Ipilimumab and immune-mediated adverse events: a case report of anti-CTLA4 induced ileitis

Authors: Olga Venditti, Department of Medical Oncology, Universita’ Campus Bio-Medico, via Alvaro del Portillo 200, Rome, Italy. Tel. (+39) 06225411244, Fax : (+39) 06.22541.1227, o.venditti@unicampus.it

Delia De Lisi, Department of Medical Oncology, Universita’ Campus Bio-Medico, via Alvaro del Portillo 200, Rome, Italy. Tel. (+39) 06225411244, Fax : (+39) 06.22541.1227, d.delisi@unicampus.it

Marco Caricato, Department of General Surgery, Universita’ Campus Bio-Medico di Roma, Via Álvaro del Portillo, 200, 00128, Rome, Italy. Tel. (+39) 06.22541.1675 Fax: (+39) 06.22541.1936

Damiano Caputo, Department of General Surgery, Università Campus Bio-Medico di Roma, Via Álvaro del Portillo, 200, 00128, Rome, Italy. Tel. (+39) 06.22541.1675 Fax: (+39) 06.22541.1936

g.caputo@unicampus.it

Gabriella Teresa Capolupo, Department of General Surgery, Università Campus Bio-Medico di Roma, Via Álvaro del Portillo, 200, 00128, Rome, Italy. Tel.: (+39) 06.22541.1311 Fax: (+39) 06.22541.1936
g.capolupo@unicampus.it

Chiara Taffon, Department of Anatomical Pathology, Campus Bio-Medico University, Tel. (+39) 06.22541.1923, c.taffon@unicampus.it

Elisa Pagliara, Department of Radiology, Campus Bio-Medico, University of Rome, Rome, Italy. Tel. (+39) 06.22541.1633 e.pagliara@unicampus.it

Sofia Battisi, Department of Radiology, Campus Bio-Medico, University of Rome, Rome, Italy. Tel. (+39) 06.22541.1633 s.battisi@unicampus.it

Andrea Onetti Muda, Department of Anatomical Pathology, Campus Bio-Medico University, Tel. (+39) 06.22541.1106 Fax: (+39) 06.22541.1923 a.onetti@unicampus.it

Giuseppe Tonini, Department of Medical Oncology, Universita’ Campus Bio-Medico, via Alvaro del Portillo 200, Rome, Italy. Tel.: (+39) 06.22541.1201 Fax 06.22541.1227 g.tonini@unicampus.it

Daniele Santini, Department of Medical Oncology, Universita’ Campus Bio-Medico, via Alvaro del Portillo 200, Rome, Italy. Tel.: (+39) 06.22541.1243 Fax: (+39) 06.22541.1933 d.santini@unicampus.it

Corresponding author: Olga Venditti, Department of Medical Oncology, Universita’ Campus Bio-Medico, via Alvaro del Portillo 200, Rome, Italy. Tel. (+39) 06225411244, Fax : (+39) 06.22541.1227, o.venditti@unicampus.it

ABSTRACT:
**Background:** Ipilimumab is a fully human monoclonal antibody directed against cytotoxic T-lymphocyte antigen-4 (CTLA-4), a key negative regulator of T-cell activation approved by the Food and Drug Administration as of March 2011 for the treatment of metastatic melanoma. As a result of the up-regulation of the immune system, several immune-mediated adverse effects have been reported including colitis, dermatitis, hepatitis and rarely hypophysitis. The most frequent immune-mediated adverse effects described in literature include gastrointestinal toxicity such as diarrhea, colitis and case of colitis and ileitis.

**Case presentation:** In this article we describe an interesting case of immune-mediated ileitis without colitis in a 54 years old woman with metastatic melanoma treated with ipilimumab. We also discuss the management of this case and possible pathological mechanisms in the light of previous reports. **Conclusions:** The aim of this paper is to suggest further investigations concerning epigenetic and genetic analysis in order to personalize biological therapy and to reduce immune related adverse events related to ipilimumab administration.

**Key-words:**
Melanoma
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**ARTICLE**

**BACKGROUND:** Ipilimumab is a fully human monoclonal antibody directed against cytotoxic T-lymphocyte antigen-4 (CTLA-4), a key negative regulator of T-cell activation approved for the treatment of metastatic melanoma. Due to this mechanism this antibody contributes to activate immune response against tumore cells. Despite these characteristics, Ipilimumab treatment has been
associated with severe and potentially fatal immunological adverse effects due to T cell activation and proliferation. Most of the serious adverse effects are associated with the gastrointestinal tract and include diarrhea, colitis and case of colitis and ileitis. In this paper we describe a case of immune-mediated ileitis without colitis in a 54 years old woman with metastatic melanoma after three ipilimumab administrations. We also report histological and CT findings that respectively show extensive superficial ulceration, full-thickness inflammatory infiltrate and indirect sign of necrosis of the ileum wall. This findings show how a disregulation of the immune system induced by Ipilimumab can result in severe and fatal immune-mediated adverse reactions due to T-cell activation and proliferation.

CASE PRESENTATION

A 54 years old woman with previous history of malignant cutaneus melanoma came to our attention in April 2013. Due to the finding of a nodular mass located in the right iliac fossa, she underwent surgery in 2009. Pathology specimens was consistent with pigmented nodular melanoma, with vertical growth, Clark level III, Breslow tickeness 9mm. The excision margins were negative, right inguinal sentinel lymph node was positive and a subsequent dissection excluded further lymphnodal involvement (stage III B: pT4a, pN1a, pMx). A staging Fluorodeoxyglucose-PET (FDG-PET) scan was negative for local and distant disease. She started a follow up program until January 2012, when a CT scan showed multiple bilateral lung metastases and the FDG-PET scan showed pathological finding in the right iliac fossa and lumbar vertebra L3. BRAF V600E mutational analysis was carried out with the detection of exon 15 mutation. The patient started a first line treatment with Dabrafenib (150 mg orally subministrated twice daily) from May 2012 to February 2013. The FDG-PET scan performed in October 2012 proved a complete metabolic response in right iliac fossa and a partial response in L3; moreover, the CT scan demonstrated a reduction in number and size of lung metastases. The FDG-PET scan of January 2013 showed progressive disease in lung and bones (D11, L3, 4th right rib and pelvis) as well as the onset of liver metastases.
In April 2013 the patient started a second line treatment with Ipilimumab (3 mg/kg every 3 weeks for a total of 4 doses). On June 2013 two days after the third cycle of Ipilimumab the patient was admitted to our oncology unit for fever (body temperature >38.5°) without shiver, Grade 2 asthenia and nausea and Grade 1 diarrhea. The blood cultures performed during the admission were negative for bacterial growth. From the recovery metilprednisolone 2mg/Kg die intravenously was administered with clinical benefit but without a complete resolution of the fever. Considering the significant clinical benefit the patient was dismissed prescribing oral prednisone 1 mg/kg daily.

Given previous toxicity, according to the drug schedule, we omitted the 4th dose of ipilimumab until the toxicities returned to Grade 0 or Grade 1 toxicity. After two weeks, in July 2013 the patient was recovered yet to our oncology unit for persisting and deteriorating Grade 3 asthenia, Grade 2 nausea and vomiting, Grade 3 diarrhea and dehydration, even thought she was under treatment with oral corticosteroid drug.

Physical examination proved a poor hydration of skin and mucosal membranes, a diffuse pain of the abdomen, in particular in the right iliac fossa; blood examination proved anemia (Hemoglobin-Hgb- 9.60 g/dL) and hypoalbuminemia (1.74 g/dL). During the hospital admission fluids, corticosteroids (metilprednisolone 2mg/Kg die) and albumin were administered with partial resolution of symptoms. Few days later, clinical conditions worsened, because of the development of gastrointestinal (GI) hemorrhage, severe anemia (Hgb 5.20 g/dL), thrombocytopenia (platelets 52.00 x10^3/uL) and coagulation impairment (INR 1.58). Red blood cells, platelet and plasma were transfused with little benefit. In order to exclude an immune-mediated colitis [1] [2] (since none comorbidity such as intestinal bowel disease or hematological disorder, were referred at the moment of hospital admission), described in literature as a possible side effect under ipilimumab treatment, a CT scan of the abdomen was performed showing colon mucosa hyperemia and submucosa edema (figure 1).
In consideration of the CT findings a total colonoscopy was done showing red blood in the ampulla, rectum and sigmoid colon, without mucosal alterations and a hyperemic and edematous colic mucosa with extensive loss of substance. Terminal ileum biopsies confirmed the presence of superficial loss of substance, and an intense inflammatory infiltrate rich of lymphocytes and granulocytes with sporadic cryptic abscesses extending up to the muscularis mucosae tonaca. Since gastrointestinal (GI) bleeding did not stop with medical therapy, the patient underwent surgery. A subtotal colectomy and the resection of the last tract of terminal ileum was performed, with the small bowel appearing necrotic and perforated in several points for at least 40 cm of length (figure 2). Pathology showed extensive superficial ulceration and full-thickness inflammatory infiltrate rich of lymphocytes, granulocytes and eosinophils, associated with acute serositis and vessels rupture (figure 3) even if these findings, where not described in the colic tract where a normal colonic mucosa with colic glands without inflammatory infiltrate or ulceration has been found (figure 4). The patient continued steroid therapy with metilprednisolone 2mg/Kg die, and no further episodes of diarrhea or GI bleeding were reporter after surgery. A post-operative CT scan showed disease progression in all the site previously detected and appearance of diffuse peritoneal carcinomatosis; in consideration of this findings, the patients was started on a palliative care program.

Discussion and conclusions

Stage IV melanoma patients need to be treated and discussed in an interdisciplinary tumor board at centers with broad experience in this disease. Several studies investigating the mechanism of the pathogenesis have been done, showing multiple pathway involved in cellular invasion and drug resistance [3] [4]. Cytotoxic drugs such as dacarbazine (DTIC), temozolomide, taxanes, fotemustine [5] and platin should be considered as a valid choice in the management of metastatic melanoma even if new
therapeutic strategies such as immunotherapy using Ipilimumab or anti-PD1 antibodies, selectiveʈ
BRAF inhibitors like vemurafenib and dabrafenib, c-Kit inhibitors and MAPK/ERK kinase (MEK)
inhibitors have demonstrated impressive antitumor activity in clinical trials.

Ipilimumab is a fully human monoclonal antibody directed against cytotoxic T-lymphocyte antigen-
4 (CTLA-4), a key negative regulator of T-cell activation. CTLA4 is constitutively expressed on
inhibitory CD25+ CD4+ regulatory T cells (Treg) and plays a key role in Treg control of the
immune response. CTLA-4 thereby works as a physiologic “brake” on the activated immune
system. Monoclonal antibody against CTLA-4, such as Ipilimumab, prevent this feedback
inhibition, enhancing the immune response against the tumor [6] . A disregulation of the immune
system induced by Ipilimumab can result in severe and fatal immune-mediated adverse reactions
due to T-cell activation and proliferation. These immune-mediated reactions (irAEs) can potentially
involve any organ system but the most common severe immune-mediated adverse reactions are
enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and
endocrinopathy.

In the phase III trial that demonstrated an increase in survival, immune-related adverse events
occurred in approximately 60 percent of patients treated with ipilimumab; they typically tend to
occur after several weeks on treatment. Overall, severe or life-threatening (grade 3 or 4) toxicity
was seen in 10 to 15 percent of ipilimumab-treated patients, compared to 3 percent in those
receiving only gp100. The most frequent irAEs described in literature include GI AEs such as
diarrhea and colitis.

In the phase III study, severe, life-threatening, or fatal (diarrhea of 7 or more stools above baseline,
fever, peritoneal signs; Grade 3–5) immune-mediated enterocolitis occurred in 34 (7%) patients and
moderate (diarrhea with up to 6 stools above baseline, abdominal pain, mucus or blood in stool)
Grade 2 both ileitis and colitis occurred in 28 (5%) Ipilimumab-treated patients. Across all
Ipilimumab-treated patients (n=511), 5 (1%) patients developed intestinal perforation, 4 (0.8%)
patients died as a result of complications, and 26 (5%) patients were hospitalized for severe enterocolitis [7].

Although clinical presentation is similar to the one of inflammatory bowel disease (IBD), lesions distribution and pathological characteristics are different from Crohn’s disease (CD), ulcerative colitis (UC) or graft-versus host disease. The predominantly diffuse nature of the active inflammation in colonic biopsies from patients after onset of diarrhea or colitis are similar to ulcerative colitis but features of chronicity and diffuse colonic involvement distally (hallmarks of UC) were not observed. Not of all were the distinctive features of CD, including granulomas, aphthous or fissuring ulcers, and bowel wall thickening secondary to transmural inflammation. CD is primarily a disease of the proximal colon and terminal ileum whereas the majority of abnormal histologic findings in patient treated with Ipilimumab were located distally; finally, the histologic findings observed were also distinct from graft-vs.-host disease, which is characterized by prominent epithelial apoptosis and glandular destruction [8].

Berman D. et al. try to explain these different pathological findings in a recent study, showing that blockade of CTLA-4 by Ipilimumab may cause dysregulation of GI mucosal immunity as pointed out by fluctuating antibody titers against enteric flora, increased levels of neutrophil-derived fecal calprotectin, and immune infiltration into the mucosa. This autoimmune deregulation is completely different from those observed for classic IBD; the pattern of positive antibody against enteric flora observed in this study was not consistent with that for classic UC or CD. In CD, approximately half of patients are positive for anti-Saccharomyces cerevisiae antibody (ASCA), CBir flagellin antibody (anti-CBir1), and anti-I2, and <25% are positive for perinuclear antineutrophil cytoplasmic antibody (pANCA); in UC, approximately half of patients are positive for pANCA, but <10% are positive for ASCA, anti-CBir1, anti-I2, and antiOmpC [9]. In this study, the most common positive titers in patients with grade 2 or higher irAEs were to pANCA and antiOmpC, with <10% of patients positive for anti-I2 and ASCA, and <15% positive for anti-CBir1.
Finally, the fluctuating antibody titers observed in this study were also inconsistent with CD, where titers are stable over time and despite changes in disease activity. This fluctuation may reflect changes in the state of T-cell activation as Ipilimumab concentrations cross an unidentified threshold. The parallel and transient changes in antibody levels in conjunction with an increase in fecal calprotectin are consistent with dysregulated mucosa induced by CTLA-4 blockade in these non-IBD patients [10].

The autoimmune disregulation reported in some patient treated with ipilimumab can be explained by common genetic variation in the CTLA4 gene. Sanderson et al., hypothesized that the GG allele of rs7565213 (JO30), reported to have lower CTLA4 activity, correlates with a higher change of developing autoimmune symptoms and subsequently could be associated with improved prognosis. In their study of 19 patients, 3 out of 4 patients with the GG allele developed autoimmune symptoms [11]. Despite these interesting data, a subsequent study did not confirm this hypothesis since a significant association between the G allele of re7565213 (JO30) and the development of autoimmune reactions was not observed [12].

In the present case report we describe an interesting case of immune-mediated ileitis without colitis secondary to the administration of Ipilimumab. We strongly suggest clinician to consider inflammatory ileitis in differential diagnosis when the patients present persistent diarrhea/ bloody diarrhea and abdominal pain in the right iliac fossa when colitis is ruled out with colonoscopy, in order to better optimize if necessary surgical treatment.

Since the patient developed ileitis only without colitis - as reported in the most of patient in the phase III study - we can suppose that two different autoimmune pathways could be activated against colic and ileal epitopes. Further data are needed to establish which ileal cell epitopes and which specific subpopulation of the enteric flora was the main target of Ipilimumab damage. A better understanding of Ipilimumab
immune related pathway with the view of identifying a specific immune T cell subpopulation involved in these adverse reactions would also be of great interest.

Consent
Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review reported.

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Figure:

Figure 1. CT axial image during venous phase. Figure A shows a marked wall thickness (arrow) at the level of pre terminal ileum. Figure B shows a thicker wall of the ileum, with the presence of air (arrow), which is a typical sign of pneumatosis intestinalis, the lume is enlarged. These finding suggest the presence of necrosis of the ileum wall.

Figure 2. The picture show the last tract of ileum resected; as seen in this image the small bowel appearing necrotic and perforated in several points for at least 40 cm of length.

Figure 3. Terminal ileum biopsies of the last small bowel tract resected. Pathology showed extensive superficial ulceration and full-thickness inflammatory infiltrate rich of lymphocytes, granulocytes and eosinophils, associated with acute serositis and vessels rupture.
Figure 4. Colon biopsy from the colonoscopy. The pathology report describes normal colonic mucosa fragment with colic glands without inflammatory infiltrate or ulceration.

References


