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CASE REPORT
Heart failure

A case report: pause and consider the late complications of heart transplantation

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Background A 75-year-old woman with a past medical history significant for non-ischaemic cardiomyopathy status post orthotopic heart transplant, type II diabetes mellitus, hypertension, chronic kidney disease stage III, chronic anaemia, and chronic diarrhoea presented with nausea, vomiting, and an unexplained fall 23 years after original transplantation.

Case summary During her hospital stay, she had multiple episodes of sinus arrest with syncope, preceded by seizure like activity. She was stabilized, and broad work up revealed an occult brain mass that was ultimately resected and consistent with post-transplant lymphoproliferative disease.

Discussion Features that make this case study unique include the late onset and location of the malignancy, the absence of Epstein–Barr virus involvement, and asystole that was potentially neurologically mediated and induced by a brain space occupying mass. This case offers insight into potential late parasympathetic reinnervation of transplanted hearts, adds to the growing literature regarding the connection between the brain and the heart, and reviews potential complications in patients with a remote history of heart transplantation.

Keywords Orthotopic heart transplantation • Late complications • Sinus arrest • Syncope • Brain mass • Post-transplant lymphoproliferative disease (PTLD) • Case report

Learning points

- Post-transplant lymphoproliferative disease (PTLD) is a group of clinically and pathologically heterogeneous disorders presenting in patients with suppressed immune systems after organ transplantation; PTLD most commonly presents in the gut with rare initial central nervous system involvement.
- Central nervous system masses can present with a wide variety of symptoms. Less commonly, they can cause bradycardia and asystole. The mechanism for bradycardia is not well-known but thought to be mediated via the efferent vagal nerve.
- Parasympathetic reinnervation and vagal nerve activity is controversial; however, human and animal studies have shown increased parasympathetic activity the further a patient is from transplantation.

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Introduction

Heart transplantation is the gold standard treatment for patients with advanced heart failure refractory to medical and resynchronization therapy. Survival after transplantation continues to improve; however, complications including chronic allograft vasculopathy, acute rejection, malignancy, infection and renal insufficiency impact outcomes and survival after transplantation.[1]

Timeline

Timeline	Events
23 years prior to presentation, 1994	Patient undergoes orthotopic heart transplantation for non-ischaemic cardiomyopathy. No immediate post-operative complications
1994–2017	Overall post-transplantation course complicated by recurrent urinary tract infections, chronic diarrhoea, and one episode of graft rejection 4 years post-transplant. Calcineurin inhibitor discontinued in 2009 for nephrotoxicity
Hospital Day 1, September 2017	Patient admitted from home with nausea, vomiting, and a fall. Of note, she has had 60 lb unintentional weight loss over the last year. Initial work up concerning for urinary tract infection
Hospital Day 2	Code Blue called for multiple episodes of sinus arrest (lasting as long as 14 s). Temporary transvenous pacemaker placed and patient transferred emergently to cardiac intensive care unit
Hospital Day 3	Right heart catheterization with myocardial biopsy show normal cardiopulmonary haemodynamics and no evidence of rejection, respectively. Transthoracic echocardiogram shows preserved ejection fraction without valvular abnormalities
Hospital Day 4	Computed tomography chest, abdomen, pelvis show no evidence of occult malignancy
Hospital Day 6	Permanent dual chamber pacemaker placed
Hospital Day 10	EGD and colonoscopy show no evidence of clinically significant luminal irregularities
Hospital Day 12	Patient complaints of worsening headaches, nausea, vomiting, left arm numbness, and right hearing loss. Computed tomography head reveals 2.7 cm ring enhancing cerebellar lesion
Hospital Day 25	Patient undergoes posterior fossa craniotomy with resection of 2.7 cm brain mass, pathology ultimately consistent with post-transplant lymphoproliferative disease
Hospital Day 39	Patient discharged from hospital 2 weeks after operation on baseline immune suppression regimen. Close haematology/oncology follow up is arranged for chemotherapy

Case presentation

A 75-year-old woman with a past medical history significant for non-ischaemic cardiomyopathy status post orthotopic heart transplant (OHT), type II diabetes mellitus, chronic kidney disease stage III, and chronic diarrhoea presented with nausea, vomiting, and an unexplained fall. She underwent OHT 23 years prior to admission. Her post-transplant course was complicated by chronic diarrhoea as well as one episode of graft rejection 4 years post-transplant. She was followed routinely in the transplant clinic with appropriate surveillance. Echocardiogram 2 years prior to admission showed normal function. On admission, her immune suppression regimen was mycophenolic acid 720 mg b.i.d. and prednisone 2.5 mg daily.

Review of systems was notable for unintentional 60 pound weight loss over the last year in addition to her chronic diarrhoea. She had a 36-pack year smoking history but quit prior to transplantation. Physical exam was unremarkable.

On hospital day two, she had multiple episodes of sinus arrest lasting as long as 14 s (*Figure 1*) associated with loss of consciousness and seizure like activity. A pacemaker was placed emergently. Right heart catheterization to evaluate for acute rejection showed normal haemodynamics and cardiac output. Myocardial biopsy showed no evidence of cellular or humoral rejection. Transthoracic echocardiogram showed normal ventricular function without valvular disease.

Her hospital course was complicated by acute on chronic kidney injury as such left heart catheterization was deferred. Her weight loss, nausea, and diarrhoea prompted evaluation for underlying gastrointestinal malignancy. EGD and colonoscopy did not show any evidence of luminal irregularities. Non-contrast computed tomography scans of her chest, abdomen, and pelvis were unremarkable.

As her hospital course progressed, she complained of worsening headaches, nausea, left arm numbness, and right sided hearing loss. Computed tomography scan of her head revealed a 2.7 cm mass with a ring like enhancing portion in her cerebellum concerning for metastatic disease vs. abscess vs. infarct (*Figure 2*). An magnetic resonance imaging could not be done to better characterize the lesion given her recent pacemaker placement. Patient underwent posterior fossa craniotomy with resection of the mass. Pathology of the sample had a low proliferation index, Ki67 estimated at 20%. The pattern was thought to be consistent with a lambda restricted B-cell lymphoma

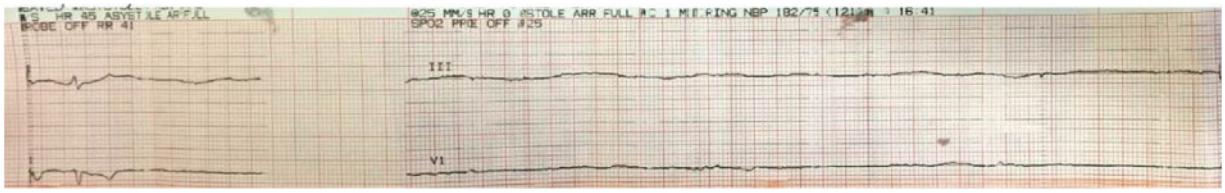

Figure 1 Rhythm strip showing onset of asystole.

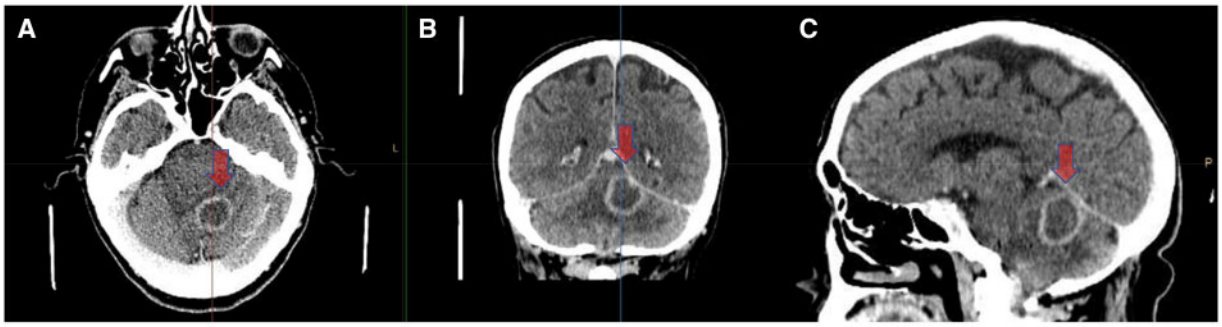

Figure 2 Computerized tomography scan of head with contrast. (*A*) Axial, (*B*) coronal, and (*C*) sagittal views of 2.7 cm ring enhancing lesion (red arrow) that was found to be post-transplant lymphoproliferative disease.

with plasmacytic differentiation favouring post-transplant lymphoproliferative disease (PTLD).

Patient followed up with haematology after resection of her mass. Bone marrow biopsy did not show evidence of marrow involvement. Serum Epstein–Barr virus (EBV) PCR was negative as was CMV PCR and HIV serology. A PET scan only localized disease to the cerebellum. Immune suppression regimen was reduced to mycophenolate 360 mg b.i.d. and prednisone 5 mg. She was started on chemotherapy, DRAG (dexamethasone, rituximab, zidovudine, and ganciclovir) and maintained close follow-up.

Discussion

Post-transplant lymphoproliferative disease is a group of clinically and pathologically heterogeneous disorders presenting in immunosuppressed patients after organ transplantation.[2] Features that make this case of PTLD unique include the late onset and location of the malignancy, the absence of EBV involvement, and asystole that was potentially neurologically mediated via a brain mass. A recent analysis from a single institution between 1984 and 2013 showed a 7.59% incidence in heart–lung transplants, 5.37% in heart transplants, and 3.1% in lung transplants. The most common sites of initial involvement were the gut, hilar lymph nodes, and lung. The central nervous system (CNS), as in our patient, was a rare site of initial involvement.[3] Another analysis identified three cases of primary CNS-PTLD in 1674 heart and lung transplants, an incidence of 0.18%. These cases occurred at 1, 9, and 17 years after transplantation and all were driven by EBV.[4] Epstein–Barr virus infection is a strong risk factor for PTLD and EBV seronegative patients at time of transplantation carry a worse prognosis.[5] Our patient had no evidence of EBV in her tumour, bone marrow biopsy, or serum. Beyond the atypical location and EBV status, the late onset nature of our patient's PTLD is unique. PTLD has a bimodal distribution with the majority of cases occurring in the first year after transplantation.[5] The average time to diagnosis after heart transplantation has been reported as 5.5 years.[6] Prior to this report, only two cases of PTLD were described 20 years post-transplantation.[7] Our patient presenting with an EBV negative primary CNS-PTLD 23 years after heart transplantation is a rare presentation of this immune system driven malignancy.

Beyond the characteristics of this patient's PTLD, the other novel aspect of this case is the bradycardia and asystole potentially of a neurological aetiology induced by the brain lesion. CNS tumours present with diverse symptoms and signs including seizures, headache, nausea, vomiting, focal deficits, and altered mental status.[8] Bradycardia and asystole, albeit not commonly, have also been reported as manifestations of tumours. In one case, a 78-year-old man with 1.4 × 2.0 cm right frontal lobe mass developed recurrent transient atrioventricular blocks followed by syncope, seizure like activity, and loss of consciousness. Interestingly, our patient had seizure like activity prior to her first episode of asystole.[9] In another case, a 48-year-old woman with a history of breast cancer was found to have a 3.5 × 2.5 × 2 cm cerebellar mass after presenting with acute onset pain, nausea, and vomiting with severe bradycardia and

hypotension.[10] The mechanism by which bradycardia occurs is not well elucidated. It can be caused by a lesion that compresses the brain parenchyma, neurosurgical procedures, epileptic and non-epileptic seizures, the trigemino-cardiac and Cushing reflex.[11] These mechanisms mediate inhibition of the cardiac conduction system via the efferent vagal nerve.

Although sympathetic reinnervation of the heart is accepted, parasympathetic reinnervation of the heart is controversial.[12] Canine models have shown evidence of parasympathetic reinnervation as early as 6–12 months after transplantation.[13,14] Human models, however, have not consistently shown parasympathetic control of donor hearts. One study evaluating the carotid baroreceptor reflex did not find evidence of vagus nerve activity in patients 2–63 months after transplant.[15] Another study evaluating the trigemino-cardiac reflex and arterial baroreceptor reflex found that the majority of patients did not have evidence of reinnervation at 96 months post-transplant. The same study, however, did observe a modest trend towards increased parasympathetic activity the later the patient was from transplant.[12] This is supported by the findings of Uberfuhr *et al.*[16] who evaluated the carotid baroreceptor reflex in patients an average of 6.7 ± 2.4 years from initial heart transplant. They found evidence of parasympathetic reinnervation in 4 of 38 heart transplant patients, all with concomitant sympathetic reinnervation.

Conclusion

Ultimately, we present a case of syncope caused by asystole in a patient with a history of a heart transplant who was found to have a CNS lesion consistent with PTLD. Although conduction system delays in heart transplants are typically due to acute rejection, surgical anastomosis failure, or chronic graft vasculopathy, there is data to suggest that reinnervation of the autonomic system occurs the further a patient is from initial transplantation. As such, we recommend pausing and considering neurally mediated aetiologies, when evaluating asystole as a late complication of transplantation.

Lead author biography

Tejas Sinha is an internal medicine resident who is currently completing his training at the Ohio State University. He completed undergraduate and medical school education at Ohio State as well. After graduating, he will serve as chief resident before applying for a fellowship in pulmonary and critical care medicine. His academic interests include critical care, obstructive lung disease, and medical education.

Supplementary material

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

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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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