Title: Acute toxic epidermal necrolysis reaction post single dose pembrolizumab with preceding cephalosporin exposure: successful rechallenge with anti-PD-1 therapy

Running head: Hyperacute TEN: anti-PD-1 & antibiotics

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Funding: nil

Conflict of interest: nil

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1111/imj.14388](https://doi.org/10.1111/imj.14388)

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Abstract

Severe immunotherapy-induced skin toxicity can be life-threatening. Guidelines suggest permanent discontinuation. Safety of rechallenge is uncertain. We demonstrate the hyperacute onset of a toxic epidermal necrolysis (TEN)-like reaction after one dose of the anti-programmed death-1 (PD-1) checkpoint inhibitor, Pembrolizumab, in a patient receiving antibiotics. Pembrolizumab rechallenge without recurrent toxicity was observed.

Case

A 78 year old woman with metastatic melanoma received one dose of Pembrolizumab and developed extensive rash. She had documented allergies: Amoxicillin; Doxycycline; Valsartan, Indapamide; Telmisartan. Regular medications: Aspirin; Paracetamol. She received Metronidazole 5 weeks earlier after a diarrhoeal illness. The patient had a symptomatic cough due to malignant left hilar involvement and mild liver function derangement thought secondary to antibiotics pre-commencement of checkpoint inhibitor therapy. She was prescribed Cephalexin for 12 days after worsening cough post endobronchial biopsy and remained on this agent at the time of pembrolizumab commencement.

Less than 12 hours after receiving Pembrolizumab, she developed fever, headache and nausea. A grade 4 (face, trunk, limbs) non-pruritic maculopapular rash occurred 2 days later. Antihistamines were commenced. Intravenous fluids were given for an elevated creatinine secondary to dehydration. She developed grade 1 diarrhoea. Liver function tests worsened: ALT/AST 6-7x and GGT 10x (grade 3) the upper limit of normal. She developed mild lymphopenia and neutropenia. Eosinophils were not elevated. Stool culture confirmed *Clostridium difficile* and detectable toxin. The fever was recurrent with rigors. Six days post Pembrolizumab, she developed a swollen upper lip, tongue discomfort and burning sensation affecting the eyes. Skin biopsy 48 hours after the development of rash confirmed an interface reaction involving epidermis consistent with early TEN (Figure 1) and CD8+ lymphocytes. PD-L1 stain demonstrated limited keratinocyte staining, predominantly in the basal layer. Her TEN severity score was 3 based on the following parameters: Age ≥ 40 years; cancer/hematologic malignancy; serum bicarbonate level < 20 mmol/L (1). Methylprednisolone 1mg/kg was given over 3 days with rapid improvement in fever, rash and resolution of diarrhoea. Prednisolone was weaned over 12 weeks to avoid rebound toxicity and for management of dyspnoea due to symptomatic endobronchial tumour. The patient required palliative radiotherapy to the hilar mass. Metronidazole was prescribed during the steroid wean due to the identification of *Clostridium difficile* toxin. The liver derangement improved with steroid therapy and may have been related to underlying TEN versus checkpoint inhibitor induced autoimmune hepatitis.

6 months later, she requested rechallenge and received Pembrolizumab with antihistamine (10mg Loratadine) and Prednisolone (10mg) for 10 days. Subsequent Pembrolizumab was given successfully without Prednisolone.

Discussion

Immunotherapy for advanced melanoma improves survival (2). The frequency of rash for anti-PD-1 therapy is 16-25% (any grade) and 0-1% (grade 3-4) (2, 3). Rates are higher with combination checkpoint therapy (any grade, 30%, grade 3-4, 3%) (2). The PD-1 receptor exerts negative regulatory effects on T-cell signalling. Pembrolizumab prevents engagement of PD-1 with its ligand, removing this inhibitory signal.

Goldinger et al performed gene expression profiling on melanoma patients that developed skin toxicity to anti-PD-1 therapy. All were classified as TEN-like reactions (4). Histopathology revealed CD8+ T-cells at the dermoepidermal junction and PD-L1 expression on keratinocytes. They concluded epidermal integrity is dependent upon the PD-1/PD-L1 interaction during these reactions. The staining pattern for our patient was similar in appearance to that seen in Goldinger et al although the intensity demonstrated was less and likely reflects the early stage of the process for our case.

Cephalosporins and checkpoint inhibitors can induce Stevens-Johnson syndrome (SJS) and TEN. Antibiotics may dampen immunotherapy effectiveness and has implications for cancer patients. Alterations of gut microbiome in mouse models and melanoma patients (5) can influence tumour growth and cancer responses to immunotherapy. A study of renal cell carcinoma patients receiving immunotherapy plus antibiotics had diminished responses than patients not receiving antibiotics (6).

The hyperacute skin toxicity in our patient may be the result of concurrent use of both drugs (pembrolizumab and cephalosporin) contributing to a 'perfect storm' with resultant TEN-like reaction. The temporal sequence is highly suggestive of an interaction between the drugs with the preceding administration of a cephalosporin and the development of systemic symptoms coinciding on the day that anti-PD-1 therapy was received.

Successful immunotherapy rechallenge in a patient that developed a TEN-like reaction after one pembrolizumab dose was demonstrated. Rechallenge can be considered in selected circumstances.

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Figure 1. Skin biopsy. Early toxic epidermal necrolysis, with multiple apoptotic keratinocytes within the basal and suprabasal epidermis (arrowheads), and a mild lymphocytic infiltrate, original magnification

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IMJ_14388_early toxic epidermal necrolysis with arrows x100 MPS133318-18T 78F back.jpg

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2019-08-01

Citation:

Lomax, A. J., McQuillan, P. I. A., Hall, A. & McArthur, G. A. (2019). Acute toxic epidermal necrolysis reaction post single dose pembrolizumab with preceding cephalosporin exposure: successful rechallenge with anti-PD-1 therapy. INTERNAL MEDICINE JOURNAL, 49 (8), pp.1051-1053. <https://doi.org/10.1111/imj.14388>.

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