Associations of Cutaneous Immune-Related Adverse Effects of Immunotherapy With Treatment Response in Patients With Metastatic Melanoma

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ABSTRACT

Background: Dermatologic toxicity is the most common immune-related adverse effect of cancer immunotherapy.

Methods: We retrospectively reviewed the health records of adult (≥18 years) melanoma patients who received ipilimumab, nivolumab, or pembrolizumab from January 1, 2011, through September 15, 2017, at Mayo Clinic. The χ² test was used to assess the association between development of a cutaneous immune-related adverse effect and antitumoral response to the immune checkpoint inhibitors. Odds ratios were calculated with logistic regression models and were adjusted for sex and immunotherapeutic drugs. We described the various cutaneous immune-related adverse effects and assessed the response to immunotherapy (each patient's objective clinical response was categorized as favorable [complete or partial response] or unfavorable). We then determined whether development of a cutaneous immune-related adverse effect was associated with the clinical response.

Results: Of 690 melanoma patients, 232 (33.6%) had a cutaneous immune-related adverse effect. The most common effects were dermatitis (21.4%), pruritus (5.5%), and vitiligo (4.2%). Median (range) time to onset of dermatitis was 3 (0-7) weeks; lichenoid dermatitis, 12 (6-18) weeks; and vitiligo, 40 (12-96) weeks. Development of a cutaneous immune-related adverse effect was significantly associated with favorable clinical response.

Conclusions: Development of cutaneous immune-related adverse effects is associated with favorable responses to nivolumab, ipilimumab, pembrolizumab, and ipilimumab plus nivolumab therapy in patients with metastatic melanoma.

INTRODUCTION

Immune checkpoint inhibitors (ICIs), such as ipilimumab (I), pembrolizumab (P), and nivolumab (N), have drastically improved the survival of patients with melanoma. Although these immunotherapeutic agents act by harnessing the immune response to fight melanoma, they are also associated with unique immune-related adverse effects (irAEs). Regardless of the precise mechanism involved, all irAEs occur because of excessive immune activation.
Any organ can be affected, but cutaneous irAEs are the most common toxicities of ICIs.1

Previous clinical trials and studies have reported incidence rates of 30% to 40% for cutaneous irAEs associated with I, P, and N.1-3 Studies have also shown that development of vitiligo is associated with better treatment response and prognosis of melanoma.4,5 However, sparse data describe the various cutaneous irAEs and their associations with immuno-therapy in a large cohort of patients with melanoma. We sought to describe the various cutaneous irAEs, associations between these irAEs and I, N, and P, and associations between skin reaction and antitumoral response to immuno-therapy in melanoma patients.

### METHODS

This study was approved by the Mayo Clinic Institutional Review Board, and informed consent was waived for this retrospective study. We conducted a retrospective review of electronic health records of adult (age ≥18 years) melanoma patients who received ICI therapy with I, N, or P from January 1, 2011, through September 15, 2017, at Mayo Clinic in Rochester, Minnesota; Phoenix, Arizona; and Jacksonville, Florida. Patients were categorized into 2 groups: those who had a cutaneous irAE and those who did not. Cutaneous irAEs were graded according to the Common Terminology Criteria for Adverse Events version 4.03.6

To assess response to immuno-therapy, we graded each patient’s objective clinical response as favorable (ie, complete or partial response) or unfavorable. For those who did not have a cutaneous irAE while receiving any ICI, the best response achieved while receiving immuno-therapy was recorded. We excluded patients who had a concomitant second tumor (n=5); received chemotherapy and immuno-therapy (n=8); received follow-up at other facilities, and therefore their responses could not be determined (n=7); and stopped ICI because of intolerance (n=6).

We used the χ² test to assess the association between development of a cutaneous irAE and antitumoral clinical response to ICI therapy. Odds ratios (ORs) and 95% CIs were calculated with logistic regression models and were adjusted for sex and immuno-therapeutic drugs. P<.05 was considered significant.

### RESULTS

#### Demographic Characteristics

We identified 690 melanoma patients (486 men and 204 women) who received I (n=228), N (n=16), P (n=297), or I+N combination therapy (n=149). Of these, 232 patients (33.6%) reported a skin reaction to immuno-therapy. The median (range) age of the patient cohort was 66 (26-93) years, and the median (range) age at diagnosis of melanoma was 61 (24-91) years. Among those who had a cutaneous irAE, 155 (66.8%) were men and 77 (33.2%) were women.

The most common cutaneous irAE was grade 1 dermatitis (103 patients [14.9%]), and other patients had vitiligo (29 [4.2%]), lichenoid dermatitis (7 [1.0%]), flare of preexisting psoriasis (7 [0.7%]), sclerodermoid reaction (2 [0.3%]), tumoral melanosis (2 [0.3%]), and bullous pemphigoid (1 [0.1%]) (Table 1).

Duration, management, and outcome of the cutaneous irAEs are summarized in Table 2. After treatment initiation, the median (range)
Table 1. Cutaneous Immune-Related Adverse Effects due to I, P, and N in Melanoma Patients (N=690)

| Diagnosis                          | No. of Patients (%) | Grade (No. of Patients) | Time to Onset, Median (Range) | Site (No. of Patients) |
|------------------------------------|---------------------|-------------------------|------------------------------|------------------------|
| Any cutaneous condition            | 232 (33.6)          | Not determined          | 3-40 wk                      | Self-reported maculopapular rash (24) |
| Dermatitis                         | 148 (21.4)          | Grade 1 (103)           |                              | Generalized (14), torso (71), extremities (59), and face and neck (4) |
| Maculopapular rash                 | 145 (21.0)          | Grade 1 (103)           |                              |                        |
| Acneiform rash                     | 1 (0.1)             | Grade 1 (103)           |                              |                        |
| Urticarial plaques                 | 2 (0.3)             | Grade 1 (103)           |                              |                        |
| Pruritus without dermatitis        | 38 (5.5)            | Grade 1 (32)            | 4 (0-12) wk                  | Generalized (21), torso (10), extremities (4), and face (3) |
| Vitiligo                           | 29 (4.2)            | Grade 1 (26)            | 40 (12-96) wk                | Extremities (13), torso (10), face (2), and generalized (4) |
| Lichenoid dermatitis^b             | 7 (1.0)             | Grade 2 (7)             | 12 (6-18) wk                 | Extremities and torso (4), torso (2), and extremities (1) |
| Worsening psoriasis                | 5 (0.7)             | Not graded              | 18 (9-30) wk                 | Extremities (3) and chest (2) |
| Sclerodermoid reaction^b           | 2 (0.3)             | Grade 2 (2)             | 15 and 39 wk                 | Extremities (2) |
| Tumoral melanosis                  | 2 (0.3)             | Not determined          | 40 and 56 wk                 | Chest (1) and chest and back (1) |
| Bullous pemphigoid                 | 1 (0.1)             | Grade 2 (1)             | 36 wk                        | Extremities (1) |

Abbreviations: I – ipilimumab; N – nivolumab; P – pembrolizumab.

^a Eighteen patients had vitiligo while receiving P at a median (range) of 9 (2.5-23) months after treatment initiation; 1 patient, while receiving P (the exact time could not be determined); 4 patients, while receiving I at a median (range) of 4 (3-10) months; 3 patients, while receiving I+N combination therapy at a median (range) of 11 (4-11) months; 1 patient, at 9 months after starting P and 6 months after starting I; 1 patient, 17 months after the first dose of P and 6 months after starting I+N combination therapy; and 1 patient, while receiving N (the exact time could not be determined).

^b All cases were attributed to P.

^c One patient had 4 cycles of I+N combination therapy and later continued only N for 23 more cycles before melanosis was noted on the chest and back (14 months after the first cycle of N); the other patient had 4 cycles of I+N combination therapy and later continued only N for 24 more cycles before melanosis was noted on the chest (10 months after the first cycle of N).
Table 2. Duration, Management, and Outcome of Cutaneous irAEs

| Cutaneous irAE (No. of Patients) | Duration (No. of Patients) | Management (No. of Patients) | Outcome (No. of Patients) |
|----------------------------------|---------------------------|-----------------------------|---------------------------|
| **Dermatitis (148)**<br>Maculopapular rash (145; 24 with self-reported)<br>Urticarial plaque (2)<br>Acneiform rash (1) | <1 wk (20)<br>1-2 wk (53)<br>2-4 wk (50)<br>4 wk (25) | Grade 1 and grade 2 were managed with topical corticosteroids, oral antihistamines (23), and rarely oral corticosteroids (26); grade 3 was managed with higher doses of corticosteroids and referral to a dermatologist | Responded to treatment (105)<br>Cleared on its own or with over-the-counter medication (35)<br>Required ICI interruption (7)<br>Persisted at last follow-up (2) |
| **Pruritus without dermatitis (38)** | <1 wk (6)<br>1-2 wk (6)<br>2-4 wk (21)<br>4 wk (5) | Topical corticosteroids (38)<br>Antihistamines (15)<br>Systemic corticosteroids (8) | Required ICI interruption (1) |
| **Vitiligo (29)** | Persisted at the time of last follow-up | Sun protection (29) | Persisted at the last follow-up (29) |
| **Lichenoid dermatitis (7)** | 2-4 wk (2)<br>4 wk (3) | Topical corticosteroids (7)<br>Oral corticosteroids (3) | Responded well to treatment (7)<br>Required ICI interruption (1) |
| **Worsening psoriasis (5)** | >4 wk (5) | Topical corticosteroids (5)<br>Apremilast (2)<br>Acitretin (1) | Responded to treatment (5)<br>Required ICI interruption (3<sup>a</sup>) |
| **Sclerodermoid changes (2)** | >4 wk (2) | Intravenous immunoglobulin, mycophenolate mofetil, and oral corticosteroids (1)<br>Hydroxychloroquine and oral corticosteroids (1) | Required ICI interruption (2<sup>a</sup>) |
| **Tumoral melanosis (2)** | Persisted at last follow-up | No treatment (2) | Persisted at last follow-up (2) |
| **Bullous pemphigoid (1)** | >4 wk (1) | Oral corticosteroids, mycophenolate mofetil, doxycycline, and topical corticosteroids (1) | Responded to treatment and required ICI interruption (1) |

Abbreviations: ICI – immune checkpoint inhibitor; irAE – immune-related adverse effect.<br><sup>a</sup> One of these patients required permanent discontinuation of all ICIs.
time to onset of dermatitis was 3 (0-7) weeks; lichenoid dermatitis, 12 (6-18) weeks; and vitiligo, 40 (12-96) weeks.

**Histopathologic Characteristics**  
Biopsy was not performed for all cutaneous irAEs. Of 14 patients who underwent skin biopsy for evaluation of dermatitis, 7 had characteristics of lichenoid dermatitis, such as vacuolar interface dermatitis with scattered dyskeratotic keratinocytes and mixed perivascular inflammation. The other 7 showed characteristics of subacute dermatitis. Results of skin biopsies confirmed the diagnoses of bullous pemphigoid, sclerodermoid reaction, lichenoid dermatitis, and tumoral melanosis.

**Management**  
Most cutaneous irAEs were managed by medical oncologists and treated with topical corticosteroids, with or without antihistamines. Thirty-two patients (13.8%) were referred to dermatologists. Severe cutaneous toxicity warranted hospitalization for further evaluation and aggressive management by dermatologists, in addition to permanent discontinuation of ICI therapy. Although ICI treatment was interrupted in 15 patients, at the last follow-up, only 2 patients required permanent discontinuation of all ICIs. Management strategies were based on the clinical judgment of the treating physicians and the symptoms and clinical signs at presentation.

Sex did not influence the likelihood of development of a cutaneous reaction ($P=.94$, determined with the $\chi^2$ test). Patients receiving I+N combination therapy were more likely to have dermatitis than those receiving P (OR [95% CI], 2.5 [1.2-4.8]; $P=.01$) or N alone (OR [95% CI], 4.6 [1.0-19.9]; $P=.04$). Development of a cutaneous irAE was significantly associated with favorable clinical response ($P<.001$).

The objective response rate (ORR) of patients with a cutaneous irAE was markedly greater than that of those who did not have a cutaneous irAE (67.7% vs 37.2%) (Table 3). The ORR of those with a self-reported rash was 54.5%, and that of patients with vitiligo was 86.2%. Patients who had vitiligo were more likely to have a favorable response than patients without vitiligo (OR, 7.23).

**Table 3. Antitumor Responses in Patients With and Without Cutaneous irAEs (n=664$^a$)**

| Response   | Patients Without Cutaneous irAEs, No. (%) | Patients With Cutaneous irAEs, No. (%) |
|------------|------------------------------------------|---------------------------------------|
| Favorable$^b$ | 178 (37.2)                              | 126 (67.7)                            |
| Unfavorable | 300 (62.8)                               | 60 (32.3)                             |

Abbreviation: irAE – immune-related adverse effect.

$^a$ We initially identified 690 melanoma patients who received immune checkpoint inhibitors, but to assess treatment response we excluded patients who had a concomitant second tumor (n=5), received chemotherapy and immunotherapy (n=8), received follow-up at other facilities and therefore had responses that could not be determined (n=7), or stopped immune checkpoint inhibitors because of intolerance (n=6).

$^b$ Defined as a complete or partial response.

**DISCUSSION**

**Incidence**  
Approximately one-third of our patients receiving I, N, P, or I+N combination therapy had a cutaneous irAE. Dermatitis (21.4%), pruritus without a rash (5.5%), and vitiligo (4.2%) were most commonly associated with these agents. The most common irAE described in the health records was maculopapular rash; however, acneiform rashes and urticarial plaques were also seen.

A recent meta-analysis of dermatologic toxicity due to ICIs reported a 16.7% incidence of all-grade dermatitis in patients receiving P and a 14.3% incidence in those receiving N.$^7$ Similar to the results of our study, low-grade dermatitis, pruritus, and
vitiligo were the most common toxicities in their cohort. Another meta-analysis reported a 24.3% incidence of dermatitis in patients receiving I.\textsuperscript{8} The likelihood of dermatitis is increased in patients receiving I+N combination therapy. In the current study, patients receiving I+N combination therapy were more likely to have dermatitis than those receiving P (OR, 2.5) or N alone (OR, 4.6). Hwang\textsuperscript{9} compared cutaneous toxicities in melanoma patients receiving P alone with those of patients receiving P+I combination immunotherapy. In the latter group, the incidence of cutaneous irAE was greater (88%) and the time to onset of these adverse effects was shorter.

Reports of individual cases and case series describe associations between I, P, and N and a wide range of cutaneous irAEs,\textsuperscript{10,11} including xerosis,\textsuperscript{2,12-15} stomatitis,\textsuperscript{16} urticaria,\textsuperscript{16,17} photosensitivity reactions,\textsuperscript{12} hyperhidrosis,\textsuperscript{12} exfoliation,\textsuperscript{16} alopecia,\textsuperscript{2,12,17} and hair color changes,\textsuperscript{2} psoriasis,\textsuperscript{18-20} bullous pemphigoid,\textsuperscript{21,22} lichenoid eruptions,\textsuperscript{23} lupus-like reaction,\textsuperscript{24} scleroderma reaction,\textsuperscript{25} panniculitis,\textsuperscript{26} erythema nodosum,\textsuperscript{27} and tumoral melanosis.\textsuperscript{28,29} Studies have also reported generalized eruptions,\textsuperscript{30-33} including drug reaction with eosinophilia and systemic symptom syndrome,\textsuperscript{34} sarcoidosis-like rash,\textsuperscript{35} lichen nitidus,\textsuperscript{36} amyloidosis,\textsuperscript{37} Sweet syndrome,\textsuperscript{38} acute generalized exanthematous pustulosis,\textsuperscript{39} and vasculitis.\textsuperscript{40} Nevertheless, a particular cutaneous irAE cannot be definitively assigned to a drug on the basis of a single case report.

**Onset and Management of Cutaneous irAEs**

The current practice in medical oncology for the management of dermatitis is based on extent of cutaneous eruption and symptoms.\textsuperscript{41} For patients with less than 20% body surface area (BSA) involvement, symptomatic treatment includes topical corticosteroids (triamcinolone 0.1% to torso and limbs, or hydrocortisone 1% or 2.5% to face and flexures) and oral antihistamines; 20% to 50% BSA, oral corticosteroids (eg, prednisolone, 0.5-1 mg/kg), topical therapy (similar to that used to treat <20% BSA), and possible consultation with a dermatologist; more than 50% BSA, oral corticosteroids (eg, prednisolone, 1-2 mg/kg) and referral to a dermatologist.

Interestingly, we noted that some cutaneous irAEs occurred acutely but some, such as vitiligo, bullous pemphigoid, and scleroderma reaction, occurred later in the course of treatment (ie, median time to onset ranged from 3 to 40 weeks). A recent study of 17 patients showed similar times to onset of lichenoid dermatitis and bullous pemphigoid as seen in our cohort.\textsuperscript{42} Many of our patients had grade 1 dermatitis that lasted from 1 to 2 weeks and were treated with topical corticosteroids, consistent with previous reports. Most irAEs resolve within weeks to months after initiation of immunosuppressive therapy.\textsuperscript{3} Our management strategies were in line with the recently published guidelines by the American Society of Clinical Oncology.\textsuperscript{43} These guidelines will serve as a treatment model until prospective clinical data are available.

**Histopathologic Characteristics**

The most common biopsy findings of maculopapular dermatitis include superficial perivascular lymphocytic dermatitis with eosinophils.\textsuperscript{44,45} Patterns resembling granulomatous, lichenoid, and spongiotic dermatitis are not uncommon.\textsuperscript{44} The inflammatory infiltrate mostly consists of T lymphocytes with a predominance of CD4\textsuperscript{+} cells over CD8\textsuperscript{+} cells.\textsuperscript{44} Tanaka et al\textsuperscript{46} reported an increase in interleukin 6 but not
tumor necrosis factor α in their series of 6 patients with metastatic melanoma who had N-induced psoriasis. Although previous reports have identified immune infiltrates in skin biopsy specimens from patients with irAEs, the specific antigens causing cutaneous irAEs have not been identified. The association of development of vitiligo with favorable antitumoral response has been linked to epitope spreading, in which immune activity against a tumor-specific antigen extends to an antigen shared by the tumor and noncancerous melanocytes.

**Association of Cutaneous irAEs With Response**

Lo et al reviewed the association of the development of cutaneous irAEs with cancer prognosis and highlighted the significant association of vitiligo with favorable response to therapy; however, data on nonvitiligo cutaneous irAEs were insufficient. Sanlorenzo et al reported better cancer outcomes in patients who had a cutaneous irAE due to P. They analyzed data of 83 patients with various cancers who were treated with P and reported that 42% of patients had cutaneous irAEs. Also, among patients who received P, those with a cutaneous irAE had longer progression-free survival than those without a cutaneous irAE.

In our cohort, the ORR of patients with a cutaneous irAE was markedly greater than that of those who did not. Twenty-nine (4.2%) patients had vitiligo, and the ORR of these patients was 86.2% (25 of 29 patients). Patients with vitiligo were more likely to have a favorable antitumoral response than patients without vitiligo (OR, 7.23). Previous studies have reported a survival benefit in melanoma patients who had vitiligo attributable to immunotherapy. In a study by Hua et al, the ORR was 71% for 17 patients who had vitiligo. A large meta-analysis reported that melanoma patients who had vitiligo (n=304) while receiving immunotherapy had better progression-free survival and overall survival than patients without vitiligo. The influence of lead-time bias should be considered in analyses of the association of cutaneous irAEs with favorable response to immunotherapy because patients who respond well may receive the drug for a longer duration and may have more time for long-term cutaneous irAEs to develop.

**Limitations**

This retrospective study was prone to ascertainment bias. Although our overall cohort was large, not all patients were evaluated by a dermatologist; most patients with cutaneous irAEs were successfully treated by oncologists. The cohort also included patients with self-reported, short-term skin eruptions. The precise time lines of the occurrence, treatment, and outcome of the cutaneous irAEs were compiled on the basis of the clinical notes obtained with chart review. It was also challenging to classify and to ascertain the severity of each cutaneous irAE with the Common Terminology Criteria for Adverse Events grades. Objective response rate was reported instead of overall survival or progression-free survival.

**CONCLUSION**

The cutaneous irAEs associated with immunotherapy can have diverse presentations, and physicians must understand how to recognize and to manage these various irAEs. Prospective studies would help determine the precise time to onset, course, and management of cutaneous irAEs. Emerging evidence suggests that patients with a cutaneous irAE may have a favorable response to
immunotherapy, and further research is required to evaluate this association.

**Abbreviations:**
- BSA – body surface area
- I – ipilimumab
- ICI – immune checkpoint inhibitor
- irAE – immune-related adverse effect
- N – nivolumab
- OR – odds ratio
- ORR – objective response rate
- P – pembrolizumab

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