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Cancer Immunology Miniatures

Cancer Immunology Research

Lichenoid Dermatitis in Three Patients with Metastatic Melanoma Treated with Anti–PD-1 Therapy

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Abstract

Therapies that activate the immune system through blocking the binding of programmed death ligand 1 (PD-L1) present on tumors and PD-1 (programmed death 1) present on activated immune cells are revolutionizing the care for patients with cancer. These therapies work by inhibiting negative regulators of the immune system, thereby decreasing a tumor's ability to evade the immune system. The side effects of anti–PD-1/PD-L1 therapies are generally mild and as expected are related to autoimmune reactions. Two of the most common side effects of anti–PD-1/PD-L1 therapies are rash and pruritus occurring in approximately 20% of patients. Although the rash is generally recognized to be immune mediated, the exact mechanisms of the rash remain unclear. Herein, we report three cases of lichenoid dermatitis in three patients treated with MK-3475 (anti–PD-1) that were characterized with marked T-cell infiltrates with few PD-1–positive cells. The rashes in all three patients were relatively mild, allowing treatment to continue despite the rashes. *Cancer Immunol Res; 3(1); 18–22. ©2014 AACR.*

Introduction

Activating the immune system through inhibiting negative costimulatory molecules has revolutionized treatment options for patients with metastatic melanoma (1–4). Although these agents are capable of generating strong anticancer responses, they are often limited by the toxicities of an unchecked and activated immune system.

The two main checkpoints with therapeutic targets are cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and programmed death 1 (PD-1). Inhibition of CTLA-4 with ipilimumab leads to a global activation of the immune system, thereby improving the survival of patients with metastatic melanoma (5, 6). Unfortunately, ipilimumab is limited by relatively frequent immune-mediated toxicities, including colitis (∼30%) and dermatitis (∼40%). The histologic description of ipilimumab-mediated dermatitis is marked by perivascular T-cell infiltrate with eosinophils (7). Low-grade ipilimumab-mediated dermatitis can be treated successfully with topical corticosteroids, whereas high-grade dermatitis requires discontinuation of the drug and systemic treatment with steroids (8).

The next generation of immune checkpoint blockade inhibitors that target either PD-1 present on activated T cells or programmed death ligand 1 (PD-L1) present on tumors has demonstrated marked clinical activity in patients with melanoma, lung cancer, and renal cell carcinoma (1–3). In contrast with ipilimumab, these agents are associated with only approximately 10% of grade 3 and 4 toxicities. Low-grade skin toxicities are relatively common, including rash, pruritus, and vitiligo, which occur in approximately 10% to 20% of patients. Given the relatively recent development of these agents, formal reports of pathology of drug-mediated dermatitis are lacking. Herein, we report three cases of lichenoid dermatitis in patients with metastatic melanoma treated with anti–PD-1 therapy (MK-3475).

Patients, Materials, and Methods

All clinical studies were approved by the Mayo Clinic Institutional Review Board (IRB). The patient described in case 1 enrolled in clinical trial NCT01295827, and was randomized to receive MK-3475 at 10 mg/kg every 3 weeks; the patient described in case 2 elected to receive MK-3475 at 2 mg/kg every 3 weeks through the expanded-access program NCT02083484. The patient described in case 3 was treated with MK-3475 2 mg/kg every three weeks also through the expanded-access program NCT02083484. For histologic analyses, anti-CD3 antibody was purchased from Leica Biosystems (Novocastra; ref. 9); anti-CD4 and anti-CD8 antibodies were purchased from Ventana (10); anti–PD-1 antibody was purchased from Abcam (11). All IHC analyses were performed at the Mayo Core Department using standard methods as described in the references.

Case 1

In September 2012, an 80-year-old woman presented with AJCC stage III melanoma with the presence of a dermal metastases and unknown primary. At that time of presentation, staging for additional metastatic disease was negative and her tumor was wild type for the BRAF V600E mutation. The patient underwent a wide-local excision with clear margins and a negative sentinel lymph node biopsy, and she declined adjuvant therapy. In May

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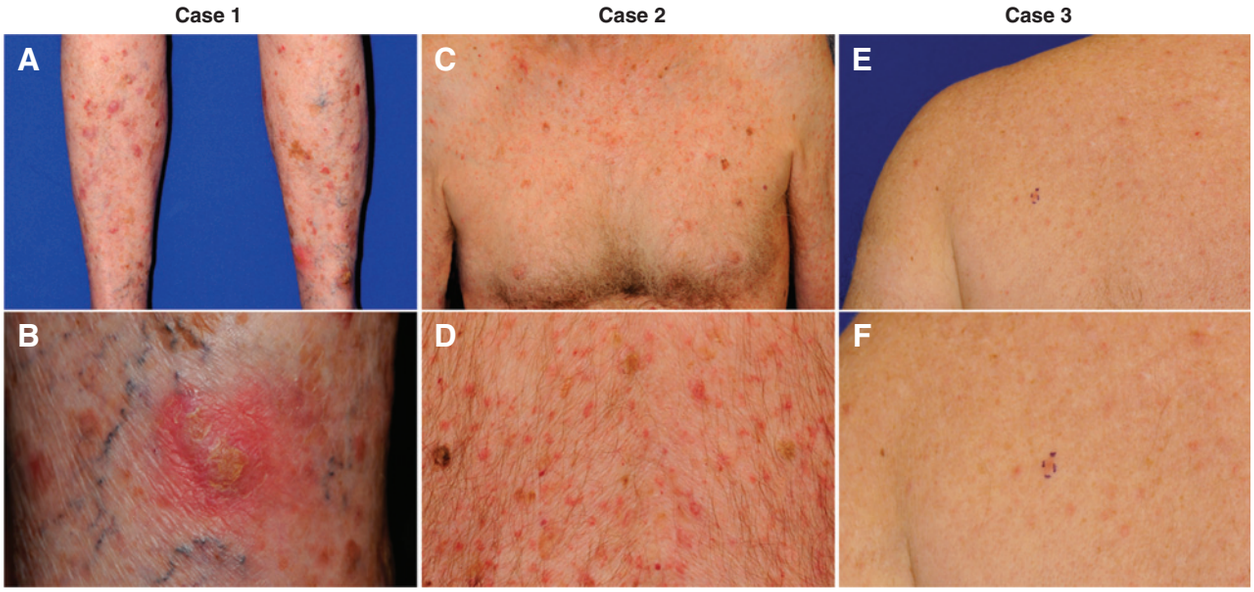

Figure 1.
Cutaneous manifestations of lichenoid drug eruption. Case 1: A, erythematous to violaceous eruption of hyperkeratotic papules and plaques on the legs of case 1. B, close-up view of lesion on upper extremity. Case 2: C, discrete, erythematous, edematous papules and plaques with minimal scaling of the torso and extremities with sparing of the face. D, close-up view of lesions on lower back. Case 3: E, papular eruption with monomorphic, flat-topped, faintly erythematous papules and plaques with fine scale distributed over his chest, back, and abdomen. F, close-up view of lesions on shoulder.

2013, routine restaging revealed multiple bilateral lung lesions, and after reviewing treatment options, the patient enrolled in the phase I clinical study of MK-3475 (NCT01295827, approval by the Mayo Clinic IRB). The patient was randomized to receive 10 mg/kg every 3 weeks. After receiving her first dose, the patient began to develop a mild pruritus that worsened after each subsequent infusion. By her fourth dose and ninth week on study, the patient developed rashes on her upper and lower extremities as well as on her trunk as described below (Fig. 1A and B). Of note, the patient's peripheral absolute eosinophil count increased from a baseline of 40 cells/μL to a peak of 140 cells/μL; however, this level was considered to be within the normal range.

Dermatologic evaluation revealed an erythematous to violaceous eruption of hyperkeratotic papules and plaques on the trunk and extremities. The face was spared, but the eruption otherwise occurred in a photodistributed pattern. There was no mucous membrane involvement or evidence of Wickham striae. The clinical differential diagnosis included papulosquamous eruptions, including lichen planus, lichenoid drug reactions, hypertrophic lichen planus, or hypertrophic psoriasis. MK-3475 was her only new medication before the eruption, although she was taking a few other drugs for several years, including lisinopril with no previous issues. A biopsy from a lesion on her upper extremity revealed lichenoid interface dermatitis with occasional eosinophils and scattered apoptotic basal keratinocytes consistent with a lichenoid drug reaction (Fig. 2). Immunohistochemical staining demonstrated a CD3-positive infiltrate with a more prominent CD4 component than CD8 with approximately 10% of the T cells staining positive for PD-1 (CD279). A course of topical steroids improved her pruritus but did not improve her rash. Given that her rash and pruritus were not overly symptomatic (grade 1), the decision was to continue MK-3475 treatment despite the rash.

Restaging at week 12 revealed a partial response in her lung with an estimated decrease of 82% of her target lesions. Given her response to therapy and ability to tolerate her lichenoid dermatitis, the patient elected to continue therapy with MK3475, and by week 36, she achieved a complete response in her lungs. However, she simultaneously developed a 0.5-cm isolated brain metastasis and was removed from the study in January 2014. For her brain lesion, she underwent a course of stereoradiotactic surgery with a 2-week taper of dexamethasone. Within days of stopping MK-3475 therapy and after beginning dexamethasone, her rash and pruritus completely resolved. The patient continues to have a complete response at 52 weeks (~24 weeks after coming off study) with no new brain or systemic lesions.

Case 2

In May 2013, a 79-year-old man presented with an ulcerated malignant melanoma of his cheek, with pathologic features consistent with spindle cell type, Breslow depth of 1.8 mm, and >1 mitosis per high-powered field. Wide local excision and sentinel node biopsies were performed with no evidence of residual tumor and 6 negative lymph nodes. In December 2013, routine restaging revealed suspicious lung nodules that were confirmed to be metastatic melanoma. Mutational analysis of the patient's tumor for BRAF V600E was found to be wild type. As per standard of care, the patient was treated with four cycles of ipilimumab at 3-week intervals that was complicated by grade 2 colitis that successfully resolved with a 1-month taper of oral steroids. Restaging after ipilimumab treatment revealed progressive disease with growth in all his lung nodules. After

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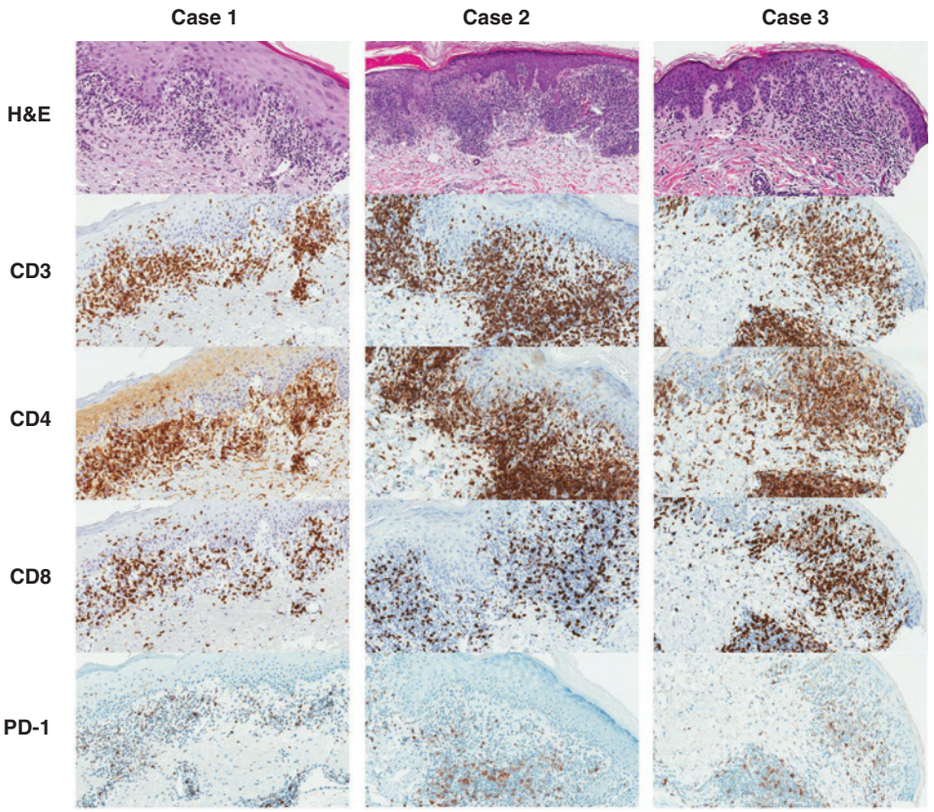

Figure 2.
Histopathologic features of all three cases. The hematoxylin and eosin (H&E)-stained specimens from all three patients have similar lichenoid band-like lymphocytic infiltrate and mild epidermal acanthosis. All three patients' biopsies are marked by an immune infiltrate that is grossly positive for CD3 with more CD4-positive than CD8-positive T cells. PD-1–positive T cells were in the range of 10% to 20% in all three cases.

reviewing treatment options, the patient elected to receive MK-3475, 2 mg/kg every 3 weeks, through the expanded access program (NCT02083484; approval by the Mayo Clinic IRB). One week after his third dose, he began to develop mild pruritus and appearance of a rash on the torso and upper and lower extremities (Fig. 1C and D), and by week 12, his rash and pruritus had significantly worsened.

A dermatologic examination revealed discrete erythematous, edematous papules and plaques with minimal scaling of the torso and extremities with sparing of the face (Fig. 1). Similar to case 1, there was no mucous membrane involvement or evidence of Wickham striae. Differential diagnosis included lichenoid drug eruption versus morbilliform eruption. Biopsies from the right abdomen and right leg revealed a superficial band-like lymphocytic infiltrate with occasional epidermal cytoid body, and scattered apoptotic basal keratinocytes consistent with lichenoid dermatitis. As in the first case, immunohistochemical staining for CD3, CD4, and CD8 revealed a CD3-positive infiltrate with a much more prominent CD4 component than CD8, with approximately 10% of the T cells staining positive for PD-1 (Fig. 2). Although the patient was taking other medications, including lisinopril, the reaction was attributed to MK-3475 as it was the only new medication before the eruption. A course of topical triamcinolone 0.1% cream resulted in resolution of symptoms and near clearance of rash within 3 weeks.

Four weeks after his fourth dose, the patient underwent restaging, revealing a near complete remission of his bilateral pulmonary nodules. As his rash and pruritus improved to grade 1, he elected to continue to receive MK-3475 in 3-week intervals without significant worsening of his rash.

Case 3

In March 2010, a 64-year-old man was diagnosed with an ulcerated superficial spreading melanoma, Clark level IV, Breslow depth of 1.7 mm, and mitotic rate of 10/mm^2 (AJCC T2b) on the right cheek. Mutational analysis of the patient's tumor for BRAF V600E was found to be wild type. The patient was treated with wide local excision and a sentinel lymph node biopsy that was positive in his right parotid gland. The patient subsequently underwent a superficial parotidectomy and neck dissection that did not show any evidence of disease in the 19 additional lymph nodes removed. Staging with a 2[18F]fluoro-2-deoxy-D-glucose PET/CT scan from the vertex through the thighs was negative for evidence of metastatic disease.

In the adjuvant setting, the patient received GM-CSF for 1 year. In September 2011, routine restaging revealed two lesions in the upper lobe of his left lung, and he was treated with stereotactic body radiation therapy followed by adjuvant GM-CSF. In September 2012, restaging revealed metastatic disease in his lungs and adrenal glands. From September 2012 to December 2012, he received oral temozolomide as a part of clinical trial (protocol MC1076) with progressive disease. From January 2013 to April 2013, patient received 4 doses of ipilimumab (3 mg/kg), resulting in stable disease. In November 2013, restaging revealed progression in the left adrenal gland and the patient underwent adrenal embolization. In June 2014, restaging demonstrated continued slight progression of disease and the patient received an additional two doses of ipilimumab (3 mg/kg), but unfortunately the disease continued to progress. In August 2014, the patient began treatment with MK-3475 (2 mg/kg) every 3 weeks.

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Ten days after his second cycle of MK-3475, he developed a mildly pruritic papular eruption on his trunk (Fig. 1E and F). The patient had taken no other medications. Dermatologic examination was notable for monomorphic, flat-topped, faintly erythematous papules and plaques with fine scale distributed over his chest, back, and abdomen. The face, mucous membranes, scalp, extremities, and nails were spared. No Wickham striae were noted. This was suspected to be a lichenoid drug reaction.

A punch biopsy of the left posterior shoulder revealed lichenoid and perivascular dermatitis with occasional eosinophils, consistent with lichenoid drug eruption. Consistent with the first two cases, immunohistochemical staining demonstrated a CD3-positive infiltrate with a more prominent CD4-positive T-cell component than CD8, with approximately 10% of the T cells staining positive for PD-1 (Fig. 2). Given the rash was mild and asymptomatic, a decision was made to continue his MK-3475 infusions, and no treatment was prescribed.

Discussion

To our knowledge, these are the first cases reported of lichenoid dermatitis in patients receiving the anti–PD-1 agent MK-3475. Given the mechanism of action of MK-3475, we expected the patients to develop T-cell–mediated rashes, and biopsies in all three cases confirmed the diffused presence of $CD3^+$ lymphocytes with relatively few PD-1–positive T cells.

Immune-mediated adverse skin findings are frequently associated with the use of immune checkpoint blockade inhibitors. The most common cutaneous findings in ipilimumab-associated rashes are discrete, erythematous, pruritic, minimally scaly papules that coalesce into plaques on the trunk and extremities (7,8). The face, hands, and feet are usually spared, and there is typically no mucous membrane involvement. Histologically, there is a superficial, perivascular CD4-predominant T-cell infiltrate with eosinophils in the dermis with mild epidermal spongiosis and rare dyskeratotic epidermal cells. Cutaneous eruptions in the setting of ipilimumab therapy are most likely a result of nonspecific T-cell activation due to blockage of CTLA-4, which may activate melanoma-associated antigen-specific CD4-positive T cells and hone to the skin.

In these three cases, the clinical and histopathologic findings differed from those typically reported with anti–CTLA-4 treatments, suggesting that anti–PD-1 induces dermatitis through a separate T-cell–mediated mechanism. Lichen planus, the prototypical lichenoid tissue reaction, is an idiopathic T-cell–mediated skin reaction to an unknown antigen that is frequently, but not always, present in patients with hepatitis C infection. The exact pathophysiology of lichenoid reactions is unclear; however, it is thought to be T cell mediated with typical histopathologic findings, including dense CD4-positive and CD8-positive T cells (12). To our knowledge, there are no published data on the presence or absence of PD-1–positive T cells in lichenoid drug reactions, and whether lichen planus or lichenoid drug reactions are mediated by dysregulation of the PD-1/PD-L1 pathway remains unknown.

The treatment of lichenoid drug reactions usually involves stopping of the culprit drug, but in the three cases described here, we felt the benefit of MK-3475 far outweighed the side effect of the rash. Treatment of lichenoid reactions can also include topical steroids. In case 1, topical steroids improved the pruritus but not the rash; in case 2, topical steroids improved both the pruritus and the rash; and in case 3, no therapy was necessary. Interestingly, ACE inhibitors such as lisinopril are associated with lichenoid drug reactions, and patients in case 1 and case 2 were taking lisinopril at the time of the reaction; however, neither had a reaction to lisinopril before starting MK-3475. Also of interest, the patients in case 1 and case 2 achieved a complete or near complete remission of their metastatic melanoma while on therapy. The significance of autoimmune reactions as a marker of response to therapy with MK-3475 remains unclear.

In summary and to our knowledge, these are the first three cases of lichenoid drug eruption associated with the use of an anti–PD-1 agent. These reactions were relatively mild, allowing patients to continue therapy, and both reactions responded to topical corticosteroids. Further work is necessary to elucidate if PD-1–positive T cells are the cause or the effect of the rash. In addition, more work is needed in developing treatment strategies for patients who develop these debilitating reactions.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: R.W. Joseph, A. Jambusaria
Development of methodology: R.W. Joseph
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): R.W. Joseph, B. Goedjen, M. Gordon, C. Gilstrap, M. Cappel, A. Jambusaria
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): R.W. Joseph, M. Cappel
Writing, review, and/or revision of the manuscript: R.W. Joseph, M. Gordon, B. Kirsch, S. Bagaria, M. Cappel, A. Jambusaria
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): R.W. Joseph

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