CLINICOPATHOLOGIC CORRELATIONS

De Subitaneis Mortibus

XXV. Sarcoid Heart Disease

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SUMMARY Postmortem findings within the cardiac conduction system are described from the case of a black woman with sarcoid heart disease who died suddenly. Her clinical course had been characterized by recurring ventricular arrhythmias and bouts of syncope. Both the sinus node artery and the atrioventricular (A-V) node artery were sites of focal fibromuscular dysplasia, which thickened slightly the wall of the former but markedly narrowed the lumen of the latter. Small foci of sarcoid infiltration were present in the sinus node and the A-V node. Fatty replacement within the His bundle was attributable to the probable ischemia caused by narrowing of the A-V node artery. Sarcoid granulomata and infiltration with epithelioid cells were present throughout the ventricular myocardium, but were considerably less prevalent in the atria. All the large coronary arteries were normal. Many small coronary arteries in the ventricular myocardium were involved by the sarcoidosis and their lumens were narrowed. These findings and analogous ones reported by others are discussed relative to the pathogenesis of syncopal attacks and sudden death which seem so peculiarly prevalent in sarcoid heart disease.

AMONG THE SEVERAL TYPES of granulomatous disease which may involve the heart there seems to be a conspicuously close association between sudden death and sarcoidosis.1-28 One gains some appreciation of the magnitude of this problem from the following observations: about one-fifth of all patients with sarcoidosis have cardiac involvement,29 and about two-thirds of the patients with sarcoid heart disease die suddenly and unexpectedly, with fully one-fourth of such deaths not having been preceded by any recognizable symptoms.10

Heart block and intractable ventricular arrhythmias are prominent clinical features of sarcoid heart disease, making syncopal attacks and sudden death expected corollaries. From clinicopathological correlative studies it has been learned that sarcoid heart disease often includes damage to various elements of the cardiac conduction system.8, 11, 12, 14, 15, 20, 22-24 The true incidence of sarcoid damage to the sinus node or atrioventricular (A-V) junctional tissues is probably greater than available reports would imply, since special studies to determine presence or absence of such involvement are still not routinely conducted in most necropsies. The purpose of the present report is to describe the findings from the cardiac conduction system of one fatal case of sarcoid heart disease, and in the context of reported observations by others, to consider some of the possible mechanisms by which lethal electrical instability could develop.

Case Report

A thirty-year-old black housewife died of sarcoid heart disease. The fact that she had a ventricular aneurysm and recurring ventricular arrhythmias was the basis of a previous report,18 but findings from her cardiac conduction system have not been published previously. During a two-year period she gradually developed exertional dyspnea, orthopnea, and numerous bouts of syncope which were thought to be due to the ventricular arrhythmias that so frequently documented (fig. 1). Despite extensive therapeutic efforts to control these arrhythmias, she continued to have syncopal attacks, one of which caused her sudden death.

At postmortem examination there were granulomata typical of sarcoidosis in several organs, including the heart. The left ventricular aneurysm was caused by a combination of confluent sarcoid granulomata and inflammation with fibrosis. There were many other areas of ventricular myocardium similarly involved (figs. 2-4), although large intervening portions of myocardium were grossly and microscopically normal. All the major coronary arteries were widely patent. The sinus node branch originated from the left circumflex coronary artery and the A-V node branch from the right coronary artery at the usual sites. The cardiac valves were essentially normal and the septa of the heart were intact. The regions of the sinus node, A-V node and His bundle with its proximal branches were removed intact for special examination as previously described in this series of Clinicopathological Correlations. Subserial sections at 2 mm intervals were supplemented by serial sections as necessary.

Both the sinus node and the A-V junctional regions were grossly normal. Microscopically, the sinus node contained scattered small foci of inflammation without granuloma formation. In one segment of the sinus node artery its wall exhibited focal dysplasia (fig. 5) similar to that reported by Morales et al.29 In general the atrial myocardium had much fewer and smaller foci of sarcoid infiltration than did the ventricular myocardium.

At its anterior margin where both bundle branches originated, the His bundle was essentially normal. In its undivided portion within the central fibrous body the His bundle contained an abnormal amount of focal fatty replacement (figs. 2 and 6) commensurate with probable local ischemia caused by marked narrowing of its nutrient supply, the A-V node artery (figs. 6 and 7). This narrowing was caused by focal fibromuscular dysplasia, a histological pro-
cess also seen in small coronary branches supplying the conduction system of other subjects who have died suddenly and unexpectedly but without sarcoidosis. However, some inflammation and epithelioid cell infiltration directly adjacent to the A-V node artery (fig. 7) in this heart suggest that sarcoidosis contributed to the pathogenesis of this focal narrowing. The lumen of the A-V node artery proximal and distal to this narrowing (total of less than 1 mm in length) was entirely normal. Several additional areas of inflammation and infiltration with epithelioid cells were present in the A-V node (fig. 8). Inflammation both with and without granuloma formation was present within and around many small coronary branches in the ventricular myocardium (figs. 9 and 10).

Discussion

Of the various electrophysiological abnormalities which could cause syncope or sudden death in patients with sarcoid heart disease, the two most often documented have been heart block and ventricular arrhythmias. Both of these occur transiently and paroxysmally, making them easy to overlook if not sought but still potentially lethal if sustained or if followed by changes such as ventricular fibrillation. Atrial arrhythmias are comparatively infrequent, particularly in comparison to their incidence in atherosclerotic heart disease or rheumatic heart disease. Other focal inflammatory diseases affecting the heart such as polyarteritis nodosa and disseminated lupus erythematosus not only involve the atrial myocardium more extensively but they are clinically characterized by atrial arrhythmias. Although there are exceptions, sarcoid heart disease appears at least relatively to spare the atria.

By contrast, sarcoid infiltration and granulomata almost have an affinity for the A-V node and His bundle, and the high incidence of reported heart block is thus unsurprising. Sarcoid heart disease resembles rheumatoid heart disease in this one respect, although the occurrence of pericarditis and of associated valvular disease is greater with rheumatoid arthritis. In the present case the amount of destruction in the A-V node and His bundle was less than has been reported in some other examples of sarcoid heart disease, wherein those regions were virtually destroyed by sarcoid infiltrations. That sarcoid infiltration which was present in this case, however, was com-

Figure 1. Typical electrocardiogram illustrating the multifocal ventricular irritability often present in this patient.

Figure 2. These two photomicrographs are made from sections taken at opposite ends of the interventricular septum (IVS). A is from the region between the coronary sinus and the A-V node; the slender arrow marks the A-V node artery which is widely patent here, while the three open arrows delineate an area of fibrosis filled with sarcoid granulomata. TV = tricuspid valve. B is from the anterior margin of the IVS and contains a portion of the undivided His bundle (AVB). Except for some abnormal fatty replacement in the AVB, virtually all the tissue shown here is normal and the IVS is free of sarcoid. MV = mitral valve. Magnification here and in subsequent photomicrographs is indicated with reference bars, and all sections were prepared with the Goldner trichrome stain.
FIGURE 3. Two examples of sarcoid infiltration of the ventricular myocardium are shown. Fibrosis surrounds a small artery in the right lower corner of A. Two multinucleated giant cells are marked with arrows in B.

Pounded in its functional significance by the impairment of arterial blood supply caused by marked narrowing of the A-V node artery. This focal fibromuscular dysplasia may have been caused and almost certainly was aggravated by the contiguous sarcoid infiltration.

Morales and his colleagues20 recently have called attention to the involvement of small coronary branches by sarcoidosis, a process made all the more impressive by the sparing of large coronary branches. While it is uncertain just where in the chronological sequence of sarcoid granuloma formation this effect on small coronary arteries occurs, narrowing of such vessels must impede any effective perfusion of local myocardium within or beyond the confines of the granuloma itself. Impaired arterial perfusion, particularly in the vicinity of sarcoid granulomata, may impede local delivery of antiarrhythmic medications and thus help explain the difficulty in treating the ventricular arrhythmias.

It seems unlikely that small coronary disease is very often an initiating factor for formation of granulomata, since they appear to develop independent of such lesions as well as in association with them.

Whatever the pathogenesis may be for sarcoid granulomata in ventricular myocardium, they can readily become foci for abnormal automaticity or serve to disperse both ventricular activation and recovery processes in a fashion conducive to re-entrant arrhythmias. Large expanses of intervening normal myocardium would magnify this disparity of electrical properties. Even though the streaky nature of sarcoid infiltration of the myocardium (fig. 4A) presents an anatomical substrate highly suitable for ventricular arrhythmias of a re-entrant nature, many other diseases produce similar streaky fibrosis and focal inflammation without as often producing recurrent ventricular arrhythmias which respond so poorly to most treatment. There must be some-
thing about the sarcoid granuloma or infiltration more than their geometric distortion of ventricular activation and recovery sequence.

In the present case and some reported by others, a ventricular aneurysm was present, and in one of these the arrhythmias were ameliorated by aneurysmectomy. Ventricular aneurysms are known to be associated with arrhythmias, but the frequent occurrence and therapeutic intractability of ventricular arrhythmias in sarcoid heart disease are equally often clinical features without the presence of ventricular aneurysm. Similarly, while intermittent or sustained heart block can facilitate the development of ventricular arrhythmias, they seem to occur just as often in sarcoid heart disease without A-V block. To know just how often transient heart block does precede ventricular arrhythmias will require prolonged electrocardiographic monitoring of patients with sarcoid heart disease.

But the greater puzzle is why sarcoid granulomata in ventricular myocardium seem to be more arrhythmogenic than other focal inflammatory processes, although the latter do sometimes behave this way as well. Processes histologically similar to sarcoidosis include berylliosis and tuberculosis (except for caseation). Tuberculosis may rarely involve the cardiac conduction system but arrhythmias are not a characteristic problem. Berylliosis seems to spare the heart entirely except for producing cor pulmonale secondary to the pulmonary involvement. Not only is sarcoid heart disease in some unexplained ways especially arrhythmogenic, this is too often a fatal aspect, even in subjects not known to have any preceding symptoms. As an insidious cause of sudden unexpected death, sarcoid heart disease is potentially lethal even in its very early form. Whether this can be attributed to early prevalent involvement of the His bundle or not should be ascertainable by special attention to this possibility in future suitable cases.

Treatments prescribed for the ventricular arrhythmias of sarcoid heart disease have included most known anti-arrhythmic agents, but despite some gratifying exceptions, their effectiveness has too often been inconsistent and disappointing. One patient did well with electronic pacing for heart block, but others so treated have not fared as well. Any evaluation of treatment is made more difficult by the known tendency of sarcoidosis for spontaneous remissions, although such improvement is less often observed once the heart becomes involved.

Treatment could become more specific if viruses are proven to be a cause of sarcoidosis, or if one or more non-infectious biochemical antigens prove to be the responsible factors in sarcoid heart disease.
Figure 6. Marked narrowing of the A-V node artery (AVNA in A) was a probable cause of focal fatty infiltration of the His bundle which is outlined with three arrows in B. See fig. 2B for low power photomicrograph; see also fig. 7.

Figure 7. Histological detail of the focal fibromuscular dysplasia of the A-V node artery is illustrated in A. Some inflammation and epithelioid cell infiltration directly adjacent to the AVNA is illustrated in B (same area boxed in fig. 6A).

Figure 8. Sarcoid infiltration was present in several areas of the A-V node (AVN). One focus is illustrated at low magnification in A and in more detail in B (same area boxed in A).
offenders, or if some consistent immunological fault is identified. A sobering lesson is provided in the history of Whipple's disease, which remained mysterious in its etiology for so long a time but now appears to be caused by one or more types of Schiff-positive bacilli. In this regard it is important that electron micrographs of sarcoid granuloma do not appear to contain microorganisms. Until more is known about the exact pathogenesis of sarcoidosis, and about the physiological and biochemical nature of the granuloma it produces within the heart, any explanation for the ventricular arrhythmias, heart block, syncope and sudden death will remain largely speculative, and treatment will continue to be empirical.

References


FIGURE 9. Two examples of sarcoid destruction and narrowing of small coronary branches are shown here. A is from interventricular septum while B is from the free wall of the left ventricle.

FIGURE 10. Just above the narrowed small artery of left ventricle illustrated in A there is a multinucleated giant cell. A small granuloma near the A-V node is shown in B, with the arrow marking an asterion cell.
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