ANTI-MYELIN ASSOCIATED GLYCOPROTEIN NEUROPATHY MEDIATED BY MGUS IN THE SETTING OF NIVOLUMAB: A CASE FOR B- AND T-CELL CROSSTALK IN THE TUMOR MICROENVIRONMENT

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Aim

- Highlight a mechanism of paraproteinemic neuropathy potentially spurred by B-T crosstalk in the setting of immune checkpoint inhibitor use

Introduction to the Case

- An 81-year-old Caucasian woman without relevant prior medical history was originally diagnosed with high-risk cutaneous melanoma of the left foot, AJCC stage IIIC.
- After surgery, she underwent one year of adjuvant anti-PD-1 therapy.
- After 10-11 months of therapy with nivolumab, she developed new onset numbness and tingling of bilateral fingers and toes, and confusion.
- Due to progression of the symptoms she was investigated for sensory motor neuropathy.
- Cell counts were normal.
- Tests for cryoglobulins and cold agglutinins were negative, blood viscosity was normal, and Bence Jones protein was present.
- Serum electrophoresis revealed IgM lambda light chain restricted monoclonal gammopathy.
- Tests for anti-myelin associated glycoprotein (MAG) antibodies were positive and felt to mediate peripheral neuropathy.
- Bone marrow biopsy did not show myeloma but did show a small clone expressing CD5, CD20, and CD23. Whole body CT did not show lymphadenopathy.
- She was diagnosed with monoclonal gammopathy of undetermined significance (MGUS), a precursor state of multiple myeloma.
- Diagnosis of polyneuropathy was made and felt to be secondary to MGUS as a result of anti-MAG antibodies.
- Her confusion, "brain fog", and memory loss raised concern for CNS vasculitis associated with IgM lambda light chains and she was started on low-dose oral steroids which were tapered and stopped within 4-5 weeks after they unfortunately did not show significant clinical improvement.
- However, she began to experience spontaneous improvement in her symptoms following cessation of nivolumab.

Results

- The melanoma sample at time of initial diagnosis was evaluated by immunohistochemistry to assess the tumor microenvironment and revealed increased infiltration of tumor site by CD3+ CD8+ T-cells and CD138+ plasma cells. Moreover, at this time there was no clear derangement of kappa:lambda ratio, suggesting development of MGUS following nivolumab administration.

Results (Continued)

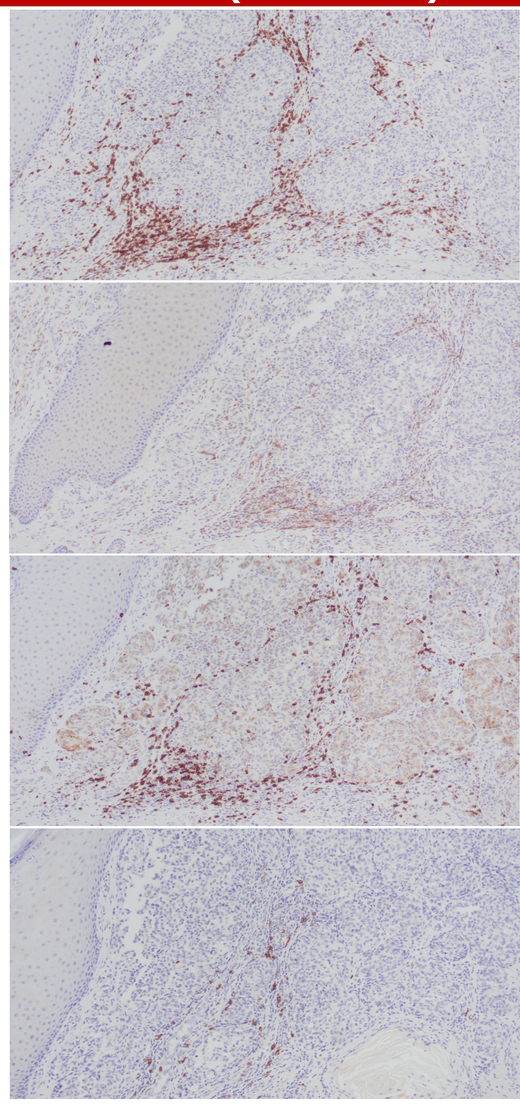


Figure 1: Immunohistochemistry results of initial melanoma excision site. Top: CD3 expression. Second from top: CD4 expression. Second from bottom: CD8 expression. Bottom: CD20 expression. Photographs by Dr. M. Murphy, UConn Health Division of Dermatopathology.

Discussion

- This patient's symptoms of neuropathy were associated with IgM anti-MAG, likely associated with nivolumab, taking into consideration the temporal relationship with nivolumab, laboratory findings, and symptoms
- Given pathology findings, we suspect B cell activation by the T cells. Among the mechanisms associated with immune-related adverse events, B-T crosstalk is a most important mechanism.
- Our patient highlights this mechanism in paraproteinemic neuropathy with anti-MAG potentially spurred by B-T crosstalk. This must be considered in the investigation of immune related adverse events.

References

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Authors have no conflicts of interest to declare.