Cutibacterium acnes endocarditis of prosthetic valves: A case series

M. Boyle[1], C. Tennyson[1], A. Guleri[2], A. Walker[1].
[1]Department of Cardiothoracic Surgery at Blackpool Victoria Hospital, UK.
[2]Department of Microbiology at Blackpool Victoria Hospital, UK.

Corresponding author information:

Dr. Mark Boyle
Department of Congenital Cardiac Surgery
Alder Hey Children's Hospital
E Prescot Road
Liverpool
UK
mark.boyle@nhs.net

Funding: None.

Conflict of Interest: None.

Data availability statement: The data that supports the findings of this paper is available from the corresponding author upon reasonable request.

Abstract

Cutibacterium acnes (*C. acnes)*, previously known as *Propionibacterium acnes* (although likely underreported), is a rare cause of infective endocarditis (IE) and often difficult to diagnose. We describe three cases from a single centre over a five-year period to provide insight into the various clinical presentations, progression and management of patients with this infection.

The primary objective of our series is to highlight the difficulty in the initial assessment of these patients with an aim to improve the time and accuracy of diagnosis and expedite subsequent treatment. There are currently no guidelines in the literature for the management of IE caused by *Cutibacterium acnes.* Our secondary objectives are to disseminate information about the indolent course of the disease and add to the growing body of evidence around this rare yet complex cause of IE. In accordance with local guidelines of the ethics commission, no ethical application was needed. Institutional review board approval or consent was not required, however verbal consent was gained from the patients or their next of kin were possible.

Background

The incidence of *C. acnes* as the causative organism for infective endocarditis is reported as 0.3%, (14). *C. acnes* IE is associated with both native and prosthetic valves but is much more commonly found on prosthetic valves. Studies show that middle aged men are mostly affected, with serious infections increasingly reported in association with bioprosthetic material (1). *C Acnes* is found in the sebaceous glands that are associated with hair follicles, this difference might account for the gender-specific bacterial colonization and subsequent male predominance seen in *C. acnes* infections (13). In a more recent study the proportion of Prosthetic Valve Endocarditis (PVE) cases due to *C. acnes* was nearly three times that previously reported from the International Collaboration on Endocarditis—Prospective Cohort Study (ICE-PCS) (23/606, 3.8% versus 13/923, 1.4%). (1)(5)

The increasing incidence of *C. acnes* endocarditis may in part be secondary to the increasing number of prosthetic valves being inserted or be a product of increased diagnosis due to the use of valve sequencing via PCR. (11) In addition, patients with *C. acnes* IE usually have advanced disease by the time they present, with a substantial proportion of patients having invasive disease and embolic complications.(1) There typically is a delayed presentation, in one case series, the mean onset of infection was 4-years from surgery. (2)

The mortality rates due to *C acnes* IE have been described in one recent study as 16%. (18) This may be due to the prevalence of *C. acnes* associated PVE, late diagnosis and subsequent delay in targeted treatment of the disease. (3) Herein we present our experience of three patients affected by *C. acnes* associated infective endocarditis.

Case Presentations

Case 1: 29 year old male with three redo aortic valve replacements.

A 29-year-old male, with a known congenital bicuspid aortic valve underwent minimal access aortic valve replacement (AVR), receiving a mechanical (25mm On-X) prosthesis in November 2015.

A routine postoperative transthoracic echocardiogram (TTE) three months later showed two distinct jets of moderate aortic regurgitation (AR), one of which was paravalvular. A subsequent Transoesophageal Echocardiogram (TOE) showed a good left ventricular (LV) systolic function with moderate to severe paravalvular AR and he was referred once more for a surgical opinion. In the interim, the patient presented to the Emergency department (6 months following his original AVR) with a two day history of rigors and a fever of 40.4 degrees Celsius. Two sets of blood cultures, taken 24 hours apart, were reported as negative in the initial 48-hour period. These cultures were observed for a further 8 days as per trust policy in suspected IE with no identifiable growth. The patient was admitted under the medical team and following satisfactory routine bloods, chest x-ray and ECG tests was discharged home with advice to seek medical attention if he developed any further symptoms.

He had intermittent rigors for several weeks following discharge, however when reviewed by his General Practitioner all observations were recorded to be within normal parameters. The patient was readmitted to hospital due to progression of his symptoms of general malaise and intermittent rigors. A full blood count on this occasion showed a raised white cell count 14.9 $x10^9$/L (WCC) and C-Reactive Protein (CRP) 96 mg/L, blood cultures were taken. He had a known penicillin allergy and so the patient was treated with empiric antibiotics as per trust guidelines (Table 1). The anaerobic blood culture on this admission was positive for *C. acnes*. A repeat TOE showed a large vegetation measuring over 3.3cm^2 on the aortic valve causing mild to moderate obstruction of left ventricular outflow tract (LVOT)(figure 2). Furthermore, he had a large aortic root abscess and new electrocardiogram (ECG) findings of a prolonged PR interval with right bundle branch block.

The patient underwent an emergency re-do aortic valve replacement with a Sorin, Bicarbon 23mm mechanical prosthesis. Intraoperatively, there was a large vegetation in the outflow tract with areas of abscess under the right and non-coronary cusps. There was a further cavity below the non-coronary cusp which was obliterated with 4-0 prolene.

The patient came off cardiopulmonary bypass and had an uneventful recovery. Intraoperative valve tissue sample was subjected to 16s rDNA Real-Time PCR and confirmed as *C. acnes*. The patient weighed 76.5kgs. Once discharged home the patient was given antibiotic therapy in the community (Table 1).

Three weeks following completion of IV antibiotic therapy he re-presented with chest pain, shortness of breath and general malaise. A full blood count showed a WCC within normal ranges but a raised CRP of 210. Blood cultures grew *C. acnes* and he was recommenced on antibiotic therapy (Table 1). Further cardiothoracic imaging was necessary and an ECG gated CT Thorax showed an irregular and slightly dilated aortic root with a small focal outpouching in keeping with a small aortic root abscess (figure 3). The patient had several episodes of supraventricular tachycardia managed with adenosine. Following a multidisciplinary team discussion, the next operation deemed appropriate would involve a homograft replacement and the patient was transferred to an appropriate surgical centre specialising in adult congenital surgery.

The third operation was uneventful. During this redo-operation, the aortic valve showed evidence of dehiscence along the non-coronary cusp (NCC) with evidence of a chronic large abscess below the NCC onto the anterior mitral valve leaflet (AMVL), there was no evidence of pus intraoperatively. The abscess was debrided and cleaned and a 27mm Perimount Magna tissue aortic valve was inserted using interrupted 2/0 ethibond sutures.

Postoperatively, a gated contrast enhanced thoracic CT was performed to examine the area adjacent to the NCC. It showed a blind ending 15mm outpouching from the left ventricular outflow tract (LVOT) adjacent to the interatrial septum, with a thin extension posterior to the annulus. There was no visible communication to the ascending aorta or evidence of vegetation or valvular dehiscence. He made an uneventful recovery and was discharged home 15 days later to complete a prolonged antibiotic course for 6 weeks from date of operation (Table 1).

4th Readmission to hospital

Unfortunately, the patient re-presented to hospital for a fourth time two weeks after his third operation with symptoms of fever and night sweats. A repeat TOE showed no evidence of valvular compromise, no dehiscence and no obvious vegetations on aortic valve leaflets. Furthermore, a PET-CT was performed and excluded an aortic root abscess and any active signs of active focal infection. The patient had a further course of antibiotics and completed a total of 8 weeks treatment.

Follow up

One year later, the patient reported feeling well in himself, reassuringly a repeat TOE showed no evidence of aortic regurgitation and he continues to be monitored closely in a clinical setting.

Table 1: Case 1 antibiotic regimen.

Case 1							
Admission 1	Vancomycin 1g IV BD 6 days	Vancomycin 1.5g IV BD 1 day	**Re-do Operation 1**	Vancomycin 1.5g BD IV 4 days	Vancomycin 3g IV continuous infusion 3 doses	**Discharged home**	Daptomycin 500mg IV OD 5 weeks
	Rifampicin 600mg PO BD 7 days			Rifampicin 600mg BD IV/PO 7 days			
	Gentamicin 80mg BD IV 7 days			Gentamicin 80mg BD IV 2 days			
				Cefuroxime 750mg IV 3 doses			
Admission 2	Vancomycin 1g BD IV 3 days	Vancomycin 1.5 gram IV continuous infusion 5 days	**Re-do Operation 2**	ceftriaxone 2gram IV OD 6 weeks			
	Rifampicin 600mg BD PO 8 days						
	Gentamicin 80mg BD IV 9 days,						
Admission 3	8 weeks 2gram OD IV ceftriaxone.						

Case 2 – 76 year old with previous CABG, followed by an AVR, pacemaker and infective endocarditis

A 76 year old gentleman with no known drug allergies (NKDA) was transferred from a local district general hospital (DGH) presenting with a four month history of progressive dyspnoea. His cardiac history included previous coronary artery bypass graft surgery in 2007 followed by a redo sternotomy for severe aortic stenosis with a sutureless bioprosthetic AVR six years later. Approximately 8-months following his aortic valve operation he had a permanent pacemaker inserted for paroxysmal narrow complex tachycardia with Type 1 second degree heart block.

The patient presented with a recent onset of worsening peripheral oedema and lethargy 17-months after his previous AVR. A chest x-ray revealed bilateral pleural effusions and a frusemide infusion was commenced, despite this the patient did not improve. He denied any new cough, fever or chest pain symptoms. A TOE showed a large abscess around the bioprosthetic AVR with evidence of valve dehiscence and significant paravalvular leak.

The patient, an 80kg gentleman, was treated initially at his parent district general hospital with various antibiotics (Table 2) for 9 days prior to being transferred to the tertiary centre. The patient's antibiotic regimen was reviewed and amended on admission. His doses of antibiotics were altered during his pre-operative period due to worsening renal function and liver function tests (LFTs).

Blood cultures highlighted gram-positive bacilli, identified as *C. acnes*, which was also subsequently confirmed by 16S rDNA Real-Time PCR identification when intraoperative valve tissue was available. Approximately 13 days following admission to the surgical unit the patient underwent an emergency re-do AVR.

Post operatively he required Noradrenaline and dopamine inotropic support for 3 days in cardiac intensive care. The patient continued to have IV antibiotics for 20 days post operatively. The patient was stepped down to oral antibiotic therapy for a final week (Table 2).

He was transferred for rehabilitation back to his local hospital 10 days after the completion of his oral antibiotics. Prior to his repatriation a post-operative TTE showed the AVR in situ to be well seated, with a central jet of moderate AR. His LV was not seen to be dilated with at least moderate systolic impairment at that time. He died in the community of unknown cause approximately one year later.

Case 2										
Admission (DGH)	Meropenem 5 days	Amoxicillin 2 days	Teicoplanin 2 days	**Transfer to Tertiary Centre**	Amoxicillin 2G QDS IV - 3 days	Tazocin 4.5gram IV TDS 10 days			**Operation**	Vancomycin 500mg/24 hrs continuous infusion 20 days	amoxi gram T 1 week
		Flucloxacillin 2 days			Vancomycin 1gram BD IV, 3 days	Vancomycin 750mg BD, 1 day	Vancomycin 2 day 1gram OD IV	Vancomycin 500mg/24 hr continuous infusion 7 days			
		gentamicin 2 days			Rifampacin 600mg PO BD 3 days	Rifampacin 300mg BD PO due to worsening liver function tests (LFTs).					

Table 2: Case 2 antibiotic regimen.

Case 3 – 74 year old – heart failure and urosepsis

A 74-year-old male, with no known allergies to antibiotics underwent a bioprosthetic aortic valve replacement for severe aortic stenosis in 2014. He had a trans-urethral resection of the prostate (TURP) 1 year later and required readmission 8-weeks following this for treatment of urosepsis. This patient had multiple subsequent admissions for management of sepsis and exacerbations of his heart

failure. It was noted that during this time *C. acnes* grew on a set of blood cultures but was considered a skin contaminant.

He was seen frequently in a heart failure clinic and optimised on diuretics, however his symptoms continued to deteriorate. Following a TTE and TOE, he was referred as an outpatient to the Cardiothoracic Surgeons with severe paravalvular aortic regurgitation and a dilated left ventricle with moderate to severe systolic impairment (Figure 4 – TTE showing severe AR)

An outpatient ECG gated Thoracic CT showed small outpouchings at the aortic root, possibly in keeping with micro abscesses. He was subsequently admitted from the outpatient clinic with evidence of acute heart failure with ongoing orthopnoea and persistent episodes of paroxysmal nocturnal dyspnoea. He was transferred to ICU for preoperative optimization with intravenous furosemide and dobutamine.

Whilst on dobutamine he had a repeat TOE which showed moderate ventricular function with mild tricuspid regurgitation (TR) and no evidence of mitral regurgitation. There was also a marked reduction in the left ventricular end diastolic dimensions (EDD). His previous TTE had suggested an end diastolic diameter (EDD) > 7cm with poor LV function and severe MR and TR. Due to this improvement with dobutamine the decision was taken to proceed with surgery for severe aortic regurgitation.

Intraoperatively, there was destruction of the strut at the NCC/RCC junction with dehiscence of the leaflets from the valve frame, leading to the prolapse of the NCC leaflet (Figure 5). A new size 23mm trifecta biological prosthesis was inserted using interrupted plegeted Ethibond sutures x 11. The excised valve was sent for microbiology PCR examination, the 16S rDNA Real-time PCR identified *C. acnes*. Blood cultures were negative.

The patient spent 4 days in CITU and was weaned gradually off dobutamine and IV furosemide infusions. He developed postoperative delirium and an acute on chronic kidney injury requiring haemofiltration for two days. Two weeks following his valve replacement he was repatriated to his district general hospital for further rehabilitation. An antibiotic protocol was detailed on discharge and PICC line inserted to facilitate a regimen of Benzylpenicillin 2.4g IV QDS for 2 weeks then changed to ceftriaxone 2g IV OD for 4 weeks.

Microbiotica

Cutibacteria (formerly propionibacteria) are part of normal flora of human skin and mucosal surfaces. They are slow growing, anaerobic yet aerotolerant, gram positive, non-spore forming, pleomorphic rods (see figure 1) of relatively low virulence. Cutibacteria, due to its low virulence, is commonly

considered contaminants of blood cultures. Infrequently it can cause significant infections of orthopaedic prosthesis, endovascular devices and cerebrospinal shunts (4)

Culture

Given the rarity of IE secondary to *C. acnes*, and that this bacterium is commonly grown as a commensal, it is pertinent to distinguish between simple culture contamination and a true bacteraemia. Multiple blood cultures must be positive with the same isolate to consider this the causative organism of infection. (5) The time to detection of the bacteria in blood cultures is 6.4 days in anaerobic bottles and 6.1 days in aerobic bottles. (5) However, the general consensus from numerous studies is; to reduce false negatives, cultures should be incubated for 10 to 14 days (5, 6, 7). Banzon et al elucidated that *P. acnes* is identified in only 12.5% of routine blood cultures, greater success is achieved with extended incubation of blood cultures to 75%. however, the gold standard of identifying P. acnes is valve sequencing - PCR base diagnosis targeting 16s rDNA - achieving growth in 95-96% of cases. (8, 9) Notably, 46% of cases in Banzon et al's study, would have found no cause for IE without valve sequencing. (8)

Clinical course

Time from symptoms including fever, chill, malaise, fatigue, myalgias and weight loss to diagnosis averages at 4 weeks, however this has been reported to be as long as 32 weeks in some studies. The bacterium can remain intracellular for weeks and months, explaining long incubation period. (10) Given the subtle nature of presentation, delayed incubation period and possibility of skin commensal contamination in blood cultures; diagnosis and subsequent early intervention can present a significant challenge to a clinician. (5, 11, 12) A clear demographic has been shown; *C. acnes* IE is typically found in middle aged men. The median age of diagnosis is 52years, with various studies reporting between 90% - 98% of cases being male. (2, 6) However the time from valve/device insertion to diagnosis of *Cutibacteria* IE is less clear, with an average of 4 years and range between 3 weeks to 23 years.(2) *C. acnes* has been associated with both native and Prosthetic valves, however the incidence is much higher in the latter.(5, 11) Prosthetic Valve Endocarditis (PVE) or IE on an annuloplasty ring accounts for 96% of cases. (8) The aortic valve is involved in the majority of cases (71%), mitral valve less so, with involvement in 24% of cases. Tricuspid valve involvement is uncommon (3%). (2)

Investigations and Findings

In this case series our main findings are that *C. Acnes* has been found to be the causative organism for infective endocarditis in 3 patients all of whom are men, all of which have prosthetic valves in situ, all with extensive valve or annulus destruction or abscess formation. Reinforced by the findings of Corvec et al, P. acnes causes extensive decalcification, abscess formation and valvular destruction. (12) Our three cases displayed systemic symptoms; this is typical in 75% of cases. Case 1 presented

primarily with a normal white blood cell count, it was not until his second presentation to hospital that he displayed leucocytosis and indeed, leucocytosis is typical in only 57% of cases. (2) Careful attention to the history and consideration of potential sources of *C. acnes* seeding should be considered. In case 2, the patient had a pacemaker inserted, a recent study evaluated the rate of cardiac device-related endocarditis at 1.9/1000 device-years. (17) All 3 patients in this case series survived until discharge. Typical complications of *C. acnes* include peripheral emboli in 16%, brain emboli in 10%, myocardial abscess in 36% and valvular insufficiency in 52%. (2) Complications such as invasive disease (71%) and embolic complications (29%) are common. (8, 11)

Management

Braun et al strongly recommend a treatment combination of rifampicin with daptomycin or penicillin G. (10) The combination of rifampicin and ciprofloxacin might be a reasonable alternative with excellent oral bioavailability for maintenance therapy in complicated IE.(10) The European Committee on Antimicrobial Susceptibility Testing (EUCAST) has set breakpoints for benzylpenicillin, advocating the use of benzylpenicillin instead of vancomycin or ceftriaxone. (7) The dose and addition of rifampicin in PVE remains to be elucidated. (7)

In summary, IE is a disease of high morbidity and mortality. Specifically, with *C. Acnes* as a causative organism it can be difficult to diagnose and when established on a prosthetic valve it is very malignant to treat. The initial treating clinician's awareness and willingness to consider the diagnosis should be encouraged. Once there is an index of suspicion, this should be preserved and the diagnosis pursued with combined modalities such as echo, CT and blood cultures, Due diligence from the multi-disciplinary team is essential in distinguishing between blood culture contamination and a true bacteraemia secondary to *C. Acnes*. The awareness of this pathogen must be highlighted in the greater cardiothoracic and microbiology community in an effort to expedite appropriate treatment and improve patient outcomes.

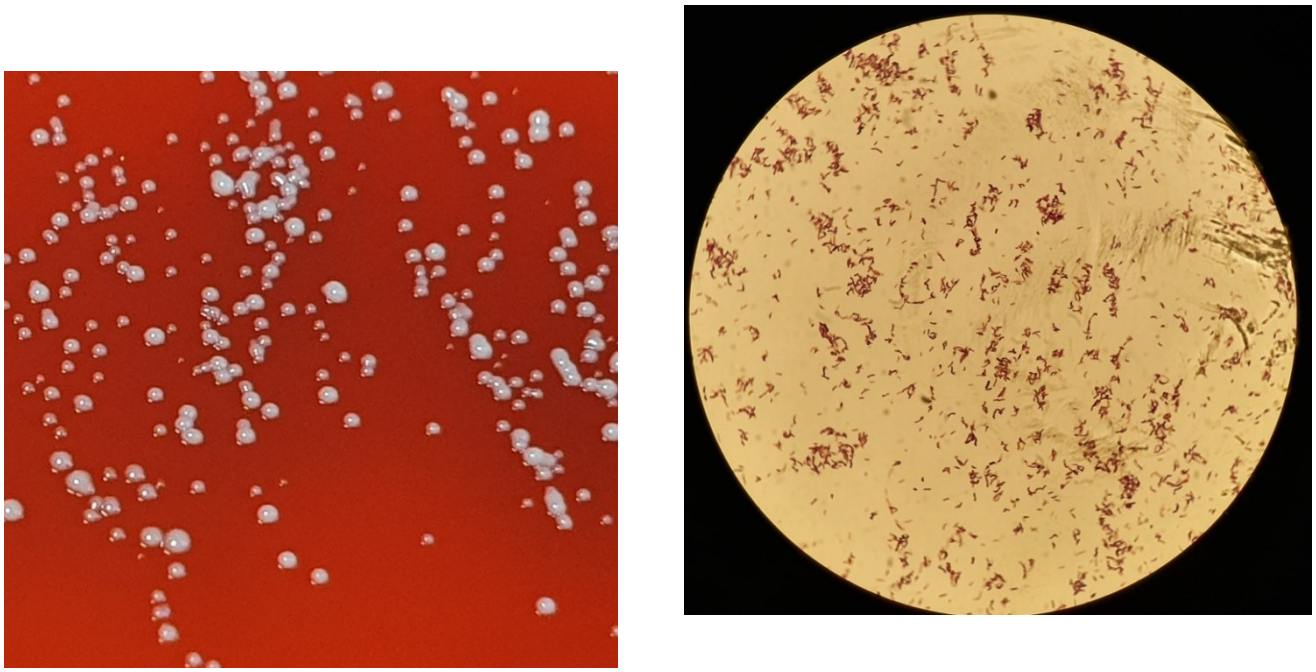


Figure 1: Propionibacterium species anaerobic, gram positive bacilli.

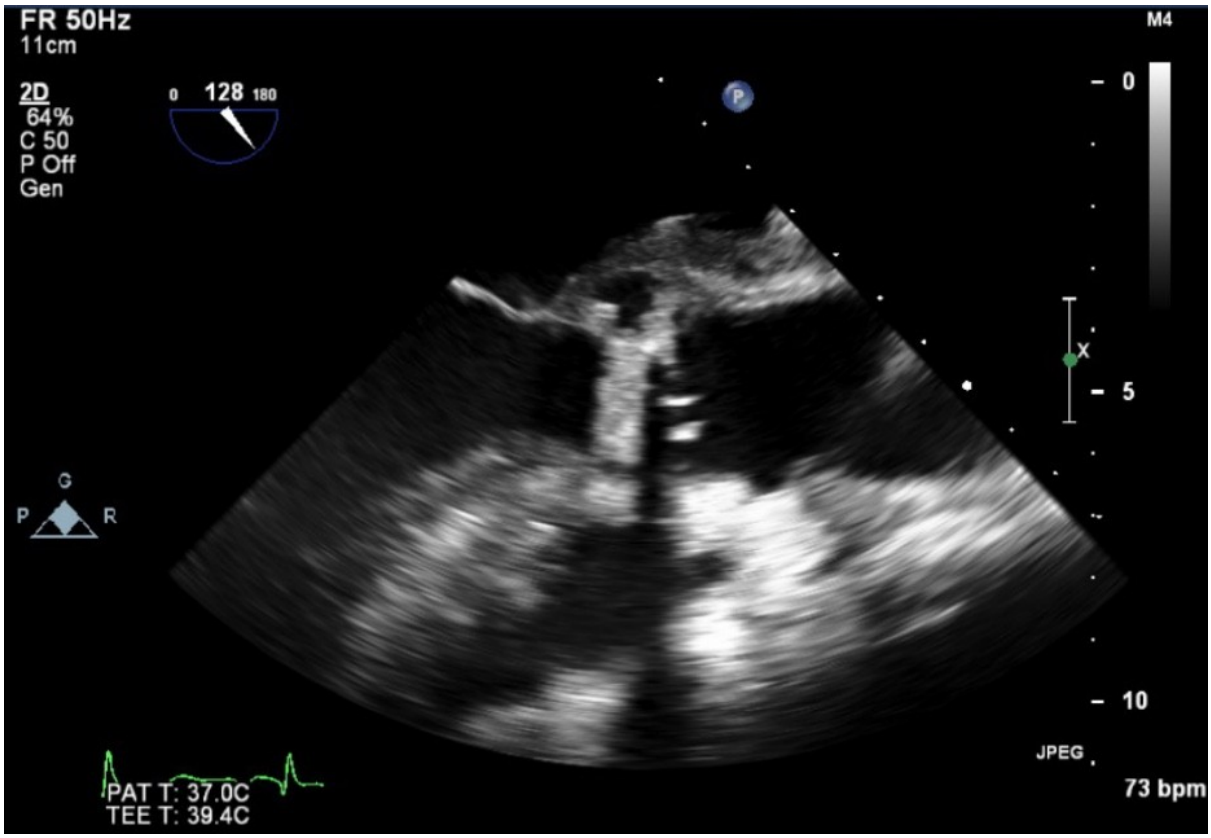


Figure 2 – TOE showing vegetation measuring over 3.3cm^2 in the aortic valve with large aortic root abscess.

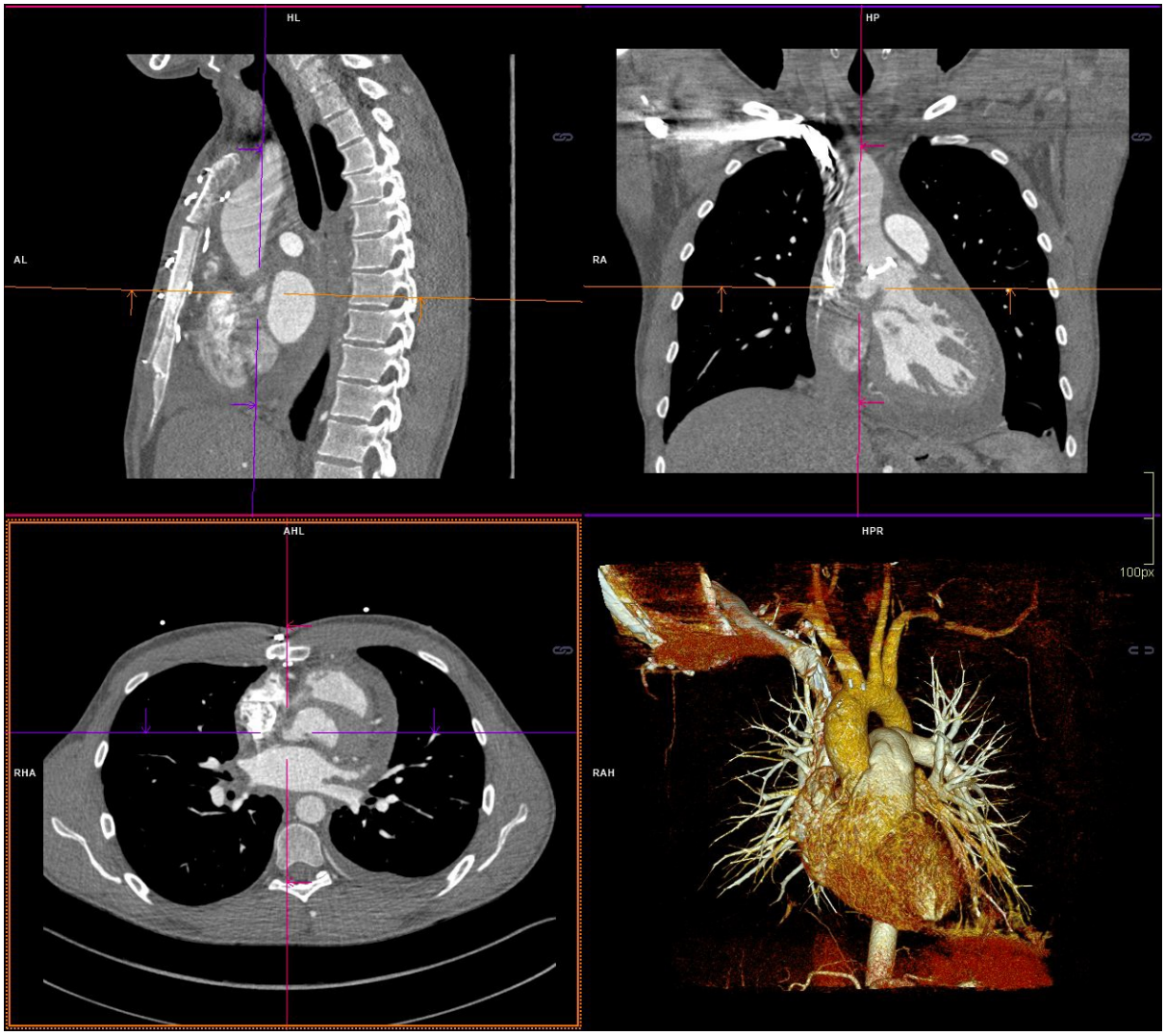


Figure 3 – CT imaging and 3D reconstruction of focal outpouchings in keeping with aortic root abscesses.

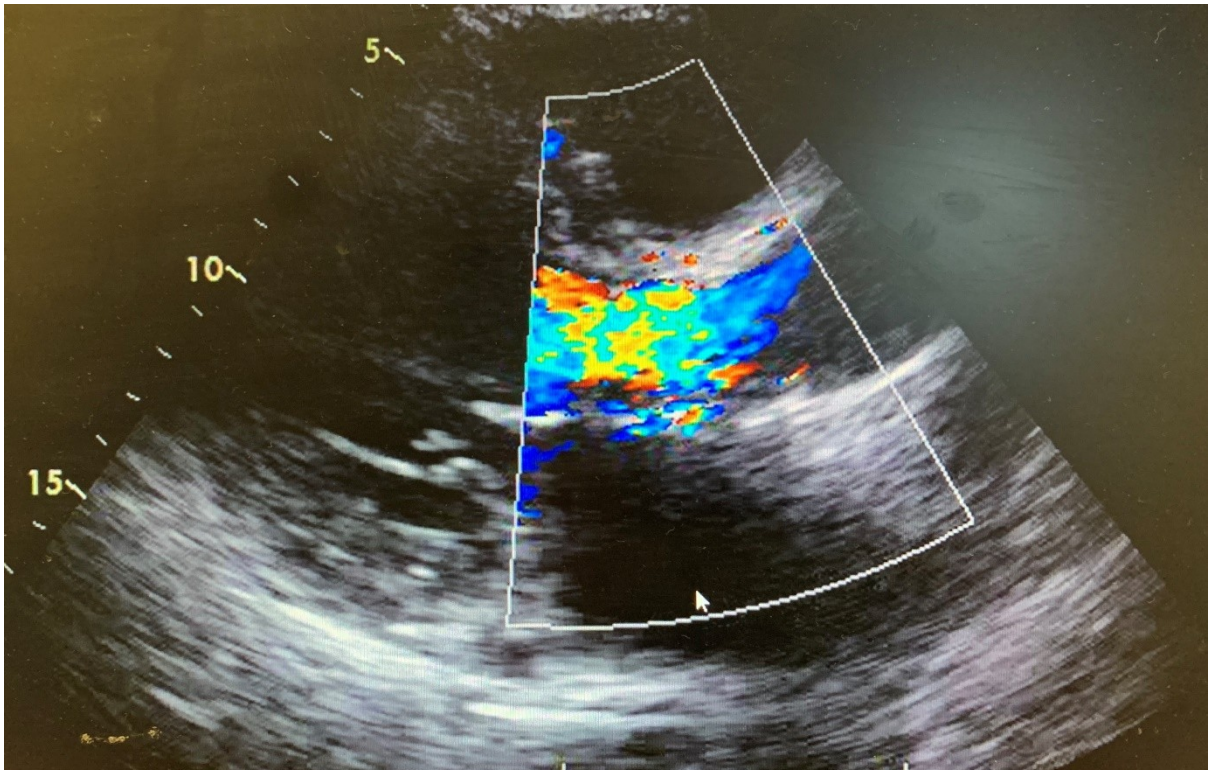


Figure 4 – TTE showing severe AR

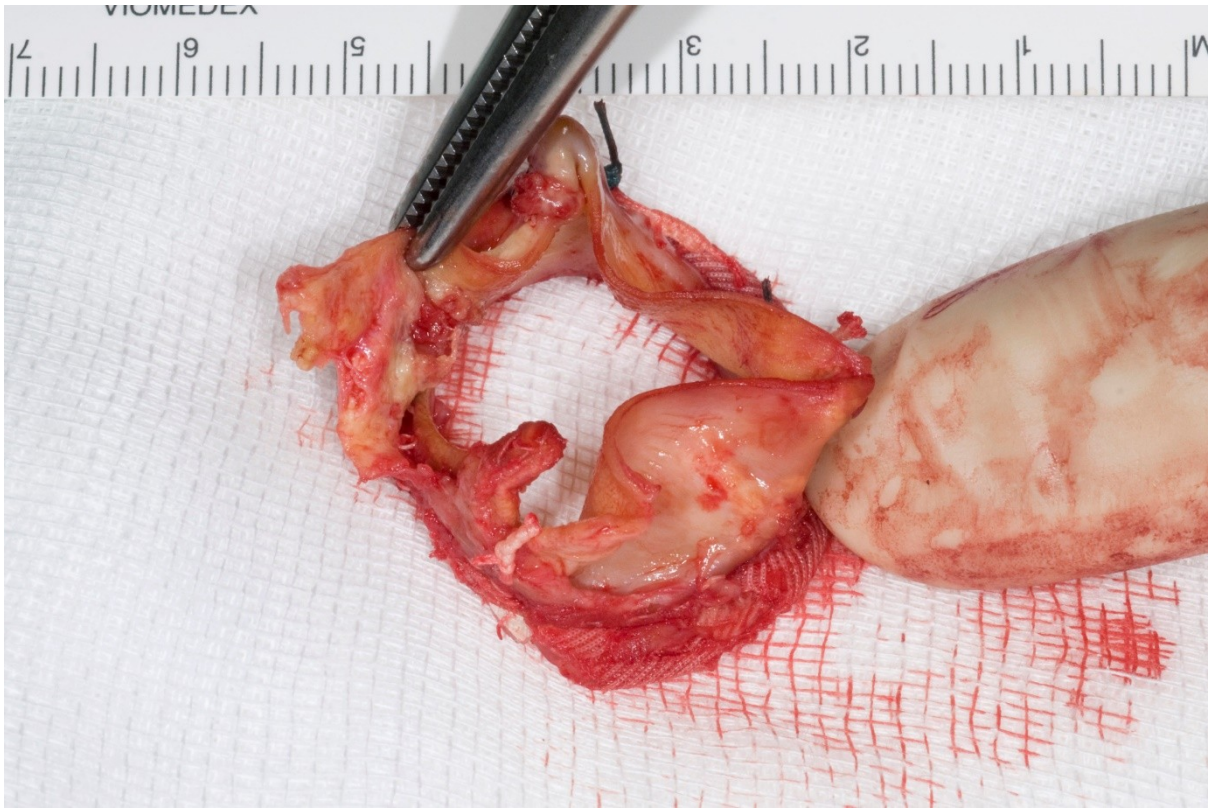


Figure 5 – Excised bioprosthetic AVR

References

(1) Lalani T, PersonAK, Hedayati SS,Moore L, Murdoch DR, Hoen B et al (2007) Propionibacterium endocarditis: a case series from the international collaboration on endocarditis merged database and prospective cohort study. Scand J Infect Dis 39:840–848

(2) Sohail MR, Gray AL, Baddour LM, Tleyjeh IM, Virk A (2009) Infective endocarditis due to Propionibacterium species. Clin Microbiol Infect 15:387–394

(3) Lalani T, PersonAK, Hedayati SS,Moore L, Murdoch DR, Hoen B et al (2007) Propionibacterium endocarditis: a case series from the international collaboration on endocarditis merged database and prospective cohort study. Scand J Infect Dis 39:840–848

(4) Kanafani, Z (2020) Uptodate. [online] Uptodate.com. Available at: <https://www.uptodate.com/contents/invasive-cutibacterium-formerly-propionibacterium-infections> [Accessed 18 June 2020].

(5) Achermann Y, Ellie J, Goldstein C, Coenye T, Shirtliff ME (2014) Propionibacterium acnes: from Commensal to Opportunistic Biofilm- Associated Implant Pathogen. American Society for Microbiology 10: 419-440

(6) Lindell F, Söderquist B, Sundman K, Olaison L, Källman J (2018) Prosthetic valve endocarditis caused by Propionibacterium species: a national registry-based study of 51 Swedish cases. Eur J Clin Microbiol Infect Dis 37: 765-771

(7) Verkaik NJ, Schurink CAM, Melles DC (2017) Letter to the editor, Antibiotic treatment of Propionibacterium acnes endocarditis. Clin Microbiol Infect 10:1016

(8) Banzon JM, Rehm SJ, Gordon SM, Hussain ST, Pettersson GB, Shrestha NK (2017) Propionibacterium acnes endocarditis: a case series. Clin Microbiol Infect 23: 396-399

(9) Yamamoto R, Miyagawa S, Hagiya H, Kimura K, Nishi I, Yamamoto N et al (2018) Silent Native-valve Endocarditis Caused by Propionibacterium acnes. Japanese Intern Med 57: 2417-2420

(10) Braun DL, Hasse BK, Stricker J, Fehr JS (2013) Prosthetic valve endocarditis causes by Propionibacterium species successfully treated with coadministered rifampin: report of two cases. BMJ Case Reports 10.1136

(11) Clayton JJ, BaigW, ReynoldsGW, Sandoe JA (2006) Endocarditis caused by Propionibacterium species: a report of three cases and a review of clinical features and diagnostic difficulties. J Med Microbiol 55:981–987

(12) Corvec S (2018) Clinical and Biological Features of Cutibacterium (Formerly Propionibacterium) avidum, an Underrecognized Microorganism. Clin Microbiol Rev 31: 1-42

(13) Patel A. Calfee R.P. Plante M. Fischer S.A. Green A. *Propionibacterium acnes* colonization of the human shoulder. J Shoulder Elbow Surg. 2009; **18**: 897-902

(14) Lalani T. Person A.K. Hedayati S.S. Moore L. Murdoch D.R. Hoen B. et al. *Propionibacterium* endocarditis: a case series from the International Collaboration on Endocarditis Merged Database and Prospective Cohort Study. Scand J Infect Dis. 2007; **39**: 840-848

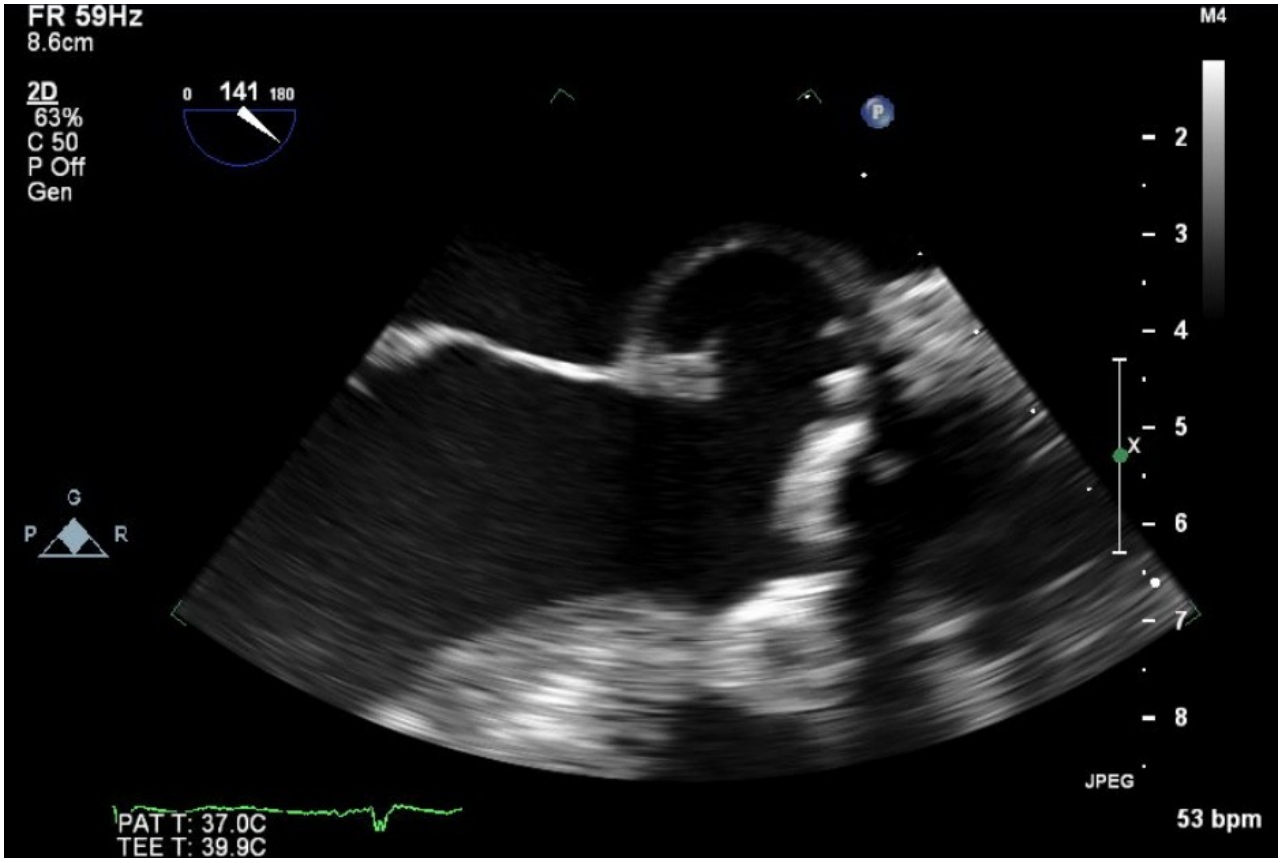
(15) https://scts.org/_userfiles/resources/SixthNACSDreport2008withcovers.pdf

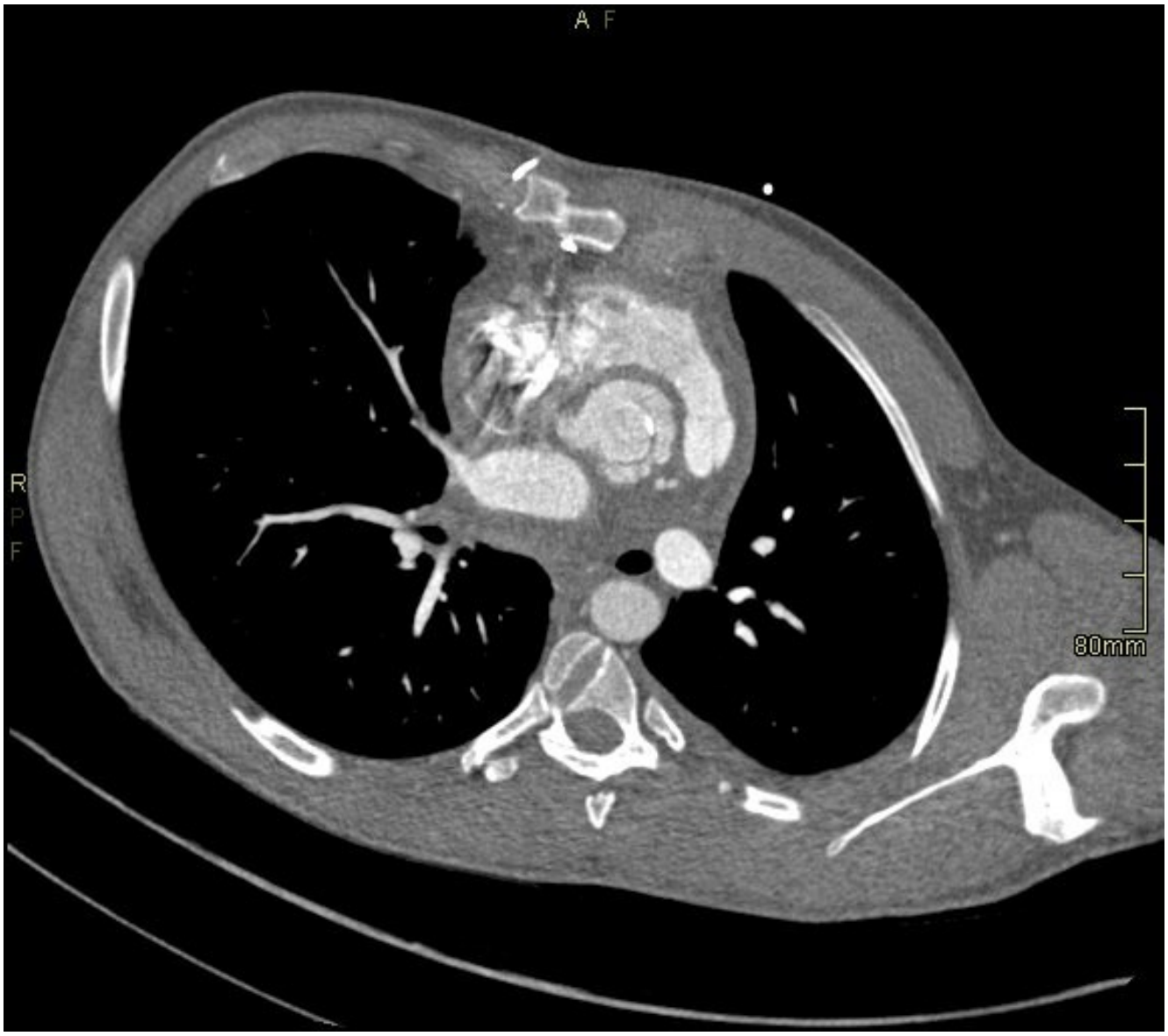
(16) Warren Noel, Nadjib Hammoudi, Elzbieta Wegorowska, Cossimo d'Alessandro, Olivier Steichen. Pacemaker endocarditis caused by Propionibacterium acnes: A case report. Heart and Lung, Elsevier, 2012, 41 (6), pp.e21-23. 10.1016/j.hrtlng.2012.04.006. hal-01172591

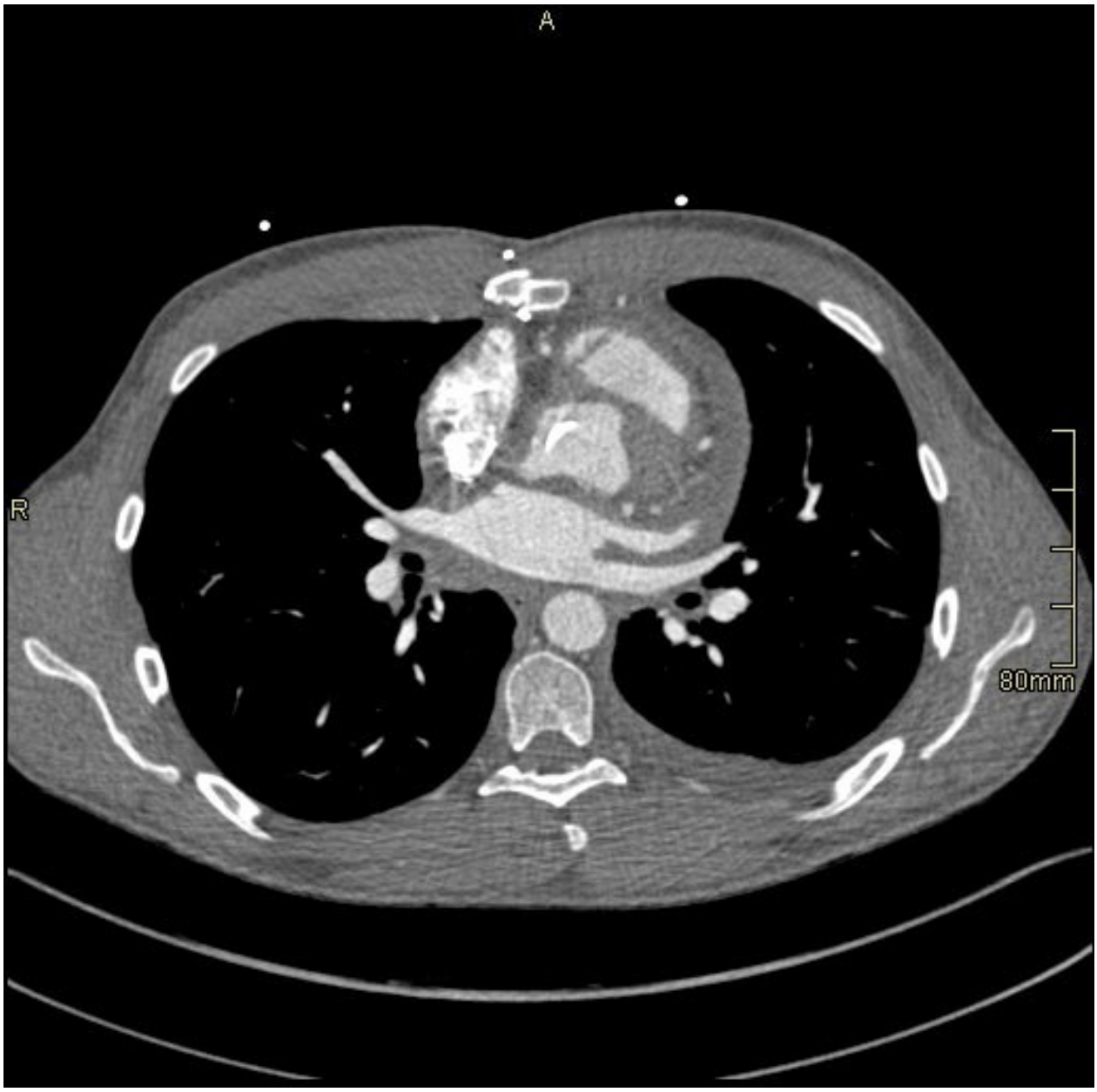
(17) Uslan DZ, Sohail MR, St Sauver JL, Friedman PA, Hayes DL, Stoner SM, et al. Permanent pacemaker and implantable cardioverter defibrillator infection: a populationbased study. Arch Intern Med. 2007;167:669-75.

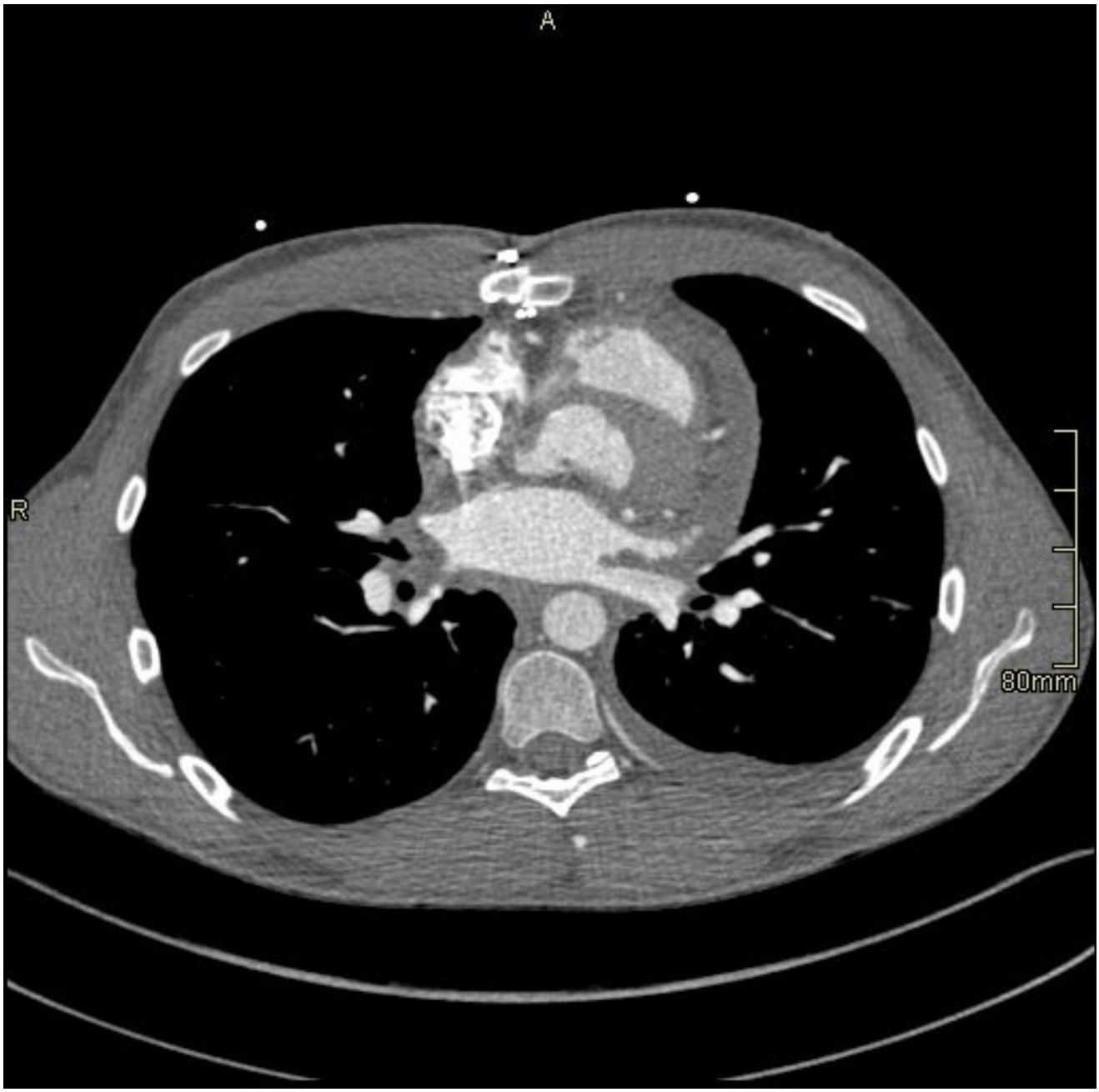
(18) https://www.sciencedirect.com/science/article/pii/S1198743X14604018

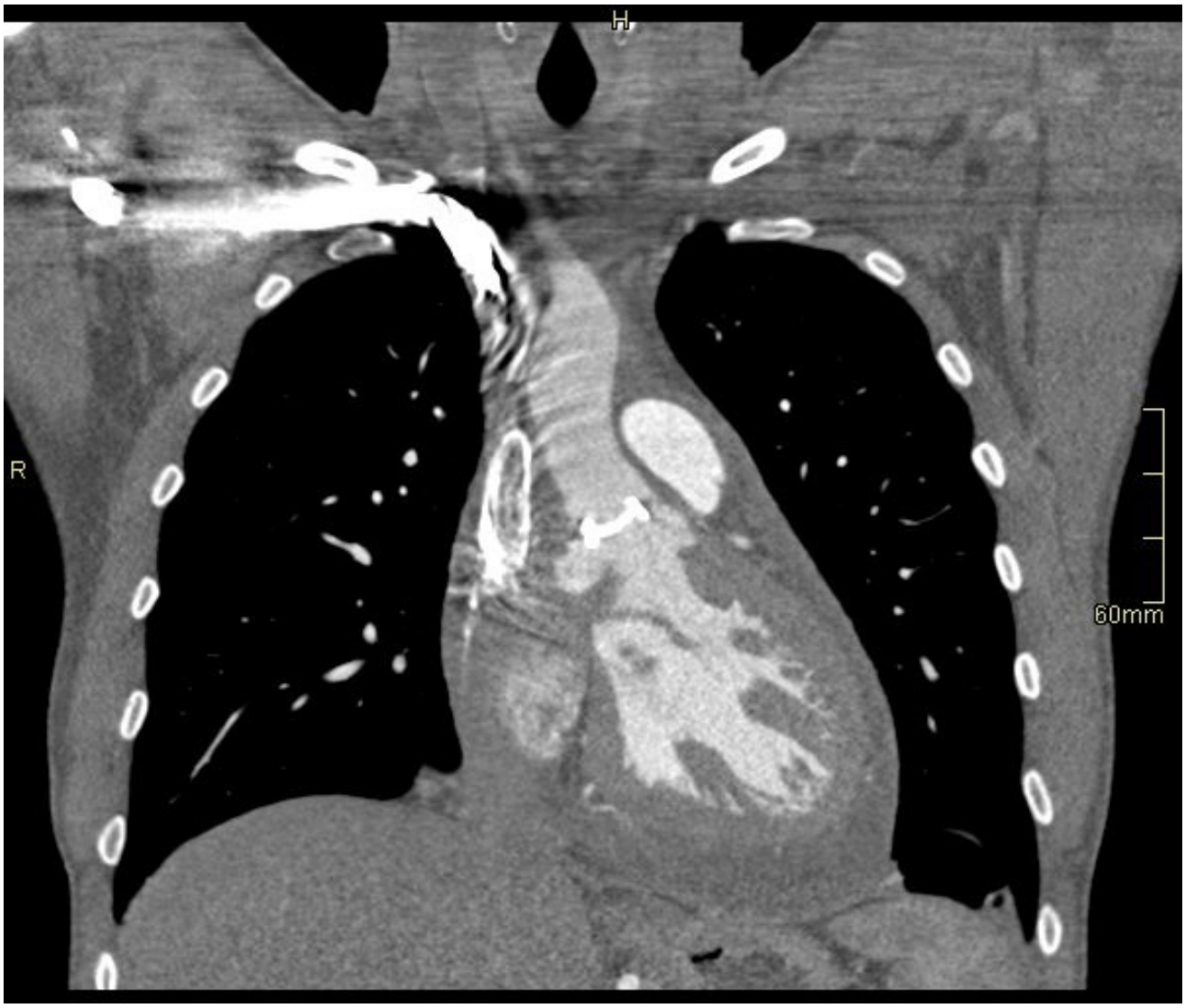
Additional images available all RE - Patient 1




A F
R
P
F
80mm


A
R
80mm


A
R
80mm


H
R
60mm