**INTRODUCTION**

- Immune checkpoint inhibitors (ICIs) are a novel group of monoclonal antibodies that target cellular surface molecules such as programmed cell death protein 1 (PD-1), programmed cell death protein 1 ligand (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4).
- ICIs such as nivolumab are known to cause autoimmune complications, but immune-mediated diabetes mellitus (DM) is rarely reported, with an incidence of < 1% (1).
- We present a case of new-onset diabetes mellitus with diabetic ketoacidosis (DKA) in a patient receiving nivolumab.

**CLINICAL CASE**

- A 74-year-old Caucasian male with no history of DM or autoimmune disease was diagnosed with stage III metastatic melanoma and started on treatment with nivolumab, an ICI. He tolerated treatment well and had no evidence of endocrine dysfunction on routine laboratory monitoring.
- Shortly after completing his 14th cycle of nivolumab therapy, he presented to the emergency department with a one-week history of fatigue, poor appetite, polydipsia, and polyuria.
- Laboratory evaluation (table 1) revealed DKA and new-onset diabetes mellitus with Hgb A1c of 7.3%, increased from 5.4% one year earlier.
- He was admitted for treatment with intravenous insulin and was later transitioned to basal-bolus subcutaneous insulin therapy, which was continued at discharge.
- Outpatient evaluation (table 2) revealed no measurable GAD65 antibodies or anti-insulin antibodies, but serum c-peptide was found to be <0.10 ng/mL on two separate occasions, five months apart. This supported a diagnosis of endocrine pancreatic insufficiency, most likely due to nivolumab therapy.
- He completed an additional 6 cycles of nivolumab with no further complications. Meanwhile his DM became well-controlled with subcutaneous insulin injections, and he was eventually transitioned to insulin pump therapy.

**LABORATORY RESULTS**

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Results</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood glucose</td>
<td>446 mg/dL</td>
<td>70-105 mg/dL</td>
</tr>
<tr>
<td>Anion gap</td>
<td>20 mEq/L</td>
<td>4-12 mEq/L</td>
</tr>
<tr>
<td>Serum bicarbonate</td>
<td>14 mEq/L</td>
<td>23-31 mEq/L</td>
</tr>
<tr>
<td>Venous pH</td>
<td>7.23</td>
<td>7.33-7.43</td>
</tr>
<tr>
<td>Urinary ketones</td>
<td>&lt;4</td>
<td>negative</td>
</tr>
<tr>
<td>Hemoglobin A1c</td>
<td>7.3%</td>
<td>4.3%-5.7%</td>
</tr>
</tbody>
</table>

**DISCUSSION**

- ICIs are monoclonal antibodies that target cellular surface molecules such as programmed cell death protein 1 (PD-1), programmed cell death protein 1 ligand (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4).
- Inhibition of these receptors triggers lymphocytic activation, enabling tumor cell recognition and subsequent attack; however, lymphocytic activation may also result in the attack of normal cells, resulting in autoinflammatory diseases (fig. 1).
- Several autoimmune manifestations have been reported in association with nivolumab therapy, including dermatomyositis, transverse myelitis, myasthenia gravis, rheumatoid arthritis, autoimmune hepatitis, dermatitis, thyroiditis, gastritis, and diabetes mellitus.
- Immune-mediated diabetes due to nivolumab therapy has been reported rarely, but progression to insulin-dependency appears to be rapid in these cases.
- It is important to recognize new or worsening DM early in patients treated with nivolumab in order to avoid life-threatening complications such as DKA.

**REFERENCES**