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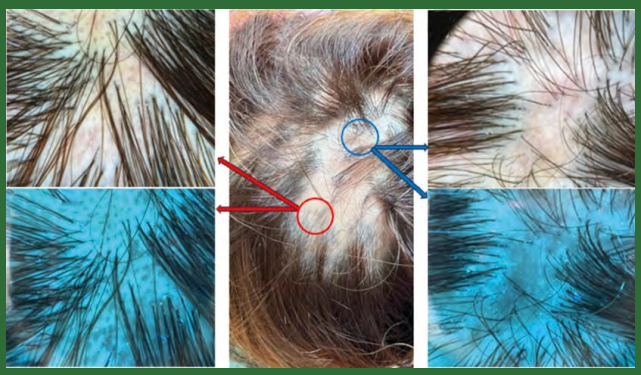

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Hereditary alpha tryptasemia: literature overview on the genetic trait and its clinical manifestations

Agnieszka Rydz[1], Magdalena Lange[2]

[1]*Student's Scientific Circle Practical and Experimental Dermatology, Medical University of Gdańsk, Poland*
[2]*Department of Dermatology, Venereology and Allergology, Medical University of Gdańsk, Poland*

ABSTRACT

Hereditary Alpha Tryptasemia (HαT) is a genetic condition characterized by an increased number of copies of the *TPSAB1* gene, resulting in elevated basal serum tryptase levels and an increased risk of anaphylaxis, especially in individuals with IgE-dependent allergies or systemic mastocytosis. The severity of clinical symptoms can vary and is influenced by the number of extra *TPSAB1* gene copies, suggesting a gene-dose effect. Approximately two-thirds of individuals with HαT show minimal or no symptoms. The remaining individuals with HαT may present with *Hymenoptera venom* allergy, flushing, urticarial/angioedema, irritable bowel syndrome, gastrointestinal reflux, hypermobility, neuropsychiatric symptoms and dysautonomia.

Recent studies revealed that α-tryptase which forms complexes with β-tryptase activate protease-activated receptor-2 (PAR2) receptors. Activation of these receptors may lead to hypotension, muscle contraction, inflammation, and trigger neuropeptide secretion, and in consequence, result in mast cell degranulation. This cycle of activation and degranulation may potentially contribute to the development of mast cell activation syndrome (MCAS).

Mast cell activation syndromes are defined by systemic, severe and recurrent mast cell activations, usually in the form of anaphylaxis. Hereditary/familial MCAS is a specific subtype of MCAS, which is associated with HαT.

Diagnostic work-up for HαT includes determination of basal serum tryptase level and the presence of additional *TPSAB1* gene copies using droplet digital polymerase chain reaction.

Further research is needed, to explore the relationship between HαT and MCAS, as well as to determine if there is a distinct form of hereditary MCAS which is independent of HαT. These investigations aim to improve diagnostic approaches and treatment strategies for individuals with HαT, enhancing their management and overall quality of life.

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Keywords: hereditary alpha tryptasemia, HAT, familial/hereditary MCAS

INTRODUCTION

Hereditary alpha tryptasemia (HαT) is an autosomal dominant genetic trait caused by an increased number of copies of the *TPSAB1* gene, which encodes for alpha-tryptase. The estimated frequency of HαT is 3–5.5% within the Western and predominantly Caucasian population [1–3]. This condition, first described in 2016, is a common cause of elevated basal serum tryptase (BST) — currently defined clinically as >11.4 ng/mL — and is associated with various clinical symptoms [4]. HαT patients may present with systemic immediate hypersensitivity reactions, particularly *Hymenoptera venom* allergy, pruritus, flushing, urticarial/angioedema, joint hypermobility, connective tissue disorders, functional gastrointestinal diseases, neuropsychiatric symptoms, and dysautonomia [4–6]. The diversity and severity of symptoms vary among affected individuals, with some experiencing milder manifestations and others displaying more pronounced symptoms. Studies have shown that the severity of symptoms in HαT patients is positively correlated with the number of *TPSAB1* gene copies, which suggests a gene-dose effect [5, 6].

Individuals with HαT are at an increased risk of developing mast cell activation syndrome (MCAS) which is defined by systemic, severe and recurrent mast cell activations, usually in the form of anaphylaxis, a substantial, event-related increase of serum tryptase level beyond the individual's baseline and a response of the symptoms to medicines directed against mast cells or antimediator therapy [7].

Address for correspondence:
Agnieszka Rydz, Student's Scientific Circle Practical and Experimental Dermatology, Medical University of Gdańsk, Smoluchowskiego 17, 80–214 Gdańsk, Poland; e-mail: agnieszka.rydz@gumed.edu.pl

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The association between HαT and MCAS is particularly significant when HαT coexists with IgE-dependent allergies or systemic mastocytosis (SM) [8, 9]. In such cases, the risk of anaphylaxis and severe allergic reactions is heightened [7].

The relationship between HαT and MCAS has gathered attention in the medical community, leading to the identification of a specific subtype of MCAS known as hereditary/familial MCAS or HαT + MCAS. In this subtype, MCAS is not attributed to any allergies or underlying clonal MC disease, but the diagnostic criteria for MCAS and HαT are met [7]. However, it is still being investigated whether a distinct form of hereditary MCAS exists independently of HαT.

This review aims to provide a comprehensive understanding of HαT including its clinical manifestations and the correlation between HαT and MCAS.

MAST CELLS AND MEDIATORS

Mast cells (MCs) are bone-marrow-derived immune cells located in peripheral tissues, particularly those near the external environment, such as the skin, airways and gastrointestinal tract [6, 10, 11]. Mast cells are the main effectors in type I allergic reactions and diseases such as urticaria, asthma, anaphylaxis, rhinoconjunctivitis and allergic rhinitis [12, 13]. Mast cells are primarily activated by IgE-antigen complexes bound to the FcεRI receptor on their surface. This interaction leads to the degranulation of MCs and the release of MC-derived mediators including histamine, cytokines, chemokines, and proteases including tryptase, which is the most specific MC product [14]. The role of MCs and MC-mediators is to further activate an immune system and to provide various adaptive immune responses by affecting T-cells and lymph node activity [15].

Mast cells can be activated in different tissues. In the gastrointestinal tract, MC activation leads to increased fluid secretion, smooth muscle contraction, and peristalsis resulting in cramps, vomiting or diarrhoea [16]. In the respiratory tract, mast cell activation (MCA) causes airway constriction, increased mucus production, and coughing. In the skin, MC activation results mainly in the occurrence of urticaria (hives), angioedema and flushing [17].

TRYPTASE AND ITS ISOTYPE DIFFERENCES

Tryptase is a protein produced by MCs and basophils [14, 18, 19]. These cells store mature tryptases in secretory granules, where they are present as tetrameric serine protease [20]. The primary function of tryptase is its involvement in allergic inflammation, as occurs in type I immediate hypersensitivity reactions, where mature tryptases are released from MCs secretory granules with other MC-derived mediators. The proteins that have not undergone enzymatic conversion into mature tetrameric tryptases are known as protryptases [21]. These monomeric proteins are consistently secreted into the serum and constitute a significant portion of the measured BST [22].

Four types of tryptase have been identified, including three soluble forms (α, β, and δ) and one membrane-anchored form (γ) [22]. The first two isoforms are essentially unique to humans, as they have undergone important evolutionary modifications, such as duplications, gene conversions missense and nonsense mutations [22, 23].

The human tryptase locus on chromosome 16 contains four paralogous genes (*TPSG1*, *TPSB2*, *TPSAB1*, and *TPSD1*) [22]. *TPSAB1* gene can produce either alpha-tryptase or beta-tryptase. On the other hand, the *TPSB2* gene encodes only beta-tryptase [24, 25]. It is important to note that approximately one-third of individuals lack alpha-tryptase, while no one has been reported to lack beta-tryptase [22, 23, 26].

HαT is defined by the presence of extra copies of alpha-tryptase encoding sequences on a single allele in approximately 5% of individuals [15, 26–30]. The presence of extra copies of alpha-tryptase encoding sequences is associated with elevated basal serum tryptase (BST) levels currently defined clinically as > 11.4 ng/mL. This increase in BST levels is likely influenced by unidentified modifiers of gene expression specific to the alpha-tryptase encoding replications [22]. Beta-tryptase, despite its similarities, does not exhibit the same clinical effect as alpha-tryptase. Therefore, variations in beta-tryptase copy numbers alone do not lead to increased BST levels [22].

PATHOGENESIS AND CLINICAL MANIFESTATIONS OF HαT AND FAMILIAL/HEREDITARY MCAS

Recently, Le QT, et al. [25] conducted a study revealing that, unlike β-tryptase, α-tryptase tetramers lack protease activity. The researchers demonstrated that the expression of α-tryptase in individuals leads to the natural formation of heterotetramers, consisting of two α-tryptase and two β-tryptase protomers, known as α/β-tryptase. These α/β-tryptase complexes specifically activate protease-activated receptor-2 (PAR2), which is found in various cell types including smooth muscle, neurons, and endothelium. Stimulation of PAR2 during MC degranulation can lead to various clinical effects. For instance, in systemic anaphylaxis, activation of PAR2 on vascular endothelium may worsen hypotension [25]. In conditions like inflammatory bowel disease and asthma, PAR2 activation on smooth muscle can result in muscle contraction, further exacerbating symptoms [31, 32]. Also, activation of PAR2 on keratinocytes and sensory nerves in the skin might intensify inflammation, pruritus, and hyperalgesia [33–36]. In addition, activation of PAR2 on sensory nerves has been found to result in the secretion of neuropeptides such as Substance P and calcitonin gene-related peptides [37]. These neuropeptides then bind to specific receptors on MCs, which triggers further degranulation

[13, 38]. This cycle of activation and degranulation may potentially contribute to the development of MCAS. These findings suggest that HαT is strongly connected with hereditary/familial MCAS presenting similar symptoms.

Based on Lyons JJ. Study [20], systemic immediate hypersensitivity reactions to stinging insects were found to be 20% more common among individuals with HαT. Moreover, flushing, pruritus, chronic gastroesophageal reflux, arthralgia, body pain, irritable bowel syndrome and sleep disruption were the most common complaints reported in symptomatic individuals.

The symptoms of MCA may resemble those of HαT and may vary among individuals. Typical clinical symptoms of MCA include pruritus, flushing, urticaria, angioedema, nasal congestion, wheezing, cough, diarrhoea, headache, and hypotension which may occur in various diseases [7].

MAIN DIAGNOSTIC FEATURES OF HαT AND FAMILIAL/HEREDITARY MCAS

The diagnosis of HαT involves several key factors as described in the Lyons study [20]. When considering HαT as a possibility, the primary indicator is BST over 8 ng/mL. This typically comes to attention following evident allergic reactions, anaphylaxis, or when diagnosing patients with *hymenoptera venom* allergy, mastocytosis symptoms, or certain haematologic malignancies. It's worth noting that nearly 80% of people with the HαT trait have BST levels surpassing the upper limit of normal cited by most laboratories, which is 11.4 ng/mL.

Tryptase genotyping is necessary to confirm the trait. A droplet digital polymerase chain reaction (ddPCR) assay is employed to demonstrate an increased copy number of the *TPSAB1* gene responsible for encoding alpha-tryptase [39, 40]. It's important to mention that routine next-generation sequencing methods may not be sufficient for characterizing tryptase gene composition or copy numbers accurately [41].

In highly symptomatic individuals, further evaluation becomes crucial. While HαT is a common condition and many patients may exhibit minimal or no symptoms, it's important to consider the possibility of coexisting disorders in those experiencing pronounced symptoms. This includes individuals displaying signs and symptoms suggestive of mastocytosis, MCAS or clonal myeloid diseases such as lymphadenopathy, hepatosplenomegaly, abnormalities in complete blood count, eosinophilic tissue infiltration, anaphylaxis (particularly hypotensive), cutaneous symptoms of mastocytosis and the presence of Darier's sign [42, 43].

To diagnose MCAS, which can present similar clinical features, three criteria must be met [7, 44]: (a) documented evidence of typical clinical symptoms that result from recurrent acute systemic MCA, resembling episodes of recurrent anaphylaxis (b) a significant and temporary increase in MC-derived mediators (e.g., tryptase, histamine, and prostaglandin D2 metabolites) in serum and urine, which should be compared to baseline levels measured before the event or at least 24 hours after all clinical signs and symptoms have completely subsided, and (c) positive response to drugs that block MCA or inhibit MC mediators, production, or effects [7].

TREATMENT STRATEGIES OF HαT AND FAMILIAL/HEREDITARY MCAS

Pharmacotherapy is the primary approach for treating symptomatic individuals with HαT, which is similar to the treatment used for clonal mast cell disorders. The treatment involves various medications such as H1- and H2-antihistamines, MC stabilizers like compounded oral ketotifen or cromolyn sodium, leukotriene modifiers, and, in some cases, aspirin or intermittent courses of oral corticosteroids [22].

Patients experiencing anaphylaxis should have at least two epinephrine autoinjectors and should be educated on their proper use.

In retrospective studies, omalizumab was found to improve cutaneous and respiratory symptoms connected with MCA [28, 45]. In a trial, described by Carter et al. [27], one individual with HαT who received omalizumab experienced a reduction in anaphylaxis episodes compared to one patient who received a placebo [27]. Moreover, a retrospective study conducted by Giannetti et al. [45], also reported a decrease in anaphylaxis episodes among HαT patients treated with omalizumab.

It is really important to monitor symptomatic individuals with HαT for bone loss, for the following reasons. Firstly, many clinical reports, have connected high BST levels with premature osteopenia and osteoporosis. Secondly, increased populations of bone marrow MCs and eosinophils have been observed in symptomatic individuals with HαT which may be a risk factor for early onset of bone loss. Lastly, symptomatic individuals with HαT often receive high-dose systemic corticosteroids, which can contribute to bone loss. Therefore, it is recommended to perform bone densitometry in symptomatic adult patients (both male and female) [30, 46].

Conclusions

In summary, HαT is a genetic condition characterized by an increased number of copies of the *TPSAB1* gene, which encodes for alpha-tryptase.

HαT may manifest with a diverse range of clinical symptoms including immediate hypersensitivity reactions, allergies, pruritus (itching), flushing, joint hypermobility, connective tissue disorders, and functional gastrointestinal diseases. However, approximately two-thirds of individuals with HαT show minimal or no symptoms.

Importantly, individuals with HαT are at an increased risk of developing anaphylaxis, particularly when they have coexisting IgE-dependent allergies or systemic mastocytosis. Currently, HαT is considered a heritable modifier of both idiopathic and *Hymenoptera venom anaphylaxis* [1].

A specific subtype of MCAS, known as hereditary/familial MCAS or HαT + MCAS, has been identified in association with HαT.

Further research is needed to delve deeper into the relationship between HαT and MCAS to determine whether MCAS exists independently of HαT or not. These investigations aim to enhance our understanding of these conditions and improve diagnostic and treatment approaches.

Article information and declarations

Author contributions

The authors confirm their contribution to the paper as follows: study conception and design: AR, ML; data collection: AR, ML; analysis and interpretation of results: AR, ML; draft manuscript preparation: AR, ML. All authors approved the final version of the manuscript.

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Conflict of interest

The authors of this publication declare no conflicts of interest.

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There is no supplementary material.

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The potential role of *Helicobacter pylori* and other gut dysbiosis factors in the development of rosacea

Zuzanna Luiza Frydrych, Natalia Chwarścianek, Karolina Błaszak, Rafał Czajkowski

Department of Dermatology and Venerology, Faculty of Medicine, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, Poland

ABSTRACT

Rosacea is a chronic inflammatory disease that presents with erythema, telangiectasia, papules, or pustules. Its mechanism of onset still needs to be fully understood. There has been an increasing number of studies and reports confirming the beneficial influence of eradication of *Helicobacter pylori* on the course of the disease. It has been recognized that the bacterium leads to the activation of the inflammatory immune response, resulting in the induction of symptoms similar to rosacea. Another thesis suggests a close connection between the gut–brain–skin axis, which relates to the influence of normal microbiota and gut health, and dermatological diseases. Correlations have been noted between the increased incidence of Crohn's disease, ulcerative colitis, and irritable bowel syndrome in patients with rosacea.

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Keywords: rosacea, *Helicobacter pylori*, eradication, microbiota

INTRODUCTION

Rosacea is a chronic skin disease characterized by papules and pustules on an erythematous base with the presence of telangiectasias and periodic paroxysmal erythema. Rosacea is divided into four subtypes: erythematotelangiectatic rosacea, papulopustular rosacea, phymatous rosacea and ocular rosacea [1]. Abnormal blood supply to the facial skin plays a major role in the development of rosacea. Enlarged sebaceous glands, dilated vessels, and features of sun damage to the skin are present in patients. Genetic predisposition, hormonal disorders and diseases of internal organs, including the gastrointestinal tract, also influence the course of the disease. Rosacea is not rare, as it affects 5% of the world's population [2]. Some authors in the literature indicate that the prevalence of the disease is similar in both sexes, while others indicate that the disease affects women more often [2]. Rosacea is usually diagnosed in adults between 30 and 50 years of age. It is most common in fair-skinned, northwestern residents with skin phototype I or II, or their relatives. However, it should be noted that in about 10% of cases, it affects dark-skinned individuals with IV, V or VI phototype (according to Fitzpatrick) [3]. In these cases, the clinical presentation is different, which can delay the diagnosis [2]. This is particularly true for erythematous lesions and telangiectasias. The pathogenesis of the disease is not yet sufficiently understood, or at least remains very unclear. There is an increasing number of studies suggesting an association of rosacea with various gastrointestinal diseases, including *Helicobacter pylori* infection [4], inflammatory bowel disease, celiac disease, irritable bowel syndrome, gastroesophageal reflux disease and small bowel bacterial overgrowth [5, 6].

A dysbiotic microbiome, dysregulation of the innate immune system and genetic factors, along with the aforementioned chronic diseases, contribute to the pathophysiology of rosacea [5]. To date, studies have reported an increased incidence of rosacea in individuals who are carriers of the gastric bacterium *Helicobacter pylori* (*H. pylori*) [5]. Based on this, a new concept of the pathogenesis of many inflammatory diseases — including rosacea — the gut–skin axis — has emerged [5].

As with many dermatological diseases, in addition to pharmacotherapy, proper skincare procedures and lifestyle changes should be followed. It is recommended to use gentle skincare cosmetics that will not further irritate the skin and cause erythema, and use high photoprotection [6, 7]. Triggers that aggravate skin symptoms such as alcohol, stress, use of saunas and pools with chlorinated water

Address for correspondence:

Zuzanna Luiza Frydrych, Department of Dermatology and Venerology Faculty of Medicine, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, Skłodowskiej-Curie 9, 85–094 Bydgoszcz, Poland; e-mail: frydrychzu@gmail.com

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should be avoided [8]. There are three types of therapeutic methods for rosacea: topical, general (oral) and selection of appropriate dermocosmetics. The choice of treatment depends on the subtype of the disease. In addition to curing skin symptoms, an additional therapeutic goal is to alleviate associated symptoms such as burning and burning sensation of the skin through excessive congestion and to reduce the visibility of erythema, which significantly affects the patient's self-esteem and comfort [9, 10].

HELICOBACTER PYLORI

H. pylori is a gram-negative bacterium found by Marshall and Warren in the early 1980^{s} [11]. The microbe may be identified in biological samples as old as several tens of thousands of years [12]. Medically, around 70% of patients diagnosed with gastric mucosa *H. pylori* colonisation are asymptomatic [13]. However, it is proven to cause various gastro and duodenal-related diseases, from which the most common ones remain peptic ulcers [14]. The bacterium is graded as a class 1 carcinogen by the World Health Organization (WHO) [15]; therefore, other reported cases of the pathogen in question infections include gastric adenocarcinoma, mucosa-associated lymphoid tissue lymphoma of the stomach (MALT lymphoma) [14].

Generally, any *H. pylori* infection is typically related to a significant number of medical conditions (Fig. 1), among which several dermatological ones may be observed. Although the direct link between *H. pylori* infection and rosacea remains the subject of controversy, many research papers suggest some influence of the microbe in triggering skin changes via two distinct mechanisms. Not only is the bacterium assumed to produce specific cytotoxins leading to the release of histamine, prostaglandins, leukotrienes and cytokines and to an inflammatory immunological reaction with the increase in nitrous oxide-related vasodilatation but it also plays a significant role in the expression of cytotoxin-associated gene A, TNF-α and IL-8. Subsequently, the entire chain of reactions is induced which may result in a symptom representation that is similar to rosacea [16]. Although antibodies against gene *CagA* (*H. pylori* virulent factor) are found in most patients with rosacea [17], as of this moment, the exact mechanism behind *H. pylori* infection and rosacea relationship remains unclear.

THE EFFECT OF *H. PYLORI* STANDARD ERADICATION PROTOCOL ON THE ROSACEA CLINICAL COURSE

While the conventional rosacea treatment protocols may be associated with frequent relapses and limited effectiveness, the use of *H. pylori* eradication may constitute an important approach. Various drug-combined therapies may be applied for *H. pylori* eradication; the latest recommended regimen, which is bismuth-based quadruple therapy, includes proton pump inhibitors (PPI), bismuth, metronidazole and tetracycline [18].

Significant research concerning the matter was conducted producing controversial and conflicting outcomes. The thesis suggesting the advantage of eradication methods in controlling symptoms of rosacea over conventional treatment, which once emerged in the 1900^{s} [19], has been widely tested in many clinical trials — both confirming its positive effect [4] on managing the course of the dermatosis and finding no relationship between the pathogen and rosacea [20]. Intriguingly, some research showed that the rosacea patients' improvement after the eradication protocol implementation was equally observed in the control group, which may suggest its placebo effect [21]. The study may be complicated by the similarity of the infection and the dermatosis antibiotic therapy; thus some cases of rosacea recoveries may only be associated with the alleviation of the inflammation process that is the key to the development of both conditions [18]. Accordingly, the link between the *H. pylori* eradication and rosacea still needs to be clarified. Indications for *H. pylori* eradication [25]:

- peptic ulcer disease,
- gastric MALT lymphoma,
- functional dyspepsia after esophagogastroduodenoscopy,
- idiopathic thrombocytopenic purpura (ITP),
- iron deficiency of unexplained cause (after adequate diagnostic investigation),
- in a patient with a history of peptic ulcer disease before the initiation of long-term treatment with acetylsalicylic acid (ASA) or a nonsteroidal anti-inflammatory drug (NSAID),
- upper gastrointestinal haemorrhage under treatment with ASA or NSAID,
- prophylaxis against gastric carcinoma in a patient at high-risk.

COMPOSITION OF GUT MICROBIOTA IN ROSACEA

Only two studies have been conducted regarding significant differences between the structure of the gut microbiota of healthy, in terms of dermatosis and rosacea patients. However, the presented data proved the limited compliance in terms of the results of both papers, in some cases making them even contradictory. Although both studies suggest some conflicting outcomes, they agree on several alterations being present in rosacea patients [26].

Nam et al. [27] found a decrease of *Methanobrevibacter*, *Slackia*, *Coprobacillus*, *Citrobacter*, *Desulfovibrio*, and *Peptococcaceae* family unknown genus and an increase of *Megasphaera, Acidaminococcus* and *Lactobacillales* order unknown family unknown genus in rosacea patients.

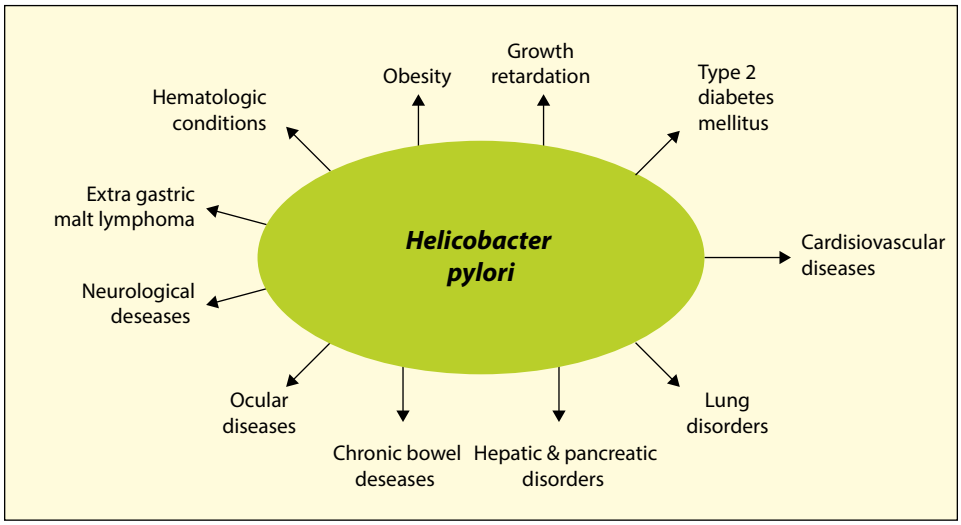

Figure 1. *Helicobacter pylori's* contribution to development of different diseases

Chen et al. found elevated presence of *Rhabdochlamydia, CF231, Bifidobacterium, Sarcina and Ruminococcus,* and reduced presence of *Lactobacillus, Megasphaera, Acidaminococcus, Hemophilus, Roseburi,* and *Clostridium* [28].

There is still a need for further research to be done on the composition of gut microbiota in Caucasian rosacea patients as these two papers cover mainly Asians as the research group and cannot pose as reliable sources of alterations that would be true for every rosacea patient [26].

GUT–BRAIN–SKIN AXIS

The GBS axis is represented by the relationship between the microbiota, neuroendocrine pathways, that the skin and gut both have, and the skin microbiome [23]. Thus several dermatological conditions may be associated with gastrointestinal health [24] and a higher risk of gastrointestinal (GI) disorders was observed in rosacea patients [25].

INFLAMMATORY BOWEL DISEASES

The term inflammatory bowel diseases (IBD) is mainly used to refer to Leśniowski–Crohn's disease (CD) and ulcerative colitis (UC). They are chronic inflammatory diseases of the GI tract which are characterized by periods of activity and remission [29]. IBD arises as a result of dysregulation of the balance between commensal microbiota and mucosal-associated immune system. The symptoms may be mild to severe, and they may appear suddenly or come on gradually. It is worth emphasizing that one in four patients with IBD has clinical manifestations of the disease which are not related to the GI system [30].

Taking into consideration that IBD and rosacea occur at the surface of skin or mucosa and involve abnormal innate immune response, it may be suggested that both of these diseases are pathogenetically similar [31]. Patients with rosacea are more likely to suffer from CD or UC than the general population [32]. That is why all patients with rosacea who suffer from GI symptoms should be investigated for IBD [33].

SMALL INTESTINAL BACTERIAL OVERGROWTH (SIBO)

The gut is inhabited by a huge number of microorganisms (bacteria, archaea, fungi, viruses) composing a vast and complex ecosystem with high intra- and inter-individual variability. In normal conditions, the cross-talk between the gut microbiota and the host is highly beneficial for both of them [34]. Gut dysbiosis is a condition caused by alterations of balance between the quantity and quality of microorganisms in the intestinal microbiota.

The small intestinal bacterial overgrowth (SIBO) is caused by excessive colonization of the small intestine by large intestine bacteria. There is no standard definition of SIBO. It is commonly used that bacterial count of at least 105 colony-forming units (CFU) per mL of small intestine fluid as the cut-off for diagnosis of this condition [35]. The altered microbiota produces a variety of inflammatory mediators and metabolites. This may lead to an immune response being triggered and may increase the risk of pathogenic invasion [36]. It is estimated that SIBO occurs 2–20 times more often in rosacea patients than in the healthy population [37]. In a randomized trial conducted by Parodi et al. [38], patients with rosacea and SIBO were randomized to receive rifaximin (1200 mg/day for 10 days) or placebo. In this study, successful treatment of SIBO resulted in almost complete regression of rosacea's cutaneous lesions [38].

According to the nationwide cohort study with 4 312 213 patients including 49 475 with rosacea, the

prevalence of SIBO was higher in patients with rosacea [32]. Some other studies point out the prevalence of SIBO in 51% of 63 patients with rosacea (based on a positive lactulose breath test) [32].

IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome (IBS) is a functional bowel disorder defined by recurrent abdominal pain for at least 1 day per week in the last 3 months that is associated either with a change in stool form or frequency [39]. Typically, symptoms occur at least 6 months prior to the diagnosis of IBS.

The pathogenesis of irritable bowel syndrome still remains uncertain [40]. The intestinal immune activation has been postulated to participate in brain-gut dysfunction which can lead to the development of IBS symptoms [41].

In 2017 new data showed a link IBS and rosacea. In a British nationwide cohort study, Egeberg et al. noticed an increased risk of new-onset IBS in subjects with rosacea. His findings may be a result of misdiagnosed IBS or they may reflect yet another comorbidity of rosacea [32].

CONCLUSIONS

Rosacea is a chronic, inflammatory, multifactorial condition whose pathogenesis still remains unknown. As the conventional rosacea treatment protocols are hardly effective, *H. pylori* eradication regimens may pose as a temporary solution producing moderately positive outcomes, until there is enough research to identify the relation between the pathogen and this dermatosis. This review found some strong associations between the course of the disease and the influence of the gut-skin axis, thus higher risk of GI diseases may be observed among rosacea patients. New influence factors that may concern the development of rosacea are found all the time, however, to be assured that they are indeed the key to inhibiting this dermatosis and not just a random correlation, we need more reliable research evidence.

Although all of the studies showed significant alterations in the composition of the skin, blood, or gut microbiome in rosacea, the results were highly inconsistent, or even, in some cases, contradictory. Major limitations included the low number of participants, and different study populations (mainly Asians). Further studies are needed in order to reliably analyse the composition of microbiota in rosacea, and the potential application of microbiome modifications for the treatment of this dermatosis.

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Conflict of interest

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Topical treatment of acne using a compounded medication based on clindamycin

Mikołaj Eryk Łanocha, Beata Bergler-Czop

Chair and Department of Dermatology, Medical University of Silesia, Katowice, Poland

ABSTRACT

Clindamycin, a lincosamide antibiotic, is widely used in the treatment of bacterial infections. It acts by inhibiting protein synthesis in bacteria, primarily targeting the peptidyl transferase centre in the bacterial ribosome. It exhibits bacteriostatic activity, inhibiting bacterial growth, and at higher doses, it can be bactericidal. In the treatment of acne vulgaris, clindamycin not only exerts direct antibacterial effects but also possesses anti-inflammatory and immunomodulatory properties. It reduces the growth of *Cutibacterium* acnes and inhibits the production of proteins and lipases, which contribute to skin inflammation. Clindamycin also enhances bacterial opsonization and phagocytosis and reduces neutrophil chemotaxis. Combination therapy with benzoyl peroxide can help minimize antibiotic resistance. Topical clindamycin, often in combination with benzoyl peroxide or retinoids, is recommended in treatment for mild to moderate papulopustular acne. In *hidradenitis suppurativa* clindamycin improves disease control and reduces cutaneous lesions, particularly superficial ones like papules and pustules. Various topical preparations containing clindamycin are available commercially, including gels, lotions, and combination products with tretinoin or benzoyl peroxide. Additionally, the registration of clindamycin as a pharmaceutical raw material allows for compounding personalized formulations, providing a cost-effective alternative. Compounded medications can be tailored to individual patient needs and increase treatment effectiveness.

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Keywords: clindamycin, acne vulgaris, acne inversa, *hidradenitis suppurativa*, treatment

INTRODUCTION

Clindamycin is an antibiotic that belongs to the lincosamide group. It is a semi-synthetic derivative of lincomycin, a natural antibiotic produced by the actinomycete Streptomyces lincolnensis. Lincomycin was discovered in 1952 and has been used in medicine to treat various bacterial infections [1].

Clindamycin was first synthesized and introduced for use in the 1960s. It was developed to enhance the effectiveness of lincomycin and improve its pharmacokinetic properties [1].

Clindamycin works on bacteria by blocking protein synthesis. The mechanism of action of clindamycin involves the inhibition of the peptidyl transferase centre within the 50S subunit of the bacterial ribosome. Peptidyl transferase is an enzyme involved in the elongation process of the polypeptide chain during protein synthesis in bacterial cells. By blocking this activity, clindamycin inhibits the further growth of bacteria and prevents their multiplication [1].

At typical doses, clindamycin primarily exhibits bacteriostatic activity, which means it inhibits the growth and multiplication of bacteria but does not cause their immediate death. However, at higher doses, clindamycin may also demonstrate bactericidal activity, meaning it directly kills bacteria [1].

The spectrum of activity of clindamycin mainly includes gram-positive cocci, such as *Staphylococcus aureus* and *Streptococcus pyogenes*, as well as anaerobic bacteria, including *Cutibacterium* acnes and *Actinomyces israelii*, while most gram-negative bacteria are resistant to lincosamide antibiotics, including clindamycin [2].

In Poland, topical preparations containing clindamycin are registered for the treatment of common acne, but its positive effects are also well-documented in the therapy of acne inversa.

ACNE VULGARIS

Clindamycin, used in the treatment of common acne, exhibits a multifaceted action. In addition to its direct antibacterial effect on *C. acnes*, it also demonstrates

Address for correspondence:

Mikołaj Eryk Łanocha, MD, Chair and Department of Dermatology, Medical University of Silesia, Francuska 20/24, 40–027 Katowice, Poland; e-mail: lanocha.mikolaj@gmail.com

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anti-inflammatory and immunomodulatory properties, contributing to the reduction of skin inflammation. Clindamycin acts directly on *C. acnes*, reducing their growth, as well as the production of proteins and lipases. Lipases as hydrolytic enzymes, break down triglycerides present in sebum into free fatty acids (FFAs). FFAs on the skin surface can have irritant and pro-inflammatory effects, as well as increase perifollicular keratinization. By reducing the number of *C. acnes*, the concentration of FFAs is decreased, favouring esters, which in turn reduces inflammation and the risk of developing comedones [3]. Clindamycin also exhibits immunomodulatory effects by inducing bacterial opsonization, increasing their susceptibility to phagocytosis, and reducing neutrophil chemotaxis [4]. Its anti-inflammatory action is manifested by reducing the release of free radicals and the production of inflammatory cytokines such as IL-1β, IL-6, INF-γ, TNF-α, and GM-CSF [5].

The treatment of acne is a complex and multifaceted process, and the choice of appropriate treatment depends on various factors such as the type of acne, its severity, the patient's skin condition, and overall health. In the management of acne lesions, multiple methods are employed, but one of the main approaches is topical treatment, which is usually sufficient for approximately 60% of patients [6].

Topical antibiotics are commonly used in acne treatment due to their good patient tolerance and rare, mild side effects. They demonstrate a rapid onset of action, particularly in papulopustular acne, but their impact on non-inflammatory lesions and comedones is less pronounced.

Two antibiotics, clindamycin and erythromycin, are registered for the treatment of acne. However, reports of increasing antibiotic resistance and declining efficacy of antibiotics raise concerns about the continued use of these preparations. The prevalence of strains resistant to at least one antibiotic in the European population ranged from 51% in Hungary to 94% in Spain, reflecting local trends in antibiotic prescribing [7]. It is important to note that due to the shared target site of action among macrolides, lincosamides, and streptogramins, cross-resistance often occurs between these drugs (MLSB resistance). In a study by Simonart et al. [8], an analysis of 75 studies conducted between 1974 and 2003 regarding the efficacy of 1–2% clindamycin and 1.5–4% erythromycin in acne treatment was performed. The analysis showed that in treatments lasting more than 12 weeks, the efficacy of erythromycin in reducing inflammatory and non-inflammatory lesions decreased by 2.1% and 2% per year, respectively. In contrast, the efficacy of clindamycin remained unchanged during the studied period. This means that over time, erythromycin became less effective in treating skin lesions, while clindamycin maintained its efficacy at a constant level [8]. These findings reflect changing trends in the prescription of topical antibiotics, with a significant decrease in the prescription of erythromycin and an increase in the prescription of clindamycin in the United States [9].

One way to reduce antibiotic resistance is by combining antibiotics with benzoyl peroxide, which exhibits synergistic bactericidal effects and has not shown any resistance to it [10]. The use of benzoyl peroxide in combination with erythromycin [11], clindamycin [12], or adapalene [13] has led to a decrease in the number of antibiotic-resistant strains of *C. acnes*. A similar effect was achieved by once-daily facial washing with a cleanser containing 6% benzoyl peroxide [14].

To limit the development of bacterial antibiotic resistance during treatment, the following principles should be followed [6]:

— Use antibiotics according to indications, for the necessary period to resolve inflammatory lesions, but not longer than 12 weeks.
— Avoid using antibiotics as monotherapy and instead prefer combination therapy with benzoyl peroxide or a retinoid (in a fixed combination or at different times of the day), which further enhances treatment efficacy, shortens its duration, and limits adverse effects.
— Do not combine topical antibiotics with systemic antibiotics, as it does not improve treatment effectiveness and increases the risk of developing antibiotic resistance.

According to the guidelines of the Polish Dermatological Society, topical antibiotics are used in the treatment of mild to moderate papulopustular acne in combination with benzoyl peroxide (preferred treatment) or topical retinoid (alternative treatment) [6]. Similar recommendations are presented in European guidelines, which recommend the use of topical antibiotics in the treatment of mild to moderate papulopustular acne in combination with benzoyl peroxide (strong recommendation) or tretinoin (moderate recommendation). However, the use of antibiotics in the treatment of comedonal acne and as monotherapy is not recommended [15].

HIDRADENITIS SUPPURATIVA

The effectiveness of clindamycin has also been demonstrated in the treatment of hidradenitis suppurativa. In a double-blind study involving 27 patients with hidradenitis suppurativa, 1% clindamycin or placebo was applied for 3 months. The clindamycin group showed improvement in disease control according to the participants' assessment and a reduction in cutaneous lesions, particularly superficial ones such as papules, pustules, and folliculitis. The effect was less pronounced for deeper lesions such as nodules and abscesses [16]. In another study, the efficacy of topical 1% clindamycin was compared to oral tetracycline (500 mg twice daily) in a group of 34 patients with *hidradenitis suppurativa*. During the first 3 months of treatment, improvement

Figure 1. Celugel® hydrogel base (**A**); Clindamycin powder (**B**); Clindamycin hydrogel (**C**)

Table 1. Examples of formulations in the form of solutions

Rp.	Rp.	Rp.
Clindamycini hydrochloridi 1.0	Clindamycini hydrochloridi 1.0	Clindamycini hydrochloridi 1.0
Glyceroli 10.0	Glyceroli 10.0	Glyceroli 5.0
Ethanoli 60% 25.0	Acidi citrici 0.07	Celugeli* 60.0
Aquae purificatae ad 100.0	Aquae purificatae ad 100.0	Acidi citric 0.07
M.f. solutio	M.f. solutio	Aquae purificatae ad 100.0
Use: two times a day	Use: two times a day	M.f. solutio
		Use: two times a day

*Ready-made hydrogel compounding base based on hydroxyethyl cellulose; M.f. — mix and make; Rp. — presciption

in overall disease assessment by both the patients and the investigator, as well as a reduction in the number of abscesses, were noted. After 3 months of therapy, a decrease in the number of nodules was also observed [17]. In a study involving 60 patients with mild to moderate *hidradenitis suppurativa*, the efficacy of topical clindamycin was compared to systemic antibiotic therapy using clindamycin and rifampicin. Although both treatment methods provided similar improvements in the IHS4 (International Hidradenitis Suppurativa Severity Score System) score and a reduction in the number of nodules and abscesses, the group using topical clindamycin showed greater improvement in the DLQI (Dermatology Life Quality Index) score, VAS (Visual Analogue Scale) score, and number of fistulas [18].

European guidelines for the treatment of *hidradenitis suppurativa* recommend the use of clindamycin in Hurley stage 1 or mild forms of Hurley stage 2 [19].

PREPARATIONS

In Poland, there are various commercially available topical preparations containing clindamycin, such as 1% gel (Clindacne®, Dalacin T®, Klindacin T®, Normaclin®), 1% lotion (Dalacin T®), as well as combination products in the form of a gel containing 1% clindamycin with 0.25% tretinoin (Acnetac®) and with 3% or 5% benzoyl peroxide (Duac®).

Thanks to the registration of the hydrogel base Celugel® as a pharmaceutical raw material in 2019, it became possible to formulate gel preparations. In March 2023, clindamycin was also registered as a pharmaceutical raw material, enabling prescriptions for compounding preparations containing clindamycin with a refund, providing a cheaper alternative to fully-paid finished medicines (Fig. 1). In addition to ready-made gel and lotion preparations, compounding formulations also allow for the creation of creams and solutions that are not available in Poland. The use of compounded medications can bring many benefits to patients. Preparing a formulation involves not only using the appropriate dosage of the active substance but also selecting other ingredients that affect the effectiveness of the medication and its tolerability by the body. Patients can receive a medication tailored to their individual needs, which increases treatment effectiveness. This way, it is possible to avoid situations where commercially available preparations are not suitable for a particular patient, for example, due to allergens they may contain. Below are several examples of compounding formulations using clindamycin in the form of gel, cream, lotion, and solutions (Tab. 1, 2) [20].

CONCLUSIONS

Topical antibiotic therapy can be an attractive treatment option for patients with common acne and acne inversa due to its quick and effective action and good tolerability. It is important to adhere to principles of antibiotic use, such as dosing frequency, duration of therapy, and combination therapy, in order to minimize the risk of bacterial resistance to the medications.

Table 2. Examples of formulations in the form of gel, cream, and lotion

Rp.	Rp.	Rp.
Clindamycini hydrochloridi 1.0	Clindamycini hydrochloridi 1.0	Clindamycini hydrochloridi 1.0
Aquae purificatae 10.0	Aquae purificatae 10.0	Lekobazae 20.0
Celugeli ad 100.0	Lekobazae ad 100.0	Aquae purificatae ad 100.0
M.f. gelatum	M.f. cremor	M.f. lotion
Use: two times a day	Use: two times a day	Use: two times a day

M.f. — mix and make; Rp. — presciption

Article information and declarations

Author contributions

Mikołaj Łanocha — wrote the paper; Beata Bergler-Czop — editorial supervision over the work

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Conflict of interest

The authors cooperate with the company Actifarm.

Supplementary material

None.

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Measuring the quality of life and itch intensity in patients with chronic venous disease using CIVIQ-20 and Pruritus Numerical Rating Scale among individuals in Poland

Justyna Putek, Aleksander Truszyński, Edwin Kuźnik

Department of Angiology, Hypertension and Diabetology, Wroclaw Medical University, Wrocław, Poland

ABSTRACT

Introduction: Chronic venous disease (CVD) is a condition affecting many people worldwide. This study aimed to measure the quality of life and itch intensity in patients with CVD using the Chronic Venous Disease Quality of Life Questionnaire (CIVIQ-20) and Pruritus Numerical Rating Scale (NRS) among individuals in Poland.

Material and methods: The study was based on an internet questionnaire fulfilled by 160 respondents. 57 (35.6%) represented grade 1 according to Clinical–Aetiology–Anatomy–Pathophysiology (CEAP) Classification, 57 (35.6%) grade 2, 26 (16.2%) grade 3, 12 (7.5%) grade 4, 5 (3.1%) grade 6 and 3 (2%) grade 5.

Results: The mean CIVIQ-20 global score for all CEAP classes was 50.1 ± 17.7. 67 (41.9%) respondents reported the presence of itch. The mean intensity of itch for individual groups was: 1.6 for C1, 1.9 for C2, 1.0 for C3, 2.3 for C4, 7.0 for C5 and 3.6 for C6. A fair positive correlation was found between the level of advancement of CVD and a global score of CIVIQ-20 ($r = 0.332$, $p < 0.001$), level of advancement of CVD and body mass index (BMI) ($r = 0.345$, $p < 0.001$), and the number of symptoms and the global score of CIVIQ-20 ($r = 0.370$, $p < 0.001$).

Conclusions: To assess the quality of life of patients with CVD, CIVIQ-20 can be used in clinical practice regarding its fair correlation with the intensity and advancement of CVD.

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Keywords: chronic venous disease (CVD), varicose veins, itch, pruritus

INTRODUCTION

Chronic venous disease (CVD) is a condition affecting many people worldwide. CVD is diagnosed more commonly in women and its prevalence increases with age. The most common symptoms are leg pain, leg heaviness, leg tingling, leg cramps or itch. Itch is an unpleasant sensation that induces a desire to scratch and occurs in many dermatological conditions e.g. atopic dermatitis, psoriasis, or urticaria. Itch is not often associated with CVD and that is why it is often neglected. However, due to skin changes which occur with CVD, pruritus can cause further skin damage and thus worsen the overall condition of a patient [1]. In the study, the authors wanted to especially focus on this symptom and measure the intensity of it in the Polish population.

The clinical spectrum of CVD ranges from asymptomatic to hard-healing ulcers and thereby impacts the physical and psychological health of individuals as well as the global economy [2]. Current papers show that higher stages of CVD are associated with lower quality of life and that the appropriate treatment greatly improves the comfort of life [3, 4]. The most common questionnaire specific to CVD regarding the quality of life is the Chronic Venous Disease Quality of Life Questionnaire (CIVIQ-20) which consists of 20 items. Pruritus often results in sleep deprivation or emotional lability, leading to a significant deterioration in the quality of life [5]. Due to a lack of research regarding the correlation between the quality of life and pruritus in CVD in the Polish population, this research was conducted. This study aimed to measure the quality of life and itch intensity in patients with CVD using CIVIQ-20 and Pruritus Numerical Rating Scale (NRS) among individuals in Poland.

MATERIAL AND METHODS

This paper was based on an internet questionnaire which was posted on Facebook's groups gathering people suffering from CVD. The data were collected between the 2nd of March 2023 to 9th of March 2023. Firstly, respondents answered general questions concerning their age, level of education, body mass index (BMI) and type of work. Then, individuals were requested to describe their stage of CVD

Address for correspondence:
Justyna Putek, Klodzka 7/10, 50–536 Wroclaw, phone: +48 603092912; e-mail: putek.justyna@gmail.com

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using pictures presenting stages of this disease according to the Clinical–Aetiology–Anatomy–Pathophysiology (CEAP) Classification [6]:

- C1: telangiectases or reticular veins,
- C2: varicose veins,
- C3: oedema,
- C4: skin changes: hyperpigmentation, eczema, atrophie blanche,
- C5: healed venous ulcer,
- C6: active venous ulcer.

The pictures represented the successive stages of chronic venous insufficiency and were accompanied by descriptions so that patients could choose the answer more reliably.

Respondents chose the photo which best reflected their skin changes. On this basis, the medical doctor classified the patient into a particular group according to the CEAP classification.

Subsequently, volunteers were asked to describe what kind of symptoms of CVD was present, and if itch was the answer, individuals assessed the intensity of it using Pruritus NRS [7]. Further, respondents were asked to say if CVD was diagnosed by a medical doctor, and what treatment was applied. Lastly, volunteers were requested to fulfil the CIVIQ-20 [8] which is a 20-item questionnaire composed of 4 quality-of-life dimensions regarding pain, physical, psychological and social life. The respondents assess how much the given statements correlate with their situation using a five-point Likert scale, which provides a global index. A low score corresponds to greater patient comfort in life.

Statistical analysis

Statistical analysis was performed using the software Microsoft Excel and XLMiner Analysis ToolPak. The mean and SD were calculated. Pearson's correlation coefficient was used to name the strength of the relationship between variables and statistical significance was set at $p < 0.05$. The data were collected and analysed anonymously.

RESULTS

The survey was completed by 160 respondents. 147 (91.9%) participants were females and 13 (8.1%) were males, aged from 20 to 83 years [mean age ± standard deviation (SD) = 42.4 ± 12.2 years]. 77 (48.1%) individuals graduated from university, 71 (45.6%) reported secondary education, 6 (3.8%) were students, and 4 (2.5%) had primary education.

61 (38.1%) respondents had normal weight, 57 (35.6%) were overweight, 32 (20%) had obesity class I, 6 (3.7%) had obesity class II, 3 (1.9%) had obesity class III and one person (0.7%) was underweight. The mean BMI for the whole group was 26.5 ± 5.3. 69 (43.1%) volunteers described that in their work they mostly sit, 38 (23.7%) that they are mostly active, 30 (18.8%) that they mostly stand and 23 (14.4%) individuals are retired.

57 (35.6%) respondents stated that they have varicose veins (CEAP class 2), and 57 (35.6%) individuals that some thread and spider veins are noticeable (CEAP class 1). 26 (16.2%) volunteers suffered from oedema on lower legs due to varicose veins (CEAP class 3), 12 (7.5%) noticed some skin damage and hyperpigmentation due to varicose veins (CEAP class 4), 5 (3.1%) had venous leg ulcer (CEAP class 6) and 3 (2%) admitted having venous leg ulcer which is now healed (CEAP class 5) (Fig. 1).

Further, respondents were requested to describe their symptoms of CVD. It was possible to give more than one answer to this question. 118 (24%) respondents admitted leg pain, 109 (22.2%) leg heaviness, 67 (13.6%) itch, 60 (12.2%) leg tingling, 50 (10.2%) "tight feeling" of legs, 46 (9.4%) leg cramps, 35 (7.1%) leg tenderness and 6 (1.2%) individuals

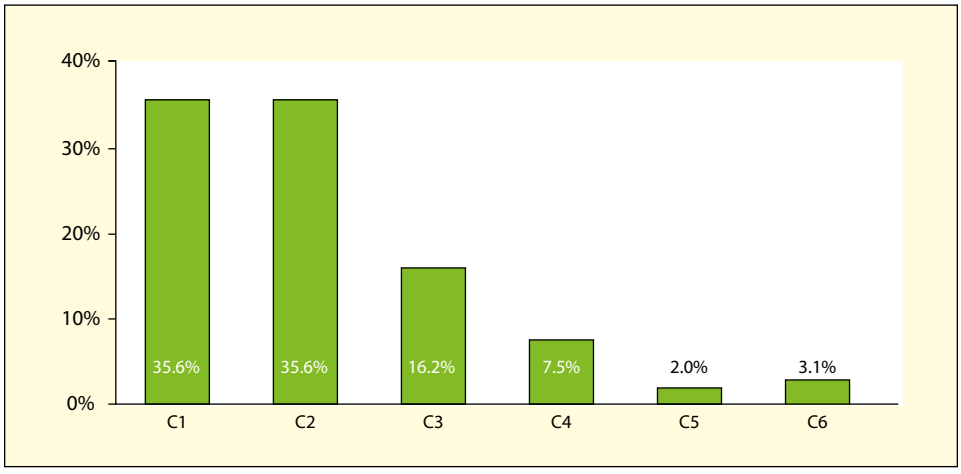

Figure 1. Advancement of chronic venous disease due to Clinical–Aetiology–Anatomy–Pathophysiology (CEAP) Classification among respondents

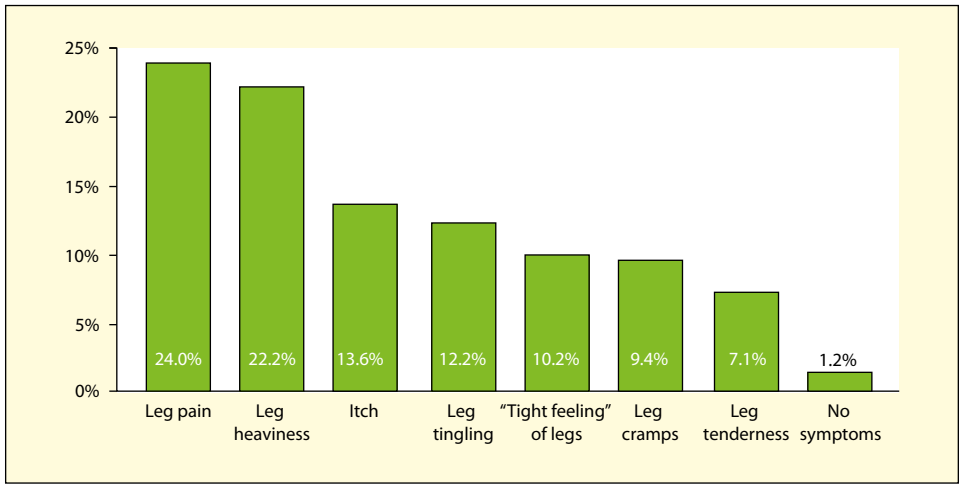

Figure 2. Symptoms of chronic venous disease among respondents

reported no symptoms (Fig. 2). The mean number of symptoms for the whole group was 3.6 ± 1.7.

This group of respondents who reported itch was asked to describe the intensity of it in the past 24 h using Pruritus NRS. Cut-off values proposed by Reich et al. [9] were used. 16 (10%) respondents reported mild pruritus (> 0–< 3 points in NRS), 38 (23.8%) moderate pruritus (≥ 3–7 points in NRS), 9 (5.6%) severe pruritus (≥ 7–9 points in NRS) and 4 (2.5%) very severe pruritus (≥ 9 points in NRS) (Fig. 3). Pruritus was reported by 19 (33.3%, n = 57) respondents with grade 1 of CVD according to CEAP classification, 26 (45.6%, n = 57) individuals with grade 2, 7 (26.9%, n = 26) volunteers with grade 3, 8 (66.6%, n = 12) individuals with grade 4, 3 (100%, n = 3) respondents with grade 5, and 4 (80%, n = 5) patients with grade 6. The mean intensity of itch was 4.4 ± 2.4.

The CVD was diagnosed by a medical doctor among 147 (91.9%) respondents. Subsequently, volunteers were asked to describe what kind of treatment was administered. It was possible to give more than one answer to this question. Among 107 (49.3%) respondents compression treatment was used, by 73 (33.6%) volunteers pharmacological treatment was applied using preparations with diosmin, hesperidin and vitamin C, 16 (7.4%) individuals had laser therapy, 5 (1.4%) sclerotherapy and 3 (1.4%) vein stripping procedure. 13 (6%) respondents remained without treatment.

The mean CIVIQ-20 global score for all CEAP classes was 50.1 ± 17.7. Global scores for individual groups were: 46.1 for C1, 47.4 for C2, 54 for C3, 59.7 for C4, 76 for C5 and 67.2 for C6. For each class the mean number of symptoms, mean intensity of itch, and mean BMI were calculated (Tab. 1). BMI and global mean score of CIVIQ-20 almost gradually increased with increasing CEAP class. Such correlations between the advancement of CVD and increasing intensity of itch and the number of symptoms were not observed.

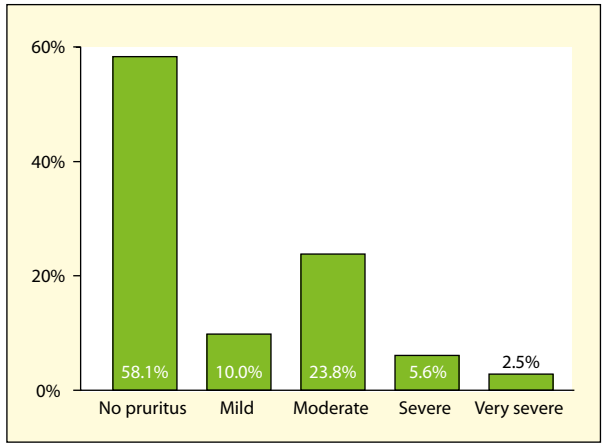

Figure 3. Self-assessment of pruritus according to the Pruritus Numerical Rating Scale (NRS) among respondents

To name the strength of the relationship between variables Pearson's correlation coefficient (r) and cut-off values proposed by Chan [10] were used. A fair positive correlation ($r > 0.3$) was found between:

— level of advancement of CVD and a global score of CIVIQ-20 ($r = 0.332$, $p < 0.001$),
— level of advancement of CVD and BMI ($r = 0.345$, $p < 0.001$), and
— number of symptoms and global score of CIVIQ-20 ($r = 0.370$, $p < 0.001$).

For all this data p-values were lower than 0.001 which means that they are strongly statistically significant (Tab. 2).

DISCUSSION

CVD is a medical condition which is caused by venous valve malfunction. The prevalence of CVD is highest in Western countries and affects about 25% of the general population [11] consuming up to 2% of healthcare bud-

Table 1. Mean values of global CIVIQ-20 score, number of symptoms, pruritus intensity and BMI for each CEAP class among respondents

Class of CVD according to CEAP	C1	C2	C3	C4	C5	C6
Global mean score CIVIQ-20 ± SD	46.1 ± 17.2	47.4 ± 15.4	54.0 ± 19.4	59.7 ± 17.3	76.0 ± 7.9	67.2 ± 13.7
Mean number of symptoms ± SD	3.4 ± 1.8	3.5 ± 1.6	3.8 ± 1.6	3.6 ± 1.7	7 ± 0	3.8 ± 1.5
Mean pruritus intensity ± SD	4.8 ± 2.1	4.2 ± 2.4	3.6 ± 1.8	3.5 ± 2.8	7.0 ± 1.0	4.5 ± 3.0
Mean BMI ± SD	26.4 ± 4.7	26.4 ± 4.7	27.1 ± 5.0	26.5 ± 5.3	33.5 ± 3.9	34.7 ± 4.9

BMI — body mass index; CEAP — Clinical–Aetiology–Anatomy–Pathophysiology Classification; CIVIQ-20 — Chronic Venous Disease Quality of Life Questionnaire; CVD — chronic venous disease; SD — standard deviation

Table 2. Pearson's correlation coefficient (r) between particular variables and their p-values

Variable	Class of CVD according to CEAP	Global mean score CIVIQ-20	Mean number of symptoms	Mean pruritus intensity	Mean BMI
Class of CVD according to CEAP	–				
Global mean score CIVIQ-20	0.332 ($p < 0.001$)	–			
Mean number of symptoms	0.153 ($p > 0.05$)	0.370 ($p < 0.001$)	–		
Mean pruritus intensity	–0.013 ($p > 0.05$)	0.280 ($p < 0.001$)	0.160 ($p < 0.001$)	–	
Mean BMI	0.345 ($p < 0.001$)	0.117 ($p > 0.05$)	0.078 ($p > 0.05$)	0.049 ($p > 0.05$)	–

BMI — body mass index; CEAP — Clinical–Aetiology–Anatomy–Pathophysiology Classification; CIVIQ-20 — Chronic Venous Disease Quality of Life Questionnaire; CVD — chronic venous disease

gets [12]. CVD presents a wide spectrum of symptoms and the severity of it can be assessed with CEAP classification. Most of the respondents in the present study represented grades 1 and 2 according to the CEAP classification.

The pathophysiology of pruritus in CVD is complex. It is presumed that macromolecules leak into the tissues causing an inflammatory response, then it comes to fibrosis and skin damage which results in incessantly dry and flaky skin which in the end leads to pruritus [1, 13]. According to the current paper, 67 (41.9%) respondents reported the presence of itch, however, treatment of CVD was more focused on the pathophysiology of CVD and not particularly focused on this symptom. The intensity of pruritus ranged from 1.0 in CEAP class 3 to 3.6 in CEAP class 6, with the highest values in CEAP class 5 (7 in NRS). Further, no strong correlation between mean pruritus intensity and mean BMI values or the mean number of symptoms was found which can supposedly mean that the advancement of pruritus is independent of weight and severity of CVD. This seems to be confirmed in the literature. In the research of Duque et al. [14] 66% of patients with CVD had itch, but no correlation with the advancement of CVD according to CEAP classification was found. According to the present results intensity of the itch weak corresponds with the worsening quality of life ($r = 0.280$, $p < 0.001$). However, research by Duque et al. [14] denies it and reports a statistically significant negative relationship between itch intensity and health-related quality of life which was measured with the Skindex-16 questionnaire ($r = 0.50$, $p < 0.001$). This difference could supposedly come from the small sample size of individuals with pruritus in particular CEAP classes.

CIVIQ-20 was developed in France by Launois et al. [8] in France, and by then many articles were published proving their good relevance, acceptability, reliability, construct validity, and sensibility [15–17]. In the current study, the global scores of CIVIQ-20 well corresponded with higher CEAP classes and the mean number of symptoms. This means that CIVIQ-20 is a good tool to screen patients with CVD in terms of quality of life. In the paper of Sinožić et al. [18] the CVDs stages significantly correlated with BMI ($r = 0.54$, $p < 0.001$). In the present research poor correlation between the global score of CIVIQ-20 and BMI was found ($r = 0.117$), however, this value was not statistically significant ($p > 0.05$). In the literature, quality of life in patients with the CVD was also measured using, for example, classification and Venous Clinical Severity Score (VCSS) [19], Dermatology Life Quality Index (DLQI) [19], Skindex-16 questionnaire [14], Chronic Venous Disease Quality of Life Questionnaire (CIVIQ-14) [15], Venous Insufficiency Epidemiological and Economic Study — Quality of life/Symptom (VEINES-QoL/Sym) instrument [20, 21] or the Aberdeen Varicose Vein Questionnaire (AVVQ) [22]. This shows that there is a huge diversity of screening tools concerning quality of life among CVD patients which are available for daily practice. A great review paper by de Almeida et al. [23] was published which sums up the best instruments. According to them the CIVIQ-14, which is a shortened version of CIVIQ-20, and CIVIQ-20 have a good potential value for assessing quality of life in patients with CVD, and emerge as reliable and valid tools which could be used by clinicians.

The authors are aware of the obvious limitations of this study: overrepresentation of women, a small sample size

of patients with CEAP class 5 and 6 or possible misinterpretations of questions. The authors admit that patients could incorrectly describe their skin lesions and thus be classified in the wrong group according to the CEAP classification, however, every effort was made to provide reliable photos of skin lesions and add descriptions to them so that the results of this study are as credible as possible. Nevertheless, the current research was conducted on a relatively big research group (n = 160), which enables us to bring forward reliable conclusions.

CONCLUSIONS

Clinicians should be aware that more than half of patients with CVD can suffer from itch, and that fact should be taken into consideration while applying treatment. To assess the quality of life of patients with CVD, CIVIQ-20 can be used in clinical practice regarding its fair correlation with the intensity and advancement of CVD.

Article information and declarations

Conflict of interests

The authors have no conflicts of interest to declare.

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VIA MEDICA

CASE REPORT

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Double trouble combat grenade allergic contact dermatitis

Agata Karny, Julia Nowowiejska, Julia Kobylińska, Zuzanna Panas, Anna Baran, Iwona Flisiak

Department of Dermatology and Venereology, Medical University of Bialystok, Poland

ABSTRACT

Allergic contact dermatitis (ACD) is a frequent inflammatory and the most common type of occupational skin disease. Chloroacetophenone (CN) has been one of the most typical riot control agents known since the end of the First World War. It is used by the armed and police forces and as pocket tear gas for personal protection. However, it is considered to be safe and, therefore, should not cause fatal health effects. Although CN is stated to provoke ACD, there are only a few cases found in the literature similar to the one shown below.

Forum Derm. 2023; 9, 4: 152–153

Keywords: dermatitis, allergic contact, tear gases, chloroacetophenone

CASE DESCRIPTION

A 21-year-old male soldier, without a personal or family history of skin diseases or allergies, was presented to the Department of Dermatology with maculopapular rash soon after exposure to tear gas — chloroacetophenone (CN) — while throwing a practice gas grenade at a military exercise. The patient had had contact with the described substance before, but this was the first time such symptoms appeared. On physical examination, skin lesions were observed mostly on the forearms, lateral surfaces of the trunk and whole neck, with no rash on the face which was covered by a face mask (Fig. 1). The skin lesions were accompanied by pruritus. The patient reported no general symptoms. The treatment with intravenous 100 mg hydrocortisone, intramuscular 100 mg phenazoline, followed by oral antihistamines and topical steroids, resulted in significant clinical improvement. The patient was referred for a follow-up at the dermatology outpatient clinic.

DISCUSSION

Chloroacetophenone probably reacts with transient receptor potential (TRP) channels, especially TRPA1, localized on the skin and mucous membranes. As a result, the gas provokes such symptoms as pain, itching, inflammation and cold [1]. Its toxicity is possibly associated with SN2 alkylation having negative effects on cellular functions [1]. The eyes and airways are irritated most frequently [2, 3]. Conjunctivitis, ophthalmalgia, intolerance to light, lacrimation and eyelid erythema, as well as cough, rhinitis, chest discomfort, pharyngitis, dyspnoea and sternutation may appear [2]. After tear gas inhalation, saliva with molecules of the toxic substance could be absorbed and cause gastrointestinal issues — sickness, emesis or diarrhoea [2]. However, the effects of CN on human health depend on the concentration of the substance and length of exposure [2]. The above symptoms did not appear in the present patient wearing a mask.

Chloroacetophenone may provoke ACD but there are only a few cases found in the literature [4–7]. Skin symptoms appear as disseminated erythematous papulovesicular lesions, pruritus, burning sensation, itchy blistering eruptions, erythema and swelling, even as a second-degree chemical burn in one case [5–8].

The dermatitis emerges first at the site of CN contact, but after a few days, the lesions may disseminate [8]. A single contact with this substance can cause primary sensitization and provoke allergic skin reactions [6]. Patch tests with CN in ACD diagnosis should be applied and they usually result in an intense eczematous reaction [7]. Furthermore, this reaction could be associated with the irritative potential of CN [4]. In the cases described canisters of tear gas and police officers' occupational exposure were the sources of CN [5, 9].

Different tear gases apart from CN, such as o-chlorobenzylidene malononitrile (CS), were proven to initiate ACD in

Address for correspondence:

Agata Karny, Department of Dermatology and Venereology, Medical University of Białystok, Żurawia 14, 15–540 Białystok, Poland, phone: +85 831 65 70; e-mail: agatakarny@gmail.com

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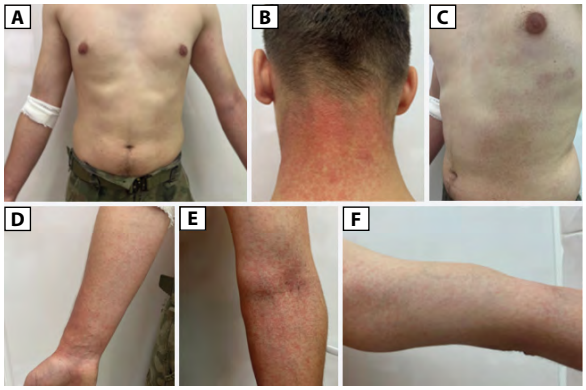

Figure 1. Maculopapular rash on the lateral surfaces of the trunk and whole neck (**A–C**); maculopapular rash on the upper limbs (**D–F**)

patients. CS action and results are similar to CN although its toxicity is lower [10].

Although the patient had had contact with CN before, that was the first time of the appearance of such symptoms. It should be emphasized that face masks can definitely reduce the risk of skin symptoms in this sensitive area. Proper diagnosis and treatment are important in the case of the exposed individuals, who may experience significant skin or systemic reactions in contact with such substances. Despite the fact that CN is used by military forces all around the world, there have been only a few similar ACD cases described in the literature so far. Therefore, research on CN's potential side effects is desired.

Article information and declarations

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Author contributions

AK — writing original draft, review & editing, conceptualization; JN — review & editing, conceptualization, visualization, patient's attending physician; JK — writing original draft, ZP — writing original draft, AB — supervision, review & editing, IF — supervision.

Conflict of interest

No conflict of interest.

Ethics statement

No ethical issues.

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Supplementary material

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CASE REPORT

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Toxic epidermal necrolysis: a study of 3 cases and review

Adam Wełniak[1], Patrycja Lipska[1], Wiktoria Watoła[1], Nicole Grabowska[1], Luiza Marek-Józefowicz[2], Rafał Czajkowski[2]

[1]*Students' Scientific Club of Dermatology, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, Poland*

[2]*Department of Dermatology and Venerology, Faculty of Medicine, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, Poland*

ABSTRACT

Toxic epidermal necrolysis syndrome is a life-threatening adverse skin reaction requiring admission to dermatology wards or intensive care units. Preceded by fever and general malaise, the condition leads to the separation of the epidermis from the dermis resulting in large erosions. Epidermal loss results in loss of fluid and electrolytes as well as an increased risk of infections. The above paper presents a description of 3 patients treated for toxic epidermal necrolysis. The first patient, in addition to typical skin involvement, had lesions on the eyes and in the throat, thus the treatments required cooperation with a laryngologist and ophthalmologist. The second patient, due to his mental disorder, caused numerous difficulties in the ward, which disrupted its work, as the ward does not have doctors on duty 24 hours a day. A third patient with cirrhosis had a rapidly progressing disease that did not respond to any form of treatment. For the first two patients, intravenous immunoglobulin therapy proved crucial for recovery, while the third patient died due to a lack of underlying disease treatment options. The most common cause of Lyell's syndrome is medications, mainly antiepileptics, and antibiotics, although the list of substances that can cause the syndrome has been growing in recent years. There are no new global guidelines and current ones emphasize drug withdrawal, topical treatment and early assessment via the SCORTEN scale. The role of systemic steroid therapy, remains unclear, although recent evidence suggests that it could potentially reduce mortality. Cyclosporine and intravenous immunoglobulins have been gaining prominence in recent years for the treatment of this condition.

Forum Derm. 2023; 9, 4: 154–161

Keywords: toxic epidermal necrolysis, drug-induced reaction, intravenous immunoglobulins

INTRODUCTION

Toxic Epidermal Necrolysis (TEN) is a rare life-threatening drug reaction characterized by the extensive destruction of keratinocytes, leading to desquamation of the epidermis and mucosal epithelium with the formation of blisters and extensive erosions [1]. Skin symptoms are preceded by fever and signs of malaise. The disease is rare, with reports ranging from 2 to 7 cases per million people yearly [2]. Medications are the most common trigger for this condition and usually cause the illness within 8 weeks of admission, in both adults and children [3]. The diagnosis is made based on the clinical presentation and the level of skin involved. If affected, is less than 10% of the skin of the whole body the authors refer to the condition as Stevens–Johnson syndrome (SJS), whereas above 30% of the skin is referred to as TEN. With patients having 10–30% of their skin involved it is considered a syndrome of overlap between SJS and TEN [4]. Epidermal loss leads to a water-electrolyte imbalance, hypoalbuminemia, impaired thermoregulation of the body and an increased risk of infection hence the mortality rate for TEN is 50% and for SJS is 10%, with a combined rate of 30%, the most common causes being sepsis and pneumonia [3]. There are no explicit drug treatment protocols in the available literature; evidence to date suggests that the outcome of patients with TEN, is largely dependent on prompt withdrawal of the causative agent, followed by supportive care and appropriate wound care [5]. Patients should be treated with extensive fluid therapy, along with 24-hour monitoring of vital signs and control of water-electrolyte balance. The following paper presents 3 patients hospitalized with TEN and provides a narrative review of the management of this condition.

Address for correspondence:

Adam Wełniak, Department of Dermatology and Venerology Faculty of Medicine, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, Sklodowskiej-Curie 9, 85–094 Bydgoszcz, Poland; e-mail: welniakadam96@gmail.com

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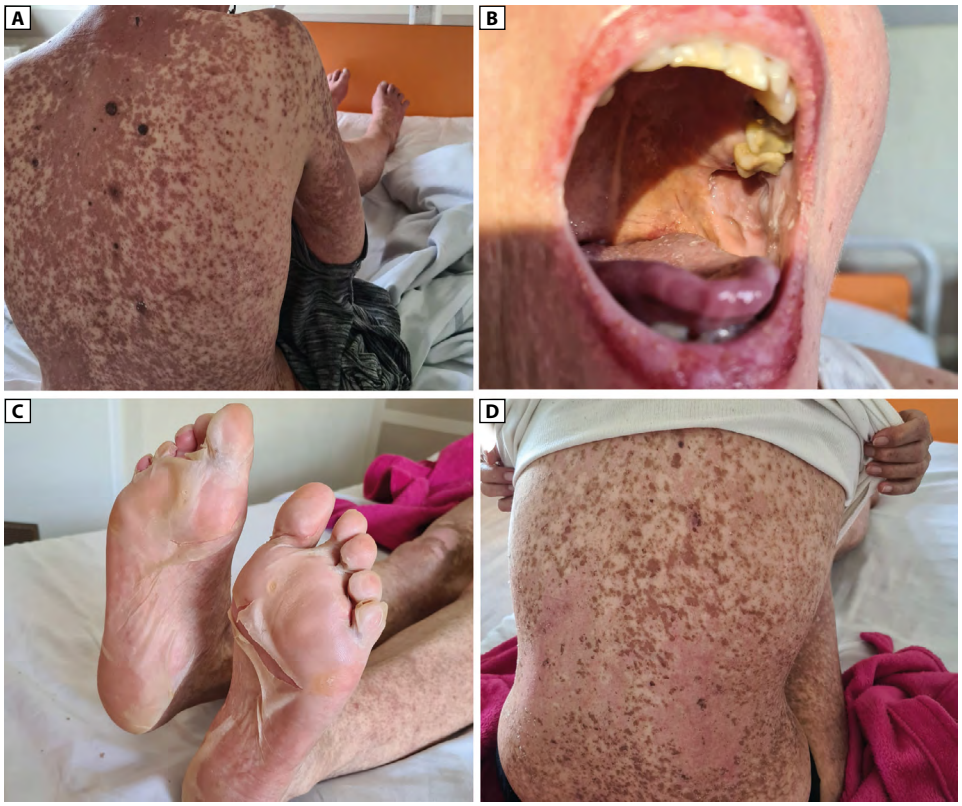

Figure 1. Maculopapular rash on the day of admission (**A**); erosions in the oral cavity (**B**); epidermal detachment (**C**), skin condition after the implemented treatment (**D**)

CASE'S DESCRIPTIONS

Case 1

The patient a 47-year-old woman with a history of skin rash in the cleavage area spreading to other parts of the body accompanied by fever and enlargement of the cervical lymph nodes was admitted for diagnosis and treatment. The patient due to the condition had previously been administered amoxicillin 1 g/day, followed by dexaven 8 mg two times. When taking a medical history, it was revealed that 3 weeks earlier, the patient started treatment with lamotrigine 50 mg/d. In the physical examination, the skin of almost the whole body presented maculopapular rash/exanthema, locally visible epidermal desquamation, on the feet, well-tight serous blisters, and erosions on the mucous membranes of the oral cavity (Fig. 1). In laboratory tests: slightly decreased total protein (5.7 g/dL), elevated CRP (12.64 mg/dL), elevated fasting glucose (110 mg/dL), elevated liver markers: ALT (102 U/L), AST (71 U/L), moreover, the morphology of blood presented a small neutrophilia, monocytosis, eosinopenia. Due to the involvement of ulceration in the oral cavity, as well as sore throat and blurred vision, the patient was consulted with laryngology and ophthalmology specialists. On ophthalmologic examination of the anterior segment of the right and left eye: the eyeball was slightly irritated, the conjunctiva was blood-stained, and there was purulent secretion in the conjunctival sac and on the eyelashes. On laryngological examination, an ulceration was present in the nasal cavity on the septal mucosa on the left side, multiple ulcerations on the mucous membranes of the oral cavity, tongue and middle pharynx, as well as a slight loss of the epiglottal margin mucosa. On the SCORTEN scale, the patient obtained two points: 1 point for age and 1 point for epidermal separation covering > 10% of the body surface area (BSA). The mortality rate for this patient was therefore 12.2%. Lamotrigine, which was an exacerbating factor in the condition, was discontinued and the treatment has been started including dexaven *i.v.*, cyclosporine 250 mg/day (4 mg/kg) and topical ointments containing 1% hydrocortisone, a bandage containing 0.5% chlorhexidine acetate solution, cholesterol ointment, and ointment containing hydrocortisone, natamycin with neomycin. In addition, a skin spray containing neomycin and dexamethasone was used. To relieve pain and other discomforts associated with ulceration of the oral cavity and middle pharynx, the patient was advised to rinse the mouth and throat with diclofenac solution, additionally take vitamin-containing chewable capsules, and for regeneration of the mucous membrane of the nasal cavity, a nasal spray containing D-panthenol and vitamin A + E was used. Due to the patient's complaint of blurred vision and purulent discharge in both eyes, the

patient was treated with the antibiotic gentamicin 0.3% in the form of drops administered directly into the conjunctival sac. However, the applied treatment did not bring improvement. Due to the patient's worsening condition, immunoglobulins in a total dose of 130 g were implemented into the treatment, after which a significant improvement in the skin condition was obtained. The patient, in generally good condition, was discharged from the hospital after 10 days with recommendations to maintain treatment with cyclosporine and topical treatment of the lesions.

Case 2

The patient is a 61-year-old male transferred from the anaesthesiology clinic to the department of dermatology for treatment of skin lesions located on the trunk and extremities. The lesions had an erythematous character, with the presence of blisters that detached at contact (Fig. 2). The condition occurred suddenly, 2–3 days ago before admission, followed by a fever of up to 39°C. The patient denied other signs of possible infection. Through the patient's medical history, a discovery had been made of an episode of cutaneous adverse reaction after carbamazepine intake in 2015 in the form of generalized drug-induced drug-induced dermatitis. Concomitant diseases were as follows: hypertension, hypercholesterolemia, hypothyroidism, schizophrenia, and mild mental retardation. On admission, the test for SARS-CoV-2 virus was positive. Laboratory tests revealed decreased haemoglobin (12.4 g/dL), erythrocyte count (3.79 × 10^6/μL) and haematocrit (36.2%). The tests also revealed thrombocytopenia (103 × 10^3/μL) and a significantly elevated C-reactive protein level (151.60 mg/dL). Also above normal were procalcitonin (6.21 ng/mL), D-dimers (4221 ng/mL), serum creatinine (1.37 mg/dL), phosphate kinase activity (1119.0 U/L). Antinuclear antibody (ANA) titters were determined — 1:320 granular luminescent type, in the specification of Mi-2 +, PM-Scl-75 (+), SRP +, Ro-52 +. Levels of tumour markers (AFP, CA 19-9, CEA, PSA) were normal. The blood cultures performed were negative. In accordance with the SCORTEN, the patient received 2 points, 1 point for age over 40 and 1 point for the initial area of epidermal detachment, which covered more than 10% of the body surface. These prognostic factors resulted in an estimated mortality rate for this patient of 12.2%. The patient proved difficult to manage due to his schizophrenia as the intravenous and intra-arterial catheterizations that had been placed continued to be removed by him. The patient was consulted by a psychiatrist, and a decision was made to discontinue ValproLEK (sodium valproate, valproic acid), as it was likely inducing epidermal necrolysis. Due to the unclear aetiology of Lyell's syndrome (risk of possible infectious aetiology), systemic corticosteroid therapy was refrained from. Treatment was limited to topical steroid therapy with hydrocortisone spray. Additional body lubrication with cholesterol ointment along with vitamin A and hydrocortisone ointment for skin lesions on the limbs and trunk was applied to erosions. Intensive fluid therapy was administered, with 24-hour vital signs and fluid balance monitoring. As the treatment was not effective, the final decision was made to include intravenous immunoglobulins. A total of 170 g of intravenous immunoglobulin (IVIG) *i.v.* was administered after which improvement has been noted. The patient was discharged home in good general condition with recommendations for further treatment and follow-up.

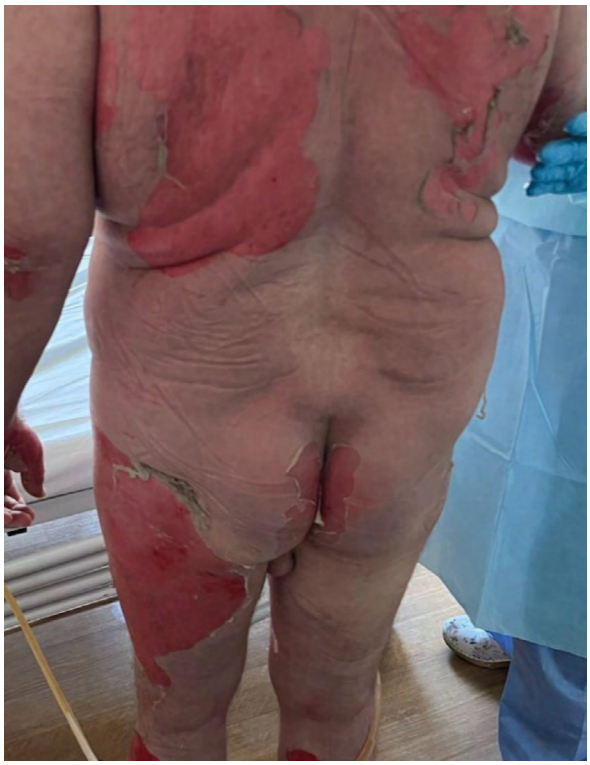

Figure 2. Massive erosions and epidermal detachment

Case 3

The patient is a 59-year-old man admitted due to extensive erythroderma that appeared 2 days before admission to the Department of Dermatology. The patient was transferred from the infectious diseases ward where he was hospitalized due to alcoholic cirrhosis of the liver. Before admission, no new medications were introduced. During the stay the following drugs were administered: ciprofloxacin, amoxicillin, metronidazole, spironolactone, ramipril, amlodipine, furosemide, pantoprazole and thiazolidine carboxylic acid. There was suspicion that amoxicillin caused the reaction however other drugs couldn't be ruled out. History

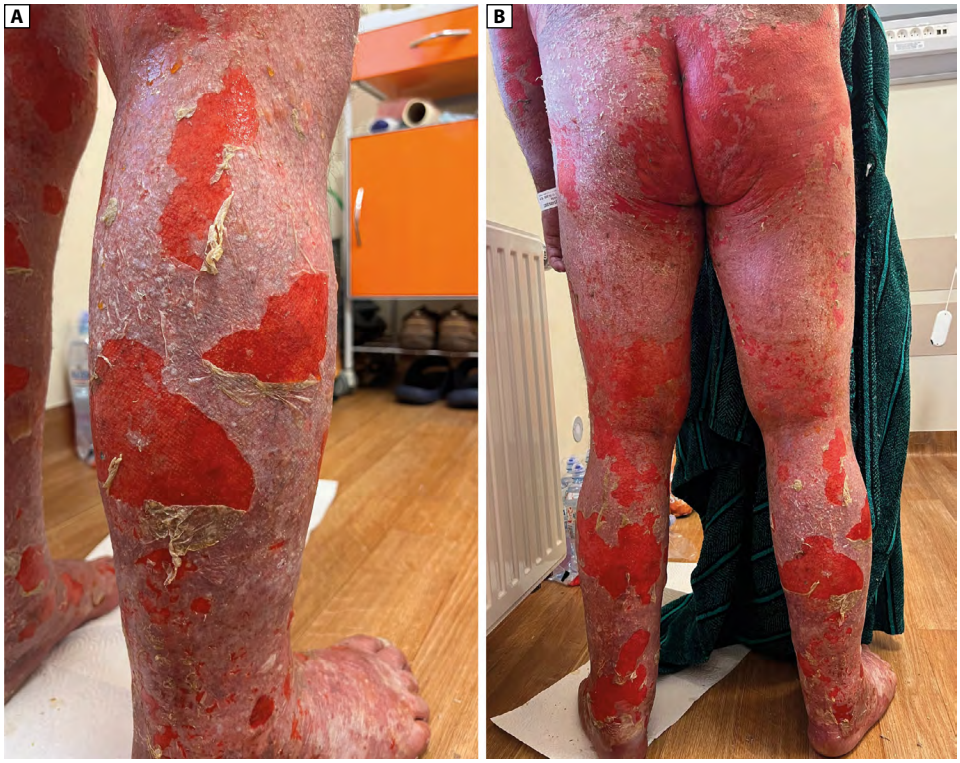

Figure 3. Extensive erythematous skin detachment (**A**, **B**)

of oedema of the lower extremities for many months, hypertension, alcoholic cirrhosis, oesophageal varices without bleeding, chronic gastritis, gastric ulcer with no mention of bleeding, diverticular disease, unspecified hyperglycaemia, anaemia, secondary thrombocytopenia and aortic stenosis. During hospitalization in the dermatology department, on admission, tests showed increased liver necrotic parameters (ALT 414 U/L, AST 294 U/L), increased total bilirubin (11.03 mg/dL), decreased albumin (2.5 g/dL), elevated creatinine (1.34 mg/dL), elevated ammonia (150 ug/dL), mild normocytic anaemia (Hgb 12.8 g/dL), hyperglycaemia (206 mg/dL) with a decrease in Hgb to 11.1 g/dL, WBC 5.23 thousand/µL. Total bilirubin increased to 16.79 mg/dL, hyperuricemia 183 ug/dL, AST 170 U/L ALT 244 U/L, hypoalbuminemia 2.2 g/dL. With reduced coagulation parameters INR 6.6 and thrombocytopenia PLT 16,000/µL. During hospitalization, the patient's condition worsened. In physical examination, the patient was connected to a ventilator without any contact, even visual. The patient obtained four points on the SCORTEN scale: point for age over 40; peeling of the epidermis covering > 10% BSA on admission, serum urea > 10 mmol/L, bicarbonate < 20 mmol/L. This means that this patient has an estimated 58% mortality rate for TEN. The entire surface of the body was peeling skin, oozing and giving off a very unpleasant smell (Fig. 3). It was unclear which drug could have caused the patient's reaction, thus most of the drugs were temporarily discontinued. Dexamethasone, vancomycin, and albumins intravenously along with topical therapy were implemented. Additionally, hypoglycaemic treatment was required. Skin condition gradually deteriorated as well as the patient's general condition resulting in cardiac arrest, after which vital functions were restored, however, the patient was maintained with a respirator. Based on the collected data and numerous specialist consultations, it was established that the patient is not eligible for liver transplantation as a causative treatment and further management should be focused on palliative treatment. Given the patient's declining vital parameters, the heart arrested again and the patient passed away.

DISCUSSION

There have been reported various triggers for TEN, amongst them infections (especially of *Mycoplasma pneumoniae* aetiology), contrast agents, herbs, vaccines, and idiopathic causes [3]. However, drugs without a doubt remain the most common trigger, especially antibiotics, and antiepileptic drugs followed by nonsteroidal anti-inflammatory drugs (NSAIDs), antiviral drugs, and allopurinol [6]. In the first case, the most likely triggering factor was lamotrigine, which is a phenyltriazine derivative, used in the treatment of

epileptic seizures, and bipolar affective disorder. According to a 2008 study called Euro-SCAR, lamotrigine was among the drugs with a high risk of TEN [7]. Despite the existence of a correlation between SJS and antiepileptic drugs, the exact mechanism of this relationship has so far not been clarified. According to some investigators, an important role in this mechanism may be played by arsenic oxide metabolites formed during the degradation of antiepileptic drugs [8]. Moreover, available studies also suggest that women are more predisposed to skin reactions after antiepileptic drugs in comparison to men [9]. A similar clinical course to that presented by patient 1 was described by Kumar et al. [10], whose patient also developed TEN 3 weeks after using lamotrigine at 50 mg nonetheless in the case of the present patient thanks to IVIG treatment the treatment in ICU was avoided. As for patient 2, the medication that most likely led to the development of the disease was valproic acid which is an anticonvulsant drug commonly also used to treat manic episodes in bipolar disorder. Many described cases of SJS or TEN were caused by the intake of valproic acid although it's worth pointing out that it happens mostly in combination therapy with another antiepileptic drug, most commonly lamotrigine or carbamazepine [11, 12]. There are also reports of SJS developing after using valproic acid in monotherapy, but these are less common [13]. In the case of patient 3, which was taking three different antibiotics: ciprofloxacin, metronidazole and amoxicillin, and each of these antibiotics has connections to SJS/TEN described in the literature. It is worth noting that the lowest number of described cases include the use of metronidazole as only a few cases have been reported [14]. On the other hand, amoxicillin is classified as one of the beta-lactam antibiotics which are considered to be one of the main causes of severe cutaneous adverse drug reactions. In a study conducted, by Kim et al. it was shown that SJS/TEN is more likely to happen when beta-lactam antibiotics are used in comparison to non-beta-lactam antibiotics [15]. The last of three is Ciprofloxacin, a fluoroquinolone group antibiotic that is a rare but determined cause of SJS [16]. Similar to patient 3 in the case presented by Cravens et al. whose patient a few days after the end of ciprofloxacin treatment, developed an itchy, blistering rash that covered 90% of his body surface [17]. Diagnosis is certain in the case of that patient as it was confirmed by biopsy.

There are two international guidelines for the treatment of TEN: one published by the British Dermatological Association and the other by the Indian Association of Dermatologists, Venereologists and Leprologists [18]. They emphasize discontinuation of suspected causative medications as soon as possible and initial assessment of the patient's condition with calculation of SCORTEN within the first 24 hours of admission. Management of patients with TEN can best be carried out under sterile conditions in an intensive care unit or a special burn unit [19, 20]. British guidelines favour primarily local treatment and early involvement of a multidisciplinary team (including an anaesthesiologist, pulmonologist, dermatologist and ophthalmologists) [19]. Patients with SJS/TEN require multidirectional treatment since most have ocular involvement complications as well as oral and genital mucosal damage. Therefore, it is so important to cooperate with physicians from other disciplines, such as ophthalmology, otorhinolaryngology or anaesthesiology, and in cases that are not promising, to involve palliative medicine specialists. Mucosal lesions occur even in 90–95% of patients and in a third of them, mucositis may precede skin lesions by several days [21, 22]. Mucosal lesions most commonly affect the mouth, throat, eyes, and genitals along with the anus, and less commonly the nose, oesophagus, trachea and bronchi resulting in s acute respiratory distress, gastrointestinal distress, and genitourinary dysfunction and denudation [21, 22]. Acute ocular complications are reported in most patients with SJS/TEN. A study by Gueudry et al. [23] found that 74% of patients experienced ocular involvement during the acute phase of the disease [19]. Ocular and eyelid blepharitis is usually accompanied by swelling, conjunctivitis, pseudomembrane formation, and corneal and conjunctival epithelial defects [23]. A study conducted by Yip et al. [24] evaluated the outcome of 117 patients with SJS/TEN; 69% of patients had ocular lesions. A classification was made according to severity; mild ocular involvement occurred in 40% of patients, moderate in 25% and severe in 4%. 50% developed late complications, the most common of which were severe dry eye and ciliary disease [19, 24]. Although not widely reported, studies show acute gynaecologic involvement occurs in up to 77% of patients with SJS/TEN [25]. Changes include vaginal erosions and ulcers, painful urination or retention, discharge, pain and bleeding [26]. Gynaecologic consultation is needed to alleviate symptoms and prevent the development of sequelae that occur in 25% of women, which are vulvar adhesions and vaginal strictures that cause, among other things, dyspareunia and difficulty getting pregnant [25]. Often the lesions also affect the genitourinary system in men. The most common symptoms are penile erosions, followed by muscle involvement, leading to dysuria and haematuria in the acute phase. Long-term sequelae are relatively uncommon and can manifest as penile adhesions, urethral strictures, and stools [25]. Also, the psychosocial consequences of the disease, should not be underestimated [27]. The guidelines also address the prevention of recurrence and the treatment of chronic complications, which, as mortality from SJS/TEN declines, are becoming more common [19]. Of great

importance in a patient's recovery are visits to a dermatology clinic for follow-up and treatment of skin complications, the most common of which are postinflammatory hyper-/ /hypopigmentation, photosensitivity, chronic pruritus, eruptive naevi, hypertrophic scarring, hair changes, like telogen effluvium, and nail changes [27]. If non-cutaneous complications occur, the patient should be referred by the coordinating physician, usually a dermatologist, to physicians of appropriate specialities. During routine follow-up, the recovering patient should be questioned about local symptoms, such as decreased visual acuity and shortness of breath, as well as generalized symptoms, including fatigue, weakness or depression, and a psychological evaluation should be considered in all patients [19, 20, 27]. In the authors' experience, the ability to work with specialists from different disciplines is of considerable value in the treatment of TEN. As in the case of the first patient, involvement of the eyes and throat lesions, required cooperation with an ENT specialist and an ophthalmologist for successful treatment. With the second patient, his schizophrenia proved his hospitalization to be quite difficult as the patient was pulling out his venipunctures requiring constant consultations with an anaesthesiologist which enabled further measures to be taken to improve treatment. The patient was also consulted psychiatrically, and this examination made it possible to identify the drug potentially causing the TEN. The third patient who was suffering from cirrhosis, had a very acute course of TEN, and any treatment provided was ineffective. In order to comprehensively evaluate his condition, the patient was repeatedly consulted by internal medicine, anaesthesiology, cardiology specialists and for pain relief, with a palliative medicine physician.

The Severity-of-Illness Score for Toxic Epidermal Necrolysis (SCORTEN) scale is a model for estimating mortality. Risk factors considered are age ≥ 40 years, heart rate ≥ 120 beats per minute, presence of cancer or haematologic malignancy, initial % BSA of detached epidermis > 10%, blood urea nitrogen > 10 mmol/L, serum glucose > 14 mmol/L and serum bicarbonate < 20 mmol/L. A score of 1 point is given for each of the conditions met. The risk of death is, respectively, for scores 0–1 — 3.2%, 2 — 12.1%, 3 — 35.3%, 4 — 58.3%, and 5 or more > 90% [28]. SCORTEN is the best-known prognostic scale and a reliable parameter in predicting mortality in patients with SJS/TEN. Analyses of several case series have confirmed SCORTEN's ability to accurately predict death [29]. However, there are papers indicating that the accuracy of this test may be limited [30]. The reliability not only of the predicted mortality risk but also of the component laboratory results and clinical features is subject to debate. There are calls to revise the score predicting death among TEN patients and to include new risk factors for death. With particular attention to the creation of more appropriate breakdowns by age and body surface area occupied, and the inclusion of more accurate renal function parameters [29, 30]. As shown in the analyses, recent studies show a much lower death rate than expected according to SCORTEN. With advances in the treatment of TEN, SCORTEN may overestimate mortality in centres with experience in treating this disease [22, 29]. In the case of the present patients, however, the SCORTEN scale was an effective predictive tool. Patients who scored 2, a predicted mortality of 12.1%, responded to treatment and survived. A patient whose condition was more severe and scored 4 on SCORTEN (predicted mortality of 58.3%) passed away.

Management of TEN relies on supportive care providing the conditions for re-epithelialization of the affected skin for which fluid resuscitation, pain management, wound care, and nutritional support are crucial [31]. The fluid resuscitation should maintain adequate tissue perfusion by achieving mean arterial blood pressure of 65 mmHg, central venous pressure in the range of 8 to 12 mmHg, and urine output in the range of 0.5 to 1 mL/kg/ hours [32]. A non-adhesive sterile dressing should be used to cover areas of skin erosion and care should be taken to prevent hypothermia, especially in the pre-hospital setting [33]. Nutritional support is critical in patients with TEN due to the hypercatabolic nature of the condition. Enteral nutrition is superior to parenteral nutrition given the reduced risk of bacterial translocation. A nasopharyngeal oropharyngeal examination may be used if the oral mucosa is significantly affected. Wound debridement of the affected area can be managed with a variety of options, including a biologic dressing (e.g., allograft, xenograft, and homograft), a biosynthetic dressing (e.g., biobrane), or a silver-impregnated dressing [31].

As for forms of systemic pharmacotherapy in TEN glucocorticoid therapy is debatable. While some studies have shown a reduction in mortality when combined with IVIG therapy, other studies have shown conflicting results. The RegiSCAR study, published in 2008, showed a statistically significant increase in survival among those who received corticosteroid therapy, supporting the view that corticosteroids may increase survival in patients with TEN [34]. The EuroSCAR study, which assessed the risk of using drugs in rare but severe cutaneous adverse reactions, including TEN, does not explicitly mention that corticosteroids decrease mortality, however, indicates that corticosteroid therapy does not increase mortality and may have a beneficial effect, however, this relation was not noticed among the present patients [8]. Cyclosporin has gained in importance in recent years. This medication inhibits the activity of T lymphocytes, which play a key role in the pathogenesis of TEN [35]. Successful treatment of SJS/TEN with cyclosporine was reported in

a study of 44 patients, which showed a significant reduction in mortality as the standardized mortality ratio of SJS/TEN treated with cyclosporine was 0.42 [36]. An analysis by Harr et al. [37] showed that patients treated with cyclosporin had a significantly shorter time to complete re-epithelization, fewer patients with multiple organ failure were observed, mortality was reduced and clinical outcomes after the use of cyclosporin were improved. Nevertheless, these effects were not present in the present study patients. Clinical evidence regarding the effectiveness of IVIG in TEN is currently inconclusive as the results of systematic reviews and meta-analyses are conflicting. While some studies suggest a great potential benefit of IVIG, especially when combined with corticosteroids, others show no significant clinical benefit to its use. The potential mechanism of action for IVIG in the treatment of TEN relies on blocking the interaction between the Fas receptor and the Fas ligand, a reported pathway for keratinocyte death that is characteristic of TENs [38]. Some systematic reviews suggest that the current evidence does not generally support the clinical benefit of IVIG in the treatment of TEN, however, it should be noted that this analysis did not consider the potential impact of the different doses used of IVIG [39]. Another meta-analysis published in the Journal of the American Academy of Dermatology in 2020 showed that combined therapy with corticosteroids and IVIG significantly reduces the observed risk of death in patients with TEN [4]. This suggests that IVIG may play a beneficial role when used in conjunction with other treatments, however, the cost of IVIG is a major limiting factor. The use of IVIG in the treatment of TEN remains controversial and guidelines contain different recommendations. According to the European guidelines (S1) on the use of high doses of IVIG in dermatology, in the absence of alternative treatment methods based on scientific evidence, early administration of high doses of IVIG (≥ 2 g/kg) may be considered [40]. In the authors' experience, IVIG is worth considering life-saving treatment in severe cases of TEN.

CONCLUSIONS

In summary, TEN also affects several internal organ systems in addition to the skin, including the eyes and mouth, respiratory, gastrointestinal/hepatic and genitourinary, which is why its treatment requires cooperation with specialists from different fields. Crucial in TEN management is potential causative drug withdrawal and topical treatment as well as early assessment with SCORTEN. Systemic steroid therapy could potentially reduce mortality, however, the evidence is lacking. Many support the role of immunoglobulins and cyclosporine in this condition management.

Article information and declarations

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Author contributions

AW, PL, WW, NG — Data analysis and preparation of the manuscript; AW, LM-J, RC — Work plan and evaluation of the content.

Conflict of interest

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Supplementary material

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CASE REPORT

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Trichilemmal carcinoma of the groin area of unknown primary site

Krzysztof Kowalik[1], Katarzyna Hetman[2], Marta Suchomska[1], Michał Falco[3], Anna Gruszczyńska[4], Krystian Kasperowicz[5], Jerzy Grabarek[6], Andrzej Modrzejewski[1]

[1]*Clinical Department of General Surgery, Pomeranian Medical University, Szczecin, Poland*
[2]*Department of Clinical Oncology, West Pomeranian Oncology Center, Szczecin, Poland*
[3]*Clinical Department of Radiotherapy, Pomeranian Medical University, West Pomeranian Oncology Center, Szczecin, Poland*
[4]*Department of Forensic Medicine, Pomeranian Medical University, Szczecin, Poland*
[5]*Faculty of Health and Life Sciences, Northumbria University in Newcastle upon Tyne, United Kingdom*
[6]*Pathomorphology Laboratory, 109 Military Hospital with Outpatient Clinic, Szczecin, Poland*

ABSTRACT

The authors present a case of a 49-year-old patient with a trichilemmal carcinoma of an unknown primary site. The groin tumour gradually enlarged over 6 months to a diameter of about 6 cm and was treated as an inguinal hernia. Specimens were taken from the tumour for histopathological examination, which revealed squamous cell carcinoma. In the meantime, ulceration of the tumour with leakage of pus appeared. The patient was referred for a computed tomography (CT) scan. A computed tomography scan exposed enlarged lymph nodes in the groin on the side of the tumour. Surgical treatment was undertaken involving excision of the tumour and a lymphadenectomy along the iliac vessels. Carcinoma was detected from the hair sheath. Chemotherapy and radiotherapy were undertaken. After four months, there were no signs of local recurrence or distant metastasis. The authors discuss the diagnostic difficulties encountered and the various treatment options for trichilemmal carcinoma.

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Keywords: trichilemmal carcinoma, metastases, lymph nodes, chemotherapy

INTRODUCTION

Trichilemmal carcinoma (TLC) is a rare malignant tumour that originates from the external root sheath of the hair. Sun exposure is considered a risk factor, as cited by other authors [1, 2]. The average age of TLC diagnosis is 70 years, with a predominance of male patients in the affected group [3, 4]. Typically, this tumour develops on hairy body parts, but it can also occur in non-UV-exposed areas in individuals with compromised immune systems [5, 6]. Other established risk factors for TLC include exposure to radiation, local injuries or burns, immunosuppression, as well as hereditary conditions such as xeroderma pigmentosum or Cowden's disease [3]. The first case of TLC was documented by Headington in 1976 [7]. He identified that TLC is composed of atypical clear cells derived from skin appendage keratinocytes. The key histological feature distinguishing TLC from other skin tumours is the presence of trichilemmal keratinization. The tumour lacks a granular layer between the spinous and keratin layers [7]. For skin-afflicted cases, local, wide excision with tumour-free margins constitutes the primary treatment. There is also growing evidence of the effectiveness of Mohs micrographic surgery, involving precise removal of tumour tissue under the microscope to spare healthy tissue [2]. In cases of TLC with metastasis, several chemotherapy options are employed. Combining cisplatin with cyclophosphamide, 5-fluorouracil, vinblastine, and bleomycin slow the progression of metastatic disease [8–10]. Literature reports indicate that recurrences of TLC after successful treatment are rare [2].

CASE REPORT

A 49-year-old female patient presented to a cardiologist due to severe abdominal pain and chest discomfort (attributed to a previous COVID-19 infection). A year and a half earlier, the patient noticed a palpable lump in the right

Address for correspondence:
Krzysztof Kowalik, MD, Clinical Department of General Surgery, Pomeranian Medical University, 9–11 Piotra Skargi Street, 70–965 Szczecin, Poland; e-mail: krzysztof.kowalik.uro@gmail.com

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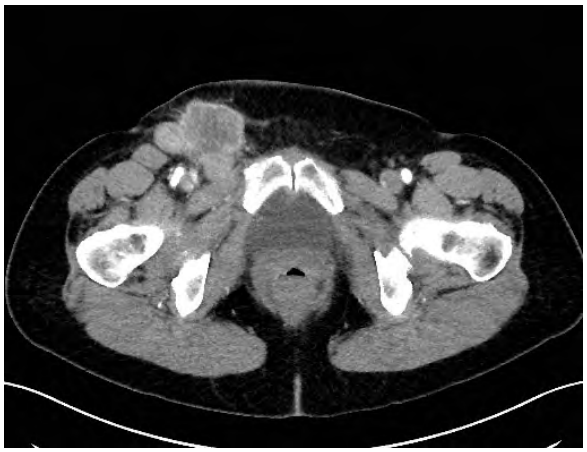

Figure 1. Computed tomography (CT) scan image of a lymph node lesion in the right inguinal region

inguinal area, which initially did not cause any pain. However, the patient observed that the inguinal lump was gradually enlarging. The patient visited her general practitioner, who recommended an ultrasound examination. On examination, bilateral inguinal hernias containing *omentum majus* was diagnosed. The patient was referred by her primary care physician for right-sided inguinal hernia repair. The surgeon, after examining the patient, clinically ruled out the presence of an inguinal hernia and requested an abdominal cavity CT scan. The abdominal CT scan revealed an irregular, strongly enhancing after-contrast administration structure measuring approximately 60 mm × 50 mm with a hypodense centre in the right inguinal area (Fig. 1). The radiologist suspected a tumour with signs of necrosis or a lymph node with signs of degeneration. Adjacent to the aforementioned lesion, two pathological lymph nodes measuring 26 mm × 21 mm and 21 mm × 21 mm were seen. Additionally, several lymph nodes up to 15 mm in size were identified around the external iliac vessels and paraaortic vessels (below the bifurcation). Enlarged lymph nodes up to 9 mm were also noted, raising concerns of tumour metastases. The CT scan also revealed an enlarged uterus with significant contrast enhancement.

The patient was referred to the surgery clinic, where a biopsy of the inguinal region lesion was performed, and the collected specimen was sent for histopathological analysis. Histopathological analysis of the biopsy sample revealed infiltrating, moderately differentiated squamous cell carcinoma (G2) with areas of necrosis. Considering the suspicion of primary cervical cancer in the patient, a gynaecological consultation was requested. A gynaecological examination revealed an irregular, enlarged cervix and uterus. A gynaecological ultrasound examination described an enlarged, heterogeneously echogenic cavity of the uterus. The cytological examination did not reveal signs of malignancy.

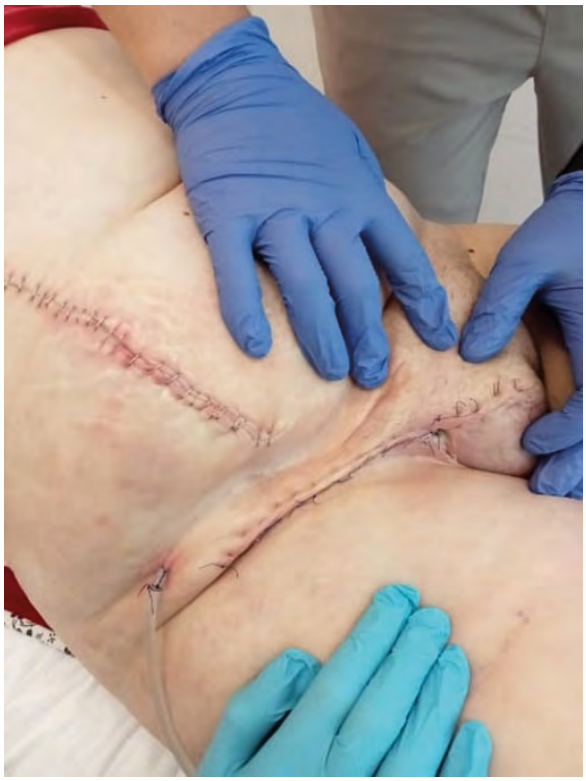

Figure 2. Image after surgery of right inguinal tumour resection with pelvic lymph node dissection

A PET scan was performed to identify the primary site of squamous cell carcinoma in the right inguinal lymph nodes. The PET scan identified a 17 mm diameter area of increased metabolism in the right adnexa. Metabolically active lymph nodes in the right inguinal region, suggestive of metastatic changes, as well as common iliac lymph node measuring up to 21 mm were also identified.

A chest CT scan of the patient did not reveal any suspicious oncological changes. Corynebacterium amycolatum was cultured from the ulceration of the inguinal tumour (but as the strain is considered to be non-toxigenic, antibiotic therapy was not recommended).

During the diagnostic process, the primary site of the tumour could not be identified. Malignancy in the genital organs was ruled out. The patient underwent surgery at the surgery clinic, where resection of the right inguinal tumour with pelvic lymph node dissection was performed.

The tumour was excised from a cut in the thigh, along and below the inguinal ligament. Upon dissecting the skin over the 8 cm × 4 cm-sized tumour, a necrotic and suppurating mass was observed. Additionally, significantly enlarged lymph nodes measuring up to 4 cm were removed from the area of the external iliac artery, common iliac artery, and aortic bifurcation by extraperitoneal incision (Fig. 2). The histopathological postoperative material (sectioned

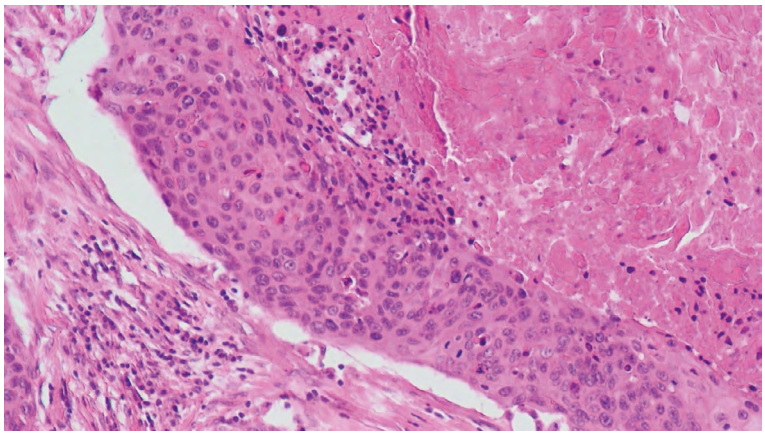

Figure 3. Visible tumour infiltration corresponding to trichilemmal carcinoma. The infiltration originates from the right inguinal tumour. Focal necrotic areas are visible in the central part

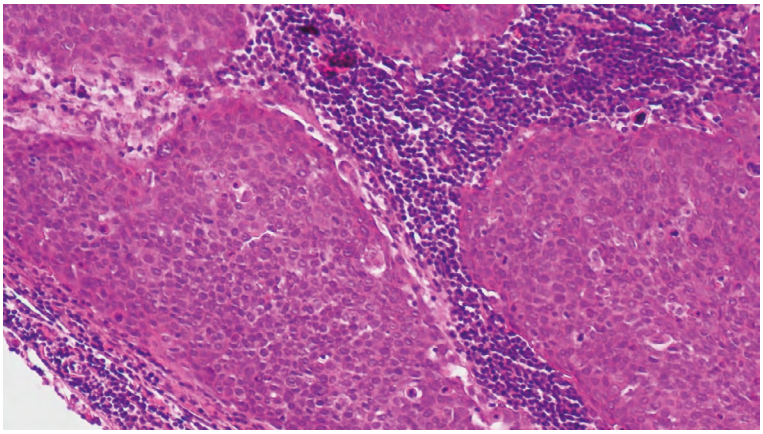

Figure 4. Section of a metastatically altered lymph node. Visible tumour infiltrations corresponding to trichilemmal carcinoma. Focal necrotic areas of the tumour are also visible in the specimen

tumour and lymph nodes) revealed metastasis of trichilemmal carcinoma cells (Fig. 3, 4). The intraoperative view of the right inguinal tumour is presented in Figure 5.

In the further stage of treatment at the Oncology Department, the patient received 6 courses of chemotherapy with cisplatin at a dose of 80 mg/m^2 in combination with radiotherapy (RT). The radiotherapy plan was developed using a 3D planning system based on the performed treatment planning with a CT scan. The radiation was delivered in 25 fractions using the volumetric modulated arc therapy (VMAT) technique on a Halcyon accelerator (Varian, a Siemens Healthineers company). A dose of 45 Gy was given to the external and internal iliac lymph nodes on the left side, while a dose of 50 Gy was given to the inguinal, external and internal iliac lymph nodes on the right side, common iliac lymph nodes, and the tumour bed (tumour bed this is what is left after the cancer has been removed surgically). During treatment, grade 1 skin erythema according to RTOG and grade 2 early gastrointestinal reactions according to RTOG (loose stools) were observed. After 6 sessions of radiochemotherapy, a follow-up computed tomography scan did not reveal local recurrence or distant metastases as of the time of publication. The patient remains under further oncological observation.

DISCUSSION

Trichilemmal carcinoma (TLC) is a rare malignant tumour arising from the outer sheath of the hair follicle and is primarily derived from the external root sheath of the hair follicle [1, 2]. It was first described by Headington [7] and is most commonly found on the face and neck of older individuals [3, 4]. Trichilemmal carcinoma is rarely documented in patients under 40 years of age, though Reis and colleagues [6] reported a case of TLC in a 9-year-old boy with xeroderma pigmentosum, followed by another case of a 25-year-old patient [11]. Clinically, TLC often presents as

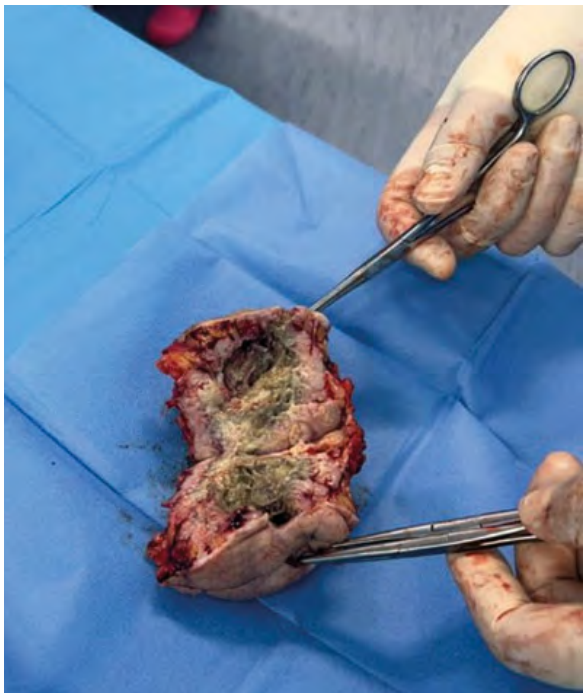

Figure 5. Inguinal tumour excised during the procedure — a bundle of enlarged lymph nodes; intraoperative image

an asymptomatic polypoid or exophytic mass. The tumour may occasionally show ulcerations, irregular borders, or "flakes" resembling basal cell carcinoma (BCC), squamous cell carcinoma (SCC), keratoacanthoma, or proliferating trichilemmal cysts [1, 6]. While TLC can exhibit local malignancy, it often has a benign nature. when treated with radical tumour resection [1, 6, 12]. In the case described by the authors, the tumour was initially misdiagnosed as an inguinal hernia. The patient sought medical attention due to the increasing size of the right inguinal mass for six months, without experiencing pain. Based on the ultrasound examination, the patient was referred for hernioplasty, but the surgeon during the physical examination ruled out the presence of an inguinal hernia. An abdominal and pelvic CT scan with contrast revealed a large enhancing metastatic tumour in the right inguinal area. Subsequent biopsy of the inguinal lymph node confirmed squamous cell carcinoma G2. The patient underwent radical tumour resection, and histopathological examination confirmed the final diagnosis of trichilemmal carcinoma. The present case highlights that TLC can also occur in the abdominal region. In a literature review conducted by other authors, only one case of abdominal TLC has been described thus far [13]. The authors recommend differentiating a suspicious mass in the groin from a neoplastic lesion.

The primary treatment for TLC is radical surgical tumour resection. In the cited literature review, 35 cases were surgically treated, with recurrence occurring in only two patients — one of whom experienced three recurrences. These patients were observed for periods ranging from 2 months to 10 years [13, 14], indicating that radical tumour resection delivers excellent treatment outcomes. Increasingly, cases of radical surgical resection of TLC using the Mohs method are being reported [5, 15–17]. This approach has also shown satisfying treatment outcomes without recurrence. Patients treated with the Mohs method were often observed for up to 20 months without recurrence [5, 15–17]. In the case of metastatic lesions, as seen in the described patient with a resected right inguinal tumour and documented lymph node metastasis, systemic chemotherapy should be considered.

In the literature, there is no specific treatment protocol described for systemic therapy in trichilemmal carcinoma (TLC) with metastases due to the limited number of cases. It is recommended to use treatment approaches similar to those used for skin cancers [3]. There are cases of TLC with metastasis after radical resection of the primary tumour, they were described and treated with cisplatin and cyclin [8, 13]. There is also data suggesting that cisplatin in combination with cyclophosphamide, 5-fluorouracil, vindesine, and bleomycin can slow down the progression of metastasis [8–10]. A case report published in 2010 described a patient aged 63 who received four sessions of combined chemotherapy (cisplatin 56 mg/m^2 with cyclophosphamide 400 mg/m^2). Partial remission with confirmed reduction of abdominal lymph nodes was achieved. This chemotherapy regimen was found to inhibit tumour growth but did not lead to remission. No serious complications were noted during treatment, but chemotherapy was discontinued as the patient requested [8]. It is suspected that the CAV regimen (cisplatin, adriamycin, vindesine) used for advanced basal cell carcinoma may be effective in TLC with metastases [18, 19]. In another reported case in 2001, cisplatin 75 mg/m^2 was administered on the first day along with etoposide 100 mg/m^2 for three days. Partial remission was achieved, and no disease progression was observed for six months [20]. Weiss et al. found a good response to cisplatin and 5-fluorouracil [21]. However, Roismann et al. [10] indicated that using four cycles of chemotherapy with 5-fluorouracil and cisplatin was associated with a poorer prognosis in the case they presented. This patient, a 35-year-old male diagnosed with basal cell carcinoma, later developed TLC in the same location. After surgery for BCC, the patient received postoperative radiotherapy with a total dose of 6000 cGy. Five years later, disease recurrence occurred, and after resection, the patient received 1000 mg/m^2 of 5-fluorouracil along with 75 mg/m^2 of cisplatin. Disease progression was observed four months after chemotherapy. Adjuvant radiotherapy was then administered with a total dose of

4320 cGy [10]. The literature includes a case of a 69-year-old woman who underwent postoperative radiotherapy. During a follow-up visit two years after completing radiotherapy, no disease recurrence or metastases were observed. Another case involved a 53-year-old woman who did not receive radiotherapy after tumour resection, as the multidisciplinary committee concluded that it would not provide significant benefit. No disease recurrence was observed during the two-year follow-up [22]. In this case the patient after radical resection, cisplatin was administered at a dose of 80 mg/m^2 in cycles every 7 days in combination with radiotherapy, achieving a good treatment response. Due to the lack of clear treatment protocols in the literature, further study is required.

CONCLUSIONS

Patients with suspected groin lesions should consider the possibility of malignant changes, not only inguinal hernias. Radical tumour excision with enlarged lymph nodes followed by postoperative radiotherapy and chemotherapy appears to be a promising approach for advanced TLC.

Article information and declarations

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Author contributions

KK, AG, KH, MF, AM — preparation of the primary version of the manuscript; JG, MS, AM — preparation of photographic documentation; KK — preparation of the English-language version of the manuscript and language proofreading; KK, AG, KH — literature review.

Conflict of interest

The authors declare no conflict of interest.

Ethics statement

No ethical issues.

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Supplementary material

None.

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CASE REPORT

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Trichoscopy-guided biopsy for the evaluation of scarring alopecia due to discoid lupus erythematosus

Kinga Kołcz[1, 2], Ewa Kaznowska[3], Adam Reich[1], Magdalena Żychowska[1]

[1]*Department of Dermatology, Institute of Medical Sciences, Medical College of Rzeszow University, Rzeszów, Poland*
[2]*The Doctoral School, University of Rzeszow, Rzeszów, Poland*
[3]*Department of Pathology, Institute of Medical Sciences, Medical College of Rzeszow University, Rzeszów, Poland*

ABSTRACT

Discoid lupus erythematosus (DLE) is an autoimmune disease that represents one of the subtypes of chronic cutaneous lupus erythematosus (CCLE). When located on the scalp, DLE may lead to the development of scarring alopecia. The following study presents the case of a 60-year-old female patient with slowly progressing cicatricial alopecia of a four-year duration. The clinical presentation did not allow for a definite diagnosis. The selection of the most representative site for biopsy was guided by trichoscopy and ultraviolet (UV)-enhanced dermoscopy. The histopathological examination was consistent with the diagnosis of DLE. This paper also discusses the most common dermoscopic findings in active and end-stage DLE. It is postulated, that in all cases of alopecia, picking the spot for biopsy should be guided by trichoscopy.

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Keywords: alopecia, scarring alopecia, discoid lupus erythematosus, dermoscopy, dermoscopy-guided biopsy

INTRODUCTION

Discoid lupus erythematosus (DLE) is an autoimmune disease that represents one of the subtypes of chronic cutaneous lupus erythematosus (CCLE). Apart from DLE, CCLE comprises chilblain lupus erythematosus (CHLE), a deep variant of lupus erythematosus (LE profundus — LEP), lupus erythematosus tumidus (LE tumidus — LET) and Blaschko's linear lupus erythematosus (BLLE) [1]. DLE lesions that develop on the scalp may lead to permanent hair loss. A patient is presented with scarring alopecia, in whom dermoscopic examination allowed a selection of a suitable site for surgical biopsy (trichoscopy--guided biopsy) and make a diagnosis of underlying DLE.

CASE REPORT

A 60-year-old woman, with a history of hyperthyroidism, was admitted to the Department of Dermatology in Rzeszow for evaluation of gradually progressing irregular alopecic patches in the parietal-occipital scalp. The first patch of loss of hair, accompanied by pruritus, started to develop 4 years before hospitalization. Her previous treatment included numerous topical corticosteroid preparations of varying potency, minoxidil and an irritant capsaicin mixture, with no clinical improvement.

Dermatological examination showed several slightly depressed confluent foci of alopecia on the vertex arranged in the pattern of "footprints in the snow". Under dermoscopy, white structureless areas on a predominantly pinkish-whitish background, and focally present honeycomb pigment pattern were observed in the parietal region. The follicular openings were absent. Dermoscopic findings differed in the occipital area, where red-brown dots, large yellow dots and pronounced honeycomb pigment pattern on a pink-white background were observed (Fig. 1). Ultraviolet (UV) enhanced-dermoscopy allowed for better visualisation of perifollicular scaling. In addition, under UV-dermoscopy dark round and oval structures, corresponding to hair follicles, were observed in place of red dots (Fig. 2).

The clinical presentation did not allow for a definite diagnosis. It was most consistent with the pseudopelade of Brocq, a controversial condition considered to be rather an end stage of various scarring alopecias than a separate entity [2–4].

Address for correspondence:
Kinga Kołcz, MD, Department of Dermatology, University of Rzeszow, Szopena 2, 35–055 Rzeszow, Poland; e-mail: kingakolcz@gmail.com

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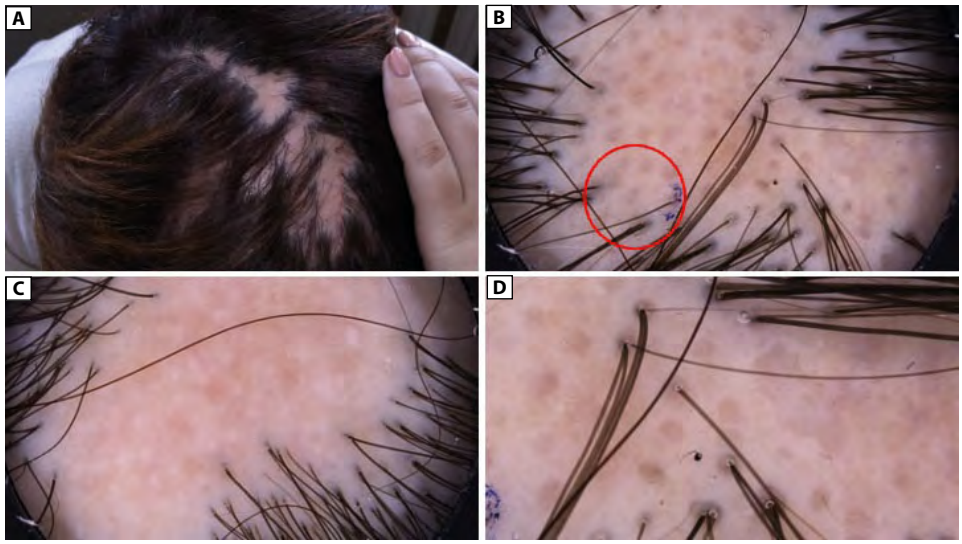

Figure 1. Clinical presentation (**A**); video dermoscopy (Canfield D200^{EVO}) performed in the parietal region — large pinkish area with fibrotic white dots and discrete honeycomb pigment pattern. No hair follicles are visible in the centre of the patch (**B**); video dermoscopy (Canfield D200^{EVO}) performed in the occipital region — red and yellow dots, corresponding with hair follicle orifices, are present. The site selected for biopsy is marked with a red circle (**C**, **D**)

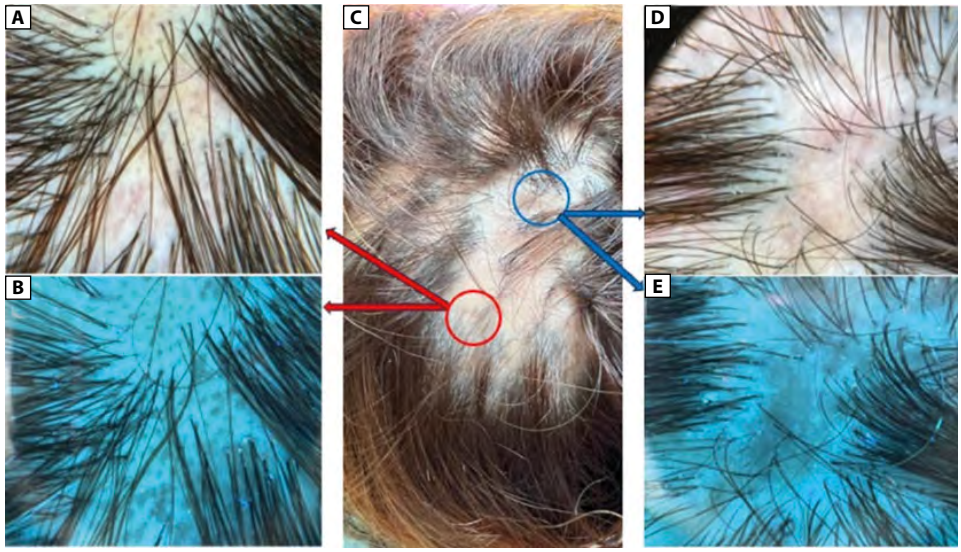

Figure 2. Comparison of the dermoscopic and ultraviolet (UV)-enhanced dermoscopic findings in the parietal and occipital location; Dermoscopy of the occipital part (marked with red circle) showing red and yellow dots (Dermlite DL5, polarized mode) (**A**); UV-enhanced dermoscopy enabled better visualization of the hair follicle ostia as dark round and oval structures (**B**); Clinical presentation (**C**); dermoscopy of the parietal part with discrete honeycomb pigment pattern (Dermlite DL5, polarized mode) (**D**); UV-enhanced dermoscopy showing an irregular structureless darkly pigment area in the centre of the alopecic patch, no round/oval structures corresponding to follicular ostia are visible (**E**)

Therefore, the decision to take a biopsy from the most representative region was made. Considering the presence of reddish dots under trichoscopy in the occipital region, this site was selected for biopsy and direct immunofluorescence. The histopathological examination showed dermal perivascular and peri adnexal infiltrate composed of lymphocytes and histiocytes; atrophic epidermis with vacuolar degeneration of the basal layer and some apoptotic keratinocytes; flattening of the rete ridges; lymphocytic infiltrate around hair follicles and vessels; as well as hyperkeratosis with condensed follicular keratotic plugs (Fig. 3). Fibrosis and scarring of the dermis were also present. Histopathology favoured the diagnosis of DLE. In extended laboratory work-up, low titters (1:160) of anti-nuclear (dsDNA) and

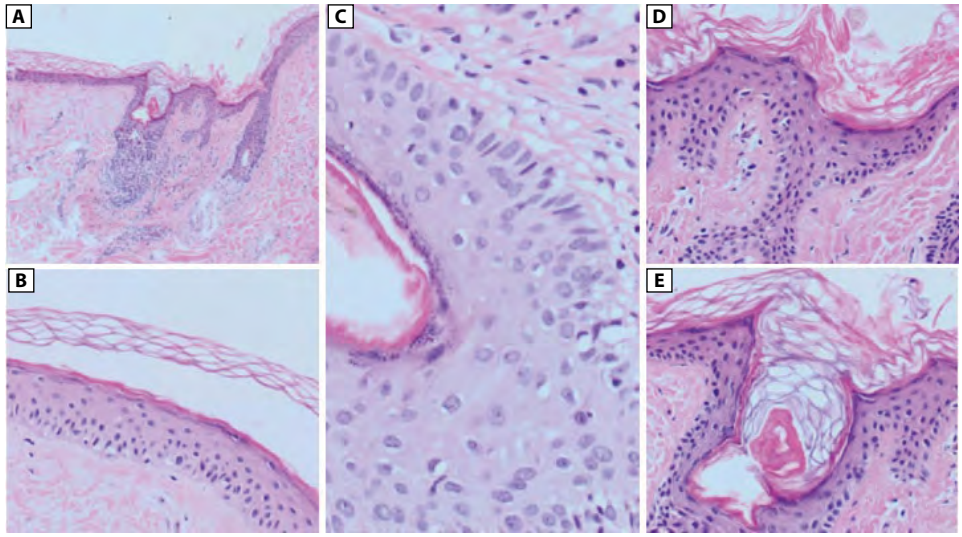

Figure 3. Histopathology. General overview (HE staining, magnification 100×) (**A**); epidermal atrophy and vacuolisation of the basal layer (HE staining, magnification 400×) (**B**); perifollicular lymphocyte infiltration (HE staining, magnification 400×) (**C**); apoptosis and vacuolization (HE staining magnification 400×) (**D**); hyperkeratosis at the hair follicle ostium (HE staining, magnification 400×) (**E**)

anti-mitochondrial (AMA) antibodies were detected. Direct immunofluorescence was negative. Complement components C3 and C4 were within reference values.

DISCUSSION

The differential diagnosis of scaring alopecia can be challenging and requires invasive biopsy. Dermoscopy is a non-invasive imaging method that is increasingly used for the evaluation of inflammatory skin conditions (inflammoscopy) and scalp diseases (trichoscopy) [5, 6].

When used to examine the scalp, this method can provide valuable assistance in the clinical differential diagnosis of different types of hair loss, both scarring alopecias (e.g. lichen planopilaris, DLE, frontal fibrosing alopecia), and non-scarring alopecias (e.g. alopecia areata, androgenetic alopecia). DLE affects the hairy scalp in up to 60% of patients [7, 8]. It accounts for about 30–40% of all scarring alopecias and about 60% of primary lymphocytic alopecias [2]. Despite such a high prevalence of conditions with permanent hair loss, one of the most common mistakes clinicians still make is taking biopsies from areas with completed scarring, as these areas are the easiest to identify. A scalp biopsy should be taken from an area where the hair follicles are affected by the inflammatory process, but still present [7].

The issue of dermoscopy-guided biopsies in scarring alopecias was initially raised by Miteva and Tosti [9]. The authors analysed 80 patients with cicatricial hair loss treated over 2 years at the Department of Dermatology, University of Miami. Patients with central centrifugal alopecia (CCCA), frontal fibrosing alopecia (FFA), lichen planopilaris (LPP), DLE and folliculitis decalvans (FD) were included in the study. Dermoscopy was used to visualize features indicative of disease activity at the margins of hairless patches. Identification of these features allowed for a definitive diagnosis in 95% of cases. When DLE is suspected, the authors strongly recommend taking a biopsy from a site showing follicular red dots under trichoscopy. On histopathological examination, follicular red dots correspond to dilated follicular ostia obstructed by keratin deposits and surrounded by dilated vessels and extravasated erythrocytes [9]. In DLE, these features are indicative of perifollicular infiltration with/without perifollicular fibrosis.

In recent years, the dermoscopic features of DLE have gained interest and have been reported by many other authors. These include red dots, large yellow dots, reduced numbers of follicles, whitish patchy scales, arborising vessels, follicular plugs and speckled pigmentation [10–13]. A summary of these features, including a division into the active and end-stage phases of DLE, is presented in Table 1.

Knowing the dermoscopic features of the active phase of the disease, it is possible to select the most diagnostic site for taking a skin specimen. This is particularly important in cases of atypical clinical presentation, in which clinical-histopathological correlation is extremely important.

Recently, there has been growing interest in UV-enhanced dermoscopy. UV light emitted by a Wood's lamp (340–450 nm) may be useful in the differential diagnosis of conditions such as tinea capitis due to *Microsporum canis* or erythrasma, a bacterial infection caused by *Corynebacterium minutissimum* [14, 15]. The increasing availability of dermoscopy/trichoscopy combined with UV light with a wavelength of 365 nm potentially opens up new possibilities in

Table 1. Early and late stages of DLE

Early (active) stages of DLE [15]	Late stages of DLE [15]
Thick arborizing vessels	Thick arborizing vessels
Big yellow dots	Yellow dots with thin spide-like vessels
Gentle scaling	Milky red areas
Scattered brown discoloration	White patches
Follicular red dots	Loss of sebaceous lobules
Reduced numbers of follicles	Absence of follicular orifices
Follicular keratotic plug	Chrysalides and rossetes [16, 17]
Peripilar sign [16] (brown hue around the hair follicle)	

DLE — discoid lupus erythematosus

the differential diagnosis of skin diseases, and thus a new direction for research. Recently, Pietkiewicz and Navarrete-Dechent described a bright-blue fluorescence of the burrow and a bright-green fluorescence of scabies mites under UV-dermoscopy [18].

In the presented patient, the use of UV-enhanced trichoscopy enabled better visualization of the follicular ostia and confirmed the initial selection of the biopsy site. It should be emphasized that the early phase of DLE, without clearly marked scarring, requires early diagnosis, as prompt implementation of appropriate treatment may prevent progression to the chronic phase and the development of permanent hair loss [19].

CONCLUSION

In scarring alopecias, early diagnosis and management are crucial to prevent permanent hair loss. Dermoscopy (trichoscopy) is a non-invasive imaging method of use for the evaluation of scalp conditions. It is postulated, that in all cases of alopecia, picking the spot for an invasive procedure of biopsy should be guided by dermoscopy (trichoscopy).

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

Kinga Kołcz, Magdalena Żychowska, and Ewa Kaznowska declare that they have no conflict of interest. Adam Reich has worked as a consultant or speaker for AbbVie, Bioderma, Celgene, Chema Elektromet, Eli Lilly, Galderma, Janssen, Leo Pharma, Medac, Menlo Therapeutics, Novartis, Pierre-Fabre, Sandoz, and Trevi, and participated as Principal Investigator or Subinvestigator in clinical trials sponsored by AbbVie, Drug Delivery Solutions Ltd, Galderma, Genentech, Janssen, Kymab Limited, Leo Pharma, Menlo Therapeutics, MetrioPharm, MSD, Novartis, Pfizer, and Trevi. Adam Reich is a member of the journal's Editorial Board.

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

None.

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