Novel Immunotherapy Treatments: The Adverse Effects of Nivolumab.

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Novel Immunotherapy Treatments: The Adverse Effects of Nivolumab

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INTRODUCTION

Nivolumab is a checkpoint immunotherapy that has become a primary treatment modality for patients with advanced melanoma and non-small cell lung carcinoma (NSCLC). New immunotherapy treatments can result in unique adverse events due to increased inflammation in any organ in the body.

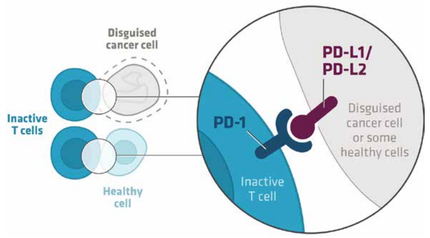

Image 1: T cells inactivated by cancer cells through PD-L1/PD-L2 receptor

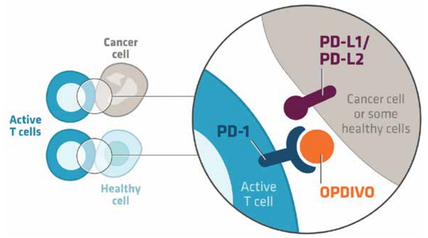

Image 2: Nivolumab utilized to maintain T cell activation against cancer cells, and some healthy cells

CASE REPORT

A 64-year-old Vietnamese male with a history of stage IIIA NSCLC was treated with Taxol, Carboplatin and radiation therapy with good response. Two years later, computed tomography (CT) scan demonstrated metastases to the liver and pancreas. The patient began treatment with nivolumab. Two weeks after the initial nivolumab treatment, the patient complained of significant abdominal pain. Repeat CT imaging showed disease progression in the liver and pancreas with mild inflammation of the pancreatic tail. Hospital admission blood work showed lipase of 4479 U/L and CRP of 179 mg/L, which is consistent with immune related pancreatitis. He was treated with methylprednisolone 1.2mg/kg/day with improvement in pain and lipase levels. Ten days after starting steroid treatment, outpatient lab work revealed significant lab derangements including blood glucose 649 mg/dL, sodium 126 mmol/L, elevated creatinine of 1.35 mg/dL and an anion gap of 14. The patient had no known history of diabetes. The patient did complain of polyuria and polydipsia for the previous 10 days. Hemoglobin A1C resulted at 11%. Glutamic acid decarboxylase antibody was negative, islet cell antibody was negative, zinc transporter 8 antibody was negative, and C Peptide level was low at 0.3 ng/mL. The patient was started on insulin as treatment for his elevated blood sugars and low insulin levels.

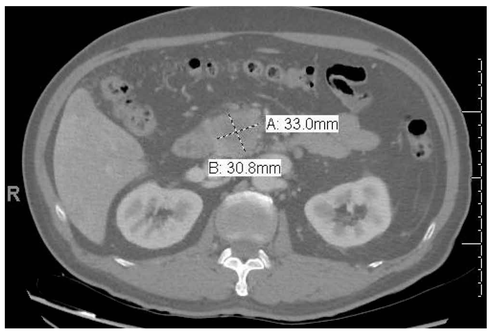

Image 3: CT Abdomen/Pelvis. Pancreatic mass noted.

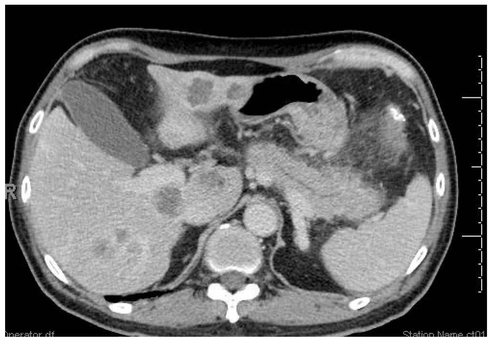

Image 4: CT Abdomen/Pelvis. Pancreatic inflammation noted.

DISCUSSION

Immune related inflammation and metastatic disease in the pancreas in combination with nivolumab immunotherapy likely caused pancreatic insufficiency resulting in new-onset diabetes. The cause of this phenomenon is presumed to be due to inappropriate activation of T-cells resulting in damage to normal tissues. Few case reports have highlighted adverse effects of nivolumab causing immune-related pancreatitis or rapid onset insulin-dependent diabetes. The case report herein demonstrates both immune-related pancreatitis and new-onset insulin-dependent diabetes developing after only one treatment with nivolumab. All medical professionals should be able to recognize immune-related adverse events due to immunotherapy medications to appropriately diagnose patients.

Immune-related adverse reaction	Severity*	Treatment Modification
Immune-related pneumonitis	Grade 2 pneumonitis	Withhold OPDIVO until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete
	Grade 3 or 4 pneumonitis	**Permanently discontinue OPDIVO**
Immune-related colitis	Grade 2 or 3 diarrhoea or colitis	Withhold OPDIVO until symptoms resolve and management with corticosteroids, if needed, is complete
	Grade 4 diarrhoea or colitis	**Permanently discontinue OPDIVO**
Immune-related hepatitis	Grade 2 elevation in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin	Withhold OPDIVO until laboratory values return to baseline and management with corticosteroids, if needed, is complete
	Grade 3 or 4 elevation in AST, ALT, or total bilirubin	**Permanently discontinue OPDIVO**
Immune-related nephritis and renal dysfunction	Grade 2 or 3 creatinine elevation	Withhold OPDIVO until creatinine returns to baseline and management with corticosteroids is complete
	Grade 4 creatinine elevation	**Permanently discontinue OPDIVO**
Immune-related endocrinopathies	Symptomatic Grade 2 or 3 hypothyroidism, hyperthyroidism, hypophysitis Grade 2 adrenal insufficiency Grade 3 diabetes	Withhold OPDIVO until symptoms resolve and management with corticosteroids (if needed for symptoms of acute inflammation) is complete. OPDIVO should be continued in the presence of hormone replacement therapy as long as no symptoms are present
	Grade 4 hypothyroidism Grade 4 hyperthyroidism Grade 4 hypophysitis Grade 3 or 4 adrenal insufficiency Grade 4 diabetes	**Permanently discontinue OPDIVO**
Immune-related rash**	Grade 3 rash	Withhold OPDIVO until symptoms resolve and management with corticosteroids is complete
	Grade 4 rash	**Permanently discontinue OPDIVO**

Adapted from the OPDIVO Summary of Product Characteristics.

*Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4)[3]
If immunosuppression with corticosteroids is used to treat an adverse reaction, a taper of at least 1 month duration should be initiated upon improvement

** Rare cases of toxic epidermal necrolysis (TEN), some of them with fatal outcome have been observed. If symptoms or signs of Stevens-Johnson Syndrome (SJS) or TEN appear, OPDIVO treatment should be discontinued and the patient referred to a specialist unit for assessment and treatment. If the patient has developed SJS or TEN with the use of OPDIVO, permanent discontinuation of OPDIVO is recommended.

Image 5: Immune related adverse reactions caused by Nivolumab.