



Acute pancreatitis linked to bevacizumab: A case report

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ABSTRACT

Introduction: The monoclonal anti-vascular endothelial growth factor antibody bevacizumab is increasingly being used in the treatment of malignant tumors. It is the first molecular-targeted agent used in the treatment of several ovarian cancers. The typical side effects of this drug are hypertension and proteinuria. Bevacizumab-related acute pancreatitis (AP) has not been described before, but AP associated with other chemotherapeutic agents has been reported. Research has shown that patients can develop AP when taking sorafenib, a multiple tyrosine kinase inhibitor that inhibits VEGF.

Case presentation: We explored the case of a 48-year-old woman who presented with undefined upper abdominal pain after receiving a cisplatin-gemcitabine-bevacizumab combination treatment as second-line therapy for metastatic ovarian cancer. Our patient was hospitalized because of AP after two cycles of this treatment. The patient started experiencing abdominal pain after the first course of chemotherapy. The severity and duration of this pain increased after the second cycle of chemotherapy. Her abdominal pain and elevated serum amylase disappeared when treated by chemotherapy without bevacizumab; this also improved her clinical pancreatitis.

Conclusions: AP without other etiological factors can occur in patients treated by chemotherapy. Furthermore, bevacizumab might induce the side effects of AP.

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1. Introduction

Acute pancreatitis (AP) is an inflammatory situation of the pancreas that is clinically characterized by elevation of abdominal pain and pancreatic enzyme levels in the blood.¹ Despite treatment, it may be associated with severe complications and high mortality rates. The mortality rate was 3% in patients with interstitial edematous pancreatitis and 17% in patients with pancreatic necrosis.^{2,3} The pathogenesis of AP is not fully understood. Nevertheless, a number of conditions are believed, with varying degrees of certainty, to induce this disorder, with gallstones and chronic alcohol abuse accounting for at least two-thirds of cases in the United States. Drug-induced pancreatitis rare (0.3–1.4%), although limited data suggest that the incidence may be increasing.^{4,5} Many drugs have been associated with drug-induced pancreatitis (DIP), or various mechanisms underlying DIP have been proposed.^{6,7} DIP has no distinguishing clinical features and is a rare variant of AP. The true incidence of DIP is not known and evidence has mainly

been derived from case reports and case series. The literature is scant regarding the association between DIP and bevacizumab. Because no bevacizumab-induced pancreatitis cases have been in the literature, our aim is to fill this gap.

1.1. Case report

We explored the case of a 48-year-old woman who presented with undefined upper abdominal pain after receiving cisplatin-gemcitabine-bevacizumab combination treatment as second-line therapy for metastatic ovarian cancer. In our case, serous carcinoma of the left ovary was detected in July 2015. Post-operative stage 3c patient had a high CA 125 level and PET had multiple LAP in the abdomen. Six cycles of carboplatin and paclitaxel chemotherapy were administered. Post-chemotherapy was clinically and radiologically responsive, and in the third month of follow-up, mediastinal, intra abdominal LAP and clinical progression were detected. Patient was accepted as progressive metastatic overcancer. Cisplatin + gemcitabine + bevacizumab chemotherapy was started. On the first day of cycle 1, the patient began experiencing spontaneously resolving, previously unexperienced, and non-localized abdominal pain. Although she experienced similar abdominal pain on the second day of the following cycle, this pain was more

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extended and more localized to the epigastric region. Therefore, she began using proton pump inhibitors. The severity of the abdominal pain decreased slightly, but still continued until the third cycle of chemotherapy. The patient was hospitalized during the third cycle of pre-chemotherapy assessment because of a high serum amylase level and ongoing, undefined abdominal pain. In the MRI and CT images of the patient; It has been stated that in all segments of the pancreas normal and T1 STIR sequence appearance of peripheral pancreatic ducts can not be selected because of delicate plan and soft pancreatic duct in the MR images. Lateral concha facies became evident, and these findings were found to be significant in favor of edematous pancreatitis. There was no history of pancreatitis; physical examination and laboratory and imaging studies also failed to reveal identify pancreatitis. Therefore, possible causes of pancreatitis, such as biliary, alcoholic, and autoimmune pancreatitis were excluded in the etiology. As a result of current clinical, laboratory and detailed contrast imaging; it was decided that this could be explained by edematous pancreatitis rather than metastatic peripancreatic lymph node involvement in the abdomen. At the patient's in hospital follow-up, oral intake of medication was stopped and intravenous hydration was started. By her subsequent follow-up, she had recovered from AP, and the third round of chemotherapy was started. Because AP developed again after the third round of chemotherapy, it was thought that her AP might be due to the chemotherapy. The patient was then treated for AP And, after showing a clinical response, she was given chemotherapy again without bevacizumab. Pancreatitis was not present during her subsequent follow-up and the AP episodes were thought to be related to bevacizumab. For this reason, her case was reported to the Turkish Pharmacovigilance Center (TÜFAM). The patient's chemotherapy treatment was not performed properly as a result of her AP and she showed disease progression during follow-ups and died in the intensive care unit from circulatory and respiratory insufficiency.

2. Discussion

There are many etiological risk factors for AP, including a history of gallstones, alcohol abuse, endoscopic retrograde cholangiopancreatography and manometry, trauma or surgical procedures near the pancreas, certain medications, infection, hyperlipidemia, drugs, and chronic hypercalcemia.^{8,9} Ascertaining the true incidence of drug-induced AP is dependent on clinicians excluding other possible causes and reporting all cases. It can be difficult to exclude the other causes of AP, especially in patients who have multiple comorbidities, use several medications, or have potentially unknown underlying risk factors. DIP is rare (0.3–1.4%), although limited data suggest that the incidence may be increasing.^{4,5} AP is an infrequent complication of chemotherapeutic agents; however, without challenge, the diagnosis of chemotherapy-induced pancreatitis is difficult. In our study, AP with epigastric pain and vomiting occurred within a few days of completion of the first cycle of chemotherapy. During the following cycles, AP became evident and was accompanied by elevated amylase and lipase levels and positive radiology findings. There have been reports in the literature of cases of AP due to chemotherapy, as in our case. For example, in 2010, Yucel and Warmerdam¹⁰ reported the case of a 40-year-old female who developed AP 1 day after completing her third course of capecitabine. The patient recovered after 5 days of appropriate treatment, as in our case. Also similar to our case report, the patient was administered a further course of capecitabine and AP again occurred. For this reason, capecitabine was clearly demonstrated to be responsible for the onset of AP. The chemotherapeutic agents that our current patient received were gemcitabine and capecitabine. However, it remains

unclear as to which drug caused her episode of AP, and by which mechanisms.

A total of three cases of capecitabine-induced AP have been previously published.^{11,12} Chan et al.¹² proposed that capecitabine-induced hypertriglyceridemia may have led to AP. However, we found no of AP cases induced by bevacizumab in the literature. Bevacizumab is a recombinant humanized monoclonal immunoglobulin G1 (IgG1) antibody that targets vascular endothelial growth factor A (VEGF-A) and is indicated in the treatment of various tumors (e.g., colon, lung, renal, and glioblastoma). The monoclonal antibody bevacizumab, which was recently approved for the treatment of ovarian cancer in various countries, targets all isoforms of VEGF-A, and is effective against platinum-resistant ovarian cancer, both as a monotherapy^{13,14} and in combination with chemotherapy.^{15,16} The most common side effects of this medication are headaches, high blood pressure, tiredness, sore mouth and ulcers, gastrointestinal perforation, bleeding, difficulties in wound healing, and arterial thromboemboli.

AP is not mentioned among the side effects of bevacizumab in the literature. On the other hand, sorafenib is a multiple tyrosine kinase inhibitor that has an effect on VEGF, similar to bevacizumab, and has been shown to cause clinical AP in case reports.¹⁷ As noted in a study, sorafenib may also cause to reflux of the duodenal contents into the pancreatic duct, because it causes gastrointestinal motility abnormalities; as a result, AP may occur.¹⁸ This situation cannot sufficiently explain the AP associated with bevacizumab in our case because of the differences in mechanisms of action between sorafenib and bevacizumab. The literature is scant regarding AP associated with bevacizumab; therefore, because no bevacizumab-induced pancreatitis has been reported in the literature, our aim was to fill this gap.

Conflict of interest

There is no conflict of interest between the authors.

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