Case Study

Management of Vascular Graft Infection

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Learning Points

This case report focuses on the risk factors, diagnosis, and management of vascular graft infections. A complex and intriguing case is presented and the latest evidence on aetiology and management of this challenging condition are summarised. The contention regarding the diagnostic criteria for graft infection is addressed, and how different imaging modalities and genetic or systemic biomarkers could aid this diagnostic process. Key management challenges are also discussed. Firstly, the difficulties of penetration and efficacy of antimicrobials and the issues surrounding biofilm formation. Secondly, the different surgical options such as graft preservation with partial excision or muscle flap coverage, or excision and revascularisation. Further, the type of explant and the latest innovations in the field of biological grafts are considered. Overall, this case report brings to the fore the lack of structured guidelines and level 1 evidence for the diagnosis and management of vascular graft infection, and calls for a more structured, unified, multi-disciplinary approach.

Introduction

Vascular graft infection occur in 4% of peripheral grafts and 1-3% of aortic grafts, but accounts for 20% of mortality in graft patients. There are several difficulties in the field surrounding prevention, diagnosis and treatment of graft infections which may account for this substantial attributed mortality. Firstly, graft infections have varied clinical presentation often delaying diagnosis. Further, a lack of clear guidelines and randomised controlled trials of sufficient size and quality mean that management is often very different and appears independent of the nature of the infection but rather depends on the clinician’s speciality. The dynamic microbiological picture of graft infection as well as development of biofilms and antibiotic resistance all hinder medical treatment. Surgical options range from graft preservation with tissue debridement, to graft excision and replacement; however judging which technique is most suitable and cost-effective is often difficult given the numerous underlying factors: surgical, patient-related and environmental, which determine the ongoing pathology and response to treatment.

The pathogenesis of vascular graft infections is varied but can include direct colonisation from skin flora, haematogenous spread (e.g. after endoscopy), spread from adjacent tissues or colonisation of plaques and thrombi around the graft. The grafts provide surfaces for biofilm formation which facilitates avoidance of immune attacks and medical therapy. Inflammation and immune dysregulation around the site of infection results in a local hyper-coagulable state and endothelial changes which may promote stenosis, graft migration and endoleaks. If untreated, the infection can progress to worsened graft function as well as bacteraemia and sepsis. Therefore, it is important that the diagnosis and treatment are prompt, but also effective. Further understanding into the mechanisms underlying clinical presentation of graft infection and response to treatment will facilitate informed clinical judgement for best medical or surgical therapy.

Case History

Patient JB, a 70 year old man, was admitted to the vascular ward on the 23/01/19 following worsening vascular graft infection, right groin sinus and femoral aneurysms. He had previously had an open 9.5cm aortic abdominal aneurysm repair in 2007. He also has a history of surgeries in his iliac and femoral arterial systems. In the 1980s he had a right femoro-femoral cross-over due to an occluded left common iliac artery which was causing symptomatic occlusive arterial disease. In 2006 he had a right femoral-popliteal bypass graft for a popliteal aneurysm. In 2018 he had a femoral artery stent, and he has had a chronic sinus in his right groin since 2016 which was treated with a silver Dacron graft.

He has a history of hypertension, left-sided weakness due to a stroke in 1996, chronic obstructive pulmonary disease (COPD), benign prostatic hyperplasia, squamous cell carcinoma and basal cell carcinoma on the scalp, and renal cysts.

He takes nicotine 21mg, chloridiazepoxide 30mg, paracetamol 1g, atorvastatin 40mg, dalteparin 5000U, dosulepin 75mg, amlodipine 5mg, aspirin 75mg, clopidogrel 75mg, omeprazole 20mg, tamsulosin 400mcg, Pabrinex, lisinopril+hydrochlorothiazide, cyclizine 50mg, fentanyl 25mcg, ondansetron 4mg.

He lives with his female partner, and has retired from a job in security services. He has a 50 pack-year history of smoking. He drinks very little, at most a couple of units per week.

Risk Factors

Risk factors for vascular graft infection can be patient-related, surgical and post-operative. Patient-
related factors include old age, male gender, high BMI, heart failure, immunodeficiency, diabetes mellitus, renal failure, COPD, bloodstream infection, skin ulcers on legs, and prolonged pre-operative hospital stay. These either promote the acquisition of infection or hinder its clearance by facilitating spread of bacteria into the bloodstream and to the graft site, reducing the flow of blood and immune mediators to the site of infection or reducing the effectiveness of the immune response.

Surgical factors include the injection site used, groin incision, length of surgery, type (emergency, re-do) and grafts used (polyester vs polytetrafluoroethylene), complications during surgery (e.g. bowel injury, tissue injury during dissection), and extensive lymphatic manipulation. These influence the spread of bacteria, the physiological stress of surgery and its effect on the patient's physiological reserve.

Post-operative complications also increase the risk of infection; for example wound infections, seroma, pseudoaneurysm and haematoma formation.

With these in mind, avoiding these risk factors are important in the care of surgical patients. For example, reducing the pre-operative hospital stay, treating infections before elective surgery, removing hair at the site of incision, limiting simultaneous GI procedures, maintaining normothermia, controlling blood glucose and eradicating nasal S. aureus colonisation have been shown to reduce infection risk.

In the context of patient JB, there are several risk factors that could contribute to the chronic graft infection. He has underlying co-morbidities such as COPD, renal cysts and chronic kidney disease, and long-standing hypertension which will all limit his physiological reserve. Furthermore, he had a wound infection in the right groin and multiple re-do surgeries which all increase the risk of infection.

**Diagnosis**

One of the main issues surrounding graft infection is early diagnosis and management, preventing progression and avoiding the necessity of graft replacement. Infection can be diagnosed with microbiology using cultures from blood, explanted grafts and surrounding tissue, clinical findings such as fever, bacteraemia, pain and erythema, imaging, and inflammatory markers. There are two main classification systems used to grade graft infection: Sizlagyi and Samson. These characterise the extent of infection: dermis, subcutaneous, contact with graft, and whether contact is with the anastomosis with the artery. However, the variable clinical presentation of graft infection makes it difficult to know when to suspect it; in diabetic patients a systemic manifestation of infection is often absent and they are often culture negative. Therefore, imaging is often required to ascertain the diagnosis and the extent of infection.

There is some contention in the diagnostic criteria for graft infection. The Management of Aortic Graft Infection Collaboration (MAGIC) have suggested a definition of aortic graft infection. Clinical/surgical major criteria include intra-operative identification of pus around graft, direct communication with prosthesis and non-sterile site including fistulae, open wounds, mycotic aneurysms. Minor clinical criteria include localised features and fever. Radiological criteria include peri-graft gas on serial CT or gas/ fluid post-implantation. Laboratory criteria include micro-organisms cultured from percutaneous aspirates of peri-graft fluid, explanted grafts, intra-operative specimens, and blood or elevated inflammatory markers. In this way, a collaboration of indices can be used to precisely diagnose and define the extent of infection, thereby informing subsequent therapy.

Imaging modalities for diagnosing infection include CTA, 18F-FDG, PET-CT, and ultrasound. While peri-graft fluid and inflammation can be quickly seen by ultrasound, CT is the diagnostic test of choice. CTA allows visualisation of ectopic gas, peri-graft fluid, soft tissue enhancement, pseudoaneurysm, and discontinuity of the aneurysmal sac. Furthermore, CT-guided puncture facilitated aspiration of peri-prosthetic fluid for culture. FDG uptake is promising and could be combined with CTA to precisely locate the abnormal glucose uptake; a recent study showed 97% accuracy for diagnosis of graft infections with FDG-PET/CT imaging.

Patient JB had a CTA in 29/10/18 which showed inflammatory changes around the sinus in his right groin, and also showed occlusion of the right common iliac and external iliac arteries, a thrombus in the right common femoral arteries, stenosis of the right femora-popliteal bypass and proximal stenosis of the mid-superficial femoral artery. In this case, the diagnosis was not the limiting factor to treatment, but actually the complexity of the case made it difficult to determine the best treatment course and also makes it very difficult to apply evidence-based practice as this patient would likely be excluded from clinical trials.

**Management**

There are several broad management options for graft infection: antimicrobial therapy, graft preservation, and graft replacement. Choosing effective antimicrobial therapy is important and empirical therapy should cover Staph and gram negatives with good biofilm penetration. The difficulty of treating biofilm infections arises from several factors including poor penetration, low metabolic activity and hence resistance to antibiotic mechanisms, genetic heterogeneity within biofilms facilitating resistance, and quorum sensing mechanisms that mediate responses to altered environmental factors and thereby mediate longevity. Therefore, efficient treatment of biofilms should include anti-quorum sensing and biofilm dispersing agents as well as well-penetrating and sensitive antibiotics. Testing for susceptibility of blood cultures will then enable more effective antibiotics to be employed and also reduce selection pressure for resistance against broad-spectrum empirical therapy. Lack of guidelines mean that the duration of treatment is uncertain but it should probably depend on the extent, location and type of graft. Treatment over 4-6 weeks followed by 6-12 months has been shown to be effective. Equally, however, 20% of patients treated without antibiotics showed good long-term results, showing that surgery can also have a curative role. Zetrenne et al. compared management techniques for different grades of vascular graft infection showing that bacteriology did not systematically alter management and that irrigation and debridement was effective for Samson group 3 but inadequate for group 4, suggesting that antimicrobial therapy should only be administered alone in less severe cases and that with increasing severity surgery is indicated.

Surgical options can be aggressive such as graft excision and replacement with homografts, allografts or antibiotic-bonded grafts, which can include in situ or extra-anatomic revascularisation, or can aim to preserve the graft. Graft preservation can involve wound therapy, partial excision and muscle flap coverage. Using vacuum-assisted
closure of graft infections can improve clinical outcomes\(^1\). Furthermore, muscle flaps can be used to cover a vascular groin wound and rectus femoris flaps are more cost and clinically effective in terms of QALY than sartorius flaps\(^2\).

Ohta et al. compared graft removal, revascularisation and different timings of excision with different materials showing that in situ had better outcomes than extra-anatomic\(^3\). Importantly, graft preservation was curative in patients with patent grafts, no sepsis, local bleeding or pseudoaneurysm, suggesting that this technique is more suitable for less severe infections\(^4\). Umminger et al. showed that graft sparing was comparable to graft replacement in terms of in-hospital mortality although the time interval from the initial surgery was shorter in the graft-sparing group and some patients in the graft-sparing group required a second operation due to graft degeneration or infection that could not be treated with antibiotic irrigation\(^5\). They concluded that sparing is only effective when the diagnosis and treatment are prompt and aggressive. In contrast to Ohta et al., comparing types of reconstruction, in situ vs extra-anatomic revascularisation, revealed no difference in pre-operative or overall mortality in 30 EVAR explant infections\(^6\). Zetrenne et al. compared the surgical management of different grades of infection, showing that although preservation was effective for Samson group 3 it was not often done. In fact, procedures were chosen more on the basis of which the surgeon was most comfortable with and the relationship between the surgeon and plastic surgeon, as opposed to infection type or severity\(^7\). This highlights the need for treatment guidelines based on systematic classification of infection type and severity. The difficulty in classifying an infection arises from its dynamic state and uncertain progression; biofilm cultures may be used to predict its biology and bloodstream markers may be isolated to evaluate the immune status of the patient as a prognostic indicator for infection progression. However, graft infection severity is a spectrum and therefore dichotomising surgical treatment between preservation and replacement will always be arbitrary.

Innovations in materials used for vascular surgery also improve outcomes of graft infection. Recent ideas have included the addition of biological factors to grafts which then act to improve endothelialisation and reduce inflammation or infection. For example, vascular grafts with immobilised VEGF and anti-GDF4 showed improved endothelialisation in vitro and in mice inferior vena cava\(^8\); this opens up the possibility of having other factors to modulate the inflammatory reaction to graft insertion, and perhaps locally hinder atherosclerosis. Coating grafts with antibiotics such as vancomycin and rifampicin has been shown to elute high concentrations in vitro and in rabbits in vivo\(^9\). However, it is still uncertain how flow and the surface of the aneurysmal sac will affect the local concentrations of the antibiotic, and what concentration of antibiotic coating is required to provide sufficient time and concentration for infection control. Bio-absorbable beads have been shown to resolve prosthesis graft infections in patients, showing proof of concept\(^10\).

In the case of patient JB, the diagnosis of vascular graft infection had not been the issue, but rather deciding what the best management would be. Initially, the right groin infection was managed with a silver Dacron graft in 2018, however there are several complications associated with these such as aneurysmal degeneration, occlusion and re-infection. Unfortunately, the graft did become re-infected. This is in line with a study in 2011, showing that 20% of patients with silver Dacron grafts were re-infected, whereas there was no re-infection in patients with cryopreserved arterial homografts, however these are more expensive and also show higher rates of aneurysmal degeneration\(^11\). Interestingly, antibiotic-impregnated grafts appear to perform worse than Silver-coated grafts in terms of latency and freedom from infection\(^12\), which may suggest that firstly systemic antimicrobial therapy is sufficient and secondly that Silver-coating improves graft longevity.

Following the re-infection, wound therapy and antibiotics were started but this did not prevent the infection from progressing. Vacuum-assisted closure was not attempted despite showing improved clinical outcomes and quality of life with the same cost as alginate wound dressings\(^13\). However, it is uncertain whether these trials apply to all patients as they excluded patients with overt bleeding and septicaemia. Given the worsening infection and femoral artery aneurysms, the decision was then made to intervene surgically. The plan was to remove the femoro-femoral bypass and the femoral-politeal bypass and replace both with biological Omniflow grafts and repair both aneurysms. This decision is supported by a prospective study in 2012 showing that biological grafts were not re-infected up to 20 months after the operation\(^14\). However, they did report that the mechanical properties of these grafts may be disadvantageous and more prone to kinking and obstruction. A recent case has also shown the utility of biological Omniflow grafts for aortic graft infection, stating that these provide better tissue integration, reduced rates of re-infection and degenerative complications\(^15\).

Evaluating the best treatment for patient JB is difficult firstly because of the lack of staging used routinely for graft infections. Without this information it is difficult to systematically classify the severity of the infection, and thereby align the patient with the evidence from the literature. If the infection was Samson grade 3, then it is clear that graft preservation would not be sufficient. The next question is whether to reconstruct the femoro-femoral cross-over or attempt in situ reconstruction of the occluded right iliac artery. The current femoro-femoral graft has lasted since the 1980s and it is a good technique and prospective studies looking over 10 years have shown that patency rates remain high throughout those years with a low frequency of complications\(^16\); further, although aortic infections are usually better treated with in situ rather than extra-anatomic revascularisation\(^17\), cross-over grafting shows better survival rates and latency than iliofemoral grafting\(^18\). In fact, in this case, with poor general health due to COPD, hypertension, chronic kidney disease and poor local health due to chronic infection, it is likely that this patient would not be suitable for major abdominal surgery to repair the iliac artery. It is unfortunate that this conclusion was not reached earlier, as the patient has had to go through a period of years of worsening right groin sinus infection and femoral aneurysms. This highlights the importance of evaluating prognostic information when giving patients the treatment options. Retrospective analyses have identified age, creatinine and C reactive protein as indicators of in-hospital mortality after graft replacement\(^19\), but the next step is to identify markers predicting the progression of graft infection, akin to working at markers for aortic abdominal aneurysm progression\(^20\), allowing treatments to be tailored to the potential course of the disease.
Conclusion
This case clearly highlights the difficulties in managing vascular graft infections. Firstly, with no systematic classification of infection severity supported by NICE, there is no set pathway for treatment and the expected response. This results in a range of treatment methods across the UK rather than a standardised approach to management based on evidence from RCTs. Secondly, this highlights the difficulty in applying RCT results to a given case. The majority of cases will have other co-morbidities and be more complex than those used in RCTs and this casts doubt on the applicability of the RCT results and the best course of action. With a growing number of RCTs on vascular graft infection, the next step is now to investigate the effect of different co-morbidities on management. Thirdly, vascular graft infection is a dynamic state with variable progression and remission, making management decisions very difficult without knowing the particular nature of the infection. There should be a new focus in the field on phenotyping infections based on their genetic picture and systemic biomarkers of infection severity and the physiological response to predict the probability, rate, and nature of progression. Armed with these prognostic information and a standardised approach to diagnosis, the minefield of vascular graft infection will become systematic and evidence-based rather than subjective and variable.

Conflicts of interest
None.

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Consent
The patient has consented for the publication of this case study.

References


