Miocarditis mortal después de la inmunización con ARNm contra la COVID-19: informe de un caso y revisión del diagnóstico diferencial

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Abstracto

La carditis en la infancia es una enfermedad rara con varias etiologías. Presentamos un caso de muerte infantil por pericarditis y miocarditis después de la vacuna de ARNm contra COVID-19 (COVIDmRNAV). Un niño varón de 7 años recibió la primera dosis de la vacuna COVIDmRNAV y presentó monoartritis y fiebre que no respondía a los antibióticos orales. La investigación de laboratorio mostró signos de infección (leucocitosis, niveles altos de proteína C reactiva). Su condición se deterioró rápidamente y el paciente murió. La autopsia identificó depósitos de fibrina pericárdica, áreas hemorrágicas en el miocardio y válvulas normales. Se identificó un infiltrado inflamatorio intermiocárdico difuso compuesto por linfocitos T CD8+ e histiocitos. Una dosis de antiestreptolisina O (ASO) mostró títulos altos. La presencia de artritis, ASO elevado y carditis cumple con los criterios de fiebre reumática. Sin embargo, la valvulopatía y los nódulos de Aschoff, presentes en el 90% de los casos de carditis reumática, estaban ausentes en este caso. La correlación temporal con la vacunación con ARNm motivó su inclusión como una de las etiologías. En los casos de daño miocárdico relacionado con COVID-19mRNAV, parece estar relacionado con la expresión de exosomas y nanopartículas lipídicas, lo que conduce a una tormenta de citoquinas. Los efectos potenciales del COVID-19mRNAV deben considerarse en la patogénesis de esta enfermedad, ya sea como etiología o como factor contribuyente a una lesión miocárdica previamente iniciada.

Palabras clave: COVID-19 (/search?q=COVID-19); **inmunización (/search?q=immunization)**; **vacuna de ARNm (/search?q=mRNA+vaccine)**; **miocarditis (/search?q=myocarditis)**; **cardiopatías reumáticas (/search?q=rheumatic+heart+disease)**; **cardiotoxicidad inducida por catecolamina (/search?q=cathecolamin-induced+cardiotoxicity)**; **Síndrome inflamatorio multisistémico (/search?q=multisystem+inflammatory+syndrome)**

1. Introducción

La carditis en la infancia es una enfermedad rara con una presentación clínica variable, a veces inespecífica y de resolución espontánea, con la posibilidad de desarrollar secuelas, que en ocasiones son graves y mortales [**1,2,3**]. La investigación etiológica precisa es crucial para el manejo terapéutico, ya que diferentes mecanismos patogénicos guían la elección de la medicación, siendo la biopsia endomiocárdica y la evaluación histológica el estándar de oro actual. [**4**].

Las causas más comunes de miocarditis son las infecciones bacterianas y virales, los trastornos inflamatorios sistémicos que afectan al tejido conectivo, la autoinmunidad y los efectos de medicamentos y toxinas [**3**]. Recientemente, un patógeno ya conocido ha ganado aún más atención: el coronavirus 2 del síndrome respiratorio agudo severo (SARS-CoV-2) [**5,6**]. También se han reportado afecciones a menudo relacionadas con la inflamación multisistémica, aunque con menos frecuencia, después de la vacunación contra la enfermedad por coronavirus 2019 (COVID-19), desarrollada principalmente con ARNm viral [7,8,9,10,11,12].

Presentamos un caso de muerte infantil por una patología desconocida que se inició tras el uso de una vacuna de ARNm frente a la COVID-19. La autopsia identificó pericarditis y miocarditis, con un amplio solapamiento morfológico entre los posibles diagnósticos diferenciales y una difícil clasificación etiológica final.

2. Caso clínico

Un niño varón de 7 años presentó mialgia y fiebre 3 días después de recibir la primera dosis de la vacuna contra la COVID-19 (BNT162b2). Los padres negaron haber tenido contacto previo con personas enfermas o antecedentes de síntomas de infección de las vías respiratorias superiores. A los siete días, presentó monoartritis en el tobillo derecho. Los análisis de sangre indicaron leucocitosis, pero una tomografía computarizada del tobillo no mostró anomalías. Se le diagnosticó artritis séptica y se le dio de alta con terapia antibiótica empírica.

Después de 10 días, el paciente fue reevaluado debido a la persistencia de los síntomas. En ese momento, la leucocitosis había mejorado y los valores de O antiestreptolisina (OAS) eran normales, lo que llevó al alta con un nuevo régimen antibiótico ambulatorio. Tres semanas después de la aparición de los síntomas, con dolor articular continuo y dificultad para caminar, se realizaron nuevas pruebas. Los niveles elevados de SAO motivaron el ingreso hospitalario para tratamiento antibiótico intravenoso con oxacilina. El dolor articular mejoró a lo largo de nueve días, pero el paciente desarrolló síntomas gastrointestinales leves como vómitos con vetas de sangre y dolor epigástrico. Su condición se deterioró rápidamente tras el

diagnóstico de hemorragia digestiva alta. Después de la intubación orotraqueal, se observó sangrado activo por el tubo, lo que llevó a una derivación al servicio de urgencias. Las pruebas de laboratorio indicaron leucocitosis, niveles elevados de proteína C reactiva y reacción en cadena de la polimerasa COVID-19 negativa (**Tabla 1**), junto con consolidaciones del lóbulo pulmonar superior e inferior derecho y opacidades en vidrio esmerilado en la TC de tórax. Desafortunadamente, el paciente falleció.

Tabla 1. Pruebas de laboratorio durante el curso de la enfermedad.

En la autopsia, el examen externo mostró anasarca y aumento del volumen abdominal. Los órganos internos presentaban edema difuso, incluido el cerebro, con derrame cavitario pleural, pericárdico y peritoneal. El corazón presentaba una superficie externa granular, opaca y blanquecina, similar a los depósitos de fibrina en el pericardio (**Figura 1**).

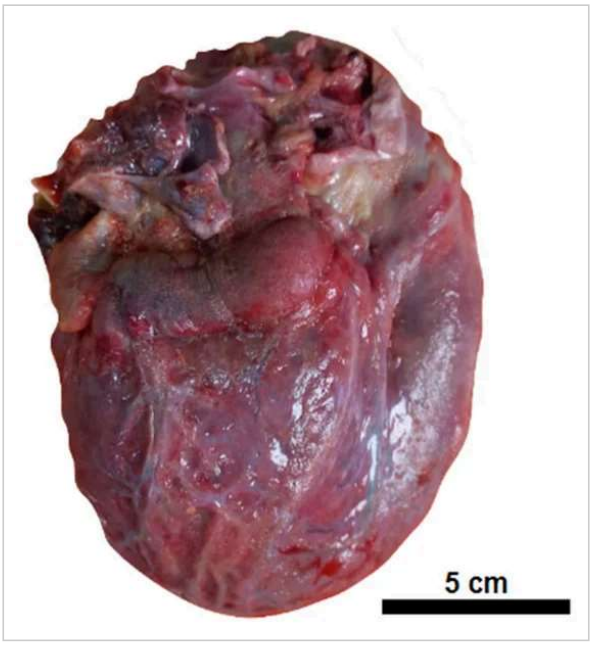

Figura 1. Pericarditis. Corazón globoso con una superficie externa opaca cubierta de granulación fina y restos fibrinosos.

The myocardium had a soft consistency, alternating between pale and hemorrhagic areas, while the valves remained preserved. Microscopy revealed disseminated vascular thromboembolism. The macroscopic and microscopic findings of the main organs are reported below (**Table 2**, **Figure 2**, **Figure 3** and **Figure 4**).

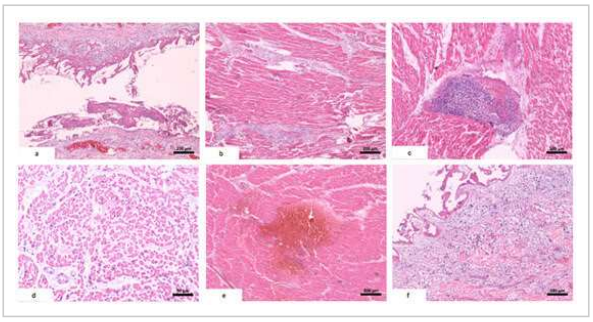

Figure 2. Histological alterations in the heart. (**a**) Pericarditis: fibrin deposition in the pericardium and lymphocytic infiltrate. (**b**) Myocarditis: inflammatory infiltrate concentrated in intermyocardial fibrotic tracts, with focal extension to cardiac fibers. (**c**) Foci of mixed inflammatory aggregate in the myocardium: plasma cells, lymphocytes, and neutrophils. (**d**) Subendocardial necrosis: myocardial fibers with eosinophilic and vacuolized cytoplasm and absent nuclei. (**e**) Myocardial hemorrhage. (**f**) Focal endocarditis: discrete mixed inflammatory infiltrate in the endocardium with fibrin deposition.

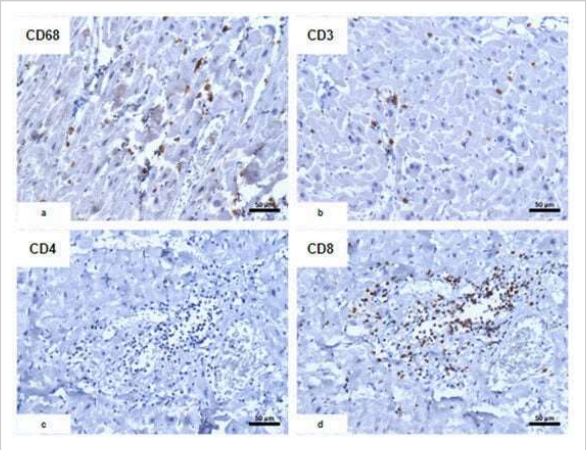

Figure 3. Immunohistochemical characterization of the inflammatory infiltrate. (**a**) CD68; (**b**) CD3; (**c**) CD4; (**d**) CD8: predominance of CD8+ T lymphocytes associated with CD68+ macrophages with an usual morphological appearance.

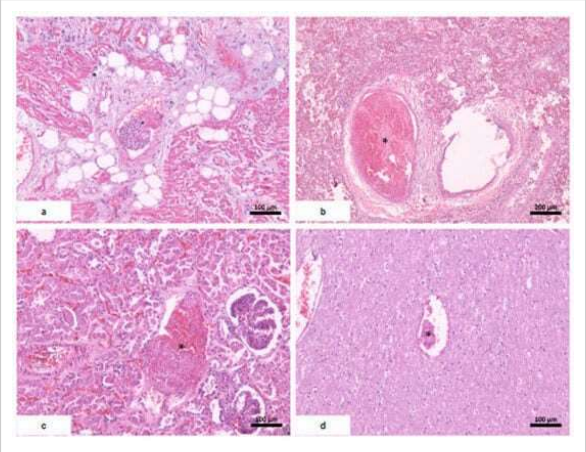

Figure 4. Systemic thromboembolism. (**a**) Heart; (**b**) lungs; (**c**) kidney with severe acute tubular necrosis; (**d**) brain. * fibrin thrombi.

Table 2. Pathological findings of the autopsy procedure.

The condition was diagnosed as acute pericarditis and myocarditis, without valve involvement, with heart failure leading to pulmonary edema, complicated by acute tubular necrosis and ischemic hepatic necrosis.

3. Discussion

This case poses a diagnostic challenge due to overlapping risk factors, symptoms, and diverse histological findings, each with variable diagnostic specificity. The main differential diagnoses will be discussed.

3.1. Rheumatic Fever (RF) and Myocarditis

The previous occurrence of an upper airway infection associated with arthritis and elevated OSA levels would fulfill the modified Jones criteria for diagnosing RF, with the presence of one major and two minor criteria: carditis, fever, and elevated serum CRP levels, respectively. However, evidence of monoarthritis is not a diagnostic criteria, as only polyarthritis is considered in diagnosing a first outbreak [**13**].

Furthermore, the morphological presentation differs from that typically seen in cardiac involvement by rheumatic fever. Most rheumatic carditis involves the endocardium [**14**], with valve disease in up to 90% of symptomatic cases [**13**]. Associated pericarditis and myocarditis, when present, show morphological characteristics reflecting the pathogenic mechanisms involved.

Cross-immune activation through antigenic mimicry with streptococcal proteins leads to the systemic inflammatory damage characteristic of RF [**14**,**15**]. Other studies have shown integration between streptococcal proteins and type IV collagen in the extracellular matrix [**16**]. In the heart, this reaction is more accentuated at the endothelium, especially in the valves, with increased expression of VCAM-1, an adhesion molecule that helps in the migration of activated leukocytes [**17**]. Moreover, the inflammatory aggregates are arranged around the cardiac connective tissue, intermingling the muscle fibers, without pronounced myocardial necrosis [**18**], which, when present, is related to local cellular aggression caused by the inflammatory process. This presentation differs from virus-related carditis, where aggression primarily affecting the myocardium results in extensive necrosis and a corresponding rise in myocardial necrosis markers [**3**].

The most specific histopathological finding of rheumatic heart disease (RHD) is Aschoff's nodules, perivascular histiocyte aggregates with characteristic nuclear changes [**14**]. Spina et al. identified the frequency of this finding in endomyocardial biopsies ranging from 19 to 67% (average: 41.8%). However, the studies failed to establish a consistent relationship with prognosis, corticoid use, or β-hemolytic Streptococcus prophylaxis [**19**].

3.2. Viral Carditis

Enteroviruses are classically associated with viral myocarditis. Over time, new entities have gained importance, such as parvovirus B19, influenza, adenovirus, cytomegalovirus, human immunodeficiency virus, and SARS-CoV-2 [**4**], accompanied by different pathogenic mechanisms. Adenoviruses and enteroviruses possess a cytolytic action profile that damages the myocardial cytoskeleton and is possibly linked to CCR5 receptor expression [**20**]. Parvovirus B19 exhibits vasculotropism and can remain quiescent in endothelial cells, causing damage to myocytes through inflammatory stimuli [**4**].

The expanding evidence on SARS-CoV-2 cardiotoxicity reveals various pathogenic mechanisms, including cardiomyotropism and cell damage via the angiotensin-converting enzyme receptor-binding protein, immune activation by the spike protein, and the production of antibodies that cross-react with cardiac cell antigens like α-myosin [**21**]. After a collaborative systematic review, Almamlouk found that 100% of studies show an association between cardiac infection with SARS-CoV-2 and myocardial necrosis, while there is no reference to signs of myocarditis, such as a pronounced inflammatory infiltrate [**22**]. The study failed to define a histological lesion pattern associated with COVID-19. Notably, a systematic review identified cardiomegaly, myocardial necrosis, an inflammatory infiltrate composed of CD3 T lymphocytes, with prominent CD8, and macrophages as the main cardiac signs identified. [**5**]. The absence of a clear relationship between viral load and cell damage, myocardial necrosis, and the low frequency of organized and pronounced inflammatory infiltrates make it less likely that the mechanism involved in COVID-19 is cytotoxic injury. The vasculitis caused by the virus, including arterial damage and occlusion, along with the systemic effects of the infection, such as adrenergic response and cathecolamin-induced cell stress, may be key contributors to its harmful effects [**23**,**24**,**25**,**26**].$^{++}$

3.3. Vaccination against COVID-19 and Myocarditis

The general population's use of vaccines, following their safety confirmation in phase 3 studies, increases exposure and enables the identification of rarer side effects. This was also true for the COVID-19 vaccine, especially the viral mRNA-based one [**27**,**28**].

Vaccine-related myocarditis is one of these adverse effects. The Adverse Event Reporting System (VAERS) included 27,229 cases of myocarditis and pericarditis until June 2023 [**29**]. With an often favorable clinical course, several studies corroborate the higher frequency of this complication after the second dose in young males under 40 years of age [**30**], especially in the 18–25 age group, with a higher risk attributed to the mRNA-1273 vaccine than to the BNT162b2 [**31**]. However, studies show that the booster dose does not lead to a substantial increase in the risk of perimyocarditis [**21**].

Giannotta et al. described the mechanisms involved in cardiac injury stimulated by the mRNA vaccine. The stimulation of the expression of exosomes, containing both the spike viral protein and inflammatory mediators, associated with the expression of adhesion factors that dysfunctionally stimulate the endothelial cell, plays an important role in this mechanism [**7**,**32**]. The spike protein leads to activation of the TLR-4/NF-kB pathway and stimulation of the cell-mediated immune response, with inflammation directed at cardiomyocytes [**33**]. In addition to the effect related to the viral structure, the composition and quantity of lipid nanoparticles in the vaccine dose, which differ between manufacturers, can show toxic activity with a potent inflammatory response already in the first moments after application [**34**]. There is also evidence that the immune cells that absorb the lipid nanoparticles distribute them throughout the body with high levels of spike protein, inflicting a continuous immune response [**29**]. The immune reaction comprises CD8 T lymphocytes, macrophages, and plasma cells, occasionally including an eosinophilic component without a characteristic morphological pattern [**35**].$^{+}$

Post-vaccination inflammatory activation is evidenced by a storm of inflammatory cytokines, such as high levels of IL-1, IL-1B, IL-6, and TNF-α. The circulation of these mediators might relate to the development of side effects and individual reactions after the first vaccine dose, but more frequently after the second dose, with varying clinical significance [**35**,**36**].

3.4. Multisystem Inflammatory Syndrome (MIS)

Multisystem inflammatory syndrome (MIS) is a condition related to COVID-19, with a predilection for children (MIS-C) [**37**]. The diagnostic criteria defined by the World Health Organization [**38**] include fever > 3 days, increased markers of inflammation, no evidence of other infections, and proof of COVID-19 infection, in addition to two of the following criteria: rash, non-purulent conjunctivitis, or mucocutaneous inflammation; hypotension or shock; myocardial dysfunction, pericarditis, or valvulitis; coagulopathy; and gastrointestinal symptoms. Diaz et al. identified a series of 35 children with defined criteria for a diagnosis of MIS-C, all with cardiac involvement. In another series of eight children with hyperinflammatory syndrome and probable COVID-19 infection, seven had gastrointestinal symptoms on initial presentation, as well as fever for 4 to 5 days [**39**].

Although rare, cases of MIS have also been reported after vaccination against COVID-19 (MIS-V) without evidence of concomitant virus infection [**40**]. Wassif et al. reported 10 cases of perimyocarditis related to COVID-19 vaccination, including 1 case associated with MIS, marked by a significant reduction in left ventricular function and requiring intensive treatment [**41**]. Ourdali identified 12 cases of MIS among over 4 million vaccinated children aged 12 to 17 with mRNA vaccines, with cardiac involvement in 83% of cases. Gastrointestinal symptoms (83%) and cytolytic hepatitis (50%) were also common [**9**].

3.5. Diagnostic Considerations

This is a case with complex clinical laboratory findings. Myocarditis and pericarditis, only suspected at the time of autopsy, developed in an indolent and nonspecific manner, which led to difficulty in raising this hypothesis for its appropriate investigation. This highlights the importance of investigating deaths with undefined causes. For comparison, **Table 3** summarizes the histological findings of the diagnostic hypothesis.

Table 3. Differential diagnosis of carditis.

The patient met the criteria defined for RHD. Nevertheless, some clinical and morphologic details raised suspicion for another causative or contributing factor since they differed from the classic presentation of rheumatic fever. The patient did not report a clinical history of streptococcal infection, despite the fact that Jones modified criteria acknowledge the possibility of subclinical infection if there is laboratorial evidence (i.e., high OSA levels). In addition, there were also criteria for MIS-C in the case, since myocardial disfunction, coagulopathy, and gastrointestinal symptoms developed related to fever > 3 days and an increase in inflammatory markers.

Previous exposure to streptococcal strains with immunogenic potential is an important risk factor for myocarditis. Still, the lack of typical findings in rheumatic heart disease, such as Aschoff nodules, even with extensive histological examination, makes the clinical pathological correlation difficult. A series of endomyocardial biopsies found a considerable prevalence of this finding, regardless of the limited material. In addition, the absence of valve disease is uncommon in RHD, reaching 10% of cases [**19**]. Unfortunately, the complementary methods for the detection of viral mRNA in the cardiac tissue were not feasible at the time of investigation.

4. Conclusions

It is reasonable to address the potential effects of the COVIDmRNAv in this setting. Temporal relationships must be evaluated carefully since they do not evoke a causal relationship. However, the growing evidence of the vaccine's systemic immunological effects allows us to deduce the possibility of the contribution of the cytokine storm to the establishment of myocardial injury, already initiated by rheumatologic mechanisms. The systemic findings developed by the patient are similar to those of MIS, which can be frequently present in patients with post-COVID-19 vaccine myocarditis.

Author Contributions

Conceptualization, G.E.B.S., J.S.L., R.d.G.C.F.C. and P.M.B.d.S.; methodology, G.E.B.S.; validation, G.E.B.S., J.S.L., R.d.G.C.F.C. and M.A.G.C.; investigation, E.A.S., P.M.B.d.S. and G.E.B.S.; resources, J.S.L. and R.d.G.C.F.C.; data curation, G.E.B.S., R.d.G.C.F.C. and M.A.G.C.; writing—original draft preparation, P.M.B.d.S. and E.A.S.; writing—review and editing, G.E.B.S., P.M.B.d.S. and M.A.G.C.; supervision, G.E.B.S.; project administration, G.E.B.S. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of the University Hospital of the Federal University of Maranhão (protocol code 4.069.664; date of approval: 6 April 2020).

Informed Consent Statement

Informed consent was obtained from the parents of the patient.

Data Availability Statement

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

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Conflicts of Interest

The authors declare no conflicts of interest.

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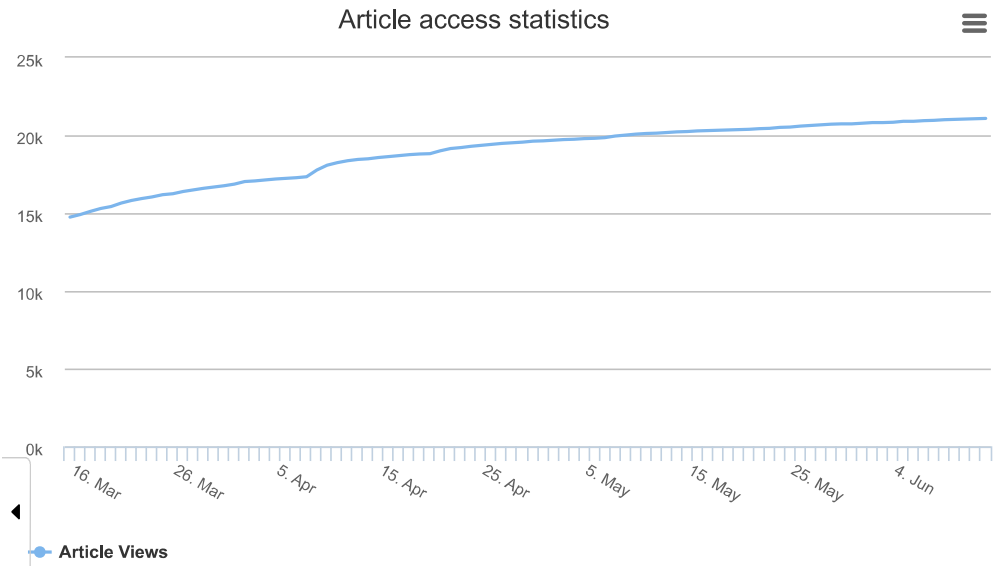

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