Dermatomyositis associated with nivolumab therapy for melanoma: a case report and review of the literature

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Abstract

We present a rare case of dermatomyositis associated with nivolumab therapy for melanoma. Nivolumab is an immune checkpoint inhibitor that blocks the programmed death-1 (PD1) receptor and has a number of associated immunotherapy related adverse events. Although most are T-cell mediated, some are antibody mediated mimics of classical autoimmune diseases. We review the characteristics of other cases of anti-PD1 associated dermatomyositis and the recent literature to better understand how to classify and treat this challenging immunotherapy related adverse event.

Keywords: dermatomyositis, nivolumab, pembrolizumab, PD1, PDL1, immune checkpoint inhibitors, immunotherapy-related adverse events, melanoma

Introduction

The programmed death-1 (PD1) receptor is presented on T-cells and when bound by its ligands PDL1 and PDL2, is inhibitory and negatively regulates T-cell effector function [1]. The ligands to PD1, PDL1, and PDL2, have constitutive low-level expression and contribute to "immune privileged status" in certain normal tissues [2]. PDL1 and PDL2 expression can be induced in malignant cells, inhibiting self-immune reaction [2]. Blockade of the PD1 pathway, known as immune checkpoint inhibition, can maintain or restore the effector activity of T-cells [1]. Cytotoxic T lymphocyte antigen four (CTLA-4) is another related pathway that has been targeted to block the inhibition of T-cell activation [1]. There are now multiple PD1 and CTLA-4 inhibitors that are being used to treat cancer. Nivolumab and pembrolizumab are PD1 blocking antibodies that are FDA-approved for the treatment of advanced melanoma and other cancers [3,4].

Immune checkpoint inhibitors have shown impressive benefits in the treatments of various cancers. However, they are associated with the occurrence of adverse events which can affect any organ of the body [5]. These are known as immunotherapy-related adverse events (irAEs), [5]. The most common irAEs include rash, colitis, hepatitis, and hypophysitis [5]. They are believed to occur owing to T-cell activation, which when aberrant, can result in these toxicities [5]. Interestingly, genetic polymorphisms in PD1 and CTLA-4 have been found in several studies to be associated with various autoimmune diseases including systemic lupus erythematosus, thyroiditis, and rheumatoid arthritis [6].

Dermatomyositis is a form of idiopathic autoimmune inflammatory myopathy. In rare situations, it is believed to result from an antibody-mediated process triggered by malignancies, medications, or infections [7].

Case Synopsis

A 40-year-old man with stage IIIc melanoma who was receiving adjuvant nivolumab 240mg every two

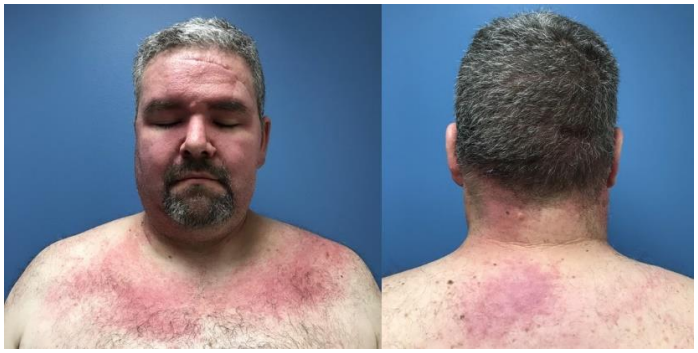

Figure 1. *Photodistributed erythema with slightly violaceous appearance involving the forehead, periorbital skin, malar cheeks (including nasolabial folds), upper chest, posterior neck, and upper back.*

weeks developed symmetrically photodistributed painful erythematous plaques one week after his seventh nivolumab infusion. The rash was associated with muscle and joint pains and weakness in the shoulders and hips. His melanoma was an invasive nodular melanoma of the left forehead with 6.5mm Breslow depth and metastases to the left parotid and left neck that was treated with wide local excision, left parotidectomy with neck lymph node dissection, and radiation therapy followed by initiation of nivolumab.

His comorbidities include hypertension, obesity, and fatty liver disease. He also reported a 20-year history of non-specific intermittent joint pain and swelling in the shoulders, wrists, knees, and ankles. Workup two years prior to rash presentation revealed normal rheumatoid factor, cyclic citrulline peptide (CCP) antibody, uric acid, erythrocyte sedimentation rate, and anti-nuclear antibodies (ANA). At that time, his C-reactive protein (CRP) was elevated at 6.8mg/L (normal range 0-3mg/L). Of note, he worked for many years lifting heavy boxes. He had no known personal history of autoimmune diseases. His concurrent medications were losartan and ibuprofen, which he had been taking for years, and doxycycline, started two months prior to rash onset for folliculitis of the face and body, which started after the second cycle of nivolumab.

On examination, the patient had brightly erythematous-to-slightly-violaceous patches over the face (sparing the upper and lower eyelids), neck (sparing the submental area), upper chest and back, dorsal forearms, overlying the metacarpophalangeal joints (these were scaly), and to a lesser extent overlying the proximal interphalangeal joints (**Figures 1, 2**). He had periorbital swelling. There was prominent periungual erythema with ragged cuticles on the fingers (**Figure 2**). His motor strength was 4/5 in the shoulder girdle and hip flexors bilaterally.

Skin biopsies taken from the chest and right forearm revealed similar histopathology: a cell poor interface dermatitis with focal increased interstitial mucin (**Figure 3**). Laboratory testing revealed positive ANA 1:640 titer with speckled pattern. Erythrocyte sedimentation rate was borderline elevated at 9mm/hr (normal range 0-15mm/hr) and CRP was

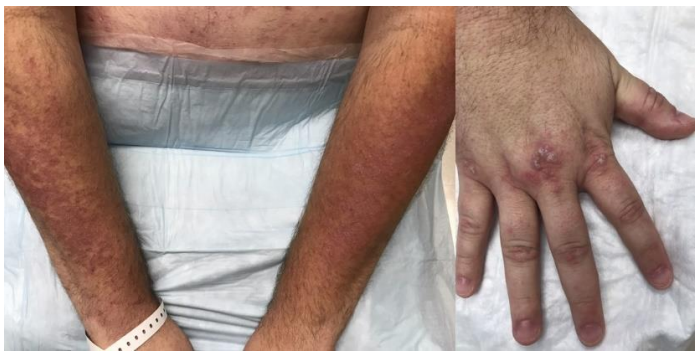

Figure 2. *Erythematous patches with slightly violaceous appearance involving the dorsal forearms. Scaly erythematous papules involving the metacarpophalangeal joints and to a lesser extent overlying the proximal interphalangeal joints. Periungual erythema is also present.*

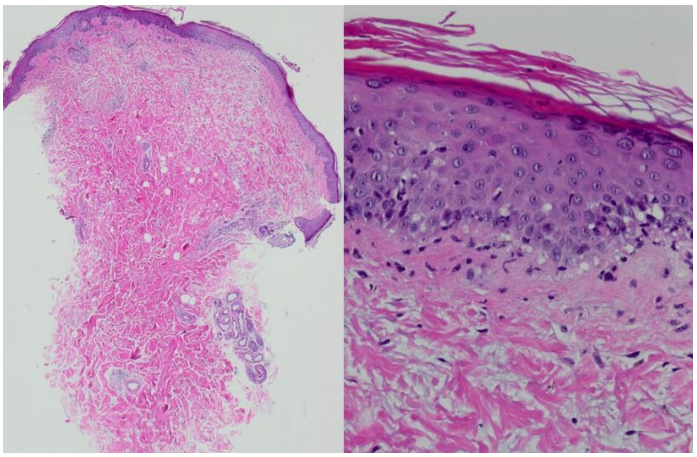

Figure 3. *Left, H&E 20x punch biopsy from the right forearm showing epidermal atrophy and pauci inflammatory lichenoid infiltrate. Right, H&E 200x showing vacuolar interface dermatitis with some lymphocyte exocytosis and substantial interstitial dermal mucin.*

elevated at 18.68mg/L (normal range <1mg/L). TIF1γ (p155/140), Jo-1, Mi-2, and PM-Scl antibodies were negative. Unfortunately, further myositis panel testing was not available. Creatinine kinase (CK) and aldolase were within normal limits initially. Alanine aminotransferase was normal and aspartate aminotransferase was slightly elevated at 47U/L (normal range <40U/L). Given the typical clinical presentation, histopathology, and positive ANA, the patient was given a diagnosis of dermatomyositis. No muscle magnetic resonance imaging was performed. Rheumatoid factor and CCP were not repeated owing to lack of synovitis on examination. At the time of diagnosis of dermatomyositis, the patient's re-staging imaging studies showed he was cancer-free.

Nivolumab was discontinued and the patient was started on prednisone 60mg daily and methotrexate 10mg weekly. Hydroxychloroquine 200mg twice daily was started four weeks after rash onset by the rheumatology service because of continued joint and muscle pains. The patient had improvement of the rash without complete clearance at his two-month follow-up while taking prednisone, methotrexate, and hydroxychloroquine but flared when the prednisone was tapered to less than 5mg daily. His repeat aldolase was elevated at 13.1units/L (normal range < 7.7unit/L) but CK remained within normal limits. The joint and muscle pains improved but did not resolve completely. Consequently, methotrexate was increased to 20mg weekly and when his symptoms persisted, the patient was given IVIG two g/kg over three days as a corticosteroid-sparing agent. His dermatomyositis was reasonably controlled. At this point, there was no melanoma recurrence.

Despite aggressive treatment of his dermatomyositis, in subsequent follow up visit months after his dermatomyositis diagnosis, the patient was noted to have a left forehead nodule and punch biopsy confirmed recurrent melanoma. He subsequently developed additional soft tissue and nodal disease of the left face and neck and was given one pembrolizumab dose that caused worsening of his rash, joint pains, muscle pains, and weakness. He continued to have dermatomyositis with arthralgias, myalgias, and worsening muscle weakness despite multiple months of therapy with intravenous immunoglobulin (IVIG) two g/kg every four weeks, prednisone, and hydroxychloroquine. He received one course of cisplatin, vinblastine, and dacarbazine, but was unable to tolerate this regimen because of thrombocytopenia. Unfortunately, the patient ultimately expired two years after his initial melanoma diagnosis.

Case Discussion

Our patient had both malignancy and exposure to nivolumab, either of which can be triggers of dermatomyositis. Dermatomyositis is a well-known paraneoplastic disease and has been reported in association with melanoma in a handful of cases [8-13]. It typically presents simultaneously with metastatic melanomas that have high mortality [8]. There have also only been five cases of dermatomyositis associated with anti-PD1 therapy reported [14-18]. We believe that our patient's dermatomyositis is more likely to be caused by anti-PD1 therapy as these medications have been associated with other antibody-mediated autoimmune diseases such as bullous pemphigoid, type one diabetes mellitus, and hepatitis. This is further supported by his flaring dermatomyositis without evidence of cancer, negative TIF1γ (p155/140) antibody, which is positive in 42-100% of patients with cancer-associated dermatomyositis, and the flare of his disease after pembrolizumab re-challenge [19]. Of note, there is a recent report of a case of dermatomyositis in a patient receiving nivolumab for gastric cancer. However, his dermatomyositis was attributed to his malignancy owing to positive TIF1γ antibody testing [20]. The characteristics of the other previous reports of anti-PD1 associated dermatomyositis are presented in **Table 1** [14-18]. Notably, all cases involve male patients when classically, dermatomyositis affects female patients two-to-three times more often [7]. Our patient also has an atypical muscle enzyme and antibody profile. Finally, it is interesting to point out that our patient was briefly on doxycycline prior to the onset of dermatomyositis symptoms. It is well known that doxycycline can cause phototoxicity

from ultraviolet (UV) radiation exposure [21] and it is suspected that UV radiation can be involved in the pathogenesis of dermatomyositis [22]. This raises the question of possible doxycycline-induced phototoxicity contributing to the development of dermatomyositis in this patient.

Aside from his rash, the patient had persistent muscle pains and joint pains. These can both be associated with dermatomyositis but are not always observed. This raises the concern for a distinct PD1 inhibitor associated myopathy and/or arthritis. The so called "PD1 inhibitor-associated myopathies" are becoming increasingly recognized. Patients have been reported to present with ptosis, diplopia, dysarthria, dysphagia, myalgias, and limb weakness [18].

Nearly all patients classified as having a PD1 inhibitor-associated myopathy have significantly elevated CK levels [18]. Interestingly, our patient had normal CK levels, but elevated aldolase levels. Two patients with anti-PD1 associated dermatomyositis had significantly elevated CK levels [14,16] and one of the patients had normal CK with elevated aldolase, similar to our patient [17]. The clinical and pathological features of elevated aldolase levels with normal CK levels are not well documented, but this phenotype may suggest pathology of the perimysium rather than the muscle fiber [23]. This is significant as aldolase levels may detect muscle involvement that can be missed when CK levels are normal.

There is probably overlap in the distinction between PD1 dermatomyositis and PD1 inhibitor-associated myopathies, analogous to classical DM versus polymyositis. Clinically, there may be important prognostic differences as death related to necrotizing myopathy of the diaphragm and myocarditis have been reported in the PD1 inhibitor-associated myopathies and not with PD1-associated DM [18].

Arthralgias occur frequently during anti-PD1 treatment and have been classified into arthritis (arthralgias with synovitis), progressive osteoarthritis, and arthralgias without evidence of joint damage [24]. In one study, rheumatoid factor and CCP were positive in 14.3% of the patients with arthritis, but not in the other two classifications [24]. Most cases were satisfactorily treated with NSAIDs and/or low-dose corticosteroids [24]. It is unknown whether the arthralgias in our patient are completely related to the dermatomyositis or if they are occurring through a separate mechanism. Regardless of the etiology, treatment with NSAIDs and/or low dose corticosteroids is likely to help in both situations, but as in our patient, may not completely mitigate the symptoms. Rheumatoid factor and CCP antibody testing seem unlikely to change management in our patient but is of academic interest to further aid in classification of the irAEs.

Typically, the initial treatment of dermatomyositis involves treatment of the underlying malignancy and discontinuation of the offending medication, if present, followed by topical and/or systemic therapies depending on the severity of disease [7]. However, discontinuation of the offending medication becomes difficult in the case of anti-PD1 therapy when it is being used to treat a life-threatening malignancy, especially with the observation of higher tumor response rates in patients with irAEs [6]. Literature recommends temporarily suspending immunotherapy for common terminology criteria for adverse events (CTCAE) grade two reactions, suspending immunotherapy and discussion of risk/benefit ratio with the patient before resumption for CTCAE grade three reactions, and permanent discontinuation of immunotherapy for CTCAE grade four reactions [6]. It is also recommended that the systemic corticosteroids be employed at initial doses used to treat autoimmune diseases, but for a shorter period of time to avoid compromising anti-tumor activity [6]. In all reported cases of anti-PD1 associated dermatomyositis, immunotherapy was held and the patient was started on a prednisone taper. Methotrexate has been added in some cases and in one particular case, the regimen cleared the rash within one month and the patient remained clear off all treatments with no evidence of disease after nine months [15]. In other cases, hydroxychloroquine and IVIG have been added with varying success.

With the limited number of reports, it is difficult to predict how long the dermatomyositis symptoms last after discontinuing anti-PD1 therapy. With antibody-mediated bullous pemphigoid, the course can be quite long [25]. Evaluating the natural history of irAEs in patients taking immune checkpoint inhibitors is problematic because of the premature death that can occur with advanced cancers. Both nivolumab and pembrolizumab have long half-lives, 25 and 22 days, respectively [3,4]. This indicates that anti-PD1 levels can persist for months after discontinuation. Not to mention that immune checkpoint blockade can provide long-term clearance of malignancy perhaps suggesting that irAEs could also persist or occur up to several years after discontinuation of treatment [6].

Immunotherapy related adverse events are not uncommon and can be associated with significant morbidity and mortality, both directly and indirectly by withdrawal of potentially life-saving treatments. Reporting of irAEs is important and as it becomes more enhanced [26], it would be useful to assess which patient characteristics and which types of anti-PD1 are associated with the development of different types and severities of irAEs. Patient characteristics could result in preemptive autoantibody testing, but thus far little is known in the literature about screening patients for autoimmune disease prior to initiation of therapy. It is important to mention that many of the initial studies for immune checkpoint inhibitors excluded patients with pre-existing autoimmune diseases [27]. However, a recent study examined patients with pre-existing autoimmune disease and found that although they were more likely than those without pre-existing autoimmune disease to develop an irAE, the anti-PD1 antibodies seem to be just as safe and effective with appropriate management [27].

Conclusion

Our case highlights that dermatomyositis and comparable PD1 inhibitor-associated myopathies are becoming increasingly recognized irAEs associated with anti-PD1 therapy. Continued and improved irAE reporting can help to better define and distinguish these and other irAEs and their responses to particular treatments. Finally, irAEs offer a unique way to better understand the immune system's function in the context of malignancy and autoimmunity.

Potential conflicts of interest

The authors declare no conflicts of interest.

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Table 1. *Patient characteristics of other previous reports of anti-PD-1 associated dermatomyositis.*

Report	Marano et al. [14], (Case 1)	Yu et al. [15]	Berger et al. [16]	Liewluck et al. [18], (Patient 4)	Kudo et al. [17]	Messer et al. (this case)
Therapy	Nivolumab 3mg/kg every 2 weeks	Nivolumab 3mg/kg + cabiralizumab 4mg/kg	Pembrolizumab	Pembrolizumab	Nivolumab 3mg/kg every 2 weeks	Nivolumab 3mg/kg every 2 weeks
Primary Malignancy	Small Cell Lung Cancer	Renal Cell Carcinoma	Melanoma	Non-Hodgkin lymphoma	Lung Adenocarcinoma	Melanoma
Patient Demographics	Man, in 60s	67-year-old man	83-year-old man	55-year-old man	42-year-old man	40-year-old man
Diagnosis	1) Subacute cutaneous lupus erythematosus and then 2) dermatomyositis	Wong-Type Dermatomyositis	Dermatomyositis	Early Dermatomyositis	Dermatomyositis	Dermatomyositis
Description of Symptoms	1) Photodistributed, pruritic annular rash. 2) Fatigue, jaw claudication, muscle weakness and ulcerations on dorsal distal and proximal interphalangeal joints	Photodistributed rash, facial edema (periocular), Gottron's papules; no muscle weakness	Asthenia, diffuse edematous syndrome, muscle weakness, dysphagia, Gottron's papules, rash on neck and trunk	Diplopia, dysarthria, dysphagia, rash	Heliotrope rash, shawl sign, periungual erythema, muscle weakness	Painful photodistributed rash, Gottron's papules, periungual, periorbital swelling, muscle pain and weakness, arthralgias
Development of Symptoms	1) After 2nd dose 2) 2 months after restarting nivolumab	After 13th dose	After 6th dose	After 4th dose	After 3rd dose	After 7th dose
Skin Pathology	1) Interface dermatitis and increased dermal mucin.	Superficial perivascular lymphocytic infiltrate with epidermal atrophy, vacuolar change, and dermal mucin. DIF negative	Lichenoid dermatitis with some dermal mucin	Lichenoid interface dermatitis	Not reported	Interface dermatitis + dermal mucin
Laboratory Testing	1) ANA 1:40, then 2) 1:640 2) ESR 33mm/hr (elevated) 2) CRP 4.94mg/dL (elevated) 2) CK 1657units/L (elevated) --	-- -- -- CK Normal Aldolase Normal	ANA 1:1280 (speckled) -- -- CK 1883UI/L (elevated) Aldolase 15.5UI/L (elevated)	-- -- -- CK 72U/L (normal) --	-- -- CRP 0.65mg/dL (normal) CK 137units/L (normal) Aldolase 23.7units/L (elevated)	ANA 1:640 (speckled) ESR 9 mm/hr (normal) CRP 18.68mL/L (elevated) CK Normal Aldolase 13.1units/L (elevated)
Other Testing	1) Anti-Ro positive	dsDNA, Smith, RNP, Ro, La, Jo1, Mi2, SRP all negative	TIF1γ positive ENMG: net myogenic involvement in	EMG: normal repetitive nerve stimulation and normal R1	Jo1 tRNA negative EMG: myogenic involvement	TIF1γ, Jo1, Mi1, PM-Scl all negative

			deltoid Biopsy deltoid: myositis with vasculitis and necrosis	latency with mildly prolonged bilateral R2 latencies Muscle biopsy: focal reduction of capillary density and membrane attack complex deposition of intramuscular capillaries		
Treatment	1) Stopped nivolumab. Started 60mg PO prednisone + topical corticosteroid + hydroxychloroquine 200mg BID + sun protection for 8 weeks. 2) Nivolumab stopped + prednisone taper + IVIG 2g/kg monthly	Immunotherapy held + topical corticosteroids + prednisone taper (started at 1mg/kg/day) + methotrexate 10mg weekly	High dose oral corticosteroids (initially 1.5mg/kg/day) + IVIG 2g/kg	Prednisone (initially 1mg/kg/day)	IV corticosteroids (0.6mg/kg/day)	Stopped nivolumab. Prednisone + methotrexate 20mg weekly + hydroxychloro-quine 200mg daily + IVIG 2g/kg ×5 infusions
Outcome	1) SCLE resolved with therapy above. 2) Rapid normalization of CK and improved ulcers and claudication. Ultimately progression of disease, patient deceased	Rash resolved in 1 month. Clear and in remission at 9-month follow-up	Swallowing and rash improved, but muscle weakness persisted	Not reported	Some improvement of rash, muscle weakness persisted. Patient died from lung cancer progression five months after the start of nivolumab therapy	Some improvement of rash. Minimal improvement of muscle and joint pains, weakness. Patient ultimately expired 2 years after his initial melanoma diagnosis

Abbreviations: PD1: programmed death-1, PD-L1: programmed death-ligand 1, PD-L2: programmed death-ligand 2, CTLA-4: cytotoxic T lymphocyte antigen four, irAEs: immunotherapy-related adverse events, CCP: cyclic citrulline peptide, ANA: anti-nuclear antibodies, CRP: C-reactive protein, CK: creatinine kinase, intravenous immunoglobulin (IVIG), UV: ultraviolet, NSAIDs: nonsteroidal anti-inflammatory drugs, CTCAE: common terminology criteria for adverse events.