

LETTER TO THE EDITOR



Ulcerative lymphomatoid papulosis following immune checkpoint inhibition and autologous stem cell transplant in a patient with recurrent Hodgkin lymphoma: a case report

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To the Editor

The use of immune checkpoint inhibitor (ICI) therapy in cancer treatment has improved patient outcomes by increasing the immune response to fight tumor cells [1]. However, overactivation of the immune response is also responsible for immune-related adverse events (irAEs) [2]. Cutaneous irAEs occur in up to 30% of patients treated with ICIs and encompass a wide range of events including lichenoid reactions, eczema, vitiligo, and pruritus (Table 1) [4]. Although cutaneous irAEs secondary to ICIs are common, they can vary in presentation and may go underdiagnosed or underreported. There has been only one report of lymphomatoid papulosis (LyP) secondary to an ICI in a patient with renal cell carcinoma [4,5]. Additionally, there has been one report of CD30+ cell infiltrate secondary to an ICI in a patient with stage IV metastatic melanoma, for which malignancy was excluded but no formal diagnosis was made [6]. There have been no reports of LyP secondary to an ICI in a patient with Hodgkin lymphoma or an autologous stem cell transplant (autoSCT). Here we present a case of a patient with recent autoSCT for Hodgkin lymphoma taking ICIs who developed ulcerative LyP.

Case report

A 63-year-old male with recurrent Hodgkin lymphoma, initiated on treatment with nivolumab and brentuximab and followed by autoSCT 2 months later, presented to dermatology 2 months after autoSCT with 2 weeks of mildly painful leg ulcers. Nivolumab was held due to rash. The lesions began as papules that evolved into blisters, some pus-filled and ruptured into ulcers. The patient denied systemic symptoms and recent travel. Examination revealed grouped pink firm nodules on the right medial thigh, scattered round crusted plaques on the bilateral thighs, and grouped red ulcerated papules and plaques with a violaceous rim on the right medial leg (Figure 1). Differential diagnoses included lymphoma

cutis, LyP, neutrophilic dermatosis, bullous/erosive lichen planus, and infection.

A punch biopsy demonstrated a superficial and deep perivascular and interstitial mixed inflammatory cell infiltrate with many enlarged lymphocytes. Immunohistochemical staining of the infiltrate consisted of mostly CD3+ T-cells with a predominance of CD4 over CD8. The large lymphocytes expressed CD30 but not CD15 or ALK1. A T-cell receptor gene rearrangement study demonstrated evidence of monoclonal T-cell proliferation. A separate punch biopsy was performed for tissue cultures, which were negative for bacteria, mycobacteria, and fungi. Histopathology and clinical presentation were consistent with a diagnosis of LyP, however, the presence of activated T-cell lymphocytes was unusual. This histopathology differed from the patient's prior histopathology on diagnosis of Hodgkin lymphoma, in which large Reed Sternberg cells positive for both CD30 and CD15 were identified. The patient was managed with supportive wound care with improvement, nivolumab was resumed 6 weeks after the initial presentation, and resolution was achieved 8 weeks after the initial presentation without LyP recurrence.

Discussion and conclusion

There is a spectrum of primary cutaneous and systemic CD30+ lymphoproliferative diseases linked by the expression of CD30+ tumor cells [7,8]. This spectrum includes benign and premalignant diseases, such as LyP, and malignancies such as anaplastic large-cell, B-cell, T-cell, and classical Hodgkin lymphoma [7,8]. LyP is a benign, chronic, CD30+ cutaneous lymphoproliferative disorder that is characterized by crops of papules, plaques, or nodules that often self-resolve and can recur [9]. Given our patient's clinical and histologic features, our patient was diagnosed with ulcerative LyP potentially occurring as a reaction to immune checkpoint inhibitor exposed T-lymphocytes from nivolumab therapy later activated by autoSCT.

Table 1. Cutaneous immune-related adverse events (irAEs) secondary to immune checkpoint inhibitors (ICIs) and differential diagnoses [13].

Cutaneous immune-related adverse events secondary to immune checkpoint inhibitors	
Cutaneous irAEs secondary to ICIs	Differential diagnoses
Acantholytic dermatitis	Pemphigus Hailey-Hailey disease Darier disease Acantholytic acanthoma
Acneiform/follicular dermatitis or rosacea	Acne vulgaris Seborrheic dermatitis Suppurative folliculitis
Acute generalized exanthematous pustulosis	Pustular psoriasis Impetigo Candida infection Subcorneal pustular dermatosis
Bullous pemphigoid	Bullous arthropod reaction Allergic contact dermatitis Drug reaction Pemphigus vulgaris
CD30+ lymphomatoid reaction	Lymphoma Lymphomatoid papulosis
Dermatomyositis-like reaction	Lupus erythematosus
Drug reaction with eosinophils and systemic symptoms	Spongiform dermatitis Pustular dermatitis Interface dermatitis Interstitial granulomatous dermatitis
Sarcoidal granulomatous dermatitis	Infection (including tuberculoid leprosy) Foreign body granuloma Sarcoidal variant of granuloma annulare Cutaneous Crohn's disease Necrobiosis lipoidica Granuloma annulare
Interstitial granulomatous dermatitis	Interstitial granuloma annulare
Lichenoid dermatitis	Lichen planus Lichenoid keratosis Lichen nitidus Lichen Striatus Fixed drug reaction Discoid lupus erythematosus
Neutrophilic dermatosis of the dorsal hands	Infection Vasculitis Pyoderma gangrenosum Granuloma faciale Bechet disease
Panniculitis	Erythema nodosum Lupus panniculitis Other panniculitides Infection
Photosensitivity	Other spongiform dermatitides
Prurigo nodularis	Verruca vulgaris Pseudocarcinomatous hyperplasia Keratoacanthoma
Psoriasis	Chronic spongiform dermatitis Seborrheic dermatitis Pityriasis rubra pilaris Syphilis Lichen simplex chronicus
Pyoderma gangrenosum	Infection Vasculitis Sweet syndrome Granuloma faciale Bechet Disease
Sclerodermoid reaction	Morphea Sclerodermoid GVHD Chronic porphyria cutanea tarda Keloid Late-stage radiation dermatitis Lichen sclerosus Borrelia infection
Spongiform dermatitis	Allergic contact dermatitis Atopic dermatitis Psoriasis Stasis dermatitis Id reaction Pityriasis rosea Tinea infection

(continued)

Table 1. Continued.

Cutaneous immune-related adverse events secondary to immune checkpoint inhibitors	
Cutaneous irAEs secondary to ICLs	Differential diagnoses
Stevens-Johnson syndrome/toxic epidermal necrolysis-like reaction	Erythema multiforme
	GVHD
	Lupus erythematosus
	Dermatomyositis
Superficial perivascular dermatitis	Urticaria
	Arthropod bite reaction
	Drug reaction
	Scabies
	Urticarial bullous pemphigoid
	Allergic contact dermatitis
	Itchy red bump disease
Sweet syndrome	Infection
	Vasculitis
	Pyoderma gangrenosum
	Granuloma faciale
	Bechet disease
Xerosis	Ichthyosis
	"Invisible" dermatoses (macular amyloidosis, dermal melanocytosis, mastocytosis, anetoderma, vitiligo, tinea infection)



Figure 1. Pink firm nodules, round crusted plaques, erosions with violaceous rim at initial presentation (A–C) and 2 weeks after initial presentation (D). A) Right groin. B) Right thigh. C) Right medial ankle. D) Right medial ankle.

Little is known about the dynamics of PD-1 expression on immune effector cells after SCT, however, there is evidence that PD-1 inhibition improves the antitumor effect of transplantation procedures [10]. Malignant cells can compromise the antitumor effects of SCT by misusing the self-limiting system of the immune response by overexpressing inhibitory molecules that interact with immune cells, resulting in immune exhaustion [11]. ICIs prevent the activation of the immune system in order to prevent autoimmunity and maintain peripheral tolerance. Nivolumab inhibits a transmembrane protein known as PD-1 that is expressed on T-cells, B-cells, and NK-cells [11]. The ligand of PD-1 is PD-1L and is not only expressed on hematopoietic and non-hematopoietic cells but also on various solid tumor and hematologic cancer cells [11]. The use of ICIs should decrease the activation of T-cell lymphocytes, thereby decreasing the likelihood of immune exhaustion [11]. Our patient was first treated with ICIs, inhibiting T-cell activation, followed by autoSCT, which we believe activated the T-cells that were previously inhibited by nivolumab and resulted in a cutaneous irAE. These activated T-cells were seen on histology in our patient who was diagnosed with LyP secondary to nivolumab. Cutaneous irAEs are a common side effect of ICIs, however, LyP secondary to ICIs is rare.

A systematic review of prospective trials evaluating the benefits and harms of nivolumab in patients with Hodgkin lymphoma after autoSCT identified 283 patients, with 12% reporting rash as an irAE, however, the rashes were not described [12]. In general, skin reactions caused by ICIs include lichenoid reactions, eczema, vitiligo, and pruritus [4]. There is one report of LyP secondary to an ICI in a patient with renal cell carcinoma [4]. However, to our knowledge, there have been no reports of LyP associated with ICI in patients with Hodgkin lymphoma after autoSCT.

There are no prospective controlled studies validating treatments for LyP [13]. However, current treatment methods include therapeutic abstinence with supportive care for mild to moderate disease and oral, subcutaneous, or intramuscular methotrexate with weekly doses of 5 to 20 milligrams for moderate to severe disease [13]. Other options include phototherapy, particularly psoralen and ultraviolet A (PUVA) therapy, and local chemotherapies including mechlorethamine, bexarotene, and interferon [13]. For larger or recurrent LyP skin tumors, surgical excision or radiotherapy is another treatment option [13]. Our patient, like the majority of patients with LyP, had resolution of disease with only supportive treatment, supporting the diagnosis of LyP rather than a malignant CD30+ disease.

Here we present a case of a 63-year-old male with recurrent Hodgkin lymphoma, treated with nivolumab and brentuximab followed by autoSCT, presenting with painful leg ulcers that on clinical and on pathological examination were consistent with a diagnosis of ulcerative LyP. To our knowledge, this is the first report of LyP potentially occurring as a reaction to immune checkpoint inhibitor-exposed T-lymphocytes from nivolumab therapy later activated by autoSCT. Physicians should consider ulcerative LyP in patients with Hodgkin lymphoma or with recent autoSCT receiving ICIs

who develop painful ulcers. Clinically, these lesions may appear similar to cutaneous lymphoma or infection and biopsy is important to differentiate these entities.

Patient consent statement

Consent for the publication of all patient photographs and medical information was provided by the authors at the time of article submission to the journal stating that all patients gave consent for their photographs and medical information to be published in print and online and with the understanding that this information may be publicly available.

Prior presentation

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