Nivolumab Induced Hemolytic Anemia in Patient with Advanced Squamous Cell Lung Cancer (SCC)

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Abstract
Nivolumab, a humanized IgG4 programmed death-1 (PD-1) inhibitor antibody, is approved in Italy for advanced non small cell lung cancer (NSCLC), for advanced melanoma in association with ipilimumab, in second line renal cell carcinoma (RCC), in Hodgkin lymphoma relapsed after autologous stem cell transplantation and treatment with brentuximab vedotin, in head and neck squamous cell carcinoma progressed after platinum therapy and in locally advanced urothelial carcinoma unresectable or metastatic after failure of previous platinum therapy. Its immunogenic potential is well known, with described autoimmune-like syndromes, but no clear association is evident for hemolytic anemia. We report case of a 68-year-old man who developed hemolytic anemia after 28 cycles of treatment for advanced Squamous Cell Lung Cancer (SCC).

Keywords: Nivolumab; Hemolytic anemia; Squamous cell lung cancer; Hodgkin lymphoma; Anticancer effect; Carcinoma

Introduction
Nivolumab is a humanized IgG4 monoclonal antibody direct against T cell PD-1 receptor, avoiding interaction with tumor-expressed ligands PDL-1 and PDL-2 [1]. Restored T cell function is responsible for both therapeutic anticancer effect and immune related side effects [2].

Currently it is approved by AIFA in the treatment of advanced NSCLC, on the basis of Checkmate 017 and Checkmate 057 trials, in advanced melanoma as single agent or in combination with Ipilimumab [3], in second line treatment of advanced RCC, in second line head and neck squamous cell carcinoma after previous platinum regimen, in advanced urothelial carcinoma after platinum chemotherapy and after failure of both autologous staminal transplant and brentuximab for classical Hodgkin Lymphoma [4].

Most frequently reported adverse effects with standard dose of 240 mg every 15 days, or 480 mg every 28 days, alternative administration schedule allowed only for melanoma and RCC, include fatigue, skin rash, diarrhoea, which are usually moderate-mild graded; common clinical appearances comprehend also immune-mediated pneumonitis, colitis, hepatitis, renal disfunction, hypophysitis, adrenal insufficiency, autoimmune thyroid disorders, and type 1 diabetes mellitus. Despite autoimmune hemolytic anemia is described for other immune checkpoint inhibitors such Pembrolizumab, only few cases have been reported with Nivolumab use, often with confounding factors conditioning anemia differential diagnosis [5].

Case Presentation
A 68-years-old man, with a story of prostatic adenocarcinoma radically treated in 2011, was diagnosed in June 2015 SCC, stage IIIb (CT4 cN2 cM0), and was treated with six cycles of carboplatinum-vinorelbine and subsequent radiation therapy till May 2016. In November 2016, because of locoregional disease progression, patient started Nivolumab at standard dosage of the period of 3 mg/kg every two weeks [6].

Basal blood exams, comprehensive of endocrine function, were in range of normality; pharmacological treatment ongoing for neoplastic pain and paraneoplastic polymalgia control consisted of fentanyl 75 mcg/h every 72 h, gabapentin 300 mg/day, etoricoxib 120 mg/day, hydroxychloroquine 400 mg/die and prednisone 12.5 mg/die. The patient also took atorvastatin 10 mg/day and inhalatory beclomethasone/formoterol 200 mcg.

Twelve days after 28th infusion of Nivolumab, the patient presented shortness of breath, asthenia and tachycardia whereby he went to emergency room. Physical exam demonstrated jaundice and hepatomegaly; laboratory tests showed anemia with hemoglobin level of 5.2 g/dL; subsequent investigations were consistent with autoimmune hemolytic anemia diagnosis. The patient was then transfused with two units of packed red cells and treated with methylprednisone 40 mg by intravenous injection and oxygen therapy [7].

Hematological insights, performed subsequently, revealed positivity for cold agglutinins (title 1:8), positive direct Coombs test, reduced haptoglobin, both serum immunoglobulins IgA, IgM and IgG and complement proteins C3 and C4 were in range of normality. Mycoplasma infection was excluded in presence of cold agglutinins. Additionally, blood tests detected increased erythropoietin levels (160.8 mU/L), increased ferritin (1621 ng/mL) and iron level (239 mcg/dL). Notable, platelet levels were in range of normality, thus excluding Fisher-Evans Syndrome.

According to Nivolumab immune related adverse events management, methyl-prednisolone 1mg/kg was started and, after ten days, because of not responsiveness, intravenous immunoglobulins 0.5mg/kg were additionally administered for four days. Than hemoglobin levels gradually increased, and hemolysis quote decreased, till hospital discharge, after twenty-two days, with prescription of continuation corticosteroid therapy with dexamethasone 8 mg twice daily.

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During hospitalization CT scan was performed with evidence of thorax progressive disease, pleural and diaphragmatic infiltration and hepatic localizations. Before oncologic evaluation, the patient required new hospitalization because of febrile severe acute respiratory failure due to pleural effusion: no infective causes were detected neither hemolysis signs were identifiable [8]. Few days after patient died (Table 1).

Discussion and Conclusion

Generally, immune-related AEs occur within short time frame from immunotherapy start, nevertheless later onset have been documented until months after drug discontinuation. Therapeutic indications for anemia during it suggested by 2017 ESMO committee are high dose corticosteroids and immunosuppressive drugs and hemolytic anemia is generally managed by hematologic protocols inclusive of gradually tapering corticosteroids, intravenous immunoglobulin and, in case of refractoriness, Rituximab [9].

Only few hemolytic anemia cases have been reported, and this adverse event is still poorly documented: in most of described cases onset appeared around the first cycles of Nivolumab therapy and patients often had predisposing autoimmune conditions. This case reports a prolonged, late onset hemolytic anemia after twenty-eight Nivolumab infusions in patient with unknown autoimmune predisposing factors, not assuming chronic drugs known to be autoimmune triggers and not presenting with infectious diseases, treated with standard immunosuppressive therapy.

This adverse event showed a benign resolution with immunosuppressive medical therapy but patient died because of progressive disease.

References


Table 1: Investigations for hemolytic anemia.

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Result at baseline</th>
<th>Result at 10 days</th>
<th>Result at admission</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/dL)</td>
<td>5.2</td>
<td>5.0</td>
<td>8.2</td>
<td>13.0-18.0</td>
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<tr>
<td>RBC (10⁶/mm³)</td>
<td>1.61</td>
<td>1.30</td>
<td>2.44</td>
<td>4.50-6.0</td>
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<tr>
<td>MCV (fL)</td>
<td>111.8</td>
<td>123.8</td>
<td>109</td>
<td>80-100</td>
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<tr>
<td>Total bilirubin (mg/dL)</td>
<td>3.97</td>
<td>1.29</td>
<td>0.66</td>
<td>&lt;1.1</td>
</tr>
<tr>
<td>Direct bilirubin (mg/dL)</td>
<td>1.01</td>
<td>0.28</td>
<td>0.13</td>
<td>&lt;0.25</td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>1514</td>
<td>479</td>
<td>343</td>
<td>&lt;250</td>
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<tr>
<td>Reticulocytes (%)</td>
<td>27.43</td>
<td>16.55</td>
<td>13.46</td>
<td>0.50-1.50</td>
</tr>
<tr>
<td>Haptoglobin (mg/dL)</td>
<td>&lt; 30</td>
<td>&lt;30</td>
<td>87</td>
<td>30-200</td>
</tr>
</tbody>
</table>

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