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UNEXPECTED LARGE-VESSEL VASCULITIS IN COLON ADENOCARCINOMA TREATED WITH BEVACIZUMAB

Daniela Ribeiro Alves[1], Cátia Barra[2], João Fonseca[1], João Pedro Gomes[3], Ana Borges[2]

[1] Department of Internal Medicine, Unidade Local de Saúde da Região de Aveiro, Aveiro, Portugal
[2] Department of Internal Medicine, Unidade Local de Coimbra, Coimbra, Portugal
[3] Department of Internal Medicine, Unidade Local de Saúde Gaia/Espinho, Vila Nova de Gaia, Portugal

Corresponding author's e-mail: dralves94@gmail.com

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ABSTRACT

Large-vessel vasculitis is a rare inflammatory disorder affecting the aorta and its major branches and may, in rare cases, be drug-induced. The association with bevacizumab is highly unusual, with only 2 reported cases, both in combination therapy with granulocyte colony-stimulating factor. We report the case of a 47-year-old man with metastatic colon adenocarcinoma treated with chemotherapy and bevacizumab, who was subsequently diagnosed with inflammation of the ascending and descending thoracic aorta and the aortic arch, consistent with large-vessel vasculitis. This is the first documented case of aortitis associated solely with bevacizumab. Although rare, clinical suspicion and early diagnosis are essential, given the potential for severe complications. Imaging plays a pivotal role, particularly in the absence of suggestive clinical features.

KEYWORDS

Bevacizumab, large-vessel vasculitis, aortitis, colon adenocarcinoma, pharmacovigilance

LEARNING POINTS

- Bevacizumab, although generally well tolerated, can, in rare cases, cause large-vessel vasculitis, even in the absence of concomitant granulocyte colony-stimulating factor therapy.
- Clinical presentation of drug-induced aortitis may be subtle or asymptomatic, and imaging studies such as ^{18}F-fluorodeoxyglucose positron emission tomography or magnetic resonance angiography play a key role in diagnosis.
- Recognition and prompt reporting of unexpected vascular toxicities are essential for pharmacovigilance, particularly as antiangiogenic agents become increasingly used in oncologic treatment regimens.

INTRODUCTION

Large-vessel vasculitis is a rare inflammatory condition involving the aorta and its major branches, which may be primary or secondary, including drug-induced forms[1]. Bevacizumab, an antiangiogenic agent widely used in the treatment of metastatic solid tumours, is only rarely associated with this adverse effect. To date, 2 published cases of bevacizumab-associated aortitis have involved

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concomitant granulocyte colony-stimulating factor (G-CSF) therapy. The clinical presentation of drug-induced aortitis is often nonspecific and may go unnoticed in the absence of systemic manifestations or laboratory evidence of inflammation[2]. In such cases, imaging plays a crucial diagnostic role.

We report the case of a 47-year-old man with metastatic colon adenocarcinoma, treated with chemotherapy plus bevacizumab, in whom large-vessel vasculitis was incidentally diagnosed during oncological reassessment, without significant clinical manifestations, highlighting the importance of recognizing this potential adverse drug reaction.

CASE DESCRIPTION

A 47-year-old man, with no relevant past medical history and no regular medication, presented with several weeks of abdominal pain. Abdominal computed tomography scan revealed diffuse thickening of the descending colon wall and suspected peritoneal carcinomatosis. He underwent subtotal colectomy, sub segmentectomy and excision of peritoneal nodules. Histopathological examination confirmed colon adenocarcinoma with peritoneal metastases.

Following multidisciplinary discussion, systemic chemotherapy was initiated with 5-fluorouracil, oxaliplatin, leucovorin, and folinic acid (FOLFOX) for nine cycles, five of which were combined with bevacizumab.

Four weeks after the last chemotherapy cycle, a ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) scan was performed to reassess disease extent, revealing persistent peritoneal metastases and additional increased FDG uptake in the walls of the ascending and descending thoracic aorta and the aortic arch, consistent with active large-vessel vasculitis (SUV max: 2.7) *(Fig. 1A)*.

The patient was referred to Internal Medicine Department for etiological investigation and differential diagnosis of aortitis. On history-taking, the only relevant symptom was transient pain in the temporomandibular joint without masticatory claudication, occurring three weeks after chemotherapy initiation. On physical examination, he was hemodynamically stable and afebrile. Extensive infectious and autoimmune screening was negative, including blood cultures, serologies for human immunodeficiency virus, hepatitis B and C, syphilis, antinuclear antibodies and anti-neutrophil cytoplasmic antibodies.

Given the absence of additional clinical abnormalities and normal inflammatory markers (C-reactive protein: 0.47 mg/dl normal, range <0.5 mg/dl), and considering the hypothesis of chemotherapy-induced vasculitis, more specifically related to bevacizumab, glucocorticoid therapy was deferred, pending repeat imaging at a longer interval after chemotherapy cessation.

Four months after discontinuation of cytotoxic therapy, a follow-up ^{18}F-FDG PET scan confirmed persistent, unchanged aortitis, prompting the initiation of oral prednisolone 20 mg/day for 4 weeks, followed by a 2-month taper. Post-treatment ^{18}F-FDG PET showed persistent aortic uptake, however in less extension (SUV max: 2.5) *(Fig. 1B)*, and, at 12-month follow-up, thoracoabdominal magnetic resonance angiography demonstrated complete resolution of the inflammatory process *(Fig. 2)*.

A final diagnosis of large-vessel vasculitis associated with bevacizumab was established and the adverse event was reported to the national pharmacovigilance authority.

DISCUSSION

The present case is noteworthy as the first report of aortitis associated solely with bevacizumab, without the confounding presence of G-CSF, thus contributing to pharmacovigilance literature. Additionally, it highlights a presentation with minimal clinical symptoms and normal inflammatory markers, diagnosed incidentally on imaging.

Drug-induced large-vessel vasculitis, although rare, is a recognized complication most frequently linked to penicillins, allopurinol, thiazide diuretics, fluoroquinolones[3] and hematopoietic G-CSF[1]. Isolated G-CSF induced aortitis has been reported[4], whereas the association with

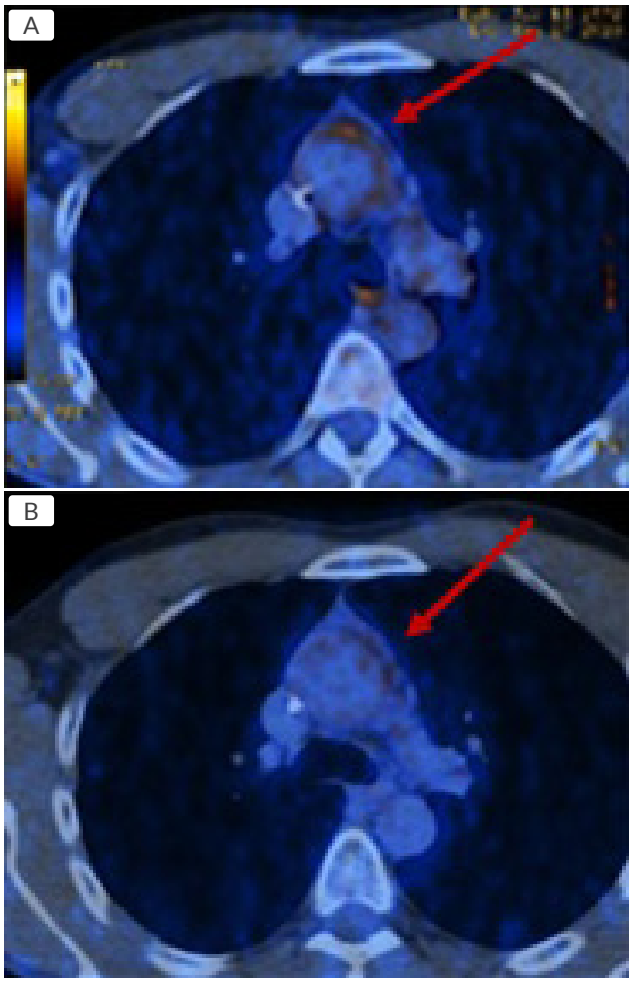


Figure 1. *A) First ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) scan showing increased FDG uptake in the walls of the ascending and descending thoracic aorta and the aortic arch (arrow); B) ^{18}F-FDG PET scan showing a decrease in aortic FDG uptake (arrow), 1 month after starting glucocorticoid therapy.*

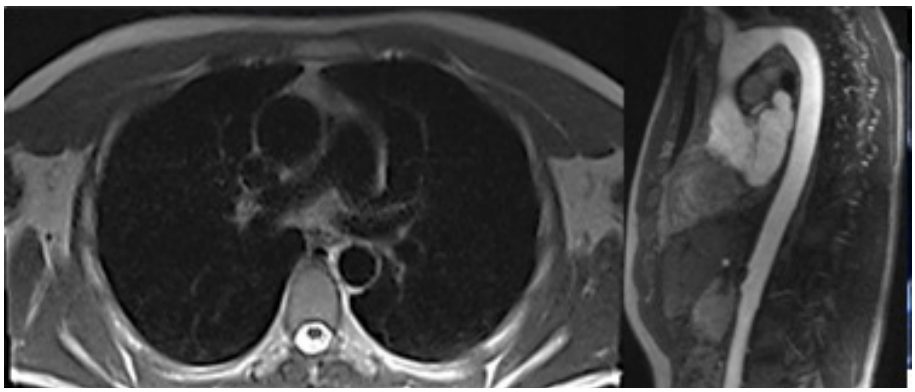


Figure 2. Thoracoabdominal magnetic resonance angiography, at 12-month follow-up.

bevacizumab is particularly uncommon, with only 2 prior cases described. The first involved a 57-year-old woman with advanced lung adenocarcinoma who developed fever on day 7 after chemotherapy with bevacizumab and G-CSF, 23 days later diagnoses as periaortitis[3]. The second case described a 47-year-old woman with ovarian carcinoma who developed fever on day 8 after chemotherapy plus bevacizumab and G-CSF, with aortitis diagnosis 18 days after treatment initiation[5].

Bevacizumab is a recombinant humanized monoclonal antibody widely used in oncology for the treatment of various metastatic cancers, including colorectal, breast, lung, renal and brain tumours. Its mechanism of action involves inhibition of angiogenesis through neutralization of vascular endothelial growth factor (VEGF) A, blocking its binding to receptors and preventing the formation of new blood vessels necessary for oxygen and nutrient supply to tumour cells, thereby slowing their proliferation[2]. Although generally well-tolerated, bevacizumab has been associated with cardiovascular adverse events such as hypertension, arterial and venous thromboembolism, haemorrhage, aneurysm formation and arterial dissection[6].

The exact pathophysiological mechanism of bevacizumab-induced aortitis remains unclear. It is hypothesized that VEGF inhibition may disrupt the balance between vascular injury and endothelial repair. VEGF is essential for mobilizing endothelial progenitor cells, which are critical for vascular repair. Its inhibition may therefore impair regenerative capacity, potentiating vascular injury induced by chemotherapy[3].

The diagnosis of aortitis can be challenging due to its nonspecific clinical presentation. In some cases, as in the present report, it is incidentally detected on imaging[7]. Other patients may present with persistent fever and upper abdominal or back pain, symptoms that in the chemotherapy setting should raise suspicion[2]. Imaging is frequently pivotal in diagnosing large-vessel vasculitis, as clinical and laboratory findings are nonspecific. Contrast-enhanced computed tomography is useful to detect aortic wall thickening indicative of inflammation. Magnetic resonance imaging, computed tomography angiography and ^{18}F-FDG PET are also valuable for demonstrating aortic wall oedema or increased glucose uptake, suggestive of inflammation[8]. Notably, the diagnostic yield of these modalities decreases rapidly after glucocorticoid initiation. Therefore, they should preferably be performed before or within the first week of treatment to preserve their diagnostic value.

Differential diagnosis should include and exclude other causes of large-vessel vasculitis such as infections, autoimmune diseases or other drugs with vasculogenic potential[7].

This case highlights the importance of recognizing unexpected vascular toxicities associated with antiangiogenic agents. Although rare, clinicians should be aware of this potentially serious complication. Reporting such adverse events to pharmacovigilance systems is essential to ensure early identification of new safety signals, especially for drugs increasingly used in combination regimens.

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