Novel cutaneous eruptions in the setting of programmed cell death protein 1 inhibitor therapy

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INTRODUCTION

Programmed cell death protein 1 (PD-1) inhibitors are checkpoint inhibitor anticancer drugs that block the regulatory activity of immune proteins present on the surface of cells.[1] Nivolumab and pembrolizumab are humanized IgG4 (Immunoglobulin G4) monoclonal antibodies against PD-1, and prevent programmed death-ligand 1 from binding to PD-1, decreasing the regulation of T-cell activation.[2] Indications for PD-1 inhibitor therapy include non-small-cell lung cancer, melanoma, renal cell carcinoma and other advanced solid tumors.[3,4]

While PD-1 inhibitors are generally well tolerated, previous work has found the incidence of cutaneous eruptions may be as high as 32.68% for nivolumab and 40.51% for pembrolizumab.[5] PD-1 inhibitor-associated cutaneous eruptions can occur anywhere from weeks to months after starting therapy, or days in the case of reexposure. The most frequently reported symptom is pruritus and patients most commonly present with morbilliform exanthems, psoriasis/psoriasiform eruptions, vitiligo-like depigmentation, and lichenoid dermatitis.[6] Less common manifestations include acantholytic dermatitis, bullous pemphigoid, acute generalized exanthematous pustulosis, and Stevens-Johnson syndrome/toxic epidermal necrolysis-like reactions.[6,7] Rarely, erythema nodosum-like panniculitis, morphea, erythema multiforme, and granulomatous dermatitis including interstitial granulomatous dermatitis, sarcoid-like reactions, and granulomatous tattoo reactions have been reported.[8]

Abbreviations used:

NSCLC: non-small-cell lung cancer
PD1: programmed cell death protein 1

We report several novel clinical and pathologic features in this setting including scleredema and pseudolymphomatous tattoo reaction. We also report cases of fixed drug eruption, extragenital lichen sclerosus, and post-herpetic isotopic response for which there are exceedingly rare reports for the purposes of adding to the current literature.

METHODS

The pathologic archives at The Ohio State University Wexner Medical Center were searched for patients who were treated with immune checkpoint inhibitors. We identified 5 patients with novel clinical and pathologic features from this group of patients.

Case 1: Scleredema

A 49-year-old man with metastatic non-small-cell lung cancer on pemetrexed/pembrolizumab for

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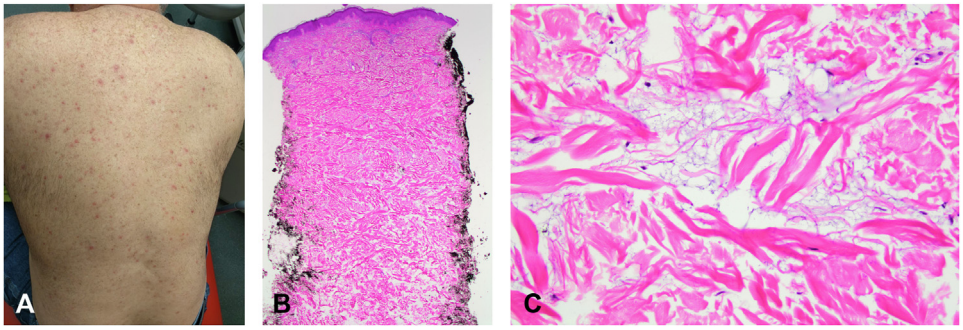

Fig 1. Pembrolizumab associated scleredema. **A,** Diffuse, poorly marginated woody induration of upper back with background folliculitis. **B,** There is splaying of collagen bundles in the deep dermis (H&E, 20×). **C,** High magnification demonstrates abundant mucin between collagen (inset, H&E, 200×).

9 months without a history of diabetes mellitus, infection, or monoclonal gammopathy presented for evaluation of pruritus of the upper back which started after initiating pembrolizumab. On physical examination there was woody, thick induration diffusely across the back (Fig 1, *A*). A 4 mm punch biopsy was performed and demonstrated prominent mucin deposition with splaying of collagen bundles in the lower dermis (Fig 1, *B* and *C*) and was consistent with scleredema.

Case 2: Fixed drug eruption

A 70-year-old man with a history of metastatic malignant melanoma on nivolumab presented for evaluation of a vesicular eruption of 2 months duration (Fig 2, *A*). He was treated previously with ipilimumab/nivolumab and had been on nivolumab as single-agent therapy for the past year. Two months prior to presentation, he developed tender, red plaques on his back shortly after receiving nivolumab. While these plaques eventually self-resolved. He then developed a recurrence of the eruption with additional similar lesions on the shoulder and chest after receiving his most recent dose of nivolumab. Importantly, this patient was not treated with agents typically indicated in fixed drug eruptions, including acetaminophen premedication for nivolumab infusion. On physical examination, he had bright red edematous plaques with central duskiness and vesiculation (Fig 2, *B*). A punch biopsy demonstrated vacuolization of the dermal-epidermal junction with aggregates of necrotic keratinocytes and a superficial perivascular lymphocytic infiltrate with eosinophils. Given the clinical history and these findings, a diagnosis of multifocal fixed drug eruption was rendered.

Case 3: Pseudolymphomatous tattoo reaction

A 24-year-old woman with a history of Hodgkin's lymphoma presented for evaluation of a lichenoid

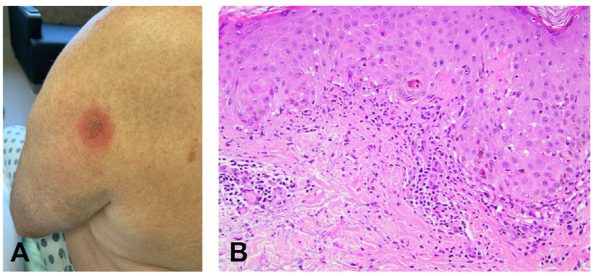

Fig 2. Nivolumab associated fixed drug eruption. **A,** Left shoulder with bright red edematous plaque with central duskiness and vesiculation/flaccid bullae noted. **B,** Histopathology demonstrates an interface reaction with numerous necrotic keratinocytes and associated inflammatory infiltrate with eosinophils, characteristic of a drug eruption (H&E, 200×).

eruption of 2 months duration, which occurred after the initiation of nivolumab. She also reported tenderness and ulceration within a tattoo (Fig 3, *A*). On physical examination she was noted to have an ulcerated scaly, edematous plaque within the red ink of the tattoo (Fig 3, *A*). A punch biopsy of the affected area revealed a diffuse dermal lymphohistiocytic infiltrate with predominantly CD4-positive T-cells (Fig 3, *B* and *C*). CD15 was positive in rare cells. Evidence supported a diagnosis of pseudolymphomatous tattoo reaction, and she had resolution of the generalized lichenoid eruption and improvement of the findings within her tattoo upon discontinuation of nivolumab.

Case 4: Post-herpetic isotopic granulomatous eruption

A 53 year-old-man with a high-grade neuroendocrine tumor of the lungs with metastases on ipilimumab and nivolumab presented for evaluation of a persistent cutaneous eruption on his right lower back. He reported having shingles at the site of the

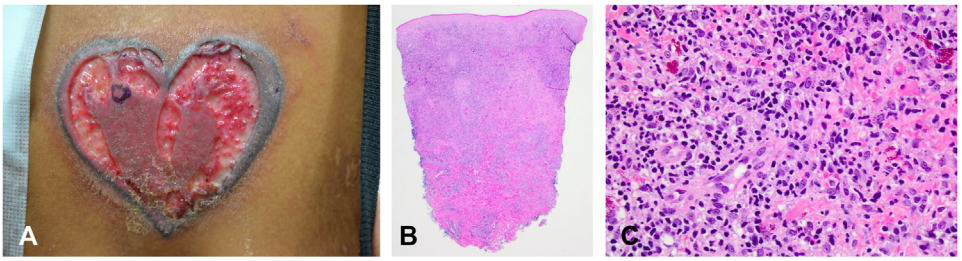

Fig 3. Nivolumab associated pseudolymphomatous tattoo reaction, **A,** Central chest tattoo with erythematous, indurated, and ulcerated plaque in areas of *red* ink. **B,** There is a diffuse hematolymphoid infiltrate in the dermis (H&E, 20×). **C,** High magnification demonstrates a mixed lymphohistiocytic infiltrate associated with *red* tattoo ink (inset, H&E 200×).

eruption 6 months prior. He noted that the eruption started shortly after the initiation of ipilimumab and nivolumab, and that it remained unchanged in appearance for 6 weeks. On physical examination he had smooth pink semi-coalescing papules in a dermatomal distribution (Supplementary Fig 1A, available via Mendeley at https://data.mendeley.com/datasets/5y8ktcft6z/1). Skin punch biopsy revealed aggregates of epithelioid histiocytes with multinucleate giant cells in the papillary dermis associated with lymphocytes. Grocott methamine silver, periodic acid Schiff, and acid-fast bacteria stains were negative for unequivocal fungus or acid-fast organisms (Supplementary Fig 1B, available via Mendeley at https://data.mendeley.com/datasets/5y8ktcft6z/1). In conjunction with the clinical presentation, these findings were felt to be consistent with a granulomatous post-herpetic isotopic response.

Case 5: Extragenital lichen sclerosus

A 46-year-old female with a history of metastatic melanoma on nivolumab presented for surveillance skin exam and was found to have several white, thin scaly plaques on her upper back (Supplementary Fig 2A, available via Mendeley at https://data.mendeley.com/datasets/5y8ktcft6z/1). She recalled these lesions appearing shortly after starting nivolumab. Shave biopsy of a representative lesion demonstrated epidermal atrophy with effacement of the rete pegs with prominent papillary dermal edema and hyalinization of the collagen (Supplementary Fig 2B, available via Mendeley at https://data.mendeley.com/datasets/5y8ktcft6z/1). These findings were consistent with extragenital lichen sclerosus.

DISCUSSION

Immune checkpoint inhibitors have proven instrumental as adjunctive therapies in the treatment of locally advanced and metastatic malignancies. While these drugs are generally well tolerated, a wide range of cutaneous eruptions have been reported.[2,6,8] A retrospective analysis of drug eruptions secondary to immune checkpoint inhibitors found that 33 of 103 (32%) were specifically due to nivolumab and 35 of 103 (34%) were due to pembrolizumab.[9]

Novel PD-1 inhibitor associated cutaneous eruptions from our investigation include scleredema and pseudolymphomatous tattoo reaction. Scleredema is a sclerotic, cutaneous mucinosis that most often occurs in the setting of diabetes mellitus, infection, or monoclonal gammopathy.[10] The patient in case 1 lacked these risk factors, supporting the notion that pembrolizumab was the culprit medication. Fixed drug eruption is a cutaneous eruption that characteristically recurs in the same location with reexposure to the culprit drug. The patient in case 2 lacked exposure to other common culprit drugs including nonsteroidal anti-inflammatory drugs, acetaminophen, antimalarial, anticonvulsants, antibiotics, and barbiturates.[11] Cutaneous pseudolymphoma refers to lymphocyte-rich infiltrates which simulate cutaneous lymphomas. Causes can include infections and foreign agents such as tattoo dye.[12] While the patient in case 3 had this tattoo for many years, her eruption appeared 2 months after nivolumab initiation and resolved upon drug discontinuation, supporting that this was likely a pseudolymphomatous tattoo reaction to nivolumab. Post-herpetic granulomatous dermatitis has been reported both weeks and months after initiation of nivolumab which is in accordance with the time course noted in case 4.[13,14] The extragenital lichen sclerosus in case 5 has also been reported in a patient with uveal melanoma on nivolumab who was also noted to have previously experienced melanoma-associated leukoderma related to nivolumab.[15]

CONCLUSION

Immune checkpoint inhibitors are associated with a wide variety of cutaneous reactions and novel

eruptions in this setting continue to be identified. Dermatologic evaluation of new cutaneous findings in patients on checkpoint inhibitors is helpful in recognizing and treating these reactions. However, further research is needed to elucidate their underlying mechanisms and to discern whether their occurrence provides prognostic information.

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Conflicts of interest

None disclosed.

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