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CASE REPORT

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Sudden Cardiac Death due to Giant Cell Inflammatory Processes*

ABSTRACT: Granulomatous inflammation of the myocardium may occur in a number of systemic disease processes including those with infectious etiologies such as fungal, mycobacterial and parasitic infections, as well as hypersensitivity reactions, and rarely autoimmune disorders. In many of these disorders, giant cells are components of the inflammatory infiltrate. Systemic granulomatous processes of unknown pathogenesis, most notably sarcoidosis, may also be associated with involvement of the myocardium. Occasionally, these disorders are associated with sudden death due to pathologic involvement of the heart. In contrast, giant cell myocarditis, also known as idiopathic myocarditis, a rare, frequently fulminant and fatal disorder of unknown etiology, is isolated to the heart and lacks systemic involvement. This disorder is most commonly diagnosed at autopsy. We present two cases in which sudden death resulted from a giant cell inflammatory process affecting the myocardium. Both individuals lacked antemortem diagnoses and collapsed at their respective places of employment. These cases compare and contrast the clinical and pathologic issues involved in the differential diagnoses of the subgroup of sudden cardiac deaths resulting from giant cell inflammatory processes that affect the myocardium, as well as the value of histologic examination and immunohistochemical studies.

KEYWORDS: forensic science, sudden death, heart, giant cells

Granulomatous processes involving the heart can occur in a number of systemic processes including those with infectious etiologies (fungal, mycobacterial and parasitic infections), hypersensitivity reactions, and rarely autoimmune disorders (1–4). Systemic granulomatous processes of unknown pathogenesis, most notably sarcoidosis, may also be associated with involvement of the myocardium (4–7). In contrast, giant cell myocarditis, also known as idiopathic myocarditis, a rare, frequently fulminant and fatal disorder of unknown etiology, is isolated to the heart and lacks systemic involvement (4,8–11).

The majority of systemic granulomatous disorders that involve the heart are diagnosed prior to death due to their protracted clinical course and symptomatology related to the involvement of other organs. Occasionally, however, these disorders are associated with sudden death due to pathologic involvement of the heart (4–6,12,13). These cases are likely to be investigated by a forensic pathologist, particularly if the affected individuals do not have an antemortem diagnosis. Because of its isolation to the heart and rapid clinical course, giant cell myocarditis is more likely to be diagnosed at the time of autopsy. Indeed, an individual may be asymptomatic, and sudden death may be the presenting manifestation of the disease. Cases of sudden death with no documented medical history are often investigated by the medical examiner or coroner.

We report two cases in which sudden death resulted from a granulomatous disorder of the myocardium. Both individuals lacked antemortem diagnoses. These cases illustrate the medical and pathological issues involved in the differential diagnoses of this subgroup of sudden cardiac deaths.

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Case 1

An 18-year-old Hispanic man had been laying tile in a new housing development. His brother found him collapsed in a shower stall at the job site with his back against the wall. Paramedics were summoned and the young man had no detectable electrical cardiac rhythm. He was pronounced dead at the scene. The man had no known past medical history with the exception of the fact that he had complained of vague abdominal pain for approximately 2 1/2 months prior to his death. He had also complained of occasional difficulty in swallowing chicken. Information about his family history was not obtainable.

Postmortem examination on the well-developed, well-nourished, 5′ 9″, 172 pound Hispanic male revealed an unremarkable external examination. The internal examination revealed cardiomegaly (700 grams) associated with concentric left ventricular hypertrophy with a left ventricular myocardial thickness of 2.2 cm. There was no discernible coronary arteriosclerosis. The left ventricle showed patchy, well delineated, yellow–white zones of discoloration, most prominent in the subendocardial region (Fig. 1). The remaining chambers of the heart were not grossly involved. The lungs, pulmonary hilar lymph nodes and kidneys were studded with 1–2 mm white-tan nodules. Postmortem toxicologic studies were significant only for the presence of caffeine in the decedent's blood and urine.

Case 2

A 43-year-old white man collapsed at work after complaining to coworkers of dizziness. Emergency Medical Services responded and discovered the individual in ventricular fibrillation. Cardiopulmonary resuscitation was unsuccessful and he was pronounced dead in the emergency room at a local hospital. His past medical history was significant for an episode that had occurred approximately 10 years prior to his death when the man had woken with a sensation of pressure in his chest. This sensation recurred periodically and his wife reported that the pressure sensation was

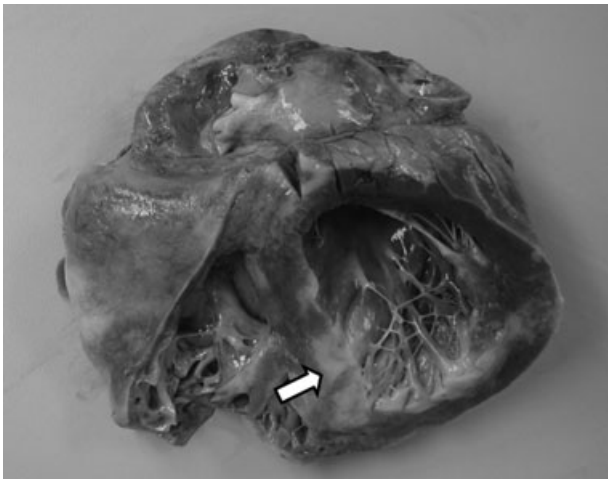

FIG. 1—*The heart in Case 1 showing subendocardial discoloration of the left ventricular myocardium (arrow).*

apparently relieved by the consumption of prune juice. The man had been evaluated by a cardiologist 4 months prior to his death. A cardiac stress test revealed frequent premature ventricular contractions and ventricular couplets associated with short runs of nonsustained ventricular tachycardia. A cardiac ultrasound revealed normal left ventricular function and mild dilatation of the right heart chambers. A 24 h Holter monitor revealed "very frequent ventricular ectopy and frequent runs of nonsustained ventricular tachycardia." The man was treated with atenolol. His past medical history was otherwise significant only for recurrent bouts of sinus infections. The family history was noncontributory.

Postmortem examination was performed on the body of the 5′ 10″, 170 pound, lean white man. The external examination was unremarkable. The heart weighed 460 grams and appeared floppy. The right dominant coronary arterial system showed minimal arteriosclerosis. The left ventricle was concentrically hypertrophied, measuring 2.0 cm. The interventricular septum and the inferior aspect of the left ventricle showed irregular, well circumscribed zones of myocardial softening associated with a central area of red–brown discoloration surrounded by a rim of pale tan myocardium. The remainder of the autopsy was remarkable only for pulmonary congestion and edema. No granulomas or other abnormalities were identified grossly in any other visceral organs. Toxicologic studies were significant for the presence of lidocaine, consistent with resuscitation efforts, and a subtherapeutic concentration of theophylline in the blood.

Materials and Methods

Formalin-fixed, paraffin-embedded tissue sections were stained with hematoxylin and eosin. Representative sections of abnormal myocardium were also stained with the Gomori's one step trichrome stain for collagen. Additionally, immunohistochemical stains were performed on the sections of myocardium using a Ventana BenchMark automated slide stainer and Ventana detection kits (Ventana Medical Systems, Inc., Tucson, AZ). Immunohistochemical staining allows the visualization of antigens via the sequential application of a specific antibody (primary antibody) to the antigen, a secondary antibody (link antibody) to the primary antibody, an enzyme complex, and a chromogenic substrate with interposed washing steps. Sections of tissue cut at 4 μm were mounted on two positively charged control slides. After optimum dilution, the reagents were applied to the tissue sections and mixed over the specimen. Each step in the staining protocol included incubation for a precise time at a specific temperature, followed by rinsing by the automated Ventana system to halt the reaction and remove unbound material that would hinder the desired reaction in subsequent steps. Staining was completed after incubation with a substrate chromogen and optional counterstaining. The slides were viewed by routine light microscopy.

The primary antibodies employed included antibodies to desmin and actin (markers of muscle cells), EMA (epithelial membrane antigen), S-100 protein, Ki 67, lysozyme (macrophages/histiocytes), CD68 (macrophages/histiocytes) CD3 and CD45RO (pan-T cell markers), CD4 (T-helper cells), CD5 (T-suppressor cells), and CD 20 (B lymphocytes).

Results

Microscopic examination of the grossly affected myocardium in Case 1 revealed the presence of an inflammatory cell infiltrate composed of epithelioid and spindle cells, lymphocytes, Langhans' giant cells (with their nuclei arranged around the periphery of the cell), and foreign body-type giant cells (Fig. 2). The process was most prominent in the subendocardial zones of the affected areas, where it was associated with collagenous fibrosis. The infiltrate extended into the deeper layers of the myocardium (Fig. 3). Rare, poorly formed granulomas that lacked necrosis were identified and focal perineural infiltration was seen (Fig. 4). Although occasional necrotic myocytes were identified, myocardial necrosis was not prominent. No fungi or acid fast bacilli were identified with special stains and no polarizable foreign material was visualized. Immunoperoxidase studies revealed positivity of the giant cells for lysozyme, CD68 and Ki 67 and absence of immunostaining for actin, desmin, EMA, S-100 protein (Figs. 5 and 6). The associated lymphocytes were predominately T-suppressor cells, with scattered T-helper cells, and rare B cells. Well-formed, noncaseating, sarcoidal-type granulomas were identified in the lungs, pulmonary hilar lymph nodes and kidneys. The cause of death was attributed to a cardiac arrhythmia due to cardiac involvement by sarcoidosis.

Microscopic examination of the involved myocardium in Case 2 revealed collagenous fibrosis associated with a prominent cellular infiltrate composed of epithelioid and spindle cells, numerous

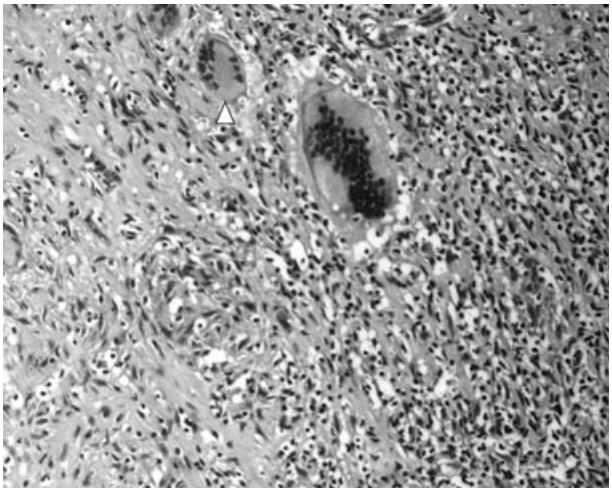

FIG. 2—*The involved myocardium in Case 1 showing the pleocytotic cellular infiltrate including foreign body-type giant cells and a Langhans' giant cell (arrowhead) (H&E, ×400).*

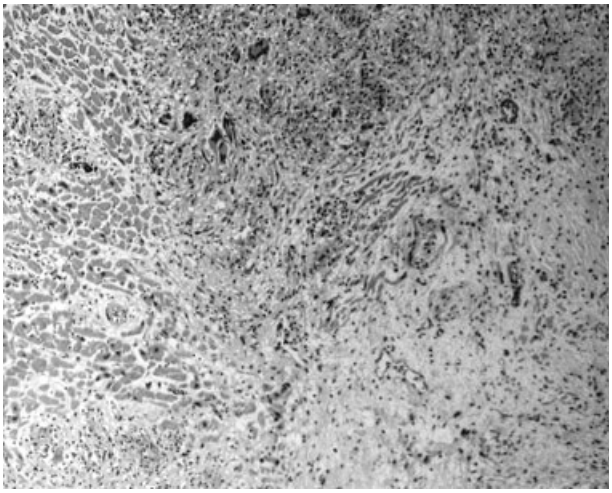

FIG. 3—*The infiltrative nature of the inflammatory cell process in Case 1 (H&E, ×10).*

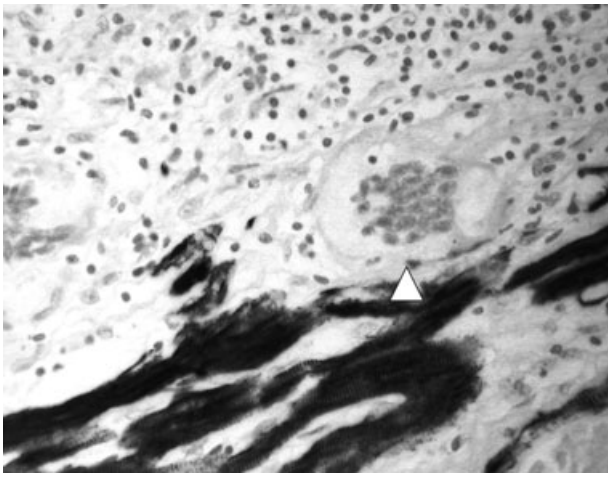

FIG. 6—*Immunoperoxidase stain for desmin showing immunoreactivity of the myocardial fibers and the absence of immunostaining of a giant cell (arrowhead) in Case1 (desmin ×400).*

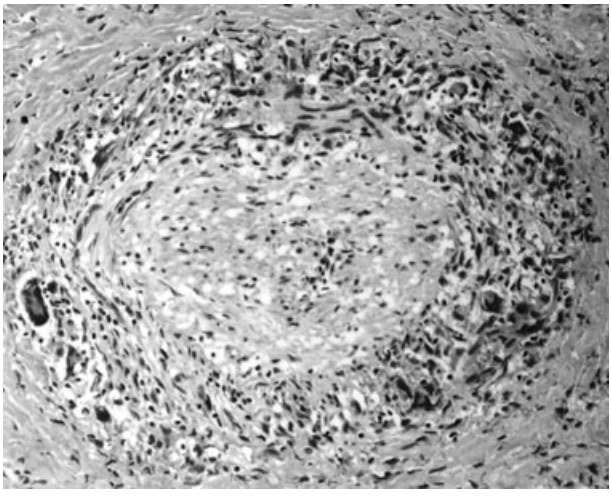

FIG. 4—*Infiltration of the perineural space in Case 1 (H&E, ×200).*

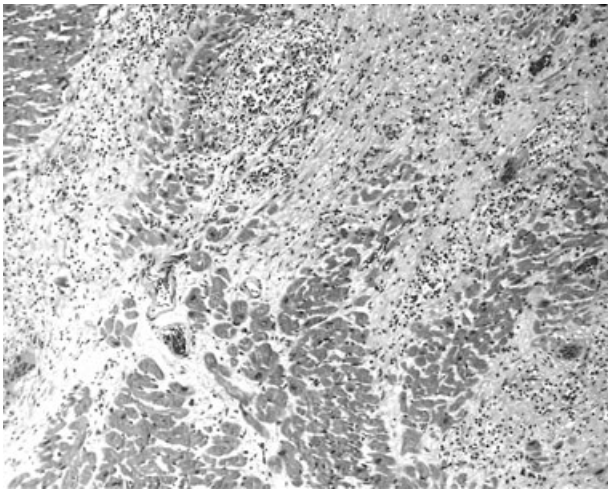

FIG. 7—*The infiltrative nature of the inflammatory cell process in Case 2 (H&E, ×10).*

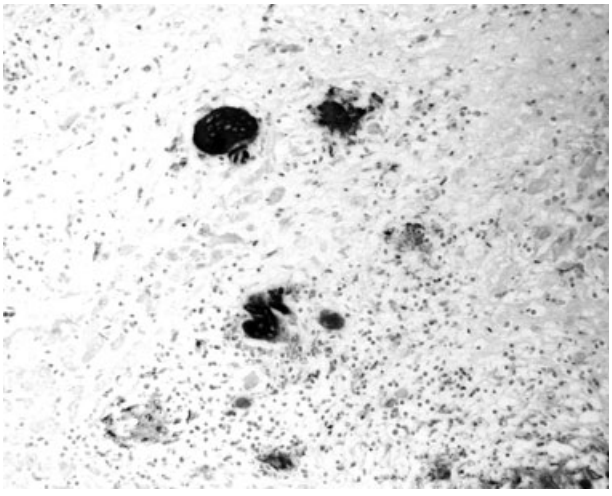

FIG. 5—*Immunoperoxidase stain for CD68 showing immunoreactivity of the giant cells in Case 1 (CD68, ×200).*

foreign body type giant cells, occasional Langhans' giant cells, lymphocytes, and scattered eosinophils (Fig. 7). The process extended in an infiltrative pattern, surrounding bundles of degenerating myocytes, and focal myocardial fiber necrosis was identified. No fungi or acid fast bacilli were identified with special stains and no polarizable foreign material was identified. Immunohistologic studies revealed a pattern identical to that seen in Case 1. The giant cells showed immunostaining with antibodies to lysozyme, CD68 and Ki 67 and the absence of immunostaining for actin, desmin, EMA, and S-100 protein (Fig. 8). The associated lymphocytes showed a striking predominance of T-suppressor cells (Fig. 9). Thorough microscopic examination revealed no granulomas or other lesions in any of the remaining organs. The cause of death was attributed to giant cell myocarditis.

Discussion

Sudden and unexpected deaths in individuals without documented disease processes that would provide reasonable explanations for the deaths are usually investigated by the medical examiner or

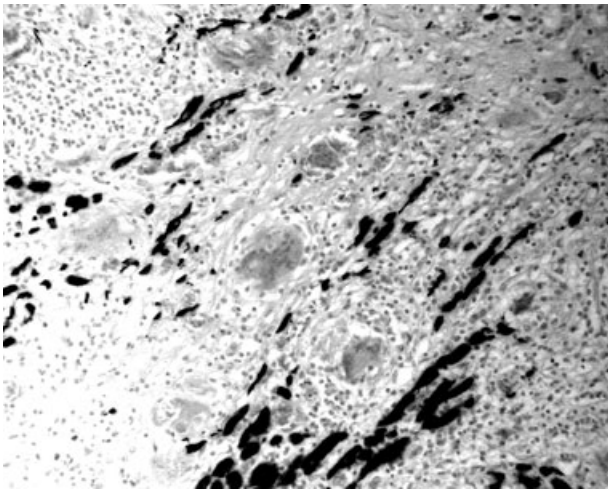

FIG. 8—*Immunoperoxidase stain for actin illustrating immunoreactivity of degenerating myocytes and the absence of immunoreactivity of the giant cells in Case 2 (actin ×200).*

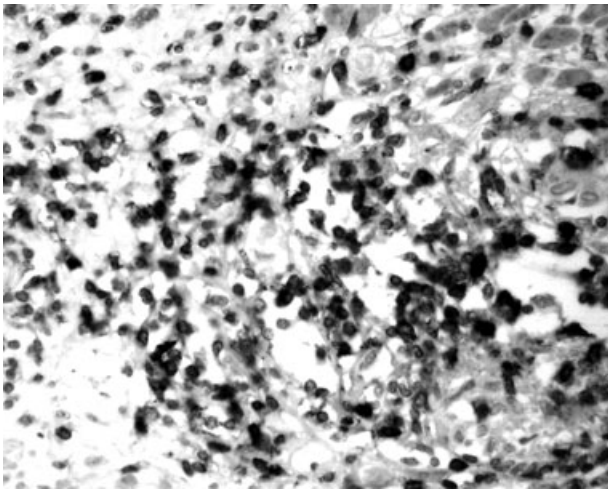

FIG. 9—*Immunoperoxidase stain for CD5 demonstrating the presence of numerous T-suppressor cells in Case 2 (CD5, ×400).*

coroner. These include the unexpected deaths of individuals who have been diagnosed with a known chronic natural disease that was not expected to cause death at that point in time as well as those cases in which the deceased had no known pre-existing natural disease at the time of death. Cardiovascular disorders, most notably arteriosclerotic and/or hypertensive cardiovascular disease, account for the majority of sudden and unexpected natural deaths. Less commonly diagnosed are disease processes directly affecting the myocardium, including inflammatory processes that contains giant cells. In these cases, histologic examination of the myocardium is often essential in reaching a diagnosis.

The differential diagnosis of myocarditis with an inflammatory cell infiltrate with giant cells includes a diverse group of disorders. The majority are systemic processes in which symptoms related to involvement of the heart are rarely the presenting or predominant manifestation of the disease.

A wide range of granulomatous infectious diseases, including fungal, parasitic and most notably mycobacterial, may affect the myocardium. Myocardial tuberculosis was first reported in 1664 (14). Although tuberculosis is now less common in this country, it is still a public health issue. Cardiac tuberculosis is most often diagnosed at autopsy in an individual with systemic disease (4,15,16). Rose (14) recently reported 19 South African cases of cardiac tuberculosis, most involving the ventricles. Eight patients had a miliary pattern of involvement of the myocardium with scattered grossly visible nodules of granulomatous inflammation surrounding central zones of caseous necrosis, while 11 had nodular involvement. Systemic symptoms overshadowed the effects of cardiac disease in the patients with miliary involvement and the nodular lesions caused no significant cardiac dysfunction. Other investigators have reported a diffuse infiltrative pattern of involvement (15,17). Clinically, myocardial tuberculosis can cause cardiac arrhythmias, complete heart block, congestive heart failure, restrictive cardiomyopathy, and left ventricular aneurysms, as well as sudden death, even in individuals without previous illness (2,4,12,13). There have also been case reports of valvular endocarditis and coronary arteritis due to tuberculous infiltration (14,18). In some cases, the lesions in the heart lack caseous necrosis and resemble the granulomas of sarcoidosis (13). The differential also includes other infectious processes such as fungal infections, tularemia, brucellosis, and syphilis (2,3). The diagnosis of myocardial tuberculosis can be confirmed by identification of the mycobacterial organisms, histochemical or *in-situ* hybridization techniques and/or by culture.

Hypersensitivity reactions, usually drug-induced, involving the myocardium may also have a semigranulomatous pattern with giant cells, although eosinophils are also typically present and caseating necrosis is lacking (1,19–22). More commonly, however, the pattern of involvement is infiltrative or perivascular. There may also be an associated non-necrotizing vasculitis (4,19). Since the advent of heart transplantation, hypersensitivity myocarditis has become much more prevalent (23–25). In individuals who have had prior cardiac surgery it should be noted that giant cells in the myocardium may be due to a reaction to foreign material. Giant cells are usually not seen in the myocardium of hearts undergoing transplant reaction (4).

Acute rheumatic fever, a systemic disease that results from an immunologically mediated reaction to a previous episode of group A (beta-hemolytic) streptococcal pharyngitis, is associated with characteristic lesions termed Aschoff nodules (26,27). In their granulomatous stage, Aschoff nodules contain a central zone of fibrinoid necrosis surrounded by lymphocytes, plasma cells, and distinctive macrophages with their nuclear chromatin in a ribbon-like configuration, termed Anitschkow cells or caterpillar cells, that may be multinucleated (27). Typical rheumatoid nodules may be found in the myocardium, pericardium, and cardiac valves in patients with rheumatoid arthritis. These nodules, which have central necrosis surrounded by a zone of palisading fibroblasts and epithelioid histiocytes and an outer zone of perivascular mononuclear inflammatory cells, characteristically do not contain giant cells (28). Giant cells have been described in the hearts of individuals with Wegner's granulomatosis and Takayasu's arteritis (29,30).

Cardiac sarcoidosis was first described by Bernstein in 1929 (7,31). Involvement in individuals with systemic sarcoidosis is a common autopsy finding, reported in 20–30% of patients, although most studies indicate that <5% of patients with sarcoidosis have symptoms related to cardiac involvement. Cardiac disease is only diagnosed prior to death in 40–50% of cases with involvement of the heart. (4,7). Roberts et al. (6), however, reported 35 autopsy cases and reviewed an additional 78 previously diagnosed cases of cardiac sarcoidosis. Eighty-nine patients had clinical evidence of involvement of the heart. The most common symptoms were

arrhythmias, particularly ventricular tachycardia. Complete heart block, ventricular aneurysms, papillary muscle dysfunction, and atrial arrhythmias were less commonly documented. Sudden death was the presenting manifestation of sarcoidosis in six cases, as has also been reported by other investigators (5). Sarcoidal involvement of the conduction system may be the origin of the cardiac arrhythmias (6,7).

Cardiac involvement in sarcoidosis is usually grossly apparent, with either small foci or grossly apparent confluent zones that are well demarcated from the uninvolved myocardium. Although any part of the heart may be involved, the left ventricular free wall and the interventricular septum are the most commonly affected (6,7). Microscopically, there may be well-formed non-necrotizing granulomas similar to those seen in other organs. The granulomas may involve intramyocardial blood vessels (32). Alternatively, the granulomas may be less well-formed and the pattern more infiltrative. The infiltrate includes lymphocytes, predominately T cells, macrophages, and giant cells. Myocyte necrosis, and eosinophils are uncommon (4). Later stages of sarcoidal involvement of the heart result in dense fibrosis. The diagnosis is one of exclusion and is based on the involvement of lymph nodes and/or other visceral organs and the ruling out of infectious agents. Although the etiology of sarcoidosis is currently unknown, it is likely to be immunologically mediated (33).

In contrast to the systemic nature of sarcoidosis, idiopathic giant cell myocarditis, formerly known as Fiedler's myocarditis, a disorder of unknown etiology, occurs predominately in young adults and is confined to the heart (9,11). Involvement of the heart is usually extensive. The clinical course is most commonly fulminant, with a rapid onset, although prolonged survival has been reported (4,8,9,11). Clinical symptoms frequently include refractory ventricular tachycardia (9,10,34). Progressive heart failure, conduction system abnormalities and high grade atrioventricular block have also been documented (10). Sudden death has been reported, and the diagnosis is most commonly made after postmortem examination (10,11). Giant cell myocarditis has been reported in association with thymomas, thyroid disorders, systemic lupus erythematosis, myasthenia gravis, pernicious anemia, and inflammatory bowel disease (9,11,35–38). Because of these associations, an autoimmune etiology has also been postulated for giant cell myocarditis. Immunosuppressive therapy has proven useful in some cases, although cardiac transplantation has been required in others (9,39–43). Recurrence of the disorder in transplanted hearts has been described (8,40,44,45).

Acute, healing, and healed stages of giant cell myocarditis have been described histologically, although the three phases may co-exist in one heart. Similar to sarcoidosis, the acute phase has a mixed inflammatory cell infiltrate containing histiocytes, T lymphocytes, and plasma cells in addition to multinucleated giant cells. Although the histologic distinction between cardiac sarcoidosis and giant cell myocarditis is controversial, most investigators have reported that the latter disorder is characterized by the presence of myocyte necrosis and eosinophils, which are usually not prominent in cardiac sarcoidosis (5,8,46,47). Well-formed granulomas in the myocardium are not common in either disease. Davies et al. (11) stated that the histologic appearance of giant cell myocarditis is diagnostic and histologically distinct from sarcoid. These authors describe serpiginous areas of myocardial necrosis associated with giant cells. In contrast, Rashid and Williams (33) reported that the diagnosis of giant cell myocarditis cannot be made on examination, but necessitates a thorough exclusion of involvement of other organs or lymph nodes. Long (48) has postulated that giant cell myocarditis may be a rare form of sarcoidosis.

The origin of the giant cells in giant cell myocarditis is also controversial (8,10). One report has described the presence of birefringent material within the giant cells (33). Some investigators have postulated that these cells arise from damaged myocardial fibers. Pyun et al. (49) and Davies et al. (11) reported the presence of degenerating myocardial fibers by electron microscopy, and stated that they demonstrated the transition between these fibers and the giant cells. These investigators also ruled out the presence of viral particles. Davies et al. (11) reported the presence of giant cells deriving from viable myocyte fibers at the periphery of the areas of necrosis. In contrast, Wilson et al. (43) demonstrated the presence of cytoplasmic lysozyme within the giant cells using immunoperoxidase stains, indicating a macrophage/histiocyte origin. Other investigators have reported the expression of macrophage markers in the giant cells and the absence of staining for muscle-associated markers using immunoperoxidase studies in cases of giant cell myocarditis and in animal models (8,35,46,50). Tubbs et al. (51) reported the lack of immunostaining for muramidase (lysozyme) and Tanaka et al. (52) reported a case in which many of the giant cells were positive for myoglobin, a marker of muscle cells.

The two cases presented in this report illustrate the difficulties involved in the differential diagnosis of sudden cardiac death due to involvement of the heart by infiltrative processes that include giant cells. Both individuals collapsed at work. In the first case, the decedent had no history of symptoms referable to the heart, having complained only of vague abdominal pain. However, at autopsy he was found to have widespread sarcoidosis. The clinical history is similar to that described by other investigators in the occasional subgroup of individuals with previously undiagnosed sarcoidosis who present with sudden dearth due to cardiac involvement (5). In contrast, the second individual had a 10-year history of cardiac-related symptoms, and at autopsy was found to have a giant cell process isolated to the left ventricular myocardium. This protracted course is uncommon in cases of giant cell myocarditis, which usually follows a rapid clinical course, in contrast to the more typically protracted course of sarcoidosis (4,8,9,11,43,52).

Gross and microscopic examination of the hearts in these two individuals showed very similar processes, distinguished histologically only by the subtle findings of individual myocardial fiber necrosis and scattered eosinophils in the case of giant cell myocarditis. The results of the immunophenotypes of the giant cells and lymphocytes were identical in the two cases. Our findings support those of previous investigators who have reported that the giant cells in giant cell myocarditis express markers indicating a macrophage/histiocyte origin, similar to the giant cells seen in sarcoidosis (8,35,43,46,50,53). In contrast to other earlier studies (11,49,52), we found no evidence to support the theory of a myocyte origin for the giant cells.

These cases illustrate that the differentiation of giant cell myocarditis from sarcoidosis involving the heart is very difficult on the basis of clinical history and morphologic examination alone. Only subtle histologic differences exist between the two processes and immunohistologic studies are of no value in making the distinction. The differentiation in our two cases was based on the presence of involvement of the lungs and lymph nodes, characteristic of sarcoidosis, in Case 1, and by the localization of the granulomatous process to the myocardium in Case 2, diagnosed as giant cell myocarditis. Our findings support those of Rashid and Williams (33), and indicate that thorough gross and microscopic examinations of other organs and lymph nodes are necessary to exclude a diagnosis of sarcoidosis in a case of suspected giant cell myocarditis.

Acknowledgments

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