Abdominal Aneurysm Rupture with Aorto-Caval Fistula after Bevacizumab Therapy: A Case Report

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Abstract

Bevacizumab is a monoclonal antibody, commonly used for treatment of stage IV non small cell lung cancer. We report the case of a patient which presented with a bevacizumab-induced aorto-caval fistula. The causality is based on the fact that no pre existing vascular abnormality was described on previous CT-scan. A surgical treatment was realized and is described in this report.

Keywords: Abdominal aneurysm rupture; Bevacizumab; Anti-angiogenic; Aorto-caval fistula

Introduction

Aortic abdominal aneurysm is an under diagnosed pathology with several major complications that can lead to death. Natural expansion of the aneurysm exposes the patient to the risk of rupture, with a poor prognostic. In rare cases, this rupture arises under the form of an aorto-caval fistula which leads to high-output cardiac failure thus requiring immediate surgery treatment. Bevacizumab is a monoclonal antibody aimed at inhibiting vascular endothelial growth factor (VEGF). It is widely used against cancer owing to its anti-vascularisation effect and is associated with an increased risk of thromboembolic events, hypertension and myocardial ischemia. We report a case of abdominal aortic aneurysm rupture leading to an aorto-caval fistula in a patient with unknown fast-expanding aneurysm after bevacizumab therapy.

Case Presentation

We present a 66-year-old man diagnosed with lung adenocarcinoma discovered at a metastatic stage. The only cardiovascular risk factor he presented is smoking for 45 years. He never had signs of hypertension, hypercholesterolaemia or arterial ischemic events. According to standards of care, he received a first chemotherapy with cisplatine perometrexed and bevacizumab. As planned, he came into the service 21 days after to receive a second chemotherapy injection.

He presented with a general asthenia. He had sleeping troubles and temporary back pain treated with anti-inflammatory drugs at home. On examination, blood pressure was 105/56 mmHg and he had a temperature of 38.6 °C. The abdomen was not pathological, there was no rigidity or pain, no palpable mass. There was no urination complain. The pulmonary auscultation found localized crackles in the right inferior lobe. Blood samples were taken in peripheral and central catheters, as well as urine sample. A thoracic radiography found a right inferior opacity and the patient was treated with ampicillin and levofloxacin. The blood investigations found an inflammatory syndrome with C-reactive protein (CRP) 171 mg/L, no change in white cells count but low platelet count 48 x 10⁹/L. In the urine sample, white cells count was elevated to 2500/mm³. The blood and urine cultures were positive in all sites with an Escherichia Coli fully sensible to the given antibiotherapy. After 48 hours, blood inflammatory syndrome decreased, CRP 99 mg/L, fever and clinical status were stable.

The patient had a sudden hemodynamic deterioration with cardiac frequency 128 bpm, blood pressure 85/56 mmHg and temperature 40.8°C. His general condition worsened rapidly and he went into shock. Blood lactates were elevated to 5 mmol/L. In the absence of specific complains or findings on examination, a computed tomography (CT) scan was performed. It found an aortitis with aorto-ilio-caval fistula explaining the shock (Figure 1). The aortic rupture was precisely localized on the iliac bifurcation in front of the right iliac vein. Owing to the patient’s background (metastatic
lung cancer) and the localization of the fistula, an emergency hybrid surgical treatment was performed.

Under general anesthesia, an approach to the right common femoral artery was first performed in order to set a covered aorto-uni-iliac endograft (reference ZAUI-28-130-ZT, Cook) deployed under scopic control just below renal arteries. In a second time, an approach of the left scarpa was performed to set an endovascular occluder in the left iliac artery (reference ZIP-20-ZT) and the left lower limb was revascularized by performing a right-left femoral crossover bypass (Figure 2). Immediately after exclusion of the fistula, haemodynamics greatly improved and amine drugs were stopped during the intervention. The patient could get out of the intensive care unit after 48 hours.

The recovery was very satisfying and the patient went back home 10 days after. On leaving the hospital, the patient was significantly improved in terms of cardio-respiratory function with a well-functioning bypass. On an oncological point of view, the response was almost complete after a single chemotherapy treatment. After one month recovery, his performans status was evaluated to 1 and a surveillance could have been proposed. The follow-up CT scan showed a well-standing endograft with permeable renal arteries and the absence of type 1 endoleak. However it showed a type 2 endoleak in front of a pair of lumbar arteries without refilling the aorto-caval fistula. The vena cava was fully permeable.

**Discussion**

Aorto-caval fistula is a rare complication of abdominal aortic aneurysm (AAA), occurring in 3-6 % of AAA ruptures. Clinical presentation is usually acute with high-output cardiac failure, abdominal pain and shock [1]. The most frequent cause is the expansion of atheromatic aneurysm resulting in inflammation-mediated adhesion to the adjacent vena cava. Other causes include penetrating abdominal trauma, iatrogenic trauma at lumbar disc surgery and connective tissue disorders [2]. An infectious etiology is not common though Belyavskaya et al. [3] reported one case of aorto-caval fistula due to *Salmonella typhimurium* infection [3].

In our case, the patient was not known for having abdominal aortic aneurysm. The pre-therapeutic CT scan performed one day before treatment did not find evidence for abdominal aneurysm (Figure 3). Less than one month after, CT found a ruptured aneurysm of 60 mm diameter with aorto-caval fistula. The growth of an aortic abdominal aneurysm is commonly 2-3 mm/year in average [4,5]. In the published literature, factors associated with an increased rate of AAA expansion are aneurysm size, smoking, chronic obstructive pulmonary disease, female gender and hypertension [6]. In addition, some drugs have been suspected to play a role in AAA expansion or rupture, mainly due to hypertensive action. For instance, long-term treatment with glucocorticoids has been associated with aortic aneurysm ruptures in numerous case reports, though it is not clear whether the ruptures have been caused by the underlying disease, the drug treatment, or combinations thereof [7].

Our patient had no cardiovascular risk factors as he had stopped smoking but he was treated with chemotherapy including bevacizumab. In a single-center retrospective study over 10 years, Martin et al. did not find an increased aneurysm growth with cytotoxic chemotherapy compared with patients not undergoing treatment for malignancy [8]. We found only one case from Palm et al. [9] reporting AAA enlargement and rupture in a patient receiving chemotherapy. However in this case, chemotherapy was including steroids and the expansion time to the rupture took almost one year [9].

Our patient presented a very fast aneurysm growth with aorto-caval fistula in a septic context but which was not on the first plane. Bacteriological documentation was available and response to
antibiotherapy was clinically and biologically satisfying. Symptoms stopped as soon as the fistula was controlled by endograft; urine, blood and catheters cultures remained sterile after intervention. Among all risk factors that could explain such evolution, bevacizumab therapy remains the most plausible.

Anti-angiogenic therapies have been developed in the last decade in order to interact with tumor growth angiogenesis. Anti-VEGF molecules like bevacizumab have shown successful results in lung cancer [10]. However, systemic VEGF inhibition disrupts endothelial homeostasis and accelerates atherogenesis [11]; it has serious cardiovascular side effects including hypertensive emergencies and arterial thromboembolic events encompassing myocardial infarction, cerebrovascular insults, and peripheral or mesenteric ischemia [12]. A recent meta-analysis confirmed an increase of the risk of hypertension, arterial thromboembolism, cardiac ischemia and cardiac dysfunction under angiogenesis inhibitors in treatment of malignancy [13].

Finally, though there is theoretical background, bevacizumab is not specifically incriminated in abdominal aneurysm rupture or expansion. Baek et al. [14] reported a case of AAA rupture in a patient receiving intravitreal bevacizumab recurrently [14], and Jeanny et al. [15] presented a case of aortic dissection in a patient treated for malignancy with bevacizumab [15].

We report here for the first time the case of a major and fast expansion of abdominal aortic aneurysm in a patient with no specific risk factors after treatment with bevacizumab. Owing to a close surveillance during chemotherapy, the patient could have been treated successfully. This reinforces the idea of a dedicated vascular surveillance for patients receiving bevacizumab, which may not be a rare situation as pulmonary cancer is the most frequent cancer associated to AAA [8]. A systematic and exhaustive vascular exploration could be of interest before treatment with anti-VEGF.

References