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A Very Rare Case of Esophagitis Due to Nivolumab Immunotherapy

Sujata Sajjan*, Deepika Savant, Rebecca Thomas, Nina Haghi, Margaret Cho

Department of Pathology and Laboratory Medicine, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, 6 Ohio Drive, Suite 202, Lake Success, New York, 11042.
*Corresponding author: ssajjan@northwell.edu

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Abstract A 72-year-old woman with Renal Cell Carcinoma, on Nivolumab therapy for extensive metastatic disease, presented with dysphagia. Endoscopy revealed Grade 2 esophagitis with biopsy confirming active esophagitis. There was no histological evidence of an infectious or lymphoproliferative etiology. Nivolumab-induced esophagitis was suspected, and the medication was discontinued. There was dramatic clinical improvement with steroids. Immune checkpoint inhibitors are novel immunotherapeutic agents designed to restore the patient's own antitumor immune responses. Nivolumab, an IgG4 monoclonal antibody that acts as an inhibitor of programmed death-1, is currently approved for clinical use in treatment of advanced stage malignancies. As Nivolumab is increasingly used in clinical oncology due to its efficacy and better tolerance compared to other chemotherapeutic agents, we present the second reported case of Nivolumab-associated esophagitis. Pathologists and clinicians should be aware of this possible complication to ensure its timely diagnosis and management.

Keywords: *nivolumab, esophagitis, immunotherapy, cancer chemotherapy*

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1. Introduction

Recent advances in the understanding of immunology and cancer biology have resulted in the development of newer classes of drugs, specifically immunomodulatory therapy in the management of cancers. Nivolumab, an IgG4 monoclonal antibody that inhibits the programmed death-1 (PD-1) receptor, has revolutionized management of patients with cancer, and has been approved for treatment of metastatic melanoma, advanced non-small cell carcinoma (NSCLC) and renal cell carcinoma. As Nivolumab is increasingly used in oncology, the immune-related adverse events may be more frequently being observed. Therefore, early recognition of pathological injury is critical.

2. Case Report

A 72-year-old woman with stage 4 Renal Cell Carcinoma, status post nephrectomy with lung and liver metastases, on Nivolumab therapy for the last 9 months, presented with difficulty in swallowing both liquids and solids of one-week duration. There was no history of diarrhea, constipation, abdominal pain or fever. An upper gastrointestinal endoscopy revealed Grade 2 esophagitis (Figure 1).

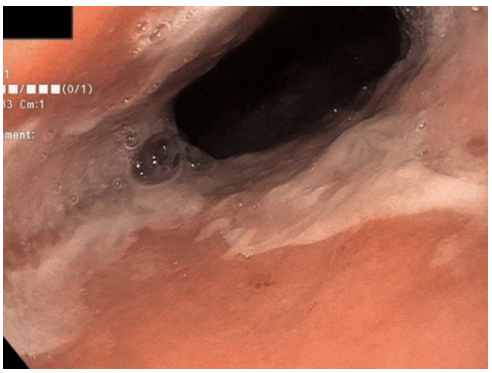

Figure 1. Upper gastrointestinal endoscopy revealing Grade 2 esophagitis

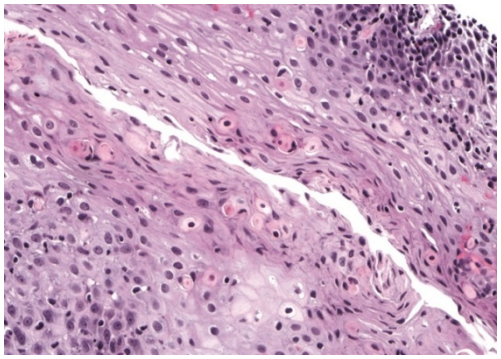

Figure 2. Active esophagitis with intraepithelial lymphocytes, scattered eosinophils, and few neutrophils with dyskeratotic keratinocytes (H&E Original magnification × 400)

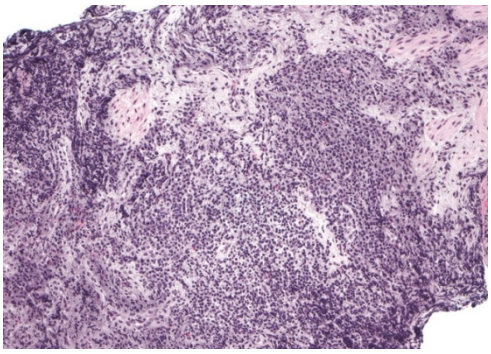

Figure 3. Granulation tissue with lymphocytes, plasma cells, neutrophils, and scattered eosinophils in the lamina propria (H&E Original magnification x 400)

Esophageal biopsy demonstrated active esophagitis with intraepithelial lymphocytes, scattered eosinophils and few neutrophils with dyskeratotic keratinocytes (Figure 2). Granulation tissue was present with lymphocytes, plasma cells, neutrophils, and scattered eosinophils in the lamina propria (Figure 3).

There was no histological evidence of fungal (Grocott's methenamine silver stain was negative) or viral infections (Cytomegalovirus immunostain and Epstein-Bar Virus-Encoded RNA (Ribonucleic Acid) In Situ Hybridization were negative). There was no evidence of a lymphoproliferative disorder; immunohistochemical stains showed a mixture of T-cells (CD3, CD5, Bcl-2, and CD43) and B-cells (CD20, Pax-5; negative for CD5, CD43); Cyclin D1 was negative; CD138 highlighted plasma cells which were polytypic (supported by kappa and lambda in situ hybridization). Nivolumab-induced esophagitis was suspected, and the medication was discontinued. There was a dramatic clinical improvement with initiation of steroids. The patient continued to do well and did not report dysphagia on follow up visits over the next two months.

3. Discussion

Targeted therapies acting on specific molecular targets are the new frontiers of cancer management. Immunotherapy is one such therapeutic approach in several malignancies such as non-small cell carcinoma of the lung, renal cell carcinoma, Hodgkin's lymphoma and melanoma. Checkpoint inhibitors, like Pembrolizumab and Nivolumab are increasingly used in management of metastatic malignancies because of their greater efficacy and tolerance [1,2,3].

Nivolumab is a fully human immunoglobulin (IgG4) monoclonal antibody that interacts with the programmed death-1 (PD1), a cell surface transmembrane immune checkpoint receptor present on activated T-cells that plays a vital role in immune inhibition and antineoplastic activities. Blockade of the interaction of PDL1 with PD1 enhances immune function and mediates antitumor T-cell activity against tumor cells. Since the mechanism of action includes promoting T-cell responses, enhanced autoimmunity involving various organ systems, including the skin (rash and pruritus), gastrointestinal system (colitis and gastritis), endocrinopathies (hypophysitis, hypothyroidism), liver (hepatitis), kidneys (nephritis) and lungs (pneumonitis) are described side effects. [4,5,6,7] Unlike other are IgG1 subtype and cause antibody-related cell cytotoxicity.

Since Nivolumab is an IgG4 subtype of monoclonal antibody, it is not associated with antibody-related cell cytotoxicity, resulting in improved tolerance. In phase I human studies, skin (20%), gastrointestinal (15%), and pulmonary (9%) toxicities were observed, while in the phase II studies skin (31%), rash (12%), pruritus (9%), vitiligo (3%), gastrointestinal (11%), and pulmonary (3%) were reported. In general, toxicities with anti-PD-1 antibodies appear to be less common and less severe when compared with anti-CTLA-4 monoclonal antibodies [8,9,10]. Dermatologic toxicity is the most common immune-related adverse event associated with checkpoint inhibitors which is usually seen 3-4 weeks after the initiation of therapy. Diarrhea/colitis is the most common gastrointestinal symptom presenting approximately 6-8 weeks after the commencement of therapy. [2,8,9,10,11]

Boike et al. have previously reported endoscopic and histopathological features of esophagitis related to Nivolumab therapy. [2] They noted marked intraepithelial T-cell lymphocytic infiltrates with dyskeratotic keratinocytes. Similar to our case symptoms improved dramatically with steroid therapy. Nivolumab associated colitis is characterized by lymphocytic infiltration in the lamina propria and epithelium of the involved mucosa. In some cases, it is characterized by active colitis with neutrophilic crypt microabscesses, prominent crypt epithelial cell apoptosis and crypt atrophy/dropout. After exclusion of other etiologies, management includes initiation of corticosteroid therapy and cessation of Nivolumab in severe cases. [2,10] Interestingly, involvement of the rest of the gastrointestinal tract is rarely reported in the literature.

4. Conclusion

Advances in immuno-oncology have led to the development of newer immune-response-modifying agents like Nivolumab. Although promising, physicians and pathologists should be vigilant for toxicities associated with this medication, such as esophagitis, that will likely become more commonplace with the emergence of additional formulations and indications. Awareness of this clinical scenario should allow pathologists and physicians to facilitate its timely diagnosis and management.

Statement of Competing Interest

The authors declare that they have no competing interests.

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