Acute Aortic Thrombosis Related to Adjuvant Capecitabine-Oxaliplatin in a Chinese Patient with Resected Adenocarcinoma of Sigmoid Colon

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Abstract

Aortic thrombosis is a rare disease entity which has been reported to be related to malignancy and chemotherapeutic agents. Here we present the first case in literature about a colon cancer patient with well-controlled vascular risk factors who developed acute aortic thrombosis after the first cycle of adjuvant chemotherapy with capecitabine-oxaliplatin. Risk factors and causal relationship between systemic anti-cancer agents and this condition are reviewed and discussed.

Keywords: Aortic thrombosis; Arterial thromboembolism; Capecitabine; Oxaliplatin

Introduction

Aortic thrombosis in the absence of atherosclerosis, dissection and aneurysm is extremely rare but potentially devastating due to embolic events to the brain, coronary vessels, intra-abdominal organs and extremities. Cancer therapeutic agents including chemotherapy and vascular endothelial growth factor inhibitors were reported as risk factors [1,2]. We herein present a case to describe the relationship between acute aortic thrombus and adjuvant capecitabine-oxaliplatin in a colon cancer patient without any predisposing factors.

Case Presentation

A 64-years-old Chinese lady presented with acute left lower quadrant abdominal pain. She had history of well-controlled hypertension on amlodipine 10 mg daily and hyperlipidemia on dietary control. Computerized Tomography (CT) of the abdomen and pelvis showed irregular mural thickening at sigmoid colon with uterine and small bowel invasion alongside presacral and left iliac lymph node metastasis. Sigmoidoscopy revealed an obstructing tumor 25 cm from anal verge with biopsy confirmed adenocarcinoma. Preoperative bloods including blood counts, organ function tests and coagulation profile were normal. Carcinoembryonic Antigen (CEA) was 85 ng/L (normal range <5 ng/L).

She underwent low anterior resection, total abdominal hysterectomy and bilateral oophorectomy with a defunctioning ileostomy created. Pathology showed moderately differentiated adenocarcinoma of the sigmoid colon with uterine invasion. Nine out of forty-two resected lymph nodes were involved. Overall, she had T4bN2M0, stage III colon cancer (American Joint Committee on Cancer Staging Manual 8th Edition) [3]. Her postoperative recovery was uneventful. One month after surgery, her CEA normalized to 3.7 ng/L and loopogram showed no evidence of anastomotic leak.

Six weeks post-operation, she was started on adjuvant chemotherapy with oral capecitabine at 1000 mg/m² on days one to fourteen and intravenous oxaliplatin at 130 mg/m² on day one. Her Eastern Cooperative Oncology Group (ECOG) performance status was zero. On the fifteenth day of the first cycle, she was admitted for malaise, epigastric pain and high output stoma. She reported no suspicious food intake. She was clinically stable and afebrile, but dehydrated. Abdominal examination showed mild tenderness over epigastrium with no peritoneal signs or organomegaly. Greenish loose stool was noted from her ileostomy.

Blood results showed dehydration picture with elevated white cell count to 9.8 × 10⁹/L (normal 3.7 × 10⁹/L to 9.2 × 10⁹/L), raised hemoglobin to 17.1 g/dL (normal 11.7 g/dL to 14.9 g/dL) and acute kidney injury with serum creatinine at 232 umol/L (normal 40 umol/L to 90 umol/L). Liver function was normal. Electrocardiogram showed sinus rhythm with no acute ischemic changes. Chest and
abdominal X-ray were unremarkable.

She was treated with intravenous fluid replacement. On the second day, she had severe abdominal pain, shock and hypothermia. Abdominal examination found generalized guarding and fresh blood from ileostomy. Abdominal X-ray demonstrated “stack-of-coin appearance” suspicious of ischemic bowel (Figure 1). Bloods showed picture of disseminated intravascular coagulation with pancytopenia and deranged clotting profile, and metabolic acidosis with pH of 7.20. She was immediately started on intravenous pantoprazole and broad-spectrum antibiotics. An urgent CT of the abdomen and pelvis demonstrated a thrombus in the descending thoracic aorta above the celiac axis and right portal vein, associated with extensive ischemic involvement of the small bowel, both kidneys, spleen and liver (Figure 2 and 3).

Exploratory laparotomy and resection of ischemic organs were offered. Family opted for conservative management after discussion due to expected high risk of “open-and-close” and intra operative mortality. The patient developed rapid deterioration and succumbed on the same day.

Discussion

The cause of death in this patient was extensive ischemia of the abdominal viscera secondary to an aortic thrombus. This condition is a rare life-threatening event more commonly associated with an atherosclerotic aorta, large embolus, or acute occlusion of an abdominal aortic aneurysm [4]. Although our patient had hypertension and hyperlipidemia, they were under control. Besides, neither did she have other risk factors of atherosclerosis such as smoking and diabetes, nor risk factors for embolic events including valvular heart disease or arrhythmias. Pre-operative imaging also did not reveal any evidence of aortic calcifications, atherosclerotic plaques or aneurysmal changes.

Without the above-mentioned factors, thrombosis in a non-aneurysmal, non-atherosclerotic aorta is exceedingly uncommon. Other reported risk factors for arterial thromboembolism include hypercoagulable disorders such as Protein C or S deficiency, antithrombin III deficiency, Factor V Leiden and underlying malignancy [5]. However, patient’s age being older than the typical onset of thrombotic events in familial disorders (before 50 years old) and absence of active cancer make these factors less likely to be the explained cause of our patient [6]. Without other apparent underlying causes of thrombotic tendency, chemotherapy is postulated to be the cause based on the timing of the event in relation to the initiation of therapy. This is the first report to describe a possible relationship between capecitabine-oxaliplatin and acute aortic thrombosis.

One large population based matched-cohort study using Surveillance, Epidemiology, and End Results (SEER) data identified a two-fold higher risk of arterial thromboembolism six months after cancer diagnosis (4.7% vs. 2.2%; hazard ratio 2.2; 95% confidence interval 2.1 to 2.3), which generally resolved by one year [7]. Some respondents raised the importance of vascular toxicities of cancer therapies in contributing the higher arterial thromboembolism [8].

Cisplatin is the most commonly reported culprit, with an 8.3% incidence noted in a retrospective analysis of 932 patients [1,9-13]. Underlying mechanisms include hypomagnesemia causing arterial spasm, endothelial injury, and increased von Willebrand factors [14]. Our patient was treated with oxaliplatin, which is another platinum-based chemotherapy with similar mechanism of action. Karabacak et al. [15] reported a metastatic colon cancer patient who developed upper limb ischemia after three cycles of 5-fluorouracil and oxaliplatin but not when previously given 5-fluorouracil alone, demonstrating a possible causal relationship between oxaliplatin and arterial thrombosis. A study on advanced gastric cancer also described an 1.1% incidence of arterial thrombosis in patients treated with oxaliplatin-based triplets, but was less compared to cisplatin-based triplets with incidence of 2.9% (p=0.044) [16].

Capecitabine, which is a prodrug of 5-fluorouracil, is more reported to cause coronary artery thrombosis resulting in cardiotoxicity; vascular complications in large vessels are less described. Potential mechanisms hypothesized for capecitabine/5-fluorouracil induced cardiotoxicity include vasospasm, endothelial injury, and an increase in thrombogenic substances such as fibrin peptide a [17]. These postulations could theoretically result in large vessel thrombosis as well. This was illustrated by a recently published case report involving a Korean patient with no known vascular risk
Acute aortic thrombosis could be a rare complication of chemotherapy with capecitabine and oxaliplatin. Further studies are required to understand the mechanism and predictive factors for this life threatening complication especially in patients without preexisting vascular risk factors.

References

1. Fernandes DD, Louzada ML, Souza CA, Matzinger F. Acute aortic thrombosis in patients receiving cisplatin-based chemotherapy. Curr Oncol. 2011;18(2):e97-100.
2. Herrmann J, Yang EH, Iliescu C, Marmagkiolis K. Response by Herrmann et al to Letter Regarding Article, "Vascular Toxicities of Cancer Therapies: The Old and the New-An Evolving Avenue". Circulation. 2016;134(20):e466-7.
3. Amin MB ES, Greene F, Byrd DR, Brookland RK, Washington MK, Gershewenfeld JE, et al. AJCC Cancer Staging Manual. 8th ed. Springer International Publishing; 2017.
4. Kaschwitz M, Behrendt CA, Tsilimparis N, Kolbel T, Wipper SH, Debus ES. Management of acute aortic thrombosis. J Cardiovasc Surg (Torino). 2017;58(2):313-20.
5. Tsilimparis N, Hanack U, Pismisiss G, Yousefi S, Wintzer C, Ruckert Rl. Thrombus in the non-aneurysmal, non-atherosclerotid descending thoracic aorta—an unusual source of arterial embolism. Eur J Vasc Endovasc Surg. 2011;41(4):450-7.
6. Murin S, Marelich GP, Arroliga AC, Matthey RA. Hereditary thrombophilia and venous thromboembolism. Am J Respir Crit Care Med. 1998;158(5):1369-73.
7. Navi BB, Reiner AS, Kamel H, Iadecola C, Okin PM, Elkind MSV, et al. Risk of Arterial Thromboembolism in Patients With Cancer. J Am Coll Cardiol. 2017;70(8):926-38.
8. Frere C, Martin-Toutain I, Thuny F, Bonello L. Risk of Arterial Thrombosis in Cancer Patients: Which Role for Cancer Therapies Vascular Toxicities? J Am Coll Cardiol. 2018;71(2):260.
9. Apipaisawat S, Wongpraparut N, Jacobsson L, Berkowitz H, Jacobs LE, Kotler MN. Cisplatin induced localized aortic thrombus. Echocardiography. 2003;20(2):199-200.
10. Chin SO, Lee JJ, Hwang YH, Han Jj, Maeng CH, Baek SK, et al. Aortic thrombosis resolved with enoxaparin in a patient treated with cisplatin-based regimen for small cell lung cancer. Int J Hematol. 2015;2015:248748.
11. Doganci S, Kadan M, Kaya E, Erol G, Gunay C, Demirkilic U. Acute arterial thrombosis following chemotherapy in a patient with a gastric carcinoma. Cardiovasc J Afr. 2013;24(2):e7-9.
12. Ito S, Nakamura Y, Nouni T, Sasaki Y. Acute aortic thrombosis during cisplatin based chemotherapy for gastric cancer. Intern Med. 2013;52(9):973-5.
13. Moore RA, Adel N, Riedel E, Bhutani M, Feldman DR, Tabbara NE, et al. High incidence of thromboembolic events in patients treated with cisplatin-based chemotherapy: a large retrospective analysis. J Clin Oncol. 2011;29(25):3466-73.
14. Doll DC, List AF, Greco FA, Hainsworth JD, Hande KR, Johnson DH. Acute vascular ischemic events after cisplatin-based combination chemotherapy for germ-cell tumors of the testis. Ann Intern Med. 1986;105(1):48-51.
15. Karabacak K, Kadan M, Kaya E, Durgun B, Arslan G, Doganci S, et al. Oxaliplatin Induced Digital Ischemia and Necrosis. Case Rep Vasc Med. 2015;2015:248748.
16. Starling N, Rao S, Cunningham D, Iveson T, Nicolson M, Coxon F, et al. Thromboembolism in patients with advanced gastroesophageal cancer treated with anthracycline, platinum, and fluoropyrimidine combination chemotherapy: a report from the UK National Cancer Research Institute Upper Gastrointestinal Clinical Studies Group. J Clin Oncol. 2009;27(23):3786-93.
17. Sorrentino MF, Kim J, Foderaro AE, Truesdell AG. 5-fluorouracil induced cardiotoxicity: review of the literature. Cardiol J. 2012;19(5):453-8.
18. Lee MK, Kim EY, Kim YS, Sym SJ, Kim Jh. Acute Aortic Thrombosis Following Cisaplatin Chemotherapy in a Patient with Colon Cancer. J Korean Soc Radiol. 2018;79(3):166-170.
19. Choukroun EM, Labrousse LM, Madonna FP, Deville C. Mobile thrombus.
of the thoracic aorta: diagnosis and treatment in 9 cases. Ann Vasc Surg. 2002;16(6):714-22.

20. Boon IS, Boon CS. In the nick of time: arterial thrombosis on starting combination chemotherapy in metastatic gastric adenocarcinoma. BMJ Case Rep. 2016;2016.

21. Kim JH, Jeon YS, Cho SG. Successful management of four unusual cases of acute aortic thrombus induced by chemotherapy. Clin Imaging. 2016;40(2):224-7.

22. Mathews J, Goel R, Evans WK, Shamji F, Stewart DJ. Arterial occlusion in patients with peripheral vascular disease treated with platinum-based regimens for lung cancer. Cancer Chemother Pharmacol. 1997;40(1):19-22.

23. Weijl NI, Rutten MF, Zwinderman AH, Keizer HJ, Nooy MA, Rosendaal FR, et al. Thromboembolic events during chemotherapy for germ cell cancer: a cohort study and review of the literature. J Clin Oncol. 2000;18(10):2169-78.

24. Kawachi Y, Watanabe A, Uchida T, Yoshizawa K, Kurooka N, Setsu K. Acute arterial thrombosis due to platelet aggregation in a patient receiving granulocyte colony-stimulating factor. Br J Haematol. 1996;94(2):413-6.

25. Spiel AO, Bartko J, Schwameis M, Firbas C, Siller-Matula J, Schuetz M, et al. Increased platelet aggregation and in vivo platelet activation after granulocyte colony-stimulating factor administration. A randomised controlled trial. Thromb Haemost. 2011;105(4):655-62.