CASE REPORT

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The Spectrum of Intramyocardial Small Vessel Disease Associated with Sudden Death

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ABSTRACT: Intramyocardial small vessel abnormalities are not commonly recognized. The best known abnormality is fibromuscular dysplasia involving the sinoatrial or atrioventricular nodal arteries. Small vessel disease has been reported as an isolated cardiac anomaly in individuals with sudden death, and may also be associated with other cardiac conditions including hypertrophic cardiomyopathy and mitral valve prolapse. The nature of the association is unknown, and the mechanism causing sudden death is sometimes obscure. We describe pathological changes of the intramyocardial small vessels of three individuals with sudden death. Abnormalities involved small vessels at different levels. In all the cases, the abnormalities were thought to have caused or contributed to the individual's death. The possible mechanisms of this are discussed.

KEYWORDS: forensic science, fibromuscular displaysia, blood vessel, sudden death, conduction system

Disease involving the small intramyocardial arteries of the heart has been proposed as a cause of sudden death in young adults with otherwise structurally normal hearts (1–6). These abnormalities are probably under-recognized owing to their variable pathologic appearance, patchy nature, and the considerable time commitment required for their rigorous assessment during pathologic examination of the heart. Differentiation of pathological changes from those related to normal aging can also be a challenge (7–9).

Pathologic changes may occur in small arteries ranging in size from the sinoatrial (SA) or atrioventricular (AV) nodal arteries, to the small terminal arterial branches in the atria or ventricles (1–3,8). The nodal arteries of the conduction system are probably the best known to be affected (7,8).

We describe the pathologic changes involving the intramyocardial small vessels in three young individuals with sudden death. All had previously unrecognized intramyocardial small vessel disease that caused or contributed to their death. The spectrum of pathology and mechanism of sudden death is discussed.

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Case Histories and Pathological Findings

Case 1

The patient was a 24-year-old female, healthy except for mild asthma, which was aggravated by cigarette smoking. Her only medication was a salbutamol inhaler. She complained of fatigue, retired to bed, and was discovered dead 11 h later.

Toxicology, including general drug screen, cocaine and metabolites, ethanol, barbiturates, and morphine was negative.

Complete autopsy examination showed no significant findings except for the cardiovascular system. No evidence of pulmonary changes associated with asthma were seen. There was mild pulmonary edema and acute passive congestion of the liver. The heart was dissected in detail and showed mild biventricular dilatation with no evidence of significant hypertrophy. There was no evidence of myocarditis, neoplasm, right ventricular cardiomyopathy (ARVD), hypertrophic cardiomyopathy, or coronary artery distribution abnormalities.

Conduction system examination showed remarkable vascular changes localized to the summit of the ventricular septum. These changes were not noted in the other microscopic sections of the ventricles or atria. There was marked vascular dilatation and congestion (Fig. 1*a*). Adjacent to this, the intramyocardial small arterioles showed prominent medial and fibrointimal thickening (Fig. 1*b*). No PAS positive intimal "humps" were found. The arterial changes were associated with patchy myocardial fibrosis, weeks in age. These findings were consistent with the entity that has been termed "localized fibromuscular dysplasia of the intramural arteries of the interventricular septum."

Case 2

The patient was a 20-year-old female who had complained of a sore throat a few days before her death. She took an antihistamine "sleeping" pill and retired to bed. She was found dead in bed at the end of the next day. Myocarditis was clinically suspected as the cause of her death.

Interestingly, she had undergone an EKG examination several months prior to her death. The clinical indication for this could not be determined. The EKG was interpreted as showing benign

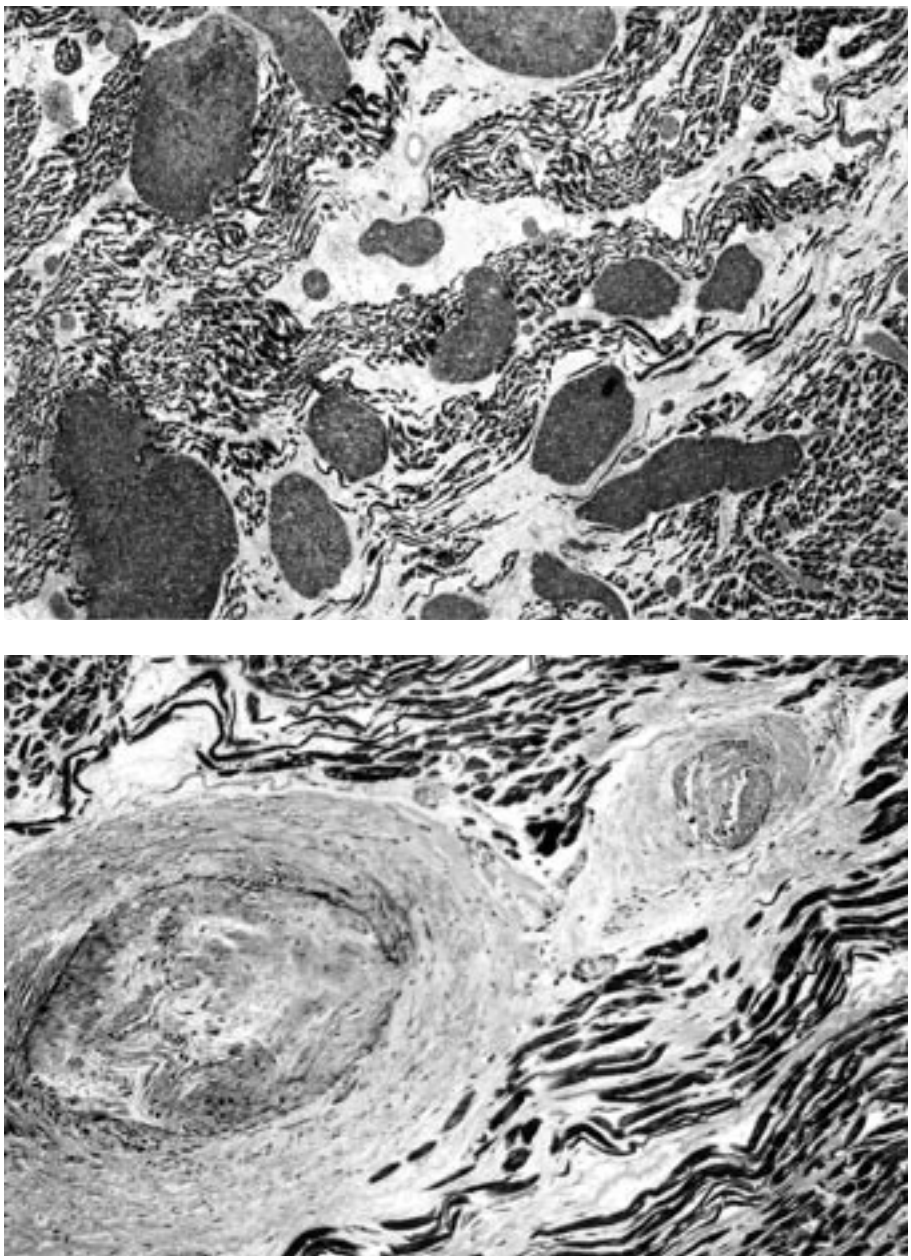

FIG. 1—a) *Photomicrograph of upper ventricular septum myocardium with prominent vascular dilatation and interstitial edema.* b) *Photomicrograph demonstrating marked vascular narrowing of the intramyocardial arterioles due to fibromuscular dysplasia.*

premature ventricular beats. A cardiologist, with expertise in arrhythmias, reviewed the study and also thought the changes benign. There was no evidence of a prolonged QT interval. The premature ventricular beats were thought to have probable origin in the right ventricular outflow tract. The possibility of arrhythmogenic right ventricular dysplasia (ARVD) was also raised since the patient had subsequently died suddenly.

Toxicology, including general drug screen, cocaine and metabolites, ethanol, barbiturates, and morphine was negative, except for a low level of diphenhydramine (0.01 mg/100 mL).

Complete autopsy examination revealed significant findings in only the cardiovascular system. There was mild pulmonary edema. Detailed heart dissection showed no visible gross abnormalities. Microscopic sections of her heart, including multiple sections of the right ventricle, showed no evidence of ARVD, neoplasms, or myocarditis. No significant myocardial disarray or fatty infiltration was found and there were no cardiomyopathic changes, including no evidence of hypertrophic cardiomyopathy. There were no coronary artery distribution abnormalities.

A conduction system examination showed significant changes of the small intramyocardial arteries of the high ventricular septum. These changes were prominent only in this region, and rarely noted in the other ventricular sections. There were a range of arterial changes including eccentric intimal obstructive "humps," and larger vessels with obstructive medial and intimal hyperplasia (Figs. 2, 3). The intimal humps were PAS positive and Congo red negative. By elastic stain (Movat pentachrome), redundant internal elastic lamina was noted to be a component of some of the luminal vascular protrusions (Fig. 2*a*). The myocardium showed patchy fibrosis adjacent to the small vessels.

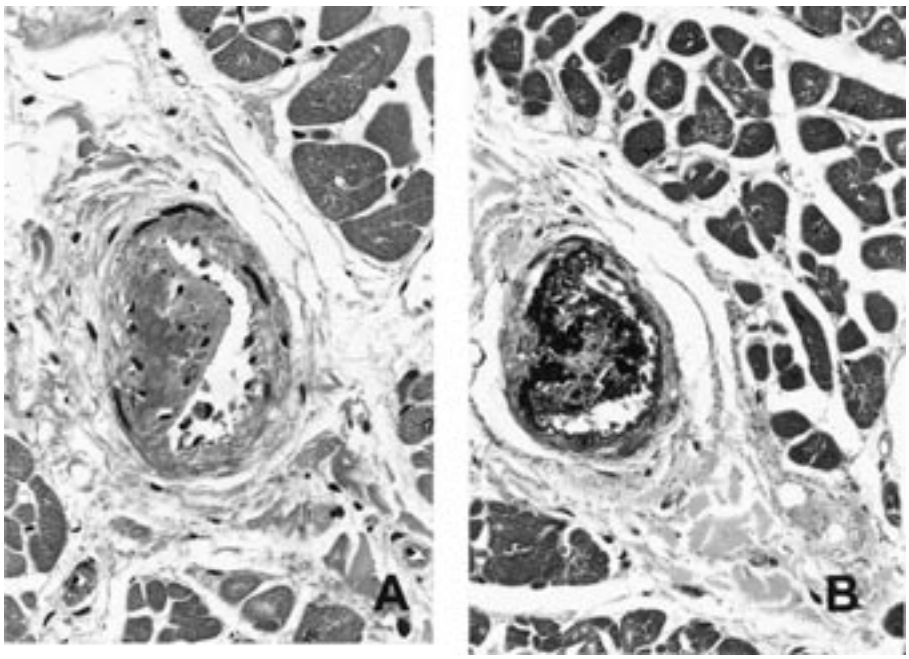

FIG. 2—A) *Photomicrograph of the intramyocardial arterioles of the upper ventricular septum. These have intimal "humps" with variable degrees of luminal stenosis.* B) *Arteriole stained with elastic Movat pentachrome stain demonstrating irregular disrupted elastic lamina in the intimal protrusion.*

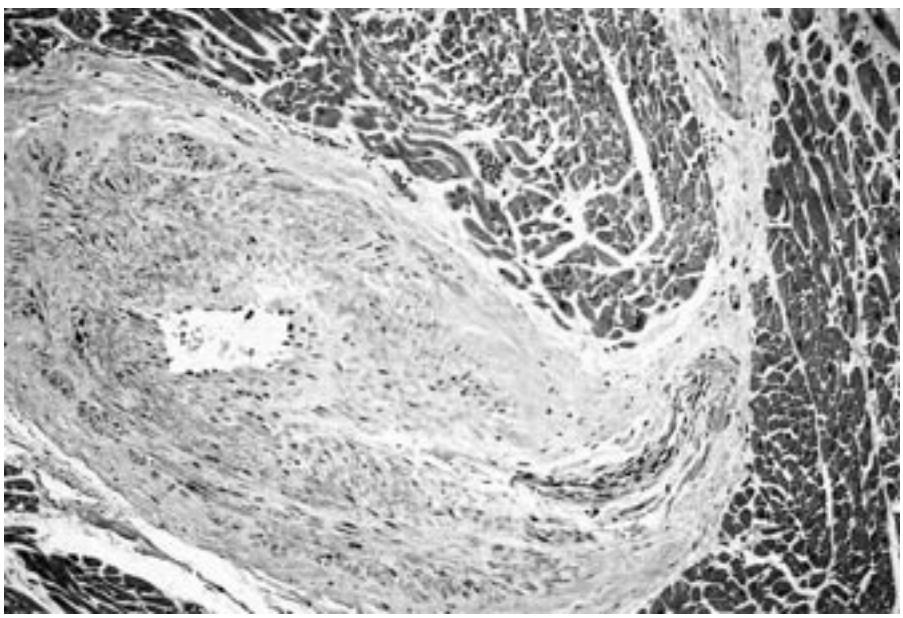

FIG. 3—*Photomicrograph of an intramyocardial arteriole with fibromuscular dysplasia causing severe luminal narrowing.*

Case 3

The patient was a 15-year-old male. He was healthy, but had pectus excavatum. Due to parental concerns about athletic activity with his pectus and the possibility of cardiac abnormalities, he had undergone an echocardiogram a few weeks prior with no significant abnormalities noted. Specifically, there was no evidence of a dilated aortic root or significant mitral valve prolapse or regurgitation. While playing baseball, he had a witnessed cardiac arrest, and died. There was no history suggestive of commotio cordis. Toxicology, including general drug screen, and cocaine and metabolites was negative.

Complete autopsy revealed abnormal findings only in the heart. There was no evidence of hypertrophic cardiomyopathy, ARVD, neoplasms, myocarditis, and no coronary artery distribution abnormalities. The chest wall had pectus excavatum, but no evidence of trauma.

Detailed heart dissection showed a heart of normal weight and size. The mitral valve had mild myxomatous degeneration with chordal elongation and leaflet thickening. The underlying posterior

left ventricle endocardium had small endocardial friction lesions due to chordal trauma on the wall. The conduction system had mild fibromuscular dysplasia of the sinoatrial (SA) node artery (Fig. 4). The atrioventricular (AV) node and His bundle had a disorganized appearance with multiple irregular fascicles of muscle in the area of the His bundle. This was considered to be persistent fetal dispersion of the AV region. The aorta had no significant medial degenerative changes (cystic medial necrosis).

Comment

The pathologic changes described in small intramyocardial vessels have been divided into embolic, inflammatory, and a large group of noninflammatory causes (1,2). These include thromboemboli, nonthrombotic emboli (sutures, air, catheter material), inflammation, thrombosis, intimal proliferation, medial necrosis, dissection, fibrinoid necrosis, and fibromuscular dysplasia (1,2,9). These changes are often associated with myocardial fibrosis or necrosis (2,3,6,9).

Abnormal small intramyocardial arteries have been associated with numerous systemic conditions, many of which are associated with sudden death (1,2,4,9,10). Fibromuscular dysplasia, in particular, has been described in patients with Friedreich's ataxia, scleroderma, Marfan's syndrome, and the long QT syndrome (1–5). Small arteriolar abnormalities, usually intimal thickening, are also prevalent in hypertrophic cardiomyopathy (83% vs. 9% of controls), and mitral valve prolapse (75% vs. 25% of controls) (3,11). Diabetes mellitus and even normal aging have also been associated with thick small intramyocardial vessels (1,2,4,7,10).

Among individuals not dying suddenly, one finds similar vascular abnormalities, but not as commonly as the sudden death group (3,7,11). One must always be skeptical and consider whether such changes are an incidental finding, unrelated to the cause of death, or whether they actually could play a role. This is a similar problem that one encounters with other pathological findings, including tunnel segments of epicardial coronary arteries. Such changes do occur in "normal" individuals, but also have been associated with sudden death. In such cases it is critical to consider all the information available concerning the death of the individual. The individual's age and medical history are vital in this assessment. The type and severity of the abnormality must be considered with other anatomical findings, the statements of witnesses of the arrest, the individual's age and past history, the toxicology, and the circumstances surrounding the death.

Since the mechanism of sudden death is most often ventricular arrhythmia, it is important to look for other pathologic changes associated with these vascular abnormalities. In the case of abnormally thick small intramyocardial vessels, the presence of myocardial fibrosis and necrosis are important associated findings.

The mechanism of death secondary to small vessel disease is thought to be a ventricular arrhythmia, secondary to the myocardial fibrosis in the territory supplied by the abnormal small arteries. Death could arise from acute ischemia, either global or limited to the conduction system. As small arteries are crucial for collateral blood flow, their compromise could provoke or aggravate regional ischemia (2,4,5,7). In addition, bradyarrhythmia may result from ischemia to the sinoatrial or atrioventricular nodes. A vicious circle may be set up with arrhythmia leading to poor perfusion in a myocardium compromised by fixed lesions in small vessels.

The third patient had possible additional predisposing features for sudden death including mitral valve prolapse, and persistent fetal dispersion of the atrioventricular region (12–14). Sudden death in individuals with mitral prolapse may occur even in those without significant mitral regurgitation. This has been explained by implicating electrical instability due to traction on the papillary muscle by the leaflets, stimulation of the endocardium by the chordae, co-existent autonomic nervous system abnormalities, and underlying cardiomyopathic findings (14). In this group of individuals, examination of the conduction system has sometimes found small vessel anomalies (3). How commonly this occurs, and in which subset of people, is still unknown.

Fibromuscular dysplasia of the sinoatrial (SA) nodal artery was observed in one of the two individuals with sudden death and with persistent fetal dispersion of the AV node and His bundle. In persistent fetal dispersion, the isolated myocardial nests or loops may

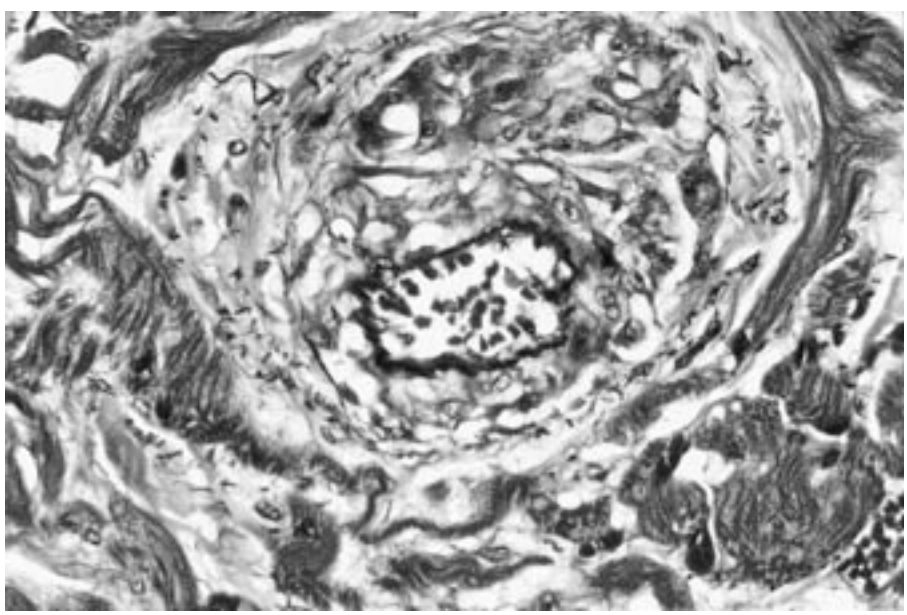

FIG. 4—*Photomicrograph of the sinoatrial node artery of the patient. The media is thick, disorganized, and has caused vessel narrowing.*

be a source of impulse generation or a potential abnormal conduction route (13).

It has been proposed that small coronary artery dysplasia is likely genetic (2,5). However, it is unknown whether this association with other genetic cardiac conditions is the result of a common abnormality. Mutations of contractile proteins are seen in hypertrophic cardiomyopathy, and mutations of potassium and sodium channels have been identified in the long-QT syndrome (15). Neither contractile protein or ion channel abnormalities have an obvious link to small vessel changes.

In conclusion, small vessel disease of the intramyocardial vessels is not limited to involvement of the nodal arteries. Abnormalities may occur in the distal intramyocardial vessels, as an isolated finding, or associated with other systemic conditions or cardiovascular disease. With, or in the absence of, myocardial damage the abnormal small vessels may give lead to poor collateral blood flow, inadequate perfusion, arrhythmias, and sudden death.

Conduction system examination is useful in the investigation and workup of individuals that die suddenly. Conduction system vascular disease may be a sole cause, or a contributory factor in explaining sudden death, especially in those patients in which the initial impression is of a grossly normal appearing heart.

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