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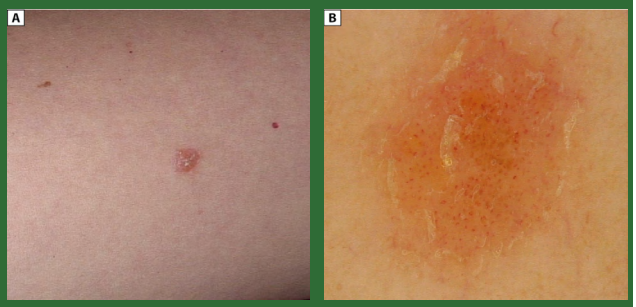

Clinical presentation — amelanotic nodule on the right arm

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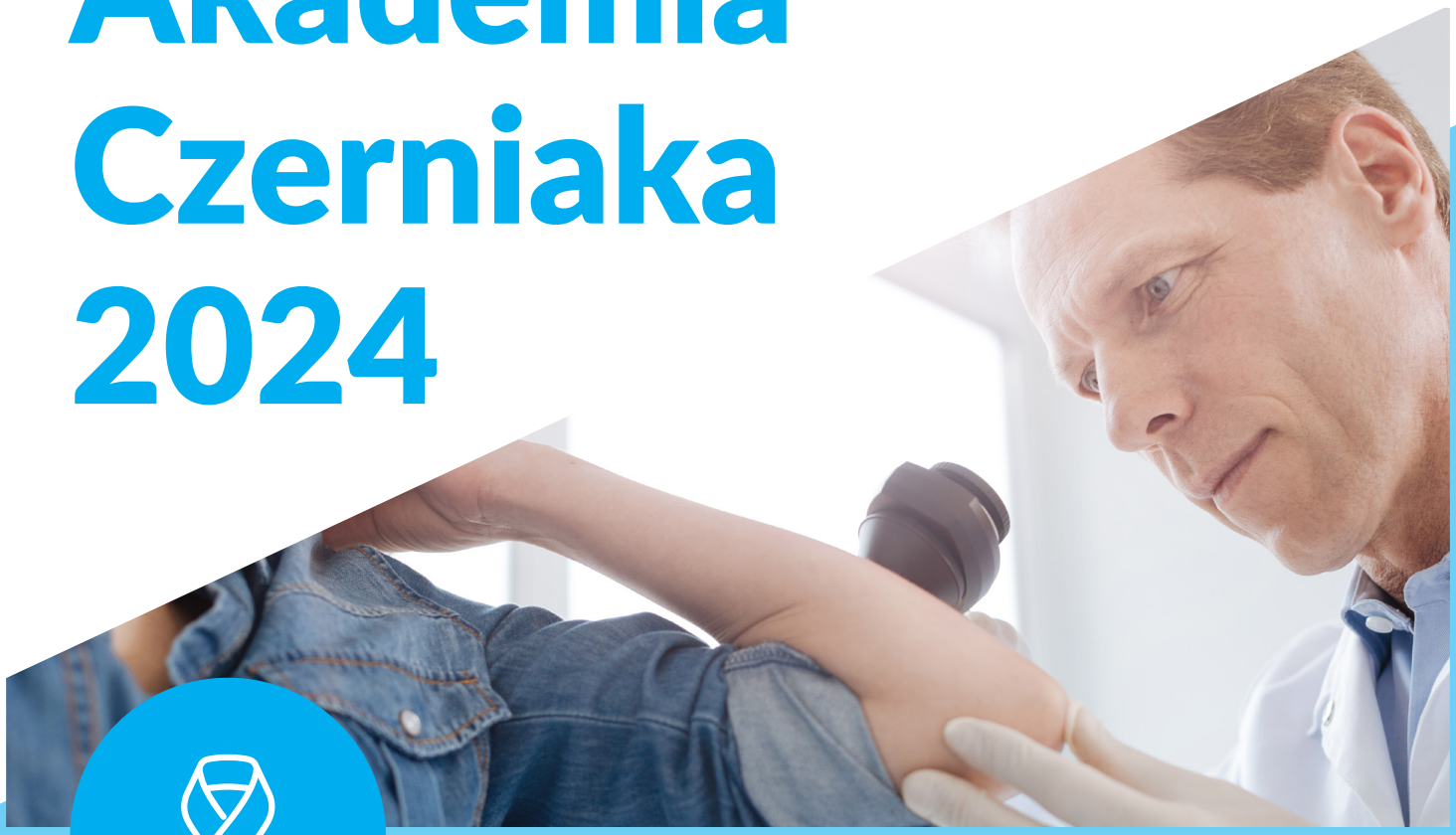

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REVIEW ARTICLE

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Pruritus in elderly patients: review of literature

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ABSTRACT

Pruritus is the most common symptom reported by dermatology patients, including the geriatric patient population. Due to population ageing, pruritus will be an increasingly common reason for medical consultations. Pruritus can involve both previously affected and unaffected skin, occurring as the only manifestation of the disease. Chronic pruritus lasting more than six weeks has a significant impact on patients' quality of life, often resulting in sleep disorders and depressive-anxiety disorders. Mechanisms responsible for pruritus in the elderly include abnormal dermal-epidermal barrier, age-related changes in the immune system, and central and peripheral neuropathy. Xerosis is considered the most common cause of pruritus in geriatric patients. Chronic pruritus occurs in the course of many dermatological conditions, as well as Internal diseases, and neurological or psychiatric disorders. The treatment of chronic pruritus in elderly patients may sometimes be a therapeutic challenge due to comorbidities or the complexity of the mechanisms leading to its onset. Each patient needs an individual and often multidisciplinary approach, taking into account comorbidities and polypragmasia. In addition to emollient skincare — which is the basis of skin care — and topical anti-inflammatory preparations for inflammatory skin disorders, biologics are increasingly being used in the treatment of pruritus, as well as drugs with antidepressant and antiepileptic effects.

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Keywords: senile pruritus, immunosenescence, xerosis, pruritus treatment, quality of life

INTRODUCTION

Pruritus is the most common symptom reported by dermatology patients. Pruritus can involve both previously affected and unaffected skin, occurring as the only manifestation of the disease. Pruritus is also associated with internal diseases such as inter alia, chronic kidney disease (CKD) and cirrhosis, or neurological/psychiatric diseases. Chronic pruritus, which is defined as an unpleasant sensation resulting in the scratch reflex that lasts for more than six weeks, is often the cause of sleep disorders, depression or anxiety disorders, significantly affecting patients' quality of life [1]. Chronic pruritus is also one of the most common symptoms in geriatric patients [2]. It represents a significant health problem among people aged 65 years and older. Studies on the impact of pruritus on patients' quality of life and the relationship between pruritus and chronic pain have shown that most patients would prefer to live a shorter life and be free of symptoms rather than live longer and struggle with chronic pruritus, as the detrimental impact of chronic pruritus is comparable to that of chronic pain [3, 4].

EPIDEMIOLOGY

According to a study by Matterne et al. [5], the lifetime risk of chronic pruritus was estimated to be approximately 23%, with an estimated prevalence of 13.9%. The prevalence of pruritus is thought to increase with age. A survey of employees at 144 German companies found that the prevalence of chronic pruritus increased with age from 12.3% in those between the ages of 16–30 to 20.3% in those aged 61–70 [6]. In studies conducted on other patient populations, the prevalence of pruritus did not differ significantly between the paediatric and adult populations and was above 8% [7] and ranged from approximately 12% to 41% for elderly patients [8]. In addition, pruritus appears to be the most common symptom reported in elderly patients. This is supported, among other things, by a study of 149 Thai patients [9] and 68 patients aged 50–91, in which 83% of those aged 80 and 90 years reported pruritus as the most common symptom [10]. A study conducted in Thailand revealed that 41% of patients suffered from pruritic conditions, of which xerosis was the most common (38.9%) [8]. Other studies of elderly patients found that the prevalence of pruritus ranged from 11 to 78% [2, 11, 12]. Nowadays, there is recognition that chronic pruritus will become a growing health problem due to an ageing population, especially in economically developed countries. The population aged 60 and older is growing at a rate of approximately 3% per year. It is estimated that the number of elderly people in the

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world will be 1.4 trillion in 2030 and 2.1 trillion in 2050 [13]. Consequently, the number of patients with chronic pruritic skin conditions will also increase.

PATHOPHYSIOLOGY

Several mechanisms are responsible for the development of pruritus in the elderly. These mechanisms include abnormal skin-epidermal barrier, age-related changes in the immune system, and central and peripheral neuropathy [14]. In addition, factors such as dermatoses and systemic or psychiatric disorders may cause pruritus in elderly patients [14, 15].

The changes in the immune system that result from ageing are called immunosenescence [16–19]. This process affects both acquired and innate immunity and induces increased autoreactivity of the immune system [20, 21], which may lead to autoimmune disease. Nonbullous pemphigoid, which is manifested by chronic pruritus associated with nonspecific skin lesions and the presence of circulating antibodies, is increasingly becoming the focus of research. In this case, pruritus may be the only symptom of the disease or may precede bullous pemphigoid for many years [22]. The immune system becomes increasingly inefficient with age. There is a several-fold increase in proinflammatory cytokines and acute phase proteins in the bloodstream of the elderly. The consequence is the appearance of chronic inflammation of low intensity. In addition, the function of T and B lymphocytes is significantly impaired. This is related, among other things, to the loss of naive T cells, which leads to a reduced ability of the immune system to respond effectively to infectious agents to which the elderly person has not previously been exposed [23]. It is implied that with the progression of immunosenescence, the balance between two main subclasses of helper T cells — Th1 and Th2 — is altered [24], exhibiting mutual antagonism. As a result of immunosenescence, Th1 lymphocyte-dependent cellular immunity loses importance in favour of defence mechanisms that are dependent on an "allergic" Th2-dependent response [25], making elderly patients more susceptible to chronic pruritus. Elderly patients with chronic pruritus also exhibit immune dysregulation in the form of lymphopenia, eosinophilia or hypogammaglobulinemia [25].

Xerosis, or dry skin, is considered the most common cause of pruritus in the elderly population. Its prevalence is estimated to range from 38% to as high as 85% [26–29]. Many changes in the skin of the elderly are associated with xerosis and include an increase in skin pH and protective function of the epidermal barrier and increased protease activity, reduced activity of sweat and sebaceous glands or reduced oestrogen levels [30]. From approximately 55 years of age, the epidermal pH becomes more alkaline [31, 32]. This affects the activity of the enzymes of the stratum corneum, resulting in reduced production of natural moisturizing factor [33] and ceramides [31, 34] through reduced activity of enzymes that affect their production and reduced secretion of lamellar bodies [35]. As pH increases, serine protease activity also increases, leading to the activation of protease-activated receptors (PARs) that induce pruritus in the skin [33, 35]. Pruritus induced by PAR-2 receptor stimulation is also observed in dermatoses such as atopic dermatitis (AD) [36]. The stratum corneum, as the outermost part of the epidermis, acts as a barrier against external factors and protects against transepidermal water loss (TEWL) [37]. As the skin ages, the normal process of exfoliation can be disrupted, leading to the appearance of dry skin [38, 39]. A link has been suggested between xerosis/pruritus and an acquired abnormality of keratinization and a reduced amount of water in the stratum corneum [39]. The intercellular lipid matrix is one of the components of the stratum corneum that determines epidermal barrier function [40]. The matrix consists of ceramides, cholesterol and free fatty acids [40]. On the other hand, lipids of the matrix originate from the lamellar bodies of the stratum granulosum (granular layer) [41]. In older and elderly patients, there is a reduced secretion of lipids of the lamellar bodies into the intercellular spaces, which is also affected by the aforementioned alkalinization of skin pH. These abnormalities significantly impair the epidermal barrier, leading to an increased risk of developing allergic contact dermatitis (ACD) and irritant contact dermatitis (ICD) [42]. Therefore, special caution is recommended in terms of the use of topical anti-inflammatory preparations in geriatric patients [43]. In addition, when the epidermal barrier is impaired, proinflammatory cytokines are released to repair it, which leads to dermatitis [20]. Other factors that lead to xerosis include the aforementioned reduced activity of the sweat and sebaceous glands [44, 45] and endocrine disorders, mainly those related to reduced oestrogen levels in women with age [46].

Chronic pruritus may also be associated with neuropathic changes, resulting from damage to the central and peripheral nervous systems acquired with age [20, 21, 47]. In the elderly, neuropathic pruritus (NP) is found in several conditions such as shingles, diabetes, radiculopathies, and — in rare cases — neurodegenerative diseases of the central nervous system [48]. In the case of shingles, which is the most common viral skin infection in the geriatric population [11, 49], the prevalence of pruritus that persists after the disease — postherpetic pruritus — is 36% [50], while activation of pruritus-inducing neurons in the affected dermatomes is cited among the causes [51]. Diabetic patients may develop NP as a result of polyneuropathy [52]. A study of pruritus in diabetics revealed that pruritus of the trunk can be a common manifestation of diabetes-induced

peripheral nerve damage [52], while a link with scalp pruritus was established in geriatric patients with diabetes [2]. Brachioradial pruritus (BRP) and *notalgia paresthetica* are two radiculopathies associated with NP in elderly patients. In most cases, BRP affects the upper half of the body, involving the distal parts of the arms and the extensor parts of the forearms on both sides and sometimes can also be found on the proximal parts of the arms, neck, back or chest. In rare cases, BRP can be generalised or affect only one side of the body or the lower limbs. *Notalgia paresthetica* causes topical pruritus of the interscapular region in the T2–T6 dermatomes, which is often associated with pain, a tingling or prickling sensation. The secondary symptoms of pruritus are areas of hyperpigmentation.

CLASSIFICATION OF PRURITUS

The first step in the management of geriatric patients suffering from pruritus requires confirmation of the presence of primary skin lesions. Most patients with chronic pruritus can be diagnosed with inflammatory skin diseases. If no primary skin lesions are found, it may be a case of an invisible dermatosis or metabolic cause of pruritus, especially when the lesions on the skin are very subtle or only lesions secondary to scratching are visible. The IFSI (International Forum for the Study on Itch) classification distinguishes three groups of patients, taking into account the clinical picture of skin symptoms: 1) group 1 — pruritus involving previously affected skin; 2) group 2 — pruritus involving unaltered skin; 3) group 3 — pruritus associated with skin lesions secondary to scratching (neurotic excoriations, lichenification, papules, nodules). In the second stage of pruritus classification, the patient is classified into one of six categories: 1) skin-derived pruritus; 2) systemic pruritus; 3) neurological pruritus; 4) psychogenic pruritus; 5) mixed pruritus; 6) pruritus of unknown cause.

PRURITIC DERMATOSES

In the elderly, many dermatological conditions are associated with chronic pruritus, which shows higher intensity [2]. These include seborrheic dermatitis, contact dermatitis, psoriasis and scabies, among others. Seborrheic dermatitis is marked by erythematous and scaly lesions on the face, chest and scalp. The prevalence of seborrheic dermatitis in the geriatric population is 31% [52], and the associated pruritus is localized [53, 54]. In elderly patients, this dermatosis particularly often presents with Parkinson's disease, depression or anxiety disorders [55]. The increased risk of seborrheic dermatitis in patients with Parkinson's disease may be related to parasympathetic overactivity and increased melanocyte-stimulating hormone levels [56]. It is increasingly believed that seborrheic dermatitis is one of the first symptoms of Parkinson's disease, occurring even before motor dysfunction [57].

A disease whose prevalence is increased in the elderly due to long-term stays in hospitals or nursing homes is scabies [58]. Patients are observed to have scattered papules or erosions, scabs or neurotic excoriations secondary to scratching. These lesions are often very discrete, hence the need for a thorough examination of the patient, taking into account the spaces between the toes, soles, genitalia, nipples or umbilicus. The associated pruritus is very intense and generalised, often with greater intensity at night; however, this should not determine the diagnosis. Patients under immunosuppression resulting from systemic conditions or secondary to treatment with topical or systemic immunosuppressants are at particular risk of developing hyperkeratotic (Norwegian) scabies [59].

Chronic prurigo is a dermatosis that occurs in all age groups but is more commonly diagnosed in middle-aged women. It presents with chronic pruritus and lesions secondary to chronic scratching, for example, scratch marks and scars. Moreover, due to the complex clinical picture of chronic prurigo, several subtypes of the disease are distinguished according to predominant skin lesions observed: nodular prurigo, papular prurigo, plaque prurigo, umbilicated prurigo and linear prurigo [60]. Skin eruptions are usually located symmetrically on the distal parts of the limbs, buttocks or trunk. Intense pruritus is a characteristic symptom of the disease; however, some patients also experience burning or stabbing pain [61].

Contact dermatitis — both allergic and irritant — is also common in the elderly population; its prevalence ranges from 33% to 64% [62]. This is most likely related to immunosenescence and abnormal epidermal barrier function [63]. The development of contact dermatitis in the elderly is most common on the lower limbs.

Nummular eczema, considered a type of contact eczema, is an inflammatory dermatosis characterised by severe pruritus and the presence of round erythematous plaques, within which exfoliation is visible in the chronic phase. The peak incidence is between the ages of 50 and 70, occurring more often in men [52]. Some researchers consider frothy nummular eczema to be a variant of AD that appears in late life [64].

Psoriasis as a chronic inflammatory dermatosis is another condition prevalent in the geriatric population [65]. Pruritus is the most common symptom among this group of patients [66] and is often observed in the genital area [67, 68], hence the need for careful evaluation of genital involvement.

Grover's disease, a transient acantholytic dermatosis, is more commonly seen in elderly men. Numerous papular and papulovesicular eruptions are found mainly on the

trunk and proximal parts of the limbs. Its primary symptom, however, is pruritus. Causes of the occurrence of the disease in the elderly include immunosenescence [20]. Factors that stimulate the appearance of skin lesions are sunlight and infections [68]. Cases of the disease were described in patients with malignant neoplasms of the kidney, stomach or genitourinary system [69–71].

Intense pruritus also occurs in cutaneous T-cell lymphomas, especially in the advanced stages of the disease. Often, pruritus is the predominant symptom of slow-onset T-cell lymphomas. Its occurrence is associated with increased expression of interleukin-31 (IL-31) [72].

PRURITUS WITHOUT VISIBLE SKIN SYMPTOMS

In the absence of primary skin symptoms, consideration should be given to a metabolic cause of pruritus and pruritus associated with systemic diseases, neurological pruritus and psychogenic pruritus or so-called invisible dermatosis. The most common condition causing pruritus without visible skin symptoms is xerosis, which was discussed earlier. Scabies is sometimes included in this group due to its very discrete skin lesions or lack thereof. A number of drugs responsible for the induction of pruritus, sometimes without visible exanthema, have also been described. This is confirmed by a large study from the 1980s, which found that pruritus without skin rash represented 5% of adverse drug reactions among inpatients [73]. In another study, drug-induced pruritus without visible exanthema was reported in 12.5% of cases [74]. Some of these drugs can cause liver and biliary tract dysfunction and thus generate pruritus. Hydroxyethyl starch may cause pruritus with a delayed onset, without visible skin lesions. Intense pruritus with minimal or no skin lesions was also described in the course of lichen planus, dermatitis herpetiformis, urticaria or bullous pemphigoid.

There are increasing reports of pruritus as a single or early manifestation of various autoimmune conditions such as systemic sclerosis [75] or bullous pemphigoid. The course of bullous pemphigoid traditionally involves intense pruritus and well-tense blisters on an erythematous background [76]. The frequent co-occurrence of psychiatric and neurodegenerative diseases was described [77]. One in five patients with pemphigoid does not have typical blisters, and such a condition is called nonbullous pemphigoid [78], which can develop severe pruritus and a wide spectrum of clinical manifestations resembling other pruritic skin conditions [79–81]. The most common lesions observed are papules or nodules and urticarial lesions [79–81]. Bullae may occur in 10% of patients as the disease progresses [82]. For this reason, the disease is usually diagnosed after a long delay [82]. A study of seven Dutch nursing homes found the prevalence of pemphigoid to be 6%, with more than half of the patients having no previously established diagnosis and presenting no blisters [83]. Nonbullous pemphigoid appears to be an unrecognised cause of pruritus [84], and this is facilitated by its atypical clinical presentation. Indirect and direct immunofluorescence tests should be performed to diagnose the condition, revealing linear deposits of IgG and/or C3 at the dermal-epidermal junction. Occasionally, IgE deposits may be present as the only immunological component or in addition to IgG, along with circulating antibodies [78]. Histopathology is nonspecific and should not determine the diagnosis [79].

Pruritus may be associated with many internal conditions such as CKD or chronic liver disease, as well as endocrine and haematological diseases, which statistically tend to develop with age. Elderly patients are also more likely to develop cancer, and malignancy-associated pruritus is called paraneoplastic pruritus. Pruritus can also occur as an adverse drug reaction. This is facilitated by the phenomenon of polypragmasia in geriatric patients. Drugs with the greatest known pruritogenic potential include calcium channel blockers (particularly popular in elderly patients), angiotensin-converting enzyme inhibitors, thiazides [85], salicylates, opiates and antimalarials [54]. New drugs for melanoma therapy, such as vemurafenib and ipilimumab, may also cause pruritus — according to literature, in 29% [86] and 31% [87] of patients, respectively. Drug-induced pruritus occurs by several mechanisms, including the induction of drug-induced skin rashes, phototoxicity, neuropathies, xerosis or deposits of drugs or their metabolites in the skin [88].

Pruritus may be associated with mental disorders such as depression or be the only symptom present in patients — in both of these situations, it is psychogenic pruritus. In the case of psychiatric conditions, pruritus may be a symptom of these or lead to the development of psychiatric disorders, so it is necessary to determine which disorder appeared first. In patients suspected of psychogenic pruritus, other possible causes of pruritus should be ruled out first. Furthermore, the patient should meet at least three of the seven supporting criteria developed in 2007 by the French Psychodermatology Group [89].

TREATMENT

Selecting an appropriate treatment for pruritus can be problematic due to diagnostic difficulties, comorbidities or the complexity of the mechanisms leading to pruritus. If possible, the primary cause of pruritus should be determined before implementing treatment. In certain cases, such as scabies, paraneoplastic pruritus, CKD-associated pruritus or cholestasis-associated pruritus, treatment of the underlying disease is often sufficient.

The fundamental therapy of pruritus in geriatric patients, regardless of the cause, is the use of emollients and gentle skin care. Patients should avoid high-pH cleansers and those containing alcohol [90]. The most recommended emollients are those with ceramides, cholesterol or free fatty acids in their composition, allowing the regeneration of the epidermal barrier. Preparations containing urea (usually at a concentration of 5–10%), menthol and other cooling agents or topical anaesthetics also reduce the severity of pruritus. Moisturising creams with fragrances and preservatives should be avoided because of the possibility of causing allergic contact dermatitis.

Topical glucocorticosteroids or calcineurin inhibitors should be used in the case of pruritic inflammatory skin conditions. Topical glucocorticosteroids are not antipruritic drugs, however, by reducing inflammation they reduce the associated pruritus. In addition, they bring rapid improvement and stop the vicious circle mechanism of itching-scratching. Topical glucocorticosteroids should be used briefly due to the risk of skin atrophy. Moreover, long-term use can exacerbate pruritus due to inhibition of prostaglandin D2 production [91]. Calcineurin inhibitors such as tacrolimus and pimecrolimus, unlike glucocorticosteroids, do not cause skin atrophy, which is why they are recommended for long-term therapy [92]. They are particularly popular in the treatment of AD, seborrheic dermatitis and contact eczema [93]. Despite much debate, their effect on the risk of developing cutaneous lymphomas or non-melanoma skin cancers was not proven [94–96].

Oral, especially second-generation, antihistamines are considered relatively safe and thus are often used in the treatment of pruritus. First-generation antihistamines (hydroxyzine, diphenhydramine, dimethindene) not only block histamine H1 receptors but also other receptors, including muscarinic or serotonergic receptors. Therefore, they should not be used in elderly patients due to adverse effects such as drowsiness or anticholinergic symptoms. In addition, hydroxyzine (which is heavily used by the elderly) is thought to increase the risk of delirium or dementia in addition to its high anticholinergic activity [97, 98]. Data supporting the efficacy of antihistamines in the treatment of pruritus other than chronic spontaneous urticaria are severely limited [99].

The treatment of choice in patients with multiple chronic diseases and associated pruritus appears to be ultraviolet-B phototherapy and UVA photochemotherapy. It is particularly popular in inflammatory dermatoses such as psoriasis and AD, cutaneous T-cell lymphomas or cholestatic or uremic pruritus [100]. In the case of phototherapy, it is important to be mindful of accelerated ageing and an increased risk of skin cancers.

Immunosuppressive drugs are also used in the treatment of pruritic dermatoses. Cyclosporine is effective in reducing pruritus in AD and chronic urticaria. Methotrexate reduces pruritus sensation in patients with psoriasis, and azathioprine at a dose of 50–200 mg/day was found to be effective in inhibiting pruritus in patients with bullous pemphigoid [101].

Recent studies reveal the antipruritic properties of various biologics. An example is dupilumab — a monoclonal antibody that inhibits IL-4 and IL-13 cytokine-induced responses, which is used in the treatment of AD. When applied subcutaneously every fortnight, dupilumab significantly reduces pruritus and disease activity [102, 103]. Until recently, it was used off-label for the treatment of diseases with severe pruritus, such as nodular prurigo [104, 105], chronic spontaneous urticaria [106], allergic contact dermatitis [107] and pemphigoid [108, 109]. In September 2022, the U.S. Food and Drug Administration (FDA) registered dupilumab for the treatment of patients with nodular prurigo. In December 2022, dupilumab received the same registration in Europe as well. Nemolizumab, a monoclonal anti-IL-31 receptor antibody, which is in final phase III trials in patients with nodular prurigo, also causes reduced pruritus sensation and improved sleep quality [110]. Upadacitinib, abrocitinib, and Janus kinase inhibitors were found to significantly reduce pruritus in AD patients compared to a placebo [111, 112]. Omalizumab (a humanised monoclonal anti-IgE antibody that binds to high-affinity IgE receptor) was found to rapidly and effectively reduce pruritus and the number of skin lesions in chronic spontaneous urticaria [113]. A meta-analysis confirmed the inhibition of blistering and reduction of pruritus in patients with bullous pemphigoid [114]. In cases of pemphigoid refractory to conventional treatment, omalizumab was also used in combination with the previously mentioned dupilumab [115].

Opioid receptor agonists and antagonists are another group of drugs used in various forms of pruritus, especially in cholestasis and uraemia. Difelikefalin is an opioid, a kappa-opioid receptor agonist, which in April 2022 was approved in Europe for the treatment of moderate to severe CKD-associated pruritus in haemodialysis patients [116]. Butorphanol reduces the severity of pruritus in patients with non-Hodgkin's lymphoma or cholestasis. It should be noted, however, that butorphanol has no registration for these indications and is used off-label, including in refractory cases of pruritus [117]. Naloxone and naltrexone — opioid receptor antagonists — are used in the treatment of cholestatic and uremic pruritus [118]; however, opioid-induced pruritus is not an indication of their use. Anxiolytics and/or antidepressants from the selective serotonin reuptake inhibitor (SSRI) group, such as paroxetine at a dose of 20 mg/day

[119] or sertraline, are used in the therapy of psychogenic pruritus. Tricyclic antidepressants (TLPDs) are less commonly used in this context. Antidepressants from both of the aforementioned groups also show a beneficial effect in the treatment of chronic paraneoplastic pruritus, in the course of cholestasis or AD [120]. For NP, capsaicin cream and antiepileptics such as gabapentin and pregabalin [99] are used, which are also reported to be popular for postherpetic neuralgia (PHN) [121]. Gabapentin is also effective in treating CKD-associated pruritus [122, 123]. Particular caution should be exercised in elderly patients due to the numerous adverse effects.

CONCLUSIONS

Pruritus in geriatric patients is a common health problem. Due to population ageing, pruritus will be an increasingly common reason for medical consultations. Therefore, it is essential to understand the pathophysiology and complexity of the mechanisms that lead to its formation. The management of geriatric patients requires an individual and often multidisciplinary approach that takes into account comorbidities and polypragmasia, which can have a limiting effect on therapeutic options. An important diagnostic aspect of pruritus is its occurrence as the only manifestation of the disease, which triggers the need for an in-depth analysis of the problem. In this case, it is always important to be aware of rarer and less typical variants of various dermatoses, in which pruritus may precede the full-blown development of the disease for many years.

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The effect of isotretinoin therapy on the circulatory system

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ABSTRACT

Isotretinoin is a drug belonging to the group of retinoids, which is mainly used in dermatology. Through its mechanism of action, it leads to a reduction in sebum production, which effectively inhibits the formation of acne. Unfortunately, this drug exhibits numerous side effects. This study aimed to review the literature in terms of clinical cases and articles on the side effects of isotretinoin in the context of the cardiovascular system. It has been proven that isotretinoin can harm the circulatory system, causing changes in the structure of the heart walls, thromboembolic episodes, coronary events and lipid metabolism disorders. Further clinical trials are needed to better understand these side effects.

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Keywords: isotretinoin, 13-cis-retinoic acid, retinoids, acne

INTRODUCTION

13-cis-retinoic acid, or isotretinoin, belongs to retinoids, so it has the activity of vitamin A. It was first approved for the treatment of acne in 1982 by the American Food and Drug Administration (FDA), which was a breakthrough in the treatment of severe forms of acne [1, 2]. Through the mechanism of its action, it affects the life cycle of sebocytes, keratinization and sebum secretion. In this way, it inhibits the formation of blackheads and limits the development of *Cutibacterium acnes* [2, 3]. Retinoids have been divided into four generations (Tab. 1) [4]. Isotretinoin belongs to the first generation of retinoids. Individual groups differ in chemical structure, bioavailability and lipophilicity [4]. These drugs are widely used in dermatological diseases. However, they are characterized by numerous side effects such as dry skin and mucous membranes, teratogenicity, neurological disorders, nephrotoxicity and visual impairment [5, 6]. Further exploration of adverse effects of therapy, including cardiovascular effects and cardiotoxicity, with the use of isotretinoin is still the subject of much scientific research.

MECHANISM OF ACTION

Isotretinoin is a lipophilic compound, therefore carrier proteins found in plasma (RBP, retinoid binding proteins) and cytoplasm (CRBP, cellular retinoid binding proteins) are necessary for its transport. After crossing the cell membrane, it is isomerized to ATRA (all-trans-retinoic acid). This compound is then transported to the cell nucleus with the participation of CRABP-2 (cellular retinoic acid-binding protein 2) and after reaching the cell nucleus, ATRA is bound to RAR (retinoic acid receptor). This process leads to the expression of TP53 and ARF. As a result, p14 and p53 are produced. These proteins, in a cascade of successive reactions, lead to apoptosis of the sebaceous cell. In addition, p53 inhibits the action of insulin growth factor 1 (IGF-1), which is one of the main factors leading to sebaceous cell overgrowth and leads to increased sebum secretion [7].

Table 1. Classes of retinoids [4]

1st generation	2nd generation	3rd generation	4th generation
Tretinoin (all-trans-retinoic acid)	There are no second-generation topical retinoid formulations available	Tazarotene Bexarotene Adapalene	Trifarotene

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USE

Isotretinoin is most often used in the treatment of acne because it has a documented effect here and has a very good therapeutic effect. It is used in selected cases, such as:

— severe and very severe forms of acne such as acne phlegmonosa, acne conglobata, acne nodulo-cistica and acne inversa;
— if conventional treatment for severe or moderate disease has not produced the desired results within 18 months, or if the disease has relapsed despite treatment;
— in case of no improvement exceeding 50% of the initial condition after 2–3 cycles of recommended antibiotic therapy lasting 3 months each in papuloprick acne;
— cases of moderate severity with a tendency to scarring;
— fulminant acne [2].

In addition, due to its anti-inflammatory and immunomodulatory properties, isotretinoin can be used in the treatment of such diseases as genodermatosis, inflammatory diseases, skin cancers (basal cell carcinoma or squamous cell carcinoma), psoriasis and genital warts. Therapies for the above-mentioned conditions, however, require further clinical research [8, 9].

Topical retinoids work by binding to retinoic acid receptors and directly activating them with the help of ligand-receptor formation, causing retinoic acid-responsive genes to be transcribed [4]. RXR retinoid X receptors form heterodimers with various ligands important for cell function and physiology, enabling the cell to function properly [4]. Retinoids normalize abnormal exfoliation in acne by increasing hair follicle epithelial replacement and accelerating corneocyte exfoliation, leading to the removal of mature blackheads and inhibition of the formation of microcomedones [4]. In psoriasis, only topical retinoid tazarotene is indicated. Tazarotene is hydrolysed in tissues to tazarotenoic acid, which then binds to retinoic acid receptors [4]. This combination leads to the regulation of genes responsible for cell proliferation and inflammation, which is a hallmark of psoriasis, a condition characterized by increased epidermal proliferation and inflammation [4]. Tretinoin is the only retinoid with an official indication for use in photoaging and rhytides. The mechanism by which this occurs is molecular in nature and occurs in two different ways, albeit synergistically [4]. The first mechanism of action occurs as a result of blocking the activator protein 1 (AP-1), responsible for the activation of matrix metalloproteinases (MMP) that break down collagen, thus inhibiting the breakdown of collagen [4]. Topical application of all-trans retinoic acid induces collagen synthesis by increasing the expression of type 1 procollagen. Bexarotene is indicated for the treatment of retinoid X receptor-selective retinoid (RXR) cutaneous T-cell lymphoma [4]. Bexarotene binds to RXR nuclear receptors, activating them, leading to inhibition of the G1, G2 and M phases of the cell cycle, reducing proliferation and increasing apoptosis of cancer cells [4]. Adapalene modulates cellular keratinization and inflammatory process [4]. This anti-inflammatory effect is due to the inhibition of the lipooxygenase activity and also to the oxidative metabolism of arachidonic acid [4]. Trifarotene is a new fourth-generation retinoid with a selective action on RAR-γ [10]. Trifarotene, by means of RAR-γ, causes an increased expression of transglutaminase 1, promoting keratinocyte cohesion [10]. Trifarotene is an agonist of retinoic acid receptors (RAR), with particular activity at the gamma subtype of RAR [10]. Stimulation of RAR results in modulation of target genes which are associated with various processes, including cell differentiation and mediation of inflammation [10].

CLINICAL CASES

According to many scientific studies, the use of oral isotretinoin has beneficial effects in the treatment of acne vulgaris, but it is associated with many adverse health effects (Tab. 2) [11], which is why the FDA has approved its use in the case of severe, refractory nodular acne [12]. Isotretinoin, as a derivative of retinoic acid, directly inhibits the activity of sebaceous glands, resulting in a decrease in sebum production and a reduction in blackheads. Reduced sebum production leads to a reduction in the growth of *Cutibacterium acnes bacteria*, which in turn leads to a decrease in the release of inflammatory mediators and reduces inflammation of the epidermis [12]. The recommended starting dose of isotretinoin for the treatment of moderate acne is 0.25–0.4 mg/kg/d and 0.5 mg/kg for severe acne, gradually increasing to 1 mg/kg/d. Pharmacotherapy with isotretinoin should be administered until the maximum dose of 120–150 mg/kg/day is reached in order to reduce the risk of relapse [12]. A study was conducted to check whether isotretinoin affects the functioning of the heart muscle [13]. For this purpose, 20 men suffering from acne vulgaris were included in the study. Patients were treated with isotretinoin at a dose of 0.5 mg/kg/d. The study lasted 10 weeks. Doppler echocardiography was performed before and at the end of the study. During treatment, patients showed a reduction in the vertical diameter of the right atrium, the longitudinal diameter of the left atrium, the volume of the left atrium, and the diastolic diameter of the left ventricle. A significant increase in diastolic septal thickness, posterior diastolic wall thickness, relative wall thickness and left ventricle (LV) mass was observed. The LV mass index showed an increase in ventricular mass and a decrease in cavity size. When examining the systolic activity of LV, a decrease in the cardiac index was observed [13]. The study proved that isotretinoin therapy at a dose of 0.5 mg/kg/d

Table 2. Characteristics of isotretinoin. Author's own elaboration based on literature [11]

Category	Details
Indicate	Treatment of severe forms of acne (e.g. nodular, conglobation) resistant to standard therapies using systemic antibiotics and topical therapy
Dosage	• Dosage: 0.5 mg/kg body weight/day taking into account individual characteristics • Method of administration: oral • Length of treatment: usually 15–20 weeks
Treatment monitoring	• Before starting therapy: pregnancy test, laboratory tests: complete blood count, lipidogram, liver enzymes (AST, ALT) • Follow-up blood tests every 1–3 months
Interactions	• In combination with vitamin A, it increases the risk of hypervitaminosis • Do not combine with tetracyclines due to the risk of developing intracranial hypertension • Isotretinoin cyproterone acetate with ethinylestradiol, increases the risk of cardiovascular events • Drospirenone + ethinylestradiol increase the risk of thromboembolism
Side effects	• Dryness of the skin and mucous membranes • Worsening of acne at the beginning of treatment • Visual disturbances, dry eyes • Muscle and joint pain • Elevated liver enzymes • Lipid disorders • Potential risk of enterocolitis
Contraindications	• Pregnancy, breastfeeding • Hypersensitivity to isotretinoin • Hepatic • Hypervitaminosis A • Tetracycline therapy
Comments	• Due to its teratogenic nature, isotretinoin therapy requires the use of effective contraception. Contraception contributes to an increased risk of thromboembolic events • Therapy poses a risk of mental disorders, including depression and suicidal thoughts • May affect the ability to drive and use machines, due to the risk of visual impairment and dizziness

ALT — alanine aminotransferase; AST — aspartate aminotransferase

promotes concentric cardiac remodelling due to the occurrence of two related cardiovascular events during treatment: cardiac hypertrophy and hypovolemia in the studied patients [13]. These lesions were not accompanied by clinical symptoms [13]. A comprehensive research acquisition strategy was conducted using Ovid/MEDLINE, EMBASE, and grey literature (1960–1 August 2013) to identify all relevant results on the use of isotretinoin in the treatment of acne vulgaris [14]. The inclusion criteria for the study were: clinical trials with oral isotretinoin at doses of 40 mg/d or greater of at least 4 weeks, patients aged 9 to 35 years with acne vulgaris, and a minimum number of 10 or more participants. Studies from all countries published in any language are included. The exclusion criteria were: the use of modified isotretinoin products, isotretinoin therapy for the treatment of conditions other than acne vulgaris, and concomitant treatment of acne. The initial search yielded 342 records, of which 116 were subjected to full-text examination [14]. Laboratory evaluation of lipid levels, liver function and total blood cell count was performed in the study. A total of 26 studies (1574 patients) were included in the meta-analysis. Mean (99% CI) triglyceride values during treatment (beyond baseline) were 119.98 mg/dL (98.58–141.39 mg/dL); for total cholesterol 184.74 mg/dL (178.17–191.31 mg/dL); for low-density lipoprotein cholesterol 109.23 mg/dL (103.68–114.79 mg/dL); for high-density lipoprotein cholesterol 42.80 mg/dL (39.84–45.76 mg/dL); for aspartate aminotransferase: 22.67 U/L (19.94–25.41 U/L); for alanine aminotransferase 21.77 U/L (18.96–24.59 U/L); for alkaline phosphatase 88.35 U/L (58.94–117.76 U/L); and white blood cell counts were 6890/µL (5700/µL–8030/µL) (Tab. 3) [14–16]. This meta-analysis showed that (1) isotretinoin is associated with a statistically significant change in mean laboratory parameters from several studies (it affects white blood cell counts and hepatic and lipid panels), but (2) mean changes across the patient group did not meet the high-risk criteria, and (3) the proportion of patients with laboratory abnormalities was low.

In August 2021, an 18-year-old man was admitted to the emergency department (ED) with a history of acne vulgaris due to left hip fossa pain and exertional dyspnoea [17]. Computed tomography (CT) scans revealed left renal infarction and echocardiography showed global left ventricular dilatation with a significantly reduced left ventricular ejection fraction (LVEF) (Fig. 1). Coronary artery disease, autoimmune, infectious or hereditary causes of dilated cardiomyopathy (DCM) have been excluded [17]. Cardiac magnetic resonance imaging revealed late gadolinium enhancement

Table 3. Laboratory parameters of patients aged 9–35 years with acne vulgaris taking isotretinoin at a dose of 40 mg/d for at least 4 weeks [14–16]; however, there are also reports indicating the emergence of a high cardiovascular risk associated with the use of isotretinoin in young patients [17–22]

Laboratory parameters	1574 patients (average value)	Normal value (European Society of Cardiology standards)
TG	119.98 mg/dL	< 150 mg/dL
TC	184.74 mg/dL	< 190 mg/dL
LDL	109.23 mg/dL	< 115 mg/dL
HDL	42.80 mg/dL	Women > 46 mg/dL Men > 40 mg/dL
AST	22.67 U/L	< 40 IU/L
ALT	21.77 U/L	< 40 IU/L
ALP	88.35 U/L	< 270 U/L
WBC	6890/μL	4000–10,000/μL

ALP — alkaline phosphatase; ALT — alanine transaminase; AST — aspartate aminotransferase; HDL — high-density lipoprotein; LDL — low-density lipoprotein; TC — total cholesterol; TG — triglycerides; WBC — white blood cells

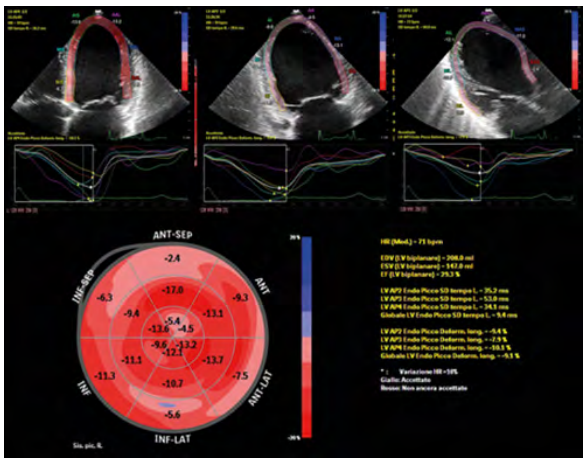

Figure 1. Echocardiography of an 18-year-old patient treated with isotretinoin admitted to the ED due to sudden pain in the left iliac fossa and exertional dyspnoea [17]

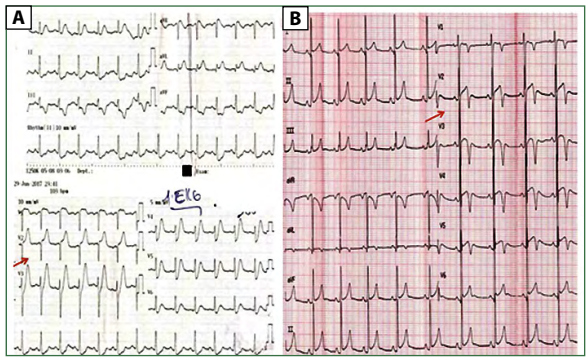

Figure 2. (**A**) Imaging of first-contact electrocardiography with sudden onset of chest pain (arrow indicates peak T-waves in the V1–V5 wires); (**B**) Imaging of follow-up electrocardiography after tirofiban infusion (arrow indicates biphasic T-waves in leads V1–V5) [17]

in the medial wall of the left ventricle, and ECG monitoring revealed several unfixed episodes of ventricular tachycardia (Fig. 1). Accordingly, bisoprolol, sacubitril/valsartan, and eplerenone were initiated and subsequently increased to the maximum tolerated doses, with only a weak improvement in LVEF [17]. This is the first reported case of renal disease thromboembolism and DCM requiring implantation of a subcutaneous implantable cardioverter defibrillator (S-ICD) and heart transplantation, occurring during isotretinoin treatment [17].

Another case report of the patient indicates a correlation between isotretinoin treatment and the occurrence of Kounis syndrome [18]. The diagnosis of Kounis syndrome is based on the clinical picture, observed signs and symptoms, especially after an allergic episode that is the result of a hypersensitivity reaction [18]. This is a multifactorial pathophysiological mechanism that is still unclear. A 25-year-old patient was admitted to the emergency department complaining of acute chest pain lasting for 1 hour [18]. Physical examination showed a systolic blood pressure of 120 mmHg, a diastolic blood pressure of 80 mmHg, and a heart rate of 100 beats per minute [18]. Auscultation of the heart did not reveal any abnormalities. Acute changes in the T-wave and dynamic ST segment were detected in V1–V5 electrocardiography derivatives (Fig. 2) [18]. Laboratory analysis revealed a high cardiac troponin I level of 4.1 ng/mL (normal range: 0.0–0.1 ng/mL) and a cardiac creatine kinase fraction concentration in the patient's blood of 8.2 ng/mL (normal range: 0.0–3.2 ng/mL) [18]. No risk factor for coronary artery disease was detected in the hospitalized patient, with the exception of smoking. There was no family history of coronary artery disease, no allergy or allergic reaction, and no substance abuse. The patient stated that he had been treated with isotretinoin (20 mg/day) for 1 week due to an acne diagnosis and that he had received the last dose 1 hour before the onset of chest pain [18]. Coronary angiography revealed

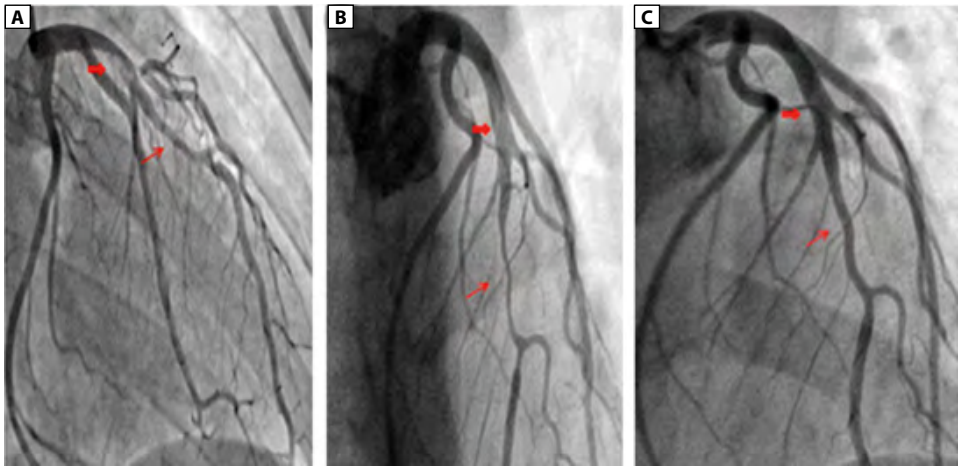

Figure 3. (**A**) Angiographic imaging of the left anterior descending (LAD) thrombotic lesion (thin arrow indicates the bridge of the myocardium, thick arrow indicates thrombus); (**B**) imaging of reduced LAD arterial thrombus after tirofiban infusion (thin arrow indicates myocardial ridge, thick arrow indicates thrombus); (**C**) imaging of dissolved LAD thrombus at 1 week (thin arrow indicates the area of the myocardial sternum, thick arrow indicates the area of dissolved thrombus [18]

thrombus and distal flow in the proximal left anterior descending coronary artery with a muscle bridge resulting in stenosis from 70% to 80% (Fig. 3) [18]. An infusion of tirofiban at a dose of 0.15 µg/kg/minute was administered over 18 hours. Chest pain has been completely eliminated. The assessment of thrombophilia, including mutations of the Leiden factor V gene and prothrombin, proteins C and S, antithrombin III, homocysteine levels, and resistance to active protein C, was completely negative [18]. Blood lipid and lipoprotein levels were within normal limits. Anti-nuclear, anti-dsDNA, and anticardiolipin antibodies were also within normal limits, ruling out the possibility of vasculitis and connective tissue diseases [18]. Subsequent follow-up coronary angiography showed that the thrombus had shrunk (Fig. 3). Biphasic negative T waves in V1–V5 derivatives were observed on electrocardiography (Fig. 2). Echocardiography showed mild hypokinesia of the anterior myocardial wall with no valvular abnormalities, intracardiac mass, or thrombus. Antiplatelet and anticoagulant therapy was continued, and 1 week later additional follow-up angiography showed that the thrombus had resolved (Fig. 3). The patient was discharged home without symptoms after administration of 200 mg of metoprolol, ticagrelor acetylsalicylic acid and atorvastatin. Isotretinoin treatment was not discontinued. A month later, there were no signs of ischaemia in the imaging of myocardial perfusion scintigraphy in the function performed in the described patient [18].

According to the literature to date, systemic isotretinoin treatment may cause some cardiac adverse reactions, such as atrial tachycardia, congenital heart defects and cardiac remodelling, as mentioned in the case reports [19]. A 26-year-old woman came to the emergency department as a result of sudden fainting after a prolonged episode of palpitations [19]. Physical examination showed no abnormalities, except for the presence of tachycardia. The woman was treated with isotretinoin at a dose of 0.5 mg/kg/day for 4 months due to nodular acne and did not take any other medications [19]. On ECG, the patient had atrial tachycardia in a 12-lead electrocardiogram and a heart rate of 149 beats/min. After an intravenous bolus injection of 25 mg of diltiazem hydrochloride, atrial tachycardia resolved and normal sinus rhythm was maintained [19]. Laboratory tests and chest X-rays were normal. Echocardiography revealed normal left ventricular function and pericardial effusion of 0.8 cm in the posterior part, 0.9 cm in the right atrium and 1.3 cm in the right ventricle [19]. Holter ECG revealed several episodes of atrial tachycardia. In the longest episode of atrial tachycardia, the heart rate was 149 beats/min [19]. After consultation with a dermatologist, isotretinoin was discontinued. Holter analysis showed a circadian sinus rhythm below 149 beats per minute only 2 months after discontinuation of drug therapy. Echocardiography revealed a gradual regression of pericardial effusion [19].

The subject of another case is a 16-year-old boy who, after three months of treatment with isotretinoin, began to experience episodes of palpitations both during physical exertion and at rest [20]. He started isotretinoin therapy due to cystic acne lesions on the face, initially receiving a dose of 30 mg/day for a month, and then 70 mg/day (1 mg/kg/day). The patient had a negative cardiac history and also denied taking cardiac drugs and dietary supplements. An ECG revealed a sinus rhythm with an incomplete right bundle branch block (iRBBB) [20]. Holter ECG showed a high incidence of isolated premature atrial excitations and

episodes of vestibular tachycardia that occurred ≥ 106 times daily, with the shortest lasting 3 beats and the longest 11 beats. The symptoms almost completely disappeared within a week of stopping the isotretinoin treatment. Follow-up ECG-Holter examinations performed 4 and 6 weeks after discontinuation of the drug showed sinus rhythm with an average heart rate of 62 and 58 beats per minute, respectively, and sporadic premature vestibular excitation in the number of 2 per day and none, respectively [20]. The results of the study clearly indicate a temporal relationship between isotretinoin treatment and the patient's symptoms in the presence of documented arrhythmias, suggesting a drug-related cause [20].

Another study shows a link between isotretinoin intake and a change in the lipid profile fraction in treated patients [21]. Sixty patients (32 men and 28 women) aged 18 to 50 years with an average age of 27 years were enrolled in the study. Patients were administered from January 2015 to December 2015. orally 20 mg of isotretinoin (according to a low-dose schedule) [21]. A thorough medical history and a thorough clinical examination were conducted. A medical history of concomitant medications that may interact with retinoids was collected. Laboratory tests such as a complete haemogram, liver function tests and a lipidogram were performed [21]. In the study population, hyperlipidaemia occurred in 25% (15 out of 60) of patients. Among hyperlipidaemias, hypertriglyceridemia was the most common (16.67%, 10 out of 60 patients), with increased levels of very low-density lipoprotein (VLDL) (11.67%, 7 out of sixty patients), increased low-density lipoprotein (LDL) (10%, 6 out of 60) and hypercholesterolaemia (5%, 3 out of 60). A combination of hyperlipidaemia occurred in 11.67% (7 out of 60) of patients. No changes in high-density lipoprotein (HDL) levels were observed. Among men, hyperlipidaemia after 3 months of isotretinoin treatment was 28.12% (9 out of 32), while in women the incidence of hyperlipidaemia was 21.43% (6 out of 28) [21]. Among women with hyperlipidaemia, hypertriglyceridemia occurred in 83.3% (5 out of 6) patients, while in men 55.5% (5 out of 9 patients). There was no statistical significance between hyperlipidaemia occurring in men and women with hyperlipidaemia ($p = 0.6869$) [21]. A 34-year-old female patient with no known cardiovascular disease, a non-smoker, and no diagnosed lipid disorders was admitted to the ward [22]. The patient was transported to the Cardiology Clinic on 6 October 2012 in a very serious condition due to sudden out-of-hospital cardiac arrest [brought by the ambulance after successful defibrillation (ventricular fibrillation) and cardiopulmonary resuscitation previously performed by her husband] [22]. It was determined that the patient did not smoke or drink alcohol. In biochemical tests, the concentration of total cholesterol was normal, and LDL cholesterol was 61 mg/dL. From the age of 18, the patient was treated for severe acne — she started the therapy by first taking isotretinoin for 5 months and cyproterone acetate and ethinylestradiol as an adjunct. After the acne lesions disappeared, she started taking the contraceptive drospirenone and ethinylestradiol, but due to the increase in acne symptoms, she returned to cyproterone acetate and ethinylestradiol about 2 years before her heart attack, taking it for 10 months. In addition, in 2010 she was given another one-year treatment with isotretinoin, which was discontinued due to pregnancy, after which the patient returned to taking cyproterone acetate and ethinylestradiol [22]. The patient underwent coronary angiography, which revealed amputation of the anterior descending branch, just behind its departure from the left coronary artery [22]. Aspiration thrombectomy (evacuation of a large thrombus) and left anterior descending (LAD) primary anterior descending coronary artery disease (LAD) with implantation of 2 amfillimus CRE 3 × 25 mm, 3.0 × 16 mm stents and administration of abciximab were performed simultaneously, achieving full vessel opening and TIMI 3 peripheral inflow. To sum up, the long-term anti-acne therapy that was applied to the patient may have contributed to the occurrence of sudden thromboembolic changes. Drugs such as isotretinoin and cyproterone acetate together with ethinyl oestradiol, as well as their side effects, may have significantly contributed to the development of thrombosis and myocardial infarction complicated by sudden cardiac arrest in a hospitalized woman [22]. According to previous studies, the contraceptive therapy used in the patient drospirenone and ethinylestradiol could also affect thromboembolic disorders [23–25].

Although cases such as those described in the following article (Tab. 4) and other articles (Tab. 5) may indicate a potential cardiovascular risk, an overall correlation between isotretinoin and cardiovascular disorders has not been proven in large population-based studies [26]. This is important in the context of assessing the risks and benefits of using isotretinoin to treat acne.

SUMMARY

Isotretinoin is definitely effective in dermatological treatment, but unfortunately, it has numerous side effects, including those related to the cardiovascular system. Studies have shown that it affects lipid metabolism, especially the concentration of triglycerides in the blood. However, it is worth noting that these values do not exceed the ceiling considered a high cardiovascular risk. Isotretinoin also directly affects the heart, causing it to remodel and resulting in a decrease in the cardiac index. Particular attention should be paid to young patients with thromboembolic events,

Table 4. Summary of cited clinical cases

Reference	Cardiac abnormalities	Patient	Indications for isotretinoin	Treatment data	Evidence suggesting isotretinoin as a cause of cardiovascular disorders
Pepe et al. [17]	Global left ventricular dilatation with a significantly reduced left ventricular ejection fraction	18-year-old man	Acne vulgaris	5 months	The patient was healthy before starting isotretinoin therapy, which he took for five months. Investigations, including cardiac MRI, ruled out ischaemic, autoimmune, infectious and hereditary dilated cardiomyopathy causes
Akçay et al. [18]	Kounis syndrome	25-year-old man	Acne	1 week	There was no family history of coronary artery disease and no risk factor, except smoking. Symptoms of Kounis syndrome appeared after 1 week of starting isotretinoin treatment
Güler et al. [19]	Pericardial effusion with atrial tachycardia	26-year-old woman	Nodular acne	4 months	Symptoms of pericardial effusion with atrial tachycardia appeared during treatment with isotretinoin. The woman was not taking any other medications, laboratory tests and a chest X-ray were normal
Hasdemir et al. [20]	Episodes of palpitations both during physical exertion and at rest	16-year-old boy	Cystic acne lesions on the face	3 months	The patient had no previous episodes of palpitations. His symptoms almost completely disappeared within a week after stopping treatment and has remained asymptomatic since discontinuing the drug
Sarkar et al. [21]	Change in the lipid profile fraction in treated patients	Sixty patients (32 men and 28 women) aged 18 to 50 years (an average age of 27 years)	Various skin diseases	January 2015 to December 2015	Regular observation of changes in the lipid profile during isotretinoin treatment indicates a direct link between the therapy and lipid disorders
Figiel et al. [22]	Cardiac arrest	34-year-old female	Severe acne	One-year	Patient without diagnosed cardiovascular disease, non-smoker and without diagnosed lipid disorders was transported to the Cardiology Clinic after long-term anti-acne therapy

Table 5. Some of the isotretinoin-associated cardiovascular side effects reported in the literature

Age and gender	Drug use time	Symptoms	Risk factors	Diagnosis	Therapy	Imaging	Physiopathology
35-year-old female [27]	One month	Palpitation	No	Premature ventricular contractions	Drug cessation	No	Unknown
18-year-old male [28]	Three months	Palpitation	No	Sinus tachycardia and right bundle branch block	Drug cessation	No	Unknown
28-year-old female [29]	One year	Chest pain	Cigarettes, oral contraceptives, high glycaemia and cholesterol levels	Inferior-STEMI	Thrombus aspiration and stent implantation	Optical coherence tomography	Complicated atherosclerotic plaque

Inferior-STEMI — inferior ST-elevation myocardial infarction; non-STEMI — non-ST-elevation myocardial infarction

coronary events and cardiac arrhythmias. It should be noted that the cases of cardiotoxicity that occur are singular in relation to the number of people who are successfully treated with isotretinoin without cardiovascular effects. Therefore, isotretinoin should be considered a relatively safe drug.

Despite the positive effects of isotretinoin, it is still necessary to monitor its effects through subsequent clinical trials so that the effectiveness of the therapy is fully evaluated and its use is safe.

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The contribution of each author in the creation of the review article was equal, accounting for 25% per author. The tasks performed by the authors included selecting the topic, conducting a literature review, performing an in-depth analysis of the subject, and writing the manuscript.

Conflict of interest

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Discoid lupus erythematosus and cutaneous squamous cell carcinoma

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ABSTRACT

Discoid lupus erythematosus (DLE) is a chronic autoimmune skin disorder characterized by inflammatory skin lesions. Patients with DLE often exhibit photosensitivity, scarring, and a higher susceptibility to skin cancers. This systematic review aims to comprehensively evaluate the existing literature to better understand the relationship between DLE and cutaneous squamous cell carcinoma (cSCC). A systematic search of major medical databases was conducted to identify relevant studies published between 1978 and 2023. Studies were included if they explored the association between DLE and cSCC and reported epidemiological data, clinical features and outcomes. Evidence shows a correlation between DLE and squamous cell carcinoma. The study aimed to find literature about DLE and squamous cell carcinoma (SCC) and analyse potential risk factors. Healthcare providers should be aware of the increased cancer risk in DLE patients, emphasizing the importance of regular skin examinations and sun protection.

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Keywords: discoid lupus erythematosus, squamous cell carcinoma, systematic review

INTRODUCTION

Discoid lupus erythematosus (DLE) is distinguished by well-defined, red, and scaly discoid plaques that undergo healing accompanied by atrophy, scarring, and alterations in pigmentation. Neoplastic transformation is a rare complication of this condition. The development of squamous cell carcinoma (SCC) within pre-existing DLE lesions has been regarded as the most severe consequence associated with DLE. The association between DLE lesions and SCC has not been fully investigated or integrated, despite the significant reporting of cases revealing SCC complicating DLE lesions. Early detection of SCC in a patient with DLE is crucial for effective treatment.

Aim

A literature study was conducted to identify and summarize the characteristics and meta-analysis of existing studies in this particular field.

MATERIAL AND METHODS

On September 26, 2023, a study was conducted to identify relevant literature. The PubMed and Medline databases were searched using different variations of two primary keywords: "discoid lupus erythematosus" and "squamous cell carcinoma". Additionally, additional variations of the aforementioned key terms, namely "DLE" and "SCC", have been used in the following study. The selected publication dates encompassed the period from 1978 to 2023. A total of 153 papers, including abstracts, original texts, and case reports, were identified. A total of 93 publications were removed from the analysis. The literature review only comprised original publications written solely in the English language, focusing on a research population consisting of individuals with discoid lupus erythematosus (DLE) and squamous cell carcinoma (SCC). The review included case series, case reports, and experimental randomized controlled trials. The analysis focused on the general characteristics of the patient (age, sex, potential risk factors), on the side of characteristics of patients with DLE (age, duration of DLE, location of the lesions, treatment), and on the side of characteristics of patients with SCC (age at the time of diagnosis, location of SCC, stage of malignancy, metastasis, cancer treatment, mortality rate). A total of 84 patients diagnosed with DLE and SCC were included in the study. The study selection process is depicted in Table 1. The literature incorporated in this review consists of a total of 48 original papers [1–48].

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RESULTS

All the case reports and series fulfilled the minimum standards for quality assessment. The process of identifying the data proved to be challenging, primarily attributable to their scarcity. The majority of the papers consisted of case reports, with authors applying varying criteria in the evaluation of each case. Initially, the attention was directed towards patient demographics and overarching characteristics, followed by a comprehensive analysis of SCC data, specifically regarding SCC characteristics. Although some authors did not provide extensive information on histological details, patient details, and attempted treatments, the overall methodological quality of the selected articles was assessed as satisfactory.

DLE patients' general characteristics

A total of 84 cases were included in this analysis. General DLE patients' characteristics are detailed in Table 2. The majority were male patients — 57.14% (48 male cases *vs.* 36 female cases). The mean age of the patients was 51.93 years. Discoid lupus erythematosus duration time to SCC diagnosis (mean) was 14.83 years. Most patients had systemic treatment (71.74%), mainly antimalarial drugs. Only 5 patients were reported to be using only topical treatment for DLE.

Squamous cell carcinoma's general characteristics

The location of SCC on the DLE lesions was analysed. The majority was located in sun-exposed areas (91.67%). The most common locations were lips (35.71%; lower to upper lip ratio 1, 14:1), scalp (20.24%), and face and ears (19.04%). The authors also focused on metastatic status, where it was found that 65.9% of the included patients had no metastatic data. The majority of patients diagnosed with squamous cell carcinoma (75%) used surgical intervention as their primary treatment modality. A smaller proportion of patients (18.33%) received chemotherapy, while the remaining patients (6.67%) were treated with radiotherapy. General characteristics of SCC in DLE patients are shown in Table 3.

Table 1. Study selection

Identification of studies via databases	
Records identified from PubMed and Medline databases (n = 153)	Records removed before screening: duplicate records removed, records removed for other reasons (non-English papers, not SCC patients) (n = 93)
Record screened (n = 60)	
Full texts assessed (n = 48)	
Total number of detailed cases in all included papers (n = 84)	

SCC — squamous cell carcinoma

Table 2. Discoid lupus patients erythematosus patients profile

Characteristics of DLE patients		Number of patients
Sex	Males	48
	Females	36
	Total	84
Age, mean [years] (range)	[51, 93] (35–78)	–
DLE duration time [years]	14.83	–
Mean DLE duration time to SCC diagnosis (range)	1–44	–
DLE treatment (n = 46)	Topical	5
	Systemic	33
	No treatment	8

DLE — discoid lupus erythematosus; SCC — squamous cell carcinoma

DISCUSSION

Discoid lupus erythematosus (DLE) is a benign skin condition characterized clinically by red, scaly areas that heal with atrophy, scarring, and pigmentary changes, and histopathologically by vacuolar degeneration of the epidermis's basal cell layer and patchy dermal lymphocytic infiltrate. DLE can be classified into two distinct forms: a localized variant characterized by lesions limited to the face and neck, and a disseminated variant where lesions are present in other areas of the body as well. The areas of the body most frequently affected by this condition are the sun-exposed regions of the head and neck, including the scalp, face, and ears [49, 50]. DLE typically does not involve the internal organs, as is the case with systemic lupus erythematosus (SLE). DLE can lead to the development of high-risk skin malignancies, which, although infrequent, pose significant health risks. DLE complicated by SCC was first mentioned in 1953 and has since been the focus of many case studies. The incidence of SCC in instances of long-standing chronic DLE ranges from 2.3% to 3.4%, with a higher prevalence observed in males [34, 37, 51]. There is a documented four-fold increase in the probability of cutaneous squamous cell carcinoma (cSCC) formation in patients with DLE [51]. Other neoplastic lesions in DLE, such as basal cell carcinoma, malignant fibrous histiocytoma, and atypical fibroxanthoma, have occasionally been reported [41]. Previous research has provided evidence of a latency period ranging from 7 to 30 years for the formation of SCC in DLE lesions. However, more recent investigations have indicated that this latency period can occur as early as 1–3 years [33]. Cutaneous squamous cell carcinoma (sSCC) exhibits a spectrum of clinical characteristics, varying from less aggressive forms to more aggressive forms that have

Table 3. General characteristics of squamous cell carcinoma in in patients with discoid lupus erythematosus

Characteristics of SCC		Number of patients	Percentage of cases [%]
Location of SCC on DLE lesions (n = 84 patients)	Upper lip	14	16.67
	Lower lip	16	19.04
	Scalp	17	20.24
	Face and ears	16	19.04
	Limbs	14	16.67
	Sun protected areas	7	8.33
Metastatic status (n = 44 patients)	No metastases	29	65.91
	Metastases	15	34.09
SCC treatment (n = 60 patients)	Surgical excision	45	75
	Radiotherapy	4	6.67
	Chemotherapy	11	18.33

DLE — discoid lupus erythematosus; SCC — squamous cell carcinoma

a notable propensity for metastasis. Predisposing factors such as scarring and immunosuppression have been identified as related to high-risk subtypes [52]. Squamous cell carcinoma is often associated with prolonged sun exposure and can occur anywhere on the body. The potential variables contributing to the development of SCC include genetic predisposition, the severity of discoid lesions in DLE, and human papillomavirus (HPV) infection.

Squamous cell carcinoma typically appears as a firm, red bump or a scaly patch that can ulcerate and bleed. Cutaneous squamous cell carcinoma ranks as the second most prevalent form of non-melanoma skin cancer. It constitutes 20% of reported instances of skin cancer [53]. The occurrence of SCC as a complication of persistent DLE lesions has been well-documented in the literature, and SCC has been regarded as the most serious consequence associated with DLE.

Although there are a significant number of documented cases that describe the occurrence of SCC in individuals with DLE lesions, the precise pathophysiological mechanisms contributing to the development of cSCC in individuals with DLE have not yet been fully elucidated. However, various factors may confer a susceptibility to the development of skin cancer in individuals with DLE. There is a notable correlation between cutaneous malignancies and autoimmune connective tissue diseases (ACTDs) such as SLE, systemic sclerosis, dermatomyositis, and Sjögren syndrome. This association can be attributed to various potential pathogenetic mechanisms, including chronic scarring, exposure to ultraviolet (UV) radiation, inflammation, immunosuppressive therapies, viral infections, and smoking [54]. Various characteristics have been proposed as potential predisposing factors for the development of malignancy in DLE lesions, such as the presence of chronic ulcers and inflammation associated with DLE. The prolonged scarring process could potentially contribute to the development of SCC originating from Marjolin's ulcers, as it may include a similar underlying pathomechanism [55].

Ultraviolet radiation is widely recognized as a significant risk factor for cSCC and DLE lesions, which tend to occur mostly in sun-exposed regions of the body. Possible pathogenetic processes include immune system dysfunction related to disease and cutaneous inflammation. The potential impact of UV light exposure is likely to be substantial in the context of DLE, particularly when combined with the reduced presence of protective melanin in individuals with hypopigmentation and those with fair skin [56]. The role of immunosuppressives in encouraging the development of cSCC has been under consideration. However, a study revealed an identical prevalence of cSCC in individuals with DLE, regardless of their history of immunosuppressive medication use [51]. Additionally, it has been noted that early anti-inflammatory medication can reduce the chance of cSCC developing in DLE, despite the clinical presentation's potential for difficulty [57, 58]. In their study, Ju et al. [59] presented a clinical case involving an individual of African American descent who exhibited the development of squamous cell carcinoma on a pre-existing discoid plaque of extended duration. The examination of the lesion indicated a pattern of p53 protein expression characterized as null type, along with a significant presence of CD123+ plasmacytoid dendritic cells. These findings suggest that the p53 protein may play a role in driving oncogenesis, while the abundance of CD123+

plasmacytoid dendritic cells may contribute to inflammation [59]. Gao et al. [60] conducted a study to investigate the immunoexpression of podoplanin in samples obtained from patients diagnosed with DLE and to examine its potential link with the risk of developing lip squamous cell carcinoma (LSCC). The findings of the study indicate a substantial correlation between the expression of podoplanin and the malignant transformation of DLE into LSCC. Hence, the expression of podoplanin has the potential to identify a specific subgroup that carries a heightened risk of malignant development in DLE [60]. Long-standing discoid lesions appear to be a crucial determinant of cSCC emerging in DLE, as previously published patients often presented with a long-term DLE history [19]. The clinical progression of cSCC as a consequence of DLE might exhibit an aggressive nature, characterized by the occurrence of early metastases and an elevated risk of mortality. compared to spontaneous cSCC cases [5, 9, 19].

The long-term prognosis of such instances exhibits considerable variability. Squamous cell carcinoma that arises in DLE is commonly recognized as a carcinoma of low grade with a locally aggressive nature, characterized by recurrences and infiltration into the underlying tissue. A study conducted by researchers found that approximately 20% of individuals experienced local recurrences, whereas 30% of cases exhibited metastasis [17]. Multiple metastases have also been documented as a cause of mortality [39].

The prompt and adequate management of DLE has the potential to reduce the probability of occurrence of this uncommon complication. Furthermore, alongside the implementation of UV protection and the use of anti-inflammatory topical treatments such as corticosteroids or calcineurin inhibitors, antimalarial medications have been widely recognized as the prevailing therapeutic approach [61]. It is recommended that smokers abstain from smoking, as the efficacy of the latter is diminished in this population. If a patient experiences mild intolerance reactions or if the antimalarial medicine is not sufficiently effective, it may be advisable to consider transitioning to another antimalarial agent [62].

The precipitating variables associated with SCC include individuals aged 40 years or older, male gender, exposure to sunlight or UV radiation, skin pigmentation, and chronic inflammatory processes. The development of SCC is inversely related to skin pigmentation due to the preventive properties of melanin [63]. To minimize the risk of SCC and maintain overall skin health, individuals with DLE should take measures to protect their skin from UV radiation, such as wearing sunscreen and protective clothing and avoiding excessive sun exposure.

Regular follow-up of patients with DLE is strongly advised, especially for those who exhibit the following traits: (1) male; (2) early onset of DLE; (3) involvement of lips; (4) resistance to treatment; and (5) cigarette usage.

Although SCC remains a rare complication of DLE, healthcare providers and individuals with DLE should remain vigilant, recognizing the importance of ongoing monitoring and preventive measures to minimize the risk of SCC development and ensure timely intervention if needed. This multifaceted approach contributes to improved outcomes and a better quality of life for individuals living with DLE. Once SCC has been established, it is imperative to allocate adequate focus towards monitoring potential recurrences and/or metastasis due to their heightened aggressive nature.

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VIA MEDICA

CASE REPORT

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Difficulties in the diagnosis of erysipelas in immunosuppressed patients

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ABSTRACT

Introduction: Erysipelas is an acute inflammatory condition of the skin and subcutaneous tissue caused by *Streptococci*. The lesions usually affect the lower limbs or face unilaterally and are characterized by erythema, oedema and pain. By the definition, the disease is accompanied by high fever. On the laboratory investigations, elevated C-reactive protein and leukocytosis are observed. However, in immunocompromised patients, the diagnosis might be unclear.

Case description: This study presents cases of three patients admitted to the department of dermatology with erysipelas: a 51-year-old woman with rheumatoid arthritis treated with tocilizumab, methotrexate and methylprednisolone, a 51-year-old woman with systemic lupus erythematosus treated with prednisone, and a 75-year-old woman with rheumatoid arthritis treated with methotrexate. Clinical pictures shared common symptoms in all cases: oedema, erythema and pain in one of the limbs. However, none of the patients had a fever on admission. On laboratory tests, in two cases, there was no significant increase in inflammatory markers. The treatment with intravenous antibiotics and low-molecular heparin resulted in good clinical improvement.

Conclusions: Chronic immunosuppressive treatment acting due to inhibition of pro-inflammatory cytokines reduced patients' immune response, which resulted in the absence of fever and no significant increase in the inflammatory parameters. Presented cases show some peculiarities of erysipelas in the distinct group of immunosuppressed patients and draw attention to unusual manifestations. Nowadays, there are more and more patients treated with biological agents for different diseases, including dermatoses. Hence, the number of atypical erysipelas cases may rise.

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Keywords: erysipelas, immunosuppressive therapy, immunosuppression, biological treatment, infection

CASES DESCRIPTION

Case 1

A 51-year-old female with a long-standing history of rheumatoid arthritis, treated with tocilizumab, methotrexate, and methylprednisolone was admitted due to oedema, erythema and pain in the area of her left lower leg. Initial treatment with oral amoxicillin did not lead to clinical improvement after 4 days, and the skin lesions expanded in the proximal direction. Importantly, the patient suffered from chronic venous insufficiency, and in the past, she had had erysipelas in the same lower leg.

Case 2

A 51-year-old female with a history of systemic lupus erythematosus, managed with prednisone, presented to the dermatology department due to oedema, erythema and pain in the upper limb. The symptoms have been present for two weeks. The patient had been previously treated with amoxicillin with no improvement.

Case 3

A 75-year-old female with rheumatoid arthritis, treated with methotrexate, presented with oedema, erythema, and pain in the right foot and lower leg (Fig. 1, 2). Despite receiving ciprofloxacin for 3 days, there was no improvement in the skin condition. It was discovered that the patient had suffered an injury to the toes of her right foot two months prior. Notably, the patient had previously suffered two episodes of erysipelas in her right lower limb.

The clinical presentations of all cases displayed common symptoms, characterized by the presence of oedema, erythema, and pain in a single limb (Tab. 1). However, none of the patients exhibited fever, and in two instances (cases 1 and 3), there was an absence of significant elevation in

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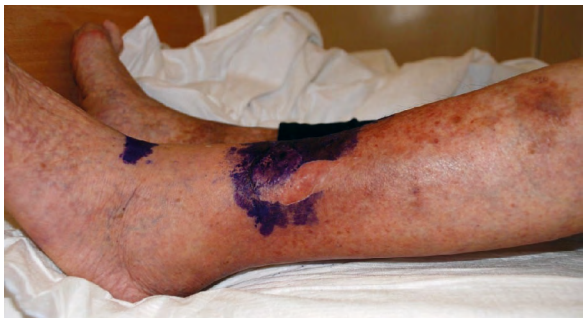

Figure 1. Erythema and oedema of the left lower limb with the presence of vesicles

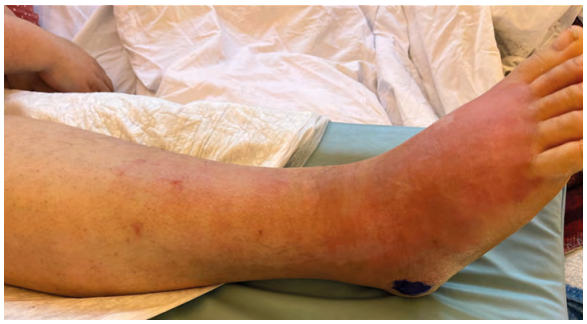

Figure 2. Oedema and erythema of the right foot and lower leg in a patient on admission

Table 1. Comparison of three cases

	1st patient	2nd patient	3rd patient
Patient age and sex	51-year-old female	51-year-old female	75-year-old female
Underlying disease	Rheumatoid arthritis	Systemic lupus erythematosus	Rheumatoid arthritis
Treatment of the underlying disease	• Methotrexate 15 mg/week *s.c.* • Tocilizumab 1 ×/week • Methylprednisolone 2 mg/d	• Azathioprine 150 mg/d • Methylprednisolone 16 mg/d	• Methotrexate 15 mg/week *s.c.*
Concomitant diseases	• Chronic venous insufficiency	• Arterial hypertension, • Osteoarthritis, • COPD	• Arterial hypertension • Heart failure • Diabetes mellitus • Gastritis • Cardiac achalasia
Onset of symptoms	For 5 days: erythema, oedema, pain, increased warmth around left ankle joint	For 2 weeks: erythema, pain, oedema, increased warmth of the forearm and right hand	Oedema, erythema and pain in the foot and right lower leg
Treatment applied before admission to the clinic	Amoxicillin 1 g every 12 hours for 4 days (without clinical improvement), expansion of skin lesions in a proximal direction	Amoxicillin 1 g 2×/d, for 9 days (without improvement)	Ciprofloxacin for 3 days (without improvement)
The occurrence of fever before starting antibiotics on an outpatient basis	No fever	No fever	No fever
Occurrence of erysipelas in the past	Erysipelas of the same lower leg	–	2 episodes of erysipelas within the right lower limb
Symptoms on admission to the clinic	• Erythema • Oedema • Pain • No fever	• Erythema • Oedema • Pain • No fever	• Erythema • Oedema • Pain • No fever
Laboratory results (on admission → on discharge) Reference values CRP < 5.0 mg/L WBC 4.0–10.0 k/μL	CRP: 4.3 → (< 1) WBC: 8 → 3.5	CRP: 501.7 → 115.8 WBC: 19 → 10	CRP: 8.2 → 5.8 WBC: 7.7
Imaging tests	Deep vein thrombosis in the lower left limb was excluded from the Doppler ultrasound examination	Deep vein thrombosis in the upper right limb was excluded from the Doppler ultrasound examination	Deep vein thrombosis in the lower right limb was excluded from the Doppler ultrasound examination
Respiratory rate	15/min	19/min	13/min
Pulse	75/min	81/min	66/min
Causative factor of the disease	Unknown	Unknown	2 months earlier, an injury to the toes of the right foot with a skin fissure

s.c. — subcutaneous; COPD — chronic obstructive pulmonary disease; CRP — C-reactive protein; WBC — white blood cell

Table 2. Treatment of all cases

	1st patient	2nd patient	3rd patient
Systemic treatment	• Ceftriaxone 2 g 1×/d *i.v.* (10 days)	• Ceftriaxone 2 g 2×/d *i.v.* (10 days), next 1×/d *i.v.* (5 days) • Vancomycin 1 g *i.v.* (14 days)	• Ceftriaxone 2 g 1×/d *i.v.* (10 days)
Anticoagulant treatment	• Enoxaparin 0.4 mL 1×/d *s.c.* (10 days)	• Enoxaparin 0.4 mL 1×/d *s.c.* (10 days)	• Enoxaparin 0.4 mL 1×/d *s.c.* (10 days)
Other systemic treatment medications	• Ketoprofen • Ac. Folicum • Omeprazole • Diosmectite	• Omeprazole • NSAIDs	• Ac. Folicum • Spironolactone • Hydroxyzinum • Ramipril • Gliclazide • Naproxen • Tramadol • Isosorbide
Topical treatment	• Aluminium acetate tartrate • Ichthyol ointment • Allantoin	• 10% borax with glycerine	• Aluminium acetate tartrate • Vaselinum album • Fusidic acid
Limb elevation	Applied	Applied	Applied
Treatment effects	The patient responded well to the applied treatment and managed to reduce skin lesions	Significant clinical improvement of general condition, local improvement and decrease in blood inflammatory parameters were obtained	The reduction of oedema and erythema of the lower leg was achieved. The patient was discharged home with the local improvement
Relapse prevention	After discharge, the patient was referred to the clinic for the prevention of recurrent erysipelas with phenoxymethyl penicillin or debecillin	–	After discharge, the patient was referred to the clinic for the prevention of recurrent erysipelas with phenoxymethyl penicillin or debecillin

i.v. — intravenous; NSAIDs — non-steroidal anti-inflammatory drugs; *s.c.* — subcutaneous

inflammatory markers such as C-reactive protein (CRP) or leukocytosis. In all cases, clinical improvement was obtained after intravenous antibiotic therapy, encompassing the administration of ceftriaxone, thromboprophylaxis, and topical treatment, along with limb elevation (Tab. 2).

DISCUSSION

Erysipelas is an inflammatory condition of the dermis and subcutaneous tissue, caused by the infection with streptococci, mainly from group A (*Streptococcus pyogenes*) but also serotypes C and G [1]. It is estimated that a small percentage of infections are caused by Group A *Streptococcal* (GAS) alone, and in most cases, a mixed group of bacteria is the cause [2]. Lipoteichoic acid molecules and F protein are factors facilitating host cell adherence and successful colonization by GAS. The production of streptolysin and hyaluronidase, on the other hand, allows the destruction of host tissues and the dissemination of GAS in the host. Moreover, the M protein found in GAS cells is believed to inhibit phagocytosis by host immune cells [3].

The clinical manifestation of erysipelas is characterized by a well-demarcated, warm oedema, most often involving the lower limbs, while the second most frequently affected site is the face [4]. Lesions are usually asymmetrical. However, sometimes the clinical picture might be atypical.

Studies indicate that the incidence of erysipelas has decreased since the improvement of sanitation and the development of antibiotic therapy. Although erysipelas can affect any age group, it most often occurs at elderly age [5]. Infection can be facilitated due to breaks in the skin barrier, particularly those caused by insect bites or athlete's foot. Other risk factors that predispose individuals to erysipelas development include surgical incisions, obesity, lymphedema, ulcers, poorly controlled diabetes, and liver disease. Noteworthy, cases of recurrent erysipelas are reported, most often within the same site as the primary infection [6, 7].

Laboratory tests are not required to make the diagnosis of erysipelas, however, they may affect the treatment plan [4]. The most important tests are complete blood count with white blood cell count and CRP. Moreover, in more severe cases it is worth performing procalcitonin concentration.

In the case of the presented patients, the course of erysipelas was atypical due to the absence of fever, and in two patients no increase in inflammatory parameters. It can be suspected that the cause of the atypical presentation of the disease was the immunosuppressive drugs taken permanently by each of the three patients. It has been noted that in severely immunocompromised patients, although rare, local or systemic infections may occur without fever. It can also be suppressed by the immunosuppressants themselves [8].

Two of the described patients received methotrexate. It can inhibit the production of pro-inflammatory cytokines: interleukin-4 (IL-4), interleukin-13 (IL-13), interferon-gamma (IFN-γ) and tumour necrosis factor-alpha (TNF-α) [9, 10]. It can also reduce inflammation by capturing free radicals, suppressing intracellular oxidative stress and inhibiting the formation of immunogenic protein complexes (called MMA adducts) [11]. Similarly, prednisone, which activates certain nuclear receptors, changes gene expression and inhibits the production of pro-inflammatory cytokines. In addition, it reduces the number of circulating lymphocytes, induces cell differentiation, and triggers apoptosis in susceptible cell populations [12].

The presence of fever is associated with endogenous pyrogens such as interleukin-1 (IL-1), tumour necrosis factor (TNF) and interleukin-6 (IL-6), which indirectly increase the body temperature. After reaching the hypothalamus, they stimulate the production of cyclooxygenase 2, which induces the synthesis of prostaglandins (especially prostaglandin E2). In turn, the presence of prostaglandins in the hypothalamus changes the biological set point [13]. The influence exerted on the cytokines by the drugs taken by the study patients may result in a lack of fever and no elevation in inflammatory markers.

Immunocompromised patients are more susceptible to opportunistic infections, which are typically controlled by a healthy immune system but can cause severe illness in individuals with compromised immunity [14]. There are various factors and medical conditions that can lead to immunocompromised states, and these individuals are at a higher risk of developing infections and experiencing more severe illness when exposed to pathogens. Common causes and conditions associated with immunocompromised states include cancer treatment, organ transplantation, human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), primary immunodeficiency disorders, and autoimmune diseases such as systemic lupus erythematosus (SLE) or rheumatoid arthritis. Moreover, within the category of immunocompromised individuals, some individuals receive immunosuppressive therapy, which includes antimetabolites, biologic drugs, and high doses of glucocorticoids [14, 15]. It's essential to provide extra care and precautions for immunocompromised individuals to reduce their risk of infections and support their overall health. In the treatment of erysipelas in immunocompromised patients, broad-spectrum parenteral antibiotic therapy is recommended according to the following scheme: Intravenous vancomycin plus cefepime 2 g intravenously (IV) every eight hours [16]. Vancomycin loading dose: 20 to 35 mg/kg. Vancomycin initial maintenance dose and dosing interval: 15 to 20 mg/kg every 8 to 12 hours. Once clinical improvement is observed, it is appropriate to switch to an oral antibiotic regimen. If a specific pathogen is identified during therapy, antibiotics should be adjusted to target that particular pathogen. For immunocompromised patients without an identified pathogen, it is recommended to use amoxicillin-clavulanate (875 mg orally every 12 hours) in combination with either doxycycline (100 mg orally twice daily) or trimethoprim-sulfamethoxazole (TMP-SMX; one to two double-strength tablets orally twice daily). The duration of antibiotic treatment should be adjusted according to the individual's clinical response. If there is a severe infection, a delayed response to treatment, or if the patient is immunosuppressed, it may be necessary to consider an extension of antibiotic therapy for up to 14 days. In certain cases, it can be beneficial to seek a dermatologic evaluation and perform a skin biopsy.

Although the clinical presentation of erysipelas seems to be quite characteristic, there are unusual situations that make accurate diagnosis difficult. Chronic immunosuppressive treatment results in the inhibition of pro-inflammatory cytokines, and thus a decrease in the immune response, hence the absence of fever. Nowadays, there are many subjects treated with immunosuppressants and even more and more patients are treated with biological agents for different diseases, including dermatoses. Hence, the number of atypical erysipelas cases may rise. Physicians should be aware of such possibilities to introduce proper treatment, even despite the obvious symptoms of erysipelas.

Article information and declarations

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Author contributions

JN: conceptualization, patient's attending physician, writing — original draft preparation, writing — review and editing; AB: writing — review and editing, supervision; IF: supervision; MC, KB, MD: writing — original draft preparation.

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VIA MEDICA

CASE REPORT

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A collision tumour of basal cell carcinoma and melanocytic nevus mimicking a melanoma — a case report and review of the literature

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ABSTRACT

A collision tumour is characterized by the presence of at least two different skin neoplasms in the same lesion. Collision skin tumours develop quite rarely. The case presents a 58-year-old woman in whom an asymmetric skin lesion of undetermined duration was noted during routine dermoscopy. The skin lesion consisted of two clinically distinct components. The patient remained under a 4-month follow-up. At the next visit, a change in the appearance of the previously present lesion was observed. The lesion was excised and submitted for histopathological examination, which was consistent with the diagnosis of a collision tumour composed of dysplastic nevus and basal cell carcinoma. This article discusses the characteristics and diagnostic difficulties in the diagnosis of collision tumours based on the available English literature. Furthermore, highlighted is the value of a non-invasive imaging modality which is dermoscopy in diagnosing not only melanoma and non-melanoma skin cancer but also complex lesions such as collision tumours.

Forum Derm. 2024; 10, 1: 29–31

Keywords: collision tumour, basal cell carcinoma, dysplastic nevus, dermoscopy

CASE REPORT

A 58-year-old Caucasian male, with a negative family history of melanoma, was referred to the Dermatology Clinic in March 2021 for a routine nevi check-up. Under dermoscopy, attention was drawn to an asymmetric lesion of unknown duration located in the lumbar region. The lesion consisted of two components — the left part showing under dermoscopy typical brown pigment network, and the right part composed of an unspecific pink structureless area (Fig. 1A). The patient was invited for a follow-up visit in July 2021 (Fig. 1B). Digital dermoscopy showed growth of the pink structureless area and development of punctate erosions (Fig. 1C). In addition, short fine serpentine vessels became apparent (Fig. 1D). The collision lesion was not taken into consideration, and malignant melanoma was the main suspicion. The whole lesion was surgically excised with a 3-mm margin. Histopathology was consistent with the diagnosis of a collision tumour composed of dysplastic nevus with cytologic low-grade atypia (left part) and basal cell carcinoma (right part) — Figure 2.

DISCUSSION

Collision skin tumours develop quite rarely, and largely because of that, pose a diagnostic challenge. Thus, only a small number of descriptions of them can be found in the English-language literature [1–15]. They are characterized by the presence of at least two different skin neoplasms in the same lesion [1]. They were found to be histopathologically diagnosed and not suspected based on clinical examination in 51.2% of cases [1]. A collision tumour may be composed of benign associations, malignant associations, or benign-malignant associations. The confusing terminology that has been present in the literature so far was finally systematized by Satter et al. [2], who distinguish four types of lesions: collision tumours (composed of originally separate neoplasms with a tendency for merging),

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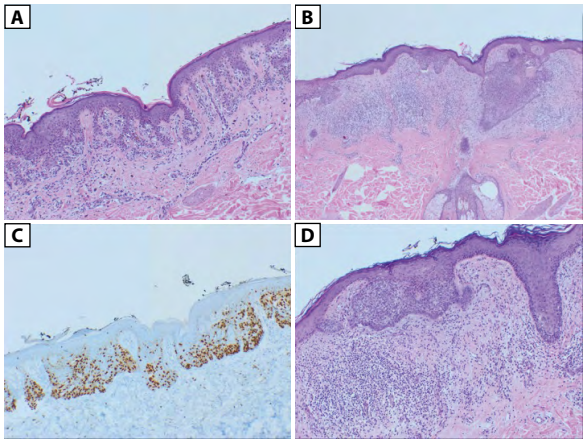

Figure 1. Dermoscopy of the lesion at initial consultation showing regular brown pigment network on the left and pink structureless area with single fine linear vessels on the right (**A**); clinical presentation of the lesion at follow-up visit after 4 months — peripheral spreading of the right component and single crusted erosions were present (**B**); dermoscopy at the follow-up visit showed evident erosions and linear vessels on pink background (**C**); video dermoscopy (×30) showing multiple linear vessels (yellow arrows) and crusted erosions (red arrows) (**D**)

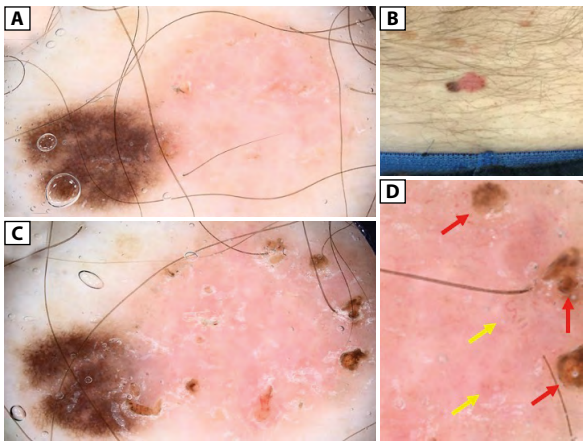

Figure 2. Histopathological examination showing both features of (**A**, **C**) melanocytic nevus (left part of the collision lesion) and (**B**, **D**) basal cell carcinoma (right part of the collision lesion); lentiginous hyperplasia and irregular nests of melanocytes with cytologic low-grade atypia (haematoxylin & eosin, ×100) (**A**); positive SOX10 staining (SOX10, ×100) (**B**); basaloid lobules projecting from the lower margin of the epidermis with peripheral palisading (haematoxylin & eosin, ×40) (**C**); basaloid lobules with peripheral palisading (haematoxylin & eosin, ×100) (**D**)

combined tumours (composed of intimately admixing cell populations), colonized tumours (composed of one cell population has a tendency for colonizing an underlying second cell population), and biphenotypic tumours (composed of cell populations arising from a common precursor but undergoing divergent differentiation) [3]. If a malignant component is present, correct diagnosis is crucial for proper management [1].

In the study of 41 collision tumours by Fikrle et al. [1], over half of the lesions were misdiagnosed clinically and dermoscopically. Twenty-eight out of 41 collision lesions consisted of at least one malignant component. However, only 3 cases were a collision of two malignant tumours. Melanoma was found to collide most frequently with seborrheic keratosis [1]. Therefore, older patients with multiple seborrheic keratosis undoubtedly require thorough dermoscopic examination in order not to miss melanoma.

Basal cell carcinoma (BCC) was also found to frequently collide with seborrheic keratosis [1]. In the study by Zaballos et al. [4], a collision of BCC and seborrheic keratosis constituted 37.9% of histopathologically proven malignant collision tumours. In the same study, collision tumours composed of BCC and melanocytic nevus accounted for 19.9% of cases [4]. In the study by Fikrle et al. [1], collision tumours composed of BCC were predominantly located on the head and neck area (58.3%).

Three larger histopathological studies on collision tumours have been published to date, all showing a very low rate of collision tumours among biopsied lesions [3, 13, 14]. In the study by Boyd and Rapini, the collision of BCC and melanocytic nevus was found to be predominant [3].

It should be taken into consideration that collision lesions, consisting of benign components in particular, are encountered in daily clinical practice much more frequently than estimated. Most of these lesions, such as a collision of seborrheic keratosis and cherry angioma, are easy to diagnose with the naked eye and they are never biopsied. Therefore, a thorough examination, including dermoscopy, is so important in order not to miss the malignant component, which may be overshadowed by the dominant benign part of the collision lesion.

Dermoscopy facilitates the detection of collision tumours [4, 6, 11]. In the study by Fikrle et al. [1], dermoscopic structures corresponding to the histopathological diagnosis were present in all 41 cases of collision tumours [1]. Therefore, routine use of dermoscopy for evaluation of all skin tumours and close examination of all quadrants of the lesion in order not to miss a minor colliding tumour is recommended [1]. Reflectance confocal microscopy (RCM) has also proved to be of help in the early recognition of collision tumours [15]. Cooperation with histopathologists is crucial. In the above-mentioned study by Fikrle et al. [1], six collisions were initially missed in histopathology. Enough clinical and dermoscopic information should be provided to the pathologist to avoid even a minor element of the collision tumour being unrecognized.

CONCLUSIONS

In conclusion, thorough physical examination, detailed dermoscopic analysis of all four quadrants of the lesion, RCM in case of equivocal lesions, and good cooperation with the dermatopathologist are necessary to increase early clinical diagnosis of collision tumours.

Article information and declarations

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Author contributions

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrality of the work as a whole, and have given their approval for this version to be published.

Conflict of interest

The authors of this publication declare no conflicts of interest.

Ethics statement

Informed consent was obtained from the patient for participation in the study and publication of the article, including publication of clinical photographs.

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Supplementary material

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VIA MEDICA

CASE REPORT

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Amelanotic Meyerson's nevus dermoscopically mimicking amelanotic melanoma

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ABSTRACT

Meyerson's nevus (MN) is a term describing melanocytic nevus with a surrounding symmetrical halo of erythema and scaling. It most commonly presents as an itchy or asymptomatic lesion on the trunk or proximal part of the upper limbs in young individuals, with male predominance. The underlying cause of MN has not been explained. Histopathologically, the features of associated spongiotic reactions are observed, including spongiosis, acanthosis, parakeratosis, lymphocytic exocytosis, as well as intraepidermal spongiotic vesicles. Dermoscopy of this phenomenon was rarely reported. No dermoscopic report on amelanotic Meyerson's nevus has been found.

The study reports a 29-year-old woman (phototype II), with a previous history of papillary thyroid carcinoma, who presented with an amelanotic nodule on her right arm. The patient reported enlargement of the lesion within the previous several weeks. Dermoscopy showed the presence of dotted, glomerular and short linear irregular vessels over a pink-yellowish background as well as the presence of a white scale. Due to the history of a growing, amelanotic lesion with polymorphic vessels, an excisional biopsy was performed. Based on histopathology the diagnosis of Meyerson's nevus was made.

Forum Derm. 2024; 10, 1: 32–34

Keywords: Meyerson's nevus, dermoscopy, dermatoscopy, melanocytic nevus, amelanotic lesion

CASE REPORT

A 29-year-old woman (phototype II), with a previous history of papillary thyroid carcinoma, presented with an amelanotic nodule on her right arm (Fig. 1A). The patient reported enlargement of the lesion in the previous several weeks. On dermoscopy, it showed dotted, glomerular and short, linear, irregular vessels spanned over a pink-yellowish background together with the presence of a white scale (Fig. 1B). Due to the history of a growing, amelanotic lesion with polymorphic vessels, excisional biopsy was performed. Based on histopathological evaluation the diagnosis of Meyerson's nevus (MN) was made (Fig. 2).

DISCUSSION

Meyerson's nevus usually presents as an itchy or asymptomatic lesion on the trunk or proximal portion of the upper limbs in young individuals, with male predominance. Histopathologically, an associated eczema-like reaction is observed, including spongiosis, acanthosis, parakeratosis, and lymphocytic exocytosis, as well as intraepidermal spongiotic vesicles. Although the classical description of Meyerson's phenomenon concerned nevi with an erythematous halo, later studies showed that in the case of mild spongiosis, it may be absent, as in the described case [1]. The underlying cause of MN has not been explained so far. Of note, Meyerson's phenomenon, apart from common acquired melanocytic nevi, has been described also in relation to dysplastic nevi, congenital melanocytic nevi, melanoma as well as other benign and malignant skin tumours [1–6]. There are few dermoscopic descriptions of melanocytic nevi with Meyerson's phenomenon, and to the authors' knowledge none of them concerned amelanotic MN [1–4]. It was previously stated that Meyerson's phenomenon does not modify the dermoscopic feature of the melanocytic lesion, but sometimes it may be difficult to assess due to the presence of overlying yellowish crust [1]. On the other hand,

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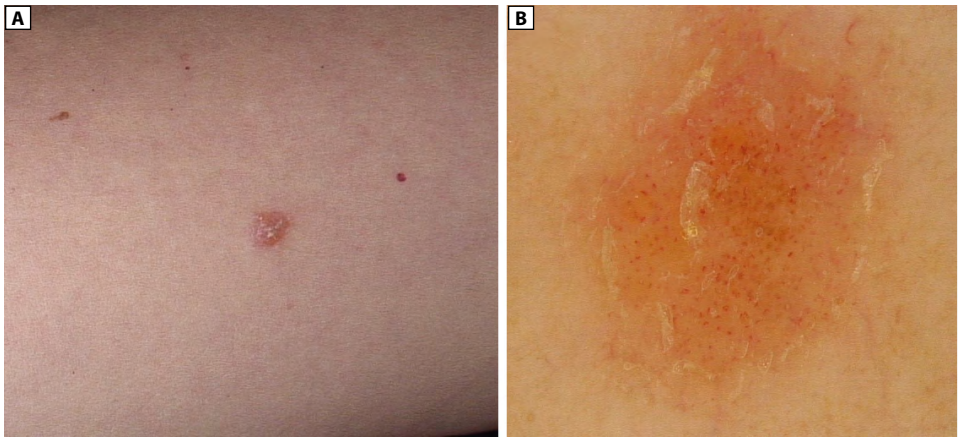

Figure 1. Clinical presentation — amelanotic nodule on the right arm (**A**); dermoscopy shows the presence of dotted, glomerular and short linear irregular vessels over a pink-yellowish background as well as the presence of white scale (FotoFinder, camera Medicam 800 HD, ×20 magnification, non-polarized mode with ultrasound gel as an immersion fluid) (**B**)

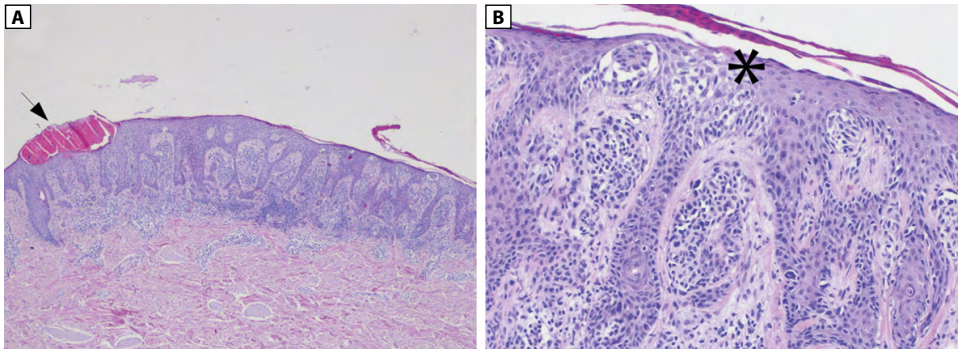

Figure 2. A symmetrical melanocytic nevus with focal presence of a vesicle (**A**, arrow) and spongiosis with exocytosis of single lymphocytes and parakeratotic scale on the surface (**B**, asterisk) is a typical microscopic presentation of Meyerson's nevus (magn. A — ×20, B — ×100, H&E staining)

a recent report by Di Altobrando et al. [2] describing clinical and dermoscopic features of two congenital melanocytic nevi with this phenomenon showing worrisome dermoscopic patterns raises a question of whether this statement is still actual. The lack of the classical erythematous halo and fast growth of the lesion reported by the patient with previous oncological history influenced the decision of prompt excision of the lesion in the described case.

CONCLUSIONS

In contrast to pigmented Meyerson's nevus, when diagnosis is possible in most cases based on clinical and dermoscopic features, dermoscopic presentation of its amelanotic counterpart seems to be unspecific. Amelanotic Meyerson's nevus is another lesion that should be considered in differential diagnoses of fast-growing tumours presenting with polymorphic vascular patterns.

Article information and declarations

Prior presentation

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Author contributions

U.M.: writing — original draft preparation; M. Sławińska: conceptualization, patient's attending physician, supervision; JŻ, RJN, M. Sobjanek: writing — review and editing; WB: figures preparation, review and editing.

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Ethics statement

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Supplementary material

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