Ipilimumab and Nivolumab induced Colitis

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Background:

Ipilimumab and Nivolumab are monoclonal antibodies specifically target cytotoxic T lymphocyte associated protein 4 (CTLA 4) and programmed cell death protein (PD1). Both of these medications increase the activity of T cells against cancerous cells as well as stimulating T cell against non-cancerous tissues, such as the gastrointestinal tract. It has been reported that the incidence of colitis with Ipilimumab is five time higher than that with Nivolumab, and 13.6% with combination therapy. In this case, we present a 54 years old male who developed severe immunotherapy induced colitis with significant fluid loss as a result of combination of Nivolumab and Ipilimumab immunotherapy for advanced melanoma with metastasis to the scalp and brain. [1,2,3]

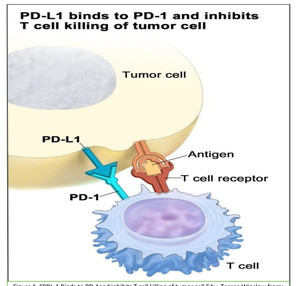

Figure 1, "PDL-1 Binds to PD-1and inhibits T cell killing of tumor cell " by Terese Winslow from: National Cancer Institute

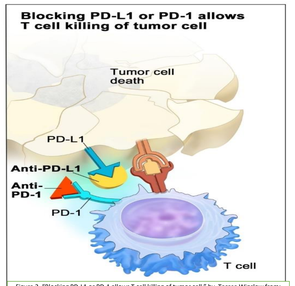

Figure 2, "Blocking PD-L1 or PD-1 allows T cell killing of tumor cell " by Terese Winslow from: National Cancer Institute

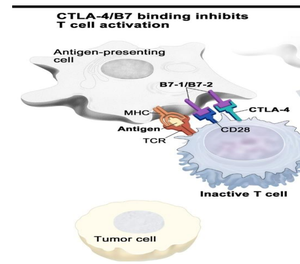

Figure 3, "CLTLA-4/B7 binding inhibits T cell activation " by Terese Winslow from: National Cancer Institute

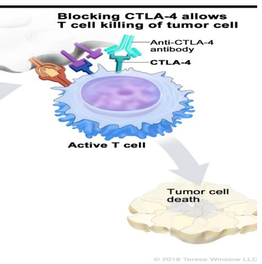

Figure 4, "Blocking CTLA-4 allows T cell killing of tumor cell " by Terese Winslow from: National Cancer Institute

	Colitis[5,7]	Diarrhea[5,7]
Grade 1	Asymptomatic	Increase of <4 stools/day
Grade 2	Abdominal pain, mucus, blood in stool	Increase of 4-6 stools/day
Grade 3	Sever pain, fever, Peritoneal signs	Increase of >7 stools/day
Grade 4	Life-threatening consequences (perforation, ischemia, necrosis, bleeding, toxic megacolon)	Life-threatening consequences such as hemodynamic collapse
Grade 5	Death	Death

Case Background:

A 54 years old male was found to have advanced Melanoma with metastasis to the scalp and brain. Thus, the patient was eligible for induction of Ipilimumab and Nivolumab.

The patient began the first cycle of therapy with single dose of Ipilimumab 246mg, and Nivolumab 82mg. One week later, prior to any additional immunotherapy, patient presented to oncology nurse clinic with history of nausea, retching, Vomiting and increased diarrhea. The patient had diarrhea with mucous but no blood probably more than six times per day after using maximum dose Loperamide. A diagnostic colonoscopy revealed mild colitis and CT scan showed thickening of large bowel from rectum to hepatic flexure. This can be occurred by Nivolumab and Ipilimumab due to Immunotherapy induced colitis.

Lab result : Stool culture (-) Clostridium difficile (-)
DNA amplification stool test (-)

In addition to fluid replacement, patient was continued on Loperamide 2mg QID PRN started by his oncologist. Patient had persistent severe diarrhoea therefore the steroid regimen was started with Methylprednisolone 80mg daily for 5 days. Unfortunately, the patient did not respond to IV Methylprednisolone over the course of 5 days and a decision was made to initiate Infliximab 5mg/kg. After the start of infliximab 350mg, the patient continued to be improved.

Follow up : After confirming immune mediated colitis , treatment with steroid and Infliximab started and the patient responded well to the treatment.

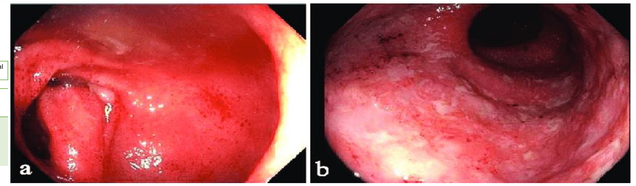

Figure 5. Endoscopic appearance of irAEs colitis in : (a) Sigmoid colon; (b) Rectum.

References:

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Discussion:

In patient with metastatic melanoma, the combination therapy of Nivolumab and Ipilimumab improved survival rate compared with monotherapy. Gastrointestinal toxicity is the most prevalent Immune related adverse events seen in immunotherapy. Immune mediated colitis is well documented as an adverse effect of immune check point inhibitors (ICIs). Combination therapy with CTLA-4 and PD1 inhibitors significantly increase immune mediated colitis and they can happen earlier in combination therapy rather than monotherapy with either of these two medications. In a large study including 676 patients, diarrhea in any grades occurred in 27-31% of patients receiving Ipilumab.[5] A literature review demonstrated that any grade colitis occurred in 45% of patients on combination therapy and 34% of patients on Ipilimumab monotherapy. PD1 inhibitors has been shown less toxic to the gastrointestinal tract than CTLA-4 agents.[1,2,3,4]

The National institute of Health and National cancer Institute "common terminology criteria for Adverse events" (CTCAE) grading scheme may be helpful for characterizing the severity of immune checkpoints induced colitis. Based on CTCAE grading scale, our patient would be categorized in grade 2 colitis due to Severe abdominal pain and mucous in the stool and grade 3 in diarrhea due to increase loose bowel to more than 6 times a day .[5]

In a recent literature review, efforts have been made to describe histology typically found in colitis caused by PD1 and CTLA4 inhibitors. This become important for the patients resistant to steroid and also important for patient facing diagnostic dilemmas.

Treatment strategies for Ipilimumab -Nivolumab induced colitis can be cessation of immunotherapy, initiation of steroid therapy and supportive treatment. In steroid refractory cases, Infliximab 5mg/kg therapy can be utilized as a second line regimen. [6]

	Management Strategies :[6 ,7]
Grade1	• **Continue immunotherapy** • Baseline investigation should be ordered • Symptomatic management: Oral fluid, Loperamide, avoid high fiber/Lactose diet
Grade 2	• Out patient management • Baseline investigation should be ordered or repeated • **Immunotherapy withheld and should not resume until symptoms or toxicity is grade One or less.** • Symptomatic management: oral fluid, Loperamide, avoid high fiber / lactose diet • if persistence of diarrhea for more than 3 days or worsens symptoms, prednisolone 0.5-1mg/kg or oral budesonide 9mg should be started • sigmoidoscopy/colonoscopy and abdominal x-ray should be arranged
Grade 3	• requires hospitalization and isolation • **Immunotherapy should permanently discontinued Anti-CTLA-4 and Withhold Anti PD-1 until toxicity is grade One or less.** • IV methylprednisolone 1-2mg /kg • gastroenterology input • CT abdomen/pelvis • daily blood test • view diet • early surgical intervention if bleeding, pain or distention • If no improvement after 72 hours infliximab 5mg/kg

Conclusion:

Immunotherapeutic agents are becoming more accessible and prevalent in medicine these days specially in Oncology field, but the side effects are not well known yet.

The wide range of presentations in immunotherapy induced side effects need early diagnosis and appropriate treatment strategies. Immunotherapy induced colitis is not an exemption from other side effects and needs early diagnosis and treatment with initiation of steroid, holding the immunotherapy agent and supportive treatment to prevent unfavourable outcomes.