

A case of hair dye-induced allergic contact dermatitis in the context of nivolumab

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KEYWORDS: 4-phenylenediamine, dermatitis, allergic contact, drug-related side effects and adverse reactions, immunotherapy, patch tests

Allergic contact dermatitis (ACD) arising during immune check point inhibitor (ICPI) therapy has rarely been reported and is likely an under-recognized cause of a number of cutaneous immune-related adverse events (IRAE), especially treatment refractory dermatitic eruptions.

rash remained quiescent. Patch testing was not performed and the patient was instructed to avoid both PPD and MI-containing products.

CASE REPORT

An 81-year-old man with Stage IV non-small cell lung cancer developed intensely pruritic eczematous fissured plaques on the scalp following the distribution pattern of hair dye, 1 year after commencing nivolumab (Figure 1). He had been self-applying the same black para-phenylenediamine (PPD)-containing hair dye every 2 to 4 weeks for 40 years, without issue. The dye was applied with polyethylene gloves for 2 min, then showered out using a methylisothiazolinone (MI)-containing shampoo. Despite the scalp eruption, he continued to use the hair dye for 8 months and in the 3 months leading up to dermatology review, the eruption was so severe he had required nivolumab dose interruptions. His lung cancer had a good partial response to nivolumab with no other IRAE. Past medical history included hypothyroidism (treated with long term thyroxine) but no atopy.

Hair dye was ceased, a non-MI-containing shampoo was substituted and 25-mg oral prednisolone and mometasone 0.1% lotion commenced. A biopsy of the anterior hairline (while on prednisolone) showed non-specific inflammation (Figure 2). The eruption resolved leaving depigmented skin in the same distribution, which fluoresced blue-white on woods lamp. A biopsy from this area showed absent melanocytes on melan A and Sox10 staining, possibly representing chemical leukoderma secondary to PPD. The eruption recurred significantly upon ceasing prednisolone requiring a further 2-month break from nivolumab. When nivolumab was restarted, his



FIGURE 1 Clinical presentation: erythematous eczematous plaques on scalp forehead and entire anterior and posterior surface of both ears, with spread to dorsal hands, back and thighs. He had androgenetic scalp hair thinning. No eyelid involvement

Abbreviations: ACD, allergic contact dermatitis; CTLA-1, cytotoxic T-lymphocyte associated protein 4; ICP, immune check points; ICPI, immune check point inhibitor; IRAE, immune-related adverse events; MI, methylisothiazolinone; PD-1, programmed cell death protein 1; PDL1, programmed death ligand 1; PPD, para-phenylenediamine; Treg, T regulatory cells.

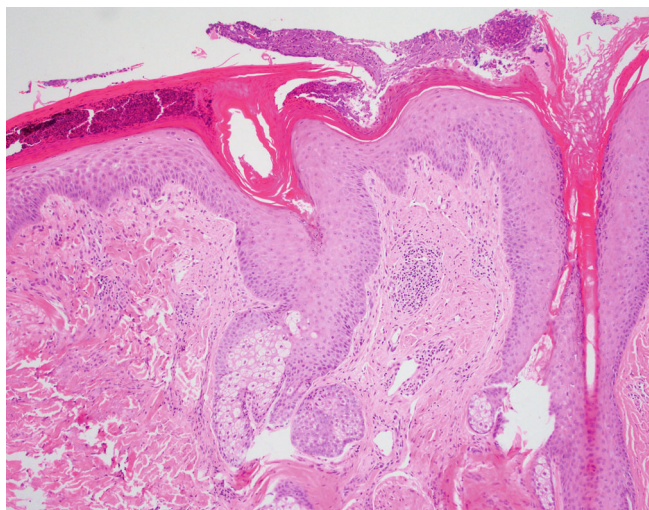


FIGURE 2 Histopathology: vertex scalp: excoriation with crust and impetiginization, adjacent epidermis slightly hyperplastic (H&E, $\times 10$)

DISCUSSION

Cytotoxic T-lymphocyte associated protein 4 and programmed cell death protein 1 (PD-1) are costimulatory molecules expressed by activated T cells, termed “immune check points” (ICPs). They act as negative regulators of immune responses, maintaining tolerance of self.¹ These ICPs are exploited by tumour cells to evade the immune system and promote tumour tolerance. ICPI, such as nivolumab, exert their anticancer effect by binding to the PD-1 receptor on T cells and preventing it binding to its ligand, PDL1 on tumour cells, allowing T cells to remain activated, recognize and destroy tumour cells.¹ ICPIs are active across an increasing spectrum of solid organ malignancies including metastatic melanoma, head and neck squamous cell carcinoma, renal cell carcinoma, among many others.^{1,2}

While enhancing the anti-tumour function of T cells, ICPIs also disrupt T Regulatory (Treg) cell homeostasis, tipping the balance from tolerance to inflammatory and autoimmune responses at different sites.¹ Eczematous dermatitis in the setting of nivolumab is common (11.7%–17%) with mean onset 6 months (range: 1–25 months).^{2,3} Patients usually respond well to topical corticosteroids and rarely require ICPI interruptions.² There are only two cases of ACD reported in the context of ICPI, both to clothing allergens, treated with short courses of topical and oral corticosteroids.^{4,5} Both patients, like ours, required periods of nivolumab withdrawal.

Interestingly, our patient developed suspected ACD a year after exposure to nivolumab and PPD/MI. Gradual depletion of Tregs in ICPI therapy is implicated in many IRAE and may explain the gradual loss of tolerance to a previously tolerated antigen over an extended period.⁶ Despite eventual allergen withdrawal and cessation of nivolumab, ACD continued for months, potentially caused by persistent T cell activation, as seen in other ICPI cutaneous reactions.² This emphasizes the importance of early

recognition of ACD and allergen withdrawal in treatment-resistant dermatitis.

Neither the previously reported cases nor our patient had patch testing, thus uncertainty remains. There are no data about the efficacy or safety of patch testing under ICPI conditions. Just as immunosuppression risks false-negative results,⁷ an immune-enhanced anti-PD-1 state could theoretically cause allergy induction, severe patch test reactions and false positives. We considered titrated PPD patch testing at 0.01%.⁸ A lymphocyte activation assay (in vitro blood test) to PPD could be an alternative but is not widely available or well established.⁸

In conclusion, we propose that the threshold for sensitisation to topical allergens is lowered by ICPI and patients undergoing this treatment are at higher risk of ACD. Dilute patch testing to limited allergens warrants further study in this setting.

AUTHOR CONTRIBUTIONS

Phoebe Star: Conceptualization; investigation; writing – original draft; writing – review and editing; project administration; resources. **Elizabeth Teng Yoke Chow:** Writing – original draft; methodology; writing – review and editing; formal analysis; supervision; resources. **Jing Jing Li:** Investigation; writing – original draft; visualization. **Victoria J. Bray:** Writing – review and editing. **Monisha Gupta:** Conceptualization; visualization; writing – review and editing; supervision.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

INFORMED CONSENT

Written informed consent was obtained from the patient for the images to be included.

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How to cite this article: Star P, Chow ETY, Li JJ, Bray VJ, Gupta M. A case of hair dye-induced allergic contact dermatitis in the context of nivolumab. *Contact Dermatitis*. 2022;87(4):377-379. doi:10.1111/cod.14169

Maculopapular rash due to delayed-type hypersensitivity from ioversol with positive patch tests

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KEYWORDS: adverse reaction (contrast media), allergic contact dermatitis, case report, cross-reactions, patch test

Non-ionic iodinated contrast media (NICMs) are the preferred option for enhanced Computerized tomography (CT) examination. Adverse reactions to contrast media occur with cutaneous manifestations to fatal, life-threatening complications.¹

Immediate hypersensitivity reactions (IHRs) occur up to 1 h after NICM administration,² mainly if the responses are 'moderate' (in contrast to severe reactions, which may indeed appear within 1H).³ HRs are delayed (DHRs) if they occur more than 1 h to 7 days

FIGURE 1 (A) Micro-maculopapular rash. (B) Difficult to interpret positive patch tests (PT) at the back 'angry back' to non-ionic iodinated media contrasts 30%, pet. and aq. (iohexol, ioversol, iopromide and iopamidol). (C) Re-test PT (reading at 2 days): upper: iopamidol 30% pet. (left) and aq. (right), both erythema (+); below: iohexol 30% (+++), pet. (left) and aq. (right). (D) Re-test PT (reading at 2 days): upper: ioversol 30% pet. +++ (left) and aq. ++ (right); below: iopromide 30%, pet. (left) and aq. (right), both negative. (E) Reading at 4 days: upper: iopamidol 30%, pet. (left) and aq. (right), both negative; below: iohexol 30% (++), pet. (left) and aq. (right). (F) Reading at 4 days: upper: ioversol 30% pet. (left, ++) and aq. (right, +); below: iopromide 30%, pet. (left) and aq. (right), both negative

