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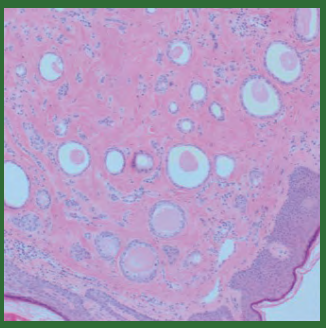

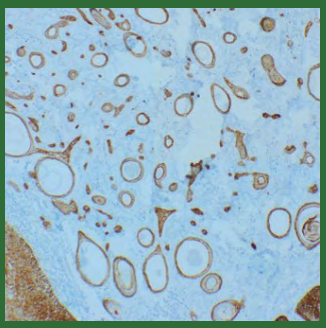

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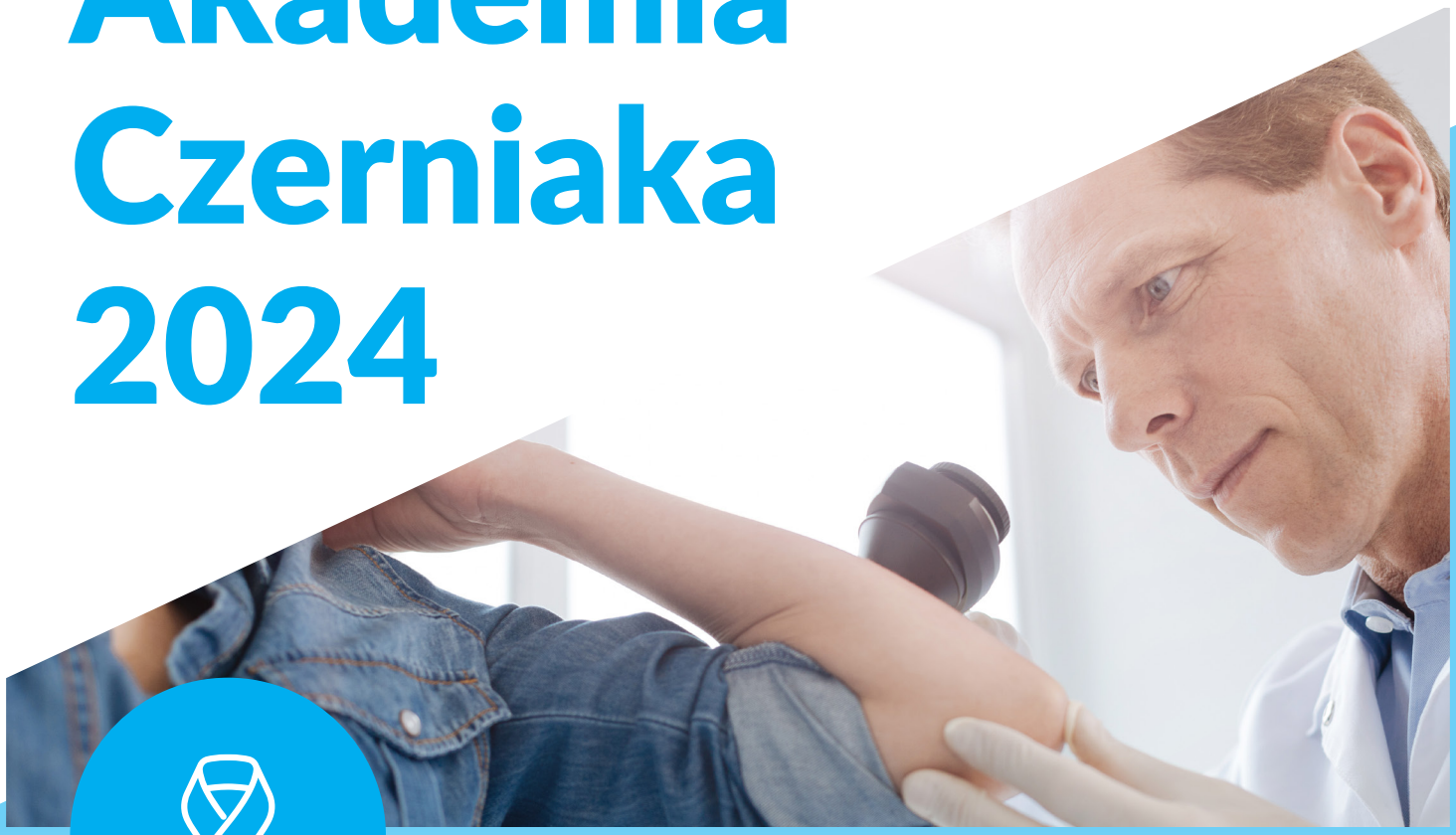

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Study of the effect of probiotics on the therapeutic effect obtained in the reduction of allergic symptoms in patients diagnosed with atopic dermatitis

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ABSTRACT

Introduction: Atopic dermatitis (AD) is a chronic inflammatory skin disease posing a significant burden on healthcare resources and patients' quality of life. It is a complex disease with a wide spectrum of clinical presentations and combinations of symptoms. Atopic dermatitis affects up to 20% of children and up to 3% of adults. Recent data show that its prevalence is still increasing, especially in low-income countries. This study aimed to check whether the use of probiotic therapy affects the reduction of allergic symptoms in patients diagnosed with AD.

Material and methods: Questionnaires of 70 respondents diagnosed with AD who took a probiotic for at least 5 days were analysed. To conduct the study, an anonymous, original survey was used in the form of a form created on Google Drive consisting of 19 questions with the possibility of answering both single and multiple choice and with the possibility of providing your own answer.

Results: The most beneficial strains affecting the reduction of allergic symptoms are bacteria of the genus *Lactobacillus*. The average duration of use of probiotic therapy to reduce allergic symptoms is from 2 weeks to 3 months.

Conclusions: The study showed that the implementation of probiotic therapy shortens the duration of therapy for AD and reduces allergic symptoms such as redness, itching of the skin and allergic rhinitis co-occurring in patients with AD.

Forum Derm. 2024; 10, 2: 35–41

Keywords: atopic dermatitis, probiotics, *Lactobacillus*, *Bifidobacterium*

INTRODUCTION

Atopic dermatitis (AD) is a chronic disease and the number of potential treatment options is growing, however, they are typically associated with immunosuppressive or immunomodulating effects, and do not guarantee a permanent cure [1]. Atopy is defined as the heritable tendency to produce immunoglobulin E antibodies in response to small amounts of common environmental proteins such as pollen, house dust mites and food allergens [2].

Probiotics are live microorganisms that, when consumed in a certain amount, exert beneficial effects on the body by improving the balance of the intestinal ecosystem [3]. The microorganisms with a positive effect on the general condition of the skin include especially lactic acid bacteria of the genus *Lactobacillus* and *Bifidobacterium* [4]. It has been shown that the use of probiotic preparations reduces inflammation due to the reduction of INF-γ, IL-4 and Th17 cytokines in splenic CD4+ T lymphocytes and increases the expression of IL-10 and cytokines associated with regulatory T cells in mesenteric lymph nodes [5]. Probiotics have an inhibitory effect on the maturation of dendritic cells, thus blocking the differentiation of naive T cells into Th2 lymphocytes, which contributes to the reduction of inflammation in the skin [5]. This study aimed to evaluate whether the use of probiotic therapy affects the reduction of allergic symptoms in patients diagnosed with AD.

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MATERIAL AND METHODS

To conduct the study, an anonymous, original survey was used in the shape of a form created on Google Drive consisting of 19 questions with the possibility of answering both single and multiple choice and with the possibility of providing your own answer. Respondents had the opportunity to select different versions of the answers.

The responses of 70 respondents diagnosed with AD who took a probiotic for a minimum of 5 days were analysed. Survey data was collected from January 18, 2022, to June 15, 2022. The author's survey was posted on social networking sites regarding the treatment of AD. The study was approved by the Ethical Committee of the Nicolaus Copernicus University in Toruń at the Ludwik Rydygier Collegium Medicum in Bydgoszcz No. 5/2022.

The criteria for inclusion of the respondents in the study were to answer all the questions asked in the author's questionnaire consisting of 19 questions, including 8 single-choice questions and 11 multiple-choice questions, including 10 questions with the possibility of giving their own answers. The criteria for inclusion in the study were the need to be at least 18 years old, a diagnosis of AD, and the need to take a given strain of probiotics for a minimum of 5 days. At the beginning, the questionnaire was completed by 76 correspondents, 6 of whom were excluded from the survey due to the failure to complete all the questionnaire questions: failure to provide symptoms of the disease, failure to provide the exact location of the atopic lesions, failure to provide information about other allergic symptoms such as rhinitis, redness or itching of the skin, failure to provide the location of allergic lesions, failure to provide pharmacological agents taken on a daily basis in the treatment of AD, failure to provide the exact type of probiotic strain in the treatment of AD, failure to specify the period of use of probiotic therapy to reduce allergic symptoms, failure to provide the exact time during which allergic symptoms have been reduced since the use of a given probiotic strain, failure to provide an answer regarding satisfaction with the implementation of probiotic therapy for the treatment of AD, failure to provide the source of information of the respondent regarding the possibility of including probiotic therapy in the treatment of AD.

Statistical analysis

The differences between the two nominal variables were analysed using the chi-square test. In statistical analyses, the significance level $p < 0.05$ was assumed. Analysis was performed using IBM SPSS Statistics version 24.

RESULTS

The study included 70 patients. Among the respondents were 64 (91%) women and 6 (9%) men. The 49% (n = 34) of respondents were between the ages of 21 and 30, 17% (n = 12) of respondents were aged 18 to 20 and 29% (n = 20) were aged 31 to 40, 3% (n = 2) were aged 41 to 50 years, and 3% (n = 2) were 51 to 60 years. 19% (n = 13) of respondents lived in the countryside 81% (n = 57) lived in cities of different sizes. 33% (n = 23) of respondents had secondary education and 59% (n = 41) had higher education. The 77 per cent of subjects (n = 54) surveyed had been diagnosed with AD for at least one year. The remaining subjects were diagnosed a year ago (15%; n = 10), half a year ago (1%; n = 1), a month ago (4%; n = 3), a week ago (1%; n = 1), a few days ago (1%; n = 1) (Tab. 1).

Table 1. Characteristics of the study population

Criteria	Number of respondents	Percentage of respondents
Sex		
Woman	64	91%
Man	6	9%
Age		
From 21 to 30 years	34	49%
From 18 to 20 years	12	17%
From 31 to 40 years	20	29%
From 41 to 50 years	2	3%
From 51 to 60 years	2	3%
Domicile		
Village	13	19%
Cities of all sizes	57	81%
Education		
Average	23	33%
Higher	41	59%
AD diagnosis time		
For at least one year	54	77%
A year ago	10	15%
Half a year ago	1	1%
A month ago	3	4%
A week ago	1	1%
A few days ago	1	1%

AD — atopic dermatitis

The most common symptoms of the disease were dry skin (86%; n = 60), skin irritation (83%; n = 58), itching (83%; n = 58), the appearance of red spots (76%; n = 53) and itchy eruptions (64%; n = 45). Less frequently, the disease was manifested by the appearance of lichen-like papules (24%; n = 17) and eruptions (17%; n = 12).

Atopic lesions were most often located on the dorsal surface of the hands, feet (54%; n = 38), face, lip, and neck (40%; n = 28), and on the skin of the eyelids (39%; n = 27). They were less common in the upper chest (31%; n = 22) or shoulder girdle (29%; n = 20).

Table 2. Clinical characteristics of the study population

Criteria	Number of respondents	Percentage of respondents
Symptoms		
Dry skin	60	86%
Skin irritation	58	83%
Itching	58	83%
The appearance of red spots	53	76%
Itchy eruptions	45	64%
Lichen-like papules	17	24%
Eruptions	12	17%
Localization of atopic lesions		
On the dorsal surface of the hands, feet	38	54%
Face, lip, neck	28	40%
On the skin of the eyelids	27	39%
In the upper chest	22	31%
Shoulder girdle	20	29%
Allergic symptoms		
Rhinitis, redness or itching of the skin	59	84%
Dry skin	51	73%
Itching	48	69%
Irritated skin	45	64%
Red spot	41	59%
Itchy eruptions	31	44%
Excoriations	12	17%
Red papules	10	14%
Localization of allergic lesions		
On the hands and feet	37	53%
In the face area	36	51%
In the upper torso area	24	34%
In the elbow and axillary bends	23	33%
Around the shoulder girdle	16	23%
Around the lower torso	14	20%
AD substrate		
Non-allergic dermatitis		
Woman	7	10.9%
Man	4	66.7%
Allergic dermatitis		
Woman	57	89.1%
Man	2	33.3%
Use of probiotic therapy in the past to alleviate AD symptoms	39	56%

AD — atopic dermatitis

The majority of respondents claimed that they had allergic symptoms such as rhinitis, redness or itching of the skin (84%; n = 59). The most common allergic symptoms are dry skin (73%; n = 51), itching (69%; n = 48), irritated skin (64%; n = 45), red spots (59%; n = 41) and itchy eruptions (44%; n = 31). Less frequent were excoriations (17%; n = 12) and red papules (14%; n = 10).

Allergic lesions were most often located on the hands and feet (53%; n = 37) and in the face area (51%; n = 36). Less often in the upper torso area (34%; n = 24), in the elbow and axillary bends (33%; n = 23), around the shoulder girdle (23%; n = 16), around the lower torso (20%; n = 14).

It is important to note the difference in the cause of AD. Non-allergic dermatitis (IgE-independent) was present in 10.9% (n = 7) of women and 66.7% (n = 4) of men. The occurrence of IgE-mediated AD with the presence of a large number of IgE antibodies and the IgE-antibody reaction caused by a given allergen manifested by allergic changes such as allergic rhinitis, redness or allergic itching of the skin was experienced by: 89.1% (n = 57) of women, including 33.3% (n = 2) of men (Tab. 2).

More than half of the respondents have used probiotic therapy in the past to relieve the symptoms of AD (56%; n = 39). Most often, the reduction of disease symptoms was observed during therapy with the following strains: *Lactobacillus* (59%; n = 41), less often with *Bifidobacterium* (28%; n = 20), *Streptococcus* (21%; n = 15), *Enterococcus* (18%; n = 13), *Saccharomyces* (18%; n = 13). No improvement during the implementation of probiotic therapy was reported by 31% (n = 22) of respondents (Fig. 1).

Most often, a reduction in allergic manifestations was observed during probiotic therapy with strains: *Lactobacillus* (54%; n = 38), less often with *Bifidobacterium* strains (23%; n = 16), *Streptococcus* (13%; n = 9), *Enterococcus* (10%; n = 7), *Saccharomyces* (10%; n = 7). Reduction of allergic symptoms was not experienced by 31%, n = 22 of respondents (Fig. 2).

All respondents who were diagnosed with AD for less than a year and used probiotic therapy showed a reduction in the severity of allergic symptoms. Among subjects suffering from the disease for more than a year, this was smaller and amounted to 59% (n = 41). This difference was statistically significant (p = 0.014). According to the subjects, the time of probiotic therapy necessary to notice a reduction in the severity of allergic symptoms ranged from 2 weeks (28%; n = 20) to 3 months (31%; n = 22), less often a few days (5%; n = 3) or a year (Fig. 3).

The 62 % (n = 43) of respondents using it were satisfied with the probiotic therapy used in the treatment of AD. All respondents who had been diagnosed with AD less than one year were satisfied with probiotic therapy (100%; n = 70), the percentage of such subjects was lower among patients with a longer period of disease (48%; n = 34). This difference was statistically significant (p = 0.004).

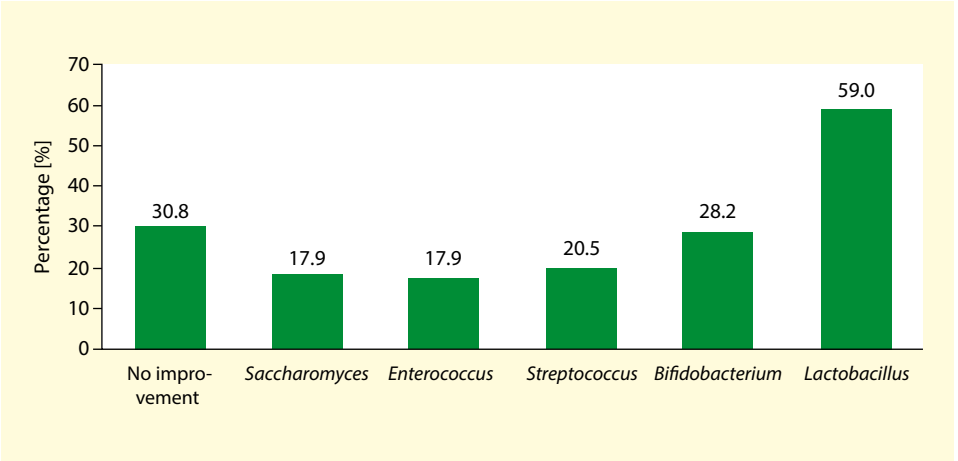

Figure 1. Types of probiotic strains that reduce the symptoms of atopic dermatitis

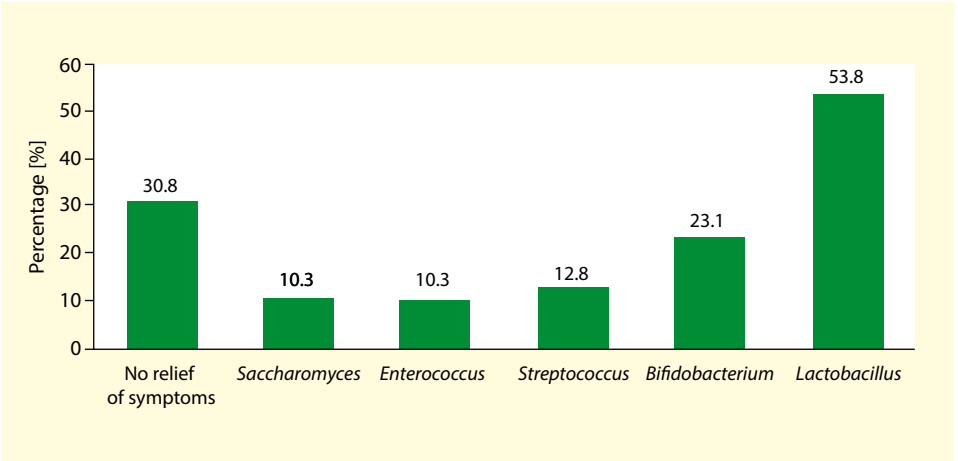

Figure 2. Types of probiotic strains that reduce the severity of allergic symptoms

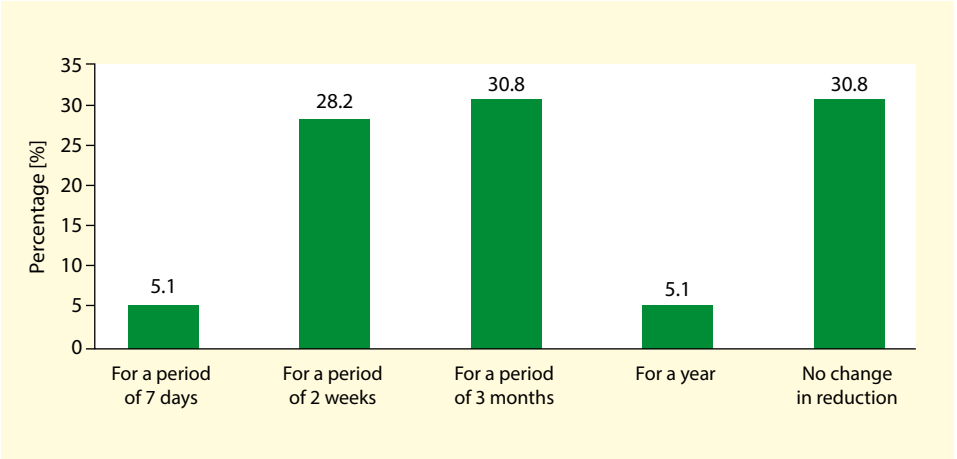

Figure 3. The duration of probiotic therapy to reduce the severity of allergic symptoms

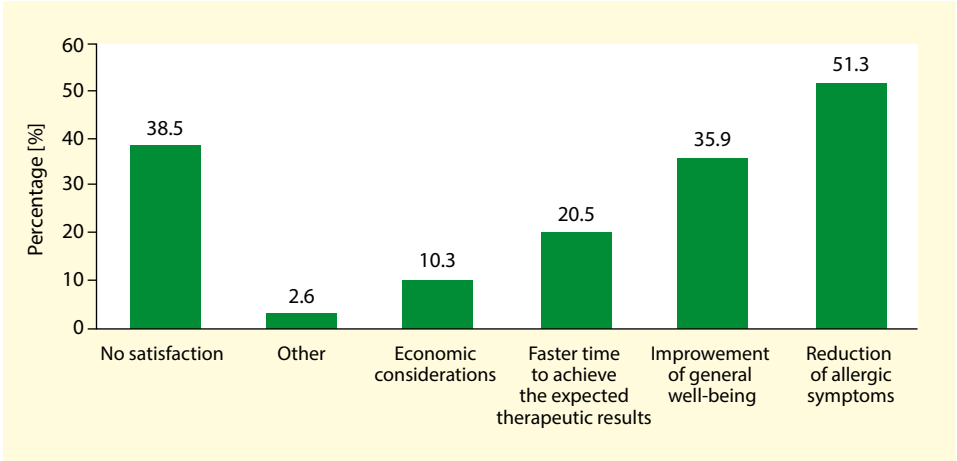

Figure 4. The time since the end of probiotic therapy from which allergic-type symptoms have decreased

The most common reason for satisfaction with the use of probiotic therapy in the treatment of AD was the reduction of allergic symptoms (51%; n = 36) and the overall improvement of well-being (36%; n = 25) (Fig. 4).

DISCUSSION

Atopic dermatitis is most often localized on the bent surfaces of the body, front and lateral neck, eyelids, forehead, face, wrists, back of feet and hands [6], which is confirmed by the majority of respondents. The latest research shows that the most effective pharmacological method in alleviating the local symptoms of atopy is emollients [7], which was also indicated by the majority of respondents in the survey (71%; n = 50). The reduction of itch sensitivity in patients with AD is attributed to the impairment of the epidermal barrier. The cause of this condition in individuals with AD is mutations in the filaggrin gene (FLG), which lead to decreased secretion of natural skin moisturizing factors [7]. Emollient therapy allows for the restoration of the damaged epidermal barrier, thereby reducing itching and skin dryness.

The implementation of probiotic therapy supports the treatment of atopy and contributes to the reduction of allergic symptoms. A significant portion of respondents (62%; n = 43) expressed satisfaction with the use of probiotic therapy in the treatment of AD, mainly due to the reduction of allergic symptoms (51%; n = 36), which were defined in the author's survey as dry skin, itching, irritated skin, red spots, itchy eruptions, excoriations, red papules. Probiotics, as living bacteria, can significantly contribute to the reduction of AD symptoms of various aetiologies. Several conducted studies, including meta-analyses, provide evidence supporting the use of probiotics as an effective method in supporting the treatment of allergic diseases [8]. Potential mechanisms explaining the health-promoting effects of probiotic bacteria may involve restoring the normal gut microbiome through the modulation of the intestinal immune system and displacing potential pathogens through competitive exclusion.

A study conducted by Mastrandrea et al. [9] demonstrated that the administration of a mixture of *L. acidophilus*, *L. delbrueckii*, and *Streptococcus thermophilus* for 30 days in patients with clinical symptoms of asthma and/or conjunctivitis, rhinitis, urticaria, AD, food allergy, and irritable bowel syndrome resulted in a reduction in the number of circulating CD34+ haematopoietic precursor cells (HPCs). Based on this, it was inferred that an increase in circulating CD34+ HPCs is a factor in systemic allergic inflammation, suggesting that these cells may become a therapeutic target in the treatment of allergic diseases, including AD. Another analysis of flow cytometry subsets of peripheral blood lymphocytes in patients receiving probiotics showed that under the influence of probiotic therapy, the percentage of CD4+ and CD25+ lymphocytes decreased, while the percentage and absolute number of CD8+ lymphocytes increased, indicating the immunoregulatory effect of probiotics in AD patients. The authors suggest that the lymphoid tissue associated with the intestines, which remain in direct contact with probiotic bacteria, plays a role in the modulation of immunological response. The study showed a relationship between the reduction in CD4+ percentage and the reduction of typical clinical manifestations of AD [10].

Regarding the type of probiotics, the most beneficial in AD therapy is the use of gram-positive, anaerobic lactic acid bacteria *Lactobacillus* and *Bifidobacterium* [11], which is also confirmed by the data obtained in the conducted study. Lactic acid bacteria, including *Lactobacillus* and *Bifidobacterium*, exhibit a multifaceted effect on the human body [11]. They contribute, among other things, to maintaining a healthy gut flora, regulating gut motility,

improving the absorption of certain nutrients, reducing toxic metabolites, and preventing gastrointestinal infections caused by *Salmonella typhimurium*, *Staphylococcus aureus*, *Escherichia coli*, *Clostridium perfringens*, and *Clostridium difficile* [11]. These findings are confirmed by studies conducted by Hoang et al. [12], which demonstrate that *Lactobacillus rhamnosus* significantly improved the quality of life in AD patients. These strains contributed to the alleviation of skin symptoms and irritations during the day and night in supplemented individuals [12].

The results of the study indicate that the most effective strains for reducing allergic symptoms are bacteria from the *Lactobacillus* genus. Majama and Isolauri [13] linked the improvement of clinical parameters in patients with AD receiving *Lactobacillus rhamnosus* preparation with a decrease in the concentration of tumour necrosis factor α (TNF-α) and α_1-antitrypsin in the stool. In contrast, Rosenfeldt et al. [14] observed a decrease in the concentration of eosinophil cationic protein (ECP), and in subsequent years, researchers demonstrated an increase in the concentration of interleukin 10 in AD patients receiving *Lactobacillus GG* strain [15]. All these elements play a role in the comprehensive pathogenesis of AD, and the observed changes in their levels indicate the immunomodulatory effect of *Lactobacillus rhamnosus* on the body's inflammatory response. Studies on the regulation of the action of these cytokines and proteins may lead to the development of more effective methods of treatment and symptom alleviation in AD.

Most respondents reported that allergic symptoms were reduced most frequently within six months (18%; n = 13) and two months (21%; n = 15) after completing probiotic therapy. To observe changes in allergic symptom reduction, most surveyed individuals took probiotics for two weeks (28%; n = 20) or three months (31%; n = 22), less frequently for a few days (5%; n = 3) or one year. From available literature data, the time required for taking probiotics to reduce AD skin symptoms was about 56 days [16].

Clinical experience has shown that some patients with AD are resistant to conventional treatment methods such as emollients, corticosteroids, and other immunosuppressive drugs. The treatment of AD, depending on the severity of the disease according to the SCORing Atopic Dermatitis (SCORAD) scale, involves high-risk strategies for severe and serious adverse events. Therefore, it is necessary to seek alternative therapies, which is why researchers are interested in probiotics. Global literature provides numerous pieces of evidence for the effectiveness of probiotics in AD therapy in children [17–19], whereas data on the modulation of the immune system in adults with AD through probiotics use is limited. The effectiveness of probiotic therapy in adults with AD requires further research.

CONCLUSIONS

The study showed that all respondents who had been diagnosed with AD for less than a year and used probiotic therapy demonstrated a reduction in the severity of allergic symptoms. Among patients with the disease for more than a year, the reduction was smaller at 59%, which was statistically significant (p = 0.014). All respondents diagnosed with AD in less than a year were satisfied with probiotic therapy, while the percentage (48%) was lower among patients with longer disease duration. The difference was statistically significant (p = 0.004). The study also showed that Lactobacillus strains were more effective than Bifidobacterium strains in alleviating atopy symptoms. The study shows that the majority of the surveyed women had atopic changes caused by a concomitant allergic disease.

Article information and declarations

Acknowledgements

None.

Data availability statement

The study was based on an anonymous, proprietary questionnaire in the form of a Google Drive form consisting of 19 questions with the ability to make both single-choice and multiple-choice answers, and with the possibility of reply.

Ethics statement

Consent of the Bioethics Committee No. 5/2022 Nicolaus Copernicus University in Toruń at the Ludwik Rydygier Medical College in Bydgoszcz.

Author contributions

The largest contribution was made by the first author (50%). The contribution of the second and third authors in the creation of the review article was equal, accounting for 25% per author. The tasks performed by the authors included selecting the topic, conducting a literature review, performing an in-depth analysis of the subject, and writing the manuscript.

Conflict of interest

The authors declare no conflict of interest.

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Supplementary material

None.

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ORIGINAL ARTICLE

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The application of repeated whole-body cryotherapy in atopic dermatitis and its impact on *Staphylococcus aureus* colonization — pilot study

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ABSTRACT

Introduction: *Staphylococcus aureus* can directly penetrate the *stratum corneum* and epidermis, which explains why this microorganism can disrupt the immune homeostasis of the skin and potentially influence skin diseases. Whole-body cryotherapy (W-BC) is one of the methods used in cryotherapy. It is well known that exposure to extremely low temperatures in the human body induces metabolic, hormonal, and thermoregulatory reactions. The study aimed to investigate whether repeated whole-body cryotherapy treatments would have an impact on the colonization of *Staphylococcus aureus* in individuals with atopic dermatitis (AD).

Methods: Fourteen adults with a mean age of 32 ± 10.8 and mild to moderate AD (mean of SCORAD index 36.5 points) were enrolled in the study. Whole-body cryotherapy comprised a total of 15 treatments, once a day.

Results: In the following research, it has been observed that whole-body cryotherapy treatments have an impact on the colonization of *Staphylococcus aureus* on the skin of patients with AD. It would be beneficial to include a larger sample size of AD patients, including both those receiving W-BC treatments and those who do not.

Conclusions: Based on the following research, W-BC can be considered an effective adjunctive method in the treatment of AD.

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Keywords: body cooling, cryotherapy, swabs, *Staphylococcus aureus*, atopic dermatitis

INTRODUCTION

The cause of eczema is multifactorial, involving both genetic and environmental factors. These factors affect both the epidermal and immune phenotypes, with T helper 17 (Th17) cells playing a contributing role. *In vitro* studies have demonstrated the impact of immune cell mediators, such as histamine, on keratinocyte differentiation, highlighting the close relationship between the epidermis and the immune system. Environmental exposure and individual susceptibility may impact multiple pathways, leading to varying degrees of dysfunction in the skin barrier and immune system regulation [1]. As a result, the common symptom of atopic dermatitis (AD) is pruritus, which can reduce patients' quality of life. Additionally, itching of the skin is exacerbated by emotional stress or sleep [2].

Research has indicated that individuals with atopic dermatitis possess a less diverse skin microbiome, which is identified by an elevated abundance of *Staphylococcus aureus* (*S. aureus*). This, in turn, has been associated with the severity of the disease in patients with AD [3]. *Staphylococcus aureus* not only causes skin infection but also produces virulence factors such as biofilm, superantigens, α-toxin, and protein A. The biofilm's role is to protect pathogenic bacteria from host immune cells [4].

Whole-body cryotherapy (W-BC) is one of the methods used in cryotherapy. The procedure is based on the effect of a thermal stimulus at an extremely low temperature ranging from –100°C to –160°C for a short period, typically 2–3 minutes on the human body [5, 6]. Whole-body cryotherapy has been used as a physiotherapy method for a long time,

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utilizing cryogenic temperatures (below –100°C) to induce and exploit physiological reactions in the human body to extreme cold. This action occurs in two stages. The first phase is characterized by stimulation of the sympathetic nervous system, resulting in vasoconstriction of the blood vessels in the skin and subcutaneous tissue. Blood pressure and metabolic activity increase as a result of the body's defensive reaction to the cold, although temperature decreases. Vasoconstriction leads to tissue cooling and poorer oxygen and nutrient supply, slowing down metabolic processes. This stage is relatively short. Then, there is vasodilation and tissue hyperaemia [5–7].

Increased blood flow and oxygenation of the muscle tissue can reduce lactate and histamine levels, increase bradykinin and angiotensin levels, and stimulate the release of endogenous beta-endorphins [7, 8]. The intended effect of this cold exposure is to reduce pain, inflammation, and post-traumatic swelling [5, 6]. Cryotherapy has also shown a marked effect on the psychological condition of the patient, leading to a more positive attitude and mood. Many individuals experience a sense of relaxation, calmness, and overall relief. Physical relaxation is also reported as a beneficial effect. Discomfort associated with pain and fatigue decreases, despite their intensification before the treatment. The state of well-being persists for several hours after the procedure, or even longer. The physiological benefits of exposure to extremely low temperatures have practical applications in biological rejuvenation, various sports disciplines, and the treatment of anxiety and depression [5–7].

The study aimed to investigate whether repeated whole-body cryotherapy treatments would have an impact on the colonization of *S. aureus* in individuals with AD.

MATERIAL AND METHODS

Patient characteristics

This study does not include randomization (single-arm clinical trial). The participants were recruited *via* a posted advertisement at the health clinic in Krakow. Inclusion criteria included age over 18 years, no contraindications to W-BC treatment and clinical diagnosis of atopic disease (mild to moderate). Study exclusion criteria included: lack of informed consent for the study; patients being treated for AD with phototherapy, cyclosporine A, oral corticosteroids, topical calcineurin inhibitors such as pimecrolimus and tacrolimus; patients during or after immunotherapy; children and adolescents under 18 years of age; lactating mothers; pregnant women; and patients with inflammatory, infectious, autoimmune, or cancerous diseases. An analysis of AD was conducted based on a questionnaire completed by patients in the presence of a dermatologist [8]. The questionnaire included basic information such as disease duration, symptoms, treatment, allergy diagnostics, and family history. The next stage involved assessing the level of AD advancement based on the SCORing Atopic Dermatitis (SCORAD) [9]. The major and minor AD criteria presented by Hanifin and Rajka [10] were also taken into consideration. Fourteen adults with a mean age of 32 ± 10.8 (7 men and 7 women) and mild to moderate AD (mean of SCORAD index 36.5 points) were enrolled in the study. The subjects were adults who lived in a big city and had been suffering from AD for a long time. Most of them experienced disease exacerbations every few months, and the severity of AD showed annual seasonality [8].

The study was conducted by the Declaration of Helsinki. All subjects gave their informed consent for inclusion before they participated in the study. The methodology of the scientific project was approved by the Bioethics Committee at the District Medical Chamber in Krakow, Poland, with opinion No. 239/KBL/OIL/2018. The study was registered at ClinicalTrials.gov under the number NCT03761199.

Sample collection

All samples were obtained from AD patients at the Centre for Microbiological Research and Autovaccines in Krakow, Poland. Nasal swab specimens were collected using a sterile cotton-tipped swab by approaching upward toward the top of both nares, followed by a 360° twist to cover the entire vestibule. In addition, skin swabs were taken from the AD patients by rolling a sterile cotton-tipped swab stick over their worst affected skin areas twice for at least 5 seconds [11] (right elbow flexion, left elbow flexions, neck, the area between the shoulder blades, lumbar region, right knee flexion, left knee flexion).

Laboratory analysis of *S. aureus* isolates

Bacterial cultures of the nasal and skin swabs were performed using standard laboratory techniques. The identity of *S. aureus* was confirmed based on colony morphologic features, coagulation of citrated rabbit plasma with EDTA, and production of clumping factor and protein A [11]. Bacterial growth was classified as follows: (0) no bacteria, (1) single < 10 CFU/mL, (2) few 11–50 CFU/mL, (3) plentiful 50–200 CFU/mL, (4) connected uncounted > 200 CFU/mL.

Whole-body cryotherapy procedures

Whole-body cryotherapy comprised a total of 15 treatments, once a day, at the Malopolska Centre for Cryotherapy, al. Pokoju 82, in Krakow, Poland. After consulting with a physician to exclude contraindications for W-BC, patients were referred for treatments. Patients entered the cryogenic chamber wearing special shoes, thick socks, shorts, gloves,

Table 1. The skin swaps measured before the first treatment (I), after the 15th treatment (II) and after 3 weeks from the end of W-BC therapy (III)

Part of the body	I	II	III	p-value
		M (Q25–Q75)		
1. Nasal swap right side	1 (0–2.75)	1.5 (0–3)	1.5 (0–3)	II *vs.* I III *vs.* I
2. Nasal swap left side	1.5 (0.25–2)	2 (0.25–3)	2 (0.25–3)	II *vs.* I
3. Right elbow flexion	1 (0–3)	1 (0–1.75)	1 (0–1.75)	NS
4. Left elbow flexions	0 (0–2.5)	0.5 (0–1)	0.5 (0–1)	II *vs.* I III *vs.* I
5. Neck	0 (0–1)	0 (0–1)	0 (0–1)	NS
6. The area between the shoulder blades	0.5 (0–1)	0 (0–1)	0 (0–1)	NS
7. Lumbar region	0 (0–1)	0.5 (0–1)	0.5 (0–1)	II *vs.* I III *vs.* I
8. Right knee flexion	1 (0–1.75)	1 (0–1)	1 (0–1)	II *vs.* I III *vs.* I
9. Left knee flexion	0.5 (0–1)	0.5 (0–1)	1 (0–1)	II *vs.* I III *vs.* I

(I–III) — measurement number; *vs.* — *versus*; NS — non-statistical; $p < 0.0001$; M — median and (Q25–Q75) the value of the lower and the upper quartile of classification of bacteria; (0) — no bacteria, (1) — single < 10 CFU/mL; (2) — few 11–50 CFU/mL, (3) — plentiful 50–200 CFU/mL, (4) — connected uncounted > 200 CFU/mL

and headwear. To acclimate the body to low temperatures, patients spent 1.5 minutes in the main chamber on the first day, 2 minutes on the next day, and then 3 minutes for the remainder of the therapy. The W-BC sessions took place during the winter of 2018/2019. Patients refrained from using local anti-inflammatory preparations and systemic antihistamine drugs for one week before the therapy and throughout the study. Participants began the cooling process in the vestibule, where the temperature was –60°C, for 30 seconds. They then proceeded to the main chamber, where the temperature was –120°C. Patients were continuously monitored by an operator inside the chamber using thermal glass and intra-chamber monitoring. A phonetic communication system allowed the operator to inform patients about the remaining treatment time. In case of feeling unwell, patients had access to an alarm button and an exit device designed to open the door from the inside [8].

Statistical analysis

Non-parametric statistics (Wilcoxon signed-rank test) were used to compare post-treatment data with the baseline due to the small number of participants and the lack of normal data distribution. Throughout the subsequent sections and tables, the median (M) and the values of the lower and upper quartiles (Q25–Q75) are reported. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using Statistica 13 software (StatSoft, Inc., USA).

RESULTS

Eight out of fourteen patients completed the treatment period (5 women and 3 men). Two patients discontinued the study due to worsening dermatitis, while the other four patients left for reasons unrelated to their skin condition. In one subject with AD, no *S. aureus* was detected in the tested swab areas. In the remaining individuals, MSSA bacteria were present, and the result depended on the swab site and the number of W-BC procedures [8].

Significant differences were observed in the nasal swab samples, showing an increasing trend in the number of *S. aureus* compared to the pre-W-BC result ($p < 0.0001$). On the other hand, in exposed body parts such as the neck and the area between the shoulder blades, no statistically significant changes were observed, but a decreasing trend was noticed. However, in covered body parts such as the lumbar region, left and right knee flexion, and the exposed left elbow flexion during cryotherapy, an increase in the number of *S. aureus* was observed when comparing the second and third measurements to the pre-W-BC state ($p < 0.0001$), as shown in Table 1.

DISCUSSION

The presented study aimed to examine the impact of a series of W-BC treatments on *S. aureus* colonization in individuals with AD. There is very limited data in the available literature regarding the use of whole-body cryotherapy in dermatological issues, including AD therapy. To the best of the authors' knowledge, this study is the first to demonstrate the influence of low temperatures on *S. aureus* colonization in patients with AD.

It is estimated that *S. aureus* is present in over 90% of AD skin lesions. In contrast, only 5% of healthy individuals are carriers of this organism, with the main site of colonization being the nose [11]. In the following study, only one subject

with AD did not show any detectable *S. aureus* in the tested swab areas, while the remaining individuals had MSSA bacteria detected, consistently confirmed in each swab sample. The subjects were carriers of *S. aureus*, as indicated by the presence of the bacteria consistently.

It is widely known that exposure to extremely low temperatures in the human body induces metabolic, hormonal, and thermoregulatory reactions. Low temperatures also stimulate the sympathetic nervous system and cause vasoconstriction, which persists for about a minute after the procedure. Following the treatment, the dilation of internal organ blood vessels reduces the levels of lactate and histamine, alleviates pain and has a positive influence on morphological, rheological and biochemical blood parameters [5–8, 12]. The lowering of body temperature also leads to a decrease in nerve impulse transmission. Another significant effect of prolonged cold exposure is the increased secretion of thyroid and adrenal hormones, as well as an elevated cellular metabolism. The impact on sensory receptors results in reduced pain sensations, as nerve impulses do not reach the neural cortex. Additionally, cold exposure activates the "endogenous opioid system", responsible for the production of β-endorphins, which are endogenous substances similar to morphine [5–8]. These findings explain the observed beneficial changes in skin parameters in previous studies. The series of W-BC treatments reduced skin irritations, including itching and inflammation (a mean SCORAD index decreased after cryotherapy treatments) in patients with AD. Furthermore, in healthy and AD individuals, cryotherapy did not lead to any adverse effects and was well tolerated [8, 9].

During W-BC treatments, the skin temperature rapidly decreases. The lowest temperatures are observed on the forearms and lower limbs (calf), while the highest temperatures are found on the palms and the soles of the feet, as they are protected by gloves and socks [13]. As reported by Cholewka et al. [14], the decrease in skin temperature also depends on the magnitude of the low temperature that affects the body and the duration of time spent in the cryogenic chamber. In the present study, a decreasing trend in the number of *S. aureus* was observed in exposed areas, while a slight increase was noticed in the covered body parts. Comparing the measurements between the third and second sessions (in each of the tested body areas), it was observed that the number of *S. aureus* remained at the same level. This suggests that cryogenic temperatures may influence the activity of bacteria on the skin by inhibiting the proliferation of *S. aureus*, especially in areas of the body exposed to low temperatures.

CONCLUSIONS

Due to the limited sample size, the results of this study are considered hypothetical. Based on the present research, W-BC can be considered an effective adjunctive method in treating AD. W-BC treatments have an impact on the colonization of *S. aureus* on the skin of individuals with AD. Depending on the body area, a decreasing trend in the number of *S. aureus* (in exposed body areas) and an increasing trend (in covered body areas) were observed. However, there is still limited data available in the scientific literature regarding the impact of cryogenic temperatures on skin parameters in patients with AD. The present study has several limitations. It would be beneficial to include a larger sample size of AD patients, including both those receiving W-BC treatments and those who do not.

Article information and declarations

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Data availability statement

The data used to support the findings of this study are included in the article.

Ethics statement

The study was conducted by the Declaration of Helsinki. The methodology of the scientific project was approved by the Bioethics Committee at the District Medical Chamber in Krakow, Poland, with opinion No. 239/KBL/OIL/2018. The study was registered at ClinicalTrials.gov under the number NCT03761199. All subjects gave their informed consent for inclusion before they participated in the study.

Author contributions

Study concept and design — MK-Sz, AM, MK-M, KR; methodology and investigation — MK-Sz, AM, MK-M, KR; data collection — MK-Sz, AM, KR, MK-M; data analysis — MK-Sz, AM; writing-original draft preparation — MK-Sz; writing-review and editing — MK-Sz, AM. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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Supplementary material

None.

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VIA MEDICA

CASE REPORT

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Vulvar syringomas — an underrecognized condition

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ABSTRACT

Syringoma is a benign neoplasm originating from the eccrine ducts of the sweat gland. Lesions are most commonly located on the face. Rarely, do syringomas develop in the vulvar region, where they may be accompanied by persistent pruritus. The article presents the case of a 34-year-old female patient, in whom small nodules and pruritus of the vulva had persisted for approximately two years. The paper includes a description of the dermoscopic features of the skin lesions. The final diagnosis was made based on the histopathological examination. The paper also discusses the most used therapeutic methods in this rare entity.

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Keywords: vulvar syringoma, dermoscopy, dermatoscopy, pruritus vulvae

INTRODUCTION

Syringomas are benign neoplasms of the adnexa, most commonly presenting as multiple skin-coloured nodules located on the face, especially on the lower eyelids, neck, and trunk. Uncommonly, the occurrence of syringomas is limited to the vulva, without involvement of extra-genital locations [1].

CASE REPORT

A 34-year-old woman presented to the Department of Dermatology with a two-year history of periodically itchy lesions in the form of several millimetre nodules located on the labia majora. In addition, the patient reported an occasional, peri-menstrual swelling in the affected area. A dermatological examination revealed the presence of confluent flesh-coloured nodules extending from the posterior conjunctiva of the labia majora to the urethral region (Fig. 1A). Videodermoscopic examination (Canfield D200^{EVO}) showed a reticulated network of thin telangiectatic blood vessels accompanied by multifocal areas of hypopigmentation (Fig. 1B, black arrows) and numerous shiny white clods located in clusters on a cobblestone-like background (Fig. 1B, 1C, blue arrows).

The clinical presentation did not allow for a definite diagnosis. Syringomas, steatocystoma multiplex and amyloidosis were considered in the differential diagnosis. A biopsy was taken for histopathological examination, which showed double-layered ductules, nests and small cysts of epithelial cells without atypia in fibrosing stroma. The final diagnosis of genital syringomas was unequivocally made (Fig. 2). The patient was informed about the benign nature of the condition.

DISCUSSION

Syringomas are benign adnexal tumours originating from the intraepidermal sweat duct of the eccrine gland. They are estimated to affect 1% of the population, with a predilection for women during puberty and the second or third decade of life [2]. Most cases are sporadic, but approximately 11.5% of patients may have a familial variant associated with an autosomal dominant mutation of 16q22 [3]. A higher incidence has also been observed in Down syndrome, Marfan syndrome, Ehlers–Danlos syndrome and in patients with diabetes [2].

Syringomas are generally not accompanied by additional symptoms. However, lesions located in the vulvar region may be susceptible to oestrogens. During the premenstrual phase, during pregnancy, in women using oral contraception, and during the summer months, nodules may tend to be swollen, giving a sensation of change in size. Pruritus may occur, as well [4].

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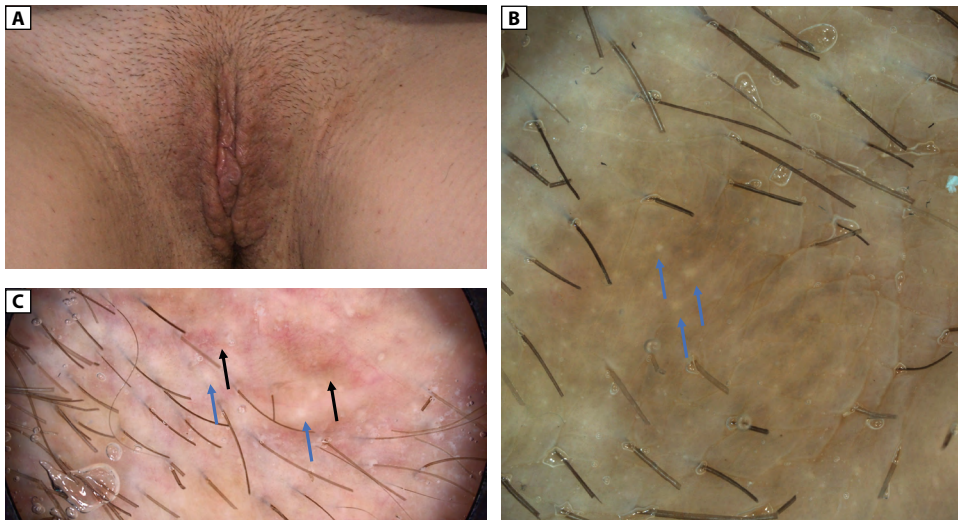

Figure 1. Clinical presentation (**A**); reticulated network of thin telangiectatic blood vessels (black arrows) and shiny white clods (blue arrows) (**B**); shiny white clods (blue arrows) (**C**)

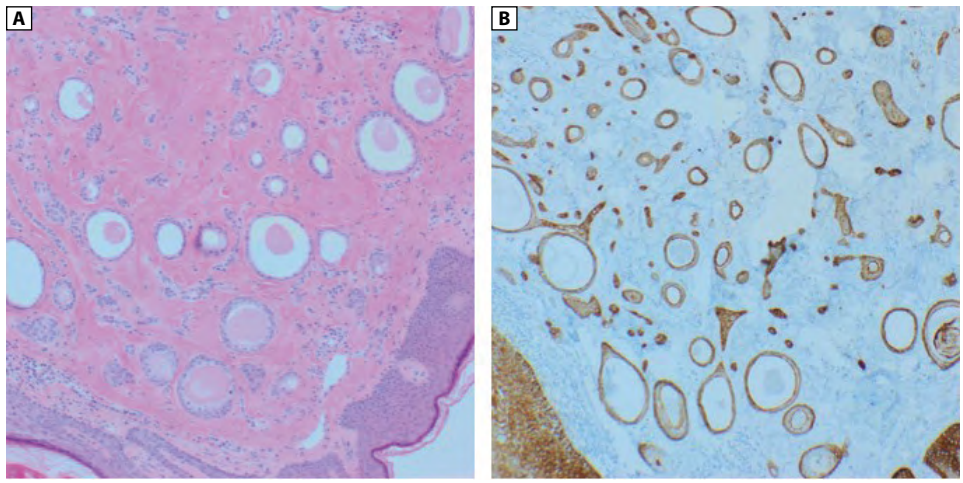

Figure 2. Syringomas — histopathological examination. Haematoxylin and eosin staining, magnification × 100 (**A**); immunohistochemical staining of cytokeratin (CK) 5.6, magnification × 100 (**B**)

Three clinical presentations of vulvar syringoma skin lesions have been identified. The most common presentation is that of multiple flesh-coloured or brownish papules located symmetrically on the labia majora. Cystic lesions or lichen planus-like plaques may also be present [5]. Cutaneous mastocytosis, fibrofolliculomas, velus hair cysts, steatocystoma multiplex, Fox–Fordyce disease, lichen simplex and lichen planus should be considered in the differential diagnosis [6].

Undoubtedly, the unspecific clinical presentation can be confusing both for gynaecologists and dermatologists. An unequivocal diagnosis is made on histopathological examination, which shows a dermal proliferation composed of cells arranged in nests and channels with fibrous stroma. Some of these channels have characteristic small tails of comma-shaped epithelioid cells, resembling tadpoles [1]. An auxiliary non-invasive method is being sought to make a preliminary diagnosis. For this purpose, dermatoscopy has been used, which showed the presence of shiny whitish-yellow oval or round structures on a pink background, histologically corresponding to small colloid deposits in cystic ducts. In addition, a reticulated vascular network consisting of short telangiectatic vessels accompanied by areas of hypopigmentation was reported in the literature [2, 7, 8].

Syringomas are benign tumours, usually asymptomatic. Their treatment is mainly for aesthetic reasons. There are various therapeutic options: cryosurgery, dermabrasion, chemical peels, electrocoagulation, surgical excision and lasers [9]. High-energy devices, such as carbon dioxide

laser, argon laser, and erbium-YAG laser are the most common choices. However, it is important to note that these methods may lead to the development of blisters or leave post-inflammatory hyperpigmentation, scarring, and delayed wound healing [10]. Aksoy Sarc and Onder [11] have also successfully used a yellow laser with a wavelength of 577 nm. Topical therapies reported so far include tretinoin and atropine [12, 13]. For syringomas located in the periorbital region, successful treatment attempts have been made using botulinum toxin type A in monotherapy or combination therapy with carbon dioxide laser or Erb-YAG laser [14, 15]. However, reports of the use of botulinum toxin for vulvar syringomas are lacking in the English-language literature.

CONCLUSIONS

Syringomas should be considered in the differential diagnosis of lesions occurring in the vulvar region. Dermoscopy can be used as an auxiliary method, but a definite diagnosis is made based on histopathological examination. In the authors' opinion, both dermatologists and gynaecologists must be aware of this entity to properly evaluate and treat patients with nodular skin-coloured lesions accompanied by vulvar pruritus.

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 integrity of the work as a whole, and have given their approval for this version to be published.

Conflict of interest

KK, MŻ, and AK declare that they have no conflict of interest. AR 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.

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VIA MEDICA

CASE REPORT

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Choose your biopsy site wisely — the utility of dermoscopy in the diagnosis of Bowen's disease of the face

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ABSTRACT

Precise assessment of facial lesions in photo-damaged skin could be challenging. A collision of benign, premalignant and malignant tumours is not uncommon. Selecting the biopsy site is fundamental for making a proper diagnosis. Therefore, biopsies should not be taken blindly but should be preceded by a detailed preliminary evaluation with dermoscopy, in particular. The article presents a case of a 78-year-old female patient, in whom dermoscopy-guided incisional biopsy of an irregular erythematous plaque led to the diagnosis of *in situ* squamous cell carcinoma.

Forum Derm. 2024; 10, 2: 50–53

Keywords: Bowen's disease, squamous cell carcinoma, dermoscopy guided biopsy, dermatosurgery, dermoscopy, dermatoscopy

CASE REPORT

A 78-year-old woman was referred to the Department of Dermatology for evaluation of a pink, scaly plaque of unknown duration located on the right zygomatic arch. She reported chronic occupational and recreational sun exposure over the years. The lesion had been treated with cryotherapy twice, however, it was still slowly growing. The patient reported a history of basal cell carcinoma (BCC) on the nose 6 years earlier and another lesion located above the current plaque that had been surgically removed. However, the histopathological diagnosis was not available.

On physical examination was observed an irregular ill-defined, oval-shaped plaque of a pink-to-red colour, measuring around 3 cm in diameter. There were also white-to-yellowish scales randomly distributed over the lesion (Fig. 1).

Dermoscopic examination showed sparse linear branched and dotted vessels irregularly distributed over the pinkish background. Patchy white-to-yellow fine scales were also seen. In the upper part of the lesion, a pinpoint erosion was present (Fig. 2, 3). At that point, an incisional biopsy was randomly taken from the upper part of the lesion.

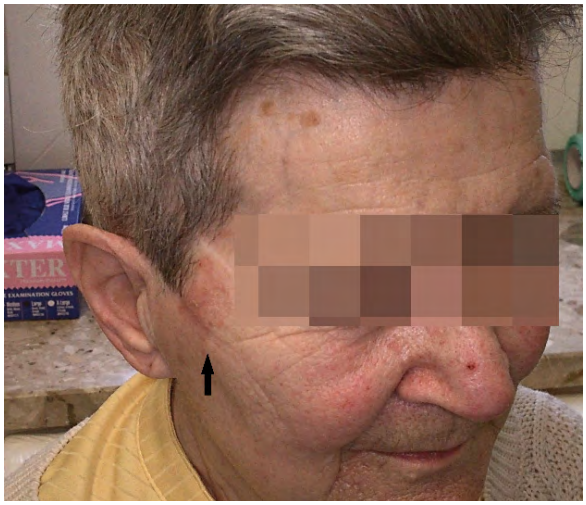

Figure 1. Clinical presentation — an ill-defined oval-shaped erythematous plaque on the right zygomatic arch

Histological examination showed degenerative changes due to chronic sun exposure: atrophy of the epidermis with low-grade dysplasia, lymphocytic-histiocytic inflammatory infiltrate around vessels of the superficial plexus and skin

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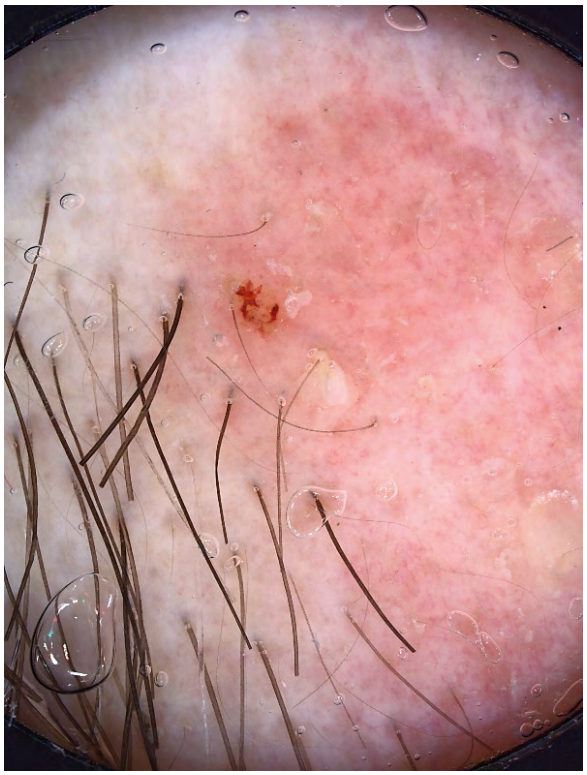

Figure 2. Dermoscopic presentation: sparse dotted and linear branched vessels randomly arranged over a pinkish background and patchy white-to-yellow scales. In the top left corner of the lesion, a pinpoint erosion is present

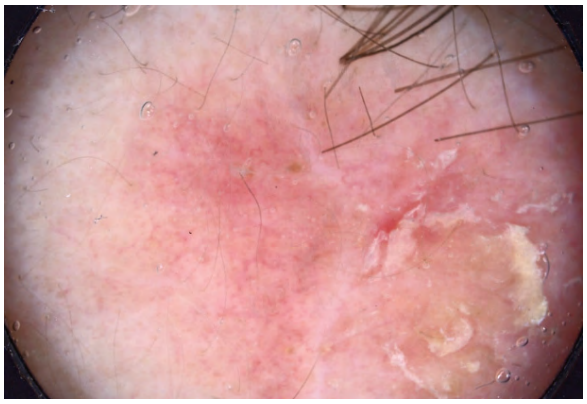

Figure 3. Dermoscopic examination showing the white-to-yellow surface scale

appendages, and stromal oedema. The findings were consistent with early actinic keratosis (Fig. 4).

The patient came for a follow-up visit a month later, after applying an exfoliating cream for a few days. A dermoscopic examination was performed once again and showed coiled vessels in a clustered arrangement in the lower part of the lesion, previously covered with scales (Fig. 5, 6). Because of a strong suspicion of squamous cell carcinoma *in situ*/Bowen's

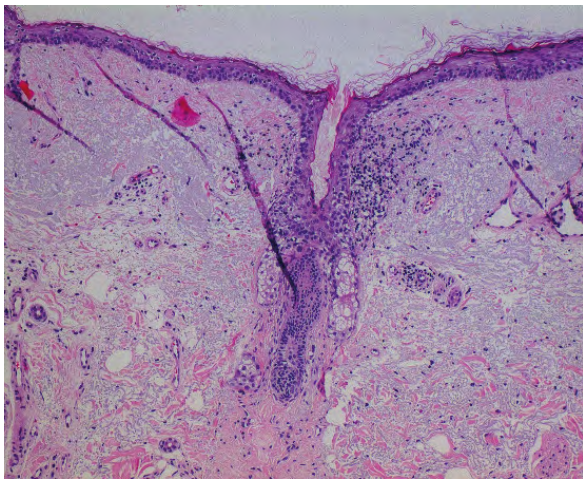

Figure 4. Histological view: atrophy of the epidermis with a low--grade dysplasia (actinic keratosis). Degenerative changes due to chronic sun exposure with no signs of invasive neoplasm

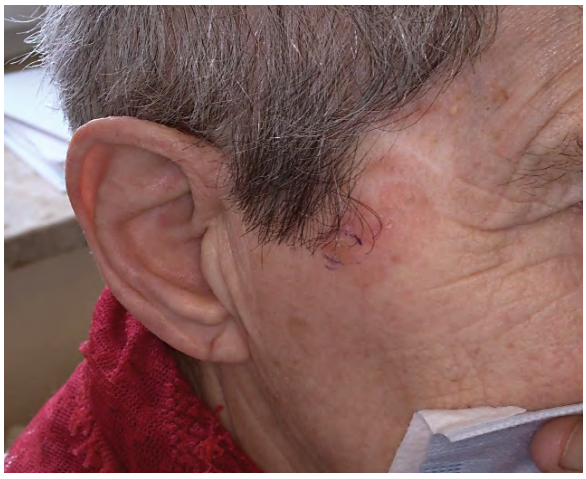

Figure 5. Clinical presentation of the patient at a follow-up visit. A scar after the first incisional biopsy is visible in the upper part of the lesion. The site for the second, dermoscopy-guided, incisional biopsy is circled in blue

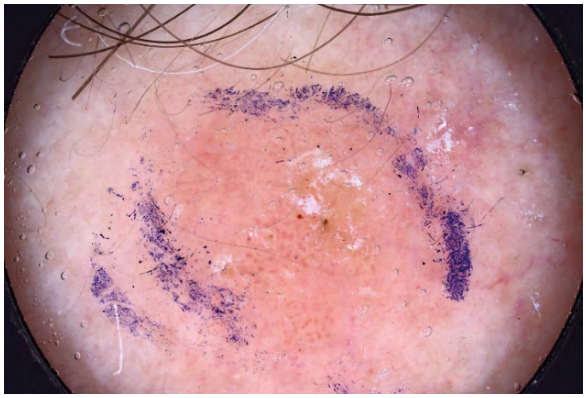

Figure 6. Dermoscopic view of the site selected for biopsy: coiled vessels in a clustered arrangement

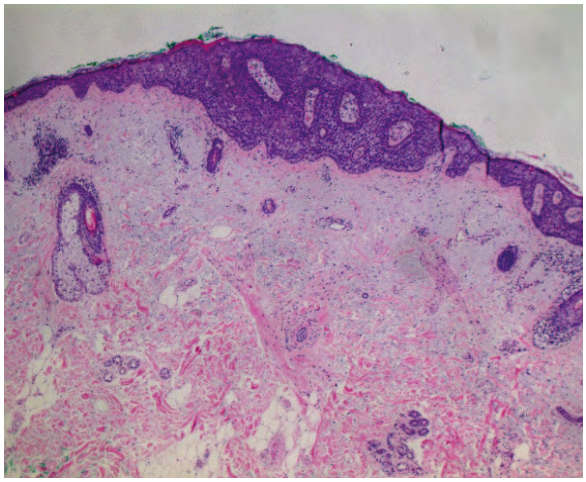

Figure 7. Histopathological examination showed full-thickness epidermal dysplasia with numerous abnormal mitoses, indicating carcinoma *in situ*/Bowen's disease

disease, a second biopsy, guided by dermoscopy, was taken. This time, histological examination showed high-grade atypia of the epidermis, with numerous abnormal mitoses, indicating carcinoma *in situ* [Bowen's disease (BD)] — Figure 7.

DISCUSSION

BD is an *in situ* squamous cell carcinoma (SCC) of the epidermis that was first described by John Templeton Bowen in 1912 [1]. It is estimated that around 3% to 5% of BD transform into invasive squamous cell cancer [2].

BD most commonly develops in photo-exposed areas of the skin, especially in the Caucasian race and in patients with low skin phototypes. The predisposing factors of BD include ultraviolet light exposure, psoralen-ultraviolet A (PUVA) therapy, thermal injury, ionizing radiation, immunosuppression, arsenic exposure, inflammatory dermatoses such as chronic lupus erythematosus or lupus vulgaris, and human papillomavirus (HPV) infections [3]. BD usually presents as a slowly enlarging, well-defined, skin-coloured, erythematous to pigmented scaly and/or crusted plaque. The plaque can rarely be eroded or ulcerated [4].

The differential diagnoses include the spectrum of premalignant and malignant keratinizing lesions: actinic keratosis (AK), keratoacanthoma (KA) and SCC [5]. In addition, inflammatory dermatoses such as psoriasis and nummular eczema should be taken into differential diagnosis.

Under dermoscopy, BD should be suspected when white-to-yellow surface scales and coiled vessels in linear or clustered arrangement on an erythematous background are present [5]. In a pigmented variant of BD, small brown globules and/or homogeneous pigmentation can be additionally observed [6]. However, these features are still not pathognomonic for BD and a biopsy must be taken to confirm the diagnosis [3].

The available therapeutic modalities of BD include topical chemotherapy (imiquimod 5% cream, 5-fluorouracil cream), light-based modalities (photodynamic therapy, radiotherapy, CO_2 laser), destructive therapies (curettage with cautery, cryotherapy) and surgical modalities (excision, Mohs micrographic surgery) [3].

Dermoscopy has already been reported as a useful tool for the selection of a biopsy site and therefore facilitation of the diagnosis of melanocytic lesions [7, 8], cicatricial alopecia [9–13], extramammary Paget's disease [14], melanonychia [15] and penile sclerosing granuloma [16]. Dermoscopy may not only aid selection of the biopsy site but also guide nail abrasion for mycological samples in case of onychomycosis [17]. By better detection of margins, dermoscopy may help to guide resection of lentigo maligna [18], squamous cell carcinoma [19–21] and basal cell carcinoma [22–24]. The real-time use of dermoscopes during surgical excision of intradermal naevus for optimal cosmetic outcomes has also been reported [25].

Precise assessment of facial lesions in photo-damaged skin could be challenging. A collision of benign lesions (*e.g.* solar lentigines, seborrheic keratosis, sebaceous hyperplasia *etc.*), premalignant lesions (actinic keratosis) and malignant tumours (*e.g.* BCC, SCC, lentigo maligna) is not uncommon. In addition, extensive erythematous or pigmented macules, with dermoscopic phenomena varying depending on the zone of the lesion, may be encountered on photo-damaged skin. Complete excision of large lesions may require advanced surgical skills, and still, this does not guarantee satisfying cosmetic outcomes. Therefore, less invasive proceedings are preferred for benign or premalignant conditions. In all these cases, if the diagnosis is uncertain or a malignant lesion is suspected (*e.g.* lentigo maligna), an incisional biopsy should be taken first. And the larger the lesion, the greater the importance of dermoscopy in selecting the best site for biopsy.

CONCLUSIONS

An incisional biopsy of extensive facial lesions should not be taken blindly but should be preceded by detailed preliminary evaluation based on non-invasive imaging methods, particularly dermoscopy. Early and accurate diagnosis of BD is essential for treatment initiation and preventing its transformation into invasive SCC.

Article information and declarations

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Author contributions

Conceptualization — MŻ and IW; resources — MŻ, EO and KKW; writing: original draft preparation — IW; writing: review and editing — MŻ and AR; visualization — MŻ and EO; supervision — MŻ and AR. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

Ethics statement

Informed consent was obtained from the patient described in the article.

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Supplementary material

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VIA MEDICA

CASE REPORT

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Refractory bullous pemphigoid during treatment with pembrolizumab in the first-line treatment of advanced non-small cell lung cancer

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ABSTRACT

Dermatological toxicity is one of the most common immune-related adverse events (irAEs) of treatment with immune checkpoint inhibitors (ICIs). Bullous pemphigoid (BP) is a rare and serious complication of these drugs that can be difficult to establish, as its initial symptoms may be indistinguishable from mild skin lesions. This paper presents the case of a 68-year-old patient who developed BP after receiving one of the ICI therapies, pembrolizumab, for advanced non-small cell lung cancer (NSCLC). After approximately 7 months of therapy, a grade 3 skin toxicity in the Common Terminology Criteria for Adverse Events (CTCAE) occurred in the form of rash and pruritus. Pembrolizumab was then held and prednisone and antihistamines were introduced. When dermal toxicity improved to grade 1, pembrolizumab was resumed and prednisone was kept at a dose of 10 mg. Immunotherapy was discontinued 3 months later, after the recurrence of grade 3 skin toxicity symptoms. When the patient developed blisters filled with clear fluid, dermatologists suspected pembrolizumab-induced bullous pemphigoid. Bullous pemphigoid was subsequently confirmed using a direct immunofluorescence test and histopathological examination. The patient's skin condition improved after the use of steroid therapy and methotrexate, and the cancer process stabilized for over one year. Cancer progression and deterioration of the patient's general condition were observed approximately 4 months after the termination of pembrolizumab therapy. The paper also discusses the key aspects of ICIs-induced BP, especially pembrolizumabinduced BP in the first-line treatment of metastatic NSCLC. Early diagnosis of skin lesions and the initiation of appropriate treatment may lead to better outcomes for patients and prevent disruptions in immunotherapy.

Forum Derm. 2024; 10, 2: 54–57

Keywords: bullous pemphigoid, pembrolizumab, immune adverse events, immune checkpoint inhibitors, immunotherapy

INTRODUCTION

Immune checkpoint inhibitors (ICIs) have revolutionized the oncological treatment of many solid tumours. One of the ICIs is pembrolizumab, a humanized anti-programmed cell death-1 (PD-1) monoclonal antibody. Pembrolizumab is currently registered for many indications. Its effectiveness as a monotherapy has been demonstrated in the first-line treatment of metastatic non-small cell lung cancer (NSCLC) in adults whose percentage of tumour cells expressing programmed death-ligand 1 (PD-L1) tumour proportion score is at least 50% (KEYNOTE-024 study) [1]. On the other hand, ICIs non-specifically activate the immune system, thereby inducing immune-related adverse events (irAEs), including severe ones [2]. Cutaneous toxicity is one of the most common irAEs, occurring in 30–40% [3] of patients treated with ICIs (according to other sources, 30–50% of patients [4]). The most common dermal irAEs include pruritus, rashes, vitiligo, and lichenoid reactions [3, 4]. The development of bullous pemphigoid (BP) has been reported in approximately 1% [4] or 0.6% [2] of patients treated with anti-PD-1/PD-L1 antibodies. In the following section of the paper, a case of a patient with pembrolizumab-induced BP during first-line treatment of advanced NSCLC is described.

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CASE REPORT

The patient, a 68-year-old male ex-smoker with metastatic squamous cell carcinoma of the right lung with PD-L1 70%, was admitted for treatment to the oncology department in August 2021. The patient was qualified for immunotherapy with pembrolizumab. In the first computed tomography assessment in October 2021, the disease was stable according to the Response Evaluation Criteria in Solid Tumours (RECIST 1.1) criteria. It was also the best possible response to treatment obtained during immunotherapy.

In April 2022, the patient reported the appearance of a rash and itching. Physical examination of the trunk and upper limbs skin revealed flat-convex papular lesions with an erythematous base and excoriations. Because of a suspicion of a grade 3 dermal irAE [according to the Common Terminology Criteria for Adverse Events (CTCAE)], pembrolizumab was discontinued, and prednisone at a dose of 0.5 mg/kg and antihistamines were introduced following the European Society for Medical Oncology (ESMO) guidelines.

At the end of April 2022, dermal toxicity decreased to CTCAE grade 1. Pembrolizumab was resumed and prednisone was kept at a dose of 10 mg. In June 2022, the patient reported severe pruritus and rash. Immunotherapy was permanently discontinued due to recurrent skin toxicity in CTCAE grade 3. According to the dermatologist's recommendations, the patient took prednisone at a dose of 20 mg, antihistamines, and an anti-inflammatory ointment.

Over 10 months, the patient received a total of eleven pembrolizumab infusions: nine cycles of 200 mg every 3 weeks and two cycles of 400 mg every 6 weeks. The last cycle of pembrolizumab was administered in May 2022 at a dose of 200 mg. At the end of July 2022, blisters developed on the patient's trunk and limbs. Blisters, filled with transparent fluid, left painful erosions after rupture (Fig. 1).

Bullous pemphigoid was diagnosed histopathologically in August 2022. A direct immunofluorescence examination (DIF) confirmed the diagnosis. Positive pemphigoid antibodies were detected at a titre of 1:80 in the IgG class. Pembrolizumab-induced pemphigoid was suspected. At the turn of August and September 2022, due to the significant severity of skin lesions, the patient was hospitalized in the dermatology department. The treatment included an intravenous steroid, hydrocortisone (3 mg/kg/day), and subcutaneous methotrexate at a dose of 15 mg once a week. After the first week of treatment, hydrocortisone was replaced with oral methylprednisolone (0.4 mg/kg/day) and topical clobetasol propionate 0.05% cream twice a day over the entire body, except the face (30––40 g daily). Methylprednisolone and clobetasol propionate 0.05% cream were gradually reduced from an initial dose,

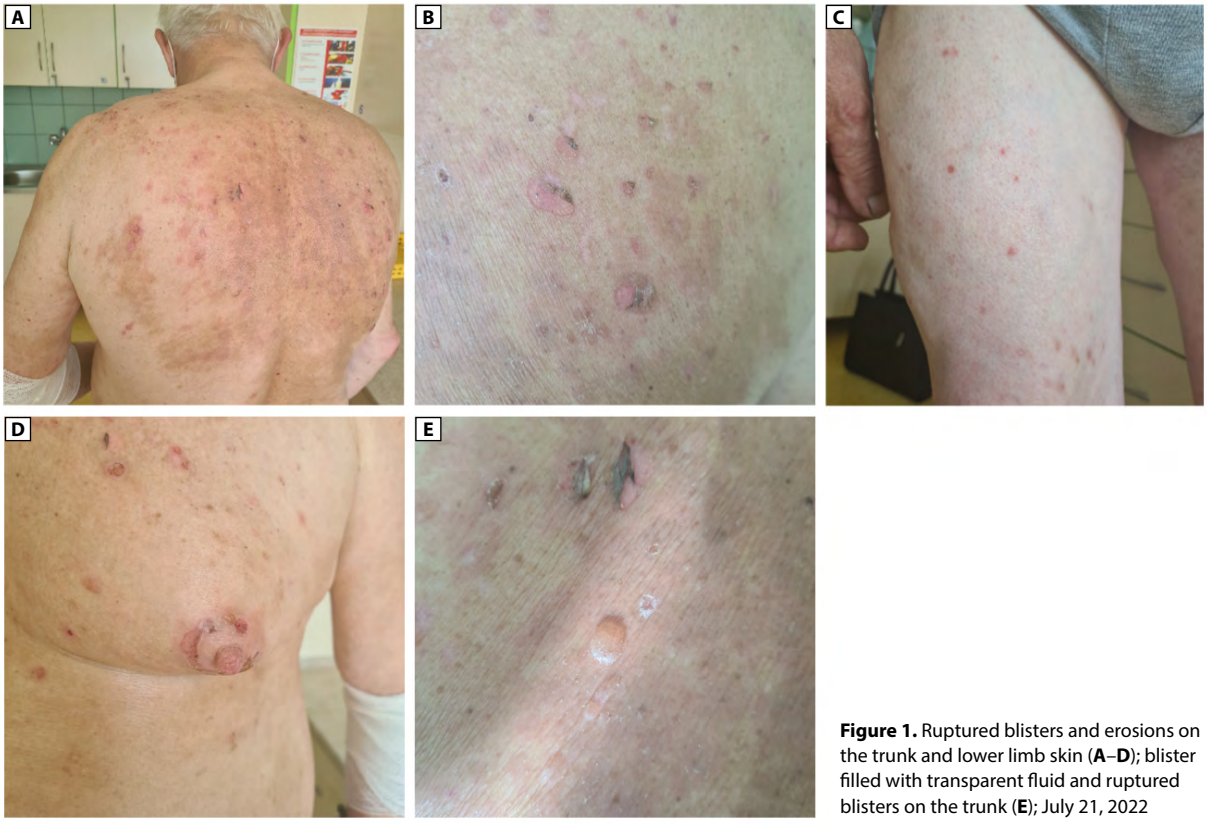

Figure 1. Ruptured blisters and erosions on the trunk and lower limb skin (**A**–**D**); blister filled with transparent fluid and ruptured blisters on the trunk (**E**); July 21, 2022

and methotrexate therapy was continued at a dose of 15 mg subcutaneously every 7 days. The symptoms of pemphigoid disappeared, but within a short period, the patient experienced abdominal pain, weight loss, and hyperglycaemia. Magnetic resonance imaging of the abdomen, performed in September 2022 during hospitalization, revealed the presence of a pathological, ill-defined mass of approximately 85 × 60 × 55 millimetres in retroperitoneal space on the left side. During the diagnosis, which was delayed due to COVID-19, the progression of cancer was confirmed. Due to the deterioration of the patient's general condition, further oncological treatment was discontinued.

DISCUSSION

Accounting for 80% of cases, bullous pemphigoid is the most common autoimmune subepidermal bullous disease with autoantibodies directed against the antigens BP180 (BPAG2 or type XVII collagen) and BP230 (BPAG1). Antigens BP180 and BP230 are parts of hemidesmosomes, responsible for adhesion between epidermal keratinocytes and the basement membrane zone. BP most commonly occurs in patients between the ages of 60 and 80. Because BP mainly affects the elderly population, the mortality rate is increased and ranges from approximately 10 to 40% [5].

Bullous pemphigoid may be induced by drugs such as diuretics, gliptins, beta-blockers, and PD-1/PD-L1 inhibitors [5]. The overall incidence rate is 4.19 per 100,000 person-year [2]. The symptoms of drug-induced BP are similar to idiopathic ones. They appear within 3 months after starting treatment and are usually observed in younger patients. In the prodromal phase of pemphigoid, the symptoms are often non-specific and include itching occurring without skin lesions or with papular or urticarial lesions. Within a few weeks or months, blisters appear over normal skin or an erythematous background. They are most often located on the flexural surfaces of the limbs and the lower part of the trunk [5, 6]. Lesions in the oral cavity occur in approximately 10–30% of patients. [6] The blisters have a tight lid and contain clear fluid, sometimes tinged with blood. After rupturing, they leave erosions and scabs. Eosinophilia may be present in blood laboratory tests [5–7].

Most cases of pemphigoid caused by anti-PD-1/PD-L1 described in the literature concern mainly male patients with an average age of approximately 72 years, diagnosed with melanoma, followed by NSCLC [2, 8].

Compared to most skin toxicities, which are usually the earliest irAEs to appear during the use of ICIs, pemphigoid develops with a delay, on average after approximately 14 weeks after the initiation of anti-PD-1/PD-L1 therapy [7]. According to other analyses, pruritus appears later, on average between weeks 19–21, while blisters may occur in weeks 20–39 of therapy [6]. According to available reports, in patients treated with pembrolizumab, the median time to dermal toxicity was 4 months, and the median time to bullae formation was 7.35 months [2]. Unlike traditional drug-induced BP, ICIs-related BP may persist for several months after discontinuation of immunotherapy due to persistent immune system activation [7] and, as a result, can be difficult to diagnose. To diagnose BP, it is necessary to confirm the presence of typical skin lesions and the result of a direct immunofluorescence examination, which shows linear deposits of IgG and/or C3 at the dermal-epidermal junction. In individual cases of BP, linear IgE deposits occur along the basement membrane zone as the only immunological component or in addition to IgG. Histopathological examination is helpful in the diagnosis but cannot be used for its basis. To determine the characteristics of the antigen or antigens recognized by autoantibodies, enzyme-linked immunosorbent assay (ELISA) tests are performed. ELISA results correlate with the extent of skin lesions and disease activity and can be a tool for monitoring treatment and predicting the recurrence of skin lesions. Additionally, an indirect immunofluorescence (IIF) test can be performed, where BP is characterized by a linear basement membrane zone staining pattern with IgG [9].

The pathogenesis of BP during ICI treatment is still unclear; it is possible that ICIs cause de novo induction of BP or unmask subclinical disease [4]. The mechanism of pemphigoid formation induced by anti-PD-1 and PD-L1 antibodies is probably related to a reduction in the number of regulatory T cells, which leads to increased T cell activation, B cell proliferation, and autoantibody synthesis [6]. Moreover, BP 180 is an antigen that also occurs in cancer cells, melanoma, and NSCLC. Some studies suggest that BP occurs as a result of the binding of overactive T lymphocytes to the BP180 antigen on both cancer cells and the basement membrane of the skin [4, 8].

ESMO guidelines for dermal irAEs recommend using topical and systemic steroid treatments and depending on the severity of BP and the response to medication, temporary or permanent discontinuation of ICI therapy [10]. Alternative treatment modalities include, among others, tetracyclines, niacinamide, methotrexate, dapsone, azathioprine, mycophenolate mofetil, plasma exchange, intravenous immunoglobulin, rituximab, infliximab, omalizumab, and dupilumab [2, 8, 9, 11, 12]. Most patients treated with PD-1/PD-L1 inhibitors who developed BP had to discontinue immunotherapy [2, 3, 8]. In reported cases, patients were treated with local therapy, and most of them required additional systemic treatment with corticosteroids. However, routine glucocorticoid application may lessen the effectiveness of immunotherapy [2, 8]. Certain

dermal irAEs (namely lichenoid and vitiligo) occurring during anti-PD-1/PD-L1 therapy were associated with better response and overall survival [8, 13, 14]. Some retrospective data link the development of BP with improved response to PD-1 treatment, but others do not support these reports [2, 8]. Further observations are therefore necessary.

Due to the increasing morbidity and significant mortality associated with bullous pemphigoid and its often-non-specific course, it is important to remain vigilant in the event of skin lesions appearing during ICI treatment.

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CASE REPORT

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Facial herpes zoster complicated by cerebral oedema in the course of encephalitis

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ABSTRACT

Herpes zoster is the result of the reactivation of the varicella-zoster virus (VZV), which remains dormant in the sensory ganglia. The clinical presentation is characterized by a unilateral vesicular rash occurring on an erythematous background and most commonly affecting one dermatome of the skin. An extremely rare complication of herpes zoster is encephalitis, which occurs in approximately 0.2% of cases. It involves fever, headache, nausea, vomiting, impaired consciousness, hallucinations, and balance disturbances in addition to the rash. The study presents a case of a 71-year-old female patient hospitalized in the Dermatology Clinic due to zoster on the left side of her face, accompanied by the above symptoms that occurred 2 days before admission and brain oedema observed in the head computed tomography, constituting the clinical picture of VZV-related encephalitis.

Forum Derm. 2024; 10, 2: 58–60

Keywords: herpes zoster, varicella-zoster virus, encephalitis, cerebral oedema

INTRODUCTION

Herpes zoster accounts for 1% of infectious skin diseases. The etiological agent is varicella zoster virus (VZV), a pathogenic human herpes virus that causes varicella (chickenpox) as a primary infection and becomes latent in the peripheral ganglia. Varicella zoster virus reactivates either spontaneously or due to several triggering factors, involving reduced immunity, to cause herpes zoster (shingles). The clinical picture of a zoster is a unilateral, small vesicular erythematous skin lesion, corresponding to one or more skin dermatoses. The lesions can burst easily and leave scars. Most often, the skin lesions do not cross the midline of the body. The lesions may be accompanied by tingling, burning, itching or significant pain in the dermatomes. In 70–80% of cases, these symptoms precede the onset of skin lesions by 3–4 days. The most common complication of herpes zoster is postherpetic neuralgia with a benign course, which reduces the quality of the patient's life. Other neurological complications of herpes zoster include central nervous system (CNS) pathologies, including cerebellar ataxia, cerebral arteritis, myelitis, meningitis and encephalitis. Central nervous system infection can occur in the course of primary or secondary reactivation of VZV [1].

CASE REPORT

A 71-year-old woman presented to the Dermatology Department due to left side facial zoster. The first skin lesions appeared 2 days before hospitalization and were preceded by a severe headache, nausea and vomiting, which had occurred 4 days earlier. The patient began treatment with acyclovir on an outpatient basis but was unable to take the prescribed medication due to severe vomiting. Symptoms on admission to the Dermatology Department involved numerous small vesicles on an erythematous background, crust and erosions on the skin of the forehead, temple, and parietal area on the right side, and swelling of the left eyelid (Fig. 1). No other abnormalities and meningeal symptoms were found. Laboratory tests revealed anti-VZV antibodies in both IgM and IgG classes. Due to persistent vomiting and headaches responding poorly to analgesics, a head computed tomography (CT) scan without contrast was performed, which revealed cerebral oedema (Fig. 2). As

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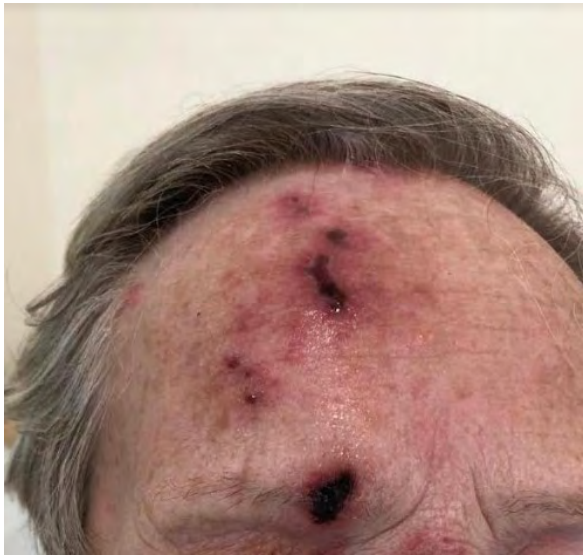

Figure 1. Numerous small vesicles on an erythematous background, crust and erosions on the skin of the forehead, temple, and parietal area on the right side

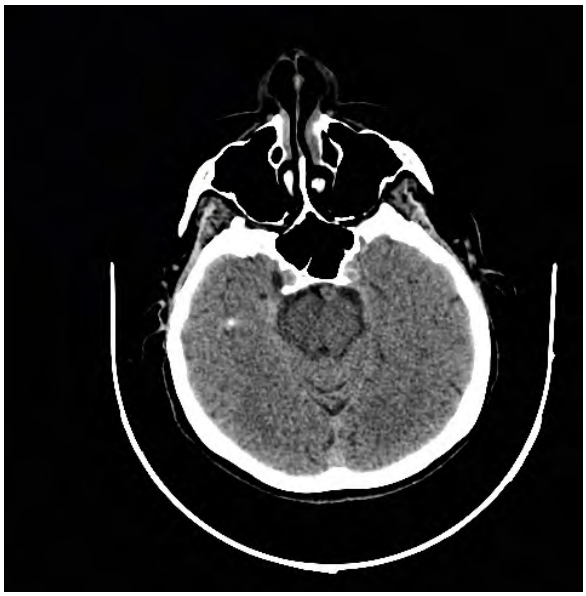

Figure 2. Rubbing of the furrows in both hemispheres of the brain especially in the temporal lobes, occipital lobes and subthalamotically

a result a lumbar puncture for further diagnosis was abandoned. Based on the clinical picture and additional tests, a diagnosis of VZV encephalitis was made and intravenous acyclovir at the dose of 500 mg 3 times daily was administered. Symptomatic treatment of cerebral oedema involved a parental dosage of 100 mL 20% mannitol with 40 mg of furosemide, dexamethasone (16 mg — 8 mg — 0 mg *i.v.*) and metoclopramide. The pain and nausea resolved on the day of the anti-oedema therapy. During hospitalization in the Dermatology Department, the patient reported an increasing cough, without dyspnoea. In laboratory tests SARS-CoV-2 antigen was positive. The patient was transferred to the Department of Infectious Diseases hospitalizing patients with COVID-19 for further treatment. Over the next few days, the patient's vital signs deteriorated, and respiratory and multi-organ failure worsened, which unfortunately led to the patient's death in the Intensive Care Unit.

DISCUSSION

Varicella zoster virus is the second most common cause of viral encephalitis and viral meningitis, affecting only 0.1––0.25% [2, 3] of patients with zoster. It is more common in disseminated cases and *foci* involving dermatomes in close proximity to the vicinity of the central nervous system. Two main risk factors for developing the zoster are the impaired immune system and the age of patients over 65. This is particularly crucial in cases of potential virus transmission from grandchildren, as previously described [4]. In a retrospective analysis, Skripuletz et al. [3] reported an isolated vesicular rash as the most common manifestation among 282 patients diagnosed with zoster and hospitalized at the Department of Neurology in Hannover. In half of those patients, it originated from the trigeminal ganglion and 90% of these cases involved an ocular nerve as the first branch of the trigeminal nerve. In 21% of patients, it initiated in the spinal ganglia and almost half of them had involved dermatomes of the thoracic spinal nerve. In the same study, the nervous system was affected in 12% of patients with zoster. The mortality rate of VZV encephalitis in immunocompetent patients is about 15% and almost 100% in immunosuppressed patients, especially in cases of additional liver or lung involvement. This group of patients requires special attention, and VZV encephalitis must be considered in cases of both drug- and disease-induced immunosuppression [5, 6]. Clinical signs of VZV encephalitis are headache, fever, nausea, vomiting, disturbance of consciousness, and productive symptoms such as hallucinations or convulsions. These symptoms can often be misdiagnosed as side effects of valacyclovir used in zoster therapy, especially in patients with impaired renal function. The rash may precede or occur after the onset of neurological symptoms. As for the present patient, the rash appeared 3 days after the headache, nausea and vomiting. Neurological symptoms accompanying skin lesions and hemiplegia oblige us to perform brain imaging studies — non-contrast CT or magnetic resonance imaging (MRI). They can show reduced hypodensity of the temporal lobes, with possible involvement of the frontal lobe, sparing of the basal nuclei (in CT) or features of oedema with excessive density in the mentioned locations and sparing of the brain base (in MRI). The gold standard for diagnosing VZV encephalitis is a lumbar puncture and examination of cerebrospinal fluid. This procedure can detect signs of viral

infection, characterized by clear fluid, a slightly increased number of cells, and normal or slightly decreased glucose levels [4, 5, 7]. It also allows for the identification of viral DNA or anti-VZV antibodies, leading to a correct diagnosis [5, 6]. However, it should be remembered that lumbar puncture is contraindicated in the case of cerebral oedema, and any features of cerebral oedema should be excluded by CT scan or ophthalmoscopic examination. Due to the features of cerebral oedema on CT in the study patient, lumbar puncture was abandoned. The treatment of choice for zoster with encephalitis remains intravenous acyclovir. Many authors have noted the clinical efficacy (defined as reduced mortality or neurological complications) of acyclovir and ganciclovir in the treatment of VZV encephalitis in HIV-infected [8], immunocompromised [7, 9–11] and immunocompetent patients [12–14]. Broucker et al. [11] and other authors [15, 16] have not observed a significant impact of different doses of acyclovir (from 10 to 15 mg/kg/8 h) and time of therapy (from 14 to 21 days) on the clinical outcome in patients. Due to a lack of other clinical evidence for the efficacy of a higher dose of acyclovir and the optimal length of therapy, the majority of recommendations are 15 mg/kg body weight/8 h for 10 to 14 days and prolonging the duration of therapy in immunocompromised patients. In the present case, additional symptomatic treatment of cerebral oedema was implemented.

CONCLUSIONS

Clinical observations suggest that in the case of vomiting and severe headaches non-responding to treatment, one should consider the possibility of neurological complications of a common infectious disease such as varicella zoster. In such a case, diagnostic imaging tests (CT and/or MRI) should be performed. The length of intravenous acyclovir therapy for VZV encephalitis has not been precisely established. The effective dose of acyclovir is 10–15 mg/kg/8 h and the optimal duration of therapy is from 10 to 21 days. There is an increased risk of neurological complications in the course of VZV infection in elderly patients, burdened with additional diseases. Early diagnosis and inclusion of appropriate treatment significantly reduce the risk of death. The case presented here is intended to sensitize doctors to the rare neurological complications in the course of a zoster.

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Author contributions

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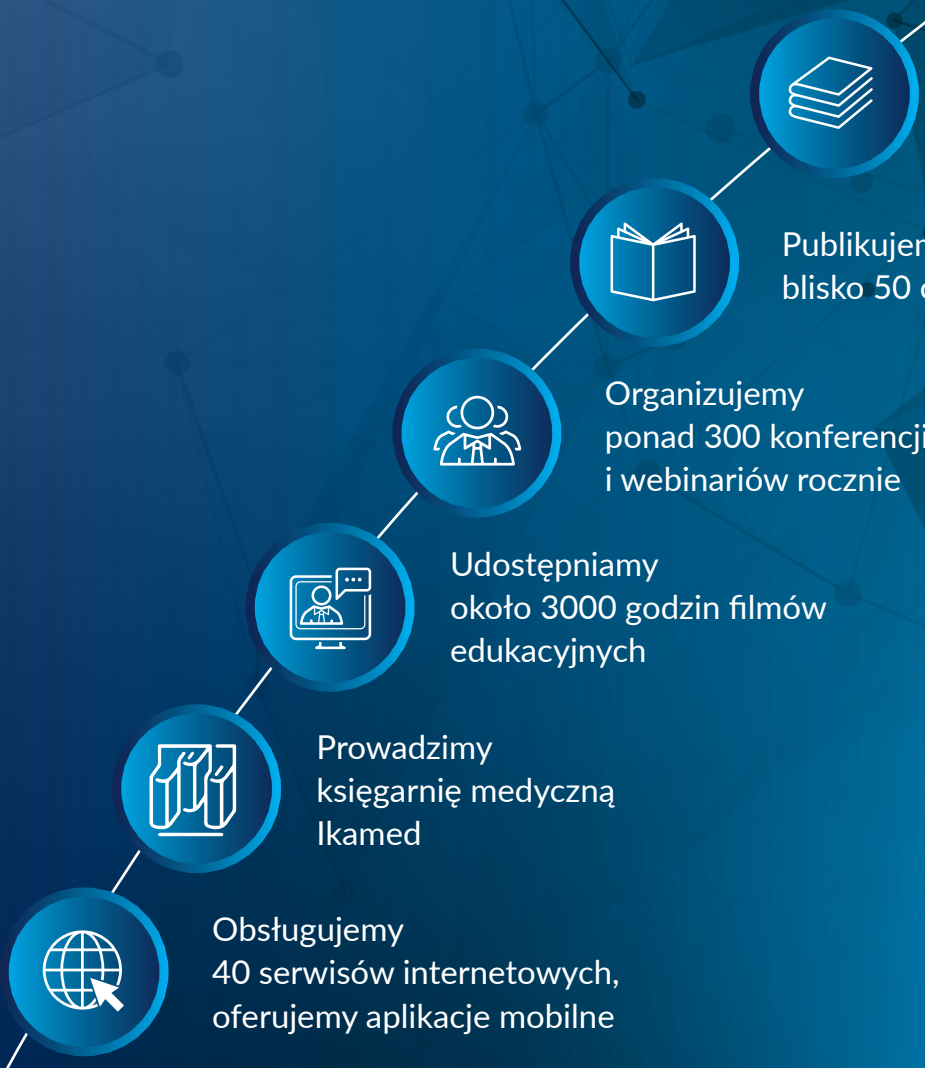

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