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Brief Report

A Dobutamine paradox: eosinophilic myocarditis in the explanted heart of a 9-year-old girl undergoing cardiac transplantation

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Abstract We describe a 9-year-old girl who was noted to have eosinophilic myocarditis in her native heart after it was explanted during cardiac transplantation. On the basis of absence of evidence for primary or secondary eosinophilia, we suggest that the prolonged use of dobutamine prior to transplantation might have induced the eosinophilic myocarditis.

Keywords: Cardiomyopathy; inotropes; children

Dobutamine is widely used for inotropic support in children. Recently, eosinophilic myocarditis has been reported in association with infusions of this inotrope.[1] Others have pointed to the potential for this inflammatory process to lead to a reduction in cardiac function, paradoxical to the indication for inotropic support. We are unaware of any previous cases reported in children, and because of this, we believe our own experience may be important for physicians using dobutamine to support cardiac output in the young. Thus, we present a case of eosinophilic myocarditis diagnosed in the explanted heart, following transplantation for severe cardiac failure.

Case report

A 9-year-old girl first presented at seven weeks of age to her local hospital with acute deterioration over a period of 24 hours. She required resuscitation and ventilation on the paediatric intensive care unit, where the diagnosis of severe left ventricular dysfunction was made, in association with endomyocardial fibroelastosis. There was suspicion of a metabolic disorder at this time, but despite extensive investigation, no diagnosis was possible. She was ventilated for three weeks during her first admission, with cardiac biopsies at that time demonstrating endomyocardial fibroelastosis, but in the absence of any eosinophilic infiltration. Additional electron microscopy performed on the initial biopsy, due to metabolic disease being considered a differential diagnosis, revealed unremarkable infrastructure without evidence of inflammation, necrosis or storage disorder.

She made a good recovery after her initial presentation, but continued to have poor left ventricular function, with a fractional shortening ranging from 15 to 20%, and an increased left ventricular end-diastolic volume. During follow-up she was treated with diuretics and inhibitors of angiotensin converting enzyme until, in July of 2000, she experienced an episode of marked deterioration. This change was represented by a worsening of her symptoms of cardiac failure, with consistently poor cardiac function on echocardiography. She had also developed severe mitral regurgitation. After detailed discussion, mitral annuloplasty was performed early in 2001. After surgery, her cardiac symptoms improved for a short time, but she was readmitted in March, 2003, with severe deterioration, a dilated left ventricle, and fractional

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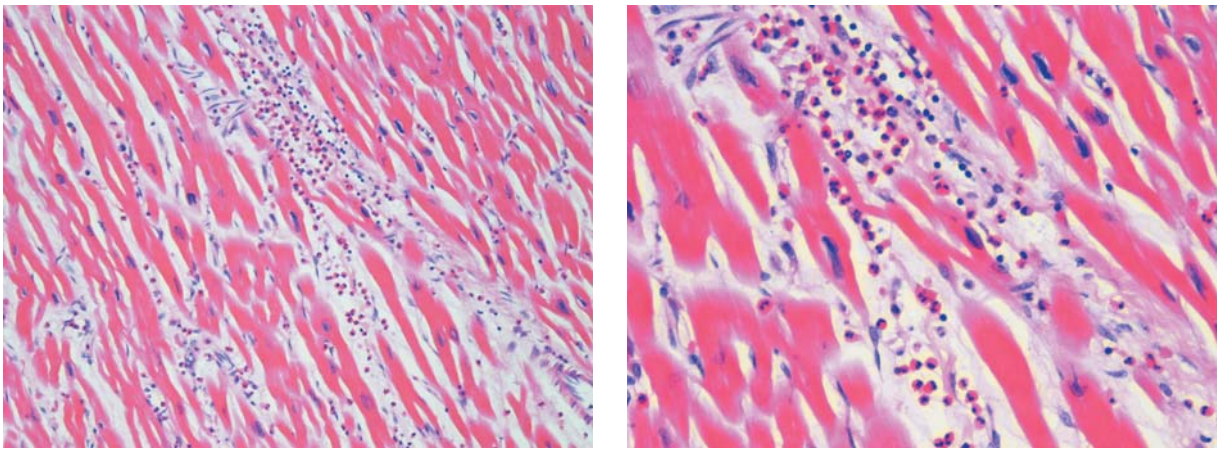

Figure 1.
Photomicrographs demonstrating eosinophilic myocarditis in the explanted specimen from a 9-year-old girl requiring cardiac transplantation for severe cardiac failure. There is a florid interstitial and perivascular inflammatory infiltrate with interstitial oedema and myocyte damage, the infiltrate being composed of lymphocytes, macrophages and large numbers of eosinophils (left, H&E, original magnification ×100; right, H&E, original magnification ×250.

shortening of 9%. She was started on Dobutamine at 5 micrograms per kilogram per minute for 16 days, and listed for cardiac transplantation.

An orthotopic cardiac transplant was carried out, and sections of the explanted heart were submitted for histopathological examination. Sections of right and left ventricle demonstrated a moderate diffuse interstitial inflammatory infiltrate, composed of lymphocytes, macrophages, and large numbers of eosinophils. There was associated interstitial oedema and focal myocytic damage. The features indicated eosinophilic myocarditis (Fig. 1). There was no history of atopy and, during the four years of follow up at Great Ormond Street, peripheral blood eosinophilia had never been present. No further cardiac biopsies had been performed after her initial presentation.

Discussion

Most cases of histologically proven myocarditis associated with cardiac failure demonstrate lymphocytic inflammatory infiltration in association with myocytic damage and interstitial oedema. In a minority of cases, however, there may be features indicating unusual diagnoses, such as giant cell or eosinophilic myocarditis.[2] The histological phenotype of eosinophilic myocarditis has been reported in around one-twentieth of explanted hearts,[3] and in about one-twentieth of endomyocardial biopsies showing myocarditis in patients presenting with cardiac failure.[4] This is a histopathological diagnosis that may be associated with several clinical syndromes.

First, some cases appear to represent primary eosinophilic myocarditis, in which there is no peripheral blood eosinophilia, and no apparent history of either infection or autoimmune disease, but which may result in severe myocarditis with myocardial necrosis and even sudden death.[5] Secondly, eosinophilic myocarditis may be associated with conditions in which peripheral blood eosinophilia is present, such as Lofflers syndrome and parasitic infestations.[6] Thirdly, some cases are reported following an apparent clear history of precipitating viral infection, suggesting an uncommon immunological response to a common antigen, the pathogenesis of the cardiac dysfunction presumably being similar to lymphocytic post-viral myocarditis.[7] Finally, eosinophilic myocardial infiltration has also been reported in association with the use of intravenous dopamine/dobutamine as therapy for severe cardiac failure.[1]

In our patient, eosinophilic myocarditis was not shown on the biopsies performed as an infant, and absence of eosinophils in the peripheral blood excludes Loffler's syndrome. During the course of her deterioration prior to transplantation, she had no clinical evidence of acute infection, implying that the eosinophilic infiltration was not related to an unusual viral infection. Neither the total count of white cells, nor the count of eosinophils in the peripheral blood, was raised in the weeks prior to transplantation. Absence of supporting evidence for other causes, through a diagnosis of exclusion, makes the use of dobutamine a factor in the eosinophilic infiltration seen in the explanted heart.

There is good evidence that eosinophilic infiltration of the myocardium may have direct pathological effects on cardiac function. Patients with a history of chronic peripheral eosinophilia are known to be at risk of significant progressive endomyocardial disease, as in Loffler's endocarditis, or even acute necrotising

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eosinophilic myocarditis.[7] The mechanism involving direct effects of products of the eosinophil granules on cardiac myocytic function is well described in experimental studies.[8]

Eosinophilic myocarditis is uncommonly encountered in children. Cases of severe necrotising eosinophilic myocarditis, however, have been reported in childhood.[5] We are unaware of the mechanism that causes infiltration of the eosinophils into the myocardium, but it is possible that the pathogenesis is related to a hypersensitivity reaction related to the diluent, sodium bisulfite, rather than the active compound itself.

In summary, we report a patient with dilated cardiomyopathy in whom eosinophilic myocarditis was discovered in the explanted heart subsequent to transplantation. We believe that, in the presence of normal early biopsy, absence of eosinophilia and acute myocarditis, this may be related to the use of dobutamine. The induction of eosinophilic myocarditis by an inotrope, with the potential to cause deterioration of cardiac function, may be an important consideration in the long-term management of children requiring haemodynamic support.

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