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Isolated Myocardial Fibrosis As a Cause of Sudden Cardiac Death and Its Possible Relation to Myocarditis

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ABSTRACT: In performing medicolegal autopsies on sudden deaths, there occur a number of cases in which no cause of death can be found. In particular, no evidence of macroscopic cardiac abnormalities can be observed. However, extensive histological screening may reveal isolated areas of myocardial fibrosis. The five cases presented discuss the etiology of this fibrosis and its possible relation to myocarditis. The cases involve white women between the ages of 19 and 25 with no previous medical history. The weight of the heart in all five cases was normal. Macroscopic evidence of fibrosis was visible in four out of five cases. No other macroscopic abnormalities were observed. Histologically, there was evidence of scarring or interstitial fibrosis in all five cases. In four of the cases, additional screening permitted the observation of dispersed inflammatory foci consisting of lymphocytes, plasmocytes and macrophages. Two of the cases demonstrated eosinophil and neutrophil agregates in the center of necrotic foci. No evidence of vascular inflammatory phenomena was observed in any of the five cases. According to the Dallas criteria, three of the five cases fulfill the requirements for myocarditis and one of the five cases for borderline myocarditis. The Dallas criteria, however, do not take into consideration the possible association between inflammation and myocardial fibrosis since many of the reported series of myocarditis have been from hospital autopsies or endomyocardial biopsies and have not taken into account sudden death from fibrotic sequelae of myocarditis. The following 5 cases demonstrate that: 1) to demonstrate inflammatory foci, extensive sampling (>10) is required, due to their sparse distribution; 2) inflammatory foci may be associated with myocardial fibrosis (Cases 1, 2, 3 and 5), and additionally, fibrosis may be the only evidence of a previous inflammatory process (Case 4). This fibrosis provides a predisposition to electric instability, re-entry circuits and fatal arrythmias. Such cases are not only of forensic interest, but may have far reaching scientific implications. The origin of this myocarditis, whether viral or autoimmune, remains to be elucidated.

KEYWORDS: pathology and biology, sudden cardiac death, myocardial fibrosis, myocarditis

Myocarditis is commonly mentioned among causes of sudden cardiac death in young people [*1–4*]. A survey of the literature on the subject shows that the frequency of reported myocarditis in such a setting is heavily dependent on diagnostic criteria. Most observations were recorded before precise diagnostic criteria were firmly established [*5*]. Moreover, relevant information on prodromes preceding death and personal antecedents

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is frequently missing. Actually, a detailed review of the published observations with enough pertinent data show that death is almost never completely sudden, but occurs in the context of previous symptoms of acute myocarditis.

We describe five cases of sudden cardiac death occurring in young people without any previous evidence of cardiac disease. In each case, the only autopsy findings were myocarditis and myocardial fibrosis as shown by microscopic examination of heart samples.

Case Reports

Case No. 1

Patient A, a 23-year-old female, died suddenly while with friends in a bank. She had no history of past disease, took no medication, and enjoyed perfectly good health the days preceding her death.

The heart weighed 300 g. There was no abnormal macroscopic feature. The coronary arteries were normal.

Microscopic examination of myocardial samples taken as a matter of principal demonstrated small foci of loose fibrosis replacing myocardial fibers. There was evidence of focal necrosis of myocardium and numerous small but more diffuse inflammatory infiltrates (Fig. 1).

Case No. 2

Patient B, a 22-year-old female, died during an evening party with friends. The investigation showed that she was in good health and had taken no medication.

The heart weighed 250 g. There was extensive fibrosis involving the middle third of the left ventricular wall. The fibrosis was transmural, but predominated in the subendocardial muscle.

Microscopic examination confirmed presence of scar tissue (Fig. 2). There was also a

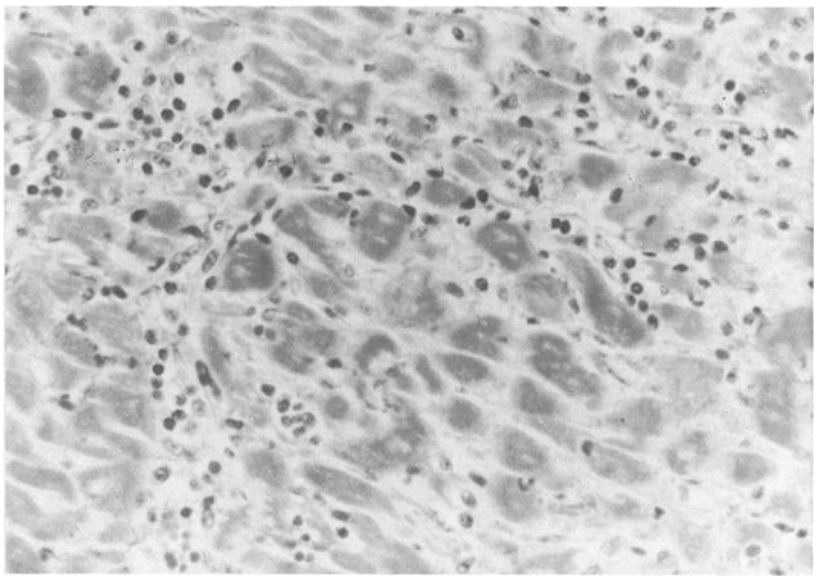

FIG. 1—*Small diffuse inflammatory infiltrates (Masson's trichrome stain: original magnification, × 250).*

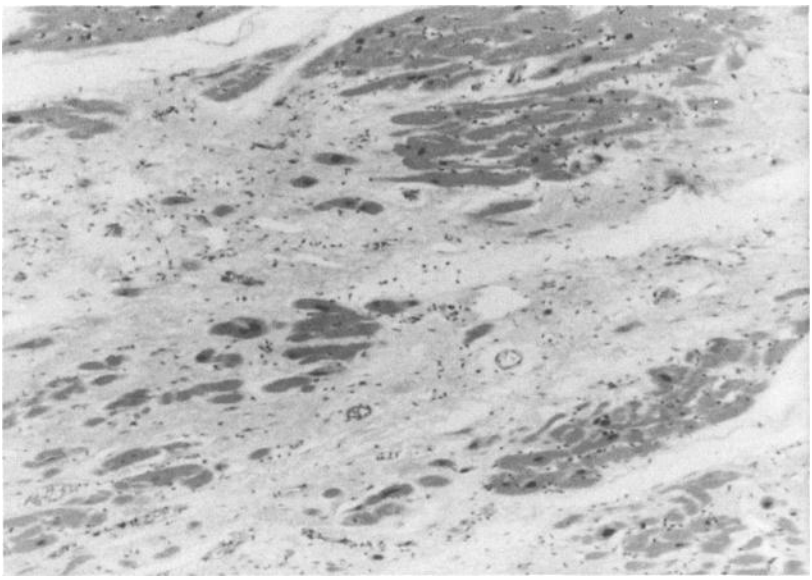

FIG. 2—*Scar tissue containing mononuclear inflammatory cells (Hematoxylin and eosin stain; original magnification × 100).*

looser fibrosis containing polymorphonuclear and mononuclear inflammatory cells. Foci of muscle cell necrosis were to be seen in the surrounding tissue.

Case No. 3

Patient C, a 21-year-old female, died suddenly at work, while with colleagues. Her family did not know of any disease or any treatment she might have taken.

The heart weight was 233 g. There was extensive fibrosis of the septum and the anterior part of the left ventricular wall. The coronary arteries were normal.

Microscopic changes included areas of fibrous scarring and foci of mononuclear inflammatory cells between myocardial fibers, some of which were damaged (Fig. 3).

Case No. 4

Patient D, a 23-year-old female, died suddenly, while touring downtown with her boyfriend. Interrogation of family members showed that she was a healthy person free of any past disease or medication.

The heart weighed 284 g. The coronary arteries were normal. But fibrosis extended to the septum and to the middle thirds of the anterior and posterior left ventricular walls.

Microscopic features consisted of areas of scarring and a diffuse mononuclear infiltrate surrounded by degenerated myocardial cells.

Case No. 5

Patient E, a 19-year-old female student, died suddenly in her bed at home. She was in good health, and had never seen a doctor, her family said.

The heart weighed 250 g. Areas of fibrosis were found in the septum and the middle third of the posterior left ventricular wall.

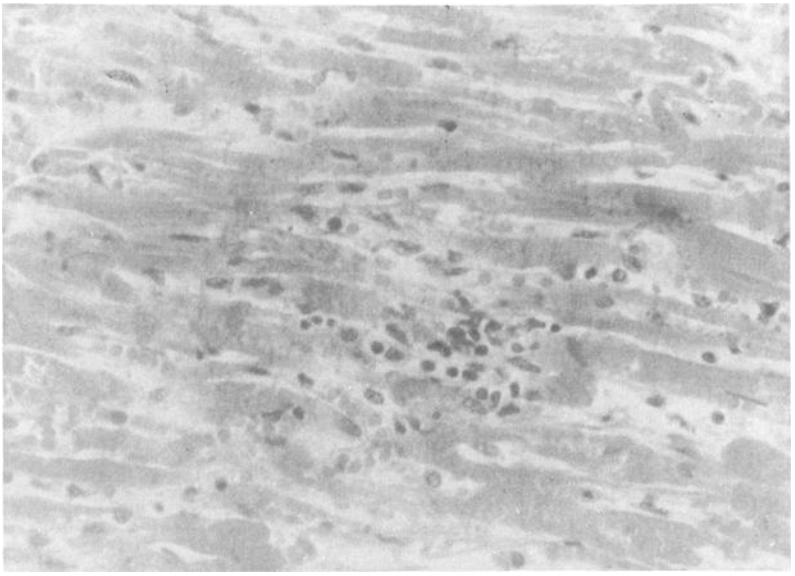

FIG. 3—*Focus of mononuclear inflammatory cells between myocardial fibers (Hematoxylin and eosin stain; original magnification × 250).*

Histologically, there was widespread, loose, edematous fibrosis which contained many fibroblasts and mononuclear inflammatory cells. Foci of myofiber necrosis were seen in the surrounding tissue. These changes were more obvious in the septum and the left ventricular wall. The coronary arteries were normal.

Comments

We have grouped these 5 cases, because they share common distinctive features:

1) These sudden deaths occurred in active young women, less than 25 years old, with no previous known disease or cardiac signs or symptoms.
2) The heart weight was always normal (less than 300 g).
3) The coronary arteries were normal.
4) In 4 cases, macroscopic examination found areas of fibrosis in the left ventricular wall. The myocardium appeared normal in one case, however.
5) No other anatomic change or toxic pathology was found despite complete autopsy.
6) Finally, diagnosis was established on the basis of microscopic changes consisting of inflammatory infiltrates and areas of fibrosis.

These observations perfectly fulfill the Dallas criteria [5] for the diagnosis of active myocarditis, for example, myocardial cell necrosis or degenerative change with surrounding inflammatory infiltrates. Diagnosis of primary idiopathic cardiomyopathy, either in the dilated-congestive form or in the hypertrophic form, was eliminated. First, the heart was grossly normal. Second, on microscopic examination distinctive myocardial changes associated with hypertrophic cardiomyopathy were lacking. Furthermore, microscopic examination in our cases showed extensive areas of replacement fibrosis at different stages of development. Microscopic evaluation of heart samples was very important for diagnosis, whereas macroscopic examination of heart was in one case unconclusive.

Recent literature on myocarditis in patients hospitalized for an acute or chronic febrile

cardiac failure has stressed the importance of endomyocardial biopsy [6]. In this context, fibrosis is not always found, and when so is not extensive in chronic presentations of the disease. In acute forms myocardial changes tend to regress, so that after the initial acute episode prognosis is good. These findings are in marked contrast with our present report, which is characterized by sudden cardiac death being the initial and only symptom of the disease and by severe myocardial changes on microscopic examination.

Data derived from other series of sudden cardiac death give myocarditis as a cause in widely varying proportions ranging from 1% to 17% [1–7]. Such a large variance may be explained by the differences in criteria used to define sudden death on the one hand, and myocarditis on the other. In most of these reports, death is not completely sudden, but occurs in a clinical setting characterized by fever, tachycardia and dizziness [1,4]. Moreover, the incidence of myocarditis can be overestimated. In an autopsy study of 263 pilots involved in air crashes, Stevens found six cases of "focal myocarditis," associated with encephalitis in one case [8]. This report stressed that there was no direct relationship between the cause of death and microscopic changes and that focal myocardial inflammatory infiltrates are never sufficient to diagnose myocarditis.

Conclusions

Our report on five cases shows that myocarditis can be responsible for sudden cardiac death in young and active healthy people without any previous symptoms.

Similar cases are not really found in the literature on the subject. Such observations can easily be missed if a microscopic examination of heart samples is not performed. Microscopic changes due to myocarditis can be observed in hearts with grossly normal appearance.

Further studies are required to establish the relative frequency of myocarditis as a cause of sudden death. The precise mechanism by which death is caused by myocarditis remains to be determined. It is not known why such extensive myocardial damage can be clinically silent with sudden death as the initial sign of the disease.

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