Nivolumab Induced Steroid-Refractory Cold Agglutinin Disease Successfully Treated with Rituximab

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Introduction

Nivolumab is a fully human immunoglobulin (Ig) G4 monoclonal antibody directed against the negative immunoregulatory human cell surface receptor programmed death-1 (PD-1, PCD-1) with immune checkpoint inhibitory and antineoplastic activities. It has significant anti-tumoral activities against several cancers including Hodgkin Lymphoma and urothelial carcinoma. However, immune-related adverse events (irAEs) such as rash, hypothyroidism, diarrhea, colitis, pneumonitis, and nephritis are reported with the use of nivolumab that can cause interruption or cessation of the therapy. In this poster, we presented a novel nivolumab induced cold agglutinin syndrome that is successfully treated with rituximab therapy.

Case Presentation

- An 89-year-old Caucasian woman with metastatic urothelial carcinoma presented with fatigue and dyspnea on exertion after she completed 7 cycles of nivolumab therapy with the dose of 6 mg/kg every 4 weeks.
- Her past medical history was significant for hypertension, hypothyroidism, chronic kidney disease, breast cancer and marginal zone B cell lymphoma in complete remission for 9 years.
- Physical exam was only notable for conjunctival pallor.
- Investigations at the clinic were evident with hypochromic and microcytic anemia, the rouleaux formation of the RBC in the peripheral smear (Figure 1), positive direct antiglobulin test with positive C3d and negative IgG, cellular bone marrow biopsy results supporting peripheral destruction (Figure 2). Cold agglutinin titer was positive (>64).
- Patient was on clonidine, olmesartan, melatonin and levothyroxine and none of these medications are known to cause cold agglutinin disease.
- There was no history of positive red blood cell antibodies or autoimmune hemolytic anemia in the patient prior to this diagnosis.

Case Presentation Con't

- The patient was diagnosed with nivolumab induced cold agglutinin disease after ruling out other possible causes of the disease.
- Nivolumab was discontinued.
- The patient did not respond to steroids and required multiple red blood cell transfusions.
- Patient was started on rituximab at a fixed dose of 1000 mg every two weeks and completed a total of 4 doses.
- Patient responded well to rituximab with clinical improvement, stable hemoglobin and undetectable cold agglutinin titer after the completion of the therapy.
- Nivolumab was not re-introduced since she was in complete remission after seven cycles of therapy.

Figures

Figure 1. H&E stain of peripheral blood smear shows anisocytosis, rouleaux and agglutination formation few hypochromic red blood cells, microspherocytes and nucleated red blood cells, scattered platelet clumping and moderate to severe neutropenia.

Figures

Figure 2. H&E stain shows hypercellular for the age (70-80%) bone marrow with increased elements of all three lineages (A). Reticulin stain show no bone marrow fibrosis (Not shown). Anti-CD3 (B) and anti-CD20 (C) antibodies show scattered small T-cells and B-cells, respectively; no clusters of B-cells and no large B-cells are detected. Anti-CD11c (D) antibody decorates increased myeloid elements. Anti-CD71 (E) antibody highlights increased erythroid elements. Anti-CD61 (F) antibody decorates markedly increased left-shifted megakaryocytes, no atypical megakaryocytes and no megakaryocyte clustering are detected.

Discussion

- This is the first case reported cold agglutinin syndrome secondary to nivolumab therapy and in the context of a urothelial carcinoma.
- Possible causes of cold agglutinin syndrome such as medications, lymphoma and metabolic causes were all ruled out before diagnosing the nivolumab induced cold agglutinin syndrome.
- Autoimmune hemolytic anemias secondary to check point inhibitors are not related to dose or the duration of the therapy. It can be seen at any time from the 2nd to 8th cycle of the therapy and at a dose of 3mg/kg to 6mg/kg every 4 weeks.
- Steroid refractory cases require multiple blood transfusions but respond well to rituximab.

Conclusions

- Cold agglutinin syndrome (CAS) is one of the rare immune related adverse events of Nivolumab.
- Early recognition and effective treatment are key to its management and prevention of morbidity and mortality.
- Rituximab should be considered for treatment of Nivolumab induced cold agglutinin syndrome.

References

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