Novel Use of Combination Therapeutic Plasma Exchange and Rituximab in the Treatment of Nivolumab-Induced Bullous Pemphigoid

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Introduction

Immune checkpoint inhibitors are a new class of medication for the treatment of metastatic melanoma. Recently, there have been seven documented cases of bullous pemphigoid (BP) associated with the programmed death-l (PD-1) and programmed death-ligand-1 (PD-L1) inhibitors. While corticosteroids are effective in Bullous Pemphigoid, we report a case of severe, refractory nivolumab-associated BP successfully treated with plasmapheresis and rituximab, to maintain the enhanced cellular immunity without need for further oral corticosteroids.

Clinical Case

A 67-year-old male with stage IV BRAF- and c-KIT-negative, NRAS-positive melanoma of unknown primary with metastases to the liver, lung and brain was started on nivolumab 3 mg/kg every two weeks. After 16 cycles over 32 weeks, he presented to the emergency department with a new, severe, pruritic, bullous eruption covering approximately 90% body surface area, and altered mental status. (Fig. 1)

Therapeutic Challenges:

• Finding an effective treatment that balanced immunosuppression with immune checkpoint inhibitor mechanism of action
• Failure of first line agents
• Therapy with a rapid onset of action
• The need to resume therapy for underlying metastatic melanoma

Laboratory Studies

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Pre Treatment</th>
<th>Post Treatment</th>
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<tr>
<td>BP-180</td>
<td>&gt;150.00 Units</td>
<td>29.32 Units</td>
<td>&lt;9.0 Units</td>
</tr>
<tr>
<td>BP-230</td>
<td>6.50 Units</td>
<td>&lt; 5.0 Units</td>
<td>&lt;9.0 Units</td>
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Biopsy:

Histopathology: Subepidermal bulla, few eosinophils

Direct Immunofluorescence: Linear deposition of IgG, C3 and C5b9 complex at the dermoepidermal junction

Initial Treatment

• Prednisone up to 1 mg/kg daily
• Betamethasone dipropionate 0.05% cream twice daily
• Deferral of nivolumab until completion of steroid taper

Complications:

• Bacteremia
• Worsening of BP
• Inability to taper the patient to low dose steroids

Therapeutic Challenges:

• Of the reported cases of PD-1/PD-L1 inhibitor-induced BP, the majority were controlled with topical and/or oral steroids alone.1-2
• Plasmapheresis:
  • Targeted immunosuppressive effects
  • Rapid onset of action
  • Used successfully to treat BP3
• Rituximab:
  • Previous single agent success in treating and preventing relapse of nivolumab-induced BP4
  • Anti-CO20 may assist in treatment of melanoma if tumor has a CO20 positive cell population5

Autoimmune bullous dermatoses are a recently described adverse event to the PD-1/PD-L1 inhibitors.1 The pathogenesis of BP may be due to excessive B-cell co-stimulation and increased autoantibody production with blockade of PD-1/PD-L1 receptors.2,3 None of the prior patients mentioned neurologic or cutaneous metastases, which potentially could have an effect on exposing epitopes for the development of BP. A diagnosis of lichen planus pemphigoides instead of BP is another consideration given that BP-180 is elevated in lichen planus pemphigoides and lichenoid eruptions are a common cutaneous adverse effect to immune checkpoint inhibitors. However, none of the patients had coexisting lichen planus or a lichenoid infiltrate on pathology.

Given that all the patients have been elderly and the majority displayed the characteristic distribution of BP, it is possible that some of the patients previously could have had low titer autoantibodies, yet clinical significance of their disease was precipitated by the PD-1/PD-L1 inhibitors.

Conclusion

This case is novel because it demonstrates the potential for rapid and sustained improvement in nivolumab-induced BP with plasma exchange and rituximab for targeted immunomodulation in the increasing population of patients presenting with unique autoimmune phenomenon with checkpoint inhibition.

References

2. Dominy W, Kari L, Song YY. Development of bullous paraplegia during nivolumab therapy. AAD2020 Case Reports. 2020;2020(1-2):e29. doi:10.1097/01.DER.0000656088.01570.6c

Figure 1: Coalescent bullous eruption covering approximately 75% of body surface.

Figure 2: Post-treatment with healing erosions and post-inflammatory hyperpigmentation.

Figure 3: Subepidermal bulla with few eosinophils.