Clinical Oncology: Case Reports

Case Report

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Ipilimumab and Nivolumab-Induced Pancreatitis and Hepatitis in Malignant Melanoma

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Abstract

Immune checkpoint inhibitors are an effective therapy option for patients with high immunogenicity malignancies, tumors that express checkpoint proteins that send an "off" signal to the body's T cells [1]. Altering the activity of T cells can help improve killing of cancer cells at the consequence of losing their ability to identify host cells. As a result, Immune-Related Adverse Effects (irAE) can occur [2]. We present a case of ipilimumab and nivolumab-induced pancreatitis and hepatitis in a woman who was treated for malignant melanoma. After two cycles of ipilimumab and nivolumab, the patient was admitted for abdominal pain, fever, and weakness, with workup revealing elevated transaminases, hyperbilirubinemia, elevated amylase, and elevated lipase. A diagnosis was made for immunotherapy-induced hepatitis and pancreatitis. Combination immunotherapy was discontinued. Treatment with oral steroids was initiated with minimal response. Mycophenolate mofetil was started and later transitioned to tacrolimus immunosuppression due to progressive neutropenia, and ultimately tapered off completely with resolution of clinical and laboratory symptoms. Early identification and prompt treatment of irAE such as pancreatitis can lead to decreased long-term consequences and morbidity including diabetes and chronic pancreatitis.

Keywords: Checkpoint inhibitors; Pancreatitis; Hepatotoxicity; Nivolumab; Ipilimumab; irAE

Introduction

Programmed Death-1 (PD-1)/ligand-1 (PD-L1) and Cytotoxic T-Cell Lymphocyte-4 (CTLA-4) inhibitors are used in combination to treat malignant melanoma [3]. Nivolumab is a human Immunoglobulin G4 (IgG4) monoclonal antibody that selectively inhibits Programmed Cell Death-1 (PD-1) activity by binding to the PD-1 receptor [1]. This interaction promotes tumor-killing effects of T cells. Ipilimumab binds to CTLA-4, an antibody that helps to boost the immune response and increase the function and growth of T cells. The combination has been effective in melanoma treatment, but results in increased irAE including diarrhea and colitis [3-6]. Almost every organ can be affected by irAE. Hepatitis can be seen as high as 13%-30% in combination therapy [7] . Asymptomatic pancreatitis can occur in 8%-27% of patients on combination therapy.

We report a unique case of acute hepatitis and pancreatitis following the use of ipilimumab and nivolumab combination therapy for a patient with malignant melanoma.

Case Presentation

A 39-year-old female with malignant melanoma of the right upper extremity was first diagnosed in 2020. She was lost to follow up until 2.5 years later when she underwent right axillary lymph node excision, received one dose of adjuvant nivolumab, experienced a seizure approximately two months after, and was found to have new brain metastases (Figure 1). She underwent a right frontal craniotomy and received one week of radiation to the brain lesion. A month after the brain metastases diagnosis, she began Cycle 1 of combination ipilimumab 3 mg/kg and nivolumab 1 mg/kg every 3 weeks. She received Cycle 2 three weeks later.

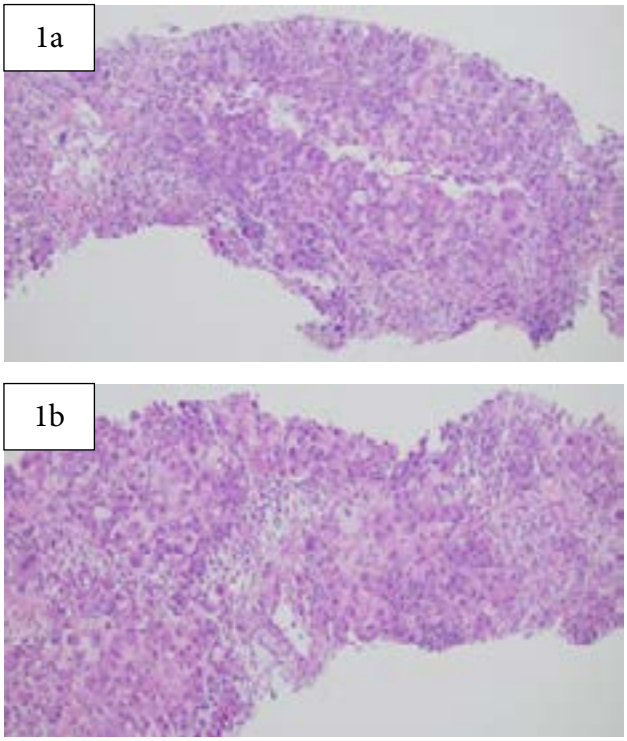

Figure 1. (1a) Liver biopsy images showing acute hepatitis pattern, with hepatocytes necrosis/dropouts, predominantly in the zone 3 (around central vein area). (1b) Hepatocytes show ballooning changes. Scattered inflammatory infiltrates are present, predominantly composed of lymphocytes and a few neutrophils. Focal cholestasis is present and there is minimal to mild portal fibrosis. Considering patient's history of immune check point inhibitor therapy, together with negative viral serology and negative markers for autoimmune hepatitis, the morphologic features are compatible with immune checkpoint inhibitor-induced liver injury.

Approximately two weeks after the second dose of ipilimumab and nivolumab (Day 37 after first dose of nivolumab), the patient presented to an outside hospital for complaints of generalized abdominal pain to the right upper quadrant lasting 5 days, weakness, and fever. Her lipase was elevated at 1454 U/L, total bilirubin 5.7 mg/dL, AST 1007 U/L and ALT 1416 U/L; her hepatitis panel was nonreactive. Imaging, including US, CT, and MRCP, were completed. Patient was transferred

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to our facility on Day 40 for further care where GI was consulted. Imaging US, CT, and MRCP all showed a non-dilated, normal biliary system. Surgical gallbladder was excluded as nonspecific gallbladder findings could be explained in context of hepatitis. Choledocholithiasis was very low on the differential given lack of corresponding imaging findings. Based on the diagnosis of exclusion, there was high suspicion for immunotherapy-induced hepatitis and pancreatitis.

As her total bilirubin continued to rise, treatment was started on Day 41 with IV fluid and electrolyte repletion, methylprednisolone IV 1 mg/kg daily, and N-Acetyl Cysteine (NAC). Her labs on Day 42 continued to elevate, with total bilirubin 15.2 mg/dL, direct bilirubin 8.8 mg/dL, AST of 1315 U/L, ALT of 1839 U/L, lipase 536 U/L, and amylase 403 U/L. Phytonadione was started for an elevated INR at 1.9. She was additionally started on diphenhydramine for significant maculopapular rash on her lower chest, abdomen, flanks, back and arms (Figure 2).

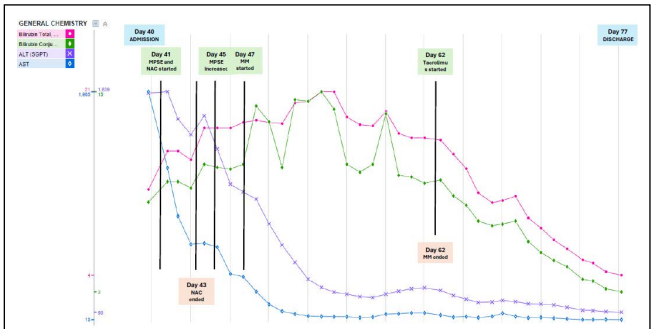

Figure 2. Graph of laboratory values throughout hospital admission.

On her third and final day of NAC, her labs were at total bilirubin 14.4 mg/dL, direct bilirubin 8.4 mg/dL, AST 662 U/L, ALT 1494 U/L, lipase 359 U/L, amylase 272 U/L, and INR 1.9. The day after discontinuing NAC her liver enzymes increased. Her steroids were increased from methylprednisolone IV 1 mg/kg daily to 1.5 mg/kg/day IV divided into two doses daily on Day 45. Minimal response was seen and mycophenolate 1000 mg twice daily was added on Day 47. A liver biopsy on Day 49 showed moderate to severe active hepatitis with bridging necrosis and cholestasis, findings compatible with checkpoint inhibitor-induced liver injury.

On Day 52, mycophenolate was tapered down to 500 mg twice daily for neutropenia. Her LFTs began to trend down, and steroids were tapered starting Day 60 to prednisone 80 mg daily. Due to persistent pancytopenia mycophenolate was discontinued, and the patient started on tacrolimus 2 mg by mouth every 12 hours with tacrolimus trough goal of 6 ng/mL to 10 ng/mL drawn three times a week (Figure 3).

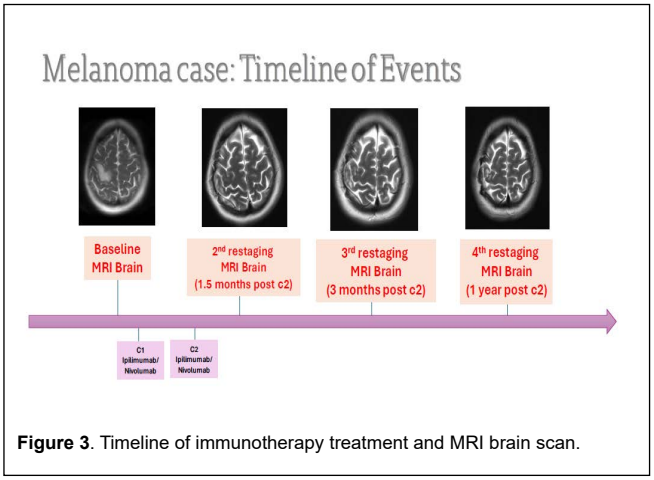

Figure 3. Timeline of immunotherapy treatment and MRI brain scan.

The patient's hospital stay was complicated by pulmonary aspergillus pneumonia found on bronchoscopy on Day 67 with a several days history of fever, chills, and cough associated with neutropenia. The patient initiated amphotericin B liposome 3 mg/kg on Day 66 and switched to isavuconazonium on Day 72. She started a slow prednisone taper on Day 71 and continued to have improved total bilirubin 3.9 mg/dL and LFTs (ALT 60 U/L; AST 18 U/L) towards the date of discharge. The patient was discharged home on Day 77 with tacrolimus 3 mg by mouth twice daily and a prednisone taper. Her tacrolimus was tapered off completely on Day 197. Post-treatment PET CT scan continued to show no evidence of FDG-avid metastases. Ultimately, the patient initiated next-line therapy with dabrafenib and trametinib (Table 1).

Discussion

Immunotherapy is an effective therapy option for patients with melanoma because the disease has high immunogenicity [1]. Cancer cells suppress T-cell mediated cytotoxicity mechanisms through checkpoint inhibition which can be overcome with the use of immune checkpoint inhibitors.

Patients receiving combination therapy with nivolumab and ipilimumab experience a higher percentage of Treatment-Related Adverse Events (TRAEs) compared to that of monotherapy. The CheckMate 067 trial reported grade 3 or 4 TRAEs in 16.3% of the patients in the nivolumab group, 55.0% of those in the nivolumab-plus-ipilimumab group, and 27.3% of those in the ipilimumab group [7]. Immunotherapy-induced hepatotoxicity is a diagnosis of exclusion. The timing of liver injury to immunotherapy treatment is a useful indicator, as hepatotoxicity onset is usually 8 weeks to 12 weeks after initiation of treatment [4-5]. Immunotherapy-associated pancreatic injury can be asymptomatic or symptomatic, with diagnosis of acute pancreatitis depending on identification of at least 2 of the following features: (1) severe epigastric pain often radiating to the back; (2) elevated serum lipase/amylase levels (at least three times the upper normal limit); and (3) characteristic findings of acute pancreatitis on abdominal imaging [6]. In a study by Friedman et al, 119 patients treated with nivolumab and ipilimumab therapy showed 20% of these patients manifested grade ≥ 3 amylase elevations, 6.3% had grade ≥ 3 lipase elevations, 20% had increased levels of both enzymes, and 1.7% developed immune-related pancreatitis [8].

Treatment of irAE is largely limited to steroids because of the inflammatory nature of the reactions [4-6]. A previous case presentation reported a 62-year-old male diagnosed with squamous cell carcinoma of lung metastatic to vertebrae on nivolumab immunotherapy who presented with severe abdominal pain and nausea and vomiting was initiated on corticosteroids and had complete resolution of symptoms [9]. Less guidance is available in the setting of steroid-refractory immunotherapy induced adverse effects. Second line therapy with mycophenolate mofetil may be considered in steroid refractory cases, and infliximab in steroid-resistant colitis and pneumonitis (without liver injury) and ATG can be trialed (acts to deplete CD4 lymphocytes) [10]. A subsequent trial of tacrolimus or sirolimus after poor response to second line therapy in irAE hepatitis can be considered. Tomsitz et al describes a case of immunotherapy-induced hepatitis requiring 5 years of treatment with tacrolimus and failure in dose tapering.

Conclusion

We describe the first case of a steroid-refractory, immunotherapy-induced hepatitis and pancreatitis in a malignant melanoma patient successfully treated with mycophenolate and transitioned to tacrolimus upon discharge. The patient's tacrolimus was successfully tapered, and she has been in remission for 16 months so far without further therapy for her malignant melanoma.

	C1D1 Ipi Nivo	C2D1 Ipi Nivo			
	Baseline (Day	**Day 21**	**Day 40**	**Day 42**	**Day 43**
	–3				
Tbili	0.2	0.2	11.7	15.2	15.2
Direct bili	-	-	7.5	8.8	8.8
Indirect bili	-	-	4.2	6.4	6.4
ALP	83	73	162	137	134
ALT	25	27	1828	1839	1620
AST	16	16	1965	1315	903
LDH	-	-	1095		
Lipase	-		688	536	359
Amylase	-	-	611	403	272
INR	-	-	1.4	1.9	1.9
	Day 44	**Day 45**	**Day 46**	**Day 47**	**Day 48**
Tbili	14.4	17.3	17.3	17.3	17.8
Direct bili	8.4	9.9	9.7	9.6	9.9
Indirect bili	6	7.4	7.6	7.7	7.9
ALP	135	155	133	129	114
ALT	1494	1645	1377	1093	1031
AST	662	671	638	410	385
LDH	-	-	-	-	-
Lipase	-	679	-	507	414
Amylase	-	516	-	134	-
INR	1.8	1.7	1.8	1.6	1.7
	Day 49	**Day 50**	**Day 51**	**Day 52**	**Day 53**
Tbili	18	17.8	17.7	19.6	19.7
Direct bili	13.6	12.6	9.7	14	13.9
Indirect bili	4.4	5.2	8	5.6	5.8
ALP	123	120	106	111	110
ALT	972	773	602	463	327
AST	258	150	90	67	49
LDH	-	-	-	-	-
Lipase	339	288	251	234	210
Amylase	112	71	70	-	-
INR	1.6	1.4	1.3	-	-
	Day 54	**Day 55**	**Day 56**	**Day 57**	**Day 58**
Tbili	20.6	20.6	18.3	17.5	17.5
Direct bili	14.5	13.4	9.9	9.4	9.9
Indirect bili	6.1	7.2	8.4	8.2	7.6
ALP	112	144	149	134	143
ALT	260	222	206	186	179
AST	46	43	43	36	41
LDH	-	-	-	-	-
Lipase	140	223	265	158	352
Amylase	-	-	-	160	
INR	1.2	1.2	1.2	1.2	1.2
	Day 59	**Day 60**	**Day 61**	**Day 62**	**Day 63**

Tbili	18.8	16.8	16.4	16.4	16.2
Direct bili	13.1	9.2	9.1	8.7	8.9
Indirect bili	5.7	7.6	7.3	7.7	7.3
ALP	150	169	202	221	209
ALT	206	230	250	257	236
AST	66	69	76	76	58
LDH	-	-	-	-	-
Lipase	255	200	-	-	-
Amylase	-	-	-	-	-
INR	1.2	1.2	1.2	1.1	1
	Day 64	**Day 65**	**Day 66**	**Day 67**	**Day 68**
Tbili	14.9	13.6	11.4	10.5	10.7
Direct bili	7.9	7.3	6.3	6	6.1
Indirect bili	7	6.3	5.1	4.5	4.6
ALP	218	193	204	214	201
ALT	195	165	139	142	155
AST	40	44	36	46	73
LDH	-	-	-	-	-
Lipase	-	-	-	-	-
Amylase	-	-	-	-	-
INR	1	1	1	1.1	1
	Day 69	**Day 70**	**Day 71**	**Day 72**	**Day 73**
Tbili	11.1	9.1	8.2	7.1	6.3
Direct bili	6.3	5	4.3	3.8	3.4
Indirect bili	4.8	4.1	3.9	3.3	2.9
ALP	193	211	252	388	365
ALT	145	128	126	119	100
AST	46	34	36	31	25
LDH	-	-	-	-	-
Lipase	-	-	-	-	-
Amylase	-	-	-	-	-
INR	1.1	1	1	1	1
	Day 74	**Day 75**	**Day 76**	**Day 77**	-
Tbili	5.3	5	4.2	3.9	-
Direct bili	2.6	2.5	2	1.8	-
Indirect bili	2.7	2.5	2.2	2.1	-
ALP	312	332	302	280	-
ALT	76	73	64	60	-
AST	18	18	20	18	-
LDH	-	-	-	-	-
Lipase	-	-	-	-	-
Amylase	-	-	-	-	-
INR	-	-	-	-	-

Table 1. Liver and pancreatic function laboratory values during hospital admission.

Declarations of interest

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Funding

This research did not receive funding.

Abbreviations

(CT) Computed Tomography, (CTLA-4) Cytotoxic T-cell Lymphocyte-4, (IgG4) Immunoglobulin G4, (irAE) Immune-related Adverse Effects, (MRCP) Magnetic Resonance Cholangiopancreatography, (NAC) N-Acetyl Cysteine, (PD-1) Programmed Death-1, (PD-L1) Programmed Death Ligand-1, (TRAEs) Treatment-Related Adverse Events and (US) ultrasound.

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