

Peculiar Clinical Presentation of Coxsackievirus B4 Infection: Neonatal Restrictive Cardiomyopathy

Pauline Le Van Quyen¹ Philippe Desprez, MD² Angelo Livolsi, MD³ Véronique Lindner, MD, PhD¹
Samira Fafi-Kremer, MD, PhD^{4,5} Pauline Helms, MD³ Maria Cristina Antal, MD, PhD^{1,5}

¹ Département de Pathologie, Hôpitaux Universitaires de Strasbourg, Strasbourg, France

² Service de Pédiatrie, Centre Hospitalier Universitaire Pointe-à-Pitre/Abymes, Pointe-à-Pitre, France

³ Unité de Cardiopédiatrie, Hôpitaux Universitaires de Strasbourg, Strasbourg, France

⁴ Service de Virologie, Plateau Technique de Microbiologie, Hôpitaux Universitaires de Strasbourg, Strasbourg, France

⁵ Faculté de Médecine, Université de Strasbourg, Strasbourg, France

Address for correspondence Maria Cristina Antal, MD, PhD, Département de Pathologie, Hôpitaux Universitaires de Strasbourg, 1 place de l'Hôpital, 67000 Strasbourg, France (e-mail: mc.antal@unistra.fr).

Am J Perinatol Rep 2017;7:e124–e126.

Abstract

Keywords

- ▶ restrictive cardiomyopathy
- ▶ neonate
- ▶ coxsackievirus B4
- ▶ PCR

Introduction Restrictive cardiomyopathy in fetuses and neonates is extremely rare and has a poor outcome. Its etiology in neonates is elusive: metabolic diseases (e.g., Gaucher, Hurler syndrome), neuromuscular disorders (e.g., muscular dystrophies, myofibrillar myopathies), or rare presentation of genetic syndromes (e.g., Coffin–Lowry syndrome) account for a minority of the cases, the majority remaining idiopathic.

Case Study We report the case of a 17-day-old male infant presenting cardiogenic shock following a restrictive dysfunction of the left ventricle. Postmortem investigations revealed coxsackievirus B4 myocarditis with histological lesions limited to the left heart. However, polymerase chain reaction (PCR) for coxsackievirus B4 was positive in the left as well as in the right ventricular samples.

Conclusion In conclusion, coxsackievirus myocarditis is a cause of restrictive cardiomyopathy, and its diagnosis should involve PCR screening as a more sensitive technique.

The patient was born at 37 weeks of gestation in a context of maternal hyperthermia of unidentified etiology. Amniotic fluid culture revealed scarce *Staphylococcus epidermidis*. The patient received triple antibiotic therapy associating cefotaxime, amoxicillin, and amikacin for 3 days until the absence of fetal infection was confirmed (normal clinical examination, negative bacteriological samples, no biological inflammatory syndrome).

At 5 days of life, the patient displayed signs of acute gastroenteritis (hyperthermia, elevated C-reactive protein

[CRP], abdominal meteorism) requiring a transfer in the neonatal intensive care unit. Symptomatology resolved over the next 7 days, and the patient left the hospital.

The second day following hospital discharge, the patient was brought to the emergency unit. Physical examination revealed polypnea, hypothermia (34.6°C), fatigue. Biological examinations revealed unspecific inflammatory syndrome (elevated CRP, procalcitonin, hyperleukocytosis of all cell types) elevated B-type natriuretic peptide (19,000 ng/L), and troponin I (1.3 µg/L), severe metabolic acidosis. Samples

received
November 25, 2016
accepted after revision
February 9, 2017

DOI <https://doi.org/10.1055/s-0037-1601352>.
ISSN 2157-6998.

Copyright © 2017 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA
Tel: +1(212) 584-4662.

License terms



of gastric fluid, urine, stool, blood, ear and skin smear were negative for pathogenic bacteria. Rotavirus, adenovirus or norovirus research were negative in stools. Polymerase chain reaction (PCR) was negative for cytomegalovirus (CMV), Epstein-Barr virus (EBV), parvovirus B19, herpes simplex virus (HSV) 1 and 2. Serology anti-coxsackievirus (IgM) was negative. Cardiac echography revealed functional obstacle to pulmonary venous blood with dilated left auricle (left atrial to aortic root fraction: 2.4) and pulmonary veins, diminished contractility of the left ventricle, particularly the posterior-inferior wall (left ventricle ejection fraction: 44%), mitral functional insufficiency (2–3/4), isosystemic pulmonary hypertension, absence of aortic stenosis or coarctation, absence of coronary anomaly, and normal connection of pulmonary veins; electrocardiogram showed sinus rhythm, right axis, and dilated left auricle. Angiography by tomodesitometry confirmed echographic data (►Fig. 1). The Rashkind maneuver was performed to lower left auricle pressure. Following exclusion of different etiologic hypotheses (malformative, infectious, metabolic) and the failure of symptomatic treatment (intravenous immunoglobulins, cardiac support [epinephrine, milrinone, levosimendan), peritoneal dialysis), the parents were informed about the poor prognosis; extracorporeal membrane oxygenation was discussed but rejected because of the lack of evidence of reversible myocardial damage at the time. The patient died at 17 days of life.

Autopsy, limited to the cardiopulmonary system, and X-ray examination were performed 45 hours postmortem. Axial skeleton, skull, and limbs did not show epiphyseal stippling; long bones measures and skeletal maturation were normal. Macroscopic examination of the organs did not reveal cardiopulmonary malformations. The left ventricular surface was uneven, with heterogeneous consistency. Its inner surface was of normal color, excluding fibroelasto-

sis. The left auricle and the origin of the pulmonary veins were dilated. Right cavities were normal.

Examination of hematoxylin-eosin-stained slides revealed interstitial inflammatory infiltrates of all left ventricular samples, composed mainly of lymphocytes and few macrophages, forming foci without preferential localization. The affected tissue was markedly edematous, displaying cardiomyocyte necrosis. Cardiomyocytes within and in the surroundings of the inflammatory foci were depleted of glycogen (periodic acid-Schiff [PAS]-negative). The lesions were strictly limited to the left side of the interventricular septum. In the left auricle, the same inflammatory infiltrate was found, however, to a lower extent. Immunohistochemistry using antibodies against HSV1, HSV2, EBV, CMV, and toxoplasmosis were negative. Gram, Grocott methenamine silver stain, and PAS staining did not reveal microorganisms. Right heart samples and lungs were normal.

Frozen samples from left and right ventricles were addressed for virus detection by real-time PCR (Enterovirus R-gene, Biomèrieux, Marcy l'Etoile, France). Myocardial enterovirus PCR was positive; the copy number was a thousand times higher in the left than in the right ventricle. In parallel, conserved patient serum was tested and found positive for Enterovirus family. Virus genotyping identified coxsackievirus B4.

Discussion

We report the case of an infant deceased in the context of a restrictive left ventricle caused by coxsackievirus B4 infection. Postmortem investigations revealed macroscopic and histologic signs limited to the left heart myocardium and the left side of the interventricular septum. However, PCR revealed the presence of the virus in the left and the right ventricle, the viral charge being markedly elevated in the left

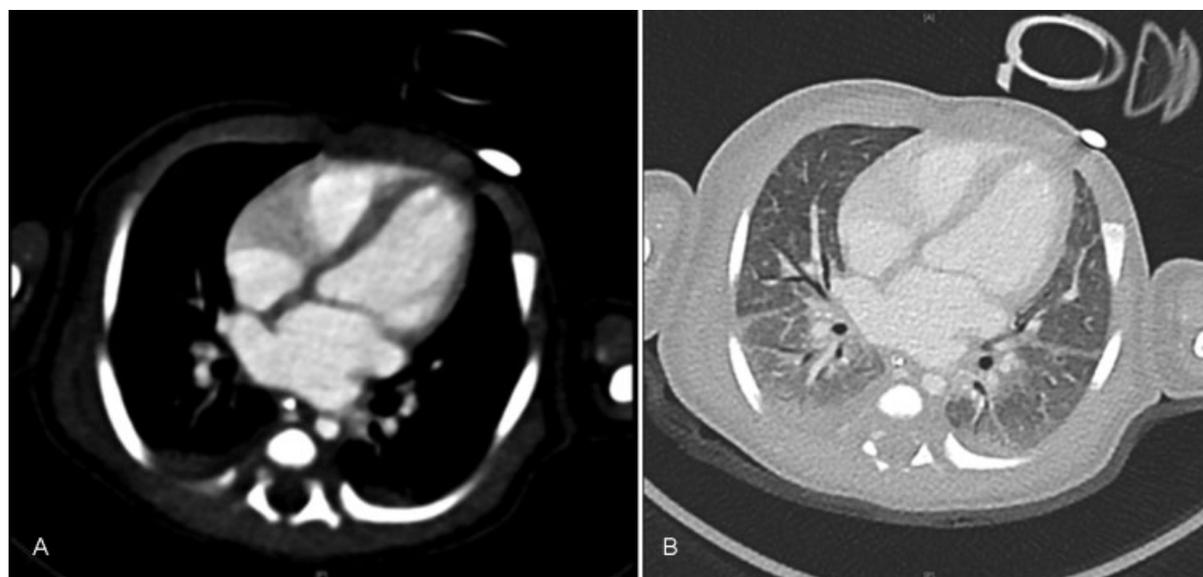


Fig. 1 Tomodesitometry showing extremely dilated pulmonary veins and left auricle (A, B) and associated venous stasis (B). Left ventricle cavity and wall thickness are normal (A, B).

samples compared with the right ones. Microscopic analysis of the left myocardium revealed, in areas surrounding inflammatory foci, that myocardium was glycogen-depleted, suggesting that the volume of the functional myocardium is lower than suspected following routine hematoxylin-eosin-stained slides examination.

Coxsackievirus B4 is an Enterovirus known for its tropism for progenitor cells, particularly neural and cardiac due to the high expression of viral receptors.^{1,2} It can cause severe disease,^{3,4} particularly myocarditis, central nervous system disease, and sepsis-like illness, particularly in neonates and infants.^{5,6} Newborns can be infected by vertical transmission (in utero or during delivery) or postnatally.⁵ Classical presentation of neonatal enterovirus infection is biphasic, with nonspecific symptoms such as fever, irritability, poor feeding, respiratory or gastrointestinal symptoms followed, in approximately half of the patients, by hepatic inflammation or myocarditis developing in a variable lapse of time.^{5,7} Myocarditis clinical presentation ranges from fulminant to asymptomatic or chronic leading to dilated cardiomyopathy. Fulminant forms are often lethal; however, surviving patients have good long-term prognosis with 93% survival at 11 years.⁸ In our patient, the infection followed a biphasic pattern, starting as acute gastroenteritis followed by general status degradation and fulminant myocarditis manifesting as restrictive cardiopathy with fatal outcome. We could not prove maternal to fetal virus transmission as, by the time of virus detection in the patient, mother serum was not available for testing.

Rare etiologies of restrictive cardiomyopathy were excluded.^{9,10} Biochemical screening for the metabolic disease was performed (blood ammonia, blood and urinary amino acids chromatography, urinary organic acids, free and total carnitine, acylcarnitine, B1 vitamin) and was found normal. The patient did not display clinical signs of syndromic disease associating restrictive cardiomyopathy to the clinical phenotype. Family history was reviewed, and no argument supporting the hypothesis of a hereditary disease was found.

Histologically, the lesions matched the typical aspect of viral myocarditis: interstitial lymphohistiocytic inflammatory infiltrate, cardiomyocyte necrosis, edema, and fibrosis.^{11,12} In our case, adjacent to foci of necrosis, we highlighted a zone of glycogen-depleted cardiomyocytes. As glycogen is a substrate to contractile function, we assume that the glycogen-depleted zones may be less functional. Interestingly, the topography of the lesions is asymmetric, strictly restricted to the left cavities. Recently, European Society of Cardiology proposed the systematic use of endomyocardial biopsy in patients with stringent criteria for clinically suspected myocarditis and recommended the use of the material collected not only for histology but also for

immunohistochemistry and molecular biology.¹³ In the case of our patient, histology only would not have been sufficient as right ventricle was spared; however, PCR would have allowed diagnosis.

Key Message

Coxsackievirus B4 infection should be evoked in the presence of left heart restrictive cardiomyopathy in neonates. PCR detection of the viral genome is more sensitive than histology and methods detecting circulating antibodies. The involvement of the two ventricles can be different which is of importance if subendocardial biopsy followed by histological analysis of the biopsy is considered.

References

- Muehlenbachs A, Bhatnagar J, Zaki SR. Tissue tropism, pathology and pathogenesis of enterovirus infection. *J Pathol* 2015;235(02): 217–228
- Sin J, Mangale V, Thienphrapa W, Gottlieb RA, Feuer R. Recent progress in understanding coxsackievirus replication, dissemination, and pathogenesis. *Virology* 2015;484:288–304
- Sekar P, Hornberger LK, Smallhorn JS. A case of restrictive cardiomyopathy presenting in fetal life with an isolated pericardial effusion. *Ultrasound Obstet Gynecol* 2010;35(03):369–372
- Zangwill S, Hamilton R. Restrictive cardiomyopathy. *Pacing Clin Electrophysiol* 2009;32(Suppl 2):S41–S43
- Tebruegge M, Curtis N. Enterovirus infections in neonates. *Semin Fetal Neonatal Med* 2009;14(04):222–227
- Tseng F-C, Huang H-C, Chi C-Y, et al; CDC-Taiwan Virology Reference Laboratories and Sentinel Physician Network. Epidemiological survey of enterovirus infections occurring in Taiwan between 2000 and 2005: analysis of sentinel physician surveillance data. *J Med Virol* 2007;79(12):1850–1860
- Woodruff JF. Viral myocarditis. A review. *Am J Pathol* 1980;101(02):425–484
- McCarthy RE III, Boehmer JP, Hruban RH, et al. Long-term outcome of fulminant myocarditis as compared with acute (nonfulminant) myocarditis. *N Engl J Med* 2000;342(10):690–695
- Finsterer J, Stöllberger C, Wahbi K. Cardiomyopathy in neurological disorders. *Cardiovasc Pathol* 2013;22(05):389–400
- Martinez HR, Niu MC, Sutton VR, Pignatelli R, Vatta M, Jefferies JL. Coffin-Lowry syndrome and left ventricular noncompaction cardiomyopathy with a restrictive pattern. *Am J Med Genet A* 2011; 155A(12):3030–3034
- Gaaloul I, Riabi S, Harrath R, Evans M, Huber S, Aouni M. Coxsackie B3 myocarditis in a case of sudden unexpected death in young athlete: histopathological, immunohistochemical and molecular-pathological for diagnosis. *Forensic Sci Int* 2011;208(1-3): e10–e14
- Guarner J, Bhatnagar J, Shieh WJ, et al. Histopathologic, immunohistochemical, and polymerase chain reaction assays in the study of cases with fatal sporadic myocarditis. *Hum Pathol* 2007; 38(09):1412–1419
- Caforio ALP, Marcolongo R, Basso C, Iliceto S. Clinical presentation and diagnosis of myocarditis. *Heart* 2015;101(16):1332–1344