Drug-Associated Dermatomyositis Following Ipilimumab Therapy
A Novel Immune-Mediated Adverse Event Associated With Cytotoxic T-Lymphocyte Antigen 4 Blockade

Shirwa Sheik Ali, BSc; Allison L. Goddard, MD; Jason J. Luke, MD; Hilary Donahue, PA; Derrick J. Todd, MD, PhD; Andrew Werchniak, MD; Ruth Ann Vleugels, MD, MPH

Despite recent therapeutic advances, metastatic melanoma has a poor median patient survival and limited treatment options. In 2011, ipilimumab, a human monoclonal antibody targeted against cytotoxic T-lymphocyte antigen 4 (CTLA-4), was approved for use in patients with unresectable or metastatic melanoma. Cytotoxic T-lymphocyte antigen 4 normally serves to transduce a negative costimulation signal when bound to ligand B7 on antigen-presenting cells. When expressed on activated T cells, CTLA-4 counteracts costimulatory signaling through CD28, thus limiting anticancer immunity. Blockade of CTLA-4 releases this negative regulatory checkpoint and can facilitate an effective immune-mediated antitumor response. Phase 3 clinical trials of ipilimumab have demonstrated an improvement in overall survival in patients with unresectable stage III or IV melanoma.

Ipilimumab has been associated with multiple immune-related adverse events (irAEs), reflecting its immunomodulatory mechanism of action. A retrospective review of safety data from 14 phase 1 to 3 trials of ipilimumab administered at various doses demonstrated that irAEs of any grade occurred in 64.2% of patients. A substantial majority of irAEs were graded as mild to moderate, with death due to irAEs occurring in less than 1% of patients. Immune-related adverse events were thought to be dose related and most frequently affected the skin and gastrointestinal tract. The liver and endocrine glands were less often involved, and neurologic manifestations were rare. Less than 1% of patients experienced pancreatitis, uveitis, autoimmune nephritis, pneumonitis, myasthenia gravis, and other irAEs. Furthermore, in a pooled analysis of 325 patients with advanced melanoma treated with CTLA-4 blockade, grade III and IV irAEs occurred in 25.2% of patients, typically affecting the gastrointestinal tract (12%), liver (7%), skin (3%), and endocrine system (3%).

Typically, irAEs present within the first 3 months of ipilimumab therapy. Dermatologic irAEs occurred in 65% of patients and were classically of mild to moderate severity, often presenting with a morbilliform cutaneous eruption with associated pruritus. Rarely, patients present with severe or fatal dermatologic irAEs, including Stevens-Johnson syndrome or toxic epidermal necrolysis. An expanding number of irAEs attributed to ipilimumab have been described in recent literature, with a growing body of reports associating CTLA-4 blockade with conditions including polymyalgia rheumatica and gi...
We report a case of dermatomyositis developing in a patient being treated with ipilimumab for metastatic melanoma. To our knowledge, dermatomyositis is a previously unreported irAE associated with this immunomodulatory therapy. Because this is a single case report, no institutional review board approval was required. The patient provided written consent to have her case reported.

Report of a Case

A woman in her 50s presented with stage IV B-RAF V600E mutant malignant melanoma with metastases of the liver, lungs, and peritoneum. Her primary site was unknown. She was started on a course of ipilimumab, 3 mg/kg, intravenously every 4 weeks. Within 2 weeks of the first dose, she developed an erythematous and pruritic eruption on the face, upper chest, posterior neck, upper back, lateral thighs, arms, dorsal hands, and nailfolds. Following the third dose of this course of ipilimumab, the patient also developed acute proximal muscle weakness involving the upper and lower extremities, along with worsening of her cutaneous eruption.

Evaluation by the dermatology department revealed a photodistributed erythematous to violaceous eruption. The patient had diffuse erythema of the forehead and midface, involving the nasolabial folds, as well as erythema and edema of the upper eyelids (Figure 1). She also had diffuse erythema of the upper chest (Figure 1) and upper back with flagellate erythema on the posterior neck. There were few flat-topped pink to erythematous papules over the knuckles on the dorsal hands (Figure 2) as well as prominent erythema at the nailfolds, which also revealed dilated capillary loops, capillary dropout, and ragged cuticles (Figure 3). Findings on clinical examination were consistent with a diagnosis of cutaneous dermatomyositis.

The patient’s musculoskeletal examination revealed grade 4/5 strength on resisted abduction of her shoulders bilaterally as well as limited flexion of both hips. Functionally, the patient had reduced her activity level due to weakness and early fatigue. She denied symptoms of Raynaud phenomenon, dysarthria, dysphagia, or dyspnea.

Laboratory test results revealed an elevated creatine kinase of 1088 U/L (normal, 30-135 U/L), which increased to 1854 U/L on the following day (to convert to microkatal per liter, multiply by 0.0167). The patient's aldolase activity was also elevated at 28.6 mg/L (normal, 0-3 mg/L) (to convert to microkatal per liter, multiply by 0.0167). C-reactive protein was elevated at 23.0 U/L (normal, 0-7.7 U/L) (to convert to nanomoles per liter, multiply by 9.524). Antinuclear antibody titer was 1:640 with a speckled pattern. Jo-1 antibody was negative. The patient declined a skin biopsy. Findings on magnetic resonance imaging demonstrated mild short TI inversion recovery hyperintensity of the bilateral vastus lateralis and rectus femoris muscles. These imaging findings, along with the patient's classic cutaneous examination, proximal muscle weakness, and elevated serum muscle...
enzymes, were consistent with a diagnosis of dermatomyositis. A scheduled fourth dose of ipilimumab was withheld. The patient's muscle weakness progressed rapidly over 3 days. Oral prednisone, 80 mg/d, was initiated but the patient's condition continued to worsen, requiring the use of a wheelchair and hospitalization for intravenous methylprednisolone, 80 mg twice daily. A biopsy of the vastus lateralis muscle was performed, which demonstrated atrophy of type II muscle fibers but no evidence of inflammatory myositis. However, this biopsy was performed 6 days after the patient was initiated on systemic corticosteroids. Given improvement with intravenous methylprednisolone, the patient was discharged on oral prednisone, 1 mg/kg/d. Within 14 days of starting corticosteroid therapy, the patient's serum creatine kinase and aldolase activity normalized, and her strength improved dramatically. Prednisone was tapered slowly over the following 8 weeks. Despite marked improvement in her muscle enzyme levels and strength, the patient's cutaneous eruption improved only minimally during this same period.

Given the prominent toxicity to ipilimumab, this therapy was discontinued. Notably, there are no data supporting the continued administration of ipilimumab in the setting of high-dose systemic corticosteroid use. The clinical trials leading to approval of ipilimumab excluded patients who required systemic corticosteroids, and existing ongoing clinical trials require that patients taper to no more than 10 mg of prednisone daily before restarting ipilimumab to avoid suppressing the immunomodulatory effects of ipilimumab. Although the patient's metastatic disease stabilized for 4 months following reinduction with ipilimumab, she soon developed progressive disease. Subsequently, she was treated with a combination of B-RAF and mitogen-activated protein/extracellular signal-regulated kinase inhibitors (dabrafenib and trametinib) and experienced rapid and significant tumor shrinkage, but she continues to have only a partial response to this regimen.

Discussion
To our knowledge, this is the first report of dermatomyositis developing as an irAE to ipilimumab in a patient with metastatic melanoma. Considering the role CTLA-4 plays in regulating tolerance to self-antigens, ipilimumab has been associated with various irAEs, reflecting its immunopotentiating mechanism of action.²

In our patient, a diagnosis of dermatomyositis was supported by classic cutaneous findings, proximal muscle weakness, and elevated muscle enzymes. There was a lack of classic inflammatory myositis noted on muscle biopsy, but this was...
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Conclusions

The co-occurrence of drug administration and clinical findings of dermatomyositis on administration and rechallenge with ipilimumab suggest that this patient’s presentation with dermatomyositis is an irAE caused by this agent. In the context of the expanding reports of irAEs associated with CTLA-4 blockade, this report adds another entity to the growing list of potential ipilimumab-related immune phenomena. Physicians should be aware of these potential irAEs related to ipilimumab and consider drug-associated dermatomyositis when evaluating patients receiving CTLA-4 blockade therapy.


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REFERENCES


NOTABLE NOTES

Changing Skin Colors

Walter H. C. Burgdorf, MD; Leonard J. Hoenig, MD

The term chameleon frequently creeps into the dermatologic literature. Diseases with a pleomorphic presentation, such as syphilis, borreliosis, or leprosy, are often described as “chameleons.” But the usage is not very precise, because no skin disease can truly alter its colors almost instantly, whereas several groups of reptiles show physiological color change or metachrosis.

Chameleons are ancient, highly specialized lizards found in Africa, southern Asia, and even southern Europe. They are most common in Madagascar. Some can change their colors dramatically. They have other unusual features—a prehensile tail, opposing clasping toes, eyes capable of focusing independently and providing 360° surveillance, and a ballistic tongue that shoots out to capture prey.1

Chameleons have a very complex skin with a transparent outer layer covering multiple layers of pigment cells or chromatophores. The outer layer consists of xanthophores and erythrophores that contain yellow and red pigment. The next layer contains iridophores, which have reflective plates of guanine that produce blue-green color. The bottom layer contains melanophores. While mammalian melanocytes produce and then transfer melanin, melanophores can quickly disperse or condense the melanin that they do not transfer. They have a complex network of microtubules with the motor proteins kinesin and dynein carrying pigment particles peripherally and centrally, respectively.2 Cells with dispersed melanin are dark; those with condensed melanin are clear. Chameleons can create a dazzling display of iridescent colors by mixing together the colors from all their chromatophores (Figure, A).

The Carolina anole, erroneously called an American chameleon, is a widely distributed representative of the largest family of lizards. It has a simpler color range, switching between lime green and brown. A relaxed anole is green because the melanin is clumped in a perinuclear position, so that the xanthophores and reflected blue light from the iridophores can combine to produce a green hue (Figure, B). When the anole is stressed or otherwise stimulated, the melanin is dispersed, producing a brown color. It has erythrophores to create its strawberry-like red dewlap for mating displays.

Neither chameleons nor anoles change color for camouflage. Chameleons are extremely colorful and use their hues to scare predators or attract mates. In most studies, anoles have failed to match a dark or light background.3 Another factor is stress: a relaxed anole is green; an anxious one is brown. The change is mediated by neural and hormonal factors. The pituitary peptide melanophore-stimulating hormone causes dispersal of melanin; it is very similar to the mammalian melanocyte-stimulating hormone, discovered by a dermatologist—Aaron B. Lerner at Yale. Ambient temperature is another factor; a chameleon may be much darker on the side toward the sun. Perhaps we can learn from chameleons and anoles to better appreciate the wonderful diversity of human skin color.

Author Affiliations: Retired (Burgdorf); private practice (Hoenig).

Corresponding Author: Leonard J. Hoenig, MD, 601 N Flamingo Rd, Ste 201, Pembroke Pines, FL 33028 (gooddocljh@gmail.com).


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Figure. Chameleon and Anole

A, Veiled chameleon from Yemen (Chamaeleo calyptratus). B, Carolina anole (Anolis carolinensis) with brown tail tip and red dewlap. Photographs provided by Kevin M. Enge, Reptile and Amphibian Research Subsection, Fish and Wildlife Research Institute, Gainesville, Florida.