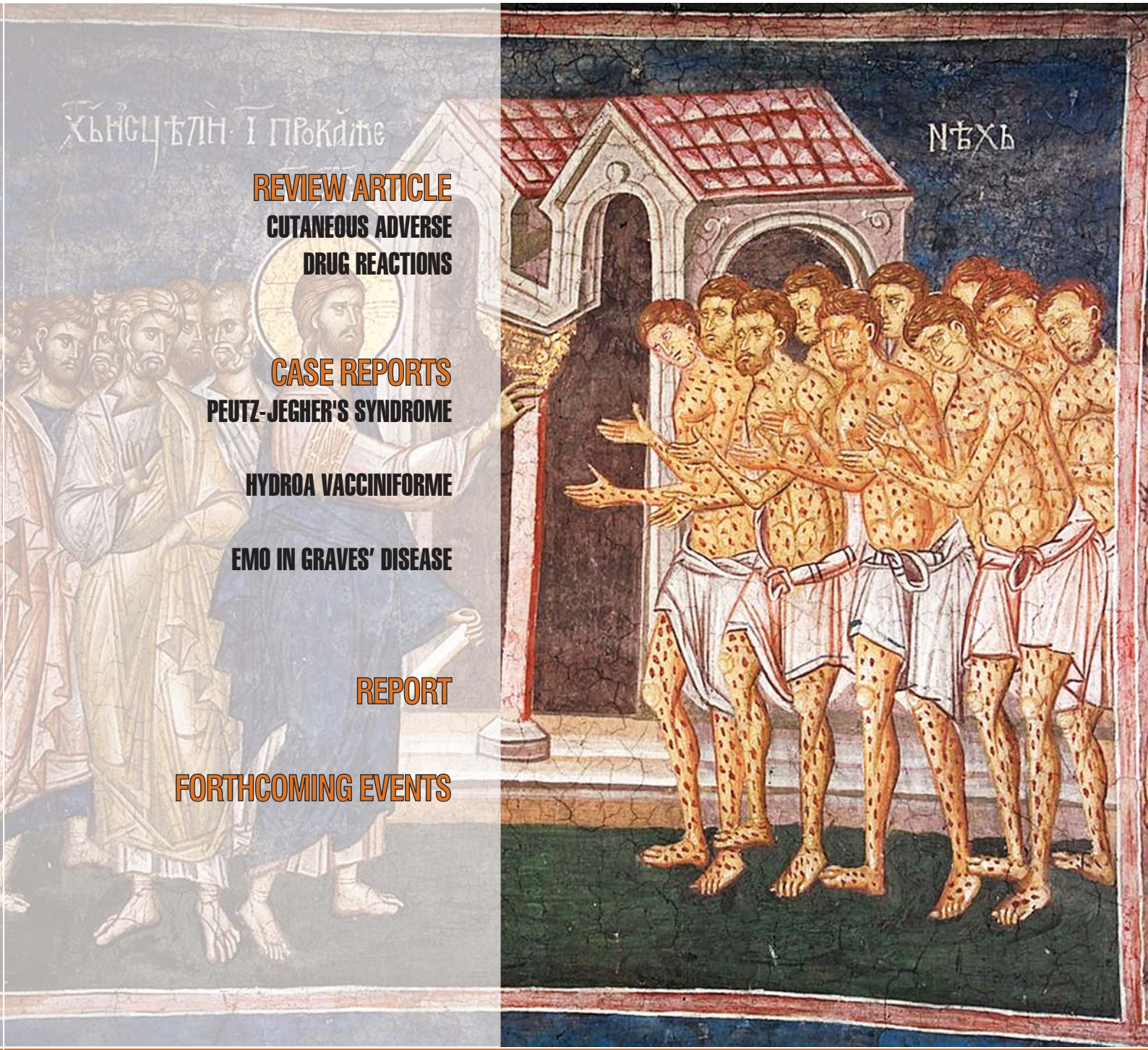

REVIEW ARTICLE

CUTANEOUS ADVERSE DRUG REACTIONS

CASE REPORTS

PEUTZ-JEGHER'S SYNDROME

HYDROA VACCINIFORME

EMO IN GRAVES' DISEASE

REPORT

FORTHCOMING EVENTS

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Cutaneous adverse drug reactions

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Abstract

Adverse drug reactions may be defined as undesirable clinical manifestations resulting from administration of a particular drug; this includes reactions due to overdose, predictable side effects, and unanticipated adverse manifestations. Adverse drug effects on the skin are among the most frequent reactions and, according to a study, account for approximately 14% of all adverse drug reactions. However, the incidence of cutaneous adverse effects in general population is unknown. Systemic drug administration results in various cutaneous adverse reactions, and medications used in the treatment of skin diseases themselves have their own adverse effects. Adverse drug reactions include a wide range of effects, from harmless exanthema of short duration, urticaria to systemic cutaneous reactions such as drug rash with eosinophilia and systemic symptoms (DRESS) or toxic epidermal necrolysis. Exanthematous eruptions and urticaria are the two most common forms of cutaneous drug reactions. Less common include fixed eruptions, lichenoid, pustular, bullous and vasculitis reactions. The most severe cutaneous and mucosal adverse drug reactions are epidermal necrolysis, which is usually drug-induced, DRESS syndrome, and acute generalized exanthematous pustulosis. Therefore, the diagnostic of adverse drug reactions requires a detailed history of drug intake and development of skin disorders, excellent knowledge of clinical presentations for a wide range of drug-induced skin reactions as well as of the very medications being taken by patients. In addition to details on drug intake, it is necessary to learn about taking herbal and alternative preparations, which may also cause adverse reactions. A drug started within 6 weeks of the development of disorders is considered the most common cause of adverse reaction, as well as drugs taken periodically but regularly. Once a reaction has occurred, it is important to prevent future similar reactions with the same drug or a cross-reacting medication. Early withdrawal of all potentially responsible drugs is essential, particularly in case of severe drug reactions.

Key words

Dermatology; Drug Therapy + adverse effects; Drug Eruptions; Drug Toxicity; Skin Diseases + etiology + therapy

Cutaneous adverse drug reactions are among the most frequent reactions and, according to one study, they account for approximately 14% of all adverse drug reactions. Although information on the incidence of cutaneous adverse effects in general population are unknown, a large prospective study has shown that 2.7% of 48.000 hospitalized patients had cutaneous adverse drug reactions, and Roujeau and Stern have estimated that 1 of 1.000 hospitalized patients had a severe cutaneous adverse drug reaction. In pre-marketing studies, the incidence of adverse reactions is 0.1%-1%, but only in the post-marketing period and after administration of the drug in large patients' series the real incidence can be estimated (1-7). For instance, in a study including 13.697 patients who were examined by a general practitioner, 2.1%, 1.6% and 1.1% had trimetoprim-sulfametoxazol-induced, fluoroquinolone-induced and penicillin-induced cutaneous adverse reactions, respectively (5). This corresponds with the estimation that adverse reactions are caused by antibiotics in 1-5% of patients (1-7). Adverse reactions have also been established to develop more commonly in females and human immunodeficiency virus (HIV) patients, and the incidence has been shown to increase with age and the number of medicines being taken by the patient, but

Table 2. Expected cutaneous and mucosal adverse drug effects

Adverse effects	The most common cases
Pharmacologic adverse effects	Cyclosporine-induced gingival hyperplasia and hypertrichosis
	Chemotherapy-induced alopecia and mucositis
	Retinoid-induced cutaneous and mucosal xerosis
	Epidermal growth factor receptor (EGFR) inhibitor-induced acneiform eruptions
Cumulative toxicity	Skin hyperpigmentation and discoloration secondary to minocycline and amiodarone
Delayed toxicity	Development of actinic keratoses, palmoplantar keratoses and planocellular carcinoma following arsenic exposure
	Accelerated skin aging, premature skin aging secondary to sunlight and skin cancer in long-term (>12 weeks) voriconazole administration
Metabolic drug effects	Bexarotene: hypertriglyceridemia and xanthomas
	Isoniazid: pellagra-like disorders
Exacerbation of skin diseases	Androgens and corticosteroids: development and acne exacerbation
	Beta-blockers, lithium, interferon-α, tumor necrosis factor
	TNF-α inhibitors: exacerbation of psoriasis

EGFR, epidermal growth factor receptor; TNF-α, tumor necrosis factor α

Immune-mediated and idiosyncratic cutaneous and mucosal reactions

Drug-induced rashes

Drug-induced morbilliform and maculopapular rash accounts for 95% of all drug-induced cutaneous reactions (1-7). Rash develops in the form of small erythematous macules with 2-3 mm in diameter (morbilliform rash) or up to 5 mm in diameter, including formation of papules (maculopapular rash) that may have a sporadic pattern on the trunk and symmetrically expand to upper and lower extremities (Figure 1).

T-cell immune response with drug-specific T-cell proliferation underlies the development of drug-induced rashes (8, 9). Rashes develop within 4-14 days of drug intake and resolve slowly following drug discontinuation, sometimes with subsequent residual hyperpigmentation and desquamation (1-9). Table 3 shows the most common causes of rashes.

Rash is a manifestation of the DRESS syndrome, but may also precede toxic epidermal necrolysis

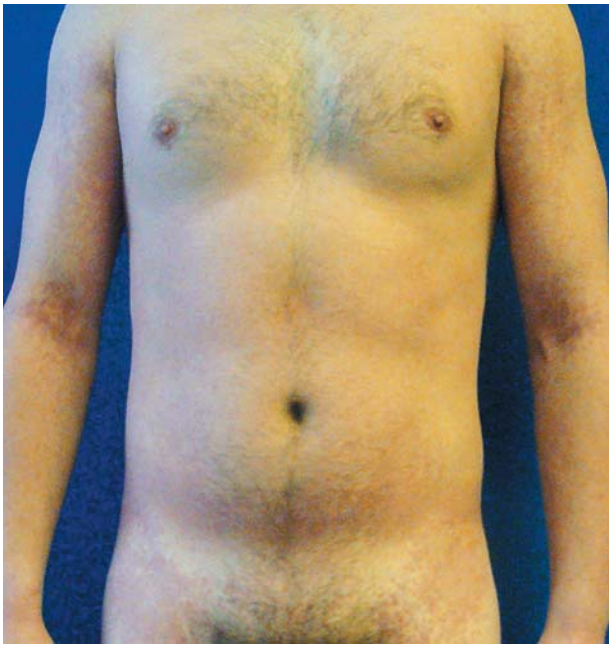

Figure 1. Ampicillin-induced rash

are histamine and prostaglandins released through the mast cell degranulation. The main characteristic of urticaria is development of transient erythematous and edematous papules and plaques which resolve in several hours but develop at other sites, with individual disorders that last not longer than 24 hours. The reaction sometimes presents with deep elastic edemas, angioedemas, isolated and without urticaria or associated with urticaria. Edema and exudation of the laryngeal, respiratory and gastrointestinal tract mucosa result in hoarseness, rhinorrhea, bronchospasm, nausea, vomiting and diarrhea, in some patients causing hypotension, tachycardia, disturbed consciousness and anaphylaxis. Anaphylaxis occurs in 1 of 5.000 cases exposed to penicillin and develops as anaphylactoid reaction with administration of radiocontrast agents (1-5, 10, 11).

Some drugs result in mast cell degranulation without the immune mechanism, whereas other drugs cause mast cell degranulation through specific IgE antibodies created at the very first contact with the drug and through the development of a specific immune reaction to the drug – an early IgE antibody-mediated hypersensitivity reaction (Table 4) (1-5, 10, 11).

Drugs most commonly cause urticaria/angioedema through an early IgE antibody-mediated hypersensitivity reaction (allergic IgE-mediated urticaria) are antibiotics, and in the era of treatment with monoclonal antibodies recognized by the body as foreign proteins, the frequency of acute urticarias will be more and more increasing due to reactions to this drug group. When diagnosing IgE-mediated drug reactions, prick tests showed as useful as well as IgE blood tests. Anyhow, prick tests bear the risk of anaphylactic reactions, so they are only performed by experienced doctors. On the other hand, blood tests for drug IgE antibodies are also useful to confirm the drug reaction if done within the first 6 months following the drug reaction, but so far there is a very small number of drugs for which there are commercially available tests (1-5, 10, 11). The most available tests are the ones used to determine IgE antibodies against penicillin, ampicillin, amoxicillin, cephalosporins, insulin, sulfametoxazole, less frequently against erythromycin and tetracyclines. Although clinicians too often attribute rash to drug reactions and recommend drug avoidance, it has been shown that only 10-20% of patients really had a genuine allergic reaction to penicillin in spite of everyone stating to have been allergic to penicillin. Therefore, in patients in need for penicillin treatment, prick test should be performed. If less than 6 months elapsed since the reaction to penicillin, IgE blood test is also useful (1-5, 10, 11).

Table 4. Agents causing urticaria and angioedema

Type of urticaria	Agents most commonly causing a reaction
Allergic autoimmune urticaria/angioedema/anaphylaxis	Penicillin
	Cephalosporins
	Sulphonamides and other sulpha group
	preparations
	Tetracyclines (minocycline)
Non-immunological direct mast cell degranulation	Opiates (codeine), contrast agents, vancomycine, relaxants, polymyxin B, dextran
Non-immunological-pseudoallergens	Aspirin, other NSAIDs
Non-immunological orofacial angioedema/urticaria	ACE inhibitors
Non-immunological contact urticaria	Sorbic and benzoic acid in the eye drops
Non-immunological systemic capillary leak syndrome	Interleukin-2

NSAIDs, nonsteridal antiinphlammatory drugs; ACE, angiotensin-converting enzyme

Fixed eruption always develops as a drug reaction, occurring 30 minutes to 16 hours after drug intake. Table 5 shows the agents most commonly causing fixed erythema.

Serum sickness-like reaction and drug-induced vasculitis

Some drugs such as cefaclor, cefprozil and bupropion may cause a serum sickness-like reaction, with febricity, lymphadenopathy and eosinophilia, and onset of urticaria and/or rash and arthralgia following 1-3 weeks after the initiation of the treatment. Unlike real serum sickness, there is no renal impairment, immune complex impairment or complement consumption or development of vasculitis (1-7).

Palpable purpura with a histopathological substrate of leukocytoclastic vasculitis may be caused by numerous drugs, most commonly within 7-21 days from the initiation of the treatment. Drug-induced vasculitis develops in 10-15% of cases of cutaneous necrotizing vasculitis (Table 6). As in idiopathic cutaneous necrotizing vasculitis, the eruptions develop on lower extremities, spreading to the trunk and less frequently to upper extremities (Figure 3). Following initial purpura, some disorders develop into bullae, ulcers and nodes, Raynaud's phenomenon or even digital necrosis. At the same time, the same vasculitic process can affect the liver, kidneys, gastrointestinal tract and CNS as well, with fatal consequences. Considering the fact that presence of p-ANCA (perinuclear antineutrophil cytoplasmic antibodies) antibodies was also shown in drug-induced vasculitis, a differential diagnosis of autoimmune systemic vasculitis may be very difficult. Sometimes the presence of eosinophils in a tissue may indicate a possible drug triggering the reaction (1-7, 13).

Drug-induced lichenoid reaction

Drug-induced lichenoid eruption is difficult to be clinically differentiated from idiopathic *lichen planus*, but skin changes are usually more widespread and most commonly there are no mucosal changes in the

Table 6. The most common agents causing cutaneous necrotizing vasculitis

Agent
Propylthiouracil/other antithyroid drugs
TNF blockers
COX-2 inhibitors
G-CSF
Hydralazine
Leukotriene inhibitors
Minocycline
NSAID
Penicillins
Quinolones
Serum reactions and antithymocyte globulin
Streptokinase

TNF, tumor necrosis factor; COX, cyclo-oxygenase; G - CSF, granulocyte colony-stimulating factor; NSAIDs, nonsteridal antiinphlammatory drugs

the drug (Table 7). In addition, a lichenoid eruption, unlike exanthematous eruptions, takes several months following the discontinuation of the incriminate drug to resolve (1-7, 14).

Lichenoid eruption may be more confidentially differentiated from idiopathic *lichen planus* using a histological finding and direct immunofluorescence examination of the skin. Histopathological analysis usually reveals significant presence of eosinophils, while direct immunofluorescence often shows lack of immunoreactant deposits (1-7, 14).

Table 7. Agents most commonly causing lichenoid eruptions

Agent	Time to reaction onset
ACE inhibitors	3 - 6 months
Beta blockers	1 year
Penicilliamine	2 months - 3 years
Antimalarial agents	

ACE, angiotensin-converting enzyme

Phototoxic and photoallergic reactions

Drug-induced photosensitivity includes reactions where the drug - light (sunlight, artificial light) interaction results in non-immune mediated phototoxicity mechanisms and an immune-mediated photoallergic reaction (1-7).

In phototoxic reactions, which may be expected in some drugs, the drug enters into interaction with light in the skin causing damage evidenced by the development of uniform erythema in areas exposed to sunlight, resolving gradually but leaving hyperpigmentation. In pseudoporphyria, it developed less commonly, most frequently as a reaction to naproxen, vesicles and erosions occur, but if the process involves nails as well, it results in nail plate elevation from the nail bed, i.e. photo-onycholysis. Phototoxic reactions, with or without photo-onycholysis, are caused by tetracyclines (doxycycline, demeclocycline), NSAIDs (nonsteroidal antiinphlammatory drugs) and fluoroquinolones, high-dose methotrexate, less frequently by psoralens (PUVA psoralen and ultraviolet A treatment), phenothiazines and amiodarone (1-7).

Photoallergic reactions include development of new antigenic determinants during the drug-light interaction, together with the immune reaction to the so-called "photoallergen". Once the reaction occurs, it does not require further exposure to sunlight to be maintained. In their clinical manifestations, photoallergic reactions resemble eczema or a lichenoid eruption, but the changes are distributed to sunlight-exposed areas, at least in the initial period. These changes are always associated with pronounced itching and later lichenification. Following the discontinuation of the drug, they resolve very slowly and sometimes remain for several months, even years thereafter. Such patients are in the range of so-called "chronic actinic dermatitis". Drugs most commonly causing such reactions usually contain sulpha group of drugs: thiazide diuretics, sulphonamides, phenothiazines and sulphonylurea. Photoallergic reactions are less commonly caused by quinine, quinidine, tricyclic antidepressants, antimalarial agents and NSAIDs 1-7).

Systemic and severe adverse drug reactions

DRESS syndrome (Drug Rash/Reaction with Eosinophilia and Systemic Symptoms)

When describing a drug reaction associated with systemic symptoms, the term DRESS has replaced the term hypersensitivity syndrome. Although the original acronym contained the term *drug rash*, it has been replaced with *drug reaction* due to isolated cases of drug reactions with eosinophilia and systemic symptoms but without rash (1-7, 15).

DRESS presents with febricity and generalized rash, morbilliform or maculopapular rash, with

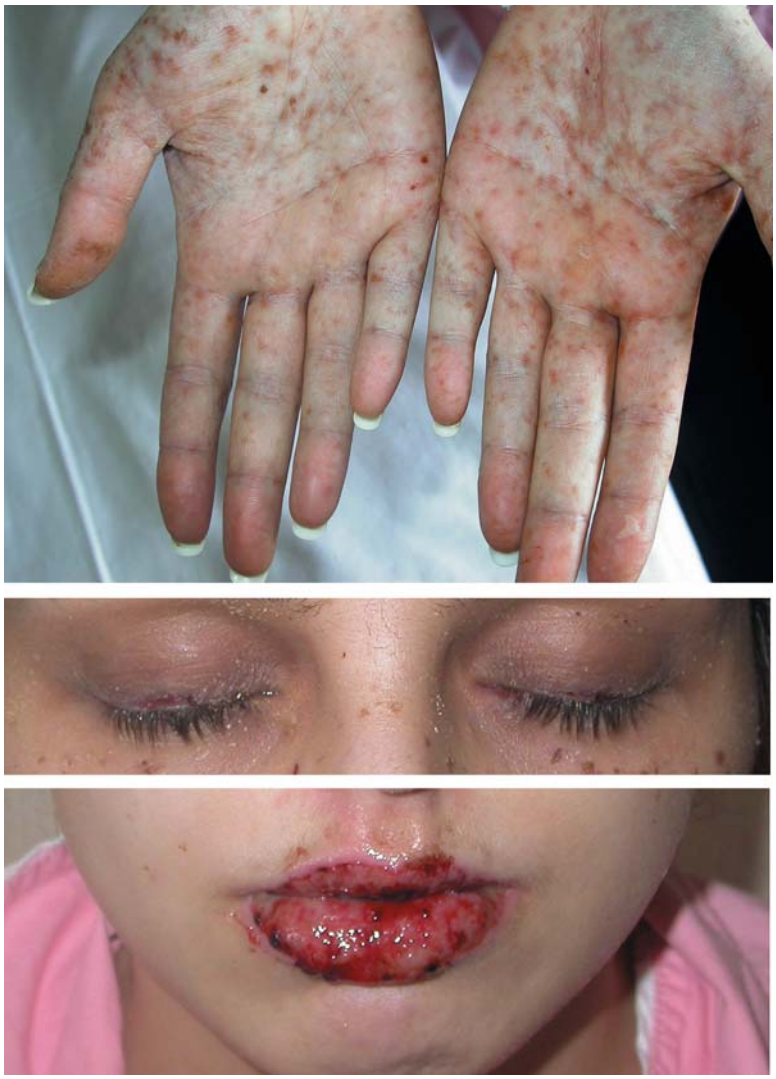

Figure 5. Stevens-Johnson syndrome (lamotrigine-induced)

macules may develop even in more intensive forms of SJS and TEN, respectively, indicating the grade of intensity of such changes as the difference between these two entities. Necrolysis involving more than 30% of the skin surface is considered a limit for the diagnosis of toxic epidermal necrolysis, and necrolysis 10 - 30% of the skin surface is considered a SJS/TEN overlap syndrome. The treatment is based on the discontinuation of the drug and a supportive symptomatic therapy. This process may be stopped by an early administration of intravenous immunoglobulins and infliximab. Administration of systemic corticosteroids over several days or weeks is contraindicated in TEN, since they slow down the healing and increase the risk of sepsis. Patients with necrolysis involving large body surfaces should be managed in sterile burn unit rooms since appropriate care and supportive therapy are necessary (1-7, 19, 20).

Differential diagnosis of SJS includes first and foremost erythema multiforme, which used to be, in its major form, considered a synonym for Stevens-Johnson syndrome, although these two entities may be both clinically and histologically differentiated, having etiologic differences as well. EM is most commonly caused by a virus, whereas SJS is most commonly caused by a drug and in less than 5% of cases by an infection. Its most common cause is *Mycoplasma pneumoniae* (1-7, 17-20).

Table 10. Adverse drug reactions manifested as idiopathic dermatoses (1-7, 22-25)

Clinical presentation	Drugs most commonly causing a reaction
Systemic contact dermatitis (reaction-inducing drugs/cutaneous allergen)	Aminophylline, hydroxyzine, cetirizine/ ethylenediamine dihydrochloride
	Disulphiram/tiuram
	Oral antibiotics/quinolones
	Streptomycin, kanamycin/neomycin
Erythroderma	Allopurinol, beta-lactam antibiotics, carbamazepine, oxcarbamazepine,gold salts, phenobarbiton, phenytoin, sulphonamides, sulphasalazine, zalcitabine
Acneiform eruptions/folliculitis	Corticosteroids, androgens, hydantoins, lithium, oral contraceptives, halogenides, rarely azathioprine, chinidine, ACTH, EGFR-inhibitor-induced acneiform eruptions
Warfarin and heparin-induced skin necrosis	Warfarin
	Heparin and low molecular weight heparin
Pemphigus	Drugs containing the thiol group: penicillamine, ACE inhibitors (capropril), gold salts, pyritinol
	Drugs not containing the thiol group: antibiotics (especially β-lactam antibiotics), pyrazolone derivatives, nifedipine, propranolol, piroxicam,phenobarbiton
Bullous pemphigoid	Furosemide, penicillin and its derivatives, sulphasalazine
Linear IgA dermatosis	Vancomycin, β-lactam antibiotics, capropril, NSAID, phenytoin, rifampicin, sulphonamides, lithium, furosemide, amiodaron,G-CSF
Pityriasis rosea	Gold salts, ACE inhibitors, metronidazole, isotretinoin, blockers (labetalol), barbiturates, arsene, sulphasalazine, bismuth, clonidine,imatinib, mercury preparations, metoxypromazine, penicillamine, ketotifen, tripelennamine
Psoriasiform eruptions	Lithium, beta blockers, antimalarial agents, interferon-α
Cutaneous pseudolymphoma	Phenobarbiton, carbamazepine, chlorpromazine, promethazine imatinib,angiotensin II receptor blockers
Systemic lupus erythematosus	Procainamide, hydralazine, chlorpromazine, isoniazid, methyldopa, propylthiouracil, chinidine, practolol, penicillamine, PUVA, anti-TNF-α agents, minocycline
Subacute lupus erythematosus	Hydrochlorothiazide, calcium channel blockers, terbinafine, NSAID, griseofulvine, docetaxel, PUVA, interferon, antiTNF-α agents
Sweet's syndrome	G-CSF, GM-CSF, all-trans retinoic acid
Neutrophilic eccrine hidradenitis	Cytarabine, mitoxantrone, bleomycin, anthracyclines, cyclophosfamide

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Dematološka neželjena dejstva lekova

Sažetak

Definicija: Neželjena dejstva lekova mogu se definisati kao nepoželjna klinička manifestacija, to jest posledica primene određenog leka što uključuje reakcije usled predoziranja lekom, predvidljive neželjene efekte i neočekivane neželjene manifestacije. Neželjena dejstva lekova na koži jedna su od najčešćih reakcija i, prema jednoj studiji, obuhvataju oko 14% svih neželjenih reakcija na lekove.

Kliničke manifestacije: Neželjene reakcije na lekove obuhvataju širok spektar manifestacija, od bezazlenih egzantema kratkog trajanja, preko urtikarije do sistemskih reakcija koje se manifestuju i na koži, poput sindroma egzantema izazvanog lekom s eozinofilijom i sistemskim simptomima - DRESS sindrom (eng. *drug induced rash with eosinophilia and systemic symptoms*) ili toksične epidermalne nekrolize. Dve najčešće forme neželjenih reakcija na koži koje izazivaju lekovi su egzantemi i urtikarija. Ređe forme neželjenih reakcija na koži koje izazivaju lekovi su fiksne erupcije, lihenoidne, pustulozne, bulozne i vaskulitis reakcije. Najteže neželjene reakcije lekova na koži i sluzokožama jesu toksična epidermalna nekroliza koja je gotovo uvek izazvana lekom, DRESS sindrom i akutna generalizovana egzantematozna pustuloza.

Dijagnoza: Postavljanje dijagnoze neželjene reakcije na lek stoga zahteva detaljne anamnestičke podatke o hronologiji uzimanja lekova i pojave promena na koži, dobro poznavanje kliničke slike velikog spektra

Peutz-Jegher's syndrome – a case report

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Abstract

Peutz-Jegher's syndrome is a hereditary disorder characterized by melanocytic macules on the lips and buccal mucosa and multiple gastrointestinal hamartomatous polyps. It is caused by a mutation localized on chromosome 19p13.3. Skin and mucosal pigmentation may be present at birth and usually occur in early childhood, but occasionally may develop later. It is associated with an increased risk of malignancy for gastrointestinal carcinoma and also for breast, ovarian, testiscular, pancreatic and gallbladder cancer. We report a 12-year-old girl who presented with disseminated petty yellowish macules on the bridge of her nose, numerous brown to bluish black macules on her lips and buccal mucosa. Mucocutaneous pigmentation has been present from the age of five, with a negative family history. In our patient, esophageal endoscopy was normal, while the endoscopy of stomach and duodenum revealed multiple diminutive polyps. After clinical evaluation, there were no indications for therapy. Further follow up was suggested. Continuous surveillance is very important for patients with Peutz-Jegher's syndrome in order to reduce risks of cancer and prevent other morbidity and mortality.

Key words

Peutz-Jegher's Syndrome; Intestinal Polyposis; Child; Hyperpigmentation; Endoscopy, Gastrointestinal; Follow-Up Studies

Peutz-Jegher's syndrome (PJS), also known as periorofacial lentiginosis, is a hereditary disorder characterized by melanocytic macules on the lips, buccal mucosa and multiple gastrointestinal hamartomatous polyps. PJS was first described by Peutz in 1921, and later, by Jeghers, in 1949.

PJS is inherited as an autosomal-dominant trait, and the gene has been mapped to chromosome 19 p 13.3, the serine/threonine protein kinase-11 gene (STK11) involved in the growth control regulation (1).

Buccal lesions tend to be permanent, while the cutaneous may fade. The acral, periorbital lesions and conjunctival pigmented macules can also be seen. The hallmark of PJS, are hamartomatous polyps that may occur in every part of the gastrointestinal tract.

The lifetime risk for gastrointestinal carcinoma is high and exceeds 50%, and there is an increased incidence of breast, ovarian, testicular, pancreatic, and gallbladder cancer (2).

Case report

A 12-year-old girl was admitted to our Clinic with disseminated petty yellowish macules on the bridge of her nose (Figure 1) and numerous brown to bluish-black macules (up to 5 mm in diameter) on her lips and on buccal mucosa (Figure 2). She was the first child from the first, well controlled, full term pregnancy. The rest of the physical findings were normal. Mucocutaneous pigmentation has been

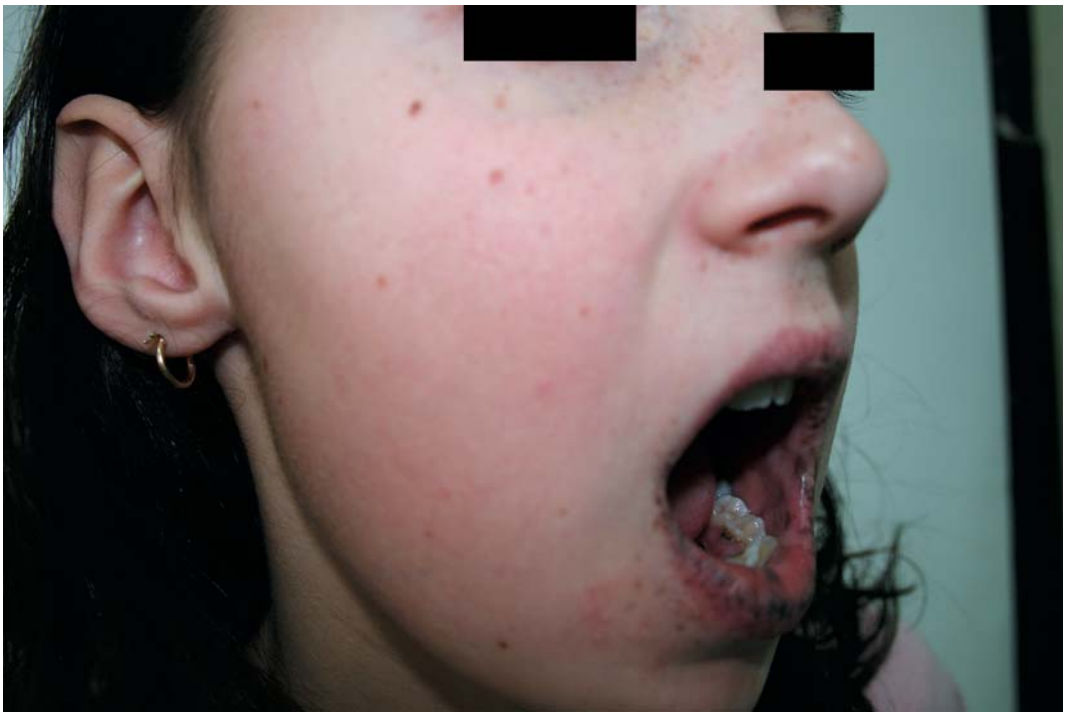

Figure 2. Brown to bluish-black macules on the lips and on the left buccal mucosa

risk for gastrointestinal cancers was 57% by the age of 70 (8). Early screening and detection of cancer were recommended to prevent morbidity and mortality (9).

Our recommendation, according to the guidelines for the management of gastrointestinal polyposis, was control endoscopy of the gastrointestinal tract every second year up to the age of 18, and later annually.

Conclusion

It is very important to bear in mind that Peutz-Jegher's syndrome presents with pigmented lip macules, because of the risk for developing gastrointestinal and other cancers in any patient who presents with pigmented lip macules.

Continuous surveillance through regular endoscopy, laboratory, radiologic investigation, referrals for genetic counseling and surgery are crucial recommendations for managing this inherited condition in order to reduce risks for cancer, and prevent other morbidity and mortality.

Abbreviations

PJS - Peutz-Jegher's syndrome
STK11 - Serine/threonine protein kinase-11 gene

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Hydroa vacciniforme - a case report

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Abstract

Hydroa vacciniforme is a rare, idiopathic, chronic photodermatosis that usually begins in childhood and resolves spontaneously in early adulthood. It is characterized by appearance of vesicles on sun-exposed areas. The vesicles crust and heal within one to six weeks, leaving vacciniform/varioliform scars. We report an 11-year-old boy with a 5-year history of recurrent blisters on sun-exposed areas that deteriorated each summer. He was treated with antimalarials, topical photoprotective agents, sun avoidance, dietary fish oil and supplementary doses of vitamin D3. Strict adherence to the regimen resulted in remission.

Key words

Hydroa Vacciniforme; Child; Treatment Outcome; Antimalarials; Sunlight + adverse effects; Vitamin D; Sunscreening Agents

Hydroa vacciniforme is a very rare photodermatosis of unknown etiology, with onset usually in childhood. It was first described by Bazin in 1862. The prevalence of this disorder is 0.34 per 100.000 children (1, 2).

Case report

An 11-year-old boy was admitted with a 5-year history of recurrent vesicles on photoexposed areas that worsened each summer. There was no family history of photodermatosis. He was firstly deteriorated with hydroa vacciniforme at the age of 9 years and treated with beta-carotene, omega-3 polyunsaturated fatty acids and topical photoprotective agents. The patient's history revealed that photoprotection was not adequately applied.

On examination, the boy presented with multiple hemorrhagic vesicles, erosions and crusts, as well as oval, pigmented, atrophic scars on the face (Figures 1a and 1b). Multiple crusted lesions and erosions were also observed on earlobes. Cursts, violaceous scars and residual pigmentations were present on the dorsal aspect of both hands, and there were discrete hypopigmentations on both forearms. Pediatric and ophthalmological results were normal. Abdominal echosonography was regular. Routine blood and urine laboratory tests were normal, as well as 24-hour urinary uroporphyrin level.

The treatment included synthetic antimalarials (initially hydroxychloroquine at 6 mg/kg, then chloroquine at 3 mg/kg), topical photoprotection (sunblocking creams with SPF 50+) and sun avoidance. Supplementary doses of vitamin D3 (1200 IU/day) were added. In February 2012, the patient had a relapse. Dietary fish oil was added to the regimen at pharmacological doses (4000 mg/day). Such a regimen resulted in an improvement and regression of vesicles, while the scars persisted (Figures 2a and 2b).

Discussion

Hydroa vacciniforme is a rare photodermatosis of unknown etiology that usually presents in childhood

(3). It is characterized by itchy, stinging, erythematous rash, occurring within a few hours after sun exposure, progressing to numerous erythematous papules and plaques undergoing vesiculation (4). The vesicles tend to become umbilicated and hemorrhagic, subsequently crusted, and heal within one to six weeks, leaving depressed vacciniform scars (2). In addition, postinflammatory hypo- and hyperpigmentation may occur.

The most accepted pathogenetic hypothesis suggests ultraviolet radiation, with wavelengths between 320 and 390 nm, as a causal agent of hydroa vacciniforme, but the chromophore leading to ultra-violet-induced damage is still unknown (2). The differential diagnosis includes erythropoietic protoporphyria, congenital erythropoietic porphyria, vesicular polymorphic light eruption, actinic prurigo, and common conditions like impetigo, herpes simplex and contact dermatitis. In our patient normal 24-hour uroporphyrin level excluded erythropoietic protoporphyria and congenital erythropoietic porphyria. Polymorphic light eruption is usually non-scarring, and has a later age of onset than hydroa vacciniforme. Actinic prurigo does show scarring, but it may also involve non-sun-exposed areas, and primary lesions are papules and nodules rather than vesicles (5).

The therapy consists of UVA sunblocking agents with high SPF and protective clothing. Antimalarials, immunosuppressives, beta carotene, psoralen with UVA exposure and prophylactic UVB phototherapy have also been reported as useful in reducing outbreaks, but they are not reliable in preventing lesions. Dietary fish oil, rich in omega-3 polyunsaturated fatty acids, has also been used with success in occasional reports, with no severe side-effects reported (6).

Our patient had a good initial response to therapy, but then suffered a relapse, because photoprotection was not adequately applied. When the combined therapy was given, including antimalarials, dietary fish oil at pharmacological doses, sun-blocking creams with SPF 50+ and avoidance of the sun, the patient was introduced into remission. Supplementary doses of vitamin D3 were added because of sun avoidance.

Conclusion

Hydroa vacciniforme is a very rare disease in childhood. Timely diagnosis and introduction of adequate therapy, including antimalarials, fish oil, and strict photoprotection may enable long remission periods and normal quality of life. The disease enters stable spontaneous remission in adolescence or early adulthood.

Acknowledgement

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A triad of exophtalmos, pretibial myxedema and acropachy in a patient with Graves' disease

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Abstract

A classical triad of extrathyroidal manifestations of Graves' disease known as EMO syndrome (exophthalmos, pretibial myxedema and osteoarthropathy) is a rare condition. This paper presents a 39-year old male patient who underwent chemo- and radiation therapy of the supradiaphragmatic area due to Hodgkin's disease at the age of 35 and 36 leading to remission. Two years later, the patient developed general symptoms of Graves' disease and ophthalmopathy, with high thyroid stimulating hormone levels. Four months later, the patient presented with pretibial myxedema. Thirteen months after the onset of the disease, higher levels of thyroxine and decreased levels of thyroid stimulating hormone were registered. The diagnosis of EMO syndrome was confirmed by radiologic and histopathological analyses. Thiamazole and intralesional corticosteroid therapy were administered, resulting in euthyreosis and decrease of pretibial myxedema. The question is whether the autoimmune thyroid disease was triggered by the previous disease, or by chemo- and radiation therapy..

Key words

Graves' Disease; Exophthalmos; Myxedema; Osteoarthropathy, Primary Hypertrophic; Syndrome

Back in 1786, Parry described the association between exophthalmos and goiter. Apart from these two manifestations, in 1935 Graves described thyrotoxicosis, and in 1840 Basedow described palpitations. Today, this disease is commonly called Graves', or Graves'-Basedow disease (1).

It is a chronic autoimmune disease characterized by diffuse goiter, hyperthyreosis, ophthalmopathy and dermopathy (2). Hyperthyreosis affects 1-2% of women under the age of 40 years, whereas in men it is about ten times less common. It occurs in 0.3% of the general population, and out of this number, 4.3% have a subacute form of the disease (3).

Not all the abovementioned symptoms are always present, and others may occur as well. Thus, Thomas (in 1933) and Diamond (in 1959) described a triad of exophthalmos, pretibial myxedema and acral osteopathy, while Braun-Falco and Petzoldt suggested the term EMO syndrome (exophthalmos, pretibial myxedema and hypertrophic osteoarthropathy) in 1967 (4).

Out of extrathyroidal manifestations, ophthalmopathy, dermopathy and acropachy are most common. Pretibial myxedema is rarely an initial symptom of Graves' disease (5). Ophthalmopathy affects about 30% of patients with Graves' disease, dermopathy about 4%, and acropachy about 1% of patients (6). Symptoms of the disease occur independently of the production of thyroid hormones. Dermopathy was also described in euthyreosis (7, 8), and in hypothyreosis with subsequent hyperthyreosis (9). Cases of exophthalmos and myxedema in Hashimoto thyroiditis were reported as well (10), generally leading to hypothyreosis. There are opinions according to which all autoimmune thyroid

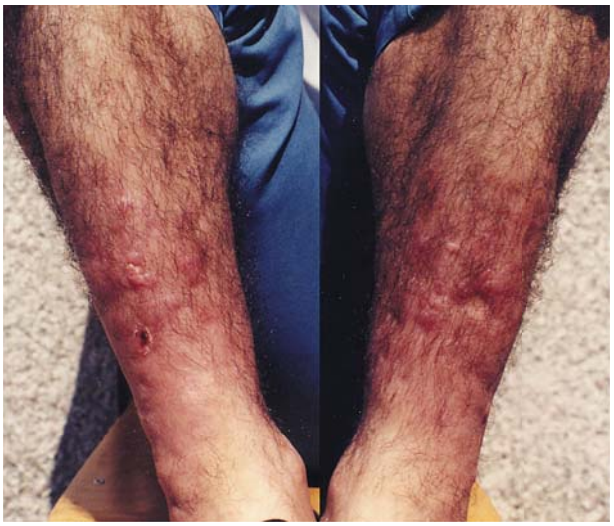

Figure 2. Pretibial myxedema: bilateral, almost symmetrical, clearly defined painless infiltrates and nodules of firm consistency, showing mild erythema and uneven surface with orange peel appearance

(Figure 5). The dermis layer was thickened and collagen fiber networks were cross-linked. Fibroblasts were present, within normal levels, some star-shaped. Mucin dermal deposits were scarce in the papillary and more prominent in the rest of the dermis, presenting between abundant collagen fibers.

Therapy

Favistan® (tiamazol) tablets of 20mg were used, 2 x 1, later 2 x ½. The treatment with topical corticosteroids showed no visible improvement. Intralesional hydrocortisone injections caused reduction of pretibial changes to some extent. Exophthalmos and acropachy remained unchanged. The patient's general condition was good all the time.

Discussion

The cause of Graves' disease is unknown. A certain genetic predisposition is indicated by several family members suffering from the disease and its association with other autoimmune diseases, for example endocrine diseases (2).

Apart from heritage, other risk factors are evident as etiologic factors of Graves' disease: smoking, immunosuppression, stress, some medications (for example amiodarone, interferon, lithium carbonate), iodine contrasts, radiation therapy of the neck, viral and bacterial infections, iodine insufficiency in the diet (4). Hyperthyroidism in Graves' disease is due to the binding of stimulatory autoantibodies to the TSH receptor (TSHr) on thyroid follicular cells. The stimulation of this G protein coupled receptor by autoantibodies leads to excessive and uncontrolled production of thyroid hormone (11).

Development of extrathyroidal manifestations, such as ophthalmopathy and pretibial myxedema, is associated with positive feedback mechanisms including mechanical (trauma/pressure), immune (accumulation of immune cells, inflammatory citokynes, incresed expression of TSHr) and cellular processes (adipogenesis, icreased production of glycosaminoglycans/prostaglandin E_2) (11). "A subclinical systemic inflammatory process might develop in Graves' disease as activated T cells and

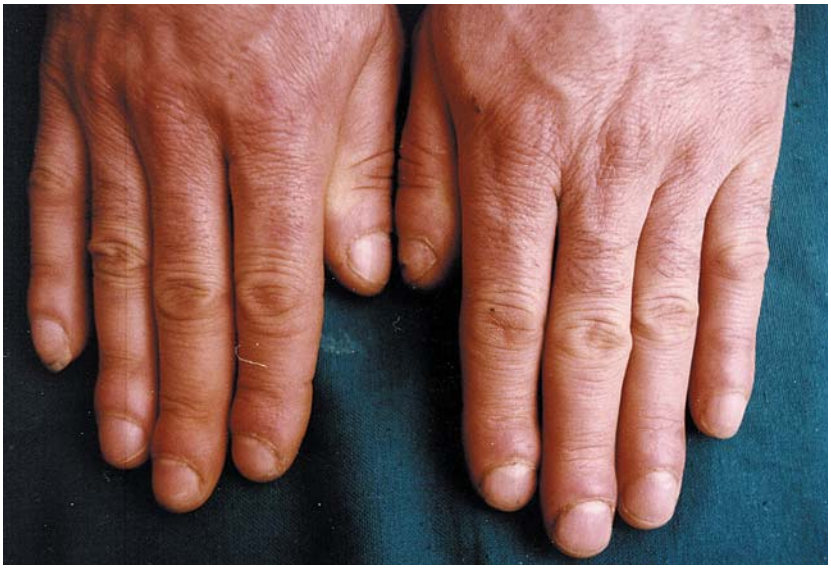

Figure 3. Clubbing of the fingernails: drumstick fingers and watch glass nails

Results of a study including 178 patients with thyroidal dermopathy showed that: only 3% of patients provided no anamnestic data and were without signs of ophthalmopathy; mild ophthalmopathy was recorded in 41% of patients, moderate in 31% and severe in 15.2%; optic neuropathy was established in 9.4% of patients with dermopathy (18). In the same study, 93.3% of patients suffered from pretibial dermopathy, 3.9% from pretibial and foot dermopathy, and 1.19% had pretibial and upper extremity dermopathy. Dermopathy manifested as non-pitting edema in 43.3% of patients, plaque dermopathy in 27.0%, nodular in 18.52% and elephantiasis in 2.8% (18). Although much less commonly, dermopathy may affect hands, arms, shoulders, head and neck, as well as sites of trauma, surgery, scars or skin grafts (5, 19, 20).

The thyroid acropachy is a rare extrathyroidal manifestation (2) with prevalence of 0.8 – 1.0%. It is a marker for severe thyroid-associated autoimmune process and ophthalmopathy (21).

The most common manifestation of acropachy is clubbing of fingers and toenails (18) - so called Hippocratic nails (1). It is characterized by clubbing and swelling of fingers, with periosteal reaction on distal bones (9). Radiography shows fusiform finger swelling and subperiosteal formation on metacarpal bones, proximal and middle phalanx and metatarsal bones and proximal phalanx of the toes (18).

In the diagnosis of Graves' disease, it is very important to control T3, T4 and TSH. Sometimes TSH is too low to be measured (2).

Histopathological changes are also characteristic and include mucin deposits, especially in the lower dermis.

The first step in the treatment of Graves' disease is elimination of risk factors, if possible. Obesity is an important risk for the development of venous stasis and edema in the lower extremities, affecting the severity of pretibial myxedema (9). Smoking has also been established as a marker of severity of autoimmune manifestations in Graves' disease (22).

Thyroid dysfunction therapy is done by endocrinologists and surgeons. It includes thyreosuppressants, medications for hormone suppression, and two forms of ablation therapy: surgical and using radioactive iodine (2).

In order to prevent extrathyroidal manifestations that may develop in some patients after therapy by radioactive iodine, concomitant corticosteroid therapy is applied (9). Apart from systemic corticosteroids, systemic immunomodulators are also used in the treatment of ophthalmopathy (cyclosporine and intravenous immunoglobulins); plasmapheresis and somastatin analogues such as octreotide (insulin-like growth factor type-1-antagonist); systemic immunomodulators are used for regression of skin lesions (18); radiation therapy is also used, while surgical orbital decompression is used in the correction of exophthalmos, and surgery of extraocular muscles in the correction of diplopia (23).

Potent topical corticosteroids under occlusion may be used in the treatment of mild forms of pretibial myxedema. Oral use of pentoxifylline and topical use of clobetasol propionate are recommended for the improvement of myxedema and ophthalmopathy (24). In severe forms of myxedema, intralesional corticosteroids are used, which had positive effects in our patient; compression and complete decongestive physiotherapy are also used (25) as well as CO_2 laser (7); surgical ablation and intravenous immunoglobulins are used in severe cases (26). In severe refractory pretibial myxedema, a combination of surgery and octreotide is performed (27), or intralesional octreotide (28).

Anyhow, the course of the disease does not only depend on applied medications, but also on the immune status of patients. Long-term remissions are possible, and in mild cases complete regressions as well.

Conclusion

This is a case report of a patient who developed exophthalmos, pretibial myxedema and hyperthyreosis after chemo- and radiation therapy of the supradiaphragmatic area due to Hodgkin's disease. Osteoarthropathy developed in the end, causing EMO syndrome. The applied therapy induced euthyreosis and regression of myxedema, but did not affect ophthalmopathy and acropachy.

Abbreviations

EMO syndrome - The combination of exophthalmos, pretibial myxoedema and hypertrophic osteoarthropathy
Gy - Gray
T3 - Thyronine
T4 - Thyroxine
TSH – Thyroid-stimulating hormone
TSHr – Thyroid-stimulating hormone receptor
GAG – glycosaminoglycans
GO - Graves′ ophthalmopathy
PTD - Pretibial dermatopathy

Prikaz slučaja**:** U ovom radu prikazan je bolesnik star 39 godina koji je u 35. i 36. godini lečen citostaticima i zračnom terapijom (supradijafragmalna regija) zbog Hočkinove bolesti i nakon toga doveden u stanje remisije. Dve godine kasnije javili su se opšti simptomi Grejvsove bolesti i oftalmopatija. Tada su registrovane povišene vrednosti tireostimulišućeg hormona TSH. Četiri meseca kasnije nastao je i pretibijalni miksedem.Trinaest meseci od početka bolesti registrovane su i povišene vrednosti tiroksina (T4) i snižene vrednosti TSH. Dijagnoza EMO sindroma je potvrđena radiološkim i patohistološkim analizama. Ordinirana je peroralna terapija tiamazol tabletama, uz intraleziono injiciranje kortikosteroida, što je dovelo do eutiroidnog stanja i smanjenja pretibijalnog miksedema.

Diskusija: Postavlja se pitanje da li je za autoimunu bolest štitne žlezde faktor okidač bila prethodno postojeća Hočkinova bolest ili tada primenjena terapija. Uzrok Grejvsove bolesti je nepoznat. Postoji izvesna genetska predispozicija, što povrđuje pojavljiva bolesti kod više članova pojedinih porodica i udruženost sa drugim autoimunim bolestima, npr. endokrinim. Pored genetskih činilaca, faktori rizika za nastanak Grejvsove bolesti su pušenje, imunosupresija, psihički stres, lekovi (npr. amiodaron, interferon, litijum-karbonat), kontrastna sredstva na bazi joda, zračna terapija vratne regije, virusne i bakterijske infekcije, nedostatak joda u ishrani.

Oftalmopatija predstavlja ekstratiroidnu manifestaciju Grejvsove bolesti. Za kliničku sliku ove manifestacije karakteristični su: proptoza, pojačana konjunktivalna injekcija i konjunktivalni edem (*chemosis*), diplopija, kornealna ulceracija, a u ekstremnim slučajevima gubitak vida zbog kompresije očnog živca.

Druga ekstratiroidna manifestacija je pretibijalni miksedem ili tiroidna dermopatija, koju karakteriše akumulacija glikozaminoglikana (GAG) u dermisu i supkutanom tkivu. Prisutna je kod 10–12% bolesnika sa Grejvsovom oftalmopatijom. Rane lezije su bilateralne, asimetrične, čvrste – u vidu napetog edema, nodusa ili plakova ružičaste, boje kože ili ljubičaste. Kasne lezije nastaju konfluencijom ranih lezija, simetrično zahvataju pretibijalnu regiju i mogu rezultirati groteksnim zahvatanjem potkolenica i stopala. Koža ima izgled „pomorandžine kore“, može biti čak i verukozna. U zavisnosti od kliničke prezentacije, u literaturi se opisuje nekoliko različitih formi dermopatije: nodularna, difuzna i elefantijazna. Iako znatno ređe, dermopatija može biti lokalizovana i na šakama, nadlakticama, ramenima, glavi i vratu, na mestima traume, operacije, ožiljaka, kao i na koži transplantiranih graftova.

Tiroidna akropatija je retka kasna ekstratiroidna manifestacija, sa prevalencijom 0,8–1 % i predstavlja marker za težinu autoimunog procesa i marker za težinu udružene oftalmopatije.

Najčešća manifestacija akropatije jeste pojava maljičastih prstiju šaka i stopala: Hipokratovi prsti. Koža prstiju može biti otečena i zategnuta, sa prisutnom periostalnom reakcijom na distalnim kostima. Radiografski se konstatuje fuziformni otok tkiva prstiju i subperiostalna formacija na metakarpalnim kostima, proksimalnim i srednjim falangama prstiju ruku i metatarzalnim kostima i proksimalnim falangama prstiju nogu.

U dijagnostici Grejvsove bolesti vrlo važno je kontrolisanje trijodtironina (T3), naročito T4 hormona i TSH. Nekad je TSH izrazito nizak i nemerljiv.

Patohistološke promene su takođe karakteristične i podrazumevaju nakupljanje depozita mucina, naročito u donjem dermisu.

Lečenje tiroidne disfunkcije spada u domen endokrinologa i hirurga: podrazumeva primenu tireosupresiva, lekova za smanjenje produkcije hormona i dva vida ablativne terapije, hirurške i zasnovane na primeni radioktivnog joda.

U lečenju oftalmopatije, pored sistemskih kortikosteroida, koriste se i sistemski imunomodulatori (ciklosporin i intravenski imunoglobulini), plazmafereza i oktreotid (eng. *octreotide: insulin-like growth factor type* 1- antagonist). Takođe se primenjuju: radioterapija, hirurška dekompresija orbite, koja koriguje egzoftalmus, i hirurgija ekstraokularnih mišića koja koriguje diplopiju.

U lečenju lakših oblika pretibijalnog miksedema primenjuju se potentni lokalni kortikosteroidi pod okluzijom. Kod izrazitijih formi miksedema mogu se primeniti: kortikosteroidi intraleziono, što je dalo pozitivne efekte i kod našeg bolesnika; takođe se koristi kompresivna i kompletna dekongestivna fizioterapija; CO_2 laser; a u težim slučajevima i hirurška ablacija i intravenski imunoglobulini. U svakom slučaju, tok bolesti zavisi ne samo od primenjenog leka nego i od imunskog statusa obolelog. Moguće su dugotrajne remisije, a kod lakših slučajeva čak i kompletna regresija promena.

Zaključak: Prikazan je bolesnik kod koga je, posle primene citostatika i zračenja supradijafragmalne regije sa ciljem lečenja Hočkinove bolesti, nastao egzoftalmus, zatim pretibijalni miksedem, a onda je registrovana hipertireoza. Osteoartropatija je nastala poslednja u sklopu EMO sindroma. Primenjena terapija je dovela do eutireoze i smanjenja miksedema bez uticaja na oftalmopatiju i akropatiju.

Ključne reči

Gravesova bolest; Exophthalmos; Miksedem; Primarna hipertrofna osteoartropatija; Sindrom

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SAMO ZA STRUČNU JAVNOST
Režim izdavanja lekova: na lekarski recept.
Datum obnove dozvole za stavljanje leka u promet:
Elocom® krem, mast i rastvor za kožu: 17.05.2007. Revizija teksta: maj 2008.
Triderm® krem i mast: 13.07.2011. Revizija teksta: jun 2011.
Diprosalic® mast: 17.05.2007. Revizija teksta: maj 2007.
Diprosalic® rastvor za kožu: 10.04.2009. Revizija teksta: maj 2007.

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FORTHCOMING EVENTS

Dermatology and Venereology Events 2012

DATE	MEETINGS, CONGRESSES, SYMPOSIA	ABSTRACT SUBMISSION DEADLINE	MORE INFORMATION AT
11-14 July, 2012	38th Annual Meeting of the Society for Pediatric Dermatology, Monterey, United States	No deadline information	www.pedsderm.net
26-28 August, 2012	6th International Congress on Dermato-Epidemiology, Malmö, Sweden	1 May, 2012	www.idea2012.net
31 August – 1 September, 2012	4th World Congress of Minimal Invasive Plastic Surgery and Dermatology, Seoul, South Korea	15 May, 2012	www.mips.or.kr
6-8 September, 2012	27th IUSTI Europe Congress (International Union against Sexually Transmitted Infections), Antalia, Turkey	8 June, 2012	www.iusti2012turkey.org
19-22 September, 2012	42nd Annual Meeting of the European Society for Dermatological Research, Venice, Italy	4 June, 2012	www.esdr2012.org
27-30 September, 2012	21st EADV Congress, Prague, Czech Republic	21 March, 2012	www.eadvprague2012.org
3-6 October, 2012	XXXIII Synposium of the International Society of Dermatopathology, Santa Cruz de la Sierra, Bolivia	No deadline information	www.isdpbolivia.org
12 October, 2012	Meeting of the Serbian Medical Society's Section of Dermatology and Venereology, Novi Sad, Serbia	No abstract submission	www.sld.org.rs
15-17 October, 2012	13th IUSTI World Congress (International Union against Sexually Transmitted Infections), Melbourne, Australia	8 June, 2012	www.iusti2012.com
19-20 October, 2012	Onychology Course, Brussels, Belgium	No abstract submission	www.onychologycourse.eu
31 October – 4 November, 2012	1st Annual Congress of the Dermatologic and Aesthetic International League (DASIL), Saint Julian's, Malta	No deadline information	www.thedasil.org
1-3 November, 2012	XVII Belgrade Dermatology Days, Belgrade, Serbia	15 June, 2012	www.udvs.org
14-17 November, 2012	6th World Meeting of Interdisciplinary Melanoma Skin Cancer Centres and 8th EADO Cingress, Barcelona, Spain	16 September, 2012	www.melanoma2012.com
29 November – 1 December, 2012	European Academy of Allergy and Clinical Immunology (EAACI) focused meeting: Skin Allergy Meeting – SAM 2012, Berlin, Germany	No deadline information	www.eaaci.net

Prepared by: Dr. Tatjana Roš, Clinic of Dermatovenereology Diseases, Clinical Center of Vojvodina, Novi Sad, Serbia

provide the context or background for the study, as well as the purpose, basic procedures, main findings and principal conclusions. Authors should avoid using abbreviations.

- An **abstract in Serbian language***, (limited to 150 words) should follow the second page. It should contain a briefing on the purpose of the study, methods, results and conclusions, and should not contain abbreviations.*

1.3. A list of abbreviations

Use only standard abbreviations, because use of non-standard abbreviations can be confusing to readers. Avoid abbreviations in the title, abstract and in the conclusion. A list of abbreviations and full terms for which they stand for should be provided on a separate page. All measurements of length, height, weight, and volume should be reported in the metric units of the International System of Units – SI, available at http://www.bipm.fr/en/si/.

1.4. Cover Letter

Manuscripts must be accompanied by a cover letter, which should include a date of submission, statement that the manuscript has been read and approved by all the authors and that the authorship requirements have been met. It should also include the name, address, and telephone number of the corresponding author, who is responsible for communicating with other authors about revisions and final approval of the proofs. The original copy of the cover letter, signed by all authors, should be enclosed with the manuscript.

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Tables *should capture information concisely and precisely. Including data in tables, rather than in the text, reduces the length of the article itself.*

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4. Additional information

Accepted manuscripts are edited and returned to the corresponding author for approval. Then a final version of the manuscript will be requested in a defined period of time. Authors will be notified of acceptance or rejection by email, within approximately 4 weeks after submission.

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