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Point of Care Ultrasound (Pocus) in Early Diagnosis of a Pediatric Pauci-Symptomatic Acute Heart Transplant Rejection

Open Access Case Report

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Delmonaco AG[1], Garrone E[1]*, Raffaldi I[1], Lauria B[1], Aidala E[2], Bordese R[2] and Bondone C[1]

[1]Department of Pediatric Emergency, Regina Margherita Children's Hospital, University Hospital of Health and Sci-ence, Italy

[2]Department of Cardiology and Cardiac Surgery, Regina Margherita Children's Hospital, Italy

***Address for Correspondence:**
Emanuela G, Department of Pediatric Emergency, Regina Margherita Children's Hospital, University Hospital of Health and Science, Piazza Polonia 94, 10126,Turin, Italy; Fax: 39 11 3135060, Email: garrone.emanuela@gmail.com

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Abstract

We report the case of a 30-month-old boy affected by severe cardiac failure in dilated cardiomyopathy requiring heart transplantation (HT), who was referred to our Emergency Department with a lightly symptomatic acute cardiac rejec-tion, suspected by point of care clinical ultrasound, performed by the Pediatrician. Despite the improvement in medical therapy and the development in mechanical circulatory support, HT still remains the best therapeutic option to im-prove survival and quality of life in patients with advanced heart failure. Rejection remains an important reason for death after pediatric HT and it can be unrecognized until more severe, because of a specific signs at presentation. Point of care ultrasound (POCUS) enhances the clinician's ability to early recognize many pathologic patterns allowing a timely and targeted treatment, as we describe in this case report report.

Abbreviations

HT: Heart Transplantation; POCUS: Point Of Care Ultrasound; FoCUS: Focused Cardiac Ultrasound; LUS: Lung Ultrasound; IVC: Inferior Vena Cava; PED: Pediatric Emergency Department; COVID-19: SARS-CoV-2; DSA: Donor Specific Antibodies; AMR: Antibody-Mediated Rejection; AHF: Acute Heart Failure; CAV: Cardiac Allograft Vasculopathy

Case Presentation

We report the case of a child with dilated cardiomyopathy which evolved in severe cardiac failure requiring heart transplantation (HT), performed when he was 11 month-old. He was then regularly followed-up by the Cardiology and Cardiac Surgery Department of Regina Margherita Pediatric Hospital of Turin. Once discharged home, the patient was treated with a maintenance therapy with tacrolimus and mycophenolate mofetil. No signs of rejection were observed during clinical follow-up and Cath-Lab evaluations.

At the age of 30-month, during COVID-19 pandemic national lockdown, the patient arrived at our Pediatric Emergency Department (PED) for mild abdominal pain from 3 days, a single vomit and asthenia during the previous week. Regular therpeutic compliance was reported. On physical examination the child showed a quite good general condition, smiling, vital signs appropriated for age. No oedemas nor cutaneous rash were detectable. A small mouth ulcer was found. No significant findings on neurologic, cardiovascular and pulmonary examination. Liver dropped 3 cm below the costal margin. The oropharyngeal swab proved negative for COVID-19 infection.

His laboratory tests showed elevated N-terminal-pro B-type natriuretic peptide (NT-pro-BNP: 16109 pg/mL - normal value ≤92 pg/mL); prothrombin time was 27.6 seconds; transaminase, bilirubin, creatinine, sodium and potassium levels proved normal. Tacrolimus level resulted within the therapeutic range. The abdominal ultrasound carried out in the Radiology Unit detected a mild perisplenic and perihepatic effusion. POCUS performed in the PED by the pediatrician confirmed these abdominal findings and detected a 2 cm bilateral pleural effusion, a 5 mm circumferential pericardial effusion, a mild cardiac sectal hypokinesis and a non-collapsible inferior vena cava (IVC). The echocardiography performed by a pediatric cardiologist confirmed mild heart failure and pericardial effusion. The patient was admitted to the Cardiology unit. Clinical acute heart rejection was diagnosed and the endomyocardial biopsy was delayed, due to child's low weight. Donor specific antibodies (DSA) were detected against HLA Class II DQ6 and DQ7, suggesting a humoral rejection. Intravenous Methylprednilosone and Immunoglobulin therapy was started and tacrolimus dosage was increased, leading to heart failure regression and absorption of pericardial, pleural and abdominal effusions. The child was discharged after 10 days, in good general condition and asymptomatic. The endomyocardial biopsy performed three weeks after discharge was negative for cellular rejection; C4d immunostaining was negative and DSA titer was decreasing.

Technique

POCUS was performed in the PED by the emergency pediatrician using a ESAOTE ultrasound system; cardiac evaluation was obtained with a FoCUS approach. The echocardiography done by the cardiologist was performed using a PHILIPS ultrasound system. A linear probe was used to detect pleural effusion, and a sector probe to perform FoCUS and echocardiography (Figure 1).

Review of Literature and Discussion

HT is a standard treatment for selected pediatric patients with

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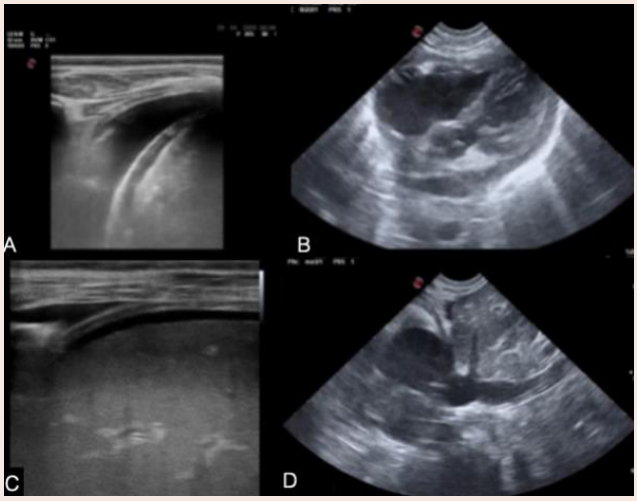

Figure 1: Pocus findings. A-B: Pleural effusion. C-D: FoCUS subcostal 4-chambers view, with 5 mm circumferential pericardial effusion. E: Pleural and subdiaphragmatic effusions. F: Non-collapsible IVC.

end-stage heart disease. With improvement in surgical techniques and immunosuppressive drugs, survival following transplantation has increased over time [2]. Nevertheless, HT recipients are exposed to the risk of several potential complications that may impair their outcome, including graft failure, rejection, infection and CAV (Cardiac Allograft Vasculopathy) [1]. Although acute allograft rejection remains an important potential cause of mortality and morbidity after HT, its incidence and impact on graft survival decreased over the years as immunosuppressive regimens have improved. Its diagnosis is a combination of clinical assessment, echocardiographic findings and endomyocardial biopsy [1-3]. Current knowledge schematically recognizes two mechanisms leading to graft injury during acute rejection: cellular-mediated and antibody-mediated rejection [1-3]. Antibody-mediated rejection (AMR) is characterized by a graft injury mediated by circulating antibodies against antigens expressed by endothelial cells. The injury may depend upon complement activation but can also be mediated by inflammatory pathways activated within the endothelial cells or mediated by natural killer cells [1,4]. Treatment depends on severity and includes immunosuppression adjustment, pulsed corticosteroids, intravenous immunoglobulins, plasmapheresis, immunoadsorption [1,5]. Acute heart failure (AHF) in HT acute rejection is a diagnostic challenge due to non-specific clinical manifestation and the urgent need for timely and tailored management. Many co-existing or alternative conditions with different pathophysiology can induce similar clinical picture, making the differential diagnosis challenging [6]. Imaging modalities are pivotal for fast triage and accurate diagnosis and for decision-making: several portable and stationary imaging modalities are being increasingly used for the evaluation of cardiac structure and function and haemodynamic and volume status. The point-of-care focused cardiac (FoCUS) and lung ultrasound (LUS) examinations are invaluable tools for rapid differential diagnosis. A full echocardiographic examination is necessary for identification of heart failure aetiology, severity, indications for specific therapy, and risk stratification during the stabilization phase [6-8]. FoCUS represents a rapid problem-oriented point-of-care protocol for the ED. FoCUS is possible to carry out with portable or handheld devices as an adjunct to physical examination. The FoCUS approach, providing a limited number of evidence-based targets [6], requires less training and expertise than full echocardiographic exam. In the early phase of AHF, FoCUS examination is useful to detect structural and functional abnormalities of ventricles and valves and presence of effusions [6]. In a case of haemodynamic instability, FoCUS is needed to identify cardiac causes and it allows to quickly differentiate the type of shock [6-9]. The integration of FoCUS and LUS into acute care at an early stage revolutionizes the urgent workup providing a prompt correct diagnosis, leading to faster clinical decisions and immediate life-saving therapy [6]. At the arrival our patient did not appear critical nor manifested signs of shock or evident heart failure. The prompt application of POCUS allowed to formulate the correct diagnosis and consequently timely target therapy.

Conclusion

Pediatric HT is standard of care for children with end-stage heart failure. Though acute rejection has decreased progressively, both diagnosis and management of antibody-mediated rejection is still challenging and complex [8]. The diagnostic yield of POCUS, providing the shortest path to life-saving therapies during first hours after admission, is emerging. Comprehensive echocardiography has the central role in the assessment of HF type and aetiology, indications for treatment, and risk stratification [6]. The diagnosis of acute rejection may be difficult due to the specific clinical presentation, especially in early stages, as we observed in our patient. A high index of suspicion by Pediatricians and the use of POCUS permit its early recognition and consequently timely targeted therapies. The POCUS evaluation could be not specific in recognizing an early acute rejection after heart transplantation, due to the low specificity of the ultrasound findings at an early stage of disease. Large, multicenter trials are necessary in order to validate POCUS role in the diagnostic assessment in the ED of patients with a suspicion for a acute rejection after heart transplantation.

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