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Case Report
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Immune-Related Omentitis Induced by Ipilimumab and Nivolumab in Advanced Melanoma: A Case Report

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Abstract

Introduction: Immune Checkpoint Inhibitors (ICIs) have revolutionized cancer therapy, particularly for advanced melanoma. However, their potent immune activation can result in immune-related adverse events (irAEs), affecting various organ systems.

Case Presentation: We report a case of a 54-year-old male with metastatic melanoma treated with combined ipilimumab and nivolumab, who developed immune-related omentitis - a rare irAE not previously described in literature. After three cycles of immunotherapy, the patient presented with nonspecific symptoms, including malaise, weight loss, and elevated C-reactive protein and alkaline phosphatase levels. Initial treatment with antibiotics on suspicion of infection was ineffective, and abdominal imaging revealed inflammation of the omentum majus. The patient responded well to corticosteroid therapy, leading to complete resolution of symptoms and normalization of biochemical markers. Subsequent imaging showed resolution of omental inflammation.

Discussion: This case highlights the importance of recognizing atypical irAEs in patients undergoing ICI therapy. Immune-related omentitis might represent an underdiagnosed irAEs needing management. Increased awareness and reporting of rare irAEs are essential for optimizing patient management. Further research is needed to better understand the underlying mechanisms and establish treatment guidelines for such uncommon presentations.

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Introduction

Immune Checkpoint Inhibitors (ICIs) have revolutionized cancer treatment and are now standard of care for multiple cancers. For patients with advanced melanoma, combined immunotherapy with an anti-CTLA-4 inhibitor (e.g. ipilimumab) and an anti-PD-1 inhibitor (e.g. nivolumab) have shown impressive survival rates, and is frequently used as first-line treatment [1,2]. The inhibition of CTLA-4 and PD-1 enhances the immune response against cancer cells by blocking inhibitory signals in the immune system, thus promoting immune-mediated destruction of tumor cells [3]. However, this heightened immune activation also results in immune-related adverse events (irAEs), which are characterized by autoimmune-like reactions in healthy tissue [4-6]. The organ systems most commonly affected by irAEs include the skin, lungs, gastrointestinal tract, endocrine system, and liver [4,5,7]. While most irAEs are mild or moderate and manageable with immunosuppressive treatment, severe and life-threatening irAEs can occur. Early recognition and appropriate management of irAEs are crucial for optimizing patient outcome. Expanding knowledge on the identification and treatment of irAEs is vital for improving treatment strategies and patient prognosis. Here, we present a case report of a patient experiencing immune-related omentitis, a complication that, to our knowledge, has not been previously described in literature.

Case Presentation

A 54-year-old male was diagnosed with metastatic melanoma in November 2023, with the primary tumor unknown and BRAF wildtype. At the time of diagnosis, the patient presented with multiple lung metastases and three symptomatic brain metastases, necessitating treatment with high-dose corticosteroids. Surgical resection was performed for the largest brain metastasis, after which corticosteroid use was reduced to a daily dose of prednisolone 25 mg. The patient then started combination immunotherapy with intravenous ipilimumab 3 mg/kg and nivolumab 1 mg/kg. After three cycles of immunotherapy administered every three weeks, he developed nonspecific

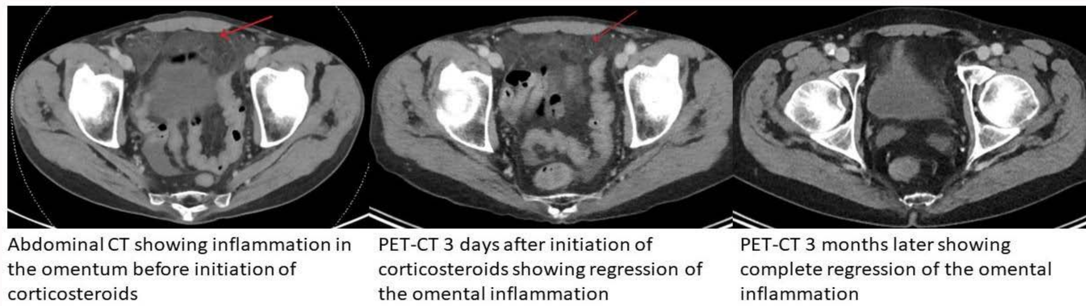

Figure 1: Inflammation of the omentum majus before and after immunosuppressive treatment.

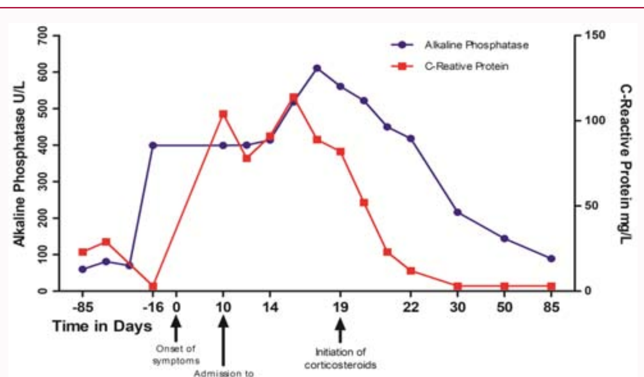

Figure 2: Changes in alkaline phosphatase (left Y-axis) and C-reactive protein (right Y-axis) for the patient experiencing immune-related omentitis. Time is described in days with day 0 representing the onset of clinical symptoms.

symptoms, including malaise, poor dietary intake, dehydration, and visual disturbances. There was no abdominal pain or stool disorder. Ten days after symptom onset, the patient was admitted to the hospital due to dehydration and significant weight loss. Blood tests showed an elevation of C-Reactive Protein (CRP) to 104 mg/L (normal range <4), and Alkaline Phosphatase (ALP) to 399 IU/L (normal range 35-105), while other laboratory results were unaffected, including cortisol ruling out adrenal insufficiency as the cause of symptoms. Except for redness of the conjunctivae, physical examination was otherwise normal. Antibiotics were initiated due to suspected infection, but all microbiological tests were negative and procalcitonin was normal, and no clinical or paraclinical improvement was observed. The patient's visual disturbances worsened, accompanied by ciliary injection in both eyes. Ophthalmologic evaluation confirmed immune-related uveitis, for which he was treated with local corticosteroids. Despite antibiotics and supportive care, the patient still experienced malaise with poor dietary intake and weight loss, CRP levels remained elevated, and ALP continued to rise, peaking at 611 IU/L. After eight days of hospitalization, an abdominal CT scan was conducted and revealed inflammation of the omentum majus, with low-grade intra- and extrahepatic biliary stasis (Figure 1). Abdominal ultrasound identified no other cause for biliary stasis, and bilirubin levels were normal, ruling out the need for surgical intervention. Due to the omental inflammation leading to low-grade biliary stasis, the patient was treated with intravenous methylprednisolone 40 mg daily. Within a few days, his clinical symptoms fully resolved, CRP normalized, and ALP levels declined. Changes in ALP and CRP are visualized in Figure 2. Three days later, a planned PET-CT scan was performed for evaluation of ipilimumab and nivolumab treatment, which revealed regression of the inflammation in the omentum majus (Figure 2). The patient was discharged from the hospital, and corticosteroids were tapered over four weeks, during which ALP levels returned to normal. Both PET-CT and MRI scans demonstrated a partial response to treatment in both intracranial and extracranial disease (Figure 3). Following corticosteroid tapering, the patient was diagnosed with adrenal insufficiency and hydrocortisone replacement therapy was initiated. Nivolumab monotherapy was continued, with no further elevations in ALP, and the patient continues to maintain a partial response to immunotherapy.

Discussion

Treatment with ICIs increases immune system activation enhancing immune-mediated destruction of tumor cells. However, this potent activation of the immune system is also associated with a range of irAEs, with approximately 90% of patients treated with the combination of ipilimumab and nivolumab experiencing an irAE of any grade [4-6,8]. While irAEs most commonly affect the skin, gastrointestinal tract, endocrine system, and liver, less common presentations are increasingly being recognized. Here, we describe a case of immune-related omentitis, that, to our knowledge, has not previously been described in literature. The patient's nonspecific symptoms, including malaise, dehydration, weight loss, and elevated ALP and CRP levels, initially led to a suspicion of infection. However, no improvement was seen after antibiotic therapy, and imaging revealed omental inflammation. Following corticosteroid treatment, both symptoms and biochemical markers normalized, suggesting that the omentitis was induced by ICI therapy. Inflammation of the omentum is a very rare condition, with only limited cases reported in the literature. In these cases, omentitis have been a result of infection, complications to surgery, or infarction [9-11]. The omentum is a layer of adipose tissue within the peritoneal cavity and acts as a protective barrier for intraabdominal infections and malignancies. It plays a crucial role in immune response and inflammation. The omentum is highly vascularized, and contains numerous immune cells organized in clusters called milky spots [12,13]. Although not previously described, it is likely that the milky spots contribute to the immune activation and inflammation observed in response to ICI therapy. The potent activation of the immune system by ICIs might cause activation of the immune cells within milky spots resulting in the inflammation seen in this case of immune-related omentitis. This case highlights several important considerations. First, clinicians should maintain a high degree of suspicion for atypical irAEs in patients receiving ICIs, especially when unexplained inflammatory markers are present. Second, immune-related omentitis might represent an underdiagnosed complication to ICIs needing awareness and management. Third, prompt initiation of corticosteroids is essential

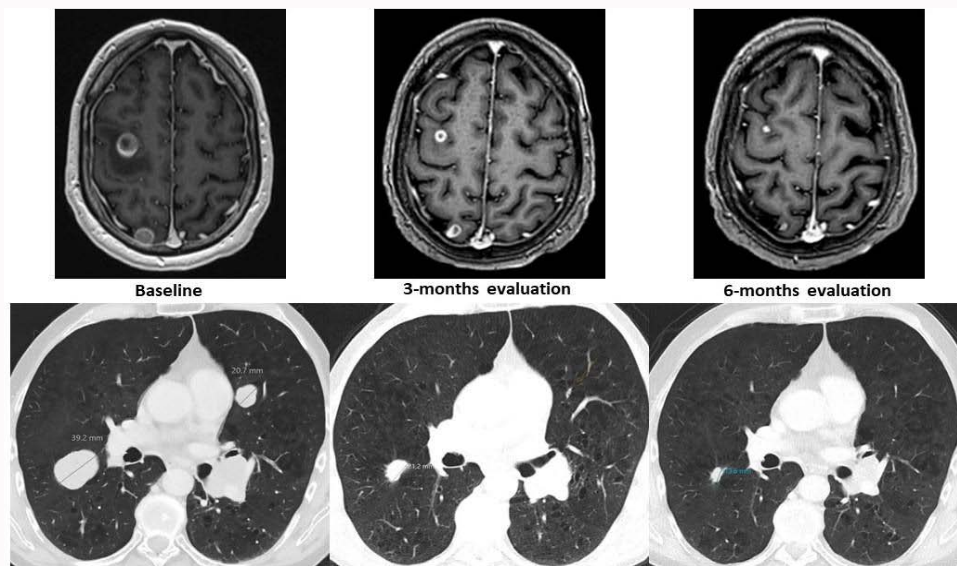

Figure 3: MRI and PET-CT at baseline, and three and six months after initiation of ipilimumab and nivolumab showing partial response on brain and lung metastases.

for controlling inflammation and preventing progression of irAEs, as demonstrated by this patient's complete recovery following treatment. Finally, this case underscores the need for increased awareness and reporting of rare irAEs like immune-related omentitis, as expanding the understanding of such events is crucial for developing more effective management strategies in the era of immunotherapy. Further research is warranted to elucidate the mechanisms behind this uncommon manifestation and to establish standardized treatment guidelines.

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