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Case series: A cautionary tale of screening methods to detect severe cardiac allograft vasculopathy.☆

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Cardiac allograft vasculopathy (CAV) remains a major impediment to long-term survival after heart transplantation (HTx) [1]. One-third of HTx patients develop CAV by 5-years and 1 in 8 HTx deaths beyond 1-year are due to CAV [2]. Whilst recognition of CAV as an adverse prognostic factor reinforces the importance of early detection, surveillance remains challenging. Despite advances in HTx, 5-year survival for CAV has only improved marginally from 71 to 76% [1].

We present a retrospective case series of severe CAV occurring at our institution over a 5-year period. Database analysis of clinical presentation including rejection profile, angiographic findings, management, as well as completeness and efficacy of non-invasive screening were analysed. Severe CAV was defined according to ISHLT definition. Screening at our institution routinely began 1-year post HTx and involved CT coronary angiography (CTCA) at years 1, 3, 5 and five-yearly thereafter as well as stress echocardiogram (SE) at years 2, 4 and years without CTCA.

We identified 6 cases of severe CAV over the last 5-years. Patient demographics, clinical presentation including rejection profile, non-invasive and angiographic findings as well as treatment are summarised in Table 1 below. Representative correlation of CTCA with invasive angiography and histopathological findings are demonstrated in Fig. 1 below. In all cases, CAV screening was either incomplete or failed to detect progression to severe CAV. All patients (including case 5) underwent HTx using a bi-atrial anastomotic approach. This made the interpretation of trans-mitral Doppler and TDI signals unreliable for the assessment of restrictive physiology which might have served as a prelude to the development small vessel disease CAV. Cases 2 and 3 had a CTCA showing non-severe disease 4-months and 1-month prior to the diagnosis of severe CAV, respectively. Cases 1 and 4 had a negative SE 6-months and 1-year prior to CAV diagnosis. Case 5 had not been screened, whilst Case 6 had no screening in the 4-years prior to diagnosis. Four patients suffered cardiac arrest or cardiogenic shock and 1 died. Importantly, CAV screening was incomplete in 5 patients and failed to detect CAV in at least 1 patient.

Early diagnosis and management of CAV is clinically challenging. Due to afferent and efferent allograft denervation, transplant patients rarely demonstrate classical symptoms of chest pain and are often asymptomatic. Many noninvasive modalities have been studied for CAV surveillance, including SE, myocardial perfusion imaging and CTCA. In regard to CTCA, one meta-analysis of prospective trials of CAV reported a 94% sensitivity, 92% specificity, 99% negative predictive value (NPV), and 67% positive predictive value for stenosis [3] but sensitivity and NPV were lower when compared directly to intravascular ultrasound. Limitations of CTCA in HTx include poor visualization of the distal coronary arteries and high resting heart rates. Coronary angiography coupled with assessment of cardiac allograft function maintains the highest level of evidence [4]. Angiography with physiology studies including fractional flow reserve and index of microcirculatory resistance within the first-year post HTx has been shown to be an independent predictor of death/re-transplantation [5].

The mainstay of treatment for CAV remains prevention with early initiation of statin and aspirin therapy, switching to mechanistic target of Rapamycin (mTOR) inhibitors at 3-months post HTx, and optimisation of immunosuppression to minimise rejection episodes [6]. Once

Abbreviations: CAV, cardiac allograft vasculopathy; CTCA, computed tomography coronary angiography; HTx, heart transplantation; SE, stress echocardiogram.

☆ Case series: a cautionary tale of screening methods to detect severe cardiac allograft vasculopathy.Dr Sara Hungerford is the corresponding author and should be contacted for submission enquiries.

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Table 1
Patient overview.

Case.	Demographics and background.	Clinical presentation.	HLA/DSA profile.	Stress echocardiogram.	CT coronary angiogram.	Diagnostic coronary angiogram & intra-procedural hemodynamics.	Management.
1	33yo M HTx for viral DCM. Late ACR (3A) with low immune-suppression levels (yr 1). CMV viraemia (yr 1).	Atypical chest pain with (yr 9).	HTx cross-match: DQA1×01:03 MFI (2659). No de novo DSAs.	Positive stress echocardiogram.	Nil.	Critical ostial left main; severe long-segment mid-RCA disease.	Cardiac arrest during angiogram requiring CPR ECMO. Failed urgent CABG. Urgent re-do HTx.
2	19yo F HTx for familial DCM. Cardiogenic shock with ICU admission secondary to late ACR (1R, post steroid) (yr 7).	Exertional angina (yr 9).	HTx cross-match: No DSA. Development of severe DSAs: DP19 (MFI:11,477), DP6 (MFI 10,843), DP9 (MFI 10,079), DP10 (MFI 9668).	Nil.	No significant coronary artery disease. No significant atherosclerotic plaque.	Triple vessel disease with 90% proximal LAD; 50% proximal LCX; 90% distal RCA. Central Ao pressure: 103/69/83 mmHg.	PCI to distal left main, proximal LAD and RCA after severe chest pain episode.
3	65yo M HTx for DCM. Early ACR (3A) on first week biopsy followed by maximum grade 1A/1R ACR thereafter.	Delayed STEMI and cardiogenic shock (yr 1).	HTx cross-match: No DSA. No de novo DSAs.	Nil.	Minor eccentric mixed plaque in the proximal LAD.	Complete occlusion proximal LAD (yr 1). Central Ao pressure: 84/74/78 mmHg.	PCI to LAD and IABP insertion.
4	67yo M HTx for ischaemic cardiomyopathy. 2 early ACR (2R) episodes with subsequent normal graft function.	Positive stress echocardiogram (yr 18).	HTx cross-match: No DSA. No de novo DSAs.	Negative stress echocardiogram.	Nil.	Critical proximal LAD, severe ostial D1 disease with TIMI 1 flow; LCX and RCA severe diffuse disease.	Failed multi-vessel PCI. CABG and failed left internal mammary graft; re-do with vein grafts to LAD and first diagonal.
5	24yo F HTx for DCM. 8 episodes of ACR (7 2R rejection and 1 3R rejection). Progressive increase in LV wall thickness but preserved systolic function.	Decompensated heart failure and acute coronary syndrome (yr 4).	HTx cross-match: No DSA. Development of moderate DSAs: DP3 (MFI 3016), DP6 (MFI 2580), DP9 (MFI 2476), DP20 (MFI 2391), DQ2 (MFI 2122).	Not screened.	Not screened.	Triple vessel disease with 50–60% mid-LAD, occluded first diagonal; severe distal LCX; occluded mid-RCA.	Died.
6	51yo M HTx for DCM.	Decompensated heart failure (yr 11).	HTx cross-match: No DSA. No de novo DSAs.	Not screened.	Not screened.	Triple vessel disease with 80% distal LAD, occluded proximal LCX and occluded proximal RCA.	Redo HTx.

Abbreviations: ACR, acute cellular rejection; Ao, aortic; CABG, coronary artery bypass grafting; CPR, cardiopulmonary resuscitation; CT, computed tomography; CMV, cytomegalovirus; DCM, dilated cardiomyopathy; DSA, donor specific antibody; ECMO, extra-corporeal membrane oxygentation; HLA, human leucocyte antigen; HTx, heart transplantation; IABP, intra-aortic balloon pump; ICU, intensive care unit; LAD, left anterior descending artery; LCX, left circumflex artery; LV, left ventricular; PCI, percutaneous coronary intervention; RCA, right coronary artery; STEMI, ST elevation myocardial infarction.

CAV has been established however, treatment requires percutaneous coronary intervention, coronary artery bypass grafting or redo HTx where anatomical revascularisation is not feasible [7].

CAV is a leading cause of death after HTx. Whilst CTCA and SE can provide useful information about the arterial lumen and wall, angiography with physiology studies remains the gold standard and should be favored in HTx patients whose risk profile is increased. Ongoing investigation into non-invasive imaging is required before it is widely adopted as part of a CAV screening program.

CRediT authorship contribution statement

Nicole K Bart: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Visualization, Writing – original draft, Writing – review & editing. **Sara L Hungerford:** Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Lucy McGrath-Cadell:** Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Peter S Macdonald:** Conceptualization, Formal analysis, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

None

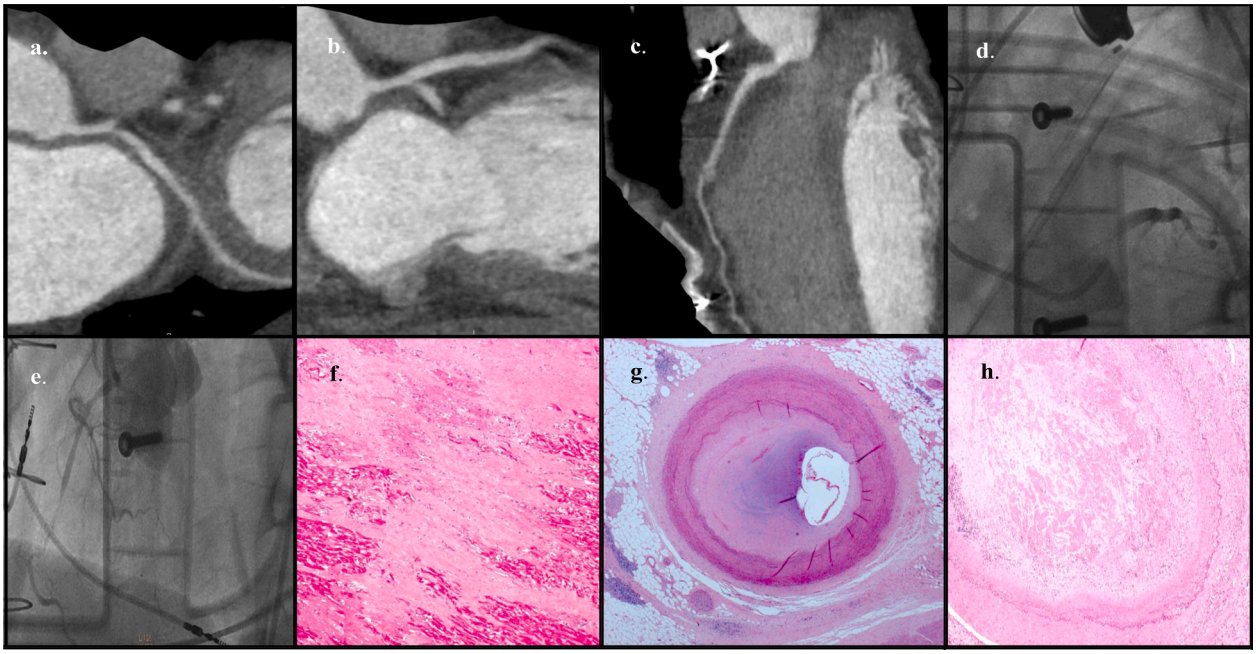

Fig. 1. Representative correlation of computed tomography with invasive angiography and histopathological findings.
Figure 1 a, b & c: Computed tomography coronary angiography demonstrating no focal stenosis in any epicardial vessel. Figure 1 d & e: Invasive coronary angiography showing no dissection. There is a critical left main lesion with retrograde filling from right system and severe long-segment mid-RCA disease. Figure 1 f: Posterior left ventricular infarction with evidence of significant scarring, fibrosis and chronic inflammatory tissue. Figure 1 g & h: Histopathology of the epicardial arteries showing overall close to complete occlusions that appear chronic. Figure 1 g: Left main stem showing marked concentric intimal thickening with greater than 90% occlusion of the lumen and no evidence of dissection. Figure 1h: Left anterior descending artery showing 100% occlusion of the lumen with small channels of early recanalization.

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