Autopsy Histopathologic Cardiac Findings in 2 Adolescents Following the Second COVID-19 Vaccine Dose

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• ***Context.***—**Myocarditis in adolescents has been diagnosed clinically following the administration of the second dose of an mRNA vaccine for coronavirus disease 2019 (COVID-19).**

Objective.—**To examine the autopsy microscopic cardiac findings in adolescent deaths that occurred shortly following administration of the second Pfizer-BioNTech COVID-19 dose to determine if the myocarditis described in these instances has the typical histopathology of myocarditis.**

Design.—**Clinical and autopsy investigation of 2 teenage boys who died shortly following administration of the second Pfizer-BioNTech COVID-19 dose.**

Results.—**The microscopic examination revealed features resembling a catecholamine-induced injury, not typical myocarditis pathology.**

Conclusions.—**The myocardial injury seen in these postvaccine hearts is different from typical myocarditis and has an appearance most closely resembling a catecholamine-mediated stress (toxic) cardiomyopathy. Understanding that these instances are different from typical myocarditis and that cytokine storm has a known feedback loop with catecholamines may help guide screening and therapy.**

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Myocarditis in adolescents (particularly teenage boys) has been reported following the second dose of the Pfizer-BioNTech COVID-19 vaccine.[1–7] Since cardiac biopsies are rarely performed in these instances with clinically stable patients, the myocardial pathology has not been clearly elucidated.[8] Myocarditis is rarely diagnosed at autopsy in deaths due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[9,10] The incidence of myocarditis, although low, has been shown to increase after the receipt of the BNT162b2 vaccine, particularly after the second dose among young male recipients.[11] In addition, the first week after the second vaccine dose was found to be the main risk window.[11] The clinical presentation of myocarditis after vaccination was usually mild.[11]

We report the autopsy results, including microscopic myocardial findings, of 2 teenage boys who died within the first week after receiving the second Pfizer-BioNTech COVID-19 dose. The microscopic findings are not the alterations seen with typical myocarditis. This suggest a role for cytokine storm, which may occur with an excessive inflammatory response, as there also is a feedback loop between catecholamines and cytokines.[12]

Also see p. 921 and p. 924.

MATERIALS AND METHODS

The Connecticut Office of the Chief Medical Examiner and the Michigan Institute of Forensic Science and Medicine investigate all unexpected and unnatural deaths in their respective jurisdictions: Connecticut and the Michigan counties of Alcona, Gladwin, Huron, Lapeer, Ogemaw, and Saginaw.

Standard medicolegal autopsies were performed including gross, microscopic, and toxicologic testing. SARS-CoV-2 nasal swab testing was performed by reverse transcriptase–polymerase chain reaction assay. Tissues were sent to the National Center for Emerging and Zoonotic Infectious Diseases branch of the Centers for Disease Control and Prevention for molecular studies.

Cardiac molecular testing with sequence analysis and deletion/duplication testing of the 100 genes listed in Invitae's arrhythmia and cardiomyopathy comprehensive panel was performed.

RESULTS

The results of autopsies for 2 teenage boys who were found dead in bed 3 and 4 days after receiving the second dose of the Pfizer-BioNTech COVID-19 vaccine are presented (Table). Both boys were pronounced dead at home without attempted resuscitation.

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Summary of Clinical and Autopsy Findings		
Patient	**Heart Gross**	**Microscopic and Molecular**
Teenage boy A, BMI = 21. History of attention deficit hyperactivity syndrome	280 g, normal	There was global myocardial injury with areas of coagulative myocytolysis and contraction bands, with a perivascular pattern of inflammation consisting of predominantly neutrophils with histiocytes, scant lymphocytes, and occasional eosinophils (Figures 1 through 4; Supplemental Figures 1 and 2). In some sections, the myocardial injury was predominantly subepicardial, and in other sections it was patchy and transmural. In the posterior wall, there was subepicardial/transmural fibrous scar, without fatty replacement. There were no acute or organizing thrombi. The overall pattern of injury was consistent with stress cardiomyopathy with contraction bands and a neutrophilic/histiocytic infiltrate
		PCR tissue testing performed by the CDC on heart and lung found no molecular evidence of SARS-CoV-2 infection
		Molecular testing on postmortem blood detected 2 variants of uncertain significance: *DOLK* (c.1257C.G [p.Ile419Met] heterozygous) and *MAP2K2* (c.581-3C>T [intronic] heterozygous)
Teenage boy B, BMI = 30 with obesity	520 g with biventricular dilatation and marked pulmonary edema (combined lung weight = 1481 g)	There was global myocardial injury similar to that seen above, but with more widespread transmural ischemic changes and more interstitial inflammation, again with a predominant neutrophil component with histiocytes and scant lymphocytes (Figures 5 through 7; Supplemental Figures 3 and 4). Several sections had transmural, confluent areas of hypereosinophilic myocytes; confluent areas of contraction bands apart from any inflammation; and florid neutrophilic inflammation with some histiocytes. In this case, a subepicardial distribution of injury was not seen. There were no acute or organizing thrombi. PCR tissue testing performed by the CDC on heart and lung found no molecular evidence of SARS-CoV-2 infection

Abbreviations: BMI, body mass index; CDC, Centers for Disease Control and Prevention; PCR, polymerase chain reaction.

Boy A complained of a headache and gastric upset but felt better by postvaccine day 3. There was no history of prior medical problems (he took prescribed amphetamine/dextroamphetamine during the school year for attention deficit hyperactivity disorder but was not currently receiving it) or prior SARS-CoV-2 infection. Boy B had no complaints, prior health issues, or prior SARS-CoV-2 infection. Neither boy complained of fever, chest pain, palpitations, or dyspnea. The autopsies were unremarkable except for obesity in one boy and the cardiac findings (Figures 1 through 7; Supplemental Figures 1 through 4 [see supplemental digital content at https://meridian.allenpress.com/aplm in the August 2022 table of contents]). Unique cardiac findings in boy A included myocardial fibrosis and in boy B cardiac hypertrophy. There were no rashes or lymphadenopathy.

Expanded forensic toxicologic testing was negative for medications and drugs of abuse. SARS-CoV-2 was not detected by postmortem swab (reverse transcriptase–polymerase chain reaction assay) in either boy. Cardiac sections were submitted from the right and left ventricles (12 sections in boy A and 29 sections in boy B). The cardiac conduction systems were not examined.

DISCUSSION

Myocarditis is an inflammatory disease of the myocardium, which may occur in isolation or as part of multiorgan/systemic immune-mediated disorders or reactions to exogenous/endogenous substances.[13] The etiologies are varied and include infectious and noninfectious causes. Noninfectious causes include immune/autoimmune conditions (autoantigens, association with immune-mediated diseases, alloantigens, and allergens), drugs/toxic substances (eg, hypersensitivity or direct toxic effects), and other causes (eg, radiation, insect stings, snake bites).[13] Lymphocytic myocarditis is the commonest histologic subtype, characterized by an inflammatory myocardial infiltrate typically comprising mononuclear cells. In the acute/active phases, it is usually accompanied by myocyte damage/necrosis.[13] Although criteria are evolving, the Dallas criteria require "inflammatory infiltrates of the myocardium with necrosis and/or degeneration of *adjacent* myocytes, not typical of ischemic damage associated with coronary artery disease."[14–16]

Toxic myocarditis is an etiologic classification involving direct myocardial injury by various drugs or substances.[13,17,18] Although variable, the histologic features consist of 2 main patterns: an early stage with foci of solely necrotic/damaged myocytes and the later phase of "myocarditis." Toxic myocarditis usually indicates inflammatory stages of catecholamine-induced myocardial injury. Catecholamine toxicity on the heart was first described in patients with pheochromocytoma.[19–21] These lesions have been described in patients with subarachnoid hemorrhages and, more recently, in donor hearts rejected for transplantation in persons declared dead by neurologic criteria, secondary to catecholamine release during the "sympathetic storm" following brain death or administered as pharmacologic support (see supplemental material).[22,23] The wide spectrum of these lesions has been studied in detail in routine pathology examination of donor hearts unsuitable for transplantation.[22]

Both teenage boys had similar clinical presentations with no obvious cardiac symptoms. Their histopathology did not demonstrate a typical myocarditis. In those instances, one sees lymphocytic (or giant cell) infiltrates with adjacent myocyte necrosis; changes such as hypereosinophilic myocytes and contraction bands are absent. In these 2 postvaccination instances, there are areas of contraction bands and hypereosinophilic myocytes distinct from the inflammation. This injury pattern is instead similar to what

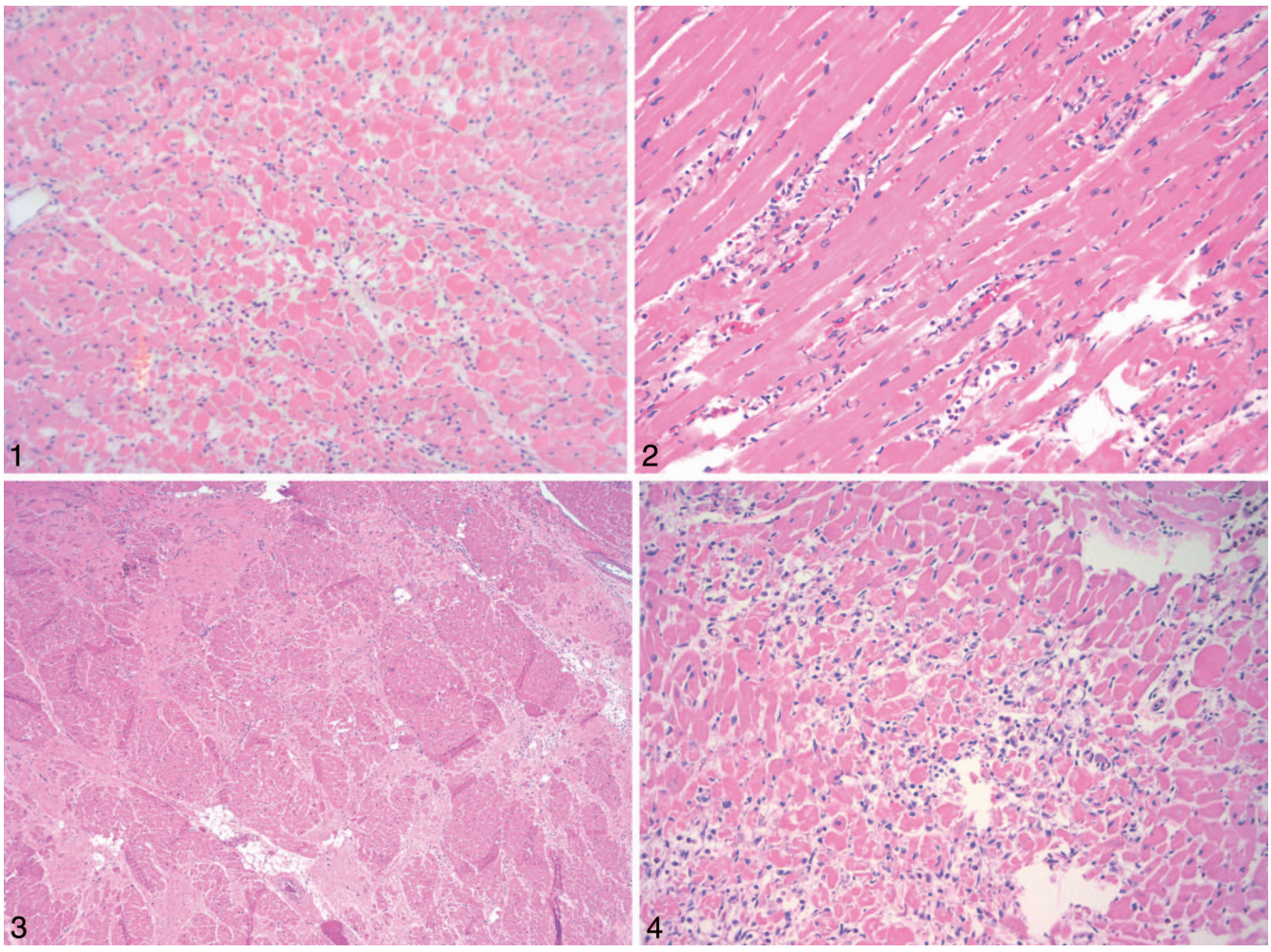


Figure 1. *Case A, heart: confluent areas of ischemia (hematoxylin-eosin, original magnification ×100).*

Figure 2. *Case A, heart: coagulative and contraction band necrosis (hematoxylin-eosin, original magnification ×200).*

Figure 3. *Case A, heart: subepicardial fibrosis. This appears older than the timing of the first vaccine dose. This is a possible arrhythmogenic cardiomyopathy, but its appearance is more consistent with healed ischemia or inflammation (hematoxylin-eosin, original magnification ×40).*

Figure 4. *Case A, heart: confluent areas of ischemia with contraction bands and coagulative myocytolysis (hematoxylin-eosin, original magnification ×200).*

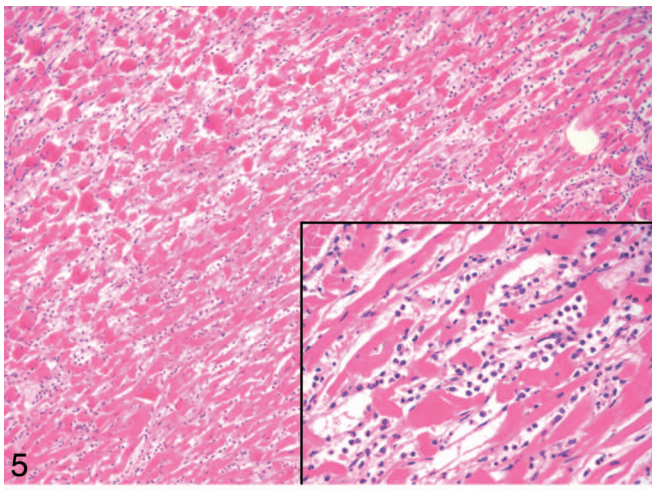
is seen in the myocardium of patients who are clinically diagnosed with Takotsubo, toxic, or stress cardiomyopathy, which is a temporary myocardial injury that can develop in patients with extreme physical, chemical, or sometimes emotional stressors.[24–31]

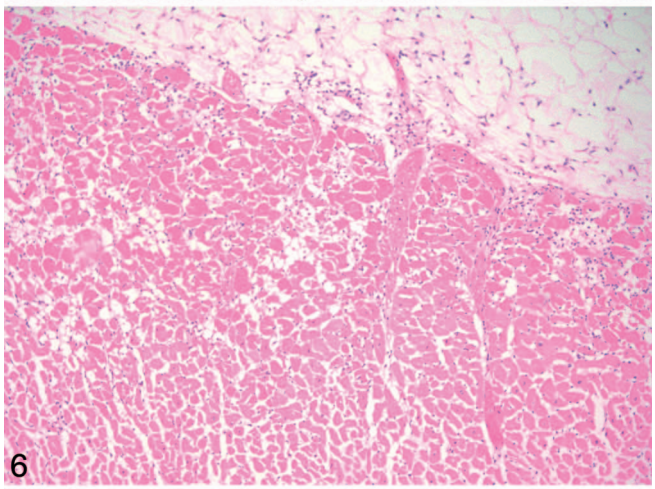
Stress cardiomyopathy is a catecholamine-mediated ischemic process seen in high catecholamine states in the absence of coronary artery disease or spasm.[17,31] It has also been called "neurogenic myocardial injury" and "broken heart syndrome."[18,24–36] Surges in catecholamines may have several triggers (fight/flight response, adrenal pathology, etc). Proposed mechanisms for catecholamine-mediated stunning in stress cardiomyopathy include epicardial spasm, microvascular dysfunction, hyperdynamic contractility with midventricular or outflow tract obstruction, and direct effects of catecholamines on cardiomyocytes.[33]

Catecholamine-mediated myocardial stunning may be due to direct myocyte injury, as elevated catecholamines decrease the viability of myocytes through cyclic adenosine monophosphate–mediated calcium overload. Catecholamines also are a potential source of oxygen-derived free radicals, which can interfere with sodium and calcium transporters, possibly resulting in myocyte dysfunction through increased transsarcolemmal calcium influx and cellular calcium overload.[37]

Histologically, catecholamine effects have been associated with contraction band necrosis, characterized by hypercontracted sarcomeres, dense eosinophilic transverse bands, and an interstitial mononuclear inflammatory response that is distinct from the polymorphonuclear inflammation seen with infarction. In addition, the mononuclear cells are not causing the myocyte necrosis; there is a distinct, separate distribution.[37]

We suspect that the acute cardiac changes seen in these 2 boys are the result of epinephrine-mediated effects on cardiomyocytes. These occurrences generally have a favorable prognosis; however, some patients may die from the underlying (noncardiac) cause of the myocardial findings





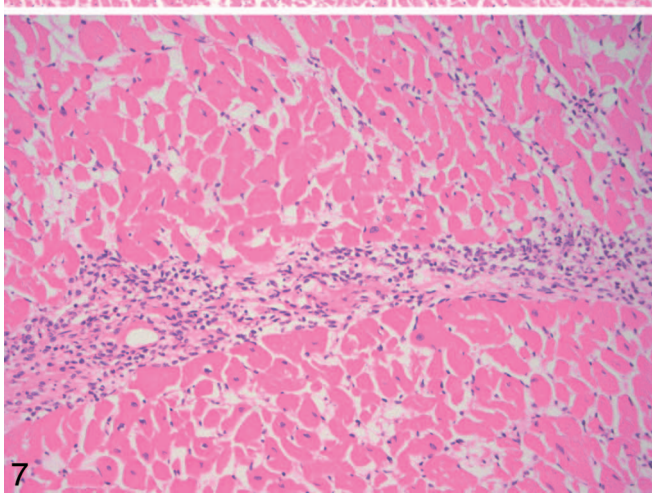


Figure 5. *Case B, heart: hypereosinophilic myocytes, contraction band necrosis, and coagulative myocytolysis. Inset: the infiltrate is predominantly neutrophilic (hematoxylin-eosin, original magnifications ×100 and ×400 [inset]).*

Figure 6. *Case B, heart: subepicardial coagulative myocytolysis/contraction band necrosis (hematoxylin-eosin, original magnification ×100).*

Figure 7. *Case B, heart: perivascular inflammation (hematoxylin-eosin, original magnification ×200).*

(eg, as with subarachnoid hemorrhage). Histologically, diffuse hypereosinophilic myocytes, contraction bands, and coagulative myocytolysis are seen, with a patchy and random pattern and a neutrophilic/mononuclear cell infiltrate. With longer survival, global myocardial ischemia may develop.[37]

This postvaccine reaction may represent an overly exuberant immune response, with the myocardial injury mediated by similar immune mechanisms to those described with SARS-CoV-2 and multisystem inflammatory syndrome cytokine storms.[38] Multisystem inflammatory syndrome is a rare systemic illness presenting with persistent fever and extreme inflammation following exposure to SARS-CoV-2. Affected children have persistent fever and may have acute abdominal pain with diarrhea or vomiting, muscle pain/malaise, and hypotension. Other reported symptoms include rashes, enlarged lymph nodes, and swelling.

A hypersensitivity reaction is in the differential diagnosis; however, infrequency or lack of eosinophils would be unusual. The common denominator of a hypersensitivity reaction is the eosinophilic infiltrate, which may be the major inflammatory component or part of a complex picture of mixed inflammation with lymphocytes, macrophages, plasma cells, poorly formed microgranulomas, and giant cells.[39] An autopsy study of 69 cases of hypersensitivity myocarditis examined the spectrum of histologic findings, including the distribution of infiltrates and the extent and composition of the infiltrates.[40] The authors reported that hypersensitivity myocarditis was "defined by the presence of eosinophils, a mixed lymphohistiocytic infiltrate along natural planes of separation, and an absence of fibrosis or granulation tissue in areas of infiltrate."[40]

Despite a molecular investigation, the etiology of the fibrosis in case A is unclear. It is conceivable that this process first started with the first vaccination dose and the initial myocardial effects resolved and healed over time. The second dose may have restarted the process. One might expect some scarring/repair after a few weeks, although the scarring in case A appears more organized than the 3-week interval between the vaccine doses. Also, it is only in one of the cases. It remains possible that the fibrosis represents arrhythmogenic cardiomyopathy. Unfortunately, cardiac molecular testing was equivocal.

Regardless of the etiology of the fibrosis, the extent of scarring by itself is potentially arrhythmogenic and may be a contributing factor with the acute postvaccine myocardial injury. Similarly, the cardiac hypertrophy in case B may have made the heart more susceptible to an arrhythmia. The key point is that since these boys died suddenly and unexpectedly in their sleep without resuscitation, if the arrhythmia had been due to the myocardial scar (boy A) or cardiomegaly (boy B), then the fulminant, global myocardial injury would not be an expected finding. These 2 clinical histories support the etiology of the acute myocardial injury as a primary factor, not a secondary agonal or postresuscitative artifact.

Two adults (ages 42 and 45 years) with myocarditis diagnosed histologically (one at autopsy and one by biopsy) following SARS-CoV-2 mRNA vaccinations were recently reported.[41] One occurred 10 days after receiving the first Pfizer-BioNTech COVID-19 vaccine dose and the other occurred 14 days after receiving the second mRNA-1273 (Moderna) dose. Histologically, both were described as "fulminant" myocarditis with "multifocal cardiomyocyte

damage associated with mixed inflammatory infiltration." In addition to areas of myocyte necrosis associated with the inflammatory infiltrate, the photomicrographs demonstrate ischemic changes distinct from the inflammation, similar to our findings.

Cytokine storm has been described with an excessive and uncontrolled inflammatory response, and there is a feedback loop between catecholamines and cytokines.[12] Clinical complications may include cardiac compromise, respiratory distress, and hypercoagulation.[42] The myocardial injury seen in these postvaccine hearts has a similar histologic appearance to catecholamine-mediated stress cardiomyopathy and severe SARS-CoV-2 infection, including myocarditis, which is associated with cytokine release syndrome.[38] Recognition that these instances are different from typical myocarditis and that cytokine storm has a known feedback loop with catecholamines may help guide screening, diagnosis, and therapy.

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