Acute severe myocarditis with cardiac thrombus formation – A therapeutic challenge

Miocardite aguda grave complicada com trombos intracardíacos – Um desafio terapêutico

Isabel Ayres Pereira¹, Cláudia Teles-Silva², Edite Serrano Gonçalves³, Teresa Cunha da Mota⁴, Maria de Lurdes Lisboa Sequeira⁴, António Ribeiro⁴

ABSTRACT

Acute myocarditis is a potentially life-threatening disease in pediatric age, with risk of severe cardiac dysfunction and intracardiac thrombus formation.

A previously healthy 16-year-old boy was admitted to the Pediatric Intensive Care Unit with suspicion of acute myocarditis with multiorgan dysfunction. He reported mucous diarrhea, vomiting, and asthenia with one week of evolution. The echocardiogram revealed moderate-to-severe left ventricle dysfunction with mitral and tricuspid regurgitation and two hyperechoic images suggestive of thrombus, later confirmed by cardiac magnetic resonance. Unfractionated heparin was started on admission. Campylobacter jejuni was isolated from feces. Despite treatment, the clinical picture worsened with systemic arterial embolization. Surgical thrombectomy was performed on day 13, and extracorporeal membrane oxygenation (ECMO) was maintained until day 28. At this time, the boy was submitted to orthotopic cardiac transplantation with favorable postoperative course.

The therapeutic approach in these cases is controversial and should always be multifactorial and multidisciplinary. Despite the inherent risk of complications, thrombectomy should be considered when conservative approaches fail.

Keywords: Campylobacter; cardiac transplant; intracardiac thrombus; myocarditis; thrombectomy

RESUMO

A miocardite aguda é uma doença potencialmente fatal em idade pediátrica, associada a risco de disfunção cardíaca grave e trombos intracardíacos.

Um adolescente de 16 anos de idade, previamente saudável, foi transferido para o Serviço de Medicina Intensiva Pediátrica por suspeita de miocardite aguda com disfunção multiorgânica. Referia diarreia mucosa, vômitos e astenia com uma semana de evolução. O ecocardiograma revelou disfunção ventricular esquerda moderada a grave associada a regurgitação mitral e tricúspide e duas imagens hiperecogênicas sugestivas de trombos intracardíacos, posteriormente confirmadas por ressonância magnética. Foi iniciada heparina não fracionada. A coprocultura foi positiva para Campylobacter jejuni. Apesar do tratamento, verificou-se agravamento do quadro clínico, com embolização sistêmica arterial,
sindo submetido a trombectomia no dia 13 e mantido em oxigenação por membrana extracorporeal (ECMO) até ao dia 28. Foi realizado transplante cardíaco ortotópico, com boa evolução pós-operatória.

A abordagem destes casos é controversa, devendo ser sempre multifatorial e multidisciplinar. Apesar dos riscos inerentes, a trombectomia deve ser considerada quando não se observa uma evolução favorável com abordagens conservadoras.

Palavras-chave: Campylobacter; miocardite; transplante cardíaco; trombectomia; trombo intracardíaco

INTRODUCTION

Myocarditis is rare in pediatric age, and a bacterial (post-)infectious etiology is uncommonly found. Despite its usually benign course, the clinical presentation may be complicated with cardiogenic shock, arrhythmia, and sudden death. Thrombotic events are rare but potentially life-threatening, and the management approach is controversial.

CASE REPORT

A previously healthy 16-year-old boy presented to the Emergency Department with a two-week history of upper respiratory tract symptoms and cough associated with vomiting. He also reported progressive asthenia and mucous diarrhea during the previous week, denying other constitutional or organ-specific symptoms. No epidemiological context of the disease was identified. The boy denied recent vaccinations, medication/toxic ingestion, suspicious food/water ingestion, or contact with animals other than a domestic bird, and the family history was unremarkable for cardiovascular or thrombotic conditions.

On physical examination, the patient appeared ill, with pallor and dry mucous membranes. He was tachycardic (108 bpm), tachypneic (28 cpm), and afebrile, with normal blood pressure and oxygen saturation while breathing. Glasgow Coma Scale (GCS) score was 15/15, cardiopulmonary auscultation was normal, and no other relevant findings were identified.

The laboratory study revealed thromboctopenia (99000 platelets/μL), kidney injury (urea 63 mg/dL, creatinine 1.29 mg/dL), hepatic dysfunction (aspartate aminotransferase 231U/L, alanine transaminase 224U/L) with elevated lactate-dehydrogenase (1285U/L), and cardiac dysfunction (T-troponin 726 ng/L, myoglobin [MB] 238.7 ng/ml, creatinine kinase MB 56.8 ng/ml, pro-brain natriuretic peptide 14585 pg/ml). Low fibrinogen (153 mg/dL), and negative for toxic drugs. Thoracic radiography revealed cardiomegaly (cardiothoracic ratio: 64%), with signs of central venous congestion. Abdominal ultrasound showed bilateral renal hyperechogenicity, hepatic dimensions on the upper limit of normal, small-volume ascites, and diffuse distention and edema of colic loops and walls with prominent mesenteric nodes. The electrocardiogram (ECG) revealed sinus tachycardia, high p waves suggestive of bilateral auricular dilation, left ventricular hypertrophy criteria, and ST-segment elevation. Intravenous (i.v.) ceftriaxone was administered, and the patient was transferred to a tertiary center due to suspicion of acute myocarditis with multiorgan failure.

On admission, he was hemodynamically stable, with a GCS score of 15. The echocardiogram revealed an apparently structurally normal heart, with moderate-to-severe left ventricular dysfunction (ejection fraction of 30-35%), mitral and tricuspid regurgitation (grades +2 and +1, respectively) with right ventricle-right atrial gradient of 30 mmHg, and an estimated pulmonary artery pressure of 35-40 mmHg. Two hyperechoic masses suggestive of intracardiac thrombus were identified in the apical region of the left ventricle, along with a small posterior apical pericardial effusion (Figure 1). The patient initiated i.v. unfractionated heparin (UFH) for thrombus resolution and i.v. furosemide for cardiac dysfunction and was transferred to the Pediatric Intensive Care Unit.

On day (D) 2, clinical worsening was observed, with increased respiratory effort, hypotension with severe metabolic acidosis (pH 7.32, pCO2 36.2 mmHg, base excess -6.2 with anion gap 20.6 mmol/L, and lactate 7.5mmol/L. The urine was positive for proteinuria (600 mg/dL) and negative for toxic drugs. Thoracic radiography revealed cardiomegaly (cardiothoracic ratio: 64%), with signs of central venous congestion. Abdominal ultrasound showed bilateral renal hyperechogenicity, hepatic dimensions on the upper limit of normal, small-volume ascites, and diffuse distention and edema of colic loops and walls with prominent mesenteric nodes. The electrocardiogram (ECG) revealed sinus tachycardia, high p waves suggestive of bilateral auricular dilation, left ventricular hypertrophy criteria, and ST-segment elevation. Intravenous (i.v.) ceftriaxone was administered, and the patient was transferred to a tertiary center due to suspicion of acute myocarditis with multiorgan failure.

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Despite maintaining aPTT in hypocoagulation range, poor perfusion signs were apparent on the right inferior limb on D9, along with small ecchymosis on the hands and feet. Cervical and limb Doppler ultrasonography revealed deep vein thrombosis of the external iliac, femoral, popliteal, and gastrocnemii veins, and right brachial and bilateral radial and cubital thrombosis. The prothrombotic study after heparin initiation revealed low protein C (PC; 0.34 U/ml) and antithrombin III (ATIII; 0.33 U/ml), with normal protein S (0.73 U/ml) and resistance to activated PC, and negative lupus inhibitor. ATIII concentrate was given on D10, and on D12, heparin was changed to argatroban. The genetic study for prothrombin 20210 and Leiden factor V mutations was negative. Anti-PF4 antibodies were negative. Executive cerebral functions were apparently normal, as well as cerebral computed tomography on D9.

Figure 1 - Echocardiogram on admission showing a hyperechoic (mobile) thrombus (arrow) proximal to the aortic truncus (•).

Figure 2 - Cardiac magnetic resonance imaging showing increased diffuse hyperintensity at the lateral and inferior walls of the left ventricle in T2 sequence, with late enhancement of the subepicardial regions suggesting myocarditis. Large thrombi were found on the interventricular septum and apical region of the left ventricle, in addition to other bilateral smaller ones (arrows).
The only relevant finding in the extensive infectious and immunological study conducted was a positive fecal culture for *Campylobacter jejuni* sensitive to azithromycin (Table 1). The patient completed nine days of i.v. ceftriaxone, five days of i.v. azithromycin, and 11 days of piperacillin/tazobactam plus gentamicin and vancomycin, which was started on D9 due to fever and rising CRP. Due to continuous worsening, bilateral ventricular thrombectomy with restrictive annular valvoplasty and myocardial biopsy were performed on D13. Postoperatively, the patient was maintained on extracorporeal membrane oxygenation (ECMO) until D28 and submitted to orthotopic cardiac transplant afterward, with no intercurrences. UFH was reinitiated, and immunosuppression was maintained with antimicrobial prophylaxis.

Endomyocardial biopsy revealed cellular hypertrophy with atrophic myocytes within interstitial fibrosis, along with lymphocytic infiltrate compatible with lymphocytic myocarditis. After transplant, macroscopy of the native heart revealed dilated cardiac cavities, with heterogeneous myocardial walls with both pale and congestive areas. Microscopically, necrosis and neutrophilic inflammatory infiltrate were evident, along with granulation tissue, fibrosis, and leukoerythrotoblastosis, possibly in the context of myocarditis and cardiac failure.

Post-surgery cardiac evolution was favorable, with cardiac function improvement and no new thrombus. The boy was discharged 60 days after transplant, maintaining normal cardiac function and immunosuppression and without major intercurrences.

**Table 1 - Infectious and immunological study performed**

<table>
<thead>
<tr>
<th>Study</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infectious etiology</strong></td>
<td></td>
</tr>
<tr>
<td>PCR for adenovirus and rotavirus in feces</td>
<td>negative</td>
</tr>
<tr>
<td>Parasitological feces culture</td>
<td>sterile</td>
</tr>
<tr>
<td>Bacteriological feces culture</td>
<td>positive for <em>Campylobacter jejuni jejuni</em></td>
</tr>
<tr>
<td>Blood PCR for hepatitis viruses A, B, and C, human immunodeficiency viruses 1 and 2, herpes viruses 1, 2, and 6, parechovirus, and adenovirus</td>
<td>negative</td>
</tr>
<tr>
<td>Serology/blood PCR for cytomegalovirus and parvovirus B19 DNA</td>
<td>negative IgM, positive IgG, negative PCR</td>
</tr>
<tr>
<td>Serology for Epstein-Barr virus</td>
<td>negative IgM, positive IgG, positive Epstein-Barr nuclear antigen antibody</td>
</tr>
<tr>
<td>Serology for varicella-zoster virus</td>
<td>positive IgG, negative IgM</td>
</tr>
<tr>
<td>Serology for Mycoplasma and <em>Chlamydia pneumoniae, Borrelia burgdorferi, Rickettsia conorii, and Toxoplasma gondii</em></td>
<td>negative IgG and IgM</td>
</tr>
<tr>
<td>Anti-Treponema pallidum antibody</td>
<td>negative</td>
</tr>
<tr>
<td>Urinary PCR for Legionella pneumophila DNA</td>
<td>negative</td>
</tr>
<tr>
<td>Blood PCR for <em>Leptospira</em> and Coxiella burnetti DNA</td>
<td>negative</td>
</tr>
<tr>
<td>Respiratory secretion PCR for syncytial respiratory virus, adenovirus, influenza A and B, parainfluenza 1-3, rhinovirus, bocavirus, and coronavirus</td>
<td>negative</td>
</tr>
<tr>
<td>Blood cultures from peripheral/central catheters</td>
<td>sterile</td>
</tr>
<tr>
<td>Bacteriologic pulmonary secretion culture</td>
<td>sterile</td>
</tr>
<tr>
<td>Urine culture</td>
<td>sterile</td>
</tr>
<tr>
<td><strong>Immunological etiology</strong></td>
<td></td>
</tr>
<tr>
<td>Immunoglobulins</td>
<td>normal IgG/IgM</td>
</tr>
<tr>
<td>Complement (C3/C4)</td>
<td>slightly elevated IgA and IgE (425 mg/dL and 532 mg/dL)</td>
</tr>
<tr>
<td>Anti-Ds-DNA, anti-cytoplasmic-neutrophil, anti-ENA antibodies</td>
<td>negative</td>
</tr>
<tr>
<td>Anticardiolipin/anti-2-glicoprotein antibodies</td>
<td>negative</td>
</tr>
</tbody>
</table>
DISCUSSION

Pediatric myocarditis has a bimodal age distribution, with peaks in infancy and adolescence. The presentation is variable and may be severe. In the present case, typical heart failure signs and symptoms were not present ad initium, possibly delaying presentation to medical services and progression to a more devastating course.

Cardiac thrombus formation is a rare myocarditis complication. It most frequently results from reduced myocardial contractility and left ventricular dilatation, aggravated by the procoagulant effect of cytokines and increased tissue factor.3-5 Hematologic and coagulation disorders can also play a role, as well as dysrhythmias and diminished fluid intake.4,14 As such, the study in this setting should always include screening for prothrombotic disorders.3 In this case, despite minor alterations in ATIII and PC levels, the absence of family history of thrombotic disorders and negative study for thrombotic genetic defects did not support coagulation disorders as etiologic or aggravating factors.

The most frequent myocarditis etiologies in children are infectious, toxic, and autoimmune. Amongst infectious causes, viruses are the most common etiologic agents, with bacteria like Salmonella and Shigella rarely reported.4,5,9,10 In this case, investigations excluded the most usually reported causes of myocarditis. The positive fecal culture for Campylobacter jejuni was in agreement with the clinical picture of mucous diarrhea and vomiting. The association of myocarditis with Campylobacter has been rarely described and is highly uncommon in pediatric range, being most frequently associated with good prognosis.5,11-13 Explanations for the pathophysiology of Campylobacter-associated myocarditis are variable and range from direct cardiac damage to toxin effects.14 A post-infectious immune-mediated mechanism resulting in myocardial damage may also play a role.3,11 The present case suggests a para/post-infectious immunological mechanism due to the time gap between the clinical presentation of gastroenteritis and onset of cardiac dysfunction, together with negative myocardial culture and lymphocytic infiltrate.

Cardiac thrombus carry significant morbidity and mortality and should thus be carefully addressed.4,15 The risk of thromboembolism and worsening cardiac dysfunction is significant. Left cardiac thrombus, in particular, can embolize to the arterial territory and elicit cerebrovascular events.6,8 As such, although no guidelines are in place and the optimal regime is not established yet, some authors suggest routine prophylactic anticoagulation for the management of these cases.3 The importance of serial echocardiograms to detect this complication cannot be overemphasized, as it probably happens more often than clinically suspected.3 The treatment of cardiac thrombus is controversial and may include thrombectomy, anticoagulation, and fibrinolysis.6,7 For left heart thrombus, as well as for pedunculated, highly mobile, or massive thrombus, surgery is frequently the main option, given the risk of dislodgment and massive embolization with anticoagulation.6,8,15 Non-surgical strategies have been increasingly reported and may be an option to minimize inherent surgical risks and risk of intraoperative embolization, particularly when heart function is severely compromised.6,7,8,15 In a large case series investigating intracardiac thrombus formation in dilated cardiomyopathy, post-Fontan surgery, and other diagnoses, medical treatment resolved the thrombus in 63% of cases.15 However, the use of fibrinolytics, as recombinant tissue plasminogen activator, could cause thrombus dislodgment/fragmentation and is underreported in children.9 Therefore, management decisions should be individualized, multidisciplinary, and holistic, accounting for cardiac function, thrombus characteristics, and risks and benefits of each approach.7 In this case, the presence of bilateral, massive, and pedunculated thrombus hampered management decisions. Despite the high risk of thrombus embolization, severe ventricular dysfunction ad initium may reduce the probability of functional recovery after surgery, justifying the initially conservative approach. However, the progressive cardiac function worsening and thrombus formation (with the large left thrombus prone to occlude the truncus bicuspidus) in the present case led to the multidisciplinary decision of surgery, which was vital to prevent a fatal outcome while waiting for cardiac transplantation.

CONCLUSION

Despite rare, myocarditis can be a devastating disease, potentially complicated with severe cardiac dysfunction, thrombus formation, and death. Management of these cases is controversial and should be multidisciplinary and individualized, considering thrombus characteristics, basal cardiac function, and available medical resources. Thrombectomy should be timely initiated when more conservative approaches fail, preventing fatal outcomes.

AUTHORSHIP

Isabel Ayres Pereira – Conceptualization; Writing – original draft
Claudia Teles-Silva – Supervision; Validation; Writing – review and editing
Edite Serrano Gonçalves – Supervision; Validation; Writing – review and editing
Teresa Cunha e Mota – Supervision; Validation; Writing – review and editing
Maria de Lurdes Lisboa Sequeira – Supervision; Validation; Writing – review and editing
Augusto Ribeiro - Supervision; Validation; Writing – review and editing

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