Case #44

NAME Educational Activities Committee

Case provided by:

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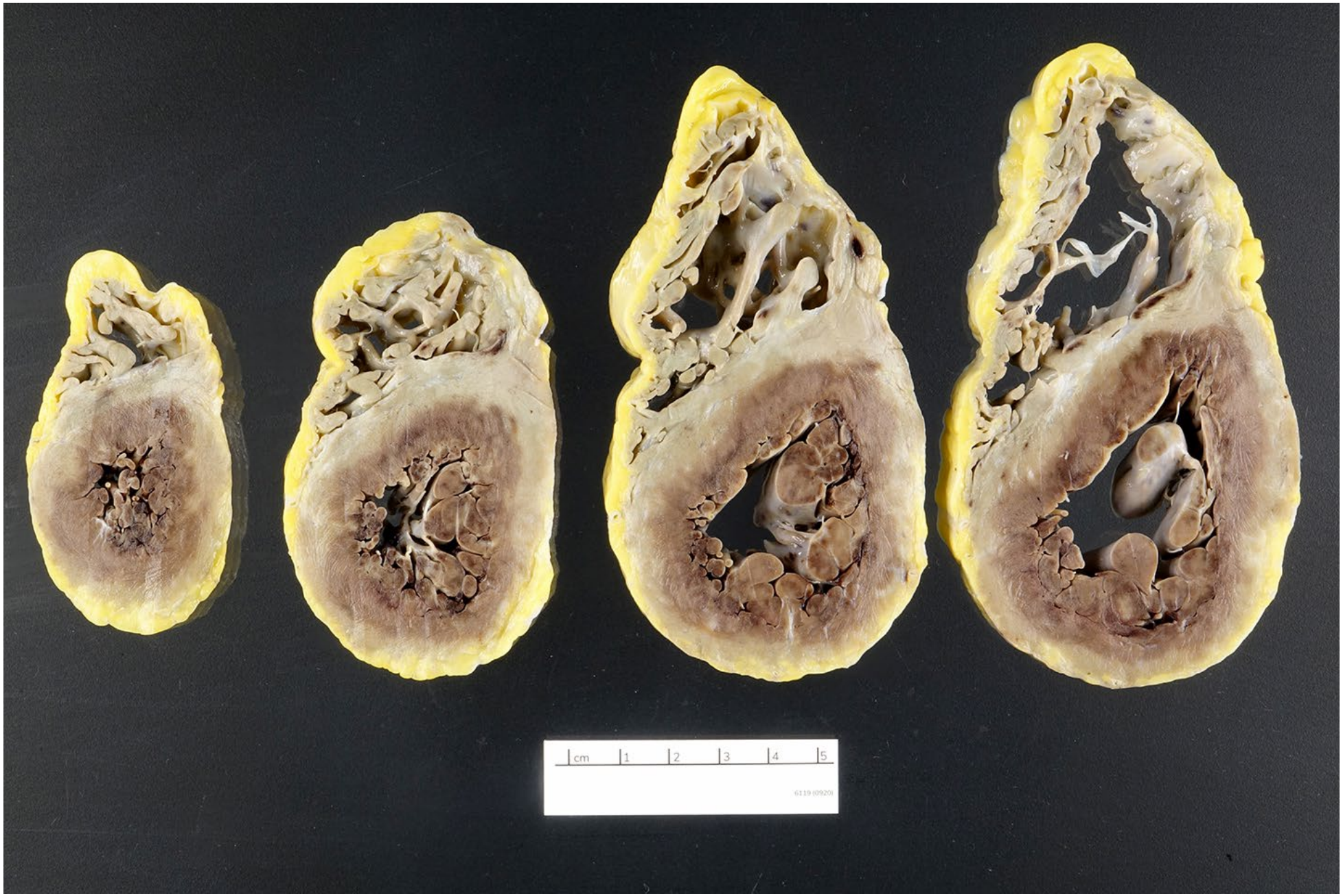
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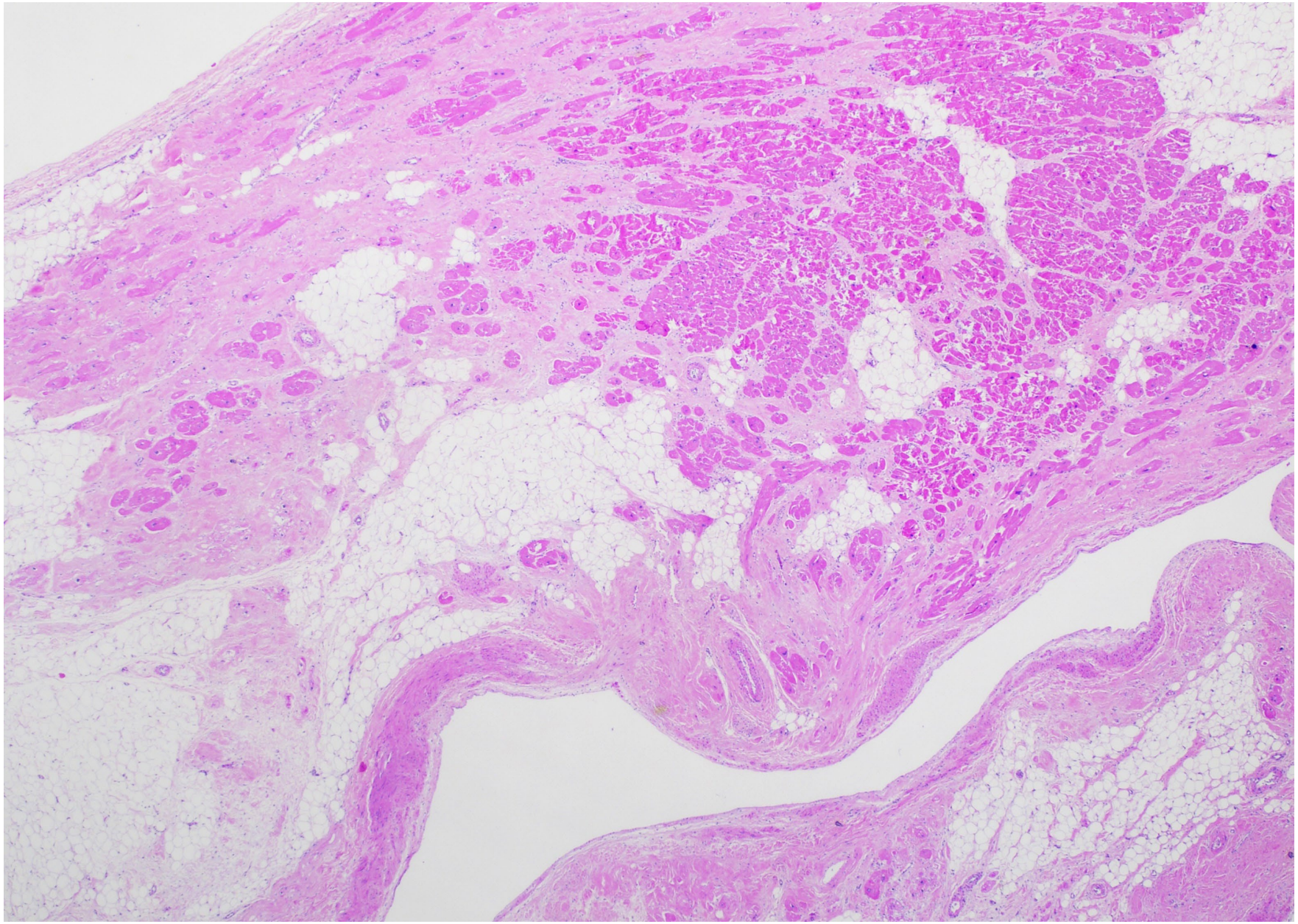
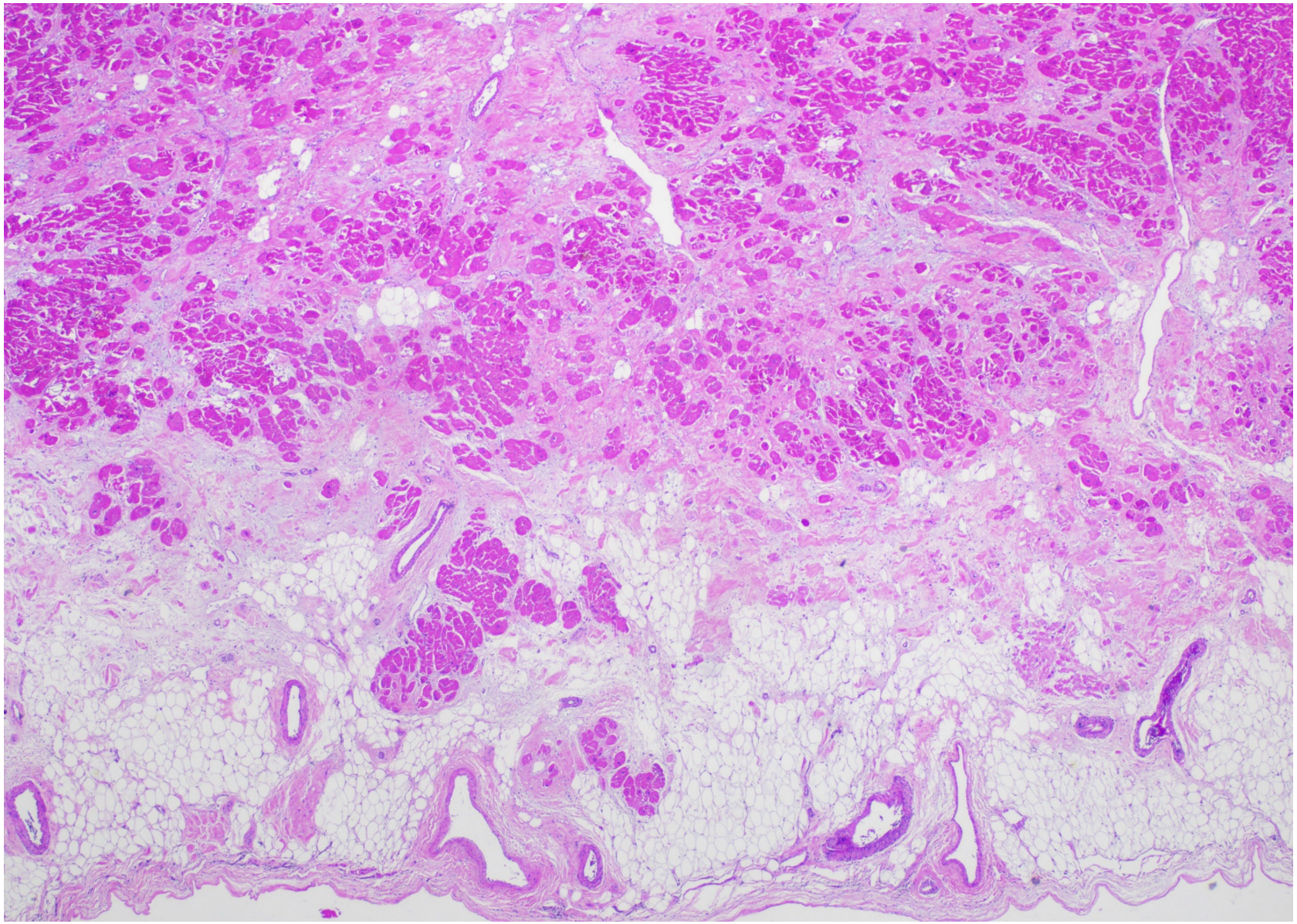
Posterior wall of the right ventricle



Posterolateral wall of the left ventricle



1. A 38-year-old man with no significant past medical history collapsed while playing basketball. Paramedics noted ventricular fibrillation on arrival and began resuscitative efforts. He was in asystole upon arrival to the emergency department and was placed on veno-arterial extracorporeal membrane oxygenation. Coronary angiogram showed no critically obstructive coronary artery disease. Computed tomography (CT) scan of the head showed findings consistent with anoxic brain injury. He was pronounced dead roughly 15 hours after presentation.

The most significant autopsy finding was noted in the heart. A gross photograph with cross-sections of the heart and microscopy from both ventricles are shown. What is the most likely cause of sudden death in this man?

- ◯ Arrhythmogenic Cardiomyopathy
- ◯ Active Infectious Myocarditis
- ◯ Commotio Cordis
- ◯ Hypertrophic Cardiomyopathy
- ◯ Ischemic heart disease

Answer...

A. Arrhythmogenic cardiomyopathy (CORRECT ANSWER, 67.0% of responses)

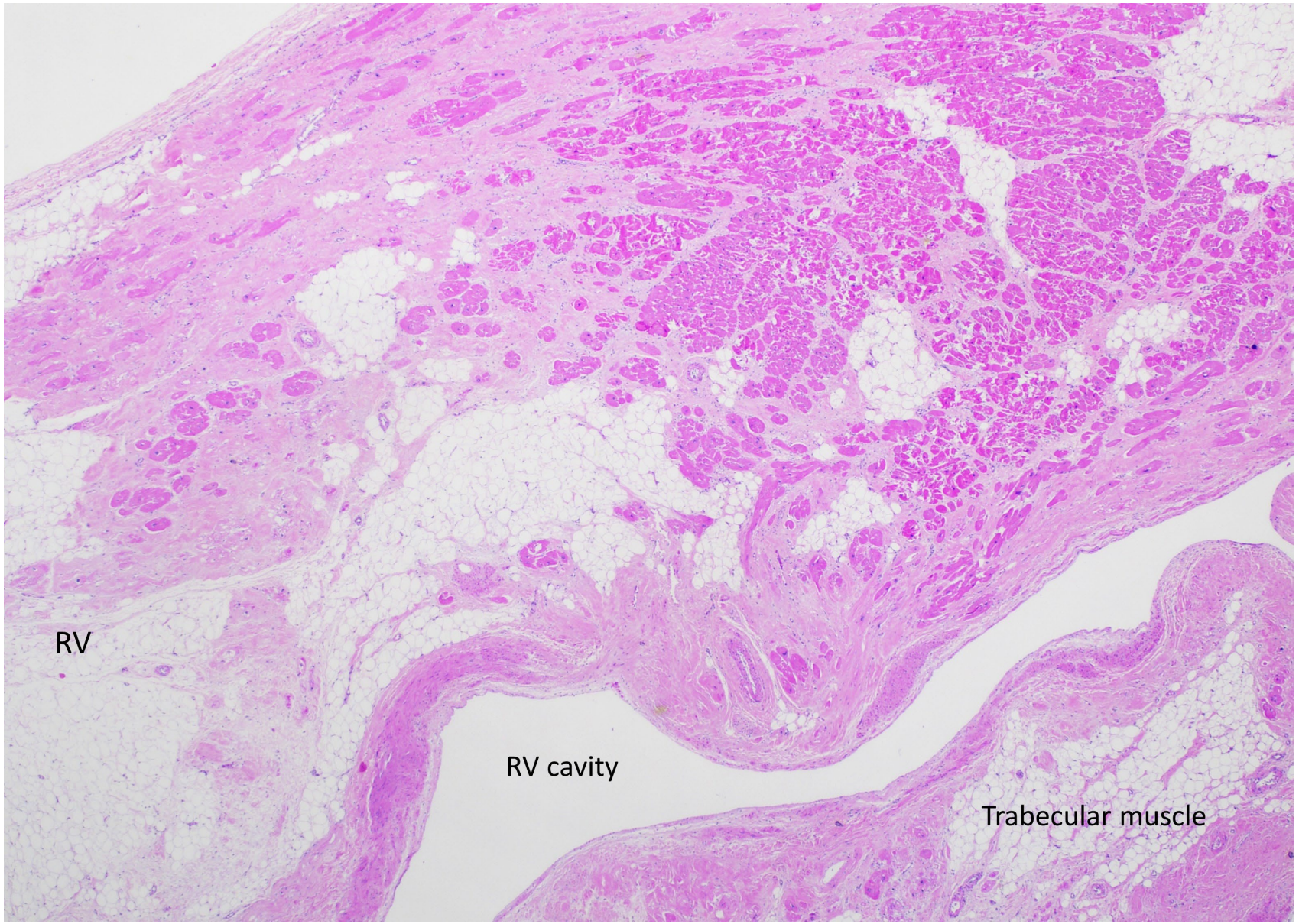
The findings are most consistent with arrhythmogenic cardiomyopathy (ACM). ACM is an underrecognized, non-ischemic myocardial disease and important cause of sudden cardiac death (SCD) in the young and in athletes (with a male predominance). It is characterized pathologically by fibrous or fibrofatty myocardial replacement and clinically by ventricular arrhythmias. Originally termed arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C), this disorder was thought to arise from a congenital defect of myocardial development limited to the right ventricle. It is now known to be a progressive, genetically mediated disease with frequent left ventricular involvement including rare left-dominant forms. This has prompted the replacement of the term ARVD/C with ACM, which encompasses all three patterns of expression (right or classic form, left-dominant, and biventricular - as seen in the current case). The majority of individuals who are diagnosed while alive are symptomatic, presenting with palpitations and syncope as manifestations of ventricular arrhythmias. Owning to the genetic underpinnings of this disease, a familial background is noted in most cases.

Replacement-type fibrosis (focal or extensive) and degenerating/atrophic cardiomyocytes should always be identified in ACM. Fibrofatty replacement in ACM shows centripetal progression - that is, from subepicardium towards the endocardium (arrow in left ventricle micrograph). There is a wide phenotypic spectrum of disease. Adequate sampling of the right and left ventricles is crucial in the diagnosis of early disease, with particular attention to the infundibulum, apex, and posterior aspects of the right ventricle ("triangle of dysplasia"). Left ventricular involvement tends to first affect the posterolateral wall. The left ventricle was near-circumferentially involved in the current case. The specialized conduction system is usually spared in ACM. Additional pathologic findings include cardiomegaly, ventricular dilatation, and inflammatory cell infiltrates. Fatty infiltration of the right ventricle is not a sufficient histologic finding for diagnosis. Physiologic fatty infiltration can be quite extensive in the right ventricular free wall and is particularly seen in the elderly and females. Physiologic fat tends to displace rather than replace cardiomyocytes.

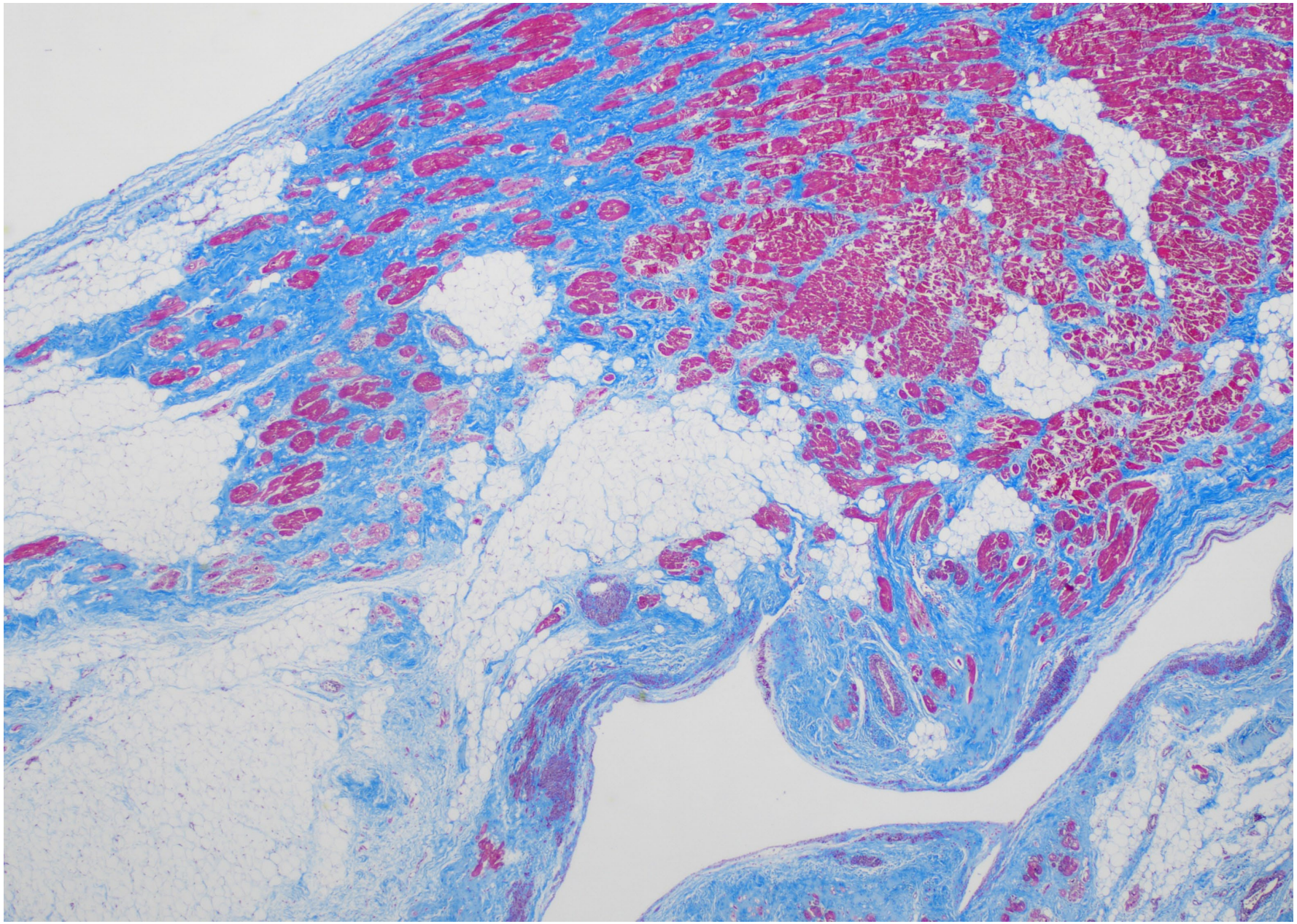
The pathogenesis of ACM is believed to be related to mutations in genes encoding proteins of the intercalated discs, namely desmosomes, resulting in loss of adhesion between cardiac myocytes, followed by myocyte detachment and cell death with replacement by fibrofatty tissue. Competitive/endurance sports increase the risk of SCD, as it may accelerate phenotypic expression in ACM.

The most commonly mutated genes are plakophilin-2 (PKP2), desmoplakin (DSP), desmoglein-2 (DSG2), plakoglobin (JUP), and desmocollin-2 (DSC2); however, genes encoding non-desmosomal proteins have also been implicated (e.g., TMEM43, RYR2). Genetic testing yields a pathogenic mutation in only ~50% of cases. The most common inheritance pattern is autosomal dominant with incomplete penetrance. All first-degree relatives of a proband should be screened, so it is imperative that the pathologist communicate findings to next of kin and/or primary physicians.

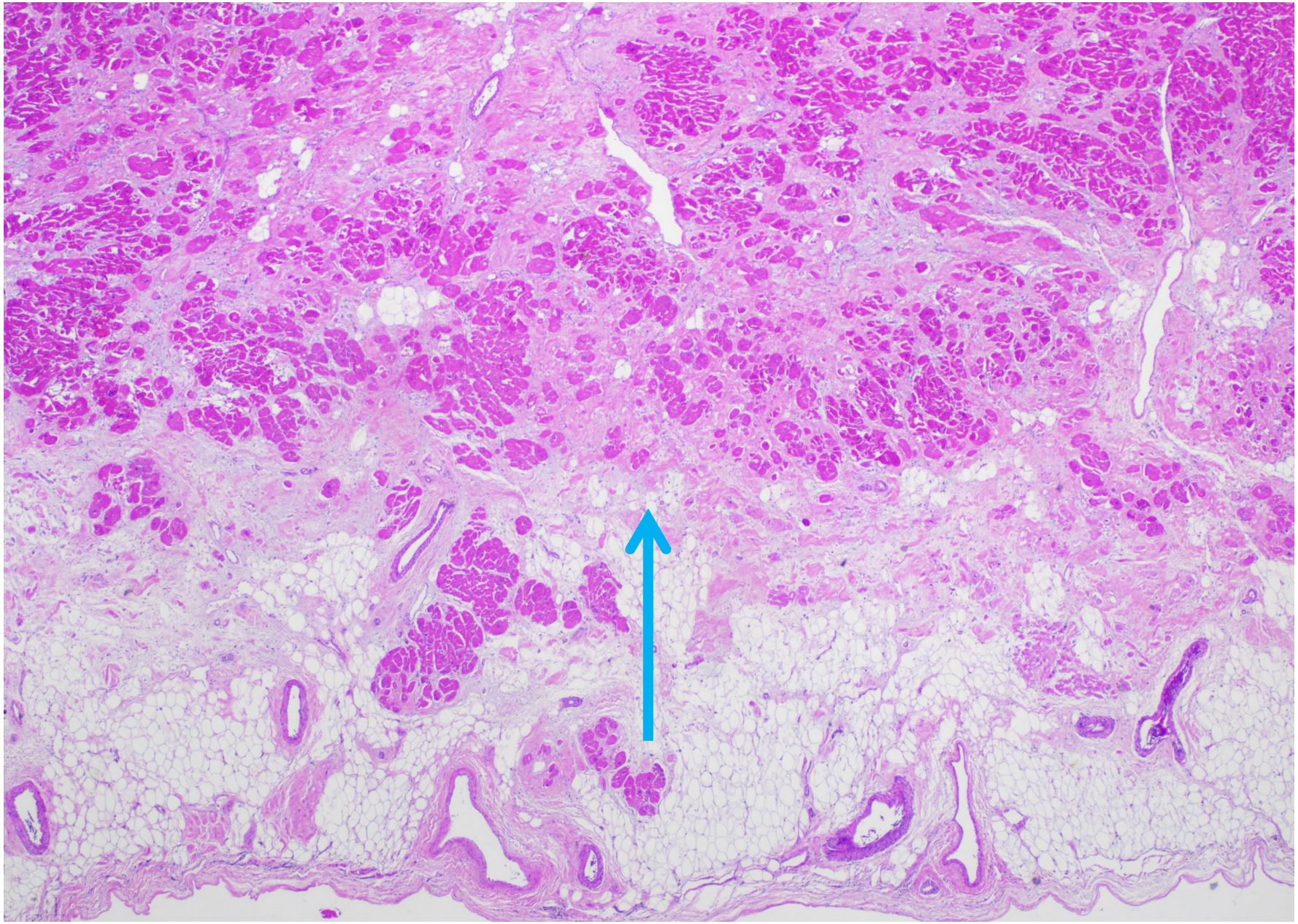
Posterior wall of the right ventricle



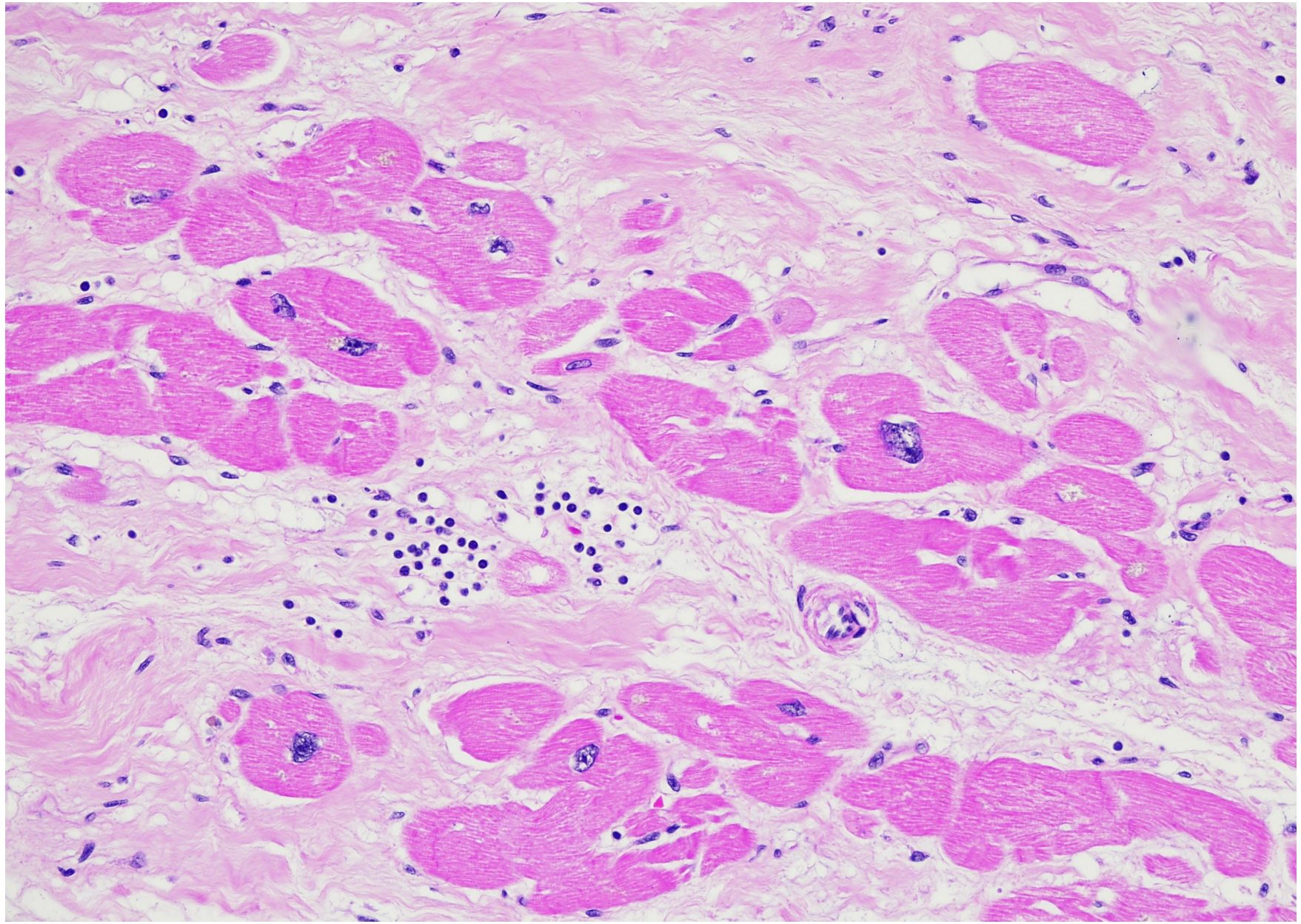
Posterior wall of the right ventricle – Trichrome stain



Posterolateral wall of the left ventricle



Residual cardiomyocytes with sparse mononuclear cell infiltrate



B. Active Infectious Myocarditis (3.91% of responses)

SCD in the setting of active infectious myocarditis (IM) may be due to several causes, including arrhythmias. Grossly, there is most often pallor of myocardium and ventricular dilation, which are nonspecific. Histologically, IM is commonly characterized by intense inflammatory infiltrate

C. Commotio cordis (1.01% of responses)

Commotio cordis (CC) is ventricular fibrillation and sudden death triggered by a blunt, nonpenetrating, and often innocent-appearing blow to the chest without damage to the ribs, sternum, or heart (and in the absence of underlying cardiovascular disease). Based on the reported circumstances prior to death in this case, there was no antemortem trauma or chest impacts during the game. Furthermore, the gross abnormalities (left ventricular hypertrophy, right ventricular dilation) and histological findings (fibrofatty ventricular infiltrate) indicate that there is an underlying cardiac etiology to this case of SCD, making CC an unlikely diagnosis.

D. Hypertrophic cardiomyopathy (21.56% of responses)

Hypertrophic cardiomyopathy (HCM) is commonly considered in the setting of exercise related SCD, especially in younger decedents. HCM is characterized by significant primary hypertrophy of the left ventricle (>15 mm). However, the presence of biventricular fibrofatty infiltrates, scattered inflammatory infiltrate, and lack of myocyte disarray found histologically makes a diagnosis of HCM less likely in this case.

E. Ischemic Heart Disease (6.51% of responses)

Death related to ischemic heart disease is most commonly a consequence of coronary artery atherosclerosis. Deaths in these cases can result from acute events (e.g. intraluminal thrombus formation with epicardial coronary artery occlusion), chronic injury leading to impaired left ventricular function, or a combination of the two (e.g. irreversible loss of myocardium due to prior myocardial infarction). There was no coronary artery vessel occlusion noted in this case, and the fibrosis identified was much more diffuse in distribution (involving the entire left and right ventricles) compared to what is more commonly seen with ischemic injury.

References

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