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Case report

Fatal acute cardiac vasculopathy during cisplatin-gemcitabine-bevacizumab (CGB) chemotherapy for advanced urothelial carcinoma

Jessica Gruenberg [a, 1], J.Carlos Manivel [a, c, 2], Pankaj Gupta [b, d, 3], Richard Dykoski [c, 4], Hector Mesa [c, *]

[a] Department of Laboratory Medicine and Pathology, University of Minnesota School of Medicine, 420 Delaware St. SE, Minneapolis, MN 55455, USA
[b] Department of Hematology & Oncology, University of Minnesota School of Medicine, 420 Delaware St. SE, Minneapolis, MN 55455, USA
[c] Department of Pathology, Minneapolis VA Health Care System, One Veterans Drive, Minneapolis, MN 55417, USA
[d] Department of Hematology & Oncology, Minneapolis VA Health Care System, One Veterans Drive, Minneapolis, MN 55417, USA

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ABSTRACT

Background: Bladder cancer (BC) accounts for ~14,680 deaths annually in the U.S. The prognosis of advanced disease remains dismal with current therapies. A phase III intergroup trial for metastatic BC adding bevacizumab to first-line cisplatin-gemcitabine chemotherapy (GCB regimen) is currently ongoing. We report the clinical-pathologic findings of a patient who developed fatal acute cardiac microvascular toxicity while receiving this regimen.

Case report: A 66 year old man consulted for epigastric pain, nausea, intermittent diarrhea and light-headedness two weeks after receiving the first cycle of GCB chemotherapy for metastatic BC. Physical evaluation, laboratory studies and electrocardiogram (EKG) were within normal limits except for marked thrombocytopenia that was attributed to his recent chemotherapy. The patient was admitted for observation, rehydrated and started on a proton pump inhibitor. The following day, however, he experienced sudden severe chest and right upper quadrant pain. EKG showed tachycardia, ST elevations in leads V2 and V3, laboratory analyses revealed marked elevation of cardiac troponin I, and an echocardiogram showed a markedly reduced ejection fraction of 10–20%, consistent with rapidly progressive cardiogenic shock. Emergent cardiac catheterization showed no significant coronary artery disease. Sepsis work-up was negative. He became progressively hypotensive, developed multi-organ failure, and died 48 h after admission. Postmortem examination showed diffuse microvasculopathy and changes due to global hypoperfusion of 12–48 h evolution.

Conclusions: We present the first case of acute, fatal cardiac failure due to microvasculopathy most consistent with bevacizumab-associated toxicity. The findings are discussed in light of the existing literature.

1. Introduction

Bladder cancer (BC) accounts for 14,680 deaths annually and is the fifth most diagnosed cancer in the United States [1]. First-line chemotherapy with cisplatin and gemcitabine is considered the standard of care for metastatic BC. Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF) [2]. It is approved in the U.S. in combination therapy for metastatic colorectal, pulmonary non-small cell, HER2-negative breast, and renal cell carcinomas [3]. Preclinical models and phase II clinical trials have shown benefit of adding bevacizumab to standard cisplatin-gemcitabine combination chemotherapy for metastatic BC, however significant toxicity was also observed [2]. A phase III intergroup clinical trial with GCB for advanced urothelial carcinoma is therefore currently underway. We describe the pathologic findings of a patient who developed acute fatal cardiac failure while receiving the CGB chemotherapy regimen on this trial.

* Corresponding author. Minneapolis VA Health Care System, Office BB-104, One Veterans Drive, Minneapolis, 55417 MN, USA. Tel.: +1 612 467 2502; fax: +1 612 725 2079.
E-mail addresses: grue0048@umn.edu (J. Gruenberg), Juan.Manivel@va.gov (J.Carlos Manivel), Pankaj.Gupta@va.gov (P. Gupta), Richard.Dykoski@va.gov (R. Dykoski), Hector.Mesa@va.gov (H. Mesa).
[1] Tel.: +1 612 242 0077.
[2] Tel.: +1 612 467 2503.
[3] Tel.: +1 612 467 4135.
[4] Tel.: +1 612 467 2444.

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2. Case report

A 66 year old man consulted for epigastric pain, nausea, intermittent diarrhea and lightheadedness. Two weeks prior, he had been enrolled in a phase III clinical trial of CGB for recurrent metastatic urothelial carcinoma (Cancer and Leukemia Group B protocol 90601). The regimen consisted of gemcitabine (Eli Lilly & Co, Indianapolis, IN) 1000 mg/m^2 IV on days 1 and 8, cisplatin (Bristol-Myers Squibb, New York City, NY) 70 mg/m^2 IV on day 1 and bevacizumab (Genentech/Roche, San Francisco, CA) 15 mg/kg IV on day 1, of 21-day cycles. The patient had received the first cycle two weeks before admission. Past medical history included radical cystoprostatectomy with regional lymphadenectomy for stage II (pT2b, pN0) BC two years prior, brachytherapy for low-grade prostate cancer (Gleason score 6) 11 years prior, hyperlipidemia, depression and anxiety. His medications were simvastatin, mirtazapine, and zolpidem. At admission, vital signs were normal, and physical examination was unremarkable except for epigastric tenderness without rebound or guarding. Abdominal and chest x-rays did not show abnormalities. Electrocardiogram (EKG) was within normal limits (Fig. 1A). Chemistry panel and complete blood count showed only severe thrombocytopenia that was attributed to recent chemotherapy (Table 1). The patient was admitted for observation, rehydrated overnight with 3 L of normal saline, and started on a proton pump inhibitor. The following day, the patient experienced sudden onset chest and right upper quadrant pain. On physical examination, he was pale, tachypneic, tachycardic, and hypotensive. Repeat X-rays of the chest and abdomen did not show abnormalities. EKG showed tachycardia, ST elevation in leads V2 and V3 and conduction abnormalities affecting the right and left posterior fascicles (Fig. 1B). Cardiac troponin I levels were markedly elevated and blood gases showed hypoxemia and metabolic acidosis (Table 1). Echocardiogram showed a markedly reduced ejection fraction of 10–20% and global hypokinesis. Computerized tomography scan of the chest and abdomen did not show acute abnormalities. Sepsis work-up was negative, but empiric broad-spectrum antibiotics were started. To evaluate the cause of cardiogenic shock an emergent cardiac catheterization was performed, but did not show significant coronary artery disease. He became progressively hypotensive, developed elevated transaminases, worsening renal function, and severe thrombocytopenia. He died in the intensive care unit 48 h after admission. Complete autopsy was performed. Postmortem examination of the heart showed borderline cardiomegaly (weight 450 g [normal range 268–467]); histologic sections showed patchy areas of hypereosinophilic myocytes, karyorrhexis, karyolysis, focal contraction bands, and mild focal interstitial neutrophilic infiltrate with intact neutrophils. These areas represent innumerable foci of acute myocardial infarction of 12–48 h duration, each measuring ≤1.5 mm in diameter throughout the entire myocardium (Fig. 2A). At high-power examination there was evidence of extensive sloughing and apoptosis of the endothelial cells of intramyocardial capillaries and arterioles associated with karyorrhectic debris, loss of capillary contours, perivascular edema and to a lesser extent extravasation of blood cells (Fig. 2B–D). Some capillaries were markedly dilated. Lymphatics were dilated but showed well

Table 1
Vital signs and laboratory studies at admission and worst values during first 24 h of hospitalization.

Parameter	Admission	Post-admission	Normal range
RR	18	24	12–20/min
HR	87	104	60–100/min
BP	106/76	82/58	120–160/80–100 mm Hg
Troponin I	–	5.07	0.021 ng/mL
pH	–	7.16	7.33–7.43
pCO2	–	23	35–45 mm Hg
pO2	–	102	80–100 mm Hg
HCO_3	–	8	14–27 mmol/L
Lactic acid	1.8	10.6	0.4–2.0 mmol/L
ALT	27	968	12–78 U/L
AST	31	1652	15–37 U/L
Creatinine	1.5	2.4	0.7–1.2 mg/dL
Hgb	14.8	14.2	13.5–17.9 g/dL
WBC	7.8	8.0	4–11 × 10^3/μL
PLT	45	18	150–450 × 10^3/μL

RR: respiratory rate, HR: heart rate, BP: blood pressure, ALT: alanine aminotransferase, AST: aspartate aminotransferase, Hgb: hemoglobin, WBC: white blood cell count, PLT: platelets.

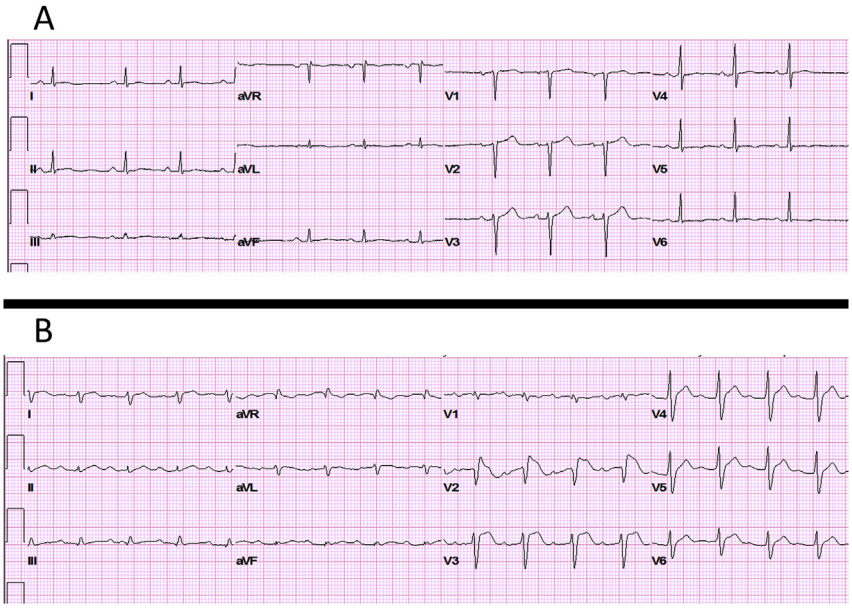

Fig. 1. Electrocardiogram (EKG). A. Admission EKG did not show abnormalities. B. EKG after 24 h. There is evidence of sinus tachycardia, broad QRS, rS pattern in leads I, aVL, V4–V6, qR in leads III and aVF, and ST-elevation in V2 and V6, consistent with acute anterior ischemia and aberrant conduction through the right and left posterior fascicles.