Nivolumab in non–small cell lung cancer: A novel case of an erythema annulare centrifugum–like eruption

Polytimi Sidiropoulou, MD,[a] Themis Sgontzou, MD,[a] Ioanna Kostara, MD,[b] Dimitrios Sgouros, MD,[a] Barbara Theologi, MD,[c] Eftychia Zouridaki, MD, PhD,[d] Georgios Kontochristopoulos, MD, PhD,[d] Dimitris Rigopoulos, MD, PhD,[a] and Alexander J Stratigos, MD, PhD[a]
Athens, Greece

Key words: drug reaction; erythema annulare centrifugum; immune checkpoint inhibitors; immunotherapy; lung adenocarcinoma; programmed cell death-1 inhibitors; nivolumab; skin reaction.

INTRODUCTION

The advent of immune checkpoint blocking therapies has profoundly enriched the anticancer armamentarium. In this evolving field, nivolumab, an anti–programmed cell death–1 (PD-1) inhibitor, is widely used in the management of late-stage malignancies, including advanced melanoma, renal cell carcinoma, and non–small cell lung cancer (NSCLC). Despite its remarkable superiority and favorable benefit-to-risk profile over conventional chemotherapy, this agent has induced unique toxicities, termed *immune-related adverse events* (irAEs). Cutaneous involvement represents a commonly encountered manifestation.[1-3] Since nivolumab has recently been licensed as a subsequent agent for advanced/metastatic NSCLC,[1,2] little is known about skin reaction patterns in lung cancer individuals. We report an uncommon case of an erythema annulare centrifugum (EAC)-like eruption in a nivolumab-treated patient with lung adenocarcinoma (AC).

Abbreviations used:

AC:	adenocarcinoma
EAC:	erythema annulare centrifugum
irAEs:	immune-related adverse events
NSCLC:	non–small cell lung cancer
PD-1:	programmed cell death–1

CASE REPORT

An 82-year-old male former smoker with a 5-year history of advanced lung AC was referred for evaluation of a pruritic exanthem existing for 4 months. He had previously undergone 6 induction cycles of combined chemotherapy with carboplatin, pemetrexed, and bevacizumab, followed by maintenance therapy with bevacizumab. Because of renal toxicity, bevacizumab was withdrawn. After 7 months without treatment, restaging images showed disease progression, and nivolumab was introduced at a dose of 3 mg/kg every 2 weeks. His medical status was otherwise notable for type II diabetes mellitus, hypertension, and cardiovascular disease managed for several years with insulin lispro, amlodipine, furosemide, and clopidogrel without skin-related reactions. No history of autoimmune disease was reported.

Ten days after commencing nivolumab, a pruritic eruption consisted of annular erythematous plaques appeared on his back. At that time, no other new medications were administered. The condition was

From the 1st Department of Dermatology-Venereology, National and Kapodistrian University of Athens, Faculty of Medicine, "A. Sygros" Hospital for Cutaneous & Venereal Diseases[a]; 1st Department of Respiratory Medicine, National and Kapodistrian University of Athens, Faculty of Medicine, "Sotiria" General Hospital[b]; Pathology Department, "A. Sygros" Hospital for Cutaneous & Venereal Diseases[c]; and State Department of Dermatology-Venereology, "A. Sygros" Hospital for Cutaneous & Venereal Diseases.[d]

Supported by the Institute of Dermatology Research and Education (IDEE).

Conflicts of interest: Prof Dr Alexander J Stratigos and Dr Ioanna Kostara have served as speakers for the Bristol-Myers Squibb. The rest of the authors have no conflicts of interest to disclose.

Correspondence to: Alexander J Stratigos, MD, Professor of Dermatology-Venereology, 1st Department of Dermatology-Venereology, University of Athens Medical School, "A. Sygros" Hospital for Cutaneous & Venereal Diseases, 5 I. Dragoumi str., GR-16121, Athens, Greece. E-mail: alstrat2@gmail.com.

JAAD Case Reports 2019;5:572-5.
2352-5126

© 2019 by the American Academy of Dermatology, Inc. Published by Elsevier, Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

https://doi.org/10.1016/j.jdcr.2019.04.007

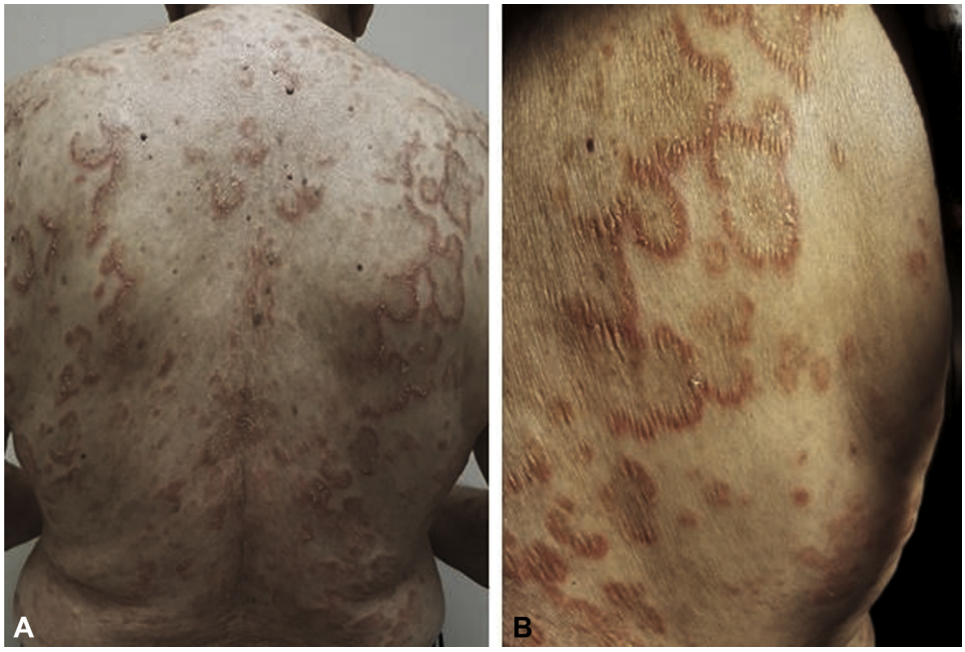

Fig 1. EAC clinical features at 4 months after nivolumab discontinuation. **A**, Pruritic arcuate, figurate and polycyclic erythematous plaques involving the back. **B**, The lesions display slightly raised borders with an inner rim of fine scale behind the advancing edges.

tolerable, yet refractory to topical steroids. Immediately after the second session of nivolumab, his course deteriorated with skin lesions involving the entire trunk, necessitating intramuscular corticosteroids (2 injections of betamethasone sodium phosphate plus betamethasone acetate [3 + 3] mg/1 mL, once weekly). Despite initial improvement, the eruption recurred upon steroid tapering. Not only was nivolumab suspended but also a dermatologic consultation was sought.

Skin examination found several annular, arcuate, figurate and polycyclic erythematous plaques on the back and upper extremities (Fig 1, *A*). The lesions displayed slightly raised borders with rims of trailing scales on the inner aspect of the advancing edges (Fig 1, *B*). The face and mucosa were intact. Intense pruritus was the only reported symptom. The general examination was found to be uneventful. A potassium hydroxide preparation yielded a negative result for a fungal infection. Routine blood tests were within normal limits besides an elevated serum creatinine level (1.92 mg/dL). Histopathologic features were supportive of nivolumab-induced hypersensitivity, including focal basal vacuolar degeneration into the epidermis and perivascular inflammatory infiltrate mainly consisting of lymphocytes along with civatte bodies, erythrocyte extravasation, and mild edema in the papillary and mid dermis (Fig 2, *A* and *B*).

The patient was initiated on topical high-potency steroids (clobetasol propionate 0.05% cream) and oral antihistamines twice daily, attaining remarkable improvement over the following month. Complete resolution of skin lesions was achieved 2 months later. At that stage, a chest computed tomography scan showed a decline in the size of the lung nodule. To date, he remains on clinical and radiologic follow-up with stable disease 1 year after nivolumab discontinuation.

DISCUSSION

EAC is a rare dermatosis characterized by asymptomatic erythematous lesions that spread peripherally while clearing centrally, resulting in an annular, arcuate, or polycyclic appearance. A rim of scale is sometimes noted behind the advancing border. Despite EAC being mainly idiopathic, it can also represent a cutaneous hypersensitivity reaction against infectious and autoimmune diseases, medications and, rarely, malignancies.[4] Although drug-induced EAC is well described, including few cases associated with targeted agents,[4,5] no known cases have, to our knowledge, been described with immune checkpoint inhibitors.

Immunotherapy differs significantly from chemotherapy in response patterns and toxicity profiles. Contrary to traditional chemotherapeutics, PD-1 axis inhibitors, including nivolumab, exert a distinct effect by restoring a suppressed immunosurveillance, thus revitalizing the body's own antitumor immunoactivity. However, this nonselective

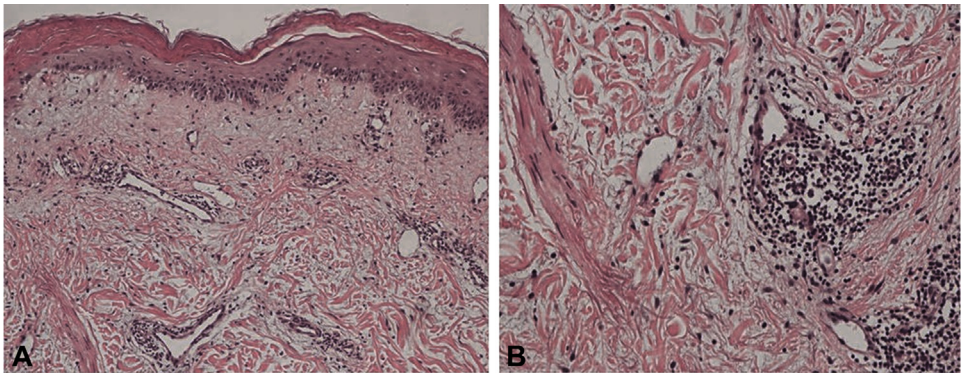

Fig 2. **A** and **B**, Skin biopsy shows focal basal vacuolar degeneration into the epidermis and subepidermal perivascular lymphocytic infiltrate in the upper and mid dermis. (Hematoxylin-eosin stain.) A high-resolution version of this image for use with the Virtual Microscope is available as eSlide: VM05504.

hyperactive immunity gave rise to novel toxicities, with several being cutaneous in nature.[1-3]

In individuals with NSCLC, these events mainly manifest as common nonspecific entities, namely morbilliform rash and pruritus.[1-3] Unusual toxicities like vitiligo,[6] psoriasis,[7] and lichenoid and bullous dermatitis[4] have also been reported. Additionally, new cutaneous effects are being documented, including the curly hair phenotype[8] and the currently described EAC. Patterns of lymphocytic tropism in skin irAEs tend to differ depending on the histologic NSCLC subtype. In squamous cell carcinoma, the lymphocyte skin infiltrates display epidermotropic distribution, whereas in AC patients such infiltrates are accentuated toward the dermis[1]; the latter was reflected by our case.

Cutaneous irAEs during PD-1 blockade are usually mild, reversible, and conservatively manageable. On occasion, however, they can be intolerable, necessitating dose modification, suspension, or discontinuation of treatment, as in the reported case. Moreover, dermatologic irAEs can persist for several months because of the prolonged in vivo drug-stimulated immunity.[1-3] Likewise, our patient exhibited ongoing skin eruptions beyond nivolumab interruption.

Although the prognostic impact of immune-mediated toxicity remains elusive, a positive correlation between skin irAEs and clinical efficacy in nivolumab-exposed NSCLC patients has already been supported.[1,9,10] Similarly, the onset of EAC coincided with tumor remission in this case. Although time to onset of irAEs has not been clearly implicated in survival benefits, it has been reported that early onset of irAEs (<6 weeks) portends a better prognosis.[10] A similar trend was observed in our case with a durable tumor response of 12 months. This finding remains to be validated.

Given that immunohistochemical studies were not performed, it would be possible to speculate that the underlying lung AC could be the initiating event. However, it should be considered that EAC occurred shortly after nivolumab initiation and peaked after the second session of immunotherapy, implicating cutaneous flare caused by repeated dosing. In parallel, the computed tomography images revealed tumor regression. Although drug-induced EAC resolves abruptly upon medication withdrawal, our patient's prolonged course may indicate both the long half-life (12-25 days) and the abiding immunologic effect of nivolumab. After all, causality assessment via the Naranjo algorithm yielded a score of 6,[8] making the possibility of drug-stimulated reaction at least probable.

REFERENCES

1. Hasan Ali O, Diem S, Markert E, et al. Characterization of nivolumab-associated skin reactions in patients with metastatic non-small cell lung cancer. *Oncoimmunology*. 2016;5:e1231292.
2. Keating GM. Nivolumab: A review in advanced nonsquamous non-small cell lung cancer. *Drugs*. 2016;76:969-978.
3. O'Kane GM, Labbé C, Doherty MK, et al. Monitoring and management of immune-related adverse events associated with programmed cell death protein-1 axis inhibitors in lung cancer. *Oncologist*. 2017;22:70-80.
4. McDaniel B, Cook C. *Erythema Annulare Centrifigum. StatPearls [Internet]*. Treasure Island (FL): StatPearls Publishing; 2018.
5. Yao CA. Sorafenib-induced erythema annulare centrifugum with spontaneous resolution after skin biopsy. *Australas J Dermatol*. 2018;59(2):e150-e151.
6. Uenami T, Hosono Y, Ishijima M, et al. Vitiligo in a patient with lung adenocarcinoma treated with nivolumab: a case report. *Lung Cancer*. 2017;109:42-44.

7. Voudouri D, Nikolaou V, Laschos K, et al. Anti-PD1/PDL1 induced psoriasis. *Curr Probl Cancer*. 2017;41:407-412.
8. Dasanu CA, Lippman SM, Plaxe SC. Persistently curly hair phenotype with the use of nivolumab for squamous cell lung cancer. *J Oncol Pharm Pract*. 2017;23:638-640.
9. Toi Y, Sugawara S, Kawashima Y, et al. Association of immune-related adverse events with clinical benefit in patients with advanced non-small-cell lung cancer treated with nivolumab. *Oncologist*. 2018;23(11):1358-1365.
10. Teraoka S, Fujimoto D, Morimoto T, et al. Early immune-related adverse events and association with outcome in advanced non-small cell lung cancer patients treated with nivolumab: a prospective cohort study. *J Thorac Oncol*. 2017;12:1798-1805.