Images and Case Reports in Heart Failure

Pericardial Constriction Attributable to Graft-Versus-Host Disease
Importance of Early Immunosuppression

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Graft-versus-host disease (GVHD) occurs as a complication of hematopoietic stem cell transplantation when donor immune cells attack host cells identified as immunologically nonself. This is beneficial in completing the eradication of residual malignant cells (the graft versus tumor effect), but detrimental through attack on other host cells and subsequent manifestations of acute and chronic GVHD. Cardiac manifestations of GVHD are rare and include pericardial effusion, coronary artery disease, and conduction abnormalities. There are only 2 previously described cases of GVHD-induced pericardial constriction. Here, we report a case of hematopoietic stem cell transplantation complicated by constrictive pericarditis associated with chronic GVHD of the pericardium, which showed rapid response to systemic corticosteroids.

Case Presentation
A 44-year-old information technology consultant and keen long-distance cyclist was referred to the cardiac clinic for investigation of dyspnoea. He was diagnosed 4 years previously with Philadelphia-positive acute lymphoblastic leukemia, and was refractory to induction chemotherapy, later achieving morphological remission with imatinib and Idar-FLAG (idarubicin, fludarabine, cytarabine, and granulocyte colony-stimulating factor). He went on to have hematopoietic stem cell transplantation with a regime involving full intensity myeloablation and total body irradiation, followed by infusion of matched unrelated donor hematopoietic stem cells. He made a good initial recovery, complicated only a pleural effusion managed conservatively, and by GVHD affecting the skin and managed successfully with prednisolone, cyclosporine, and now maintenance phototherapy. His leukemia remains in complete remission.

At cardiac referral, he described gradual onset of dyspnoea on minimal effort, severely limiting him in his home and work life. He had an elevated jugular venous pressure, left pleural effusion, ascites, and peripheral edema. B-type natriuretic peptide was 55 pmol/L (normal range: <4 pmol/L). A plain chest radiograph demonstrated bilateral pleural effusions, larger on the left (Figure 1). Transthoracic echocardiography showed normal biventricular cavity size and preserved systolic function, with exaggerated tissue Doppler velocities at the septum in early diastole (septal Ea wave of 13 cm/s; Figure 2). There was a prominent septal bounce typical of the ventricular interdependence seen in constrictive pericarditis, more prominent with inspiration (see video in the online-only Data Supplement). The pericardium seemed bright. The inferior vena cava was dilated (2.2 cm) and did not collapse with inspiration. Cardiac MRI confirmed these findings, and excluded fibrosis or infiltrative disease (Figure 4; see video in the online-only Data Supplement). A diagnosis of constrictive pericarditis was made. After multidisciplinary discussion, including the patient’s hematono-cologist, the consensus clinical diagnosis was pleural-pericarditis because of chronic GVHD. The previous pleural effusion and skin GVHD supported this. Other differential diagnoses were considered including radiation pericarditis and leukemia recurrence. The clinical team agreed to initiate therapy with high dose prednisolone (60 mg once daily).

He showed a rapid and marked symptomatic response, such that after 3 weeks he was managing 4 flights of stairs, and by 4 months he was back to work and cycling regularly. He was initiated on steroid-sparing immunosuppression with cyclosporine, with successful reduction of his prednisolone dose. Repeat transthoracic echocardiography reflected this clinical improvement, with normalization of the diastolic tissue Doppler velocities at the septum (septal Ea wave reduced to 7.8 cm/s; Figure 2), and a nondilated inferior vena cava with >50% collapse on sniffing (Figure 3), suggesting a lower right atrial pressure of 5 to 10 mm Hg. However, there were some residual features of pericardial constriction, including ongoing septal bounce and persistent mitral inflow variance with inspiration. To further characterize this, we proceeded to left and right heart catheterization, which confirmed ventricular interdependence, with elevation and equalization of end diastolic pressure between the 2 ventricles (left: 24 mm Hg, right: 23 mm Hg; Figure 5).

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Together these assessments showed greatly improved although persistent physiological constriction. He remains asymptomatic on medical therapy with prednisolone (now at 12.5 mg once daily) alongside cyclosporine at optimal dosage. We discussed the case with cardiothoracic surgical colleagues who agreed that there was no indication for surgical pericardectomy given his current clinical status. Our longer term aims will be to wean the steroid down while maintaining clinical stability on steroid-sparing therapy, and consider the surgical approach again should his condition deteriorate.

Discussion
We have described a rare but important cause of constrictive pericarditis, which is likely to increase in prevalence with further use of, and survival from, hematopoietic stem cell transplantation. Indolent onset of dyspnoea and edema is common in the postoncology population, and high degree of clinical suspicion is necessary. There was strong consensus among the multidisciplinary team on the likely underlying pathology, and the risks of biopsy to achieve histological confirmation were not considered justifiable. Our thesis in this patient is that inflammation of the pericardium driven by donor immune cells has caused the clinical phenotype of constrictive pericarditis, and the resolution of this inflammation by systemic immunosuppression has allowed complete resolution of his heart failure symptoms. As such, this case demonstrates that pericardial constriction associated with GVHD is amenable to immunosuppressive therapy, which should be instituted early in the illness with the goal of mitigating chronic inflammation that can cause permanent pericardial thickening.

Disclosures
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References

Figure 1. Plain chest radiograph at time of cardiac referral, showing bilateral pleural effusions more prominent on the left.

Figure 2. Septal tissue Doppler velocities recorded at the level of the mitral annulus before and after immunosuppressive therapy. The exaggerated longitudinal function seen initially resolves after immunosuppression. Please note the different velocity scales.

Figure 3. The inferior vena cava was dilated and noncollapsing at the time of initial assessment. After immunosuppression, it collapses >50% on sniffing.
Figure 4. Short axis cardiac magnetic resonance inversion recovery late gadolinium sequence, showing no significant enhancement.

Figure 5. Ventricular pressure recordings from left and right catheterization during follow-up. There is elevation and equalization of left and right ventricular end diastolic pressure, with rapid filling of the ventricles in early diastole manifested by the square root appearance of the trace. Left ventricular (LV) and right ventricular (RV) pressures are given as systolic/diastolic/mean (mm Hg).
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