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CASE REPORT
Heart failure

Antibody-mediated rejection 16 years post-cardiac transplantation: a case report of an uncommon late presentation in a middle-aged woman

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Background Very late antibody-mediated rejection (AMR) in heart transplant patients (over 10 years post-transplant) is very rare. It is associated with high mortality, graft dysfunction, and fulminant coronary artery vasculopathy (CAV) and should remain in the differential for patients presenting with late graft dysfunction.

Case summary A 57-year-old woman 16 years of post-heart transplant with a previously unremarkable post-transplant course including protocol driven biopsies showing no rejection and a recent unremarkable screening nuclear stress test presented to our institution with clinical heart failure. Echocardiogram revealed graft dysfunction and endomyocardial biopsy showed no signs of cellular rejection, but evidence of AMR. The patient was treated with steroid and immunotherapy with clinical improvement but suffered several infectious complications and renal dysfunction requiring haemodialysis related to her immunotherapy treatment. Despite aggressive AMR management, donor-specific antibodies and symptoms persisted and CAV progressed.

Discussion This case illustrates the poor diagnostic yield of non-invasive testing for AMR, and highlights importance to clinicians of considering AMR even if the patient over 10 years post-transplant when the diagnosis is rare.

Keywords Heart transplant • Antibody-mediated rejection • Graft dysfunction • Heart failure • Management of transplant rejection • Case report

Learning points

- Clinicians must have an index of suspicion for antibody-mediated rejection in late post-transplant patients presenting with symptoms that could indicate graft dysfunction.
- Non-invasive imaging tests frequently used in routine screening protocols of otherwise low-risk late post-transplant patients may miss this diagnosis.
- Despite aggressive immunotherapies and histological resolution this diagnosis can portend a very poor prognosis with progressive coronary artery vasculopathy and graft dysfunction.

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Introduction

Late antibody-mediated rejection [AMR, defined as allograft dysfunction with serologic evidence of donor-specific antibodies (DSAs) and endomyocardial biopsy features occurring over 1 year post-transplant[1]] is rare, but very late AMR (over 10 years post-transplant) is very rare.[2,3] It is associated with high mortality, graft dysfunction, and fulminant coronary artery vasculopathy (CAV)[2] and should remain in the differential for late graft dysfunction.

Timeline

2001	Patient undergoes successful heart transplant.
2001–13	Standard, protocol-driven endomyocardial biopsies show no evidence of rejection.
2013–16	Protocol driven screening myocardial perfusion scans demonstrate no evidence of coronary artery disease
January 2017	Patient presents with congestive heart failure. Echocardiogram reveals biventricular dysfunction. Analysis of endomyocardial biopsy tissue reveals donor-specific antibodies (DSAs) and positive C4d staining suggesting very late antibody-mediated rejection (AMR). Coronary angiogram and intravascular ultrasound demonstrate coronary artery vasculopathy (CAV). Treatment initiated for AMR with steroids and plasmapharesis, followed by rituximab and later bortezomib. Chronic immunosuppression was transitioned from cyclosporine to tacrolimus with ongoing prednisone and mycophenolate mofetil.
March 2017	Symptoms had resolved and DSAs returned to zero.
July 2017	Patient hospitalized with gastrointestinal infection that resolved with treatment. Subsequent screening nuclear stress demonstrated anterior wall motion abnormality and coronary angiogram revealed progressive CAV.
November 2017	Recurrent hospitalization for heart failure, DSAs remained elevated, but C4d staining negative for AMR.
December 2017	Patient presents with volume overload due to worsened renal dysfunction due to tacrolimus toxicity and initiates chronic haemodialysis.

Case presentation

A 57-year-old woman 16 years of post-heart transplant presented in January 2017 with several weeks of back and chest pain, shortness of breath, vomiting, generalized fatigue, and 10 pound weight gain. Her post-transplant course had been uneventful, and she had been treated with mycophenolate mofetil (MMF) and cyclosporine since transplant. Her last protocol-driven screening biopsy 12 years prior to presentation demonstrated 1B rejection. Three months prior to her presentation she had a routine exercise nuclear stress test suggesting normal graft function. Her most recent screening coronary angiogram in 2008 showed no coronary artery disease.

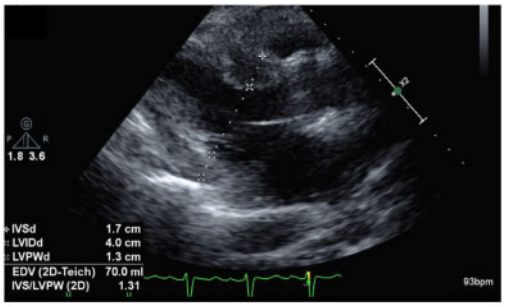

Figure 1 Transthoracic echocardiogram at initial presentation showing the parasternal long-axis view with normal left ventricular internal ventricular diameter, but increased intraventricular septal thickness and posterior wall thickness.

On exam heart rate was 110 b.p.m., with blood pressure 115/78 and she had pulmonary and peripheral oedema. Laboratory testing revealed mildly elevated LDH and troponin-I levels, significantly elevated N-terminal prohormone of brain natriuretic peptide levels (3763 pg/mL, normal 0–100 pg/mL), while other lab studies were unremarkable. An electrocardiogram revealed no ischaemic changes. A transthoracic echocardiogram demonstrated intact biventricular function without wall motion abnormalities, but increased left ventricular wall thickness (*Figure 1*). Cardiac magnetic resonance imaging with gadolinium was not performed because of concern for renal dysfunction. Right heart catheterization was significant for elevated mean right atrial pressure (20 mmHg), mean pulmonary artery pressure (27 mmHg), and mean wedge pressure (20 mmHg) with reduced cardiac index [Fick CI 2.18 L/(m^2*min)]. Left heart catheterization (*Figure 2A and B*) revealed a 40% stenosis in the mid and 60% in the distal left anterior descending (LAD) artery concerning for CAV. No other abnormalities were noted in the coronary arteries and intravascular ultrasound was not performed to avoid heparin exposure for the patient given the suspicion of rejection and urgent need for endomyocardial biopsy. Endomyocardial biopsy (*Figure 3A*) revealed no signs of cellular rejection (Grade 0), but with prominent blue staining of endothelial cells suggestive of endothelial activation. Multiple MHC Class 1 and Class 2 DSAs were positive, with mean fluorescence intensity >3000 (*Table 1*). Immunohistochemistry for C4d showed positive capillary staining consistent with AMR (*Figure 3B*). Treatment for AMR was initiated with steroids and plasmapharesis, followed by rituximab. Due to persistent symptoms and DSAs, she was later treated with bortezomib. Immunosuppression was transitioned from cyclosporine to tacrolimus with ongoing prednisone and MMF. Her symptoms resolved with these interventions suggesting that AMR was the aetiology of her initial presentation. In May 2017, repeat endocardial biopsy demonstrated negative immunohistochemistry with C4d after treatment with no staining in capillaries.

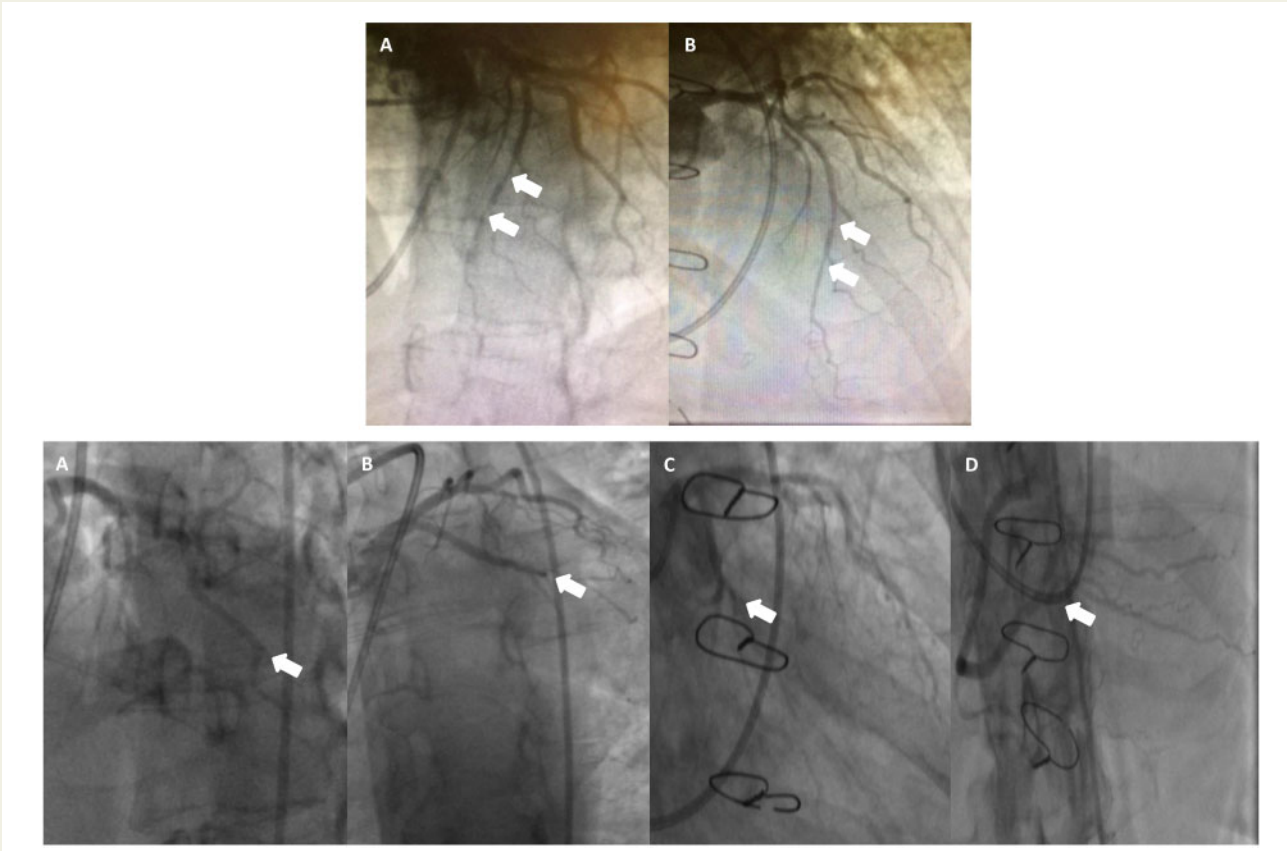

Figure 2 January 2017: antero-posterior view (*A*) and left anterior oblique view (*B*) of left main coronary angiogram showing 40% mid and 60% distal stenosis of the left anterior descending artery. August 2017: left anterior oblique view (*A*) showing moderated diffuse distal left anterior descending artery disease; right-anterior oblique view (*B* and *C*) showing sub-total occlusion of the mid left circumflex artery; right-anterior oblique view (*D*) showing severe, diffuse right posterior descending artery disease. Arrows indicate sites of stenosis.

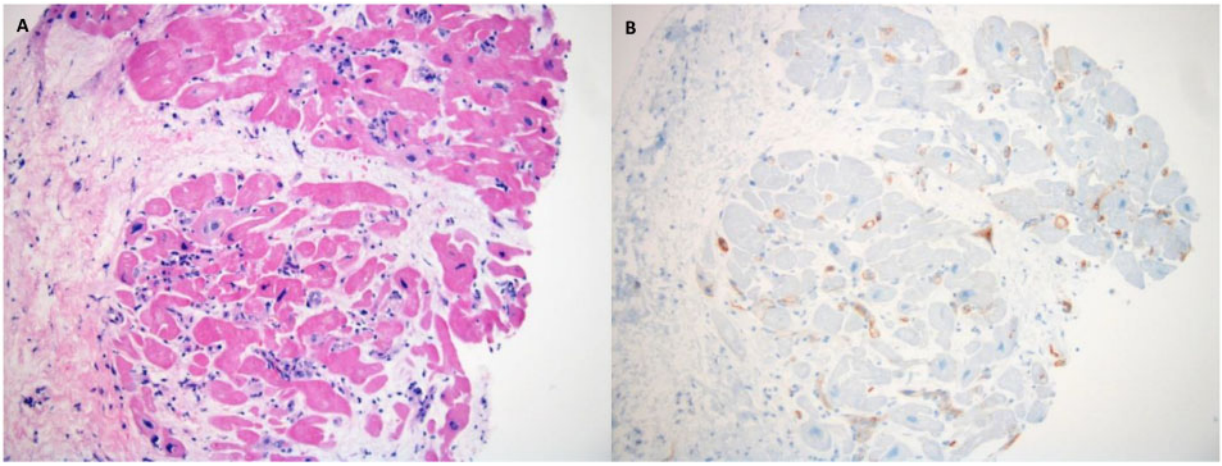

Figure 3 (*A*) Endomyocardial biopsy specimen with haematoxylin and eosin staining demonstrating endothelial activation, note prominent 'blue' staining of endothelial cells, and no evidence of cellular rejection. (*B*) Immunohistochemistry with C4d positive capillary staining consistent with antibody-mediated rejection; note brown immunostaining of endothelial cells.

Table 1 Class 1 and Class 2 donor-specific antibodies with associated mean fluorescent intensity

	Positive at diagnosis in January 2017 (MFI >3000 for each)	Positive testing November 2017
Class 1 Antigens	A2, A29, B13, B44	A2 (6090), A29 (6242)
Class 2 Antigens	DQ6, DQ8, DR53	DR53 (22171) DQ6 (23384) DQ8 (21396)

MFI, mean fluorescence intensity.

In July 2017, she was hospitalized with enterotoxigenic *Escherichia coli* infection requiring azithromycin. Screening myocardial perfusion imaging performed subsequently demonstrated a new large, severe, predominantly fixed distal anterior and apical wall defect compatible with infarct with mild peri-infarct ischaemia, as well as a medium sized, mild inferior lateral wall defect compatible with infarct. Left heart catheterization found progressive diffuse CAV with worsened involvement of the distal LAD, mid circumflex, first obtuse marginal, and right posterior descending artery (*Figure 2C–F*). No discrete lesions were amenable to percutaneous intervention. In response, her immunosuppression changed to everolimus, tacrolimus, and prednisone. In November 2017, she presented with an acute gout flare, as well as volume overload. Donor-specific antibodies checked at that time remained positive and demonstrated only two MHC Class 1 antigens greater than 3000. Repeat endomyocardial biopsy demonstrated no evidence of cellular rejection and negative immunohistochemistry staining for C4d. She presented to hospital again in December 2017 with oral HSV infection and volume overload, this time in the setting of end-stage renal disease (ESRD) attributed to tacrolimus toxicity and cardiorenal syndrome that has required ongoing treatment with haemodialysis. Because of renal dysfunction attributed in part to tacrolimus, her immunosuppression was changed at that time to everolimus and prednisone, on which she has remained clinically stable with New York Heart Association Class I–II symptoms over the past few months. As of February 2018, her left ventricular function improved to normal and no wall motion abnormalities were noted on echocardiogram. Going forward, her surveillance will include clinical follow-up and serial echocardiograms every 6 months.

Discussion

As was done for our patient, treatment for patients with late AMR and CAV includes transition to a new immunosuppressive agent, as well as plasmapheresis, immunotherapy, and steroids.[1] Percutaneous intervention is carried out on amenable coronary lesions. Our patient had a low-risk screening myocardial perfusion scan just 3 months prior to presentation in heart failure with AMR demonstrating the poor sensitivity of non-invasive tests for detecting AMR,[4] and by extension late AMR. Screening protocols for late AMR are not established. Our patient's slowly increasing left ventricular wall thicknesses on previous routine echocardiograms may have been a clue as this finding has been linked to increased mortality and CAV,[5] however, an association with late AMR has not been established. Anti-endothelial, non-HLA antibodies associated with CMV infection have been implicated in CAV and rejection in heart transplant patients,[1] and our patient did have elevated CMV DNA copies (albeit below the level that could be accurately quantified) at the time of her presentation with renal failure in December 2017. The exposure to several infections during 2017 could have led to such an immune cascade and contributed to her clinical course, although she did not have further graft dysfunction in 2017 at the time of this DNA result.

Despite aggressive AMR management, DSAs and symptoms persisted and CAV progressed. Multiple infections complicated our patient's immunosuppressive treatment and toxicity likely contributed to her development of ESRD.

Conclusions

This case of AMR greater than 10 years post-heart transplantation highlights that clinicians must have an index of suspicion of this diagnosis in late post-transplant patients with unclear cardiac symptoms as non-invasive tests frequently used in screening protocols may miss this diagnosis. Clinical deterioration of this patient after initiation of treatment highlights that further investigation is required to define optimal management.

Lead author biography

Charles Miller, MD, FRCPC, is a PGY7 clinical cardiac electrophysiology fellow at Tufts Medical Center in Boston, MA, USA. Dr Miller completed his honors undergraduate degree in Life Sciences at Queen's University, Canada and the University of Edinburgh, UK in 2007. He completed his Doctor of Medicine degree at St George's University, Grenada in 2011. After graduation, he completed internal medicine residency and chief residency at Stony Brook University Hospital in New York. He has been training in general cardiology (2015–18) and cardiac electrophysiology (2018–present) at Tufts Medical Center in Boston, MA over the past few years. He has participated in numerous research projects and held several important leadership posts during his training including patient care quality, teaching, and curriculum development. Dr Miller is an avid traveller, skier, and sailor.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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