Ipilimumab Treatment-Induced Distal Esophageal Dissection in a Patient with Advanced Prostate Cancer

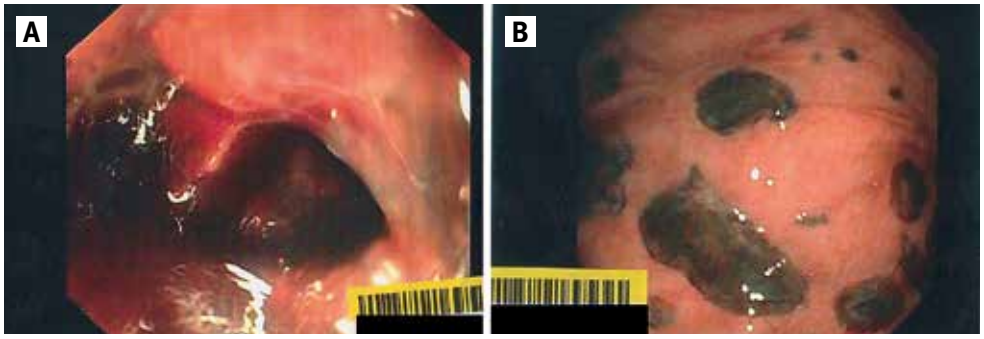
David Yardeni MD[1], Ori Galante MD[2], Lior Fuchs MD[2], Daniela Munteanu MD[1], Wilmosh Mermershtain MD[3], Ruthy Shaco-Levy MD[4] and Yaniv Almog MD[2]

[1]Institute of Gastroenterology and Hepatology, [2]Medical Intensive Care Unit, and Departments of [3]Oncology and [4]Pathology, Soroka Medical Center and Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel

KEY WORDS: necrosis, stomach, adverse reactions, monoclonal antibody, tumor cell apoptosis

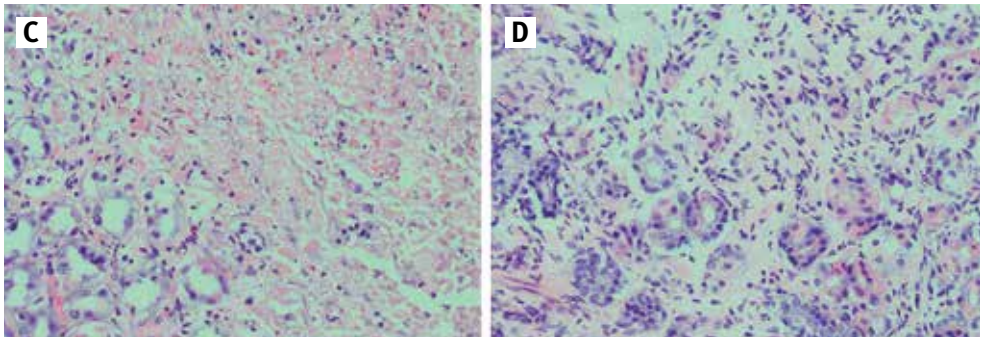
IMAJ 2016; 18: 435–436

Ipilimumab, an anti-cancer drug leading to improved overall survival among patients with metastatic melanoma [1], was recently tested as a novel treatment for advanced prostate cancer although clinical trial results are still incomplete. Ipilimumab is a fully human monoclonal antibody that blocks cytotoxic T lymphocyte antigen-4 (CTLA-4) to potentiate anti-tumor T cell response, thus promoting the activation of T lymphocytes towards proliferation. This, in turn, promotes lymphocytic infiltration in the vicinity of the tumor, increasing the probability of tumor cell apoptosis [2].



[A] Esophagogastroduodenoscopy (EGD) view of distal esophagus showing severe inflammation and esophageal dissection with true lumen on the right and false lumen on the left caused by nasogastric tube

[B] EGD view of gastric mucosa with multiple necrotic lesions



[C] Residual gastric mucosa (left lower field) adjacent to extensive necrosis represented by amorphous pink material (hematoxylin & eosin, original magnification x200)

[D] Numerous lymphocytes are evident within the gastric lamina propria (hematoxylin & eosin, original magnification x200)

In most trials the drug's adverse effects are classified as mild to moderate [3]. The main mechanism for these events was immune-related adverse events (irAE), which occurred in approximately 60% of patients. The mechanism behind the irAE is the fact that CTLA-4 is an immune checkpoint molecule involved in regulation of peripheral tolerance in order to prevent autoimmunity. Blocking of CTLA-4 is thus accompanied by adverse reactions resembling autoimmune diseases. Most irAEs affect the skin and gastrointestinal (GI) tract. Despite a benign safety profile in clinical trials, there are rare case reports of fatal lower GI complications such as severe enterocolitis [4] and colon perforations [5]. We present a case in which ipilimumab treatment was associated with high grade irAE resulting in esophageal perforation.

PATIENT DESCRIPTION

A 69 year old male with metastatic prostate cancer enrolled in a clinical trial of ipilimumab was hospitalized due to complaints of dyspnea. Because of severe hypoxemia on admission he underwent computed tomography (CT) angiography which revealed bilateral pulmonary embolism. The patient was started on subcutaneous enoxaparin. On day 2 he developed high grade fever, respiratory failure necessitating mechanical ventilation, and septic shock. The patient was transferred to the medical intensive care unit (MICU). Blood cultures yielded *Acinetobacter baumannii* bacteremia.

A nasogastric tube (NGT), inserted on admission to the ICU, drained 800 ml of fresh blood. The patient received intrave-

nous pantoprazole, and anticoagulation treatment was withheld. Nonetheless, he deteriorated to hemorrhagic shock, which was treated with massive blood transfusion. Following repletion of blood products, esophagogastroduodenoscopy (EGD) was performed revealing distal esophageal dissection [Figure 1A] and multiple diffuse necrotic lesions throughout the stomach [Figure 1B]. Retrospectively, we assume that the nasogastric tube, introduced upon admission to the ICU, had perforated the already inflamed esophageal mucosa, causing the distal esophageal perforation. Esophageal endoscopic clipping was successfully performed to obliterate the false tract and control the bleeding.

In a subsequent EGD, performed 5 days later, substantial improvement in the mucosal appearance was observed. However, 8 days after the patient's admission to the ICU, despite temporary recovery from the initial sepsis he succumbed to refractory septic shock and died.

Microscopic examination of the patient's gastric biopsies confirmed the clinical impression of multiple necrotic lesions [Figure 1C]. The necrotic foci were associated with fibrino-purulent exudate, consistent with an ulcer base. Severe chronic active gastritis with numerous lymphocytes was evident in the viable gastric mucosa [Figure 1D]. Periodic acid-Schiff stain failed to reveal fungi. Immunohistochemical stains for cytomegalovirus and herpes simplex virus were negative.

COMMENT

Based on preclinical as well as clinical studies, interference with normal ligation of CTLA-4, an immune checkpoint molecule, not only allows for activation of an anti-tumor immune response but also induction of autoimmune phenomena. Common immune related toxicities are skin toxicity, hepatitis and GI toxicity. A wide range of ipilimumab GI complications are described in the literature, ranging from simple vomiting to severe enteritis and even fatal colonic perforation. Other life-threatening non-GI adverse events include meningitis and Guillain-Barre syndrome. In the current case we present a novel fatal complication in the upper GI tract.

After ruling out other causes, our findings suggest a possible association between severe esophagogastric ulcers and ipilimumab treatment. We believe this case to be an example of high grade irAE injury. Once again, the same mechanism responsible for the medication's efficacy in cancer treatment, T cell suppression inhibitor, is also a powerful harbinger of autoimmune mediated tissue toxicity.

As far as we know, this is the first report of ipilimumab-mediated uncontrolled T cell proliferation that supposedly caused diffuse mucosal upper GI tract injury. This injury facilitated the iatrogenic esophageal dissection upon NGT insertion. These findings once again highlight the problematic nature of the use of immune tolerance-breaking biological agents that will change the course of disease in many patients on the one hand, while exposing them to new and unexpected side effects on the other. Our findings should be taken into consideration with regard to patients undergoing ipilimumab therapy for any indication.

Correspondence
Dr. D. Yardeni
Institute of Gastroenterology and Hepatology, Soroka University Medical Center, P.O. Box 151, Beer Sheva 84101, Israel
email: yardeda@bgu.ac.il

References

1. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010; 363: 711-23.
2. Peggs KS, Quezada SA, Korman AJ, Allison JP. Principles and use of anti-CTLA4 antibody in human cancer immunotherapy. *Curr Opin Immunol* 2006; 18: 206-13.
3. Haanen JB, Thienen HV, Blank CU. Toxicity patterns with immunomodulating antibodies and their combinations. *Semin Oncol* 2015; 42 (3): 423-8.
4. Beck KE, Blanfield JA, Tran KQ, et al. Enterocolitis in patients with cancer after antibody blockade of cytotoxic T-lymphocyte-associated antigen 4. *J Clin Oncol* 2006; 24 (15): 2283-9.
5. Dilling P, Walczak J, Pikiel P, Kruszewski WJ. Multiple colon perforation as a fatal complication during treatment of metastatic melanoma with ipilimumab – case report. *Pol Przegl Chir* 2014; 86 (2): 94-6.