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Review

Immune-related dermatological adverse events of antitumor immunotherapy with PD-1, PD-L1, CTLA-4 inhibitors

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ABSTRACT

The discovery of a new group of modern anticancer drugs was a breakthrough in the treatment of cancer. Immune checkpoint inhibitors that block cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein-1 (PD-1), and programmed cell death receptor ligand (PD-L1) may improve prognosis for patients with malignant neoplasms with a high level of microsatellite instability. Despite the high effectiveness of these drugs, immune checkpoint inhibitors can lead to dysregulation of immune responses and the occurrence of adverse reactions associated with an increase in the activity of immunocompetent cells in the body.

The aim of this review is to analyze the available data on the immune-related dermatological adverse events during treatment with immune checkpoint inhibitors.

Keywords: immune-related adverse events; cutaneous toxicity of immunotherapy; immune checkpoint inhibitors; antitumor immunotherapy; maculopapular rash; psoriasiform rash; lichenoid rash; vitiligo-like reaction; bullous pemphigoid; ipilimumab; nivolumab; pembrolizumab; atezolizumab; prolgolimab.

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Научный обзор

Иммуноопосредованные дерматологические нежелательные явления противоопухолевой иммунотерапии ингибиторами PD-1, PD-L1, CTLA-4

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АННОТАЦИЯ

Открытие новой группы современных противоопухолевых препаратов явилось прорывом в лечении онкологических заболеваний. Ингибиторы иммунных контрольных точек, блокирующие цитотоксический Т-лимфоцитассоциированный протеин 4 (CTLA-4), белок запрограммированной клеточной гибели-1 (PD-1) и лиганд рецептора запрограммированной клеточной гибели (PD-L1), позволяют улучшить прогноз пациентов со злокачественными новообразованиями с высоким уровнем микросателлитной нестабильности. Несмотря на высокую эффективность данных препаратов, ингибиторы иммунных контрольных точек могут приводить к нарушению регуляции иммунных ответов и возникновению нежелательных реакций, связанных с повышением активности иммунокомпетентных клеток в организме.

Целью данного обзора является изучение и анализ имеющихся данных о клинических проявлениях иммуноопосредованных дерматологических нежелательных реакций при лечении ингибиторами иммунных контрольных точек.

Ключевые слова: иммуноопосредованные нежелательные явления; кожная токсичность иммунотерапии; ингибиторы иммунных контрольных точек; противоопухолевая иммунотерапия; макулопапулёзная сыпь; псориазиформная сыпь; лихеноидные высыпания; витилигоподобная реакция; буллёзный пемфигоид; ипилимумаб; ниволумаб; пембролизумаб; атезолизумаб; пролголимаб.

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INTRODUCTION

The incidence and mortality rates of cancer are increasing. According to the World Health Organization, malignant neoplasms are one of the leading causes of death worldwide. In 2020, 19.3 million new cancer cases and nearly 10 million cancer-related deaths were recorded. The incidence is expected to increase by 50% in the coming decades, underscoring the urgent need for the development and introduction of new antitumor drugs as a priority task of modern medicine [1].

Immune checkpoint (IC) inhibitors (ICIs) are a contemporary class of antitumor drugs that have demonstrated remarkable efficacy and have become dominant in the treatment of numerous cancers. The scope of indications for this class is expanding annually. ICI therapy may be accompanied by nonspecific immune activation, which can lead to autoimmune and autoinflammatory reactions. These reactions, which are immune-mediated, can negatively affect patients' quality of life and the results of ICI therapy because of forced dose reduction or drug withdrawal.

ICIs are recombinant human or humanized monoclonal antibodies directed against cytotoxic T-lymphocyte associated protein 4 (CTLA-4) receptor (ipilimumab), programmed cell death protein 1 (PD-1) receptor (pembrolizumab, nivolumab, and prolgolimumab), and programmed cell death-ligand 1 (PD-L1) receptor ligand (atezolizumab, avelumab, and durvalumab) on the T-lymphocytes [2]. ICIs registered in the Russian Federation are presented in Table 1.

MECHANISM OF ACTION OF ICIS

ICs play a pivotal role in maintaining homeostasis and preventing autoimmune reactions and auto-damage [3–5]. The antitumor effect of iICIs is based on the blockade of two distinct signaling pathways, CTLA-4 and PD-1/PD-L1, which control different immune response stages. Ipilimumab, a monoclonal antibody, blocks the CTLA-4 receptor, which is expressed on the surface of T-lymphocytes after their activation. The binding of this receptor to molecules B7-1 (CD80) and B7-2 (CD86) on the surface of antigen-presenting cells inhibits the T-cell response at is initialization stage. The blockade of CTLA-4 activity on immune system cells reduces the influence of negative regulation, greatly realizing the immune response against detected tumor cells [6–11].

The programmed death receptor PD-1 is an immune regulator; when expressed on the surface of activated T-lymphocytes, it limits their activity. This is achieved through the binding of PD-L1 and PD-L2, which are PD-1 receptor ligands, to the corresponding receptor on the surface of the target cell [12, 13]. Increased expression of PD-1 receptor ligands is one of the most well-known mechanisms by which tumor cells evade the immune system, which suppresses the immune response. This occurs when activated T-lymphocytes, which are responsible for the tumor cell destruction, lose their activity. Consequently, the tumor can suppress the immune response and grow further [9]. PD-1/PD-L1 inhibitors prevent the interaction between the PD-1 receptor and its ligands, enhancing the immune response against tumor cells [14]. When PD-1 binding to PD-L1 and PD-L2 ligands is blocked, activated T-lymphocytes regain their ability to proliferate and initiate an antitumor response [15]. The mechanism of action of ICIs is shown in Fig. 1 [16].

Despite their high antitumor efficacy, ICIs are associated with adverse events because of autoimmunity activation. Immune-mediated dermatologic adverse reactions are often the first to occur and account for approximately 40% of all ICI-related side effects [17]. When considered separately, the incidence of immune-mediated dermatologic adverse events varies considerably among ICI classes. For instance, the occurrence of such events in patients treated with CTLA-4 inhibitors can be as high as 50%, whereas in patients treated with PD-1/PD-L1 inhibitors, it can be as low as 40%, and in patients on combination therapy it can be as high as 60% [18]. The most prevalent immune-mediated dermatologic adverse reactions include pruritus, maculopapular, lichenoid rashes, and vitiligo-like reactions. Less common adverse reactions include psoriasiform rashes and bullous pemphigoid. The oral mucosa may be affected by Sjögren's syndrome, particularly during PD-1 inhibitor therapy [18, 19]. Severe dermatologic complications of immunotherapy include drug reactions with eosinophilia and systemic symptoms, Stevens–Johnson syndrome, and toxic epidermal necrolysis.

A combination of topical glucocorticoids of medium and high activity for grade I severity, with the addition of systemic glucocorticoids for grade 2 is the current standard of care for the treatment of immune-mediated dermatologic adverse events. In more severe adverse events, ICI therapy must be discontinued, and systemic glucocorticoids added to the therapy. In grades 3 and 4, immunotherapeutic treatment is discontinued until the severity level decreases [20]. Because CTLA-4 and PD-1/PD-L1 inhibitors have different application points, if patients are intolerant to one of them, another drug may be prescribed [19].

TYPES OF IMMUNE-MEDIATED DERMATOLOGIC ADVERSE REACTIONS DURING ICI THERAPY WITH PD-1, PD-L1, AND CTLA-4

Pruritus

Pruritus is a common adverse event of immunotherapy, with a significant effect on patients' quality of life. It occurs in 14%–47% of patients receiving ICIs [8, 21] (Fig. 2, 3). It can occur as an isolated symptom or in combination

Table 1. Immune checkpoint inhibitors registered in the Russian Federation

Таблица 1. Ингибиторы иммунных контрольных точек, зарегистрированные на территории Российской Федерации

Name	Immune checkpoint inhibitors						
	CTLA-4 inhibitors	PD-1 inhibitors			PD-L1 inhibitors		
	Ipilimumab[1]	Pembrolizumab[2]	Nivolumab[3]	Nivolumab[4]	Atezolizumab[5]	Avelumab[6]	Durvalumab[7]
Type of monoclonal antibody	Human	Human	Humanized	Human	Humanized	Human	Human
Action	Binding to cytotoxic CTLA-4	Blocking the binding of the PD-1 receptor to its PD-L1 and PD-L2 ligands	Blocking the binding of the PD-1 receptor to its PD-L1 and PD-L2 ligands	Binding to PD-1 and blocking its interaction with PD-L1 and PD-L2 receptors	Binding to PD-L1 and blocking its interaction with PD-1 and B1.7 receptors	Binding to PD-L1 and blocking its interaction with PD-1 and B1.7 receptors	Blocking the interaction of PD-L1 with PD-1 or CD80 (B7.1) without affecting the interaction between PD-1 and PD-L2
Indications	Melanoma	Melanoma Non-small cell lung cancer Small cell lung cancer Head and neck cancer Classical Hodgkin's lymphoma Urothelial cancer Gastric cancer Hepatocellular cancer Cervical cancer Renal cell cancer Endometrial cancer Malignant neoplasms with high microsatellite instability	Melanoma Non-small cell lung cancer Renal cell cancer Classical Hodgkin's lymphoma Squamous cell carcinoma of the head and neck Urothelial cancer Hepatocellular cancer Colorectal cancer with high microsatellite instability	Metastatic melanoma Inoperable melanoma	Urothelial cancer Non-small cell lung cancer Small cell lung cancer Triple-negative breast cancer Hepatocellular carcinoma Melanoma	Metastatic Merkel carcinoma (monotherapy in adults, previously treated patients) Locally advanced/ metastatic urothelial carcinoma Renal cell carcinoma (in combination with axitinib)	Urothelial carcinoma Non-small cell lung cancer

VIDAL. Drug Reference:
[1] Instructions for use of the Yervoy drug (https://www.vidal.ru/drugs/ervoy);
[2] Instructions for use of the Keytruda drug (https://www.vidal.ru/drugs/keytruda);
[3] Instructions for use of the Opdivo drug (https://www.vidal.ru/drugs/opdivo);
[4] Instructions for use of the Forteca drug (https://www.vidal.ru/drugs/forteca);
[5] Instructions for use of the Tecentriq drug (https://www.vidal.ru/drugs/tecentriq-1);
[6] Instructions for use of the Bavencio drug (https://www.vidal.ru/drugs/bavensio);
[7] Instructions for use of the Imfinzi drug (https://www.vidal.ru/drugs/imfinzi)

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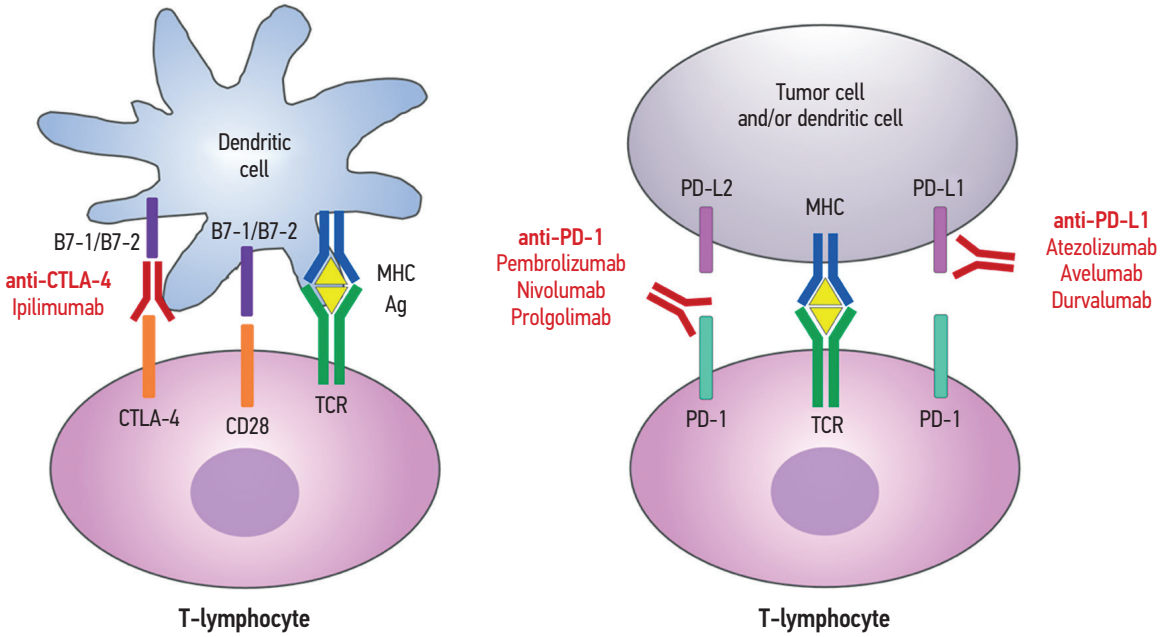

Ag — antigen; DC — dendritic cell; MHC — major histocompatibility complex; TCR — T-cell receptor; CTLA-4 — cytotoxic T-lymphocyte-associated protein 4; PD-1 — programmed cell death protein 1 receptor; PD-L1/L2 — programmed cell death ligand 1/2; CD28 — membrane protein expressed on T-lymphocytes involved in co-stimulation necessary for T-cell activation; B7-1 (CD80)/B7-2 (CD86) — membrane proteins of the immunoglobulin superfamily containing a constant immunoglobulin domain and a variable receptor-binding domain necessary for T-lymphocyte activation.

Fig. 1. Mechanism of action of immune checkpoint inhibitors (adapted from [16]).
Рис. 1. Механизм действия ингибиторов иммунных контрольных точек (адаптировано из [16]).

with other immune-mediated dermatologic adverse effects [22]. Pruritus is the most common concern among patients receiving immunotherapy, which affects the trunk and extremities but not the head and neck. Pruritus occurs in 20.2% and 13.2% of individuals receiving nivolumab and pembrolizumab, respectively. Interestingly, severe pruritus (grade 3) is relatively rare, occurring in only 0.5% and 2.3%, respectively [23]. Thus, the prevention of pruritus may be achieved through the implementation of gentle skin care practices, including gentle cleansing and moisturizing [24].

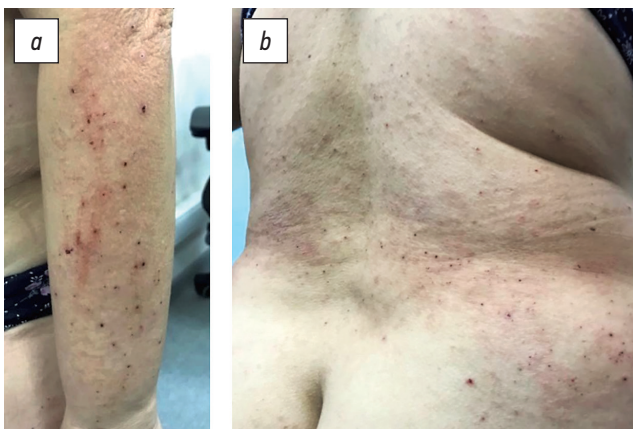

Fig. 2. Multiple excoriations with haemorrhagic crusts on the skin of the forearm (*a*) and back (*b*) due to severe pruritus on the background of nivolumab treatment.
Рис. 2. Множественные экскориации с геморрагическими корками на на коже предплечья (*a*) и спины (*b*) вследствие выраженного зуда на фоне лечения ниволумабом.

Maculopapular rash

Maculopapular rashes appear after 3–6 weeks of treatment, are dose-dependent, and may progress after each course of immunotherapy [25]. Maculopapular rashes are the most frequent immune-mediated dermatologic adverse reactions, occurring in 25% of patients receiving CTLA-4 inhibitors or anti-CTLA-4 and anti-PD-1/PD-L1 combination

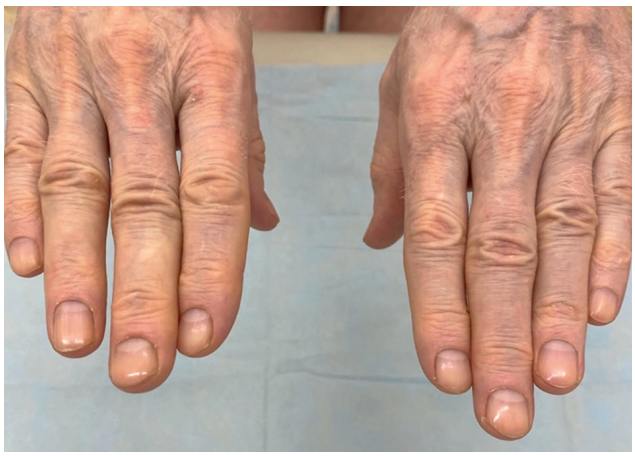

Fig. 3. Symptom of "polished nails" in severe pruritus occurring on the background of prolgolimumab treatment.
Рис. 3. Симптом «полированных ногтей» при сильном зуде, возникшем на фоне лечения пролголимабом.

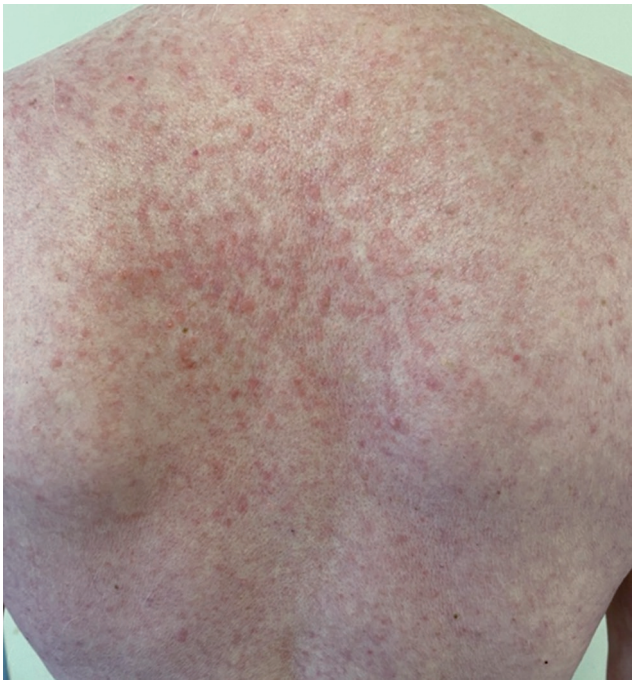

Fig. 4. Maculopapular rashes produced by treatment with nivolumab.
Рис. 4. Макулопапулёзные высыпания, возникшие при лечении ниволумабом.

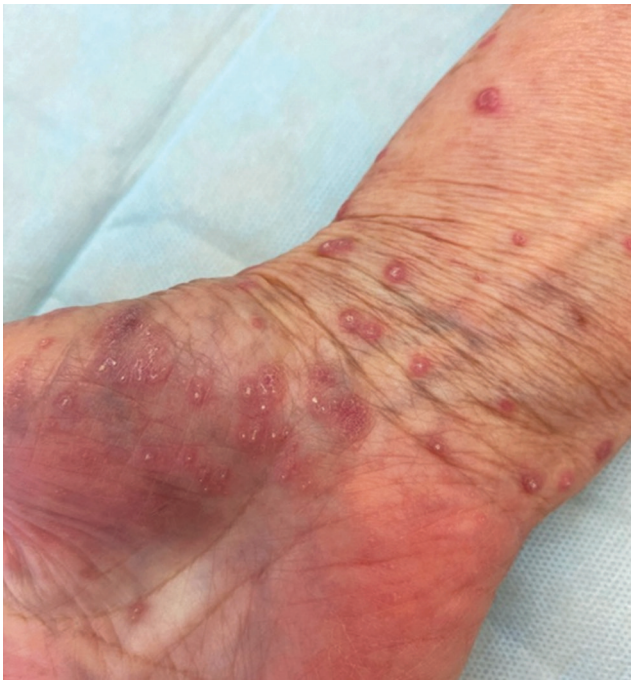

Fig. 5. Lichenoid rashes produced by treatment with pembrolizumab.
Рис. 5. Лихеноидные высыпания, возникшие при лечении пембролизумабом.

therapy, and 15% of patients on PD-1 inhibitor monotherapy [26]. Patients may present with nonspecific pale pink confluent patches and papules that occur on the trunk and extremities, except for the facial skin and palm and plantar areas. The rash is almost always pruritic and resembles the crust-like drug rash seen with antibiotics (Fig. 4). A study also reported an associated increase in the number of eosinophils in the peripheral blood. The rashes often disappear independently [27]. Notably, maculopapular rashes may be an early manifestation of other immune-mediated dermatologic adverse events such as lichenoid, psoriasiform rashes, or bullous pemphigoid. The histological picture is characterized by epidermal spongiosis, edema of the dermal papillary layer, and perivascular infiltration [28, 29].

Lichenoid rash

Lichenoid rashes typically manifest later than maculopapular rashes, with an average onset of 6–12 weeks after the initiation of immunotherapy. In patients treated with PD-1 inhibitors, lichenoid rashes were observed in 20% of cases [8, 27]. The clinical picture of lichenoid rashes varies, with manifestations frequently resembling lichen planus. These include red-purple polygonal papules and visible reticular patterns (Wickham's striae). Other presentations have also been observed. The lesions are characterized by infiltration with flaking on the surface [26, 28] accompanied by severe pruritus localized on the trunk and extremities (Fig. 5). The scalp and mucous membranes may also be involved [30]. The rashes persist for an extended period and gradually regress, leaving hyperpigmentation [8]. Cases of red squamous rash, including sclerosing and atrophic rashes, and lesions on the mucous membranes and nails have been documented [31]. The pathomorphologic features include a dense superficial band-like lymphohistiocytic infiltrate along the dermoepidermal junction and hypergranulosis [25, 31–34], which corresponds to the histologic picture of lichen planus.

Psoriasiform rash

This type of immune-mediated dermatologic reaction occurs within 5–12 weeks of initiation of ICI therapy [35]. Rashes may be either an exacerbation of psoriasis [36] or de novo [35]. Clinically, rashes correspond to psoriasis vulgaris and are characterized by infiltrated erythematous papules and plaques with clear borders and abundant scaling on the surface (Fig. 6). The pathophysiology of immune-mediated psoriasiform eruptions is similar to that of common psoriasis [37] and is based on the activation of the Th17 pathway, which is the pathogenetic mechanism of psoriasis [38, 39]. Histologic examination reveals parakeratosis, hypogranulosis, acanthosis, elongation of the dermal papillae, and superficial perivascular lymphocytic infiltrate, which corresponds to the pathomorphologic picture of psoriasis vulgaris [40].

Bullous pemphigoid

Bullous pemphigoid is a rare autoimmune disease that occurs in 12.1 per 1 million population annually in Europe [41]. In a retrospective analysis, bullous pemphigoid developed in 1% of patients treated with PD-1 or PD-L1 inhibitors [42]. The bullae may appear rapidly or after several months, on average 14 weeks after the start of therapy [43]. Patients

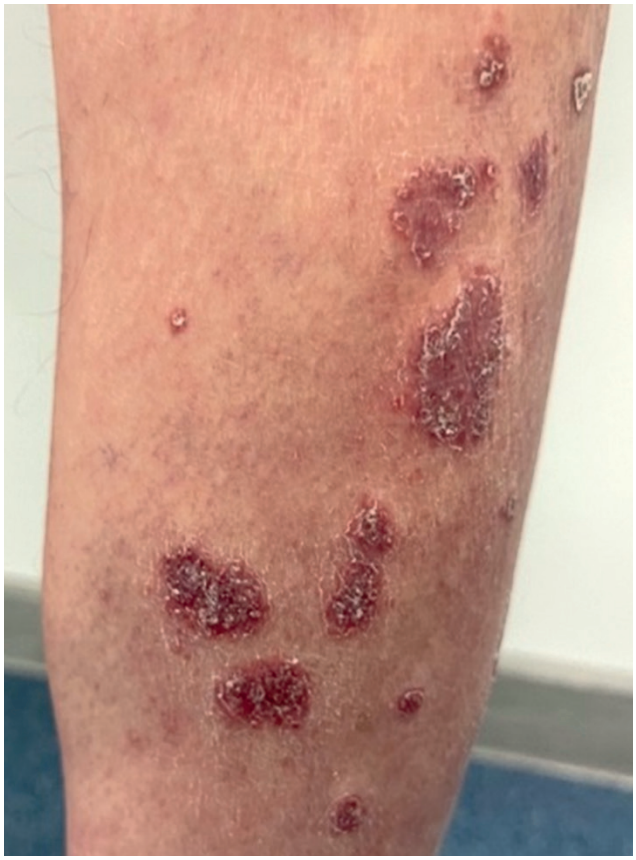

Fig. 6. Psoriasiform rashes produced by treatment with pembrolizumab.
Рис. 6. Псориазиформные высыпания, возникшие при лечении пембролизумабом.

present with pruritus, maculopapular eruptions, followed by tense vesicles filled with serous or hemorrhagic contents (Fig. 7) [22, 44]. The mechanism underlying immune-mediated bullous pemphigoid is not fully understood; however, its development is thought to be associated with the activation of B cells and humoral immunity. The diagnosis is confirmed by skin biopsy with pathomorphologic, immunohistochemical, and immunofluorescent diagnostic methods. Subepidermal rupture with an eosinophilic infiltrate is the histopathologic hallmark of bullous pemphigoid [40].

Vitiligo-like reaction

A vitiligo-like reaction is a common immune-mediated dermatologic adverse event characterized by the loss of functional melanocytes in the epidermis. In melanoma treatment, a vitiligo-like reaction was in 11% of patients receiving CTLA-4 inhibitors and 25% of patients receiving PD-1 inhibitors [45]. This side effect occurs independent of the drug dose [46]. Interestingly, a vitiligo-like reaction may develop through a distinct pathophysiologic mechanism and exhibit distinct clinical features. For instance, it may manifest in ultraviolet light-exposed areas and may exhibit less pronounced symmetry of skin lesions in the absence of the Koebner phenomenon. Furthermore, the overexpression of CXCR3-antigen by CD8+ lymphocytes was also identified,

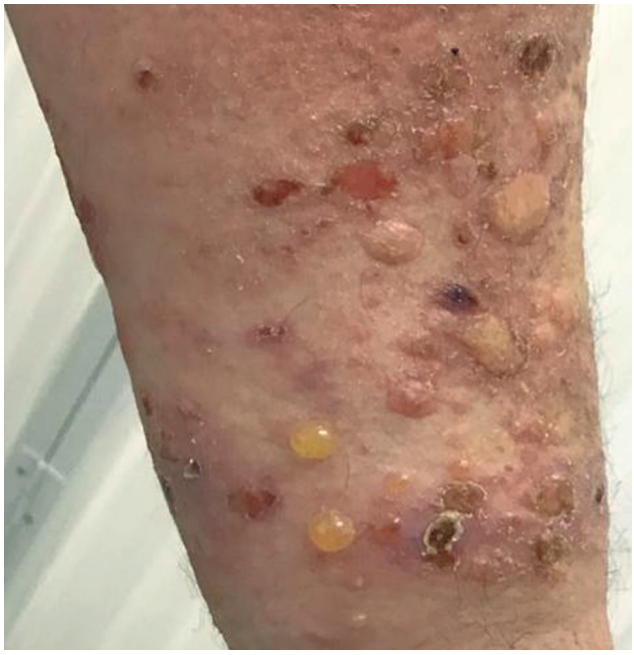

Fig. 7. Bullous pemphigoid resulting from treatment with nivolumab.
Рис. 7. Буллёзный пемфигоид, возникший при лечении ниволумабом.

indicating another potential mechanism of development [45]. Although depigmentation resulting from PD-1/PD-L1 blocker therapy is not true vitiligo, it may persist after treatment. This may manifest as an absence of hair pigmentation on the head, eyebrows, eyelashes, and body (Fig. 8) [45]. In the histological analysis, the absence of melanocytes in the basal layer of the epidermis is a defining feature, and orthokeratosis is evident in the stratum corneum [40, 44].

A summary of the characteristics of immune-mediated dermatologic adverse events associated with ICIs (CTLA-4, PD-1, and PD-L1) is presented in Table 2 [2, 26, 27, 43, 44].

CONCLUSIONS

The introduction of ICIs into clinical practice is a significant advancement in the treatment of oncological diseases. However, the rates of various immune-mediated adverse effects, particularly dermatological ones, during treatment with CTLA-4 and PD-1/PD-L1 inhibitors are extremely high. The pathogenesis of these reactions is based on the reactive activation of immune processes in the skin and a decrease in the body's tolerance to autoimmunization. Of particular importance is the assessment of the clinical picture and pathomorphologic patterns of rashes to develop the most effective accompanying therapy for patients with cancer and exclude possible reduction in the dose of antitumor drug or its withdrawal, which will allow for the initiation of the most effective antitumor treatment. This will significantly improve patients' quality of life and life expectancy.

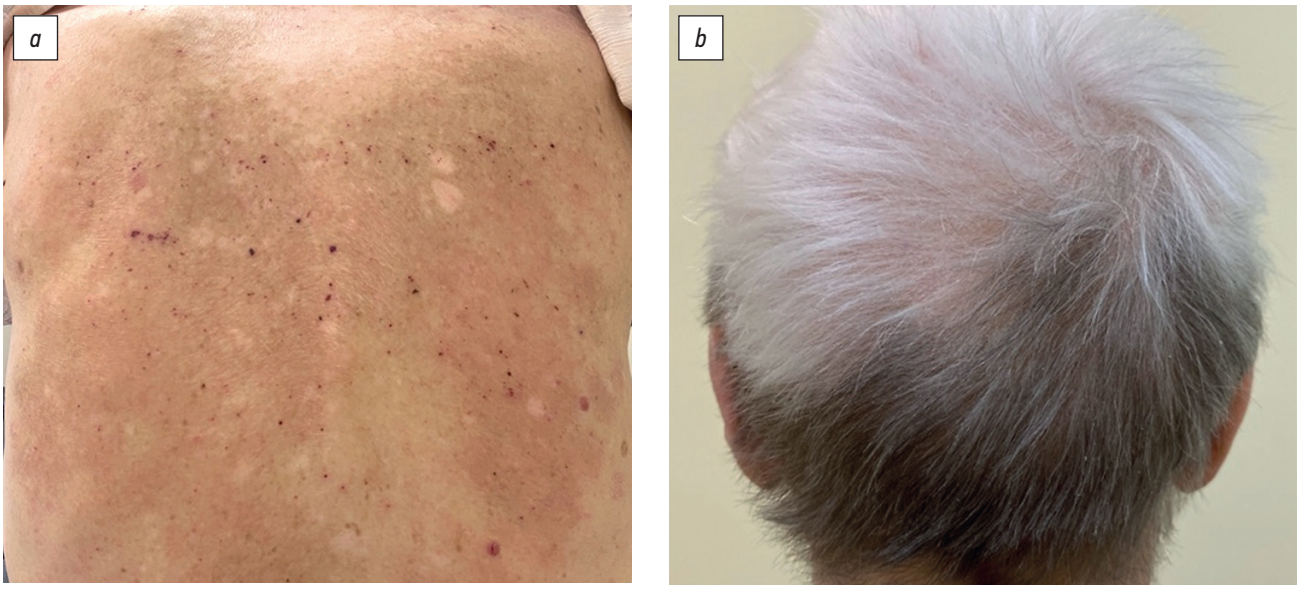

Fig. 8. Vitiligo-like reaction produced by treatment with prolgolimumab: *a* — vitiligo-like depigmentation of the skin; *b* — hair pigment loss.
Рис. 8. Витилигоподобная реакция, возникшая при лечении пролголимабом: *a* — витилигоподобная депигментация кожи; *b* — потеря волосяного пигмента.

Table 2. Immune-mediated dermatological adverse reactions of CTLA-4, PD-1, PD-L1 immune checkpoint inhibitors
Таблица 2. Иммуноопосредованные дерматологические нежелательные явления ингибиторов иммунных контрольных точек CTLA-4, PD-1, PD-L1

Reaction	Pruritus	Maculopapular rash	Lichenoid rash	Psoriasiform rash	Vitiligo-like reaction	Bullous pemphigoid	Alopecia
Period of disease onset	4–6 weeks	4–6 weeks	7–12 weeks	0–3 weeks	>7 weeks	13–15 weeks	>13 weeks
Localization	Entire skin	Trunk and extensor surfaces of the extremities	Trunk and limbs	Trunk and limbs	Trunk and extremities (mainly sun-exposed areas)	Trunk, limbs, and oral mucosa	Scalp
Clinical characteristics	The presence of rashes is optional. Pruritus bothers at any time of the day and is not controlled by antihistamines.	Erythematous spots with a tendency to merge. There may be desquamation on the surface.	Multiple red-purple papules of polygonal shape with marked infiltration and tendency to merge into plaques. Subjective itching	Erythematous infiltrated plaques with clear irregular borders and flaking on the surface	Multiple foci of depigmentation with a tendency to merge	Prodromal phase of pruritus followed by blister formation	Hair loss

ADDITIONAL INFORMATION

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Authors' contribution. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work. A.Yu. Syryseva — collection and analysis of literary sources, preparation and writing of the text of the article, analysis of patient histories, preparation of research results; E.A. Shatokhina — analysis of literary sources, editing the article, analysis of patient histories, preparation of research results; A.S. Polonskaia, I.A. Pokataev — analysis of literary sources, editing the text of the article, analysis of patient histories; L.S. Kruglova, V.N. Galkin — analysis of literary sources, editing the text of the article.
Consent for publication. Written consent was obtained from patients for publication of relevant medical information and all associated images in the manuscript.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при подготовке публикации.

Конфликт интересов. Авторы заявляют об отсутствии явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Вклад авторов. Авторы подтверждают соответствие своего авторства международным критериям ICMJE (все авторы внесли существенный вклад в разработку концепции, проведение поисково-аналитической работы и подготовку статьи, прочли и одобрили финальную версию перед публикацией). Наибольший вклад распределён следующим образом: А.Ю. Сырысева — сбор и анализ литературных источников, подготовка и написание текста статьи, анализ историй болезней пациентов, подготовка результатов исследования; Е.А. Шатохина — анализ литературных источников, редактирование статьи, анализ историй болезней пациентов, подготовка результатов исследования; А.С. Полонская, И.А. Покатаев — анализ литературных источников, редактирование текста статьи, анализ историй болезней пациентов; Л.С. Круглова, В.Н. Галкин — анализ литературных источников, редактирование текста статьи.

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