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Clinical And Histologic Features Of Cutaneous Toxicities Due To Anti-Programmed Cell Death-1 Therapy

Veronica Shi
Yale University

Clinical and Histologic Features of Cutaneous Toxicities due to Anti-Programmed Cell Death-1 Therapy

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Veronica Jennie Shi

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Abstract

Novel immunotherapies for oncologic treatment include anti-programmed cell death-1 (PD-1) and anti-programmed cell death ligand-1 (PD-L1) agents. These therapies activate the body's inherent immune response against tumor cells by stimulating T cell proliferation. With the recent approval of agents such as nivolumab and pembrolizumab for the treatment of melanoma, lung cancer, and renal cell cancer, there is a growing need to better characterize their toxicity profiles. This study sought to provide a clinical and histologic description of the cutaneous toxicities seen in patients receiving anti-PD-1/PD-L1 treatment. Cases of patients on anti-PD-1/PD-L1 therapy who developed cutaneous adverse effects were collected from a single tertiary care hospital from 2010 to 2015. Data regarding demographics of patients, concurrent medications, therapeutic regimen, clinical morphology of cutaneous lesions, and tumor response were collected. A total of 20 patients were included in the study, with the majority of patients being treated with nivolumab alone. The majority of cases had a clinical morphology consisting of erythematous papules with scale in a variety of distributions and associated pruritus. Most cases were treated with topical corticosteroids and did not require discontinuation of oncologic treatment. Out of six patients with lung cancer who were treated with an anti-PD-1/PD-L1 agent alone, five patients (83%) responded to treatment. Nearly all cases for which biopsies were available (16 of 17 cases, 94%) showed features of lichenoid interface dermatitis. In addition, 47% of the cases (8 of 17) showed features of spongiotic dermatitis. These results support a cutaneous reaction associated with anti-PD-1/PD-L1 therapies that has distinct clinical and histologic features.

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Introduction

Immunotherapy represents the next generation of anti-cancer therapy. With genetic, cellular, and biochemical advances, numerous immunomodulating agents have emerged as the most effective treatment options for cancer patients within the last several years. This represents a shift from targeting specific molecules important in tumorigenesis to disinhibiting the natural anti-tumor immune response. The idea of immunosurveillance was first developed in the 1950s by immunologists F. Macfarlane Burnet and Lewis Thomas, who both believed that immune cells of the body constantly surveyed host tissues for transformed tumorigenic cells (1, 2). This hypothesis was briefly challenged when animal models showed no differences of carcinogen-induced tumor development between normal and athymic mice (3). However, in the late 20th century, this theory was reignited when the immune response, and specifically the role of interferon-gamma, was found to be essential in preventing the development of carcinogen-induced tumors in a mouse model (4). Further support came from the clinical observation of higher incidences of specific types of cancer in immunodeficient individuals (5), as well as studies in the late 1990s and early 2000s that showed that the presence of an inflammatory lymphocytic infiltrate in a tumor correlated with increased patient survival in a variety of different cancers (6).

However, the picture is more complicated, as cancers frequently arise in immunocompetent individuals. It is thought that the immune system may also paradoxically allow for the emergence of tumor cells that are able to escape immune recognition, which was first recognized in mice models when a large percentage of

tumors isolated from normal mice had changed to progressively growing tumors, whereas none of the tumors isolated from athymic mice showed this behavior (7). This has led to the more nuanced concept of cancer immunoediting, which encompasses both the protective and the tumor-sculpting functions of the immune system. This theory proposes three phases in which the tumor interacts with the host system: 1) elimination, during which the immune system is able to eradicate nascent tumor cells; 2) equilibrium, during which the immune system controls tumor expansion and metastasis; and finally 3) escape, during which tumor cells have now developed resistance to the host immune system (8).

Communication between the cells of the immune system and tumor cells is complex and tightly controlled via a number of cell-cell receptor-ligand interactions, as well as released cytokine factors. The adaptive immune system is comprised of T lymphocytes which learn to distinguish various self-structures from non-self structures via the major histocompatibility complex (MHC) system, and B lymphocytes which recognize antigens via immunoglobulins. In the innate immune system, there are natural killer (NK) cells which recognize the lack of expression of self. Furthermore, antigen-presenting cells can recognize non-self structures and further activate adaptive cellular and humoral responses. As an added regulatory step, T cell activation requires not only the interactions between the T cell receptor and peptide-MHC complexes, but also co-stimulation with receptors such as CD28, which binds to either B7-1 (CD80) or B7-2 (CD86) (9). In addition, there are also negative co-stimulatory molecules, such as cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed cell death-1 (PD-1).

CTLA-4 Therapy

CTLA-4 is normally expressed at low levels on the surface of naïve T cells and acts by competing with CD28 by binding to CD80 and CD86 (10), which effectively shuts off T cell receptor signaling. Mouse models demonstrated that injection with a solubilized form of CTLA-4 suppressed T cell-dependent antibody responses to exogenous antigens (11). Treatment with an anti-CTLA-4-blocking antibody caused regression of tumors in mouse models of colon carcinoma, fibrosarcoma, ovarian carcinoma, and prostate cancer (12-14).

Given the importance of CTLA-4 as an immune checkpoint mediator in preclinical animal models, monoclonal antibodies for clinical use in oncologic treatment have been developed. One such antibody that blocks CTLA-4 is ipilimumab, which has been studied most extensively in melanoma. Ipilimumab binds to CTLA-4 with a greater affinity than its endogenous ligands, CD80 and CD86, and in this way is able to dysregulate the immune response. Early phase I and II trials of ipilimumab as monotherapy in patients with melanoma showed clinical efficacy. In a phase I/II study of 88 patients with unresectable stage 3 and 4 melanoma, ipilimumab was administered in single doses up to 20 mg/kg, multiple doses up to 5 mg/kg, and multiple doses up to 10 mg/kg (15). Ipilimumab had activity with a disease control rate of 19%. A larger, randomized phase II trial involved 217 patients with stage 3 or 4 melanoma, who were administered 10, 3, or 0.3 mg/kg of ipilimumab every 3 weeks for four cycles followed by maintenance every 3 months (16). The overall response rate (ORR) in this trial, defined by the patients who showed either a complete or partial response to treatment, was 11.1% for 10 mg/kg, 4.2% for 3 mg/kg, and 0% for 0.3 mg/kg.

The first randomized phase III trial compared ipilimumab alone versus ipilimumab in combination with a gp100 melanoma peptide vaccine versus the peptide vaccine alone, in patients with pretreated melanoma (17). Ipilimumab was given at a dose of 3 mg/kg every 3 weeks for four cycles. A total of 676 patients were included and the best overall response rates were 10.9%, 5.7%, and 1.5% in patients receiving ipilimumab alone, ipilimumab plus the vaccine, and the vaccine alone, respectively.

A second phase III trial randomized 502 previously untreated stage 3 or 4 metastatic melanoma patients to receive dacarbazine in combination with either ipilimumab 10 mg/kg or placebo (18). A highly statistically significant improvement in median survival from 9.1 to 11.2 months was observed in patients receiving both ipilimumab and dacarbazine. In addition, the overall response rates were higher for ipilimumab and dacarbazine at 15.2%, compared to 10.3% in patients receiving dacarbazine alone. These two phase III trials demonstrated that ipilimumab had significant clinical efficacy in patients with advanced melanoma. In 2011, the FDA approved ipilimumab at a dose of 3 mg/kg for the treatment of patients with unresectable or metastatic melanoma.

Anti-CTLA-4 Adverse Effects

From clinical trials in which patients were treated with ipilimumab monotherapy, it appears that the most common adverse events of any grade reported in these patients include fatigue (12 to 56% of patients), diarrhea (12 to 46%), nausea (11 to 35%), rash (15 to 35%), and pruritus (15 to 35%) (16, 17, 19-21). A large proportion of adverse effects associated with ipilimumab therapy appear to be immune-related, and these immune-related adverse effects (irAEs) occur with an incidence of between 60 to 78%

for any grade toxicity (17, 18, 22). The incidence of grade 3 or 4 irAEs ranges anywhere between 7 to 56% (23). The most common organ systems affected include the skin and the gastrointestinal system, with symptoms including rash, pruritus, colitis, and diarrhea. Less common toxicities involve the liver and endocrine organs, such as hypothyroidism, adrenal insufficiency, and hypophysitis. There appears to be a direct correlation between ipilimumab dose and irAE frequency and grade (16). While the majority of clinical data has come from studies investigating the use of ipilimumab in melanoma, a smaller study investigating ipilimumab in prostate cancer patients found similar incidences of irAEs. The most common grade 3 and 4 toxicities included enterocolitis (15.9%, 7 of 44 patients), hypopituitarism (13.6%, 6 of 44), hepatitis (9.1%, 4 of 44), and dermatitis (6.8%, 3 of 44) (24).

Out of a large pooled analysis of multiple ipilimumab clinical trials involving 1498 patients, dermatologic adverse effects were the most common irAE of any grade with an incidence of 44.9% (22). The majority of these irAEs were of grade 1 or 2 in severity. In terms of cutaneous toxicities specifically, the most common adverse effects were reported as rash and pruritus. A meta-analysis of 19 trials testing ipilimumab at various doses representing 760 patients total found an overall incidence of rash of any grade to be 24% (25). The overall incidence of high-grade rash was 2.4% and there was no statistical difference in the risk of rash based on dose or underlying tumor. Skin reactions in response to ipilimumab consist primarily of discrete, pruritic, erythematous papules that coalesce into thin plaques on the trunk and extensor surfaces of extremities (26). The rash and pruritus are typically mild in severity, can be managed with topical steroids and/or oral antihistamines, and are usually reversible (27). Ipilimumab treatment

typically does not need to be modified or discontinued. On histology, these lesions show perivascular infiltrates in the superficial dermis that can be comprised of both lymphocytes and eosinophils (26, 27). These lymphoid aggregates are composed of a mixture of CD4+ and CD8+ T cells. The exact mechanism leading to irAEs with ipilimumab treatment is not well understood. However, these findings suggest that immune cell infiltration may be playing a role at specific sites of toxicity. Indeed, in patients who develop colitis with ipilimumab treatment, biopsy of the colon demonstrates infiltration of neutrophils, T lymphocytes, and plasma cells (28).

PD-1 Therapy

In addition to CTLA-4, another immunoregulatory molecule that has emerged as a therapeutic target is programmed cell death-1 (PD-1). Like CTLA-4, it is involved in regulating the delicate balance between immune activation and tolerance. PD-1 is a receptor that is expressed on both activated T and B cells, as well as monocytes (29). PD-1 has two ligands: programmed cell death ligand-1 (PD-L1) and 2 (PD-L2), which are normally found on antigen-presenting cells, tumor cells, or other cells in the inflammatory microenvironment (29). Binding of PD-1 with its ligands leads to the inhibition of T cell proliferation and cytokine secretion. PD-L1 is often aberrantly expressed on tumors, which therefore allows for tumor-induced immune suppression by downregulating the T cell response. Furthermore, increased expression of PD-L1 in tumors was found to correlate with both decreased CD8+ T-cell infiltrate within the tumor, as well as with worse clinical outcome in patients in a variety of cancers, including ovarian, pancreatic, bladder, kidney, and melanoma (30-34). By inhibiting the

PD-1 receptor and blocking its interactions with its ligands, this allows for activation of an antitumor immune response.

Nivolumab

An initial phase I trial of an anti-PD-1 antibody, MDX 1106, which would later be renamed as nivolumab, included 39 patients with advanced metastatic melanoma, colorectal cancer, prostate cancer, non-small cell lung cancer (NSCLC), or renal cell carcinoma (RCC), who received treatment at doses between 0.3, 1, 3, or 10 mg/kg (35). This trial demonstrated that the therapy was well-tolerated. One patient with colorectal carcinoma achieved complete response, and two patients with RCC and melanoma experienced partial responses. Among nine of these patients whose biopsies were studied, PD-L1 expression on tumor cells appeared to correlate with the likelihood of tumor regression following treatment with PD-1 blockade. Furthermore, one patient with melanoma who underwent pre- and post-treatment biopsies of an axillary lymph node metastasis showed subsequent tumor regression after treatment accompanied by a moderate infiltration of CD8+ T cells that were not present prior to treatment. A subsequent phase II study investigated 21 patients with treatment-refractory metastatic NSCLC, RCC, melanoma, or prostate cancer who received MDX-1106 (36). In this study, one patient with RCC had a partial response, and regression of individual lesions with mixed overall responses was seen in two melanoma patients. Biopsy of a regressing lymph node metastasis showed again a moderately increased CD8+ T cell infiltrate after treatment.

Over the last several years, many large-scale clinical trials have now been done. A phase I trial of nivolumab in 296 patients that included patients with melanoma, non-

small cell lung cancer, renal cell carcinoma, prostate cancer, and colorectal cancer, found objective responses in those with NSCLC, melanoma, or RCC (37). Cumulative response rates were 18% among patients with NSCLC (14 of 76 patients), 28% among patients with melanoma (26 of 94 patients), and 27% among patients with RCC (9 of 33 patients). The responses were especially durable, with 20 of 31 responses (65%) lasting one year or more. A separate phase I trial that studied nivolumab only in melanoma, with 107 previously treated, anti-CTLA-4-naïve patients found similar results, with an objective response rate of 31% and median response duration of 2 years (38). The overall survival was 16.8 months, with a median progression-free survival of 3.7 months.

In a phase III study (CheckMate 066), 418 patients with previously untreated melanoma negative for the BRAF mutation were randomized to receive either nivolumab or dacarbazine (39). The primary endpoint measured was overall survival. At one year, the overall rate of survival was 72.9% in the nivolumab group compared to 42.1% in the dacarbazine group. The median progression-free survival was 5.1 months in the nivolumab group versus 2.2 months in the dacarbazine group. Furthermore, the objective response rate was 40% in the nivolumab group compared to 13.9% in the dacarbazine group. There was a survival benefit with nivolumab regardless of whether or not PD-L1 was expressed in tumor cells.

A separate phase III trial (CheckMate 037) looked at patients who had advanced melanoma with progression after either ipilimumab or a BRAF inhibitor if positive for a BRAF mutation (40). 631 patients were screened, with 272 patient randomized to receive nivolumab and 133 patients to receive investigator's choice of chemotherapy. Objective responses were reported in 38 of the first 120 patients (31.7%) in the nivolumab group

versus 10.6% (5 of 47 patients) in the investigator's choice of chemotherapy group, showing that nivolumab led to a greater proportion of patients achieving a response.

In addition to melanoma, clinical trials in patients with other malignancies have been done, including non-small cell lung cancer. A study investigating the overall survival and long-term safety of nivolumab in patients with previously treated NSCLC showed an objective response rate of 17% (22 of 129 patients) (41). Out of this study group, the median progression-free survival was 2.3 months and overall survival was 9.9 months. A separate study (CheckMate 063) investigating 117 patients specifically with squamous NSCLC found similar results, with a response rate of 14.5%, a median progression-free survival of 1.9 months, and overall survival of 8.2 months (42).

A larger trial (CheckMate 017) also investigated the use of nivolumab in patients with advanced squamous cell NSCLC with disease progression on previous treatment compared to standard chemotherapy (43). A total of 272 patients were randomized to receive either nivolumab or docetaxel. The median overall survival was 9.2 months with nivolumab versus 6.0 months with docetaxel. The response rate was 20% with nivolumab compared to 9% with docetaxel, and the median progression-free survival was 3.5 months with nivolumab versus 2.8 months with docetaxel. The study further found that the expression of PD-L1 in the tumor was neither prognostic nor predictive of benefit.

As for nonsquamous NSCLC, a phase III study (CheckMate 057) randomized patients who had progressed after previous platinum-based chemotherapy to receive either nivolumab or docetaxel (44). Median overall survival was longer with nivolumab than with docetaxel, with 12.2 months among 292 patients in the nivolumab group versus 9.4 months among 290 patients in the docetaxel group. The response rate was 19% with

nivolumab versus 12% with docetaxel. Although progression-free survival did not favor nivolumab over docetaxel (median, 2.3 months and 4.2 months, respectively), the rate of progression-free survival at one year was higher with nivolumab than with docetaxel (19% and 8%, respectively).

In addition to melanoma and lung cancer, nivolumab has also been shown to have activity in renal cell carcinoma. An early phase I study in 34 patients with previously treated RCC found 10 patients (29%) who achieved objective responses (45). These responses were particularly durable, with a median response duration of 12.9 months. Median overall survival in all patients was 22.4 months. A phase II study of patients with metastatic RCC randomized patients to receive varying dosages of nivolumab of either 0.3, 2, or 10 mg/kg (46). The median overall survival was 18.2 months in the 0.3 mg/kg group, 25.5 months in the 2 mg/kg group, and 24.7 months in the 10 mg/kg group. Progression-free survival and response rate showed similar trends. Median progression-free survival was 2.7, 4.0, and 4.2 months respectively. Response rates were 20%, 22%, and 20%, respectively. While no clear dose-response relationship was detected, these results showed that nivolumab demonstrated antitumor activity across all three dosages studied.

Most recently, a large phase III trial (CheckMate 025) was done involving 821 patients with advanced RCC who had received previous treatment (47). Patients were randomized to receive either nivolumab or everolimus as treatment. The median overall survival was 25.0 months with nivolumab compared to 19.6 months with everolimus. The objective response rate was greater with nivolumab than with everolimus (25% versus 5%, respectively). The median progression-free survival was 4.6 months with nivolumab

and 4.4 months with everolimus. This clinical trial was actually stopped early given the clinical benefit in overall survival shown with nivolumab.

Given the results of these numerous clinical trials that demonstrate the improved clinical benefit of nivolumab compared to previous therapies, nivolumab was approved in 2014 for patients with previously treated unresectable or metastatic melanoma. It was also approved in 2015 for the treatment of patients with metastatic squamous non-small cell lung cancer with progression on or after platinum-based chemotherapy. In late 2015, nivolumab was approved to treat patients with advanced renal cell carcinoma. Table 1 summarizes the results of the clinical trials that have been done investigating nivolumab in various malignancies.

Pembrolizumab

A second antibody that inhibits PD-1 has been developed, called pembrolizumab, also previously known as MK-3475, and appears to have comparable efficacy and tolerability. Early clinical trials demonstrated its activity in melanoma patients. A study of 135 patients with advanced melanoma showed a response rate of 38% with no significant difference between patients who had received prior treatment with ipilimumab and those who had not (48). The overall median progression-free survival among these patients was longer than 7 months. A separate phase I trial of 411 patients, of which 190 were naïve to ipilimumab and 221 had been previously treated with ipilimumab, did find a difference between these two patient groups (49). In the ipilimumab-treated group, the overall response rate was found to be 28% and in ipilimumab-naïve patients, the response rate was 40%. The median progression-free survival was similar in both groups, at 6 months in ipilimumab-naïve patients and 5.8 months in ipilimumab-treated patients. A

Table 1. Summary of clinical trials investigating the use of nivolumab in various malignancies.

Trial (*Ref #*)	# of pts	Malignancy	ORR	Median PFS (mo)	Median OS (mo)	Most Common Adverse Events (% incidence)	Rash	Pruritus	Vitiligo
Topalian et al. 2014 *(38)*	107	Melanoma	31%	3.7	16.8	Fatigue (32%) Rash (23%) Diarrhea (18%)	23%	13%	9%
Robert et al. 2015 (CheckMate 066) *(39)*	210	Melanoma	40%	5.1	Not reached	Fatigue (20%) Pruritus (17%) Nausea (17%)	15%	17%	11%
Weber et al. 2015 (CheckMate 037) *(40)*	272	Melanoma	32%	4.7	Not yet reported	Fatigue (25%) Pruritus (16%) Diarrhea (11%)	9%	16%	5%
Larkin et al. 2015 (CheckMate 067) (*21*)	316	Melanoma	44%	6.9	Not yet reported	Fatigue (34%) Rash (25%) Diarrhea (19%)	22%	19%	7%
Gettinger et al. 2015 *(41)*	129	NSCLC	17%	2.3	9.9	Fatigue (24%) Decreased appetite (12%) Diarrhea (10%)	7%	9%	-
Rizvi et al. 2015 (CheckMate 063) *(42)*	117	Squamous NSCLC	15%	1.9	8.2	Fatigue (33%) Decreased appetite (19%) Nausea (15%)	11%	6%	-
Brahmer et al. 2015 (CheckMate 017) *(43)*	135	Squamous NSCLC	20%	3.5	9.2	Fatigue (16%) Decreased appetite (11%) Asthenia (10%)	4%	2%	-
Borghaei et al. 2015 (Checkmate 057) *(44)*	292	Nonsquamous NSCLC	19%	2.3	12.2	Fatigue (16%) Nausea (12%) Decreased appetite (10%)	9%	8%	-
McDermott et al. 2015 *(45)*	34	RCC	29%	7.3	22.4	Fatigue (41%) Rash (27%) Diarrhea (18%)	27%	18%	-
Motzer et al. 2015 *(46)*	168	RCC	20, 22, 20%[A]	2.7, 4.0, 4.2[A]	18.2, 25.5, 24.7[A]	Fatigue (22-35%) Rash (22-28%) Nausea (10-13%)	9, 4, 13%[A]	10, 5, 11%[A]	-
Motzer et al. 2015 (Checkmate 025) *(47)*	406	RCC	25%	4.6	25.0	Fatigue (33%) Nausea (14%) Pruritus (14%)	10%	14%	-

ORR overall response rate, *PFS* progression-free survival, *OS* overall survival, *NSCLC* non-small-cell lung cancer, *RCC* renal cell carcinoma. The three most common adverse events are listed in order for each trial. [A]At three varying dosages of nivolumab

separate study of 173 patients who had all previously been treated with ipilimumab showed an overall response rate of 26% and median progression-free survival of 4.5 months with pembrolizumab treatment (50).

A subsequent phase II trial (KEYNOTE-002) was an international, randomized, controlled trial comparing two pembrolizumab doses with investigator-choice chemotherapy in patients with ipilimumab-refractory melanoma (51). The primary endpoint was progression-free survival, which was found to be improved in patients assigned to pembrolizumab 2 mg/kg (hazard ratio 0.57, 95% confidence interval (CI) 0.45 to 0.73) and those assigned to pembrolizumab 10 mg/kg (HR 0.5, 95% CI 0.39 to 0.64), compared with those assigned to chemotherapy. Median progression-free survival was 4.9 months averaged amongst the two dosage groups of pembrolizumab, compared to 2.6 months in the chemotherapy control group. The overall response rate with pembrolizumab was 23% compared to only 4% in the investigator-choice chemotherapy group.

Another large study compared the efficacy of pembrolizumab versus ipilimumab in advanced melanoma patients (20). This study found a response rate of 33% in the pembrolizumab group compared to 12% in the ipilimumab group. Furthermore, the patients treated with pembrolizumab had longer progression-free survival and overall survival, demonstrating that pembrolizumab has more clinical benefit compared to ipilimumab. Estimated one-year survival rates were 71% and 58% with pembrolizumab and ipilimumab, respectively.

In terms of lung cancer, only one clinical trial has been published. A large phase I trial assessed the efficacy of pembrolizumab in 495 patients with advanced NSCLC (52).

Among all patients, the objective response rate was found to be 19.4%, with a median duration of response of 12.5 months and median progression-free survival of 3.7 months. The median overall survival was 12 months. However, when looking at a subset of 73 patients who had PD-L1 expression in 50% or more of tumor cells, the response rate was much improved to 45.2%, suggesting that there may be increased benefit in those patients whose tumors strongly express PD-L1. Numerous other clinical trials studying the efficacy of pembrolizumab in NSCLC are currently underway.

Based on the results of these trials, pembrolizumab was approved in 2014 for the treatment of advanced melanoma after treatment with ipilimumab. In 2015, pembrolizumab was granted accelerated approval for the treatment of metastatic NSCLC in patients whose disease had progressed after other treatments and whose tumors specifically expressed PD-L1. Table 2 summarizes the results of recent clinical trials investigating pembrolizumab.

Anti-PD-1 Adverse Effects

The early phase I trial of nivolumab in previously treated melanoma patients investigated safety in terms of overall adverse effects and those that were specifically immune-related (38). The most common events of any grade included fatigue (32%), rash (23%), and diarrhea (18%). In particular regards to immune-related events, this was quite common as 54% of patients (58 of 107) experienced an irAE of any grade, but only 5% were grade 3 or 4. The most common irAEs of any grade included skin disorders (36%), gastrointestinal events (18%), and endocrinopathies (13%). Multiple other clinical trials have found similar incidences of these adverse effects. Table 1 lists the three most common adverse effects in each clinical trial, which include fatigue (ranging from 16 to

Table 2. Summary of clinical trials investigating the use of pembrolizumab in various malignancies.

Trial (*Ref #*)	**# of pts**	**Malignancy**	**ORR**	**Median PFS (mo)**	**Median OS (mo)**	**Most Common Adverse Events (% incidence)**	**Rash**	**Pruritus**	**Vitiligo**
Hamid et al. 2013 *(48)*	135	Melanoma	38%	>7	Not reached	Fatigue (30%) Rash (21%) Pruritus (21%)	21%	21%	9%
Ribas et al. 2014 *(49)*	411	Melanoma	34%	5.9	Not reached	NR	NR	NR	NR
Robert et al. 2014 *(50)*	173	Melanoma	26%	4.5	Not reached	Fatigue (35%) Pruritus (23%) Rash (18%)	18%	23%	7.5%
Robert et al. 2015 (Keynote 006) (*20*)	556	Melanoma	33%	4.8	Not reached	Fatigue (20%) Diarrhea (16%) Pruritus (14%)	14%	14%	10%
Ribas et al. 2015 (Keynote 002) *(51)*	361	Melanoma	23%	4.9	Not yet reported	Fatigue (26%) Pruritus (22%) Rash (11%)	11%	22%	5%
Garon et al. 2015 (Keynote 001) *(52)*	495	NSCLC	19%	3.7	12	Fatigue (19%) Pruritus (11%) Decreased appetite (11%)	10%	11%	-

ORR overall response rate, *PFS* progression-free survival, *OS* overall survival, *NR* not reported, *NSCLC* non-small-cell lung cancer. The three most common adverse events are listed in order for each trial.

41%), decreased appetite (10 to 19%), gastrointestinal symptoms such as diarrhea (10 to 19%) and nausea (10 to 15%), and cutaneous manifestations such as rash and pruritus. Rash appeared to be quite a common adverse effect of nivolumab, occurring in 4 to 27% of patients. This is with the caveat that in these oncologic clinical trials, adverse effects were tabulated separately as "rash" or as other more specific subsets such as "rash maculopapular" or "rash erythematous." Thus, the true incidence of any sort of rash may be slightly higher than these numbers suggest. Pruritus was also reported in 2 to 19% of patients.

Similar adverse effects and incidences have been found with pembrolizumab. In the phase I study of patients with ipilimumab-refractory melanoma treated with pembrolizumab, the most common drug-related adverse events of any grade were fatigue (35%), pruritus (23%), and rash (18%) (50). Adverse events that were designated by the investigators to be immune-related of any grade occurred in 24.5% of patients (25 of 173), with the most common being hypothyroidism, diarrhea, arthralgia, and rash. Table 2 outlines the incidences of the most common adverse effects found in other clinical trials of pembrolizumab, showing similar incidences to the above. Fatigue occurred in anywhere between 19 to 35% of patients, rash in 10 to 21%, and pruritus in 11 to 23% of patients. While rash was considered an immune-related adverse event, other common irAEs seen with pembrolizumab included pneumonitis, colitis, and hypothyroidism and other endocrine abnormalities (52).

PD-L1 Therapy

There are a few monoclonal antibodies directed against the PD-L1 ligand that have been developed, including atezolizumab (also known as MPDL3280A) and MDX-

1105 (also known as BMS-936559). These are currently being clinically investigated in numerous malignancies. PD-1 inhibitors block both of the ligands PD-L1 and PD-L2, and could theoretically provide more robust clinical efficacy but also increased toxicity. By blocking PD-L1 further downstream in the pathway, this could lead to slightly decreased anti-tumor response but also perhaps decreased toxicity. Preliminary data show that anti-PD-L1 agents have clinical efficacy and seem to be well-tolerated in multiple cancers. In an early study, 45 patients with melanoma were treated with atezolizumab as monotherapy (53). A response rate of 26% (9 out of 35 patients) was observed, with all responses ongoing or improving at time of analysis. Atezolizumab also appeared to be well-tolerated, with no treatment-related deaths occurring on study and the most common adverse effects being fatigue (59%), diarrhea (30%), and pruritus (25%). In a study of 207 patients with various malignancies, treatment was with MDX-1105, and the patient group was comprised of 75 patients with NSCLC, 55 with melanoma, 18 with colorectal cancer, 17 with RCC, 17 with ovarian cancer, 14 with pancreatic cancer, 7 with gastric cancer, and 4 with breast cancer (54). An objective response was observed in 9 of 52 patients (17%) with melanoma, 2 of 17 patients (12%) with RCC, 5 of 49 (10%) with NSCLC, and 1 of 17 (6%) with ovarian cancer. The most common adverse effects in this study were fatigue occurring in 16% of patients, infusion-related reactions in 10% of patients, and diarrhea in 9%. Rash and pruritus occurred in 7% and 6% of patients, respectively. While this study showed objective response rates that are lower than the large-scale trials of the anti-PD-1 agents nivolumab and pembrolizumab, whether or not there is a true difference remains to be seen with further investigation and larger sample

sizes. Further clinical trials regarding outcomes and adverse effects with anti-PD-L1 antibodies are currently underway.

Aims

While these anti-PD-1 and anti-PD-L1 therapeutic agents have shown activity in numerous different malignancies, they have only emerged recently within the last several years and remain relatively new. Thus, their safety and associated toxicity profiles are still being fully characterized. Data from existing clinical trials show that a large proportion of the associated adverse effects appear to be immune-related. These irAEs further include a significant proportion that are cutaneous in nature. However, in the large-scale oncologic trials evaluating anti-PD-1/PD-L1 agents, these cutaneous adverse effects are described only as "rash." Therefore, further investigation into the specific characteristics of the cutaneous eruptions seen with these agents is warranted to determine whether they are similar to or different from other drug eruptions. Doing so will allow for early recognition by both oncologists and dermatologists alike and allow for appropriate management and minimization of the impact of these skin toxicities. This study sought to characterize both the clinical and histopathologic features of cutaneous toxicities that developed in a series of patients receiving anti-PD-1 or PD-L1 therapy.

Methods

With the approval of the Yale University Institutional Review Board, cases were collected from Yale-New Haven Hospital from between 2010 to 2015. Patients were included if they were on treatment with either an anti-PD-1 or anti-PD-L1 agent alone, or

if there were receiving an anti-PD-1 or anti-PD-L1 agent in combination with other therapy, and if they were referred for dermatologic evaluation of rash. Data that was collected included patient demographics, concurrent medications, therapeutic regimen, type of disease, previous oncologic therapies, clinical morphology and distribution of cutaneous lesions, treatment of rash, peripheral blood eosinophil count, and tumor response. Consent was obtained from patients at time of their clinical evaluation to document photographs of their cutaneous lesions, with minimization of any identifying features. Concurrent medications at the time of presentation for each patient were recorded. The peripheral blood eosinophil count was recorded at the time of biopsy, and for those patients without biopsy, eosinophil count was recorded at the time of presentation of cutaneous toxicity. Tumor response was determined from documentation from the patients' treating oncologists, and was characterized as one of four responses based on RECIST (Response Evaluation Criteria in Solid Tumors) criteria: 1) complete response, in which there is disappearance of all target lesions, 2) partial response in which there is at least a 30% decrease in the sum of the size of target lesions, 3) stable disease, in which there is neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, and 4) progressive disease, in which there is at least a 20% increase in the sum of the size of target lesions or the appearance of new lesions. Time to disease progression was calculated from the first dose of anti-PD-1/PD-L1 treatment to progression, which was determined by imaging. Any other immune-related adverse effects that were documented were recorded. The histopathological features of available biopsy specimens were reviewed by two dermatopathologists and tabulated. For each available case, light microscopic

examination of tissue sections prepared with hematoxylin-eosin staining was performed. In addition, for three of the cases (#2, 5, and 9), a panel of immunoperoxidase stains, including stains for CD3, CD4, CD8, and CD20, was performed.

Results

A total of 20 patients were included in this study (13 men and 7 women). The median age of patients at the onset of cutaneous toxicities was 62 years old (range 46 to 86 years). Ten patients were treated with nivolumab alone, while four were treated with nivolumab in combination with ipilimumab. One patient was treated with nivolumab in combination with bevacizumab, and one patient was started on nivolumab in addition to erlotinib and subsequently continued on nivolumab alone. Two patients were treated with pembrolizumab alone, one patient was treated with the anti-PD-L1 agent atezolizumab alone, and one patient received atezolizumab in combination with carboplatin and paclitaxel. 60% of patients (12 of 20) had received prior systemic therapy for their cancer, with 3 of 20 patients having received prior immune checkpoint inhibitors. One of these patients had already received a previous course of nivolumab and ipilimumab combination therapy, while two patients had received therapy with ipilimumab. Table 3 summarizes the characteristics of the included patients.

The time of onset to cutaneous eruption was variable, with a mean time of 4 months and a range of 3 days to 13 months. The majority of cases (80%, 16 of 20) had a clinical morphology consisting of erythematous papules with scale, in either a focal distribution such as localized lesions on an extremity or the neck (55%, 11 of 20) (Figure 1A), or in a more generalized distribution of coalescing larger plaques on the trunk and

Table 3. Clinical and histologic profile of 20 patients with cutaneous adverse effects while receiving anti-PD-1/PD-L1 treatment.

Pt. #	Sex	Race	Age (y)	Cancer type	Therapeutic agent	Prior therapy	Time to rash (mo)	Morphology	Anatomic distribution	Pruritus	Was tx held for rash	Treatment of rash	Tumor response	PFS (mo)	Other irAE	Histologic pattern
1	M	C	86	Lung	Nivolumab	None	12.8	Grover's disease	Trunk	+	No	TAC	CR	33.7	None	Lichenoid, Spongiotic
2	F	C	75	Lung	Nivolumab	Carboplatin + gemcitabine, pemetrexed	1.8	Papular	Extremities	+	No	Clobetasol	PR	38.0	None	Lichenoid
3	M	C	65	Lung	Nivolumab	Carboplatin + pemetrexed	1.2	Papulo-pustular	Trunk	-	No	Clobetasol, Minocycline	PD	1.7	None	Lichenoid, Spongiotic
4	F	C	83	Lung	Nivolumab	None	4.6	Papular	Trunk, extremities	+	No	Topical steroids[A]	PR	8.9	Autoimmune DM	N/A
5	M	C	60	RCC	Nivolumab	High dose IL-2, bevacizumab	2.0	Papular	Generalized	-	No	Topical steroids[A]	PD	9.5	None	Lichenoid
6	F	C	64	RCC	Nivolumab	None	1.6	Papular, palmoplantar	Palms, soles, mouth	+	Yes	Clobetasol, PUVA	SD	10.4	Hypo-thyroidism, colitis	Lichenoid
7	M	C	67	MM	Nivolumab	High dose IL-2	13.0	Papular	Chest (shawl-like)	-	No	None	PR	75.0	None	Lichenoid, Spongiotic
8	M	C	57	Lung	Nivolumab	Carboplatin + gemcitabine	0.8	Papular	Lower back, left upper arm	+	No	TAC	CR	32.3	Possible pneumonitis	Lichenoid, Spongiotic
9	F	C	58	Lung	Nivolumab	Cisplatin + vinorelbine + cetuximab, cetuximab, gemcitabine, erlotinib, docetaxel + IPI-504	10.2	Mucositis	Mouth	-	Yes	Clobetasol, Valacyclovir	PR	55.6	None	Lichenoid, Spongiotic
10	M	C	47	MM	Nivolumab	None	0.5	Erosive LP	Penis, mouth	+	No	Clobetasol	SD	4.2[B]	None	Lichenoid
11	M	AA	58	MM	Pembrolizumab	High-dose interferon, ipilimumab	Exacerbation of existing rash in 5 days	Papular	Extremities, trunk	+	No	Clobetasol	PD	3.9	LFT elevation	N/A

12	M	C	65	MM	Pembrolizumab	Ipilimumab	2.1	Hypertrophic plaques	Lower extremities	+	Yes	Clobetasol	PR	3.5[B]	LFT elevation	Lichenoid
13	M	C	56	MM	Nivolumab + ipilimumab	None	0.1 (3 days)	Papular	Generalized	+	No	Topical steroids[A]	PR	39.5	None	Lichenoid
14	M	C	58	MM	Nivolumab + ipilimumab	Interferon, previous course of nivolumab + ipilimumab	2.8	Papular, annular, inflammation of SKs	Extremities, trunk	+	No	TAC	PD	2.8	None	Lichenoid, Spongiotic
15	M	C	75	Lung	Nivolumab + ipilimumab	None	2.5 6.0	Papular Lichenoid keratosis	Left forearm Left upper thigh	+	No	TAC	PR	10.5	None	Lichenoid, Spongiotic
16	M	C	59	Lung	Nivolumab + ipilimumab	None	4.5	Papular	Back, extensor arms, upper chest	+	No	TAC	PR	10.7	Adrenal insufficiency, AIN	N/A
17	F	AA	46	Lung	Nivolumab + bevacizumab	Carboplatin + pemetrexed + bevacizumab	1.5	Papular	Face, neck, left arm	-	No	TAC	PD	2.0	None	Lichenoid, Spongiotic
18	F	C	55	Lung	Nivolumab + erlotinib, then nivolumab alone	Erlotinib	1.9, 2.3[C]	Papular	Extremities, trunk	+	Yes	Oral prednisone	PR	35.9	LFT elevation, low TSH	Vacuolar interface dermatitis
19	F	C	73	RCC	Atezolizumab	Sunitinib	8.3	Papular, palmar	Palms, arms, mouth	+	No	Clobetasol, NBUVB	PR	31.9	None	Lichenoid
20	M	C	69	Lung	Atezolizumab + carboplatin + paclitaxel	None	3.1	Papular	Generalized	+	Yes	Clobetasol	PR	6.6[B]	None	Lichenoid

PFS progression-free survival, *irAE* immune-related adverse effect, *C* Caucasian, *AA* African-American, *RCC* renal cell carcinoma, *MM* malignant melanoma, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progression of disease, *TAC* triamcinolone, *LP* lichen planus, *SK* seborrheic keratosis, *PUVA* psoralen and ultraviolet A therapy, *NBUVB* narrow-band ultraviolet B therapy, *LFT* liver function test, *AIN* acute interstitial nephritis, *TSH* thyroid-stimulating hormone

[A] Specific strength of topical steroids unknown

[B] Response ongoing at time of data collection

[C] This patient had two acute cutaneous eruptions which appeared to be temporally related to erlotinib administration

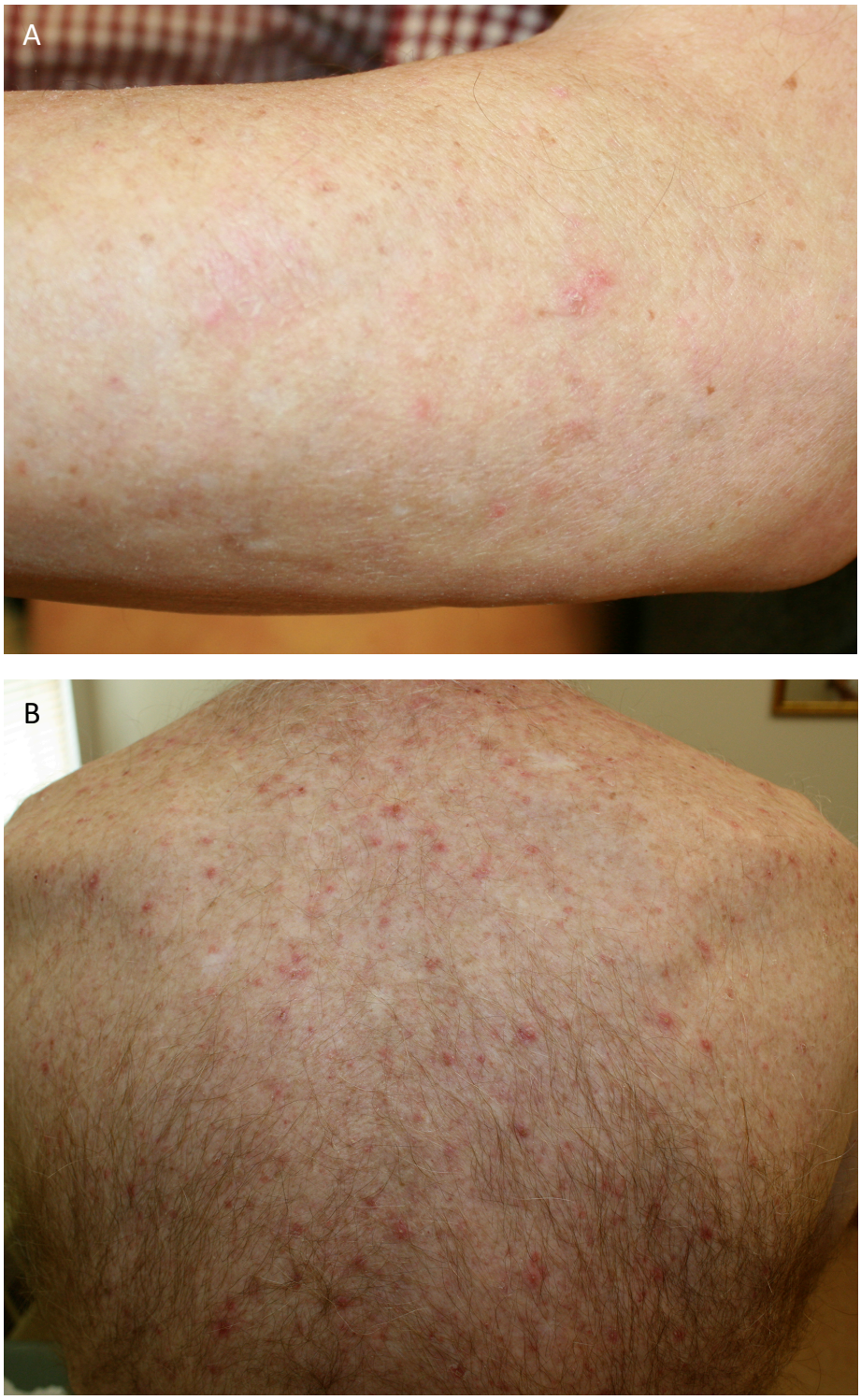

Figure 1. Erythematous papules with scale due to anti-PD-1/PD-L1 therapy. A) Example of localized lesions on the left forearm of a patient. B) Example of a generalized distribution over the back.

extremities (45%, 9 of 20) (Figure 1B). There were a few cases with distinct features. One patient (#12) developed larger 1 to 2 cm keratotic scaly plaques on the lower legs resembling hypertrophic lichen planus (Figure 2A). One patient (#7) had numerous pink thin papules and plaques forming a shawl-like distribution over the upper chest (Figure 2B). One patient (#1) presented with scaly discrete papules on the back, chest, and abdomen that looked typical of Grover's disease, or transient acantholytic dermatosis. Of note, two patients (#6 and 19) had lesions limited to a striking palmoplantar distribution with additional oral mucosal lesions. In one of these patients (#6), there was a sudden onset of small 2 to 3 mm pseudovesiculated papules in coalescent plaques covering the palms and soles. On the soles, the plaques extended laterally onto the sides of the feet but did not cross Wallace's lines (Figure 2C). In the other patient (#19), pink-red scaly thin papules limited to the palms and soles were larger (up to 1 cm), discrete, and not coalescent (Figure 2D). One patient (#14) had distinct inflammation of and around existing seborrheic keratoses (Figure 2E). One patient (#11) experienced within 5 days of starting anti-PD-1 therapy, worsening of an existing rash that had started while on previous treatment with ipilimumab. Four patients (#6, 9, 10, and 19) developed oral lesions that varied in appearance. One patient (#6) developed concurrent 1 to 2 mm whitish flat-topped papules with apparent Wickham's striae on the bilateral buccal mucosa extending onto the lateral commissures (Figure 2F), in addition to her palmoplantar lesions. The other three patients (#9, 10, and 19) developed erosions involving the tongue, buccal mucosa, lips, and/or gingivae. Lastly, one patient (#10) developed erosive lesions on the penis, clinically resembling erosive lichen planus (Figure 2G).

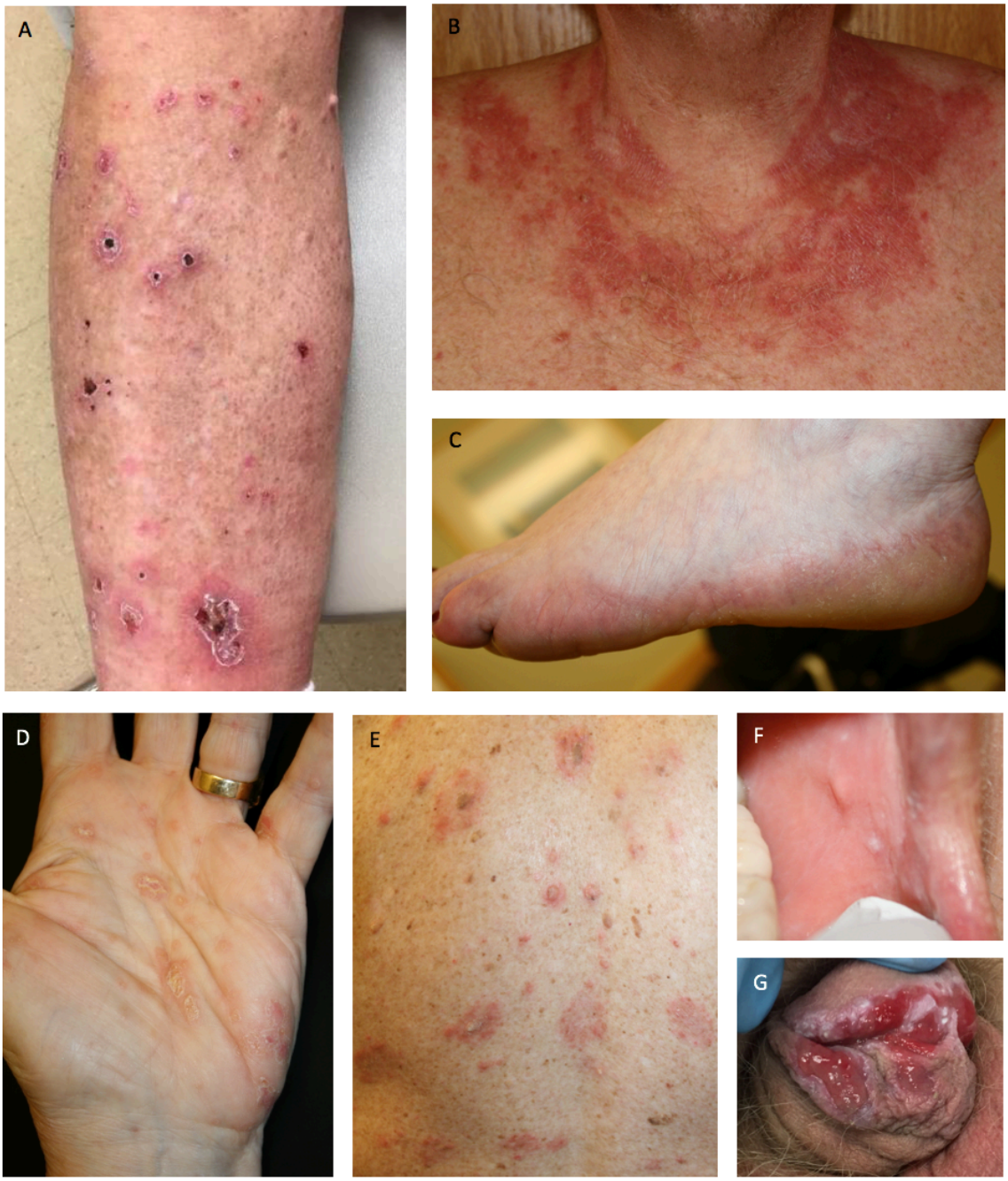

Figure 2. Additional examples of cutaneous eruptions seen with anti-PD-1/PD-L1 therapy. A) Hypertrophic scaly papules and plaques on the lower extremity. B) Thin pink papules and plaques in a shawl-like distribution over the upper chest. C) Coalescent plaques localized to the sole of the foot. D) Scaly, discrete papules on the palm. E) Inflammation of and around existing seborrheic keratoses on the back of a patient. F) Small white papules on the buccal mucosa. G) Erosive lesions on the penis, resembling erosive lichen planus.

Out of 20 patients, most (75%, 15 of 20) were noted to experience pruritus with the lesions. The most common treatment was with topical corticosteroids. One patient (#18) who developed two acute eruptions that appeared temporally related to erlotinib administration required oral prednisone. The two patients who developed palmoplantar lesions (#6 and 19) were treated with phototherapy, one with psoralen and ultraviolet A, and the other with narrow band ultraviolet B, both with improvement. Five of 20 patients (25%) required dose delay of the oncologic agent because of cutaneous toxicity. Eosinophil counts were not significantly elevated in the majority of patients (80%, 16 of 20) at the time of cutaneous eruptions. Table 4 lists the concurrent medications at the time of presentation and the absolute eosinophil counts in patients at time of biopsy or at time of presentation if biopsy was not performed.

Tumor response, time to progression, and development of any other immune-related adverse effects were also assessed (Table 3). Out of six patients with melanoma, three had a partial response, one had stable disease, and two had progression of disease. Out of 11 patients with NSCLC, two patients achieved complete response, seven had a partial response, and two had progression of disease. Out of three patients with RCC, one patient had a partial response, one patient had stable disease, and one patient had progression of disease. Excluding three patients who had an ongoing response to treatment at time of data collection, the mean progression-free survival (PFS) was 23.67 months, with a wide range between 1.73 to 75 months. This large range was due to a distinct phenomenon of quite prolonged PFS in those patients who experienced tumor response, compared to a much shorter PFS in patients who did not respond to treatment. When separating patients into two groups, those who experienced an objective

Table 4. Concurrent medications and peripheral eosinophil counts in patients.

Pt. #	Concurrent medications	Serum eosinophils (absolute count cells/ul)
1	Brimonidine, **clopidogrel**, cholecalciferol, CoQ10, iron, loperamide, **metformin**, **metoprolol**, **simvastatin**, tetrahydrozoline, nitroglycerin, **aspirin**	**1050**
2	**Aspirin**, **metformin**, coumadin, amiodarone	104
3	Rosuvastatin, zolpidem	**504**
4	Insulin	0
5	**Lorazepam**, **amlodipine**, chlorthalidine, **atenolol**	212
6	**Tiotropium**, montelukast, **metoprolol**, **HCTZ**, diphenhydramine	252
7	**Hydrochlorothiazide**, levothyroxine, tamsulosin	**747**
8	**Tiotropium**, ipratropium-albuterol, oxycontin, oxycodone-acetaminophen, **alprazolam**, fluticasone/salmeterol, rosuvastatin, fenofibrate, **aspirin**	138
9	**Ibuprofen**	84
10	**Omeprazole**, prochlorperazine, sertraline, mirtazapine, **allopurinol**, **atorvastatin**, **naproxen**	72
11	**Aspirin**, **atorvastatin**, **glipizide**, **lisinopril**, **metformin**, **metoprolol**, nitroglycerin	**930**
12	Celecoxib, levetiracetam, phenobarbital, vitamin B12	135
13	Vitamin D	310
14	**Aspirin**, **ibuprofen**, **omeprazole**, zolpidem	126
15	**Atorvastatin**, cholecalciferol, **colchicine**, rivaroxaban, famotidine, moxifloxacin	304
16	**Aspirin,** albuterol, famotidine, hydrocortisone, hydroxyzine, **lorazepam**, **omeprazole**, zolpidem, levetiracetam	150
17	**Lorazepam**, mirtazapine, morphine	66
18	**Sertraline**, eszopiclone	208
19	**Omeprazole**, levothyroxine, bupropion, **sertraline**	159
20	Acetaminophen, **atorvastatin**, bupropion, tadalafil, digoxin, fluticasone-salmeterol, **metoprolol**, morphine, **omeprazole**, ondansetron, prochlorperazine, rivaroxaban, **tiotropium**	0

Bolded medications indicate those that have been reported to cause lichenoid drug eruptions (55, 56). Bolded eosinophil counts indicate those that represent a peripheral eosinophilia, defined as greater than 500 cells/ul.

response (either complete or partial), and those who experienced stable disease or progression of disease, the mean PFS in each group was 33.8 months versus 5.1 months, respectively.

Histology was available from 17 of the 20 patients. Nearly all cases (16 cases, 94%) showed features of lichenoid interface dermatitis (Figures 3A-C). In addition, many

of the cases also showed features of spongiotic dermatitis (8 cases, 47%). One case, the patient who developed acute eruptions in temporal association with erlotinib administration (#18), showed evidence of vacuolar interface changes. Of the three biopsies for which ancillary immunostaining was performed, all showed intradermal and intraepithelial lymphocytes that were CD3-positive (Figure 3D). Intradermal lymphocytes were CD4-positive, while intraepithelial lymphocytes were CD8-positive; CD20 stains were negative (Figures 3E-G). Table 3 summarizes the predominant histopathological patterns of each skin biopsy, and Table 5 summarizes the overall findings seen in the series of cases.

Table 5. Summary of histologic features seen on biopsy of cutaneous eruptions associated with anti-PD-1/PD-L1 therapy.

		Number of cases	% of total cases (n = 17)
Reaction patterns	**Interface dermatitis**	**17**	**100%**
	Lichenoid	16	94%
	Vacuolar	1	6%
	Spongiotic dermatitis	**8**	**47%**
Diagnostic features	**Altered stratum corneum**	**15**	**88%**
	Hyperkeratosis	11	65%
	Parakeratosis	9	53%
	Parakeratotic mounds	2	12%
	Serum deposition	6	35%
	Epidermal changes	**13**	**76%**
	Premature terminal differentiation	5	29%
	Acanthosis	4	24%
	Irregular psoriasiform hyperplasia	3	18%
	Atrophy	1	6%
	Superficial reticular dermal changes	**17**	**100%**
	Lymphocytic band-like	7	41%
	Mixed band-like	4	24%
	Mixed perivascular infiltrate	6	35%
	Lymphocytic perivascular	4	24%
	Stromal edema	9	53%
	Pigment incontinence	6	35%
	Red blood cell extravasation	7	41%
Additional finding	Infundibulofolliculitis	1	6%

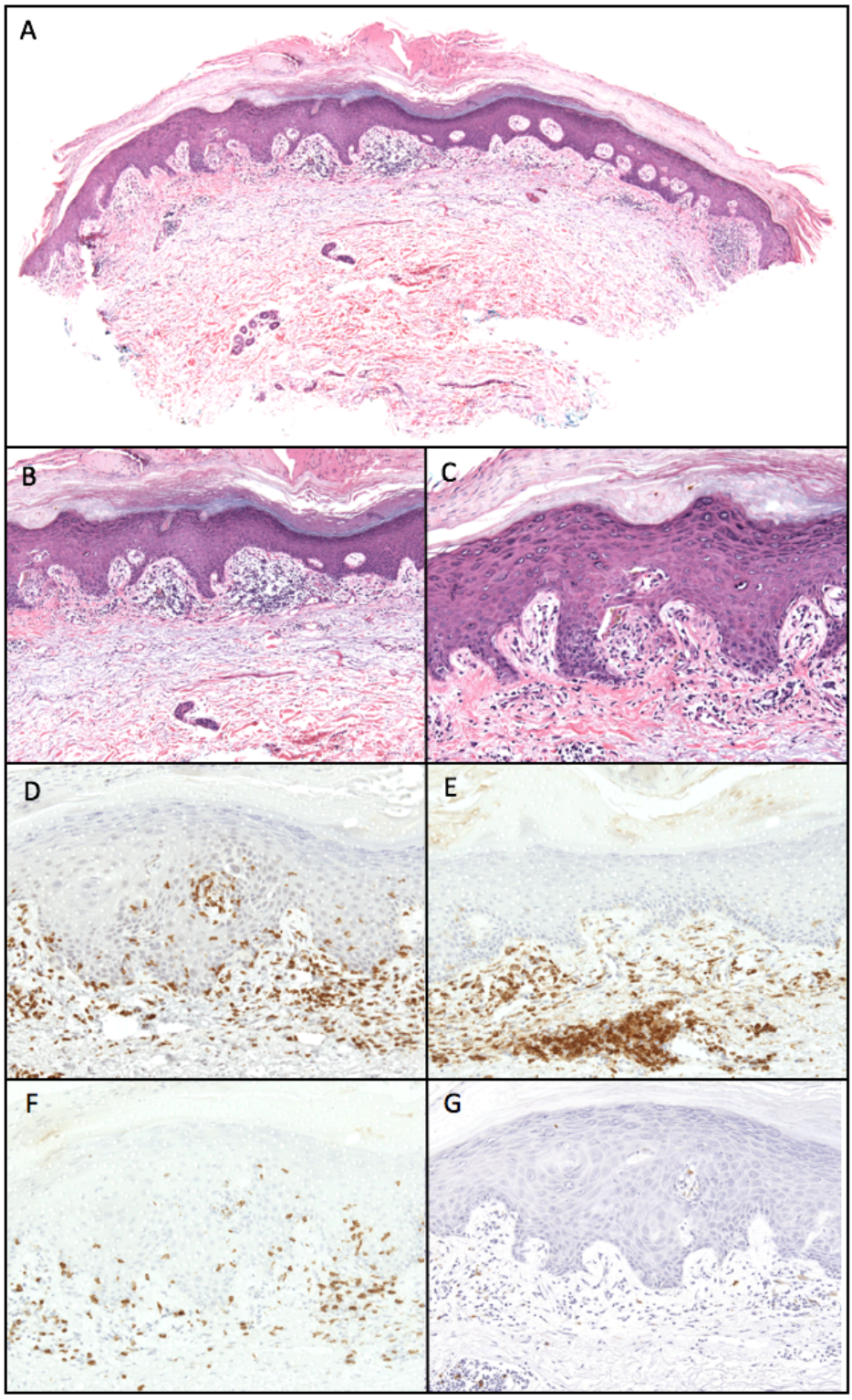

Figure 3. Photomicrographs from one representative patient showing lichenoid interface dermatitis (A-C; hematoxylin-eosin at 4x, 10x, and 20x respectively). Staining of lymphocytic infiltrate with the following immunoprofile: CD3-positive (both intradermal and intraepithelial lymphocytes, D), CD4-positive (intradermal lymphocytes, E), CD8-positive (intraepithelial lymphocytes, F), and CD20-negative (G).

Discussion

With recent advances in cancer therapy, immunotherapies have emerged as the next generation of oncologic treatment. Antibodies that block either PD-1 or its ligand PD-L1 have shown significant clinical activity and therapeutic promise. Because these agents have just recently emerged within the last decade, their full toxicity profiles have yet to be fully characterized. The main adverse effects that have been associated so far with anti-PD-1 therapy include cutaneous toxicities, gastrointestinal symptoms such as diarrhea or nausea, fatigue, myalgia, increased aminotransferase levels, and hypothyroidism or other endocrinopathies (57). Cutaneous adverse effects most commonly include rash (4 to 27% of patients), pruritus (2 to 23%), and less frequently vitiligo (5 to 11%) (see Tables 1 and 2 for complete references), with comparable incidences seen with pembrolizumab and nivolumab. Similar adverse effects are seen with anti-PD-L1 antibodies and include fatigue (59%), diarrhea (30%), pruritus (25%), and rash (16%) (53). These adverse effects are usually manageable and do not generally require discontinuation of therapy.

While "rash" has been commonly reported as an adverse effect in many oncologic trials evaluating anti-PD-1/PD-L1 antibodies, further details about the specific nature of these cutaneous eruptions are often not completely described. Our study aimed to characterize both the clinical and histologic features of cutaneous toxicities associated with anti-PD-1/PD-L1 therapy. Our group of 20 patients represented a range of different therapeutic regimens, consisting of 12 patients (60%) who were treated with anti-PD-1 monotherapy (either nivolumab or pembrolizumab alone), 4 patients (20%) who were treated with combination therapy of nivolumab and ipilimumab, 2 patients (10%) who

received PD-1 therapy (nivolumab) in addition to another agent of some kind, and 2 patients (10%) who were treated with anti-PD-L1 monotherapy with atezolizumab. Despite the differences in treatment regimen, the cutaneous eruptions that were seen with anti-PD-1, anti-PD-L1, or combination therapy shared common characteristics. Clinically, the eruption seen with these agents consisted of erythematous scaly papules or plaques that were usually pruritic. The distribution of lesions varied, with either a small number of discrete papules or plaques on a limited area of the body or a generalized distribution of larger plaques with a predilection for the trunk. A localized or generalized distribution seemed to be relatively equally as likely, with an incidence of 55% and 45% in our group of patients, respectively. There was also a wide range in time to cutaneous presentation after initiation of anti-PD-1/PD-L1 therapy, ranging from 3 days to 13 months.

While the clinical morphology varied, the histology was remarkably consistent amongst the patients. Nearly all of the cases for which biopsies were performed in our study (16 out of 17, 94%) showed lichenoid interface changes. Three biopsies for which immunohistochemical staining was available showed that this lichenoid infiltrate was composed of predominantly CD4+ T cells within the dermis, with a few CD8+ intraepithelial lymphocytes. It is interesting to note that previous trials showed a CD8+ T cell infiltrate within tumor metastases post-treatment (35, 36). In fact, one study in particular found a greater increase in CD8+ density from baseline to post-treatment biopsy that significantly correlated with a decrease in radiographic tumor size (58). Their findings seemed to suggest that therapeutic PD-1 blockade was effective through CD8+ T cells at the tumor margin. Our findings show a predominantly CD4+ T cell infiltrate, suggesting that there may be different mechanism at play in the target tumor cells than in

the skin. In addition, many of the biopsies showed concurrent features of spongiotic dermatitis. These two features of lichenoid interface and spongiotic changes represent a combination not commonly seen. A previous case series reported similar findings of lichenoid dermatitis on histology in three patients receiving pembrolizumab for treatment of melanoma (59). Clinically, the patients presented with papular lesions as well, primarily on the trunk and extremities, between four to nine weeks after starting treatment with pembrolizumab. Two of these patients had previously received immunotherapy with ipilimumab. All three cases showed a CD3-positive lymphocytic infiltrate, with a more prominent CD4+ component than CD8+, and with 10% of the T cells showing positive PD-1 expression. Tumor response was noted in two of the three patients, and consisted of one partial and one complete response. All three patients had relatively mild toxicities, and oncologic treatment was not discontinued. In another recent case series of 5 patients treated with anti-PD-1/PD-L1 agents, histologic examination again revealed lichenoid dermatitis with greater histiocytic infiltrates, increased spongiosis, and increased epidermal necrosis, compared to biopsies of non-drug-related lichen planus (60). No significant differences were seen in CD4:CD8 ratio or in expression of CD3, CD20, PD-1, CD25, Foxp3, CXCL13, or PD-L1 compared to the control lichenoid reactions. Our results are consistent with this, showing a cutaneous lichenoid eruption that is unique to anti-PD-1/PD-L1 therapy.

While PD-1 and PD-L1 inhibitors as monotherapy have shown remarkable efficacy as anti-tumor agents, combination therapy with ipilimumab appears to have more clinical benefit for patients with melanoma. A phase I trial in 53 melanoma patients receiving the combination of nivolumab and ipilimumab showed a response rate of 40%,

compared to a response rate of 20% in patients who had previously been treated with ipilimumab who then received nivolumab monotherapy (61). Another phase I trial studied 142 previously untreated patients with melanoma (62). These patients were randomized to receive ipilimumab in combination with nivolumab or ipilimumab alone. This study found an objective response rate of 61% in the group that received combination therapy with ipilimumab and nivolumab versus 11% in the group that received ipilimumab monotherapy, with the median progression-free survival not reached with combination therapy and 4.4 months with ipilimumab monotherapy. A large-scale trial of 945 previously untreated patients with melanoma randomized them in a 1:1:1 ratio to receive either nivolumab alone, nivolumab plus ipilimumab, or ipilimumab alone, with progression-free survival and overall survival as coprimary endpoints (21). While data on overall survival is not yet available, this study found significant differences in progression-free survival. The median progression-free survival was 11.5 months (95% confidence interval, 8.9 to 16.7) with nivolumab plus ipilimumab, as compared to 2.9 months (95% CI, 2.8 to 3.4) with ipilimumab alone, and 6.9 months (95% CI, 4.3 to 9.5) with nivolumab alone. The patients were also broken down into subgroups depending on whether their tumors were positive or negative for expression of PD-L1 ligand. In patients with tumors positive for PD-L1, progression-free survival was 14 months with both combination therapy and with nivolumab alone, but in patients with PD-L1-negative tumors, PFS was longer with combination therapy than with nivolumab alone (11.2 month versus 5.3 months). Therefore, it appears that in the specific subset of patients whose tumors do not strongly express PD-L1, combination therapy with ipilimumab and a PD-1 inhibitor is more effective. Taken together, these trials show that there is

significant improvement in clinical efficacy with combination therapy, and that this may be poised to become the next first-line treatment in melanoma.

However, combination therapy comes with a cost and that is a higher frequency of irAEs. The most common adverse effects related to nivolumab and ipilimumab combination therapy are rash (40 to 55% of patients), pruritus (33 to 47%), diarrhea (34 to 44%), and fatigue (35 to 38%) (21, 61). In addition to more frequent adverse effects, in particular those that are cutaneous, combination immunotherapy also seems to lead to increased severity of irAEs. One study found that the incidence of severe grade 3 or 4 adverse effects of any kind was 53% in patients on combination therapy, compared to 18% in patients on monotherapy with nivolumab (61). Another study found the incidence of grade 3 or 4 adverse events to be 54% compared to 24% in patients treated with ipilimumab alone (62). While our study only included four patients who were on combination therapy with nivolumab and ipilimumab, there were no significant qualitative differences amongst their cutaneous eruptions. They all developed papular eruptions, although interestingly, one patient also developed inflammation of and erythema around existing seborrheic keratoses. All the cutaneous eruptions were relatively mild, and none of these four patients required discontinuation of their treatment because of cutaneous toxicities. However, the caveat is that this sample size of four is quite small, and it is also possible that those adverse effects that are more likely to be severe may not be skin-related.

Given the use of these agents in oncologic patients, there is much interest in determining whether there are predictors of which patients will respond to therapy. Studies have suggested that expression of the ligand PD-L1 on tumor cells may be a

possible marker of clinical response (63). In a clinical trial that investigated patients with varying malignancies, none out of 17 patients with PD-L1-negative tumors had an objective response to nivolumab, whereas 9 out of 25 patients (35%) with PD-L1-positive tumors had an objective response (37). Another study aimed to look at tumor specimens from 41 patients with varying cancers receiving nivolumab to explore components of the tumor microenvironment (64). In this study, specimens with greater than 5% expression on immunohistochemistry staining were considered "positive." They found that when positive tumor cell PD-L1 expression was observed, it was associated with infiltrating immune cells including lymphocytes and histiocytes, and that the proportion of tumor cells expressing PD-L1 correlated with the intensity of immune cell infiltration. Furthermore, PD-L1 expression by tumor cells correlated significantly with objective response and clinical benefit. However, the presence of immune cell infiltrates and level of PD-L2 expression were not found to correlate with treatment response, suggesting that while important, it may be PD-L1 expression itself that is more closely linked to clinical response. Given the question of whether PD-L1 expression on tumor cells plays a predictive role, a large meta-analysis aimed to pool data from multiple clinical trials. Overall response rate was extracted from 20 phase I to III trials investigating nivolumab, pembrolizumab, as well as atezolizumab. A significant interaction ($p<0.0001$) according to tumor PD-L1 expression was found with an overall response rate of 34.1% in the PD-L1 positive group and 19.9% in the PD-L1 negative group (65). While the results of these various studies are certainly compelling, they do not explain the whole picture. What is still true is that there are patients with PD-L1 negative tumors that do respond to anti-PD-1 treatment, and the fact remains that the overwhelming majority of patients with PD-L1

positivity do not respond. Furthermore, the CheckMate 066 study investigated nivolumab in previously untreated melanoma patients and found a response rate of 52.6% (95% CI, 40.8 to 64.3) in the PD-L1 positive group compared to 33.1% (95% CI, 25.2 to 41.7) in the PD-L1 negative group (39). While this may represent a trend towards some improved clinical benefit with PD-L1 tumor expression, the authors of this study concluded that given the magnitude of the clinical benefit in patients receiving nivolumab versus those receiving dacarbazine, the comparison arm, PD-L1 status alone would not seem to be useful in selecting patients for nivolumab treatment. There are further added inconsistencies regarding measurement of PD-L1 expression that are assay related, in that there is no clear consensus on which antibodies to use, which cells to stain, and what cut-off threshold to use. Therefore, there is still no reliable clinical characteristic or laboratory parameter that can predict response to anti-PD-1/PD-L1 therapy.

With ipilimumab treatment, there is evidence that immune-related adverse effects may be associated with response to therapy (66). A recent study sought to investigate this idea with PD-1 therapy. This study of 83 patients treated with pembrolizumab found that those patients who developed cutaneous adverse effects had significantly longer progression-free survival, among three different groups receiving varying dosages of pembrolizumab (57). One potential caveat, however, is that patients who progress interrupt their treatment and do not receive the same cumulative dose, thereby having less likelihood of developing adverse effects. A separate study investigated the association of vitiligo with tumor response in patients with metastatic melanoma treated with pembrolizumab (67). An objective complete or partial response to treatment was associated with a higher occurrence of vitiligo: 12 of 17 patients (71%) who developed

vitiligo had an objective tumor response, compared to 14 of 50 patients (28%) who did not develop vitiligo (p=0.002). This study also found that those patients who developed vitiligo had a higher frequency and severity of other irAEs. Another study of melanoma patients treated with nivolumab found that rash and vitiligo correlated with statistically significant differences in overall survival (68). This concept is intriguing, as cutaneous adverse effects have been shown to be associated with likelihood of response to other oncologic treatments, namely the rash seen with epidermal growth factor receptor (EGFR) inhibitors (69, 70). Overall response rates with anti-PD-1/PD-L1 agents vary with tumor type. As mentioned previously, the response rates in melanoma range between 26 and 38% with pembrolizumab (48, 50), 31 to 44% with nivolumab (21, 38), and approximately 25% with the anti-PD-L1 agent atezolizumab (53) (see Tables 1 and 2 for other references). Response rates in NSCLC range between 14 to 20% for nivolumab (42, 43), and for pembrolizumab, the response rate was approximately 19% specifically in patients whose tumors expressed PD-L1 (52). In RCC, response rates range between 20 to 29% with nivolumab (45, 46). Nivolumab and ipilimumab combination therapy is known to result in greater response rates of up to 40 to 61% in melanoma patients (21, 61, 62). In our group, six patients with NSCLC were treated with monotherapy with either an anti-PD-1 or PD-L1 agent alone; five of these patients (83%) showed a response. In addition, out of four patients with melanoma treated with anti-PD-1 monotherapy, two responded, and out of three patients with RCC, one responded. Of the two patients who received nivolumab and ipilimumab combination therapy for advanced melanoma, one responded and one had progression of disease. Given the small sample size of patients, definitive conclusions about the association of cutaneous toxicities with tumor response

in this group cannot be made. Six out of 20 patients (30%) developed other definitive irAEs that were associated with anti-PD-1/PD-L1 therapy. Four of these six patients showed a response to therapy, which may suggest a possible association between irAE development and clinical response. Since the mechanism of PD-1 therapy essentially stimulates an immune response, it is of great interest whether development of irAEs is associated with clinical benefit, and this will need to be explored with further investigation in large-scale trials.

Given that some patients in our study were on combination therapy, the question arises of whether these cutaneous eruptions were truly due to anti-PD-1 therapy or whether another drug might be responsible. Indeed, four of our patients were on combination therapy with ipilimumab and nivolumab, and one might argue that the clinical appearance of cutaneous eruptions from ipilimumab versus anti-PD-1 agents is similar, consisting of erythematous papules coalescing into thin plaques. However, ipilimumab eruptions have been associated with a concurrent increase in peripheral blood eosinophil levels (26), and eosinophilia was not seen in the majority of patients in our series or in the four patients who specifically received ipilimumab. Furthermore, the changes on histology are distinct. In contrast to the superficial, perivascular CD4-predominant infiltrate with eosinophils that is seen with ipilimumab therapy, biopsies from our patients showed a lichenoid eruption. Lichenoid eruptions have not previously been reported with ipilimumab, epidermal growth factor receptor (EGFR) inhibitors such as erlotinib, bevacizumab, or traditional cytotoxic chemotherapies such as carboplatin or paclitaxel. Thus, it seems likely that the lichenoid eruptions are associated with anti-PD-1 therapy. In addition, the clinical appearance and lichenoid changes on histology are

consistently seen amongst both anti-PD-1 agents and anti-PD-L1 agents, supporting the idea that this cutaneous reaction may be a direct, on-target effect of the PD-1/PD-L1 pathway rather than a nonspecific hypersensitivity reaction.

These findings may have implications for the pathogenesis of lichen planus (LP), which is a T cell-mediated disease that affects the skin and mucous membranes, and classically presents with flat-topped, red or purple-colored papules on the flexor surfaces of extremities. LP can also affect the oral mucosa, and blockade of the PD-1/PD-L1 pathway significantly increases the proliferation of peripheral T cells in oral LP, suggesting an inhibitory role of PD-1 (71). Just as LP presents with localized lesions, perhaps the focal distribution seen in some of our patients suggests an underlying "unmasking" of an immune response to a pre-existing antigen that is localized to a specific site in the body. Only once is there blockade of the PD-1 pathway does the body now produce an inflammatory response to this antigen. Histologically, LP also shows a similar lichenoid interface dermatitis, with a dense, band-like lymphohistiocytic infiltrate at the dermal-epidermal junction. LP can be difficult to distinguish from a lichenoid drug reaction, which can show similar histologic changes, but features more suggestive of a drug reaction include fewer epidermal changes and a higher concentration of necrotic keratinocytes and eosinophils (55). Interestingly, the majority of patients in this series were also on concurrent medications that have been reported in the literature to cause lichenoid drug reactions (Table 4). Medications that have been reported to cause a lichenoid drug reaction include anticonvulsants, allopurinol, anti-inflammatory drugs, antimalarials, beta-blockers, diuretics, statins, and psychiatric drugs (55). However, these patients had all previously tolerated these medications, and the fact that anti-PD-1/PD-L1

therapy was the only new medication for these patients suggests it is the most likely drug culprit. It is possible that the administration of an anti-PD-1 or PD-L1 therapeutic agent may also further "unmask" an immune response to a medication that was previously tolerated, resulting in these lichenoid eruptions. Interestingly, one patient (#18) developed acute rashes that seemed to be temporally related to erlotinib administration, even though she had previously tolerated a course of erlotinib with no issues two years prior, possibly representing an activation of the immune system by anti-PD-1 therapy to mount a more exuberant inflammatory response.

In summary, the cutaneous eruptions described in this study represent a unique adverse effect associated with anti-PD-1 therapy that is typically papular in morphology with associated scale and pruritus. There appears to be a spectrum of clinical presentations and distributions, ranging from one or two localized lesions on an extremity to a more generalized, diffuse eruption. Yet, a lichenoid pattern on histology appears to predominate. The eruptions are usually relatively mild and typically can be adequately managed with topical corticosteroids. The cutaneous reaction associated with anti-PD-1/PD-L1 therapy appears to have distinct clinical and histologic features compared to other immunotherapies. Further investigation is needed to determine whether there is an association between cutaneous adverse effects or other irAEs and tumor response. This series of patients adds further characterization to the emerging toxicity profiles of anti-PD-1/PD-L1 therapies.

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