Methicillin-sensitive *Staphylococcus aureus* prosthetic vascular graft infection after a Fontan procedure in an adult patient: A case report

FABIO TOSTO[1,2], ANDREA MARINO[3], VITTORIA MOSCATT[1,2], FEDERICA COSENTINO[1,2], EDOARDO CAMPANELLA[1,2], CRISTINA MICALI[1], YLENIA RUSSOTTO[1], GRAZIA CACI[1], EMMANUELE VENANZI RULLO[1], GIUSEPPE NUNNARI[1], BRUNO SANTI CACOPARDO[2] and MANUELA CECCARELLI[2,4]

[1]Department of Clinical and Experimental Medicine, Unit of Infectious Diseases, University of Messina, I-98124 Messina; Departments of [2]Clinical and Experimental Medicine, and [3]Biomedical and Biotechnological Sciences, Unit of Infectious Diseases, University of Catania, I-95122 Catania; [4]Department of Biomedical, Dental, Morphological and Functional Imaging Sciences, Unit of Infectious Diseases, University of Messina, I-98124 Messina, Italy

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Abstract. Heart infections are not limited to infectious endocarditis. In fact, prosthetic vascular graft infections are among the most severe complications associated with vascular and cardiac surgery. The risk of developing an infection on prosthetic material is estimated to be ~5%. The mortality rate associated with the infection is estimated to be ~10-25% within 30 days of infection and 50% after 1 year. The present article describes a case of a methicillin-sensitive *Staphylococcus aureus* (MSSA) infection on the prosthetic material following a heart Fontan procedure. To the best of our knowledge, only one other case of extracardiac prosthesis-related infection following Fontan surgery has been reported to date in adults. Prosthetic vascular graft infections (PVGIs) are a rare complication of heart surgery. However, PVGIs can seldomly occur and are burdened by a decreased survival rate. Therefore, physicians need to promptly suspect and recognize such cases. Further studies are required however, in order to determine the feasibility and long-term survival rates of a conservative therapeutic approach.

Introduction

Infectious endocarditis is associated with an increased mortality rate, particularly when occurring on prosthetic material (1). However, heart infections are not limited to infectious endocarditis. In fact, prosthetic vascular graft infections (PVGIs) are among the most severe complications associated with vascular and cardiac surgery (2). The risk of developing an infection on prosthetic material is estimated to be ~5%. The mortality rate associated with the infection is estimated to be ~10-25% within 30 days of infection and 50% after 1 year (3,4)

A number of procedures involve the use of prosthetic material to repair or replace damaged tissues; one example of this is the extracardiac Fontan procedure. This is a palliative intervention for various forms of congenital heart disease, including univentricular heart or tricuspid atresia (5-7).

Since the first report of the Fontan procedure in 1971, several changes have made (8,9). The Fontan procedure is based upon creating serial circulation in a patient with a single ventricle physiology, exploiting the blood flow through the pulmonary circulation (10). The Fontan procedure may be performed as a single- or a multiple-stage approach, demonstrating a lower mortality and lower risk for ventricular hypertrophy (11). The extracardiac Fontan procedure, involving the use of an extracardiac polytetrafluoroethylene conduit to divert the inferior vena cava flow to the pulmonary arteries, is performed either when the classic Fontan procedure fails or according to the expertise of each center (12). The advantages of the extracardiac procedure are a reduced stasis with a decrease in the risk of thrombus formation, fewer atrial and preserved pulmonary and myocardial function (12).

The present study describes the case of methicillin-sensitive *Staphylococcus aureus* (MSSA) infection on the prosthetic material following a heart Fontan procedure.

Case report

A 38-year-old woman affected by congenital tricuspid valve atresia, who had undergone a Rashkind procedure (septostomy) at the age of 3 months, a modified Blalock-Taussig shunt at the age of 8 months, and a classic Fontan procedure

Correspondence to: Dr Andrea Marino, Department of Biomedical and Biotechnological Sciences, Unit of Infectious Diseases, University of Catania, Via Palermo 636, I-95122 Catania, Italy
E-mail: andreamarino9103@gmail.com

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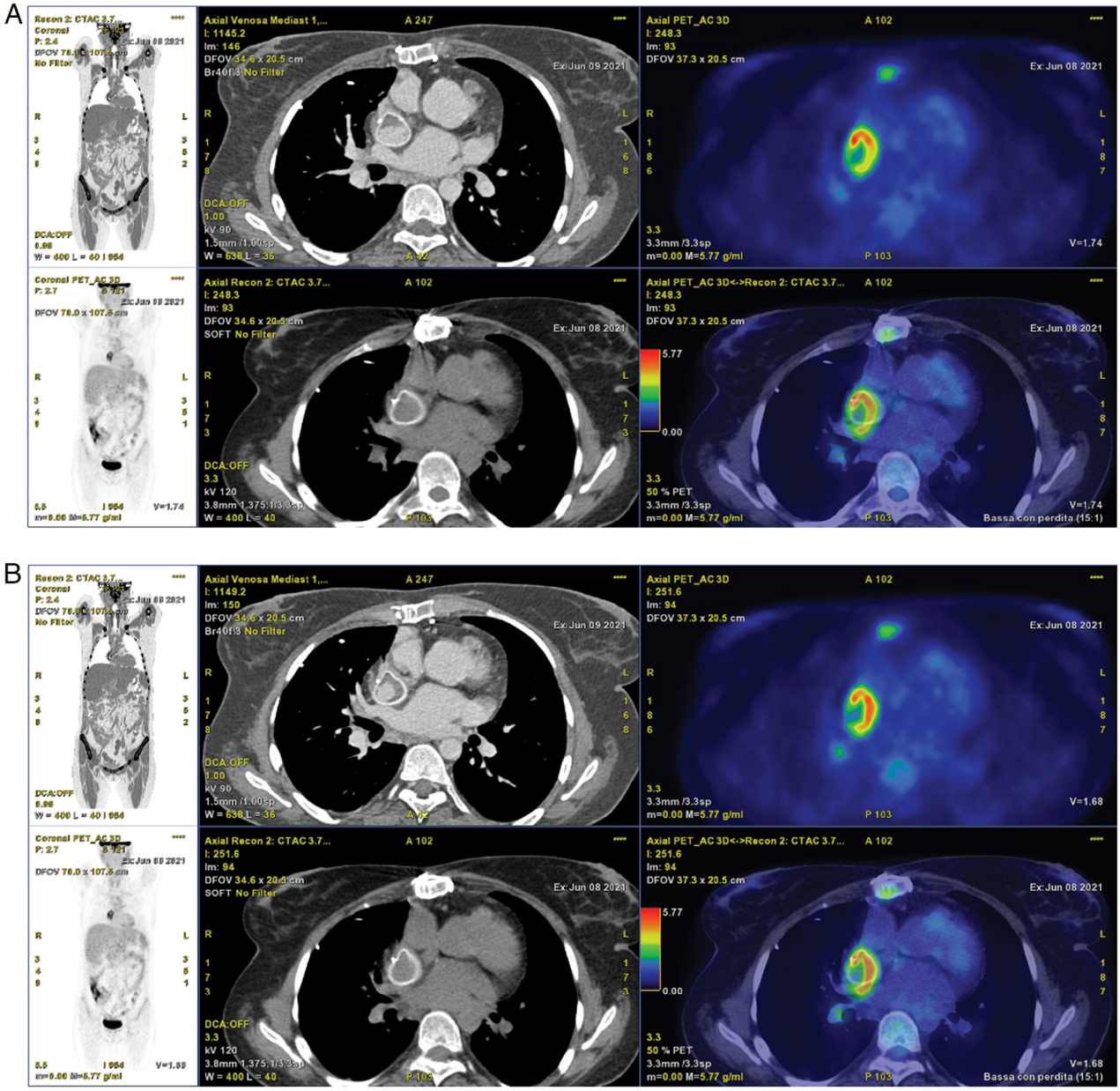

Figure 1. (A and B) PET/CT scan imaging performed using radiolabeled leukocytes, demonstrating the presence of inflammatory tissue (vegetation) within extracardiac prosthesis. Panels A and B illustrate different sections of the same PET/CT scan.

at the age of 4 years, was admitted to the Infectious Diseases Unit of Garibaldi Hospital (Catania, Italy) in June, 2021 after being diagnosed with an infection of an extracardiac prosthesis. Following the classic Fontan procedure, the patient had lived in a state of wellness until 2013 when, after giving birth, developed heart failure and deep vein thrombosis. Subsequently, the patient therefore underwent her last surgery, an extracardiac Fontan procedure with a right Gore-tex™ 22 Maze® (W. L. Gore & Associates, Inc.) and the implant of epicardial catheters, in 2017 at the San Donato Hospital (Milan, Italy). The post-operative course was complicated by a long period of subsequent pleural and atrial arrhythmias, resistant to amiodarone treatment. Therefore, catheter ablation was performed.

Following the extracardiac Fontan procedure, monthly febrile episodes (maximum temperature, 37.5-38˚C) occurred, lasting from 2 to 3 days, which became increasingly more frequent. Consequently, in May, 2021 she was admitted to the Congenital Heart Diseases Ward of the adult Unit of the San Donato Hospital, where the infection of the extracardiac prosthesis was diagnosed owing to a heart positron emission tomography/computed tomography scan performed using radiolabeled leukocytes, highlighting the presence of a vegetation (Fig. 1). The patient was subsequently discharged and admitted to the Infectious Diseases Unit of Garibaldi Hospital (Catania, Italy).

Upon admission, the patient was apyretic (maximum temperature recorded, 36.8˚C), blood pressure was measured at 100/65 mmHg, heart rate at 90 bpm, ambient oxygen saturation at 96% and the respiratory rate at 19 breaths/min.

A physical examination revealed sufficient peripheral perfusion, valid pulses, well represented subcutaneous tissues,

Table I. Results of the sensitivity tests performed on *Staphylococcus aureus* isolated using six different blood cultures.

Antibiotics	MIC (mg/l)	S/R/I
Ampicillin	4	R
Ciprofloxacin	≤1	S
Clindamycin	≤0.25	S
Chloramphenicol	≤8	S
Daptomycin	≤1	S
Erythromycin	≤0.25	S
Gentamicin	≤1	S
Levofloxacin	≤1	S
Linezolid	≤1	S
Oxacillin	≤0.25	S
Penicillin	8	R
Synercid	≤1	S
Tetracycline	≤1	S
Vancomycin	2	S
Amikacina	≤8	S
Amoxicillin/clavulanate	≤4/2	S
Cefoxitin	≤4	NEG
Ceftaroline	≤0.5	S
Phosphomycin	≤32	S
Imipenem	≤4	S
Minocycline	≤1	S

MIC, minimum inhibitory concentration; S/R, susceptible/resistant; NEG, negative.

the absence of peripheral edema, valid heart tones and the absence of murmurs. Blood chemistry tests highlighted a normal white blood cell count (5,100/μl; normal range 4,300-10,300/μl), with a normal differential count (neutrophils, 68.6%; lymphocytes, 19.0%), mild anemia (hemoglobin, 11.0 g/dl; normal range, 13.6-17.2 g/dl), a normal platelet count (149,000/μl; normal range, 156,000-373,000/μl) and a low creatine phosphokinase (CPK) level (20 UI/l; normal range, 29-59 UI/l). However, abnormally increased C-reactive protein (CRP) levels (1.77 mg/dl; normal range, <0.5 mg/dl) and an increased erythrocyte sedimentation rate (17 mm/h; normal range, <10 mm/h) were detected. The procalcitonin levels were normal (0.05 pg/ml; normal range, <0.1 pg/ml), the creatinine level was 0.53 mg/dl (the estimated glomerular filtration rate, calculated with the chronic kidney disease epidemiology collaboration method was 119.7 ml/min). Liver function indices were also normal (aspartate aminotransferase, alanine aminotransferase and international normalized ratio, and total and conjugated bilirubin). Human immunodeficiency virus, hepatitis C virus and hepatitis B virus serology resulted negative (13-15). During hospitalization, six blood cultures were taken, all of whom tested positive for MSSA (Table I).

Antibiotic treatment with daptomycin at 12 mg/kg per day (750 mg/day), gentamicin at 4 mg/kg per day (240 mg/day), trimethoprim/sulfamethoxazole at 800/160 mg b.i.d. and rifampin at 900 mg/day was then commenced. After 48 h, the patient was still apyretic, while the CRP levels decreased, reaching the normal range (0.35 mg/dl). The CPK levels were limited to below the upper level of normality (53 U/l; normal range, 29.0-200.0 U/l), demonstrating that the patient was tolerating the selected regimen (Table II).

The patient continued the antibiotic therapy for a total of 6 weeks; gentamicin treatment was terminated after 2 weeks (complying with the European Society of Cardiology guidelines for the management of infectious endocarditis) (16), and the normalization of the altered blood tests, clinical improvement and negativization of blood cultures were obtained. However, the patient refused to undergo surgery to replace the extracardiac device after completing the antibiotic treatment. Therefore, a conservative approach was selected. She

Table II. Blood test results before and during the antimicrobial therapy.

	Date (day/month)[a]									
Parameter	16/06	19/06	22/06	29/06	05/07	09/07	15/07	21/07	26/07	03/08
Hb (g/dl)	11.0	11.8	12.0	11.9	12.2	13.0	14.1	13.2	13.5	12.9
WBCs (cells/μl)	5,100	5,900	5,200	5,100	4,200	5,300	4,000	3,900	4,600	4,200
Neutrophils (%)	68.6	64.6	70.1	66.8	63.9	67.2	62.1	59.4	64.9	64.1
Lymphocytes (%)	19.0	23.9	25.0	21.5	21.2	26.0	24.3	29.0	30.0	25.4
CPK (UI/l)	-	20	28	22	57	59	58	75	-	53
Creatinine (mg/dl)	0.54	0.74	0.66	0.64	0.54	0.71	0.58	0.69	0.69	0.53
AST (UI/l)	25	24	30	19	24	-	-	-	-	24
ALT (UI/l)	35	31	48	19	20	-	-	-	-	28
ESR (sec)	17	19	13	8	7	7	-	6	6	8
CRP (mg/dl)	1.77	0.35	0.30	0.19	0.49	0.45	0.37	0.40	0.41	0.52
PCT (ng/ml)	0.05	N/A	0.02	0.01	N/A	N/A	N/A	0.02	0.01	0.01

[a]All measurements were performed in 2021. Hb, hemoglobin; WBCs, white blood cells; CPK, creatine phosphokinase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; PCT, procalcitonin; -, not tested; N/A, tested but reagent temporarily not available at the laboratory.

is currently in a good clinical condition and on an antibiotic therapy with dalbavancin and minocycline.

Discussion

As far as is known, only one other case of the infection of an extracardiac prosthesis following Fontan surgery has been reported to date in adults (17), as the majority of the cases presented in literature concern children (18).

The epidemiological study by Lee *et al* (18) on a cohort of children born between 2000 and 2008 (total no. 1,967,991) revealed an incidence of 0.184/1,000 congenital heart diseases requiring a Fontan procedure. In that study, the 10-year survival rate was 0.822 (±0.026). The causes of death included heart complications in 43.8% of cases and infections in 20.8%; other minor causes were sudden death, arrhythmias and cerebrovascular accidents. However, Lee *et al* (18) did not mention the etiological agents of the infections.

Since Fontan surgery is characterized by the use of prosthetic material, post-surgery infections can be considered and treated as vascular graft infections. Revest *et al* (19) performed a review of the literature of the medical treatment of PVGIs, approaching the issue by focusing on microorganisms and not on the procedure. In their review, among the 46 clinical studies included, there were 43 cohort studies, one case control study and four animal trials (19). They identified *Staphylococcus aureus* (20-53%) as the main etiological agent pathogen for PVGIs, followed by Enterobacteriaceae (14-41%) and others bacteria, demonstrating the optimal treatment option according to the isolated microorganism (19). However, their approach did not reveal which procedures and which materials are more burdened by infectious events.

In the case presented herein, a MSSA was responsible for the disease. *Staphylococcus aureus* is a Gram-positive bacterium involved in a large number of infectious processes, such as bloodstream infections, infectious endocarditis, skin and soft tissues infections and device-related infections (20).

The high incidence of *Staphylococcus aureus* infections of prosthetic material is justified by its ability to produce biofilm, a matrix around the bacterium that renders it difficult for the host organism's defenses to combat the infection, also hampering the penetration of antibiotics. Moreover, as prostheses are external devices, they are not vascularized by the systemic circulation, thus making it difficult for the immune system and drugs to reach and destroy the bacteria (21-23). For the present case, the combination therapy of daptomycin, rifampin and gentamicin was selected according to the current ESC guidelines for infectious endocarditis induced by *Staphylococcus aureus* on prosthetic valves. In particular, daptomycin was preferred to oxacillin and vancomycin for its easier administration (once daily vs. six times per day and four times per day, respectively), the lower number of drug interactions and incidence of side-effects (compared with vancomycin), and for its higher effectiveness in the right-side endocarditis (16,24).

The European Society for Vascular Surgery (ESVS) indicates that, in the event of a PVGI, surgical treatment with the objective of removing and replacing the extracardiac prosthesis should be preferred whenever possible (25).

According to the studies by Darouiche (26) and Revest *et al* (19), however, antibiotic treatment is recommended in all cases of endovascular prosthesis infections prior to surgical intervention. Treatment should vary from case to case. If the prosthetic material can be removed without replacement, they recommend a minimum duration of 2 weeks of intravenous therapy before surgery, followed by a further 2 weeks of oral therapy following the intervention. If the prosthetic material is replaced, 4 to 6 weeks of antibiotic therapy is recommended to prevent recurrent infections. However, some researchers recommend a treatment duration of up to 1 year following surgery. Of note, the studies by Kahlberg *et al* (27), Darouiche (26) and Spiliotopoulos *et al* (28) demonstrated that in those cases in which surgery is not recommended due to its high risks, or when it is refused by the patient, a life-long antibiotic therapy improves the survival.

In conclusion, prosthetic vascular graft infections are a rare complication of heart surgery. However, they can seldomly occur and are burdened by a low survival rate. Therefore, these need to be promptly suspected and recognized. Further studies are required however, to determine the feasibility and long-term survival rates of the conservative approach.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

FT, AM, EC and MC were involved in the conception of the study. FT, VM, FC and EC collected and analyzed the patient's data. VM, FC, YR, CM and GC were involved in the design of the study and reviewed the literature associated with the article. EVR, BSC, GN and MC obtained medical images and revised the article. AM and MC advised on patient treatment and wrote the final draft of the manuscript. All authors have read and approved the final manuscript. FT and AM confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The patient signed a written informed consent. Within the consent, it is specified that data collected during the diagnostic and therapeutic process can be anonymously used for scientific purposes.

Patient consent for publication

The patient signed a written informed consent for the publication of the data presented herein. Within the consent, it

is specified that data collected during the diagnostic and therapeutic process can be anonymously used for scientific purposes.

Competing interests

The authors declare that they have no competing interests.

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