Annals of Case Reports
D'Introno A, et al. Ann Case Rep: 9: 101859
www.doi.org/10.29011/2574-7754.101859
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Case Report

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Long-Time Conservative Treatment and Off-Label Use of Delafloxacin in Abdominal Aortic Graft Infection: Case Report

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Citation: D'Introno A, Cavallo M, Loparco F, Quarato L, Perrone L, et al. (2024) Long-Time Conservative Treatment and Off-Label Use of Delafloxacin in Abdominal Aortic Graft Infection: Case Report. Ann Case Report 9: 1859. DOI: 10.29011/2574-7754.101859

Received: 21 June 2024; **Accepted:** 26 June 2024; **Published:** 28 June 2024

Abstract

Abdominal aortic graft infection (AGI) is a rare but life-threatening disease. The diagnosis is based on clinical manifestations, laboratory tests, and imaging studies. Surgical removal of the infected graft is the cornerstone of AGI. However, in some conditions, especially for patients with a short life expectancy and high surgical risk, conservative treatment with long-life or longtime antimicrobial therapy is the only reasonable option. The antibiotic therapy represents a key issue when dealing with AGI, due to the polymicrobial nature of the infection and especially the formation of biofilm on the prosthetic graft, so that antibiotics targeting the biofilm should be chosen to eradicate the infection, particularly when the graft is not explanted. Here we describe a case of a woman with abdominal aortic graft infection who was managed with long-term conservative antimicrobial therapy and at last treated with Delafloxacin, due to the adverse effects and partial failure of other antibiotics and the documented potency and efficacy of this new fluoroquinolone against biofilms. The patient is well more than 1 year following presentation with no signs of ongoing graft infection.

Keywords: AGI; long-term therapy; Delafloxacin; PET; CT.

Introduction

Abdominal aortic graft infection (AGI) is a rare disease with incidence ranging from 0.3% to 3% [1]. Staphylococcus aureus and coagulase-negative staphylococci are the most common bacteria accounting for almost 50% of AGIs. The infection can arise from bacterial spread from contiguous tissue or septic emboli, bacterial seeding during the endovascular procedure, graft erosion or fistula to bowel, esophagus, airways. Symptoms are often nonspecific and include fever, abdominal and back pain, fatigue, malaise. Surgical intervention with removal of the infected graft is the first choice; however, in some conditions, i.e. when comorbidities make the intervention at high risk of mortality, medical conservative management with long-term or lifelong suppressive antimicrobial treatment, is recommended [1]. In this report we describe a case

of a woman with prosthetic abdominal aortic graft infection who was managed with long-term antibiotic therapy and at last treated off-label with the most recently approved fluoroquinolone Delafloxacin (DLX).

Clinical Case Presentation

A 69-year-old woman with a past medical history of chronic ischemic heart disease, 60% carotid artery stenosis, abdominal aortic aneurism status post endograft repair, multicystic dysplastic kidney disease, chronic thyroiditis and primary hyperparathyroidism treated by parathyroidectomy was admitted on December 2022 to our Internal Medicine Unit because of fever and right lower back pain for 10 days.

Physical examination revealed stable vital signs, sinus rhythm, a body temperature of 36°C, mildly tender abdomen in right lumbar region with slightly positive Giordano sign; pulmonary examination was unremarkable. Laboratory analysis showed a leucocyte count of 15,000/mcl (normal value 4,800-10,800) with 84.7% of neutrophils, hemoglobin level of 11.8 g/dl (normal value 12-16), serum sodium of 133 mmol/L (normal value 135-145), C Reactive Protein (CRP) of 43.65 mg/dl (normal value 0-1.0), erythrocyte sedimentation rate (ESR) of 116 mm/h (normal value 0-15), ferritin level of 752 ng/ml (normal value 9-250), serum iron of 10 mcg/dl (normal value 35-170), transferrin saturation of 3%, low albumin levels of 1,9 g/dl (normal value 4-4.8), fibrinogen level of 1120 mg/dl (normal value 200-400); thyroid hormones, parathormone, creatinine, transaminase, gamma glutamyl transpeptidase, bilirubin levels were within the normal values. Urine culture test was positive, and Yersinia Enterocolitica was identified. Blood cultures were negative. The patient was given intravenous Piperacillin/Tazobactam 4.5 g three times a day based on urine culture antibiogram. Abdominal ultrasound did not show pathological signs except for the presence of multiple kidney cysts. Due to the right lumbar persisting pain, abdominal computed tomography (CT) with intravenous contrast was performed that revealed inflammatory changes of infrarenal aortic aneurysm extending to right common iliac artery which were consistent with aortitis (Figure. 1).

After consulting with the vascular surgeons, fluorodeoxyglucose Positron Emission Tomography (PET) was conducted that confirmed the aortitis extending along the endograft and involving the aortic aneurysm wall (Figure. 2).

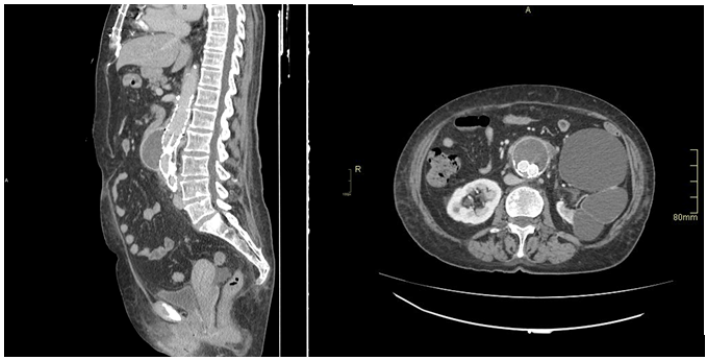

Figure 1: Contrast-enhanced CT images reveal aorto-bi-iliac stent graft with abnormal thickness of the left aortic aneurism wall and adipose tissue inhomogeneity.

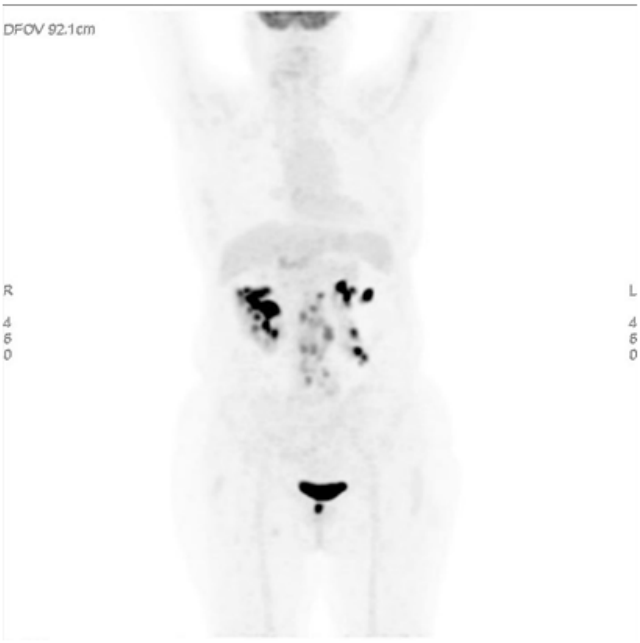

Figure 2: Fluorodeoxyglucose PET image shows abnormal tracer accumulation along the course of the aorto-bi-iliac endograft and within the aneurism wall (SUV 21.4), with involvement of the adipose perivascular tissue.

Herein a second consult with vascular surgeons was made who suggested to going on with long-term antibiotic therapy and perform PET control after 6 weeks before making the decision of

the explantation of the infected graft. According to the infectious disease specialist, daptomycin at a dose of 8 mg/Kg/day was added to the therapy. After 1 month of hospitalization and two weeks of IV daptomycin therapy, the patient was discharged at home to complete a further course of IV therapy as an ambulatory patient. On discharge from the hospital, leucocyte count was of 6.500/mcl, CRP of 1.86 mg/dl, fibrinogen level of 380 mg/dl, and the patient was asymptomatic. The inflammatory markers were followed weekly and at two weeks after discharge the patient was readmitted to the hospital for further evaluation. A daptomycin IV therapy was continued, blood cultures were obtained that were negative and PET control was performed that revealed amelioration of the aortic graft infection (SUV 10.4 vs 21.4). Unfortunately, during the hospitalization, progressive neutropenia was observed and therefore antibiotic therapy was discontinued. as long as normalization of neutrophil count. The patient was discharged at home with normalized CRP value and Levofloxacin oral treatment at a dose of 750 mg/day. She was examined every two weeks in outpatient setting and inflammation markers were constantly monitored. Vascular surgeons reassessed the patient and excluded the possibility of any surgical treatment because of patient frailty and too high risk of intervention.

On July 2023, after overall six months of antimicrobial treatment, PET was again performed showing mild progression of the infectious process; CRP value was slightly increased. Following multidisciplinary consult, decision was made to begin off-label treatment with DLX 450 mg bis in die, due to the documented DLX potency and efficacy against biofilms [2-3]. A written informed consent was obtained from the patient. The therapy was going on for 40 days, it was well tolerated, and no side effects were observed. CRP gradually reduced and consistently remains within the normal values. On October 2023, given the persistent negative CRP values, the clinical stability of the patient, and the stable improvement documented by PET, multidisciplinary decision was made to discontinue the antibiotic therapy with constant follow-up. The patient was periodically evaluated in outpatient basis at our Internal Medicine Unit and until the last visit in February 2024 she was asymptomatic and the inflammatory markers were still negative.

Discussion

Abdominal AGI is an extremely complex clinical challenge and is accompanied by high morbidity and mortality rates. In current practice, AGI is diagnosed based on clinical manifestations, laboratory tests and imaging studies. In 2016 the Management of Aortic Graft Infection Collaboration (MAGIC) introduced criteria to establish the diagnosis of an aortic graft/endograft infection which consist of clinical/surgical, radiologic, and laboratory criteria [4].

Signs and symptoms, such as fever, abdominal pain, tachypnea, tachycardia, hypotension are common although not pathognomonic of AGI. Laboratory tests usually revealed abnormally elevated inflammatory markers as ESR, CRP, WBC count which are not specific of AGI, as well. Therefore, AGI should be hypothesized based on patient's clinical history, and any differential diagnosis has to be considered. Radiological examinations play a pivotal role. Ultrasound (US) is the common, non-invasive, imaging modality to identify findings associated with AGI. However, its sensitivity for the diagnosis of AGI is low and it can be useful in the evaluation of perigraft fluid collections or abscesses, and to distinguish a fluid collection from a hematoma or a pseudoaneurysm [5]. In our patient, initial abdominal US did not show any sign of AGI, but, considering the patient's symptoms and clinical history, it allowed to exclude other disorders like pyelonephritis.

Indeed, CT is necessary to confirm the diagnosis of AGI and it is the first-choice imaging modality [6], while PET is a reliable non-invasive imaging modality to make diagnosis and map the extent of the infection [6-7]. Thus, in our patient, an abdomen CT was firstly performed revealing inflammatory changes of infrarenal aortic aneurysm and subsequently PET was carried out to better detect the graft infection.

Surgery is the cornerstone in the treatment of AGI, being the infected graft fully extracted to achieve infection eradication. However, many patients are not candidates for the preferred surgical treatment, thus conservative treatment consisting of long-term or life-long antibiotics with or without drainage is sometimes the only reasonable option. This is particularly true for patients having a greater burden of chronic diseases [8-9].

It is crucial to identify the best solution for each patient trough a multidisciplinary approach that should be involved nuclear medicine physicians, infectious disease physicians, vascular surgeons. Indeed, in our case, the decision to carry out with long-term conservative therapy was made after vascular surgeon consult that excluded a surgical approach due to the severe patient comorbidities and the high risk for explant. Appropriate antimicrobial treatment was established by an infectious disease specialist and nuclear medicine physician was crucial to evaluate the success of therapy over time.

The antimicrobial treatment represents a key issue when dealing with AGI, due to the polymicrobial nature of the infection and especially the presence of biofilm. During the acute phase when the infection is suspected, broad-spectrum intravenous antimicrobial treatment is mandatory to control the infection and prevent or cure sepsis. Blood cultures are obviously fundamental to go on with the targeted antimicrobial treatment, but sometimes they are negative and empirical antibiotic therapy must be continued. Although there are not universal recommendations on what antimicrobial

agent to use, empirical treatment should cover staphylococci and Gram-negative species, but local epidemiology and resistance patterns must be taken into consideration in the choice of therapy [10]. In our case, the patient was firstly treated with Piperacillin/Tazobactam due to the suspicion of pyelonephritis and the urine culture antibiogram results; however, when abdominal AGI diagnosis was made, given the negative blood cultures results, empiric therapy with daptomycin was administered that was discontinued after one month because of progressive neutropenia and, as long as normalization of neutrophil count, levofloxacin oral treatment was started; however, because of a documented increase of the inflammation markers during the follow-up, shift in antimicrobial therapy was made using the new fluoroquinolone DLX.

As mentioned above, one of the cornerstones in the antimicrobial treatment of AGI is the formation of biofilm on the prosthetic graft especially when the graft is not explanted, therefore antibiotics targeting the biofilms should be chosen in attempting to eradicate the infection. Study comparing DLX to daptomycin and vancomycin using biofilms produced by 7 clinical strains showed that the antibiotic penetration within the biofilms ranged from 0.6 to 52% for DLX, 0.2 to 10% for daptomycin, and 0.2 to 1% for vancomycin, highlighting that DLX potency and efficacy against biofilms are benefited by its penetration into the matrix and the local acidic micro-pH [2]. The potential utility of daptomycin and DLX for the treatment of Staphylococcus aureus biofilm-related infections was also reported in another study comparing different antibiotic activities against biofilms and examining the effects of antibiotic activities on biofilm mass [3]. Moreover, DLX showed an elevated generic barrier to resistance relative to other quinolones and lessened adverse effects on QT interval prolongation [11]. Currently DLX has been approved for the treatment of acute bacterial skin infections and community-acquired pneumonia in adults [12], however, successful off-label use of DLX has been reported in two patients with prosthetic knee infection characterized by failure of other antibiotic regimens [13]. On this basis, we administered DLX for 40 days to our patient obtaining improvement of the AGI, persistence of negative inflammation values and clinical stability of the patient without side effects. As our best knowledge, this is the first case report describing a safety long-term use of DLX in prosthetic aortic graft infection. Although shortcomings must be taken into account, such as development of drug resistance and high cost, a possible role of DLX in long-term treatment of AGI may be hypothesized.

Some studies reported poor results in patients with abdominal AGI who did not undergo explantation of the infected aortic graft and were treated conservatively, resulting in death from disease progression usually within two years of presentation [14] Anyway, a retrospective, observational, single-center cohort study from Sweden reported that conservative treatment without graft removal resulted in 98%, 88%, and 79% patient survival at 30 days, 1 year, and 3 years respectively, and concluded that antimicrobial treatment would not be needed indefinitely [15]. Similarly, in another series of patients with aortic graft/endograft infection treated with a conservative strategy without graft explantation, Caradu et al. reported in-hospital mortality rate of 20% and freedom from aortic-related death and overall survival rates of 77.1% and 70.4% at 1 year, and 61.7% and 43.1% at 5 years [16]. As well, Murphy et al showed that the overall survival for patients with abdominal endograft infection was similar between those managed surgically or selected for conservative treatment [17] Similarly to our patient, another case of successful long-term ambulatory conservative management of a patient with aortic graft infection has been described. [18]. According to a systematic review and meta-analysis of AGI, 2.5% of patients received conservative treatment [18]. Along with the cited studies, the clinical stability observed in our patient after more than 1 year of presentation suggests that in subjects with abdominal AGI, especially when surgical risk is too high, a long treatment antimicrobial course may be successful to eradicate the infection even in outpatient settings.

Conclusion

In this case report we firstly described a safety long-term off-label use of DLX in prosthetic aortic graft infection and highlighted the efficacy of long-term therapy relative to life-long therapy in patients with abdominal AGI who cannot be treated with surgical approach.

Anyway, further studies are needed to assess the possible role of DLX in prosthetic material infections and better clarify the use of long-term antimicrobial therapy in AGI.

Additional Information

Ethics Statement: Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article.

Conflicts of interest: All authors declare that are no conflicts of interest.

Financial support: A. Menarini Industrie Farmaceutiche Riunite, srl has supported the costs of publication without any further role.

Acknowledgments: We acknowledge A. Menarini Industrie Farmaceutiche Riunite srl, manufacturer of delafloxacin, for pharmaceutical support.

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