Fatal and Unanticipated Cardiorespiratory Disease in a Two-Year-Old Child with Hurler Syndrome Following Successful Stem Cell Transplant

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Abstract A 2-year-old female with Hurler syndrome (mucopolysaccharidosis type 1) died suddenly within 3 months of successful unrelated fully matched cord blood transplant, having received weekly enzyme replacement therapy (ERT) prior to transplant. Though an infectious aetiology was clinically suspected to be the cause of her unanticipated acute deterioration and untimely demise, autopsy findings suggested that a combination of pre-existing but sub-clinical Hurler related cardiopulmonary pathology and superimposed transplant related pulmonary venopathy as the basis of her death. This case highlights the limitations of ERT in ameliorating cardiorespiratory disease and the failure of standard pre-transplant investigations to detect significant abnormality related to her underlying condition. It also reinforces the importance of autopsy in explaining unanticipated events.

Introduction

Mucopolysaccharidosis type I (MPS I) or Hurler syndrome (HS) is an autosomal recessive metabolic disorder caused by the deficiency of α -L-iduronidase, resulting in the accumula-

tion of substrates including heparin and dermatan sulphate. This accretion leads to characteristic facial features, hepatosplenomegaly, skeletal abnormalities, multi-organ dysfunction and progressive mental retardation. Allogeneic haematopoietic stem cell transplantation (HSCT) is the standard of care for patients with this condition (Krivit et al. 2005; Boelens et al. 2007; Prasad et al. 2010) and results in amelioration of many of the symptoms associated with this disorder and stabilisation of neuropsychological status but has limited impact on skeletal and corneal abnormalities (Peters and Steward, 2003; Aldenhoven et al. 2008). There are now robust data to support the contention that transplantation in infancy offers superior outcomes (Muenzer et al. 2009; Boelens et al. 2007), and the possibility of newborn screening programmes is a subject of current debate (Marsden and Levy 2010). HSCT, ideally before 18 months of age, while intellectual function is still preserved, has been recommended by some (Peters and Steward 2003), while a recently published European consensus document favours transplant by 2.5 years (de Ru et al. 2011). Weekly infusions of recombinant enzyme replacement therapy (ERT) have been shown to reduce morbidity, particularly in relation to cardiorespiratory function, prior to transplant (Cox-Brinkman et al. 2006; Wiseman et al. 2012) and is now standard practice in many major centres. This report documents the unexpected course of events following HSCT in a toddler whose peri-transplant course was uneventful.

Case Report

A female infant, born to non-consanguineous parents, displaying many of the features of Hurler syndrome, was eventually diagnosed at 23 months with MPS1, genotype W402X/W402X, a known mutation generating a

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premature stop codon and associated with no enzyme production. She was asymptomatic from a cardiorespiratory perspective with serial normal blood pressure measurements and was commenced on weekly ERT while awaiting HSCT. Standard pre-transplant assessment included 2D and M mode echocardiography on three separate occasions, all of which revealed normal left ventricular function and no evidence of valvular incompetence. Respiratory status was also unremarkable. Following 4 months of weekly ERT (100 U/kg) while awaiting transplant, she underwent an uneventful HLA identical (10/10) matched unrelated cord blood transplant (CBT) following busulfan (with pharmacokinetic monitoring), fludarabine and ATG conditioning with cyclosporine and methylprednisolone as GVHD prophylaxis. Her transplant course was uneventful with normal organ function, no significant infection and without graft versus host disease. Complete donor leucocyte engraftment was documented at 28 days post transplant using molecular analysis of donor/recipient discriminatory short tandem repeats. She remained well and asymptomatic on close surveillance following discharge on prophylactic cotrimoxazole, penicillin, acyclovir and itraconazole. On D + 86, she presented with a 5-day history of dry cough; on clinical examination, she was afebrile, O₂ saturation was at 60 % in room air and chest x-ray revealed bilateral pulmonary infiltrates. No conduction abnormality or arrhythmia was documented on cardiac monitoring. She was commenced on broad-spectrum antibiotics but deteriorated rapidly over the succeeding 2–3 h, had a cardiorespiratory arrest and failed to respond to resuscitation. The clinical impression at the time of her death was of a respiratory tract infection, probably viral in origin. Pre-mortem nasopharyngeal aspirate was negative for all respiratory pathogens.

A limited post-mortem examination, confined to the chest at parent's request, identified significant pulmonary and cardiac disease. The lungs showed no evidence of any infectious process on histological examination or in microbiological investigations including both culture and serological testing. The underlying airway architecture was unremarkable but there was a range of vascular pathology. Pulmonary arteries exhibited a patchy but often profound vasculopathy with marked intimal wall thickening without aneurysmal, plexiform or necrotising changes (Fig. 1). There was also evidence of a venopathy with pronounced endothelial swelling and atypia in a majority of pulmonary veins associated with fibroproliferative changes and attempted recanalisation (Fig. 2). Peri-arteriolar foreign body giant cells and foreign body giant cell granulomas without refractile material were also detected and occasional large arteries showed eccentric endothelial cushions with cholesterol clefts present while another showed an almost

Fig. 1 Section of lung containing pulmonary artery branches with marked myointimal thickening

Fig. 2 Section of lung showing pulmonary vein with fibro-obliterative venopathy

occlusive thrombo-embolus with abundant cholesterol debris. The lung sections also showed fibrin in some alveoli and there were multiple areas of microscopic acute pulmonary haemorrhage.

Gross examination of the heart showed pericardial, endocardial and valvular thickening (Fig. 3). Histological examination confirmed conspicuous myxoid and fibromyxoid change in atrio-ventricular valve leaflets. There was profound endocardial thickening, particularly in the atrium, and areas of interstitial fibrosis were seen most notably in papillary muscles of the left ventricle. There was a profound coronary arteriopathy with substantial fibro-intimal thickening (Fig. 4). Connective tissue stains confirmed the presence of a vasculopathy and alcian blue histochemistry confirmed the presence of myxoid interstitial infiltrate within the valvular, endocardial and coronary arterial structures.

Fig. 3 Left side of the heart at autopsy showing thickened mitral valve leaflets with distinct nodularity of the free margins of the cusps

Fig. 4 Section of the proximal left anterior descending coronary artery showing marked intimal thickening

The findings suggested that a combination of pre-existing but sub-clinical Hurler related cardiopulmonary pathology and superimposed transplant related pulmonary venopathy formed the basis of the patient's abrupt clinical deterioration and death.

Discussion

Cardiac disease in MPS 1 has a prevalence and severity believed to be in the range of 60–100 % of those studied and ranges from severe dilated cardiomyopathy presenting within days or weeks of birth to identification of thickened and incompetent cardiac valves in otherwise asymptomatic individuals (Leal et al. 2010; Braunlin et al. 2011; Wiseman et al. 2012). While valvular abnormalities and coronary

artery disease are most frequently documented, vascular changes in great vessels and conduction abnormalities have also been described. Transthoracic echocardiography and 12-lead ECG remain the standard methods used to assess cardiac status in these patients, and serial monitoring, following successful transplantation, has proved a reliable indicator of cardiac function in the vast majority of patients. Other more invasive techniques, including transoesophageal echocardiography, cardiac MRI and coronary angiography, are rarely indicated and are not without risk in this unique group of patients and may also underestimate the extent of disease.

Enzyme replacement therapy (ERT), usually commenced once a diagnosis is made and continued until there is evidence of sustained engraftment, has revolutionised the management of dilated cardiomyopathy in infancy (Hirth et al. 2007; Wiseman et al. 2012) with many other centres reporting anecdotal evidence of improvement in shortening fraction and subsequent uneventful HSCT, together with alleviation of upper respiratory symptoms. Valvular thickening, on the other hand, appears irreversible and may even progress (Braunlin et al. 2003; Malm et al. 2008), reflecting the relative avascularity of these structures. While some authors suggest that the status of coronary ostia may be improved following successful transplantation (Braunlin et al. 2001), others have not supported this observation (Yano et al. 2009).

The impact of cardiac disease on survival following bone marrow transplantation is also disputed. In a study carried out in Minnesota comprising 74 patients with MPS 1 undergoing HSCT, the overall survival post transplant was 63 % and 53 % at 1 and 5 years, respectively. An assessment of pre-transplant risk factors found no clear link to cardiac status. However, patients with pulmonary complications were associated with reduced survival. Of the 33 patients who died, the largest proportion died of infection (Orchard et al. 2010).

Pulmonary veno-occlusive disease (PVOD) has been previously documented following HSCT, usually in association with haematological malignancies (Barker et al. 2003; Montani et al. 2010). It is thought that the greatest risk factor for the development of PVOD is endothelial injury from cytotoxic chemotherapy and irradiation. Several reports indicate that patients with MPS 1 may have a higher likelihood of pulmonary complications such as alveolar haemorrhage than patients of similar age transplanted for other diseases (Gassas et al. 2003; Orchard et al. 2010). Hepatic VOD has been well documented following HSCT (Barker et al. 2003; Copell et al. 2010; Corbacioglu et al. 2012), and the risk is increased when busulphan is used as conditioning agent (Vassal et al. 1996; Corbacioglu et al. 2012); PVOD is more difficult to document as lung biopsy is rarely undertaken. It is worth noting that

pharmacokinetic monitoring of intravenous busulphan was well within the therapeutic range in this patient.

In conclusion, the fulminant course experienced by our patient is a sobering reminder that standard pre-transplant evaluation may fail to detect the true extent of cardiorespiratory pathology. This experience raises the question of whether the recently recommended upper age limit of 2.5 years for HSCT in this condition (de Ru et al. 2012) is appropriate for patients with the more severe genotype as was the case in this particular patient. Consideration must also be given to the incorporation of non-busulphan conditioning regimens for this high-risk cohort of patients. This case report also reinforces the role that autopsy can play in explaining unanticipated events for both family and clinical staff, providing information that continues to impact on the shape of future practice.

Take-Home Message

Standard pre-transplant workup may underestimate the extent of cardiorespiratory disease in Hurler syndrome which may be compounded by current conditioning regimens.

Author Contributions

Sampada Gupta: Specialist registrar in histopathology, assisted with the autopsy examination and wrote the initial draft of the manuscript.

Anne O'Meara: Consultant in paediatric oncology, was responsible for the care of the patient from the time of diagnosis of Hurler syndrome and edited the manuscript.

Robert Wynn: Consultant in paediatric haematology & HSCT, was the transplant physician involved in the patient's care.

Michael McDermott: Consultant paediatric pathologist, performed the autopsy examination and edited the manuscript.

Guarantor

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Ethics and Consent

Ethical approval was not required for this report, but family members have consented to the publication of these findings.

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