

Peripheral Graft Infection due to *Staphylococcus aureus* without Abnormal Findings by ^{99m}Tc-HMPAO-Labeled-Leukocyte Scan

Enrica Fiori¹, Umberto Vespasiani Gentilucci¹, Maria Francisca Navajas¹, Giovanni Galati¹, Sara Scriccia¹, Giordano Dicuonzo², Massimo Chello³, Rosario Francesco Grasso⁴, Antonio Picardi¹ and Antonella Afeltra¹

Abstract

Here, we present the case of an extremely subtle peripheral graft infection caused by *Staphylococcus aureus*. The lack of local signs and the negativity of all imaging studies, including ^{99m}Tc-HMPAO-Labeled-Leukocyte Scan which is reported to have 100% sensitivity, delayed the diagnosis and therapy, which were both provided by surgery.

Key words: vascular graft infection, *Staphylococcus aureus*, ^{99m}Tc-HMPAO-Labeled-Leukocyte Scan

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Introduction

Since the early 60s, lower limb revascularization through crossover femoro-femoral bypass graft (CFFBG) is particularly indicated in patients with unilateral common iliac artery obstruction presenting with severe anesthesiological risk (1). Infectious complications occur in a minority of patients (2-6%) (2), but are associated with a high mortality rate (25-50%), mainly due to sepsis, and a high amputation rate (15-60%) in spite of surgical rescuing procedures (3). Unless most peripheral graft infection is readily detected based on local findings, in a minority of cases clinical presentation can be quite insidious. Low-grade fever, leukocytosis and increased sedimentation rate can be the only clinical findings, with consequent delay in diagnosis and lifesaving treatment (4). Among imaging techniques, Technetium-99 m-Hexamethylpropyleneamine Oxime (^{99m}Tc-HMPAO) - Labeled-Leukocyte Scan showed better diagnostic accuracy than any other technique, including Computed Tomography-Scan (CT-Scan) and Fluorodeoxyglucose Positron Emission

Tomography (FDG-PET) (5, 6), especially in the case of low-grade infections, with a sensitivity as high as 100%, and a specificity ranging 90-100% (7-11).

Here, we report the case of a patient presenting with a very subtle infection of the graft after lower limb revascularization by CFFBG for severe common iliac artery stenosis. The lack of local signs, together with the negativity of all the imaging studies performed, including ^{99m}Tc-HMPAO-Labeled-Leukocyte Scan, led to recurrent septicaemias, worsening of renal function, and high risk of death from sepsis. Only surgical exploration, and subsequent removal of the graft, confirmed a growing clinical suspicion and avoided the fatal outcome.

Case Report

A 54-year-old man was hospitalized in early July 2007 due to a 7-day continuous fever (max 39°C) preceded by chills, and macrohematuria. Two-day treatment with oral levofloxacin (500 mg/day) had been performed before admission on suggestion of his family physician. The patient,

¹Clinical Medicine, University "Campus Bio-Medico" of Rome, Rome, Italy, ²Department of Microbiology, University "Campus Bio-Medico" of Rome, Rome, Italy, ³Department of Vascular Surgery, University "Campus Bio-Medico" of Rome, Rome, Italy and ⁴Department of Radiology, University "Campus Bio-Medico" of Rome, Rome, Italy

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Correspondence to Dr. Antonio Picardi, a.picardi@unicampus.it

a heavy smoker, was affected by hypertension and moderate chronic renal failure secondary to IgA nephropathy (1 month before admission serum creatinine 1.4 mg/dL; baseline creatinine clearance 47 mL/min), hypercholesterolemia and severe hyperhomocysteinemia. In May 2007 he was diagnosed with a severe obstruction of the left common iliac artery (85-90% stenosis), 41 mm in length, by doppler ultrasonography and angio-magnetic resonance imaging (MRI). As the patient presented a high surgical risk and was affected by unilateral iliac artery disease, an extracavitary CFFBG was chosen and performed at the end of May 2007. An 8 mm externally supported expanded polytetrafluoroethylene (e-PTFE) graft was positioned after bilateral femoral cutaneous access and subcutaneous tunneling of the sovrapubic region. Perioperative prophylaxis was observed (cefazoline 1 gr i.v. immediately before surgery, and 1 gr i.v. every six hours on the day of surgery and on day 1 after surgery), and the patient was discharged with oral levofloxacin (500 mg/day for 7 days).

At admission to our department, five weeks after surgery, the patient was mildly febrile (37.7°C), blood pressure was 100/60 mmHg, heart rate 72 bpm, body weight 61 kg, and body mass index (BMI) 20 kg/m². Anamnesis was negative for any other symptom except for fatigue and headache, and cough, sputum and dysuria were denied. Clinical examination was not suggestive of respiratory or urinary tract infections, exploration of the inguinal regions was absolutely negative, and surgical wounds were in advanced phase of healing. On auscultation, a systolic mitralic murmur was appreciated, which was previously known and secondary to mild mitralic insufficiency. Blood tests revealed: hemoglobin 11 gr/dL, white blood cells 5.430/mm³, erythrocyte sedimentation rate 71 mm/h, C-reactive protein 94 mg/L (normal <5 mg/L), urea 112 mg/dL (normal 10 to 50 mg/dL), creatinine 5.1 mg/dL (normal 0.8-1.2 mg/dL), calculated creatinine clearance 14.5 mL/min (normal 80-120 mL/min), red blood cell carpet on urine sediment analysis. Chest X-ray and urine culture were negative. A doppler ultrasonography showed a well-positioned, completely patent graft, without any pathological finding in the periprosthetic region.

Twenty-four hours after admission the patient was afebrile, and he was maintained on observation without antibiotic treatment. After a week in which he remained afebrile and showed a progressive improvement in renal function, fever (39°C) and macrohematuria reappeared without hemodynamic derangement, and blood and urine samples were obtained for culture. While waiting for the microbiological results, empirical therapy with amoxicillin-clavulanate (1 gr bid *per os*) was administered. After 6 hours from the first dose, a diffuse erythematous rash appeared. Amoxicillin-clavulanate was discontinued, and no further attempt with beta-lactam antibiotics was made. At 48 hours from collection of samples, a methicillin-sensitive *Staphylococcus aureus* (MSSA) was isolated from blood culture, while urine culture was sterile, and teicoplanin was started on the basis of antibiogram (200 mg/die i.v. - creatinine clearance ad-

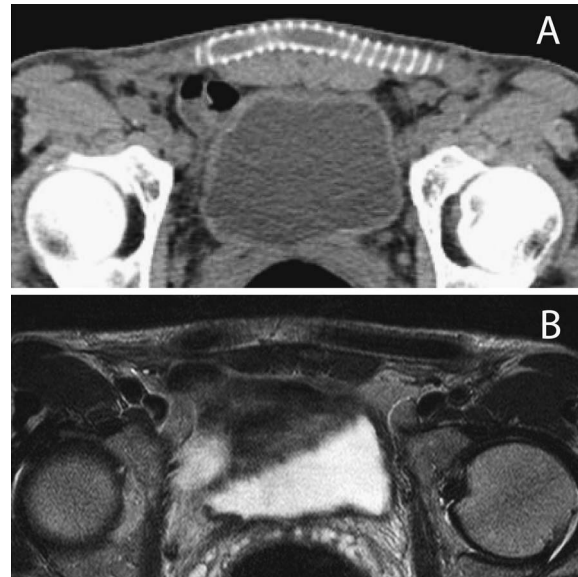


Figure 1. CT-scan (Panel A) and MRI (Panel B) images of the vascular graft: The femoro-femoral graft is completely patent. No fluid or gas-filled collections are visible in the periprosthetic region.

justed dose). Exploration of the inguinal regions persisted being completely negative, and a CT-Scan, performed without iodate medium due to the renal function, showed no abnormalities of the graft or periprosthetic tissues (Fig. 1, panel A). A trans-thoracic echocardiography was negative for valvular vegetations, and a dental-CT-Scan was negative for dental abscesses.

During treatment with teicoplanin, fever and macrohematuria rapidly disappeared, with a new progressive improvement in renal function (till creatinine 2.3 mg/dL). At day 10 of treatment, a new febrile peak occurred, accompanied by macrohematuria, and a second blood culture was collected. Twenty-four hours later creatinine was 3 mg/dL. Blood cultures showed persistence of MSSA bacteremia, with an identical antibiogram, and clindamycin (300 × 3 mg/die) was associated to teicoplanin. Trans-esophageal ecocardiography was negative for valvular vegetations, and MRI showed no fluid collection or soft tissue infiltration in the persiprosthetic region (Fig. 1, panel B). Even a ^{99m}Tc-HMPAO-Labeled-Leukocyte scan was negative for captating areas after 3 minutes, 20 minutes, and 2 hours from administration of radiolabelled cells. At day 3 of treatment with teicoplanin plus clindamycin fever had not disappeared, and renal function was not improving. In early August, while still hemodynamically stable, the patient was severely emaciated, his body weight was 51 kg and his BMI 17 kg/m². Therefore, even in the absence of any support from imaging techniques, surgical exploration of the vascular graft was carried out. Very low-grade cellulitis of the subcutaneous fat and a microabscess (3 mm) adjacent to the right surgical anastomosis were observed. The graft was consequently removed and sent to the microbiology laboratory together with fluid samples from the periprosthetic area and pus samples

from the microabscess. At gross morphologic examination, the graft was undamaged. Once opened, there were no blood clots and the luminal surface was partially lined with a thin transparent membrane presumably consisting of neointima (12). No samples were sent to the pathology laboratory since histological examination was not considered clinically relevant. All cultures were positive for *Staphylococcus aureus* with an antibiogram identical to the one isolated from blood cultures.

Postsurgically, the patient was treated with linezolid (600 mg \times 2/die i.v. for 7 days, then orally) and rifampicin (600 mg/die, orally) for three weeks. This regimen was chosen due to the lack of clinical response to the previous antibiotic treatments and because of the excellent tissue permeation of linezolid (13). Prompt resolution of fever and progressive improvement in renal function were observed. Blood cultures taken at day 8 of antibiotic treatment were negative, and he was discharged in good clinical condition. One month after discharge, the patient was well, he had gained 4 kg, and his creatinine was 1.7 mg/dL.

Discussion

Here, we present the case of a dramatically subtle post-operative graft infection, in which no instrumental technique supported the strong clinical suspicion, and surgery was finally required both to confirm diagnosis and to provide the only curative treatment, i.e., removal of the graft. Indeed, the gold standard treatment of an infected prosthetic graft in group 5 of modified Samson classification (sepsis and bleeding from anastomosis), remains total explantation of the graft and subsequent reperfusion, where possible, by placing a new conduit (14). Antimicrobial therapy is a vital adjunct to surgical management.

In the present case, the main factors leading to intervention notwithstanding the lack of support from imaging techniques were the following: recurrent septicaemias during adequate antibiotic treatment; the exclusion of other possible sources of infection; and, mainly, the type of infectious agent. In fact, *Staphylococcus aureus* is the most common cause of surgical site infection (SSI), accounting for approximately 50% of all SSIs (13) and it is also the first etiologic agent in the case of vascular graft infections (15).

Infectious complications occur in a minority of patients (2-6%) undergoing lower limb revascularization by CFFBG,

and can be divided into early (<30 days; more than 70% of total), and late infections (>30 days post-surgery) (16). While late infections are generally linked to hematogenous colonization of the graft, early infections can be considered a local complication of surgery due to intraoperative contamination of subcutaneous tissues or the graft itself by common skin contaminants, such as *Staphylococcus aureus* and, less frequently, coagulase-negative *Staphylococci* (17). In the case of infection, clinical features usually include systemic symptoms, like fever and anorexia, and local signs, i.e., cellulitis, fluid collections, wound dehiscence, and graft exposure (15). Imaging techniques, such as Doppler ultrasonography, CT-scan and MRI, usually help to confirm diagnosis, and ^{99m}Tc-HMPAO-Labelled-Leukocyte Scan is particularly indicated for low-grade infections, since it has demonstrated a sensitivity level as high as 100% and a specificity ranging 90-100% (7-11).

In the present case, two possible causes could have contributed to the negativity of all imaging studies performed. First of all, our patient was affected by chronic renal failure, which notoriously impairs innate immunity function, leading to low leukocyte reactivity at the injury site (18). Secondly, since the first appearance of fever, even before admission to our department, the patient received prompt antibiotic treatment, suspended only during the first week of hospitalization, which may have slowed the local spreading of the infection and the consequent occurrence of complications.

Noteworthy are also intermittent macrohematuria and worsening of renal function following each episode of bacteremia. Even if an established diagnosis can not be provided due to the lack of renal biopsy, it should be noted that *Staphylococcus aureus* infection has been associated with different kinds of glomerulonephritis, and has even been shown to contribute to the pathogenesis and/or reactivation of IgA nephropathy (19).

In conclusion, the present case documents the possibility that, even in the presence of a well-defined graft infection, all image techniques, even ^{99m}Tc-HMPAO-Labelled-Leukocyte Scan, may not support the diagnostic process. The strong clinical suspicion, based on the kind of infectious agent and the clinical course during antibiotic treatment, together with the accurate exclusion of other possible sources of persisting infection, should be the only guide to indicate graft removal where indicated.

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