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ORIGINAL ARTICLE

Cutaneous toxicities of antineoplastic agents: data from a large cohort of Greek patients

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Abstract

Purpose Cutaneous toxicities from novel anticancer treatments are an emerging problem in dermato-oncology. However, the prevalence of those toxicities and necessity of skin consultations are currently unknown. The purpose of our study was to perform an epidemiologic analysis of cutaneous toxicities that were referred to our cutaneous toxicity clinic in Athens, Greece.

Methods All patients examined at the oncodermatology department over a 42-month period were included. Gender, age, type of cancer, type of antineoplastic treatment, and type of toxicity were recorded and analyzed.

Results Four hundred fifty-nine patients (182 males, 277 females) with mean age (SD) 60.6 years (13.05) were included in the analysis. Six hundred seventy-two cutaneous toxicities were recorded. Chemotherapy-induced toxicities were the most commonly recorded incidents, with taxanes being the most commonly involved agent. Immune-related adverse events (IRAEs) have steadily increased over the past 3 years. Treatment modifications due to skin toxicities were more common in patients treated with targeted agents and immune checkpoint inhibitors than in those treated with chemotherapy. The toxicities that led to the most treatment modifications were acneiform eruptions and perionychias. The most common IRAEs recorded were psoriasis in 11 patients, followed by pruritus, macular rash, and lichenoid-type eruptions. In addition, 4 interesting cases of IRAEs are discussed.

Conclusion Antineoplastic treatments can lead to a wide range of cutaneous toxicities. Our study underlines the need for a multidisciplinary approach in oncologic patients. The dermatologists' role is crucial in effectively managing those reactions and preventing antineoplastic drug dose adjustments or discontinuation of treatment.

Keywords Cutaneous toxicities · Immune-related adverse effects · Acneiform eruption · Perionychia

Introduction

Over the last few decades, novel antineoplastic therapies targeting specific molecular pathways and tumor microenvironment such as epidermal growth factor or multiple kinase inhibitors have been approved for the treatment of various malignancies. Such agents have significantly improved the survival rates of patients with advanced diseases while reducing the risk of common chemotherapy-related toxicities like myelosuppression, nausea, and vomiting [1, 2]. However,

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many of these novel treatments have been associated with unique adverse events. Cutaneous toxicities are among the most common of those events and are sometimes difficult to treat and diagnose [3–5].

Since the number of cancer patients exposed to novel agents continues to expand, appropriate management of that unique spectrum of side effects will be a critical part of treatment. Therefore, highly academic study groups devoted to the understanding and treatment of cutaneous toxicities, such as the Multinational Association of Supportive Care in Cancer (MASCC), will have a crucial role in this new field of dermato-oncology. Our skin toxicity clinic at the Andreas Sygros Hospital for Skin Diseases has been operating since 2015. In this study, we analyzed cutaneous toxicities in patients referred to our department from major oncology centers in Athens.

Methods

We retrospectively reviewed all cases referred to our cutaneous toxicity clinic at Andreas Sygros Hospital for Skin Diseases, University of Athens Medical School, from January 2015 to June 2018. The type of anticancer treatment was recorded and labeled as "chemotherapy," "targeted" (epidermal growth factor receptor inhibitors [EGFRIs], BRAF inhibitors, mitogen-activated protein kinase [MAPK] inhibitors), "immune checkpoint inhibitor," "radiotherapy," "hormonal therapy," or "other therapies." If a patient had multiple treatments (e.g., immune checkpoint inhibitors and targeted therapy), the agent incriminated for skin toxicity was recorded. The gender, age, date of first visit, date of last follow-up, total number of visits, number and type of toxicities, as well as instances of anticancer therapy cessation, delay, and dose reduction, were recorded. Four interesting IRAEs are discussed.

Comparison of skin events in patients treated with chemotherapy, targeted agents, or immune checkpoint inhibitors was investigated by exploratory analysis using the chi-square test. The analysis was conducted through IBM SPSS Statistics 23.0 (SPSS, Chicago, IL, USA) while the significance level was set up at $\alpha = 0.05$.

Results

Over a 42-month period, 459 patients (182 males and 277 females) were referred to our department; they received 473 treatments. Their mean age (SD) was 60.6 (13.05) years (62.05 [13.5] years for males and 59.7 [12.8] years for females). Overall, 672 cutaneous toxicities were recorded. The patients' characteristics and treatments are presented in Table 1. Malignancies with the highest frequencies of cutaneous toxicities were breast and lung cancers. Table 2 summarizes the toxicities most commonly diagnosed at our clinic. Chemotherapy-induced toxicities were the most common toxicities, with taxanes being the most frequently implicated. Immunotherapy-induced skin toxicities have steadily increased from 2015 to 2018 (Fig. 1).

The most common chemotherapy-related toxicities were nail disorders in patients treated with taxanes (77 referrals), followed by hand-foot syndrome (HFS; Table 1). Onycholysis was the most frequently detected nail lesion, followed by subungual hematoma, melanonychia, and purulent discharge. Chemotherapy-induced toxicities were significantly more common in females than in males (159 [60.9%] female patients vs. 39 male patients [21.8%], $P < 0.001$; Table 2). The rate of treatment modifications due to skin toxicities was higher in patients treated with targeted agents or immunotherapy than in those treated with chemotherapy (13 [6.6%] chemotherapy vs 30 [15.5%] targeted agents, vs 8 [16.7%] immunotherapy, $P = 0.008$). Toxicities that led to the highest rate of treatment modifications were EGFRI-induced acneiform eruptions and perionychias. Patients who received newer agents were treated at our clinic more frequently than those who received chemotherapy (75 [38.7%] of patients on targeted agents visited our department more than three times, compared to 32 [16.2%] of chemotherapy-treated patients). In addition, multiple toxicities were much more common in patients treated with targeted agents than in those treated with chemo- or immunotherapy [16.5% for targeted agents, vs 5.1% and 4.2% for chemotherapy and immune checkpoint inhibitors respectively, $P < 0.001$] (Table 2).

The most common IRAEs recorded were psoriasis flares (11 patients), followed by pruritus, macular rash, and lichenoid-type eruptions (Table 1). Two of the patients with psoriasis had a personal history of psoriasis, while 5 had a family history of psoriasis. The psoriasis pattern with the highest frequency was guttate psoriasis (6 patients). One patient also developed psoriatic arthritis.

Severe toxicities were recorded in 3 patients, including 2 patients with Stevens–Johnson reactions. The first was a female patient with ovarian cancer treated with liposomal doxorubicin; the second was a male patient with lung cancer treated with docetaxel. Both patients recovered after hospitalization and treatment. A third patient, who was on everolimus for a gastrointestinal stromal tumor, died from skin toxicity (Fournier gangrene).

Four interesting cases of IRAEs

Case no. 1

A 49-year-old patient was treated with nivolumab for kidney cancer. He visited our clinic for a pruritic macular rash that developed after the 3rd cycle of an anti-programmed cell death protein 1 (anti-PD1) agent. He also reported a burning sensation and sun sensitivity that did not previously exist. On

Table 1 Patients' characteristics and most common toxicities recorded

	Total no. of patients = 459 (%) Total no. of skin toxicities = 672
Gender	
Males	182 (39.8)
Females	277 (60.2)
Commonest cancers	
Lung	84
Breast	129
Colorectal	59
Kidney	16
Melanoma	44
Ovarian	19
Anticancer treatment*	
Chemotherapy	198 (43.1)
Targeted agent	194 (42.3)
Immune checkpoint inhibitors	48 (10.5)
Targeted + immune checkpoint inhibitors	15 (3.3)
Radiotherapy	13 (2.8)
Other	5 (1.1)
Chemotherapy-related toxicities	198
Total toxicities recorded	256
Commonest toxicities	
Onychia	77 (38,9)
HFS	27 (13,6)
Dermatitis	25 (12,6)
Infections	24 (12,1)
Phototoxic	19 (9,6)
Macular rash	13 (6,6)
Targeted agents	
Commonest agents and toxicities	
EGFRIs, no of patients	95
Acneiform	74
Perionychia	28
Xerosis-eczema	26
Pruritus	6
BRAF/MEK, no of patients	29
Verrucous keratosis	12
KA/SCC	9
Plantar hyperkeratosis	8
Grover	3
Acneiform	3
MKIs, no of patients	26
Hand foot	13
Psoriasiform eruption	4
Phototoxic eruption	3
IRAEs, no of patients	48
Total toxicities recorded	54
Psoriasis	11
Bullous Pemphigoid	5
Vitiligo	2
Lichenoid-type eruption	7
Pruritus	9
Macular rash	8
Eczema	3
Urticaria	2
Pityriasis lichenoides	2
Lupus erythematosus	1
Other	4

*Fourteen patients (3.1%) received more than one treatments due to disease progression

close clinical examination, a total discoloration of the face was noted (Fig. 2a). Minor lesions of normal melanosis around his eyes were also present. The diagnosis of vitiligo was set and no treatment was prescribed. Interestingly, 11 months after cessation of immunotherapy, a rapid recoloration of his skin was noted (Fig. 2b).

Cases nos. 2–3

Two cases of anti-PD1-induced PLEVA have been recorded in our department. A 79-year-old male patient was referred to our department for dermatological assessment of multiple ulcerated erythematous plaques on his trunk and extremities. The patient was under nivolumab for non-small cell lung cancer. After the 4th cycle, intense pruritus appeared along with a mild maculopapular rash on his chest. The patient was treated with 5 mg levocetirizine pos and showed good response. However, after the 8th cycle, the treatment was complicated by multiple ulcerated necrotic papules on the patient's trunk and extremities (Fig. 3a, b). An incisional biopsy was performed to confirm a diagnosis of pityriasis lichenoides et varioliformis acuta (PLEVA; Fig. 3c).

A combination regimen of 10 mg prednisolone and high-potency topical steroids was initiated with significant clinical improvement. Low-dose prednisolone was prescribed for the first week after immunotherapy, during which a minor exacerbation of the skin rash was noted. Immunotherapy continued from that point on without further interruptions.

The second case of PLEVA reaction was a 65-year-old male patient, who was under nivolumab for non-small cell lung cancer, as well. After the 3rd cycle, he developed a PLEVA-like rash on his extremities. He was treated with 15 mg prednisolone p.os. combined with high-potency topical steroids, leading to remission of skin lesions. The patient continued immunotherapy without further interruptions.

Table 2 Comparison of skin events in patients treated with chemotherapy, targeted agents, or immune checkpoint inhibitors

	Chemotherapy, *n* (%)	Targeted therapies, *n* (%)	Immune checkpoint inhibitors, *n* (%)
Sex			
Male	39 (21.8)	112 (62.6)	28 (15.6)
Female	159 (60.9)	82 (31.4)	20 (7.7)
$P < 0.001$			
Treatment delays or modifications			
No	185 (93.4)	164 (84.5)	40 (83.3)
Yes	13 (6.6)	30 (15.5)	8 (16.7)
$P = 0.008$			
Total no visits			
1	89 (44.9)	52 (26.8)	11 (22.9)
2–3	77 (38.9)	67 (34.5)	26 (54.2)
> 3	32 (16.2)	75(38.7)	11 (22.9)
$P < 0.001$			
No of toxicities			
1	145 (73.2)	104 (53.6)	39 (81.2)
2	43 (21.7)	58 (29.9)	7 (14.6)
≥ 3	10 (5.1)	32 (16.5)	2 (4.2)
$P > 0.001$			

Case no. 4

A 67-year-old female patient with a history of systemic lupus erythematosus (SLE) that had been in remission over the previous 14 years began treatment with nivolumab for lung cancer under close rheumatologic surveillance. The patient had no previous signs of skin disease. Four weeks after initiation of treatment, a large erythematous plaque developed on her back (Fig. 4a). There were no laboratory or clinical signs of SLE recurrence, but an incisional biopsy was performed, and the specimen was sent for hematoxylin and eosin (H&E) staining and immunofluorescence analysis. Laboratory tests confirmed a diagnosis of discoid lupus erythematosus. Antinuclear antibodies, anti-double-stranded DNA, complement component (C)3, C4, and erythrocyte sedimentation rate were all negative. Prednisolone (15 mg/day) and hydroxychloroquine (400 mg/day) were added to nivolumab therapy. Complete resolution of the skin rash was recorded 4 weeks after initiation of therapy, and she continued immunotherapy under close surveillance by our clinic (Fig. 4b).

Discussion

Our study underlines the uprising demand for the development of dermato-oncology departments specialized in the

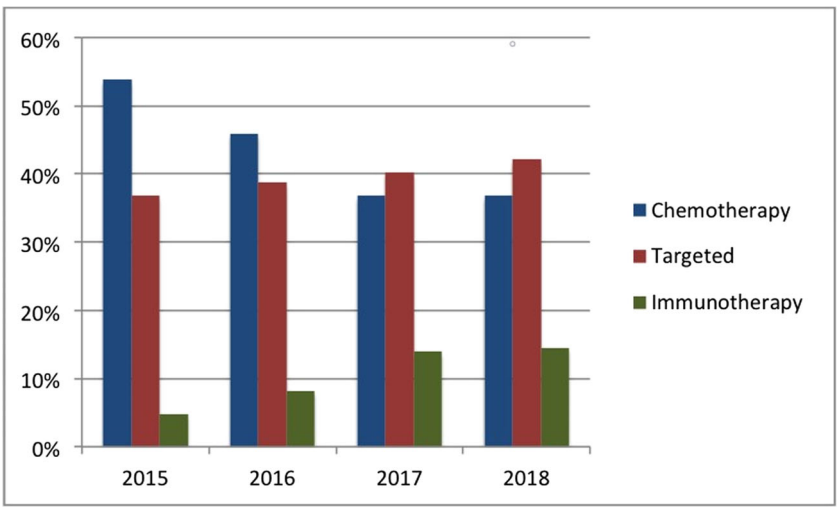

Fig. 1 Increase of immunotherapy-induced toxicities during the last 3 years

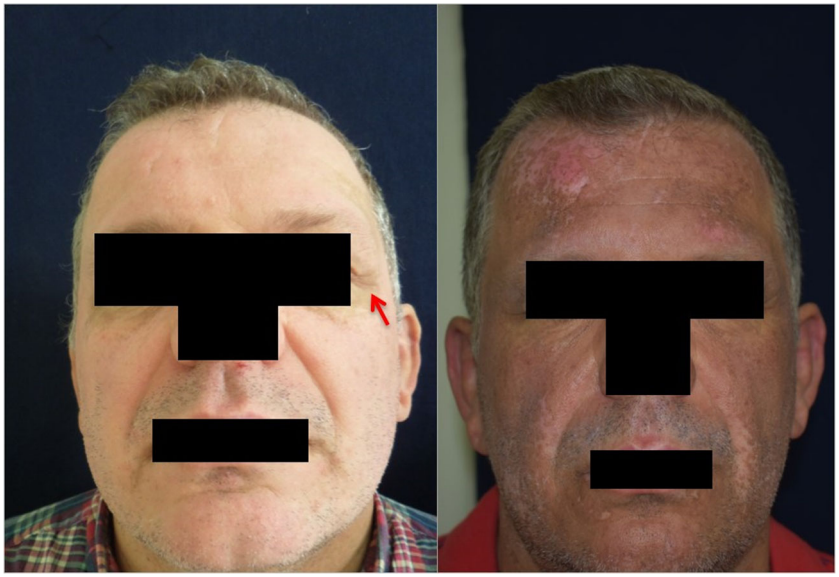

Fig. 2 **a** Total discoloration of the face due to nivolumab-induced vitiligo, with small lesions of normal melanosis around the eyes. **b** Recoloration of patient's skin after nivolumab cessation

field of skin toxicities. In our study, significantly, more female patients were recorded, supporting the notion that women have higher awareness of skin diseases and skin toxicities have more impact on their quality of life compared to that of male patients.

The majority of patients referred to our clinic presented with chemotherapy-related toxicities, with taxane-induced onychias being the most common adverse event. Sometimes, clinical oncologists underestimate this toxicity, but the impact on patients' quality of life and daily activities can be significant [6]. Literature on preventive measures and treatments is insufficient [7], as randomized blind studies of therapeutic or preemptive procedures for skin toxicities are lacking. In order to establish evidence-based guidelines, performing such studies for evaluation of treatment algorithms is recommended. One possibility that has not been widely adopted is the use of frozen gloves during chemotherapy. A less expensive option involving the application of ice packs 15 min before and after initiation of treatment may also be effective [8].

The second most common chemotherapy-induced toxicity was HFS. It is well known that HFS, although not life-threatening, can lead to reduced compliance and deterioration of patients' quality of life [9, 10]. This fact is reflected in the high mean number of patient visits in those with HFS (17 out of 27 patients visited our clinic more than twice), although only one treatment delay due to this side effect was recorded.

The clinical characteristics of HFS differ from that of palmoplantar reactions induced by the new targeted agents [11]. The latters are characterized by the development of hyperkeratosis in areas of skin trauma; they typically present as painful yellowish plaques localized mainly in pressure areas of the soles and are described under the term hand and foot skin reactions (HFSRs) [12]. Similar to chemotherapy-induced HFS, tyrosine kinase inhibitor (TKI)–induced

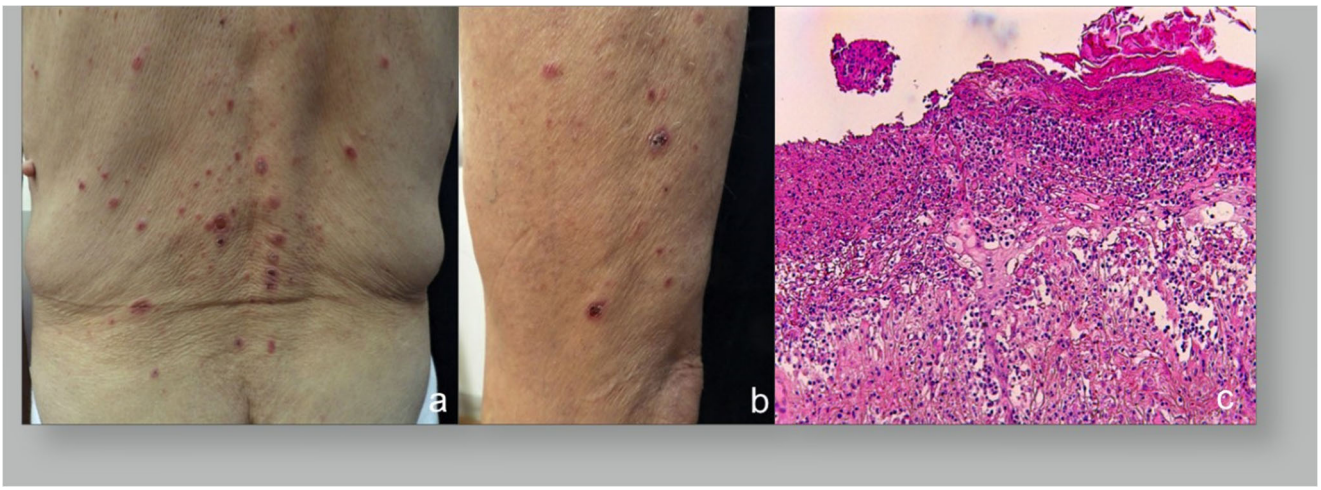

Fig. 3 **a** Pityriasis lichenoides et varioliformis acuta (PLEVA) to a patient under nivolumab **b** clinical features and **c** histopathological image

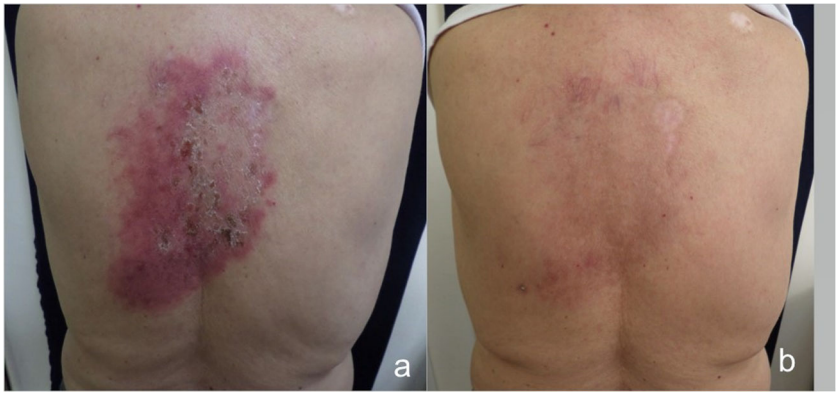

Fig. 4 **a** Discoid lupus erythematosus to a patient under nivolumab immunotherapy. **b** Resolution of skin rash after treatment with prednisolone and hydroxychloroquine

HFSRs also led to a high number of visits. However, more patients with HFSRs delayed treatment than those with chemotherapy-induced HFS (5 out of 21 HFSR patients delayed treatment).

Of the targeted agents, EGFRIs caused the highest rate of skin toxicities. As expected, acneiform rash was the most common toxicity (74 out of 95 patients), followed by perionychia and xerosis. However, only 8 patients reduced or discontinued treatment because of acneiform rash. In contrast, 6 out of 28 patients presenting with perionychia halted treatment, underlining the need for proper management and early interventions. In our experience, perionychias are the most challenging toxicity to treat. Further studies on preventive or therapeutic measures are needed.

Cutaneous immune-related adverse events (IRAEs) were the most common toxicities in patients treated with anti-PD1, anti-programmed cell death ligand 1 (anti-PDL1), or anti-cytotoxic T lymphocyte–associated protein 4 (anti-CTLA4) antibodies [13]. The proportion of patients with IRAEs referred to our department since 2015 has been steadily increasing. Although recent literature reports that maculopapular rashes and lichenoid skin reactions are the most common cutaneous side effects in patients treated with anti-PD1/PDL1 [14], such reactions were second to psoriasis flares and pruritus in our cohort. Because grade 1 macular rashes are usually treated by oncologists, we believe this rash was relatively underestimated in our patient population. Thus, psoriasis flares were the most common cutaneous toxicity reported for immune checkpoint inhibitors. Other cases of anti-PD1–induced psoriasis have recently been reported [15–17]. In 2017, we published a series on anti-PD1–induced psoriasis in 5 patients treated with anti-PD1/PDL1 agents [18]. Interestingly, 3 out of 5 patients had no personal history of psoriasis, while 2 of the patients had a family history of psoriasis. Moreover, 4 out of 5 patients developed guttate psoriasis. These findings were confirmed by the current study. Five out of 11 patients had a family history of psoriasis, 6 patients presented with guttate lesions, while 1 patient with a history of psoriasis experienced erythrodermia and discontinued immunotherapy.

In melanoma patients treated with immune checkpoint inhibitors, vitiligo is a well-recognized immune-related adverse event [19, 20]. Nevertheless, cases of vitiligo were relatively uncommon in our series. We believe that along with maculopapular rashes, vitiligo cases were underreported and not referred to our specialized center. In the vitiligo case (Case 1), three interesting points could be made. First is the appearance of vitiligo in a patient treated for kidney cancer. Despite the belief that this toxicity is unique to patients treated for melanoma [21, 22], rare cases in patients with other malignancies have recently been reported [23, 24]. Second, the patient had uniform discoloration of facial skin. The pattern of vitiligo in patients treated with targeted agents has been previously described [25]. For instance, Larsabal et al. [25] reported that vitiligo-like lesions occurring in patients under anti-PD1 therapies are clinically and biologically different from that of classic vitiligo, suggesting that the pathomechanism involved in loss of melanocytes differs between the two conditions [26]. In their series, all patients developed lesions on photoexposed areas associated with pre-existing solar lentigines, with a specific pattern of depigmentation consisting of multiple flecked macules evolving toward larger plaques. The pattern of vitiligo in our case (uniform discoloration that was difficult to detect by both patient and clinician) has never been described. The final interesting point was skin recoloration 11 months after treatment cessation. In most studies, vitiligo persists beyond the completion of immunotherapy. Recently, a case was reported in which vitiligo vanished when a patient's initial tumor recurred. No signs of recurrence were detected in our patient, although he is currently being closely monitored.

In our series, two PLEVA-like toxic reactions were recorded. These are the first reported cases of such reactions in patients treated with anti-PD1 agents. Both patients developed a rash several weeks after the appearance of a typical macular rash, suggesting that macular rashes may be the initial presentation of other toxicities. With close dermatological surveillance and management, both patients completed treatment without interruptions.

Finally, although the introduction of immune checkpoint inhibitors in patients with history of autoimmune diseases is a matter of debate, our fourth patient case supports the scenario that under close clinical surveillance, such patients can benefit from immunotherapy [26, 27]. Given the limited therapeutic options in patients with advanced cancer, clinicians should give thoughtful consideration to the use of immune checkpoint inhibitors and proceed with appropriate caution. This case highlights the necessity of a multimodal approach in oncology patients in this era of new and upcoming anticancer agents.

In conclusion, cooperation between oncologists and dermatologists is necessary in order to identify and manage any unusual or dermatological side effects that might compromise therapy and prognosis. To this end, the need for dermato-oncology departments specialized in the field of skin toxicities is rising. Expansion is needed to meet the growing demand.

Compliance with ethical standards

Disclosure of potential conflicts of interest Please find the attached disclosure forms. We have full control of all primary data and we agree to allow the journal to review the data if requested.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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