



Acute aortic thrombosis in patients receiving cisplatin-based chemotherapy

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ABSTRACT

The increased risk of thrombosis in patients with active cancer has multiple causes. Acute thrombosis of the aorta is an exceedingly rare but potentially devastating complication in patients with cancer receiving cisplatin-based chemotherapy. Prompt diagnosis and definitive treatment are imperative to decrease morbidity and mortality. Early diagnosis is difficult because initial presentation is often nonspecific, requiring a high degree of clinical suspicion. We report 4 cases of acute thrombosis of the abdominal aorta in patients with cancer receiving cisplatin-based chemotherapy. We review the clinical aspects, recommended investigation, and treatment of this potentially fatal complication.

KEY WORDS

Acute, arterial, aortic thrombosis, aortic occlusion, cisplatin, cancer

1. INTRODUCTION

The increased risk of thromboembolic events in patients with malignancy is well documented and has multiple causes such as immobilization, invasive procedures, chemotherapy, and the malignancy-induced hypercoagulable state^{1,2}. Chemotherapy is considered to be one of the most important risk factors for venous and arterial thromboembolic events in the cancer setting. A large population-based study demonstrated that patients with active malignancy have a risk of thrombosis that is 4.5 times that in the non-cancer population. In patients with cancer receiving chemotherapy, the risk increases to 6 times that for a non-cancer population².

Cisplatin, a platinum-based chemotherapy drug, is the cornerstone agent in the treatment of a variety of malignancies, such as carcinomas of the ovary and lung, lymphomas, sarcomas, and germ cell tumors. One of the most important complications of cisplatin-based chemotherapy is the high risk of

thromboembolic events, namely cardiovascular complications³. In most of the cases, heart (myocardial infarction), brain (ischemic stroke), and lower limb arteries are involved⁴⁻⁶. Acute thrombosis of the aorta is an exceedingly rare but devastating complication in patients receiving cisplatin, and it requires prompt recognition and treatment⁷⁻⁹. We report 4 cases of acute thrombosis of the abdominal aorta in patients with cancer receiving cisplatin-based chemotherapy, and we review the clinical aspects and literature relating to this potentially fatal complication.

2. CASE DESCRIPTIONS

2.1 Case 1

A 60-year-old woman with history of rectosigmoid adenocarcinoma presented with disease recurrence 3 years after surgery. She had been treated with a variant of FOLFOX chemotherapy (oxaliplatin 85 mg/m², day 1; 5-fluorouracil 1000 mg/m², days 1 and 2; and folinic acid 200 mg/m², days 1 and 2). She received intravenous cisplatin 100 mg/m², day 1; 5-fluorouracil 1000 mg/m², days 1 and 2; and folinic acid 200 mg/m², days 1 and 2. Routine enhanced computed tomography (CT) imaging 6 days after completion of the 3rd cycle revealed a large non-occlusive thrombus involving the proximal abdominal aorta and extending to the right common iliac artery (Figure 1). There was no radiologic evidence of extrinsic compression of the abdominal aorta by lymphadenopathies or masses. Upon questioning, the patient described buttock pain and calf claudication. Physical exam demonstrated preserved femoral pulses bilaterally with no bruits. Patient was conservatively treated with low-molecular-weight heparin (LMWH), and her symptoms resolved. Imaging by CT 1 year later demonstrated stable aortic thrombus.

2.2 Case 2

A 53-year-old man with small-cell lung adenocarcinoma was treated with intravenous cisplatin 20 mg/m²,

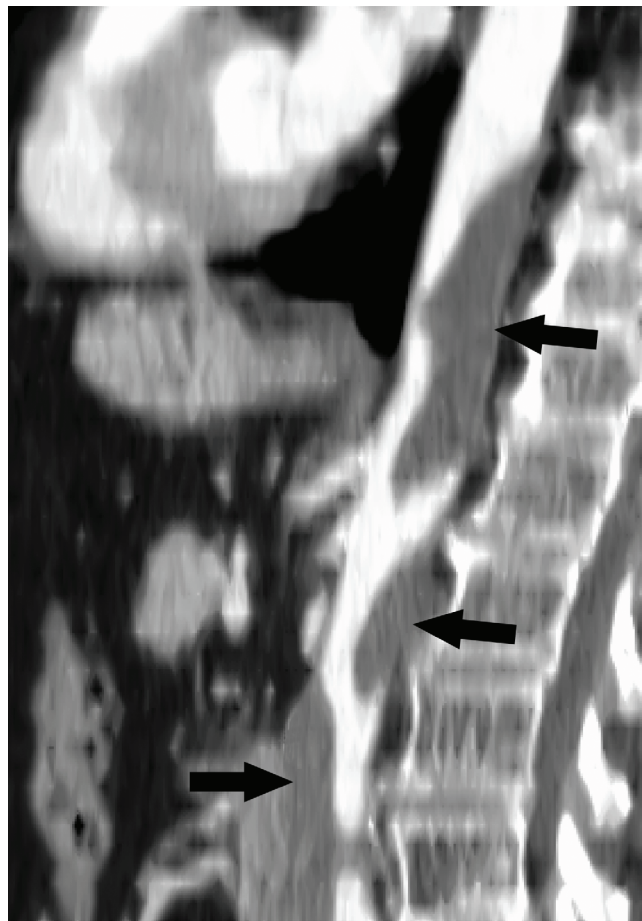


FIGURE 1 Enhanced computed tomography imaging (sagittal reformation) in a 60-year-old woman with rectosigmoid cancer receiving cisplatin-based chemotherapy shows extensive non-occlusive thrombus in the abdominal aorta (arrows).

days 1–3, and oral etoposide 100 mg/m², days 1–3, for 3 monthly cycles. Four days after completion of the last cycle, he presented with vomiting and abdominal pain. Enhanced CT imaging of the abdomen showed extensive thrombus in the abdominal aorta, extending from the level of the celiac artery to the right common iliac artery. The left renal artery was involved, and infarction of the left kidney was evident (Figure 2). There was no radiologic evidence of extrinsic compression of the abdominal aorta or above by tumour mass or enlarged lymph nodes. The patient was started on unfractionated heparin infusion, but deteriorated and died 10 days later of multiple organ failure.

2.3 Case 3

A 53-year-old man with adenocarcinoma of the lung was treated with intravenous cisplatin 75 mg/m², day 1, and vinorelbine 30 mg/m², days 1 and 8, for 4 monthly cycles. Two weeks after completion of the 4th cycle, enhanced CT imaging of the abdomen and pelvis performed for re-staging showed a large

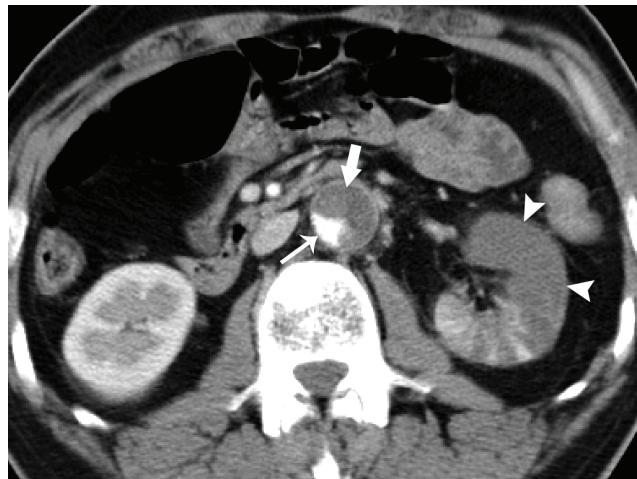


FIGURE 2 Enhanced computed tomography imaging (axial) in a 53-year-old man with small-cell lung cancer 4 days after completion of cisplatin-based chemotherapy demonstrates an acute thrombus in the abdominal aorta (arrow) causing nearly complete occlusion of the lumen (thin arrow). The left renal artery was occluded (outside current slice), resulting in infarct of the left kidney (arrowheads).

aortic thrombus originating at the level of the celiac plexus and extending into the left common iliac artery. There was no radiologic evidence of extrinsic compression of the abdominal aorta or above. Physical exam demonstrated decreased peripheral pulses, with absent posterior tibial and dorsalis pedis pulses. Even upon questioning the patient denied abdominal pain or claudication. Treatment with LMWH was started and follow-up CT imaging 9 months later demonstrated stable aortic thrombus. The patient remained asymptomatic.

2.4 Case 4

A 50-year-old woman with non-small-cell lung cancer was treated with intravenous cisplatin 75 mg/m², day 1, and vinorelbine 30 mg/m², days 1 and 8, for 4 monthly cycles. Two weeks after the last cycle, enhanced CT imaging performed for re-staging showed extensive aortic thrombus extending from the level of the superior mesenteric artery to the level above the origin of the common iliac arteries. There was no evidence of extrinsic compression of the abdominal aorta or above by tumour mass or enlarged lymph nodes. Upon questioning, the patient described mild claudication. Physical exam demonstrated absent pulses bilaterally in the dorsalis pedis and posterior tibial arteries. Patient was treated conservatively with LMWH. Follow-up CT imaging performed 6 months later showed complete resolution of the aortic thrombus.

3. DISCUSSION AND CONCLUSIONS

We report 4 cases of acute aortic thrombosis in patients with active cancer on treatment with cisplatin.

Thrombotic events tended to occur later in the treatment course, usually after cycle 3 or 4 of chemotherapy. Cisplatin is known to increase the risk of thromboembolic events and is the agent most commonly implicated in patients with cancer and arterial thrombosis^{9,10}. Cisplatin-induced vascular events tend to occur early in the course of treatment, with approximately 45% occurring during the first 2 courses of chemotherapy⁵. The mechanism by which cisplatin triggers vascular events is unknown, but endothelial damage seems to play a major role. Other proposed hypotheses are cisplatin-induced elevation of plasma levels of von Willebrand factor and drug-induced reduction of left ventricular function^{4,5,7,8}. Cisplatin is known to cause hypomagnesemia, which has been implicated in vascular events. Hypomagnesemia is associated with vasospasm, but it has not been described as a cause of thrombosis of large vessels.

Studies have suggested potential risk factors for thromboembolic complications in patients receiving cisplatin, including systemic atherosclerotic disease, liver metastasis, and antiemetic therapy with dexamethasone. In fact, most cases of cisplatin-induced arterial thrombosis described in the literature occurred in patients with at least one of the foregoing risk factors^{4,5,7,8}. None of the 4 patients described here had clinical evidence of significant peripheral vascular disease, and CT imaging demonstrated no chronic abnormalities in the abdominal aorta, such as aneurysm or atherosclerotic disease, nor enlarged lymph nodes or tumoural masses causing extrinsic compression of the abdominal aorta. In this case series, the potential risk factors for arterial thrombosis, aside from active malignancy and the use of cisplatin-based chemotherapy, were cigarette smoking in 3 patients and liver metastasis in 1 patient.

Our findings suggest an increased risk of spontaneous thrombosis of the aorta even in patients with no underlying vascular disease or other risk factors, a hypothesis that is corroborated by 3 other cases described in the literature^{7,9,11}. Importantly, as in the cases described here, symptoms may be absent or minimal. Interestingly, events tended to occur later in the treatment course, which varies from the descriptions in previous reports^{5,7,9,11}. The patient reported by Morlese *et al.*⁹ presented with an acute symptomatic thrombus in a non-atheromatous abdominal aorta, and a separate thrombus in the left ventricle 24 hours after cisplatin infusion for treatment of esophageal adenocarcinoma. The patient described by Apiyasawat *et al.*⁷ presented with symptomatic thrombosis of the aortic arch 5 days after treatment with cisplatin for cervical cancer. Her aorta was noted as non-atheromatous at surgery and pathology specimen. Recently, Dieckmann *et al.*¹¹ described a patient with germ cell tumour and with no previous cardiovascular disease or other risk factors that presented with asymptomatic abdominal aortic thrombosis diagnosed at re-staging CT after 2 cycles of cisplatin-based chemotherapy.

Early diagnosis and definitive treatment is imperative in patients with acute aortic thrombosis to prevent thrombus propagation and to obviate thromboembolism. Abdominal organ and limb ischemia is a serious complication that negatively affects outcome. Acute aortic thrombosis currently has no standardized treatment. Thrombolysis, anticoagulation, and surgery have been used with variable success in patients with cisplatin-related thrombosis. Current guidelines suggest that, in patients who suffer from acute arterial thromboemboli, initial therapy should include immediate systemic anticoagulation with unfractionated heparin. In patients undergoing embolectomy, initial therapy with unfractionated heparin, followed by long-term vitamin K antagonists or long term LMWH, is recommended^{12,13}; however, in many cases, the poor general condition of patients with cancer may contraindicate surgery.

Acute thrombosis of the abdominal aorta has a dismal prognosis if not promptly recognized and treated. As demonstrated in the cases reported here, symptoms may be subtle and underestimated by the patients. The attending physician should therefore have a high level of clinical suspicion for vascular complications in patients receiving cisplatin-based chemotherapy. Detailed clinical history and physical examination, including a check of peripheral pulses should be routinely performed. Enhanced CT imaging or duplex ultrasonography of the abdomen is recommended even when subtle clinical findings are present.

4. CONFLICT OF INTEREST DISCLOSURES

No grant support or direct or indirect sponsorship was provided by pharmaceutical companies for this study. The study was entirely conducted by the authors. DDF collected the data and wrote the manuscript. MLL and CAS wrote the manuscript. MLL also submitted the manuscript. FM elaborated the study and reviewed the manuscript.

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