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Case Report: CEA Elevation Can Be a Marker of Increased Inflammation During Treatment with Oxaliplatin

DANIEL KERR[1], DAMIAN LABER[1,2], NATHAN VISWESHWAR[1] and MICHAEL JAGLAL[1,2]

[1]*Department of Hematology, Morsani School of Medicine, University of South Florida, Tampa, FL, U.S.A.;*
[2]*Section of Satellite Oncology, Moffitt Cancer Center and Division of Hematology/Oncology, Tampa, FL, U.S.A.*

Abstract. *Oxaliplatin is a platinum-based chemotherapy that is an integral part of several regimens for colorectal cancer. We present the case of a patient, a 58-year-old male, who had initially presented aged 56 years with rectal bleeding for several months. His serum carcinoembryonic antigen (CEA) level at the time of diagnosis was 4.6 ng/ml. His CEA level increased significantly during oxaliplatin-based chemotherapy and declined to a near normal level after completion of therapy. There was no evidence of disease during this time and he remains disease-free. Oxaliplatin has been shown to cause an inflammatory response which appears to be one of the mechanisms of toxicity and high CEA levels have been correlated with increased inflammation. We postulate that this patient's rising CEA level was secondary to an inflammatory response to oxaliplatin-based therapy, which is further supported by the subsequent decrease after completion of chemotherapy. To our knowledge, this is the first published case of oxaliplatin-induced rising CEA level.*

Oxaliplatin is a platinum-based chemotherapy that is an integral part of several regimens for colorectal cancer (1, 2). Its mechanism of action involves formation of DNA adducts through various types of crosslinks (1). The most common oxaliplatin toxicities included peripheral neuropathy, gastrointestinal disturbances (diarrhea) and myelosuppression (thrombocytopenia) (2). The most common dose-limiting side-effect is peripheral neurotoxicity, which is believed to be mediated by multiple mechanisms. Acute neuropathy is believed to be related to calcium chelation by oxaliplatin that results in alterations of voltage-gated sodium channels, while chronic neuropathy is believed to be secondary to reduced cellular metabolism and accumulation of oxaliplatin in the dorsal root ganglia (3). Other proposed mechanisms of neurotoxicity involve generation of reactive oxygen species and increased inflammatory response [*e.g.* (4, 5)]. Wang *et al.* demonstrated an increase in mRNA levels of various cytokines and chemokines within the dorsal horn after treatment with oxaliplatin that was repressed with melatonin (5). Furthermore, oxaliplatin has also been shown to cause an increase in CD4- and CD8-positive T-cells, as well as a decrease in T-regulatory cells (6). Other toxicities related to inflammation have been reported in patients treated with oxaliplatin. One relatively rare but potentially fatal form of toxicity is interstitial pneumonitis, which has been reported in patients taking fluorouracil, oxaliplatin and leucovorin (FOLFOX) for gastrointestinal malignancies, for which pre-existing interstitial lung disease may be a precipitating factor [*e.g.* (7, 8)]. Moskovitz *et al.* reviewed 26 cases in the literature, 16 of which were fatal (7). This form of toxicity might be specific to oxaliplatin given it did not recur after re-initiation of 5-fluorouracil.

Carcinoembryonic antigen (CEA) is a glycoprotein that is expressed in normal mucosal cells but whose level can be significantly increased in colon adenocarcinomas. CEA has also been shown to be elevated in several non-neoplastic conditions, such as chronic obstructive lung disease, obesity, atherosclerosis and metabolic syndrome (9-12). It has also been shown to activate both monocytes and macrophages, giving a pro-inflammatory response that can increase adhesion of colorectal cancer cells, which may be a mechanism of metastasis (13, 14).

Here, we report a patient receiving adjuvant oxaliplatin who developed progressive elevation in his serum CEA level. He had no evidence of residual disease that could explain his elevated level of CEA. This phenomenon was transient and resolved after discontinuation of the drug. We include a discussion about the possible etiology of this phenomenon and clinical implications.

Case Report

The patient was a 58-year-old male who had initially presented aged 56 years with rectal bleeding for several months. Colonoscopy was performed revealing invasive

Correspondence to: Michael Jaglal, MD, MS, 3 Tampa General Circle, Tampa, FL 33606, U.S.A. Tel: +1 8138448712, Fax +1 8138448115, e-mail mikejaglal@yahoo.com

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adenocarcinoma 25 cm from the anal verge. His serum CEA level at the time of diagnosis was 4.6 ng/ml. Imaging did not reveal any metastatic lesions. The patient underwent robotic-assisted laparascopic rectosigmoidal resection with intraoperative liver ultrasound. Final pathology revealed poorly differentiated adenocarcinoma, 4.2 cm in greatest dimension, invading into the subserosal adipose tissue (pT3) with lymphovascular invasion. There were 3/33 cancer-positive lymph nodes. The final tumor stage was pT3N1bM0, stage 3B. Surgical margins were negative and there were no complications. The patient was then referred to Medical Oncology to initiate adjuvant chemotherapy and was started on FOLFOX (oxaliplatin at 85 mg/m^2) 6 weeks after resection. The patient's CEA level at the beginning of chemotherapy was 4.7 ng/ml, which increased to 7.7 ng/ml after three cycles (Figure 1). Treatment was held in order to determine possible disease recurrence. Computed tomographic (CT) scans were negative as was a follow-up positron-emission tomography (PET). The patient underwent colonoscopy which showed postoperative changes with no evidence of malignancy. Chemotherapy was resumed and he completed 12 cycles of FOLFOX. As shown in Figure 1, his serum CEA level continued to rise, peaking at 18.3 ng/ml during his last chemotherapy cycle. Follow-up imaging, which included PET/CT and magnetic resonance imaging of the abdomen, remained negative as was subsequent colonoscopy. After completing chemotherapy, the serum CEA level began to decline to 5.1 ng/ml. At 21 months post-resection the patient remains disease-free.

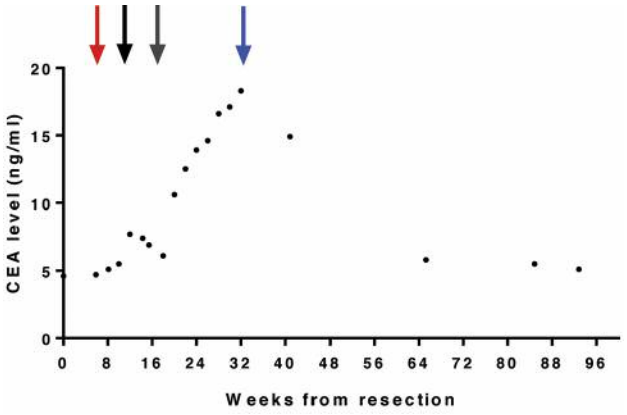

Figure 1. *Serum carcinoembryonic antigen (CEA) level for our patient from tumor resection through adjuvant chemotherapy. Fluorouracil, oxaliplatin and leucovorin (FOLFOX) was initiated 6 weeks after resection (red arrow) and held after three cycles while work-up was completed for disease progression (first black arrow). FOLFOX was restarted after work-up was negative for recurrence (second black arrow) and day 1 of cycle 12 (final cycle) was initiated 32 weeks after resection (blue arrow). CEA declined to normal after completion of chemotherapy.*

Discussion

Herein, we present a patient with colon adenocarcinoma who initially had a normal CEA level at diagnosis. His CEA increased significantly during oxaliplatin-based chemotherapy and this declined to near normal level after completion of therapy. There was no evidence of disease during this time and he remains disease-free.

For patients with colonic adenocarcinoma receiving adjuvant chemotherapy, any rise in CEA level should prompt thorough evaluation for disease recurrence; however, in the absence of disease, it should be noted that inflammatory changes could be the trigger of a CEA rise. This should especially be noted in patients who present with a normal or mildly elevated CEA level at diagnosis. While other inflammatory markers (*e.g.* C-reactive protein) were not evaluated in this patient, these may be considered in patients with a rising CEA level not explained by malignancy.

A number of studies have shown a correlation of CEA level and various inflammatory states. For example, an increased CEA level was correlated with lung disease in patients with rheumatoid arthritis (15). A study of patients with allergic bronchopulmonary aspergillosis showed an elevated CEA level that decreased after treatment (16). Furthermore, in a recent study on a large population of Korean adults (n=19,834), CEA was positively correlated with white blood cell count (17).

Oxaliplatin has been shown to cause an inflammatory response, which appears to be one of its mechanisms of toxicity, and a raised CEA level has been correlated with increased inflammation (17). Given the known inflammatory changes that can occur with oxaliplatin therapy and that the CEA level is also increased in other inflammatory conditions, we postulate that this patient's rising CEA level was secondary to an inflammatory response to oxaliplatin-based therapy, which is further supported by the subsequent decrease in CEA after completion of chemotherapy.

To our knowledge, this is the first published case of oxaliplatin-induced rising CEA level.

Conflicts of Interest

The Authors received no funding for this work and have no conflicts of interest related to this work or financial relationships to report in regard to this study.

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