CASE REPORT

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Hamartomatous Malformation of the Left Ventricle Associated with Sudden Death

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ABSTRACT: We describe unusual left ventricular cardiac lesions in a 17 year old boy who died suddenly during exertion. These consisted of two grossly evident regions of deficient myocardium, containing cavernous spaces which represented exaggerated intertrabecular regions of the left ventricular cavity. Dense fibro-elastotic tissue was deposited around these spaces along with a variable admixture of mature adipose tissue, fibrous tissue and blood vessels. The etiology of these presumably congenital developmental abnormalities is obscure. The lesions most probably represent a hamartomatous malformation, which is a poorly documented pathological entity.

KEYWORDS: pathology and biology, cardiac hamartomas, sudden death

Localized, apparently congenital abnormalities of the left ventricular myocardium may be difficult to classify and include myocardial diverticula, hamartomatous malformations and focal involvement by right ventricular dysplasia [*1,2*]. We describe a young man with unusual localized lesions in the left ventricular myocardium with no significant right ventricular pathology, who died a sudden and unexpected cardiac death. The case underscores the overlapping pathologic features that may be present in localized ventricular wall defects.

Report of a Case

A 17-year-old, white, male resident of an inpatient psychiatric hospital suddenly became unresponsive while being restrained by staff following an altercation that the patient initiated. The unprovoked and witnessed event began as verbal abuse of staff by the patient and quickly escalated with the patient striking a staff member. He was then wrestled to the floor and restrained by several staff members in a manner prescribed by their training in the physical control of violent patients. At no time during the restraint was the patient's head struck, nor was any hold placed on his neck, nor was his airway or ability to breath compromised. A careful and thorough investigation later determined that the techniques used and the forces involved in the restraint were not unreasonable or excessive. The patient was transported to the emergency room of a nearby hospital in full arrest and after one hour of aggressive resuscitation was pronounced dead. Medications at the time of his death were haloperidol deconate (depot injection) and methylphenidate, 20 mg each morning and an additional 5 mg at noon.

This young man was hospitalized for severe oppositional-defiant disorder along with an unspecified personality disorder. Oppositional-defiant disorder is defined as a "consistent pattern of disobedient, negativistic, and provocative opposition to parents and other authorities" [*3*]. The patient was adopted at an early age and no detailed family history could be obtained. However, based on what little factual history was available, a diagnosis of fetal alcohol syndrome was also entertained. The decedent's intellectual abilities were described as "borderline" with an attention deficit disorder. He was very combative with a history of verbal and physical assaults on staff and other patients and had required physical restraint on many previous occasions. He was in good physical condition and participated in strenous physical activities without restriction or complaint. His physical appearance was unremarkable. No electrocardiograms were in the medical record. At the time of his death, the patient had been an inpatient for seven months at that particular institution. For the previous four years this young man was a resident of another psychiatric hospital and was transferred after failing to progress satisfactorily.

Pathologic Findings

Gross Examination

At autopsy, the body was that of a well-developed, well nourished, muscular 17-year-old white male who weighed 205 pounds (93 kilograms) and was 74 inches (188 cm) in height. The only abnormal autopsy findings were confined to the heart which weighed 450 g and was covered by a moderate amount of epicardial adipose tissue. The lateral left ventricular myocardium contained two distinct lesions; the larger at the base of the anterolateral papillary muscle measured 3.5 cm, and the smaller at the base of the ventricle just below the atrial-ventricular groove measured 1.5

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cm in greatest diameter (Fig. 1). A small segment of grossly uninvolved myocardium separated the two abnormal areas. Each lesion was relatively well demarcated, extended from endocardium to epicardium, and contained multiple large cavernous spaces which communicated with the left ventricular chamber and appeared to represent exaggerated intertrabecular interstices. The surrounding ventricular wall had a scarred appearance, consisting of dense fibrous connective tissue admixed with small amounts of adipose tissue. The remainder of the myocardium was grossly normal. The endocardium of the left ventricle was white, thickened and fibrotic in the outflow area. The coronary arteries were thin-walled, compliant, and contained no atherosclerosis or thrombosis. The cardiac valves were normal. The atrial and ventricular septa were intact. The aorta and the major arterial tributaries arose normally and followed the usual course. The vena cava and the major venous tributaries returned to the heart in the usual fashion.

Light Microscopy

Microscopical examination revealed large endothelial-lined cavernous spaces, containing a thin subendothelial layer of smooth muscle, and surrounded by dense fibro-elastotic connective tissue (Fig. 2). These were continuous with the left ventricular cavity, and immunohistochemical studies confirmed the endothelial nature of the lining cells (factor VIII-related antigen positive, cytokeratin [cam 5.2] negative). Cardiac muscle was decreased or absent, and in some areas the cavernous spaces were in virtual continuity with the epicardium (Fig. 3). Between these spaces and at the periphery of the lesions, dense fibrous connective tissue interdigitated with and surrounded variably atrophic or hypertrophic cardiac myoctes. A small amount of adipose tissue was present in the lesions, often admixed with variably-sized blood vessels and small nerve twigs. At the edges of the lesions were foci of myocytes exhibiting vacuolar degeneration (myocytolysis) and replacement fibrosis. The lesions contained no inflammatory cell infiltrate. The left ventricular myocardium away from the grossly abnormal areas was histopathologically unremarkable as was the conduction system. The right ventricle displayed a slight fatty infiltration.

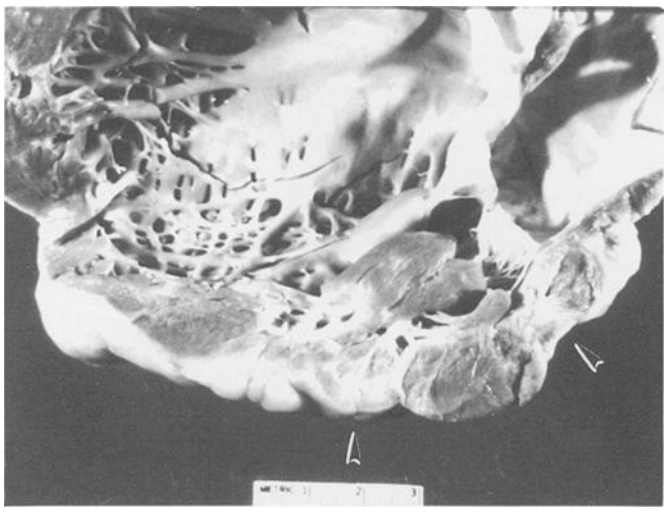

FIG. 1—*Gross photograph of the cut surface of the lateral left ventricle showing the two lesions* (arrows).

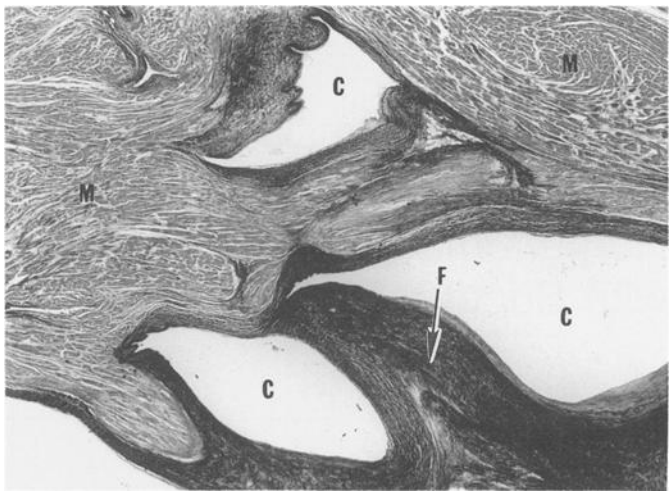

FIG. 2—*Micrograph of cavernous spaces* (C), *subendocardial fibroelastosis* (F), *and adjacent myocardium* (M), *(van Gieson elastic stain, 100×).*

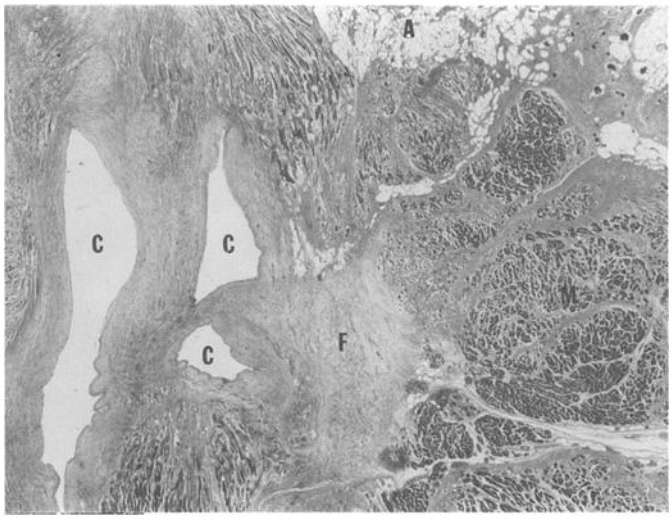

FIG. 3—*Micrograph depicting the cavernous spaces* (C), *dense fibrous connective tissue* (F), *entrapped bundles of hypertrophic myocytes* (M), *and adipose tissue* (A), *(H&E, 100×).*

Toxicology

Heart blood, stomach contents and urine were obtained for toxicological analysis. No haloperidol was detected. Methylphenidate was detected in the urine but not quantified. The heart blood level of methylphenidate was 0.83 mg/L. The gastric contents contained a total of 3.15 mg of methylphenidate, consistent with a 20 mg oral dose taken between 30 to 60 minutes before the incident.

Discussion

The pathological lesions present in this case share some features with ventricular dysplasia (replacement of myocardium with fibrous and adipose tissue), left ventricular diverticula (transmural defect in ventricular wall), endocardial fibroelastosis (dense fibroelastotic thickening of endocardium) and hamartoma (localized admixture of mature fibrous tissue, adipose tissue, blood vessels

and nerves). The unusual distribution, complex nature, lack of inflammation, focal nature, young age of the patient, and presence of normal coronary arteries and valves strongly suggest that the lesions in question are congenital in origin, possibly the result of a developmental embryological defect. The overall pattern is not consistent with an ischemic etiology. The cause of the sudden death of this young man was ascribed to an associated ventricular arrythmia during an intense physical altercation.

The patient was receiving two medications at the time of his death which can cause cardiac toxicity. The first was haloperidol decanoate. Cardiovascular side effects including arrhythmias and sudden death have been reported in association with this psychotropic drug [*4,5*]. However, no haloperidol was detected in postmortem blood. The second drug was methylphenidate. Methylphenidate (Ritalin) is a central nervous system stimulant that is extremely popular and widely prescribed in the treatment of hyperactive children and in pediatric and adult attention deficit disorder. This drug is considered to be safe and efficacious with side effects minor, subtle and dose related. Mild tachycardia and hypertension are the most common cardiovascular side effects. Overdosage can result in symptoms common to other stimulants such as nausea, vomiting, sweating, headache, tremors, delirium, and flushing of the skin. The literature contains very few reports of serious toxicity resulting from methylphenidate overdosage. Cardiac arrhythmias have been reported in individuals receiving methylphenidate intravenously [*6*]. Levine et al. reported a death of an intravenous drug abuser 1 hour after injecting 40 mg of a crushed oral preparation of methylphenidate [*7*]. The young man had received this mild stimulant drug for several years and at the time of his death the dosage was the lowest for the time period for which records were available (18 months). The methylphenidate did not directly cause the death; however, the drug cannot be ruled out as a contributing factor. This drug is known to raise plasma epinephrine levels which may act as a cardiac irritant [*8*]. The methylphenidate may have maximized the potential for the hamartomatous malformations to act as a substrate for a dysrhythmia.

This case illustrates that localized, presumably congenital myocardial defects may manifest a variety of morphological expressions, and careful pathologic examination is necessary to document the salient features.

Diffuse or focal tumorous lesions composed of more than one type of mesenchymal tissue have been variously reported as hamartoma, mesenchymoma, lymphangioma, or vascular hamartoma depending on the author's interpretation of the nature of the lesion [*9–11*]. Regardless of the appellation, these lesions are composed of abnormally arranged mature cellular elements. The question of congenital malformation vs. neoplasm of these cardiac lesions is difficult to resolve. The discriminatory differentiation between hamartoma and benign neoplasm is often tenuous and subject to interpretation. The increased incidence of these lesions in infants and children supports the belief that they are developmental abnormalities. The size, location and perhaps local growth of these benign lesions may be responsible for the clinical symptomatology.

Cardiac diverticula usually occur in the left ventricle as fibrous or muscular outpouchings of the ventricular cavity through defects in the muscular wall. Midline abnormalities in the anterior sternum or abdominal wall are associated with the muscular type. Although mural defects were present in our case, these did not protrude through the epicardial surface and therefore do not completely fit this description. Interestingly, marked fibroelastosis of the endocardium around diverticula has been reported [*12*].

Endocardial fibroelastosis, in which a dense layer of collagen and elastic tissue coats the endocardium, usually presents in infancy as a dilated or restrictive cardiomyopathy. This entity may occur in association with other types of congenital heart disease or as a primary abnormality. In the present case, fibroelastosis was predominantly localized to the endocardium of the mural defects, suggesting a secondary reaction to the presence of these lesions.

The typical morphological abnormality of ventricular dysplasia is a focal or total absence of the right ventricular myocardium with replacement by adipose and fibrous connective tissue producing a "parchmentlike" thinning of the ventricle (Uhl's anomaly) in the absence of valvular or coronary artery pathology. Case reports have described focal minor involvement of the left ventricle in conjunction with the prominent right ventricular changes, but we are unable to find documented instances of dysplasia confined to the left ventricle. The mild fatty infiltration of the right ventricle in our case might be interpreted as representing an abnormality in the spectrum of right ventricular dysplasia; nevertheless, this degree of fatty infiltration is not uncommon in otherwise normal hearts. The association with sudden death is certainly well described in arrhythmogenic right ventricular dysplasia.

On the basis of our examination, no causal agent can be offered for these congenital lesions, but in utero viral infections and exposure to teratogenic agents certainly cannot be excluded. The patient's psychiatrist postulated that fetal alcohol syndrome may have been the underlying basis of this young man's psychopathology, based on his clinical observations and the scant history available surrounding the circumstances of the adoption of this man while a young child. Although cardiac hamartomas or arrhythmogenic ventricular dysplasia have not been associated with fetal alcohol syndrome [*13*], it is a potential etiologic association.

References

[*1*] Marcus, F. I., Fontaine, G. M., Guiraudon, G., Frank, R., Laurenceau, J. L., Malerque, C., and Grosgogeat, Y., "Right Ventricular Dsyplasia: A Report of 24 Cases," *Circulation,* Vol. 265, 1982, pp. 384–397.

[*2*] Waller, B. F., Smith, E. R., Blackbourne, B. D., Arce, F. P., Sakar, N. N., and Roberts, W. C., "Congenital Hypoplasia of Portions of Both Right and Left Ventricular Walls," *American Journal of Cardiology,* Vol. 46, 1980, pp. 885–891.

[*3*] Gregory, I. and Smeltzer, D. J., *Psychiatry, Essentials of Clinical Practice,* Boston/Toronto, Little, Brown and Company, 1983, p. 329.

[*4*] Mehta, D., Mehta, S., Petit, J., and Shriner, W., "Cardiac Arrhythmia and Haloperidol," *American Journal of Psychiatry,* Vol. 136, 1979, pp. 1468–1469.

[*5*] Turbott, J. and Cairns, F. J., "Sudden Death and Neuroleptic Medication," *American Journal of Psychiatry,* Vol. 141, 1984, pp. 919–920.

[*6*] Lucas, P. B., Gardner, D. L., Wolkowitz, O. M., Tucker, E. E., and Cowdry, R. W., "Methylphenidate-Induced Cardiac Arrhythmias," *New England Journal of Medicine,* Vol. 315, 1986, p. 1485.

[*7*] Levine, B., Caplan, Y. H., and Kauffman, G., "Fatality Resulting from Methylphenidate Overdose," *Journal of Analytical Toxicology,* Vol. 10, 1986, pp. 209–210.

[*8*] Joyce, P. R., Nicholls, M. G., and Donald, R. A., "Methylphenidate Increases Heart Rate, Blood Pressure, and Plasma Epinephrine in Normal Subjects," *Life Sciences,* Vol. 34, pp. 1707–1711.

[*9*] Anabe, D. T. and Fine, G., "Cardiac Lymphangioma and Lipoma," *American Heart Journal,* Vol. 86, 1973, pp. 227–235.

[*10*] Tanimura, A., Kato, M., and Morimatsu, M., "Cardiac Hamartoma. A Case Report," *Acta Pathologica Japanica,* Vol. 38, 1988, pp. 1481–1484.

[*11*] Francoisi, R. A., Gay, R. M., and Ah-Tye, P., "Vascular Hamartoma of the Heart in a Child," *American Heart Journal,* Vol. 79, 1970, pp. 676–682.

[*12*] Bharati, S., Rowen, M., Camarata, S., et al., "Diverticulum of the Right Ventricle," *Archives of Pathology,* Vol. 99, 1975, pp. 383–386.

[13] Sandor, G. C. S., Smith, D. F., and MacLeod, P. M., "Cardiac Malformations in the Fetal Alcohol Syndrome," *Journal of Pediatrics,* Vol. 98, 1981, p. 771.

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