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Granuloma annulare associated with immune checkpoint inhibitors

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Dear Editor

Recent developments in cancer immunology have ushered in immunotherapy as a new era in anti-cancer therapy. The cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed cell death receptor-1(PD-1)/PD ligand-1 (PD-L1) signaling pathway are immune checkpoints of tumour-induced immunosuppression.¹ Immune checkpoint inhibitors (ICIs) activate cytotoxic T cells to attack tumour cells, leading to durable antitumour responses.² By unbalancing the immune system, ICIs may induce autoimmunity that results in organ dysfunction, referred to as immune-related adverse events (irAEs).² Dermatologic adverse events (dAEs) such as vitiligo, rash, and pruritus are the most common irAEs.^{1–4} Herein we report 3 cases presenting granuloma annulare (GA) during ICI treatment, a hitherto unreported dAE.⁵

A 74-year-old woman with urothelial carcinoma received 16 cycles of nivolumab, an anti-PD-1 monoclonal antibody (mAb), with a complete response. After 4 cycles, she developed erythematous plaques on the dorsal hands (Figure 1a). Next case involves a 65-year-old man with tonsillar squamous cell carcinoma, treated with durvalumab, an anti-PD-L1 mAb, with

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Conflicts of interest:

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a partial response. Eight months after the initiation of treatment, he developed pink papules on the dorsal hands and palms (Figure 1b). The third case is of a 76-year-old man with metastatic anorectal mucosal melanoma, treated with pembrolizumab, an anti-PD-1 mAb, with a complete response. After 6 months, he developed pink papules on the thighs (Figure 1c) along with vitiligo-like depigmented patches on the face.

Histopathology revealed a necrobiotic and palisading histiocytic granuloma with a lymphocytic infiltrate (Figure 1d, 1e), consistent with GA. Microbiologic stains were negative for bacterial, fungal or atypical mycobacterial organisms. Immunohistochemical studies demonstrated CD3-positive T-cells with a normal CD4:CD8 ratio. A mixed perivascular infiltrate with lymphocytes and eosinophils were found. PD1 highlighted approximately 10% of the lymphocytic infiltrate (Figure 1f).

The onset of GA ranged from 2–8 months after the initiation of ICIs. All patients showed partial to complete tumour response to ICIs. Imaging and laboratory studies showed no evidence of diabetes, hyperlipidaemia, systemic sarcoidosis or other autoimmune diseases. The skin lesions responded to topical or oral steroids but recurred after restarting ICIs. The first case was off ICI treatment after achieving a complete tumour response, and her skin lesions were resolved.

GA is a cutaneous granulomatous dermatosis, characterized by collagen degradation, mucin deposition, and a palisaded histiocytic infiltration.⁶ Recent observations indicate a role of cell-mediated hypersensitivity in the development of GA.⁶ Studies suggest that interferon-gamma (IFN γ)-producing T helper 1 (Th1) lymphocytes contribute to the activation of macrophages and subsequent inflammation and tissue destruction.⁷ Diabetes and hyperlipidemia are among the most widely reported diseases associated with GA.⁷ Several medications have been reported to induce GA.⁷

We hypothesize that ICIs block the inhibitory signal of CD4⁺ Th1 cells and subsequently lead to T cell activation and proliferation, resulting in aggregation and activation of macrophages, i.e. granuloma formation. The choronal relationship of the development of GA after the initiation of ICIs and the resolution of skin lesions after the cessation of ICIs indicate the association of GA with ICIs. The presence of a lymphocytic infiltrate with PD1 expression and coexisting eosinophils on the histopathology imply that GA may be a T cell-mediated hypersensitivity triggered by ICIs. Increasing evidence supports that vitiligo and/or cutaneous reactions emerging during ICI treatments are associated with favorable overall survival.⁸ All 3 patients showed partial to complete tumour response to ICIs. The association of GA with cancer prognosis needs to be elucidated.

Physicians should be aware of these potential irAEs in order to diagnose and properly manage them in patients receiving immunotherapies. ICI-related delayed type hypersensitivity may play an important role in the granuloma formation, and further research is needed to elucidate the pathogenesis.

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Figure 1. Granuloma annulare associated with immune checkpoint inhibitors

Photograph of case 1(a), case 2(b), and case 3(c) showed erythematous papules and plaques on the dorsal hands, palms, and thighs, respectively. Histopathology of the skin biopsy from the right dorsal hand of case 2 demonstrated a palisaded granulomatous dermatitis characterized by foci of necrobiosis with increased mucin deposition highlighted by colloidal iron stain (IHC not shown) surrounding by abundant palisading histiocytes and lymphocytes, consistent with granuloma annulare (d, e). PD1 expression was detected in approximately 10% of the lymphoid infiltrate in case 3(f).