Sudden Cardiac Death due to Coronary Fibromuscular Dysplasia: Case Report and Literature Review

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Introduction

According to the 2015 annual report on legal autopsies in Korea, 51.5% of natural deaths were diagnosed as being of cardiac origin. Among them, ischemic heart disease was the cause of death in 67.3% of people [1]. In general, most cases of ischemic heart disease are known to result from coronary atherosclerosis. However, there are several nonatherosclerotic conditions with different pathophysiologic mechanisms, causes, and risk factors. These conditions include vasospasm due to smoking, drug or alcohol use; emboli associated with atrial fibrillation or infective endocarditis; vascular diseases such as vasculitis, amyloidosis, or dissection; and systemic diseases such as shock.

In this study, we report a case of sudden cardiac death due to fibromuscular dysplasia (FMD) of the coronary artery, diagnosed by pathologic findings and

Fibromuscular dysplasia (FMD) of the coronary artery is a rare cause of sudden cardiac death; however, its prevalence and fatality may have been overlooked so far. A 47-year-old man complained of pain in his back and shoulder and became unconscious. Despite resuscitation, he died 3 hours after symptom onset. The heart weight was in the normal range; however, all three major coronary arteries showed intimal thickening without atherosclerosis or inflammatory cell infiltration. Fragmentations and duplications of the internal elastic lamina which are histologic features of intimal fibroplasia, a focal-type FMD, were observed. The prevalence of coronary FMD remains unknown, although it may be related to spontaneous coronary artery dissection and sudden death. The histopathologic confirmation of coronary FMD and exclusion of other possible coronary diseases through autopsy are essential to reveal the nature of the disease and therefore apply the information in dealing with legal problems after death.

Key Words: Fibromuscular dysplasia; Coronary vessels; Tunica intima; Cause of death; Sudden cardiac death
clinical symptoms. FMD is a nonatherosclerotic and noninflammatory vascular disease which can occur in any body part but most commonly in the renal and carotid areas. Coronary FMD is a rare example of a nonatherosclerotic cause of ischemic heart disease; however, its prevalence and fatality may have been overlooked so far. By sharing the experience of this case, recent advances in coronary FMD and potential legal issues will be reviewed.

Case Report

A 47-year-old man complained of sudden pain in his back and shoulder while resting at home with his family. Shortly thereafter, he started to vomit, and his fingers became pale and cold. On his way to the hospital, he lost consciousness and went into cardiac arrest. The emergency medical service personnel administered cardiopulmonary resuscitation; however, he died 3 hours after the onset of the symptoms. The bereaved family reported that he had presented with similar symptoms 3 days prior and had no previously known disease. His father died from aortic valve stenosis. An autopsy was performed the following day.

The victim’s height and weight were 163 cm and 69 kg, respectively, with a body mass index of 26.0 kg/m². His heart weight was 366 g, which was within the normal range for adult males. The vascular walls of all three major coronary branches were thickened circumferentially, and their lumens were narrowed by up to 85%, especially in the proximal segment. Atherosclerotic changes, such as yellowish discoloration, plaques, or calcification, were not found. The cardiac chambers did not show any morphologic changes such as hypertrophy, dilatation, fibrosis, or congenital defects (Fig. 1). Upon the microscopic examination of the major coronary branches, thickening of the coronary wall was predominantly observed in the intimal layers, without lipid deposits or inflammatory cell infiltration. The elastin stain revealed multifocal fragmentations and duplications of the internal elastic lamina (Fig. 2). According to these findings, the coronary arteries were diagnosed with focal-type FMD. In detail, the histopathologic subtype was intimal fibroplasia. Both early ischemic changes in the myocardium, such as contraction band necrosis and interstitial inflammatory cell infiltration, and typical chest pain during the perimortem period suggest that the victim died from ischemic heart damage subsequent to the coronary FMD.

Discussion

FMD is a unique vascular disease not associated with atherosclerosis or inflammation. Its pathogenesis and causative genetic alterations have not been revealed yet, although mutational variants of transforming growth factor beta receptor 1 (TGFβR1) and phosphatase and actin regulator 1 (PHACTR1) genes have been suggested as related gene alterations [2]. FMD can occur in arteries throughout the body, and its clinical features vary according to the involved location, the degree of stenosis or accompanying complications such as dissection, or aneurysms [3].

Several studies on FMD cohorts have reported that FMD occurred most commonly in renal arteries and that the prevalence of renal FMD was approximately 3%–4%. However, referral bias should be considered in these reports since their cohorts usually consisted of renal transplantation donors [2]. As proof of these results, the United States Registry for Fibromuscular Dysplasia (U.S. FMD Registry), established in 2008, found that extracranial carotid FMD occurred as frequently as renal disease [4]. Regrettably, this registry is insufficient to determine the prevalence of FMD in multiple vascular territories since most imaging studies focused on the head or abdominal areas.

Some characteristics of FMD make it difficult to determine its prevalence. Many patients with FMD have only mild or nonspecific symptoms and therefore do not visit a hospital before vascular stenosis progresses significantly. The diagnosis of FMD requires expensive and complicated techniques such as arteriography or high-resolution imaging, or even invasive methods such as vascular resection through surgery or autopsy. Unfortunately, without sufficient indications to arise suspicion, an autopsy is not a solution for diagnosis as medium- or small-sized arteries are not usually explored thoroughly during a routine autopsy. In the current case, renal and carotid arteries were not
Fig. 1. Gross findings of the heart and the coronary arteries of the deceased. (A, B) The heart was of normal weight without any abnormal features. (C–E) In the cross-sections of the major coronary arteries, the lumens were narrowed by wall thickening and there were no atherosclerotic changes (C, right coronary artery; D, anterior descending branch of the left coronary artery; E, circumflex branch of the left coronary artery).
explored during the autopsy because coronary FMD was only diagnosed after the histologic examination.

The prevalence of coronary FMD is even more controversial. More than one hundred cases of coronary FMD have been reported since 1976 [5]; however, most of them were located in small coronary branches, implying that they may be nonspecific findings of aging [6]. Only approximately 20 cases of coronary FMD involving major coronary arteries or occurring in young people are currently regarded as “true” coronary FMD [7]. Recent studies on FMD cohorts also appear unable to adequately cover or detect coronary FMDs, as pointed out by Olin et al. [8] in their review article.

The possibility that coronary FMD may be more common and fatal than previously thought is supported by several reports. First, a few cases of sudden death by coronary FMD [5] or accompanying coronary artery dissection [9] have been reported. In addition, 60 of 303 (19.8%) patients in the U.S. FMD Registry reported a family history of sudden death [4] and 19 of 32

Fig. 2. Histologic findings of coronary arteries. (A) The cross-section of the coronary artery shows circumferential thickening of the vascular wall (H&E stain, ×4). (B) The intimal layer which showed neither noticeable inflammation nor lipid accumulation contributed mainly to the thickening (H&E, ×40). (C, D) Elastin stain highlighted the internal elastic lamina and both fragmentations and duplications of the internal elastic lamina were found (C, elastin stain, ×100; D, elastin stain, ×200). These findings were consistent in all three major coronary branches.
(59.4%) patients in another case series of coronary FMD presented with myocardial infarction [8]. Moreover, the relationship between spontaneous coronary artery dissection (SCAD) and FMD has recently captured the attention of many researchers. SCAD causes acute coronary syndrome and most frequently affects young or healthy women. It has been revealed that many SCAD victims had concomitant coronary or extracoronary FMD at the time of diagnosis [3,7,10]. These findings suggest that fatal presentations, such as myocardial infarction or sudden death, may be the first indicator of coronary FMD, resulting in an underestimation of the disease.

The histopathologic classification of FMD established in the mid-1990s by Harrison and McCormack classifies the disease to three categories according to the involved layer of the arterial wall and its pathologic features. However, simplified two-tier angiographic classification has recently been suggested by several working groups. In angiographic classification, as suggested by the American Heart Association, multifocal-type FMD is indicated by a lesion with the classic “string of beads” pattern produced by medial fibroplasia, while focal-type demonstrates a limited length of stenosis, mostly generated by intimal fibroplasia. Focal-type disease also includes some cases of medial hyperplasia and adventitial-type fibromuscular dysplasia [8].

As mentioned above, the dominant histologic subtype of coronary FMD is uncertain. While the most common subtype of extracoronary FMD is known as medial-type, only few cases of coronary FMD appear to have the “string of beads” appearance characteristic of medial fibroplasia [7]. Intimal fibroplasia, a rare subtype of FMD usually found in children, may occur reasonably often in adult coronary FMD [5,7,9], as seen in the present study. The dominant subtype and histopathologic features of coronary FMD should be determined for an accurate diagnosis since intimal thickening not associated with atherosclerosis or inflammation may also be induced by traumatic endothelial injury due to hypertension, vasculitis, drug (especially cocaine) use, smoking, or congenital anomalies [5]. However, pathologic studies of coronary FMD is limited in clinical practice, considering that surgical therapy, including coronary resection, is the last choice of treatment for coronary FMD and is usually indicated for patients with multivessel involvement.

In these aspects, the role of forensic pathologists who perform the autopsy on victims of internal death is critical. Unlike angiography or optical coherence tomography used for clinical diagnosis of coronary FMD, autopsy procedures directly provide clear gross findings of coronary arteries without being disturbed by ambiguous findings of other diseases. In addition, when coronary FMD is suspected, the vascular area frequently affected by FMD may be thoroughly observed and harvested for pathologic study. Some findings that are detectable during routine gross inspections of the heart suggest coronary FMD. First, the walls of coronary arteries show obvious thickening. The range of the thickened region may be focal or diffuse in length or circumference. Second, no definite atherosclerotic coronary changes are present, including yellowish discoloration, plaques, or calcification. Third, the size, weight, and anatomy of the heart of the deceased are in the normal range for his/her population group. Histopathologic confirmation, including special staining methods for the suspected coronary arteries, would be mandatory for these people. An inspection of the frequently affected regions such as the renal and carotid areas can provide additional information. The clinical symptoms of the deceased will not differ from symptoms that are present during other cases of sudden cardiac death; however, patients may have none or mild, if present, cardiovascular risk factors and a related medical history. Information accumulated during these investigations will provide valuable assistance in revealing the pathogenesis of coronary FMD and patient demographics in the future.

Forensic pathologists also play a crucial role after diagnosis. Not only the manner of death but also the cause of death may affect several legal or administrative issues faced by the bereaved family. These situations are not restricted to unnatural deaths like accidents or homicides. For cases of natural death, the specific diagnostic entity that resulted in death can have different effects on insurance, compensation, or liability. Cardiovascular diseases, including coronary FMD, or cerebrovascular diseases are classic examples of diseases that can impact on legal or administrative issues.

Some insurance policies contain special conditions
which guarantee increased death benefits should the insured person die from one of the designated diseases. If the death certificate or autopsy report includes the exact diagnostic term as it appears on these lists and medical records show relevant descriptions, there will rarely be a problem in receiving the disbursement. However, in many cases, different terms may be selected as the final cause of death in these documents for several reasons, although they imply similar course of the diseases to those on the list. The current case with a sequence of coronary FMD, ischemic myocardial damage, and sudden death may be used as a hypothetical example to illustrate the impact of the use of varying terminology. The pathologist may select "coronary FMD" as the only cause of death without mention of "ischemic heart disease" or "acute myocardial infarction" because (1) coronary FMD was the most important cause of death and ischemic damage was an incidental or subsequent event, (2) ischemic heart damage was described sufficiently in the pathology section of the report, (3) despite a strong suspicion of ischemic changes of the myocardium, the gross and microscopic findings were not definite. These decisions are acceptable and comprehensible to the other medical experts; however, the agents of the insurance company and the contractors who lack a medical background may have problems understanding the details. They may spend additional time and effort in consulting external medical experts or even reject the insurance claim due to a misunderstanding. Without appropriate interventions, these conflicts could lead to lawsuits and a repeated waste of time and resources.

The roles of specific risk factors may also be controversial in the decision of compensation. When the risk factors are thought to be related to the victim's working conditions, his death may be the subject of a judgment for industrial death, and his employer or government-related organization may be held responsible for the management of the working environment. In the case of coronary FMD, there may be an attempt to assign a greater weight to the genetic predisposition for coronary FMD than to atherosclerosis and reduce the liability for the death. If coronary FMD and atherosclerotic coronary disease are considered to have different characteristics, legal or administrative decisions regarding related cases may be affected. Although an autosomal dominant pattern with variable penetrance has been suggested for FMD in early pedigree studies, the proportion of reported familial FMD has been substantially lower in recent studies than what was previously accepted [2]. Moreover, these studies included only a few subjects with coronary FMD. Among environmental factors, the evidence is accumulating of the association between smoking and FMD; however, to date, this has not been proven [2]. Forensic pathologists should expect and prepare for possible controversy surrounding these cases. It would be beneficial if all relevant information is included in the autopsy report from the beginning, but they should be prepared to provide suitable answers if conflict arises.

Considering that coronary FMD is usually only diagnosed after the manifestation of critical symptoms or the discovery of extracoronary disease, it is exceedingly possible that the prevalence and clinical significance of coronary FMD have been underestimated. More research is required to reveal the pathogenesis, risk factors, disease course, and mortality of coronary FMD. There should also be a consideration for reducing confusion for the person who deals with the legal or administrative issues related to these types of internal death. The role of forensic pathologists is critical in both factors. To reduce the ambiguity of diagnosis, not only the histologic confirmation of coronary FMD and subsequent myocardial damage but also the exclusion of other possible causes of sudden cardiac death, such as atherosclerotic or hypertensive cardiac disease, should be performed through comprehensive pathologic inspection and medical record review.

Conflicts of Interest
No potential conflicts of interest relevant to this article were reported.

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