CHAPTER

14 Pathology of Human Myocarditis

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INTRODUCTION

In spite of the remarkable advances in our understanding, diagnosis, and treatment of myocarditis in the last 150 years, it remains a diagnostic dilemma for many practicing pathologists. In a detailed review of the subject in 1941, Saphir[1] noted that the "incidence of the diagnosis of myocarditis has undergone more changes than perhaps the incidence of any other diagnosis." Much of the confusion can be traced to shifting diagnostic criteria, complex classifications, and changing patterns of infectious disease. The term was initially used by Sobernheim[2] in 1837 and popularized by Virchow[3] in 1858. After the recognition of distinct morphologic features of ischemic myocardial necrosis by Herrick[4] in 1912, the incidence of myocarditis diminished. The introduction of the transvenous endomyocardial biopsy in 1962 by Sakakibara and Konno[5] led to a renewed interest in the pathobiology, etiology, and treatment of myocarditis in antemortem specimens.

In 1984 a group of 8 cardiac pathologists met in Dallas, Texas, as an adjunct to the American College of Cardiology to develop a consensus definition and classification of morphologic criteria for the diagnosis and reporting of myocarditis in endomyocardial biopsy samples now known as the "Dallas criteria."[6] The primary goal was to provide reproducible criteria that allowed the discrimination of myocarditis from ischemic necrosis and other histopathologic mimics rather than to provide another complex temporal or etiologic grading scheme like classifications of Boikan,[7] Gore and Saphir,[8] Burch and Ray,[9] or Kline and Saphir.[10] The Dallas criteria were subsequently used for the multicenter National Institutes of Health myocarditis treatment trial and remain the standard for surgical pathologists.

ROLE OF THE SURGICAL PATHOLOGIST

Before the routine use of the endomyocardial biopsy in clinical cardiology practice, the diagnosis of myocarditis was often suspected but seldom proven before postmortem examination. Now, the surgical pathologist plays a pivotal role in the multidisciplinary team approach to the diagnosis and management of these patients.[11] Critical functions that the surgical pathologist performs in this endeavor can be summarized as: 1) to establish a histopathologic diagnosis of myocarditis using the Dallas criteria; 2) to exclude other morphologic and clinical mimics of inflammatory myocardial disease; 3) to classify the specific type of myocarditis for treatment and prognostic purposes (eg, lymphocytic, giant cell, hypersensitivity, toxic, infectious, sarcoidosis); 4) to monitor the effects of therapy (eg, antivirals, antibiotics, corticosteroids, and other immunosuppressive agents); 5) to evaluate for histopathologic evidence of progression to cardiomyopathy; and 6) to preserve tissue for research purposes (eg, microbiologic, immunohistochemical, molecular). Each of these

functions is predicated on the evaluation of histologic sections prepared from adequate endomyocardial biopsy samples.

In our opinion, the diagnosis of myocarditis should not be rendered before adequate clinical information has been obtained. Direct communication between clinician and pathologist promotes clinical-pathologic correlation. The information should include the clinical history, age and sex of patient, onset and duration of symptoms, ventricular function, cardiac enzyme studies, status of coronary arteries (ideally by angiographic analysis), drug history (eg, vasopressive agents, illicit drugs, cardiotoxic or hypersensitivity-provoking agents, immunosuppressive drugs), studies for infectious etiologies, systemic illnesses such as vasculitis, and results of prior endomyocardial biopsies when available.[12]

TISSUE HANDLING AND PROCESSING

Proper tissue procurement and handling is a prerequisite for optimal microscopic examination. Biopsy specimens should be extracted gently from the bioptome with a needle to prevent crush artifact. The tissue should be placed immediately in a standard fixative such as 10% neutral buffered formalin. Frozen-section immunohistochemistry and immunofluorescence are investigative studies and are not essential to establish the diagnosis. For research purposes, the specimen should be received in saline and then snap frozen in a plastic Beem capsule containing an embedding medium. Transmission electron microscopy is also considered an optional study; an appropriate tissue fixative is required such as glutaraldehyde. Any tissue set aside for research purposes should always be examined by light microscopy before a final diagnosis is rendered because of the focal nature of many types of myocarditis.

For routine diagnostic evaluation, overnight processing and paraffin embedding are sufficient. For emergent cases, a 90-minute rapid (ultra) processing cycle is preferred, and microscopic slides are available within 2 to 3 hours. All the biopsy pieces should be embedded in the same block. At least 3 slides are prepared, each sectioned at 4- to 5-micron thickness from various depths within the block, with multiple fragments or ribbons placed on each slide. Thicker sections often result in biopsy samples appearing cellular, particularly in the interstitial regions, which can be mistaken for myocarditis. This approach also diminishes the risk of missing a focal process within the myocardium. We routinely stain with hematoxylin and eosin and a connective tissue stain such as Masson trichrome to evaluate for myocyte degeneration or damage in problematic cases. Immunohistochemical and molecular studies are performed for specific indications. In some centers, frozen-section analysis on fresh, unfixed tissue by cryomicrotome sectioning is performed for emergent circumstances. Interpretation of these cases is more problematic because of additional artifacts and requires an experienced pathologist (Table 14-1).

Table 14-1
Biopsy Requirements for the Evaluation of Myocarditis

1) Adequate biopsy samples (4-5 pieces preferred)
2) Sections prepared at 4- to 5-micron thickness in ribbons and at 3-step levels
3) Optimal staining with hematoxylin and eosin and a connective tissue stain such as Masson trichrome
4) Clinical history including symptom onset, physical findings, drug history, and status of coronary arteries
5) Biopsy specimen should be obtained during acute illness

BIOPSY LIMITATIONS AND TISSUE ARTIFACTS

Myocarditis is often a focal process, and sampling error remains a major consideration in the clinical management of patients. From the cardiac transplant literature, statistical analysis has shown an expected false-negative rate of 5% with 3 pieces and 2% with 4 pieces obtained by a 9F bioptome.[13] The reported false-negative rate in myocarditis is higher than in acute cardiac rejection. A Mayo Clinic study of endomyocardial samples obtained post mortem from hearts of patients who died of myocarditis reported a false-negative rate of 37% for the right ventricle.[14] Rather than negating the role of the endomyocardial biopsy for the diagnosis of clinically suspected myocarditis, as has been proposed by some investigators,[15-17] we think it remains the standard for this purpose. Recognition of the diminished sensitivity of the biopsy, careful patient selection, adequate biopsy sampling, and liberal use of leveled sections improve the diagnostic yield. For these reasons, a minimum of 4 to 5 pieces is recommended to minimize sampling error. Samples obtained by smaller bioptomes may require at least 5 or 6 pieces.

Various artifacts occur in endomyocardial biopsy specimens, which may mimic pathologic processes, and the surgical pathologist must be aware of these patterns. These have been reviewed in detail[18] and only selected topics are reviewed here. The most common biopsy artifact is the presence of contraction bands within myocytes. They are identical to the bands observed in acute ischemic necrosis and catecholamine (pressor) effect. These changes are induced by the biopsy procedure and can be diminished by using fixatives at room temperature. In ischemic injury, the nuclei of surrounding myocytes are usually pyknotic, whereas in artifactually induced contraction bands, the nuclei appear normal.

Another frequent artifact is intussusception or telescoping of small arteries that mimics luminal occlusion by thrombus. Connective tissue stains such as Masson trichrome or elastic van Gieson highlight the internal elastic membranes of both vessel segments. Intramyocardial accumulations of mature adipose tissue can simulate epicardial tissue, especially if associated with vessels of relatively large caliber. Both can be found in the right

ventricular apical region, and adipose tissue is found not uncommonly in women and elderly patients. This should not be confused with arrhythmogenic right ventricular dysplasia or ventricular perforation; the latter is identified by the presence of mesothelial cells.

Accumulations of fresh platelet, fibrin-rich thrombus may be identified along the endocardial surface of biopsy fragments. These form by repeated placement of the bioptome along the endocardium and do not indicate chronic mural thrombi. Crush artifactual distortion of cellular components can be mistaken for inflammatory cell infiltrates. This can be reduced by gently extracting the specimen from the bioptome with a needle. Finally, artifactual widening of the interstitium may be caused by tissue procurement and processing and does not imply interstitial edema. We require the presence of interstitial, eosinophilic proteinaceous material as a minimum criterion for edema.

THE DALLAS CRITERIA

As mentioned previously, a consensus definition and classification of myocarditis were produced by a panel of cardiac pathologists at the American College of Cardiology meetings in Dallas in March 1984. The goals for the original group are enumerated in Table 14-2. Myocarditis was defined as a myocardial process characterized by the presence of an inflammatory infiltrate and myocyte damage or necrosis that is not typical of the myocardial damage of ischemic heart disease. Two distinct schemes were proposed to describe the endomyocardial biopsy findings from the timing of the biopsy procedure (Table 14-3).

The First Diagnostic Biopsy

Three diagnostic categories are possible for the initial diagnostic biopsy.[6]

Active Myocarditis — Reflecting the definitional features described above, the unequivocal diagnosis of myocarditis requires the presence of ***both*** inflammatory cell infiltrates and myocyte damage. The composition of the infiltrate should be described and can include predominantly lymphocytic, eosinophilic, neutrophilic, giant cell, granulomatous, or mixed cell types. The distribution and amount of inflammatory infiltrate should be assessed by patterns such as focal, confluent, or diffuse and mild, moderate, and severe degrees, respectively.

Table 14-2
Goals of the Dallas Criteria

1)	To provide a morphologic definition for the diagnosis of myocarditis
2)	To develop a simple, reproducible working formulation for reporting myocarditis
3)	To enumerate diagnostic mimics of myocarditis
4)	To assess the applicability and reproducibility of the classification

Modified from Aretz et al.[6] By permission of Field and Wood.

Table 14-3
Dallas Classification of Myocarditis

First biopsy
I) Unequivocal myocarditis
II) Borderline myocarditis
III) No evidence of myocarditis
Subsequent biopsies
I) Ongoing (persistent) myocarditis
II) Resolving (healing) myocarditis
III) Resolved (healed) myocarditis

Data from Billingham.[11]

A more difficult challenge is the determination of myocyte damage in the biopsy specimen. In our experience, florid myocytolysis and necrosis are not common biopsy patterns. We recognize myocyte damage by the presence of mononuclear cells that cause encroachment or scalloping of the sarcolemmal membrane of myocytes, fragmentation of myocytes with remnants of cytoplasm or bare nuclei, architectural displacement or distortion of myocytes by inflammatory cells, or partial replacement of myocytes by inflammatory cells. In equivocal cases the liberal use of leveled sections and Masson trichrome are helpful because damaged myocytes display a basophilic tinctorial quality.

Finally, the presence or absence of fibrosis should be noted for reference to changes in subsequent biopsies and the potential development of dilated cardiomyopathy. Interstitial, perivascular, and endocardial patterns can be seen. We do not attempt to quantitate the severity of fibrous replacement because it is subjective and poorly reproducible in our experience.

Borderline Myocarditis — This term is applied to biopsy samples in which the inflammatory cell infiltrate is limited and myocyte damage is not demonstrated. In some cases, unequivocal diagnostic features can be demonstrated in additional leveled sections. In others, repeat biopsies may be required.[19]

No Evidence of Myocarditis — This implies that neither diagnostic feature is present in the sample. Deeper sectioning of the paraffin blocks should be considered before this diagnosis is made because the inflammatory process may be patchy in distribution. If myocarditis is absent, attention should be focused on the presence of other myocardial disorders such as myocyte hypertrophy and interstitial fibrosis in the setting of dilated cardiomyopathy. We routinely perform histochemical stains for amyloidosis and hemochromatosis in this setting.

Follow-up Biopsy

It is not uncommon for patients with biopsy-proven myocarditis to undergo additional biopsies. In some cases, these are done after therapeutic interventions with immunosuppressive drugs to monitor the response to drug therapy. In other patients, it is used to detect disease recurrence or progression. Three categories are used that resemble the diagnostic scheme of acute cellular rejection in cardiac allograft recipients.

Ongoing or Persistent Myocarditis — This term is applied when the degree of myocarditis is unchanged or worse than the original biopsy specimen.

Resolving or Healing Myocarditis — This category implies that the degree of inflammation or damage (or both) is diminished. Reparative changes are usually evident in the form of interstitial fibroblastic or myofibroblastic cellular infiltrates, granulation tissue, and immature collagen deposition.

Resolved or Healed Myocarditis — This term is restricted to biopsy specimens lacking either cellular infiltrates or damage. Mature collagenous scar tissue may be found in some cases, whereas others are entirely normal. The distribution of cicatricial scar tissue and the compensatory myocyte hypertrophy should be noted when present. Scattered mononuclear cells can be found within scar tissue and do not imply a recurrence or exacerbation of the disease.

We have observed cases of recurrent myocarditis after tapering of immunosuppressive therapy and previous biopsy specimens showing healed myocarditis. According to the Dallas criteria, if unequivocal or borderline myocarditis recurs, the new biopsy should be interpreted as a first biopsy.[6]

SPECIFIC TYPES OF HUMAN MYOCARDITIS

The definition and diagnostic criteria described in the preceding section illustrate a crucial point for the reporting of myocarditis by the surgical pathologist. The term is primarily a descriptive one and therefore requires a qualifier to provide the clinician with important etiologic, therapeutic, and prognostic information. The remainder of the discussion focuses on specific patterns and types of myocarditis. The composition and distribution of the inflammatory cell infiltrate and the pattern and type of injury observed in the endomyocardial biopsy specimen generally offer etiologic clues. For example, infiltrates composed predominantly of polymorphonuclear cells suggest a bacterial infection; eosinophils may be found in parasitic infestations or allergic drug reactions; giant cells can be seen in mycobacterial or fungal infections, sarcoidosis, or idiopathic giant cell myocarditis; and predominantly lymphocytic infiltrates are the typical response in myocarditis associated with systemic diseases and idiopathic (postviral), viral, rickettsial, or spirochetal infections.

IDIOPATHIC (POSTVIRAL) MYOCARDITIS

In most developed countries viral agents are thought to be the primary cause of most cases of myocarditis. Historical, clinical, and experimental evidence has identified members of the genus *Enterovirus*. These include coxsackievirus A and B, echovirus, and poliovirus. The pathogenesis of these viruses is incompletely understood and is discussed in other chapters in this book. Possible mechanisms include direct viral destruction of cardiac myocytes, T-cell-mediated autoimmune injury, and viral-mediated endothelial injury with intimal proliferation and ischemic sequelae. In many clinical cases, however, a direct causative link is not established, and these cases are classified as idiopathic myocarditis. Other terms that have been used include "acute myocarditis" to reflect the clinical onset of symptoms and absence of fibrosis in the biopsy specimen or "rapidly progressive myocarditis" in cases of multifocal damage and extensive fibrosis.[20] We prefer the term "lymphocytic" or "idiopathic myocarditis" and use the criteria in the Dallas classification. We discourage the use of the term "chronic myocarditis," because these cases usually represent dilated cardiomyopathy in our experience.

The incidence and natural history of idiopathic myocarditis remain largely undetermined. Discrepancies between clinically suspected cases and endomyocardial biopsy findings are well recognized. In a previous study from Stanford University, 30% of patients presenting with unexplained heart failure of short duration had biopsy evidence of lymphocytic myocarditis.[21] Other published series reporting the prevalence of myocarditis by using the endomyocardial biopsy as the standard are presented in Table 14-4.[22-30] The low incidence is thought to relate to the focal nature of the inflammatory cell infiltrates in both pediatric and adult cases.[31,32]

Table 14-4
Prevalence of Myocarditis in the Published Literature

Reference	Year published	Positive biopsy results	
		%	Number/total number
22	1985	67	18/27
23	1989	37	38/102
24	1990	78	14/18
25	1994	51	20/39
26	1995	10	214/2,233
27	1999	9	1/11
28	1999	16	10/62
29	2000	14	252/1,757

Modified from Feldman and McNamara.[30] By permission of the Massachusetts Medical Society.

Macroscopic Findings in Idiopathic Myocarditis

In general, examination of the heart specimen at transplantation or post mortem demonstrates 4-chamber dilatation and cardiac enlargement. Patients who die of ventricular arrhythmias or florid myocarditis, however, may have normal cardiac configurations. The papillary muscles and trabeculae carneae are often flattened, and the myocardium appears pale and flabby. Thrombi are uncommon within atrial appendages or along ventricular endocardial surfaces. The cut surface of the myocardium is usually pale, and foci of hemorrhage or hemorrhagic necrosis are found. Many cases are also associated with a fibrinous pericarditis and exudative effusions.[33]

Microscopic Findings in Idiopathic Myocarditis

The resemblance of this type of myocarditis and acute cellular rejection of the cardiac allograft was described[34] (Gopal S, Achalu R, Day JD, Huang M, Narasimhan U, Day MT, Kasper EK, Trichon BH, Chen CL, Cina SJ, Berry GJ, Robertson AL, Hruban RH, unpublished data). The cardinal features of acute allograft rejection are the presence of inflammatory cells and presence or absence of myocyte damage. The category of borderline myocarditis reflects the presence of inflammatory cells without concomitant myocyte damage and resembles the categories of focal or diffuse mild acute rejection. Typically, the infiltrates are sparse and are predominantly lymphocytic in nature. Occasional neutrophils or eosinophils may be found admixed within the infiltrate. They are more commonly distributed in the perivascular tissue spaces (Fig. 14-1 *A*; see color plate 21). In more advanced or severe cases of myocarditis, myocyte damage or necrosis is conspicuous. The architectural patterns include focal (Fig. 14-1 *B*; see color plate 21), multifocal, or diffuse interstitial infiltrates (Fig. 14-1 *C*; see color plate 21). Interstitial widening by tissue edema and inflammation is seen, and interstitial hemorrhage may be either punctate or diffuse. The patterns of confluent myocyte damage and necrosis are similar in the biopsy specimens of adult (Fig. 14-1 *D*; see color plate 21) and pediatric (Fig. 14-1 *E*; see color plate 21) patients. The composition of the infiltrates in the advanced stages of both groups is often polymorphous, with a predominance of mononuclear cells but variable numbers of eosinophils and neutrophils (Fig. 14-2 *E*; see color plate 22). Scattered multinucleated giant cells of either myogenic or macrophagic origin may also be found (Fig. 14-2 *F*; see color plate 22).

The treatment of idiopathic myocarditis remains controversial and is not discussed in detail here. At Stanford University, immunosuppressive agents are used routinely for biopsy-proven cases, often with dramatic clinical and morphologic responses. The progression from florid myocarditis on the initial diagnostic biopsy (Fig. 14-2 *A* and 2 *B*; see color plate 22) to healing or healed myocarditis (Fig. 14-2 *C* and 2 *D*; see color plate 22) on subsequent biopsies is well documented. The intensity of the infiltrate is diminished

or absent. Reparative changes within the interstitium range from loose granulation tissue with minimal alteration of the myocardial architecture to replacement by collagenous scar tissue. Increased vascularity suggesting angiogenesis may also be seen, along with compensatory hypertrophy of residual myocytes. The findings on the follow-up biopsies should be graded as persistent, healing (resolving), or healed (resolved) myocarditis according to the Dallas criteria. The progression to dilated cardiomyopathy should also be recorded.

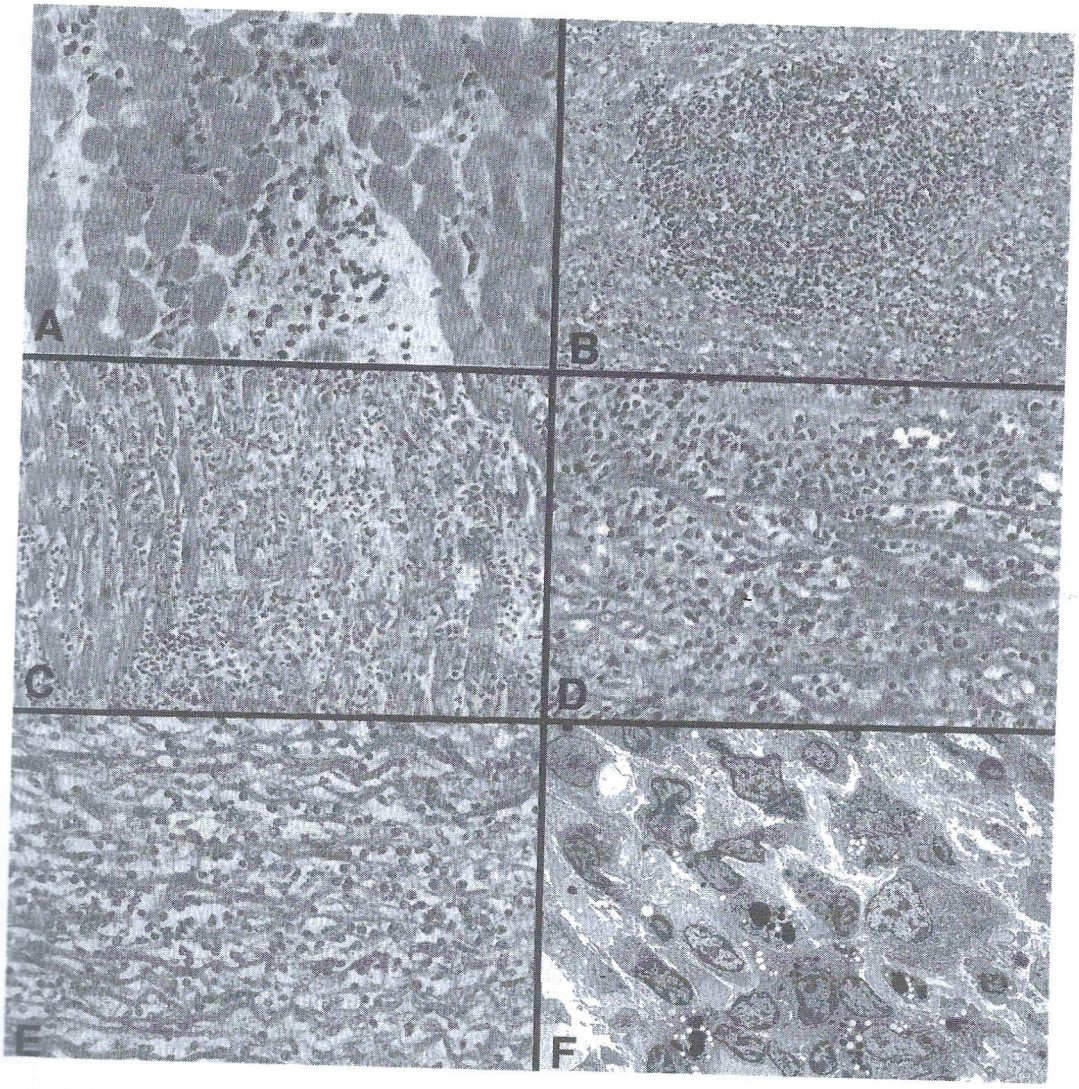

Fig. 14-1. Idiopathic lymphocytic myocarditis. See color plate 21.

Ultrastructural, Immunohistochemical, and Molecular Findings

The utility of transmission electron microscopy in the diagnosis of myocarditis is limited to research studies. Interstitial expansion by mononuclear cells dispersed among normal myocytes is observed (Fig. 14-1 *F*, see color plate 21). On occasion, myocyte necrosis characterized by lymphocytes adherent to disrupted sarcolemmal membranes, damage of the microvascular elements, and fragmented collagen bundles within the interstitium may be seen.[35] We and others have not observed viral components or immune complex deposition with these techniques.

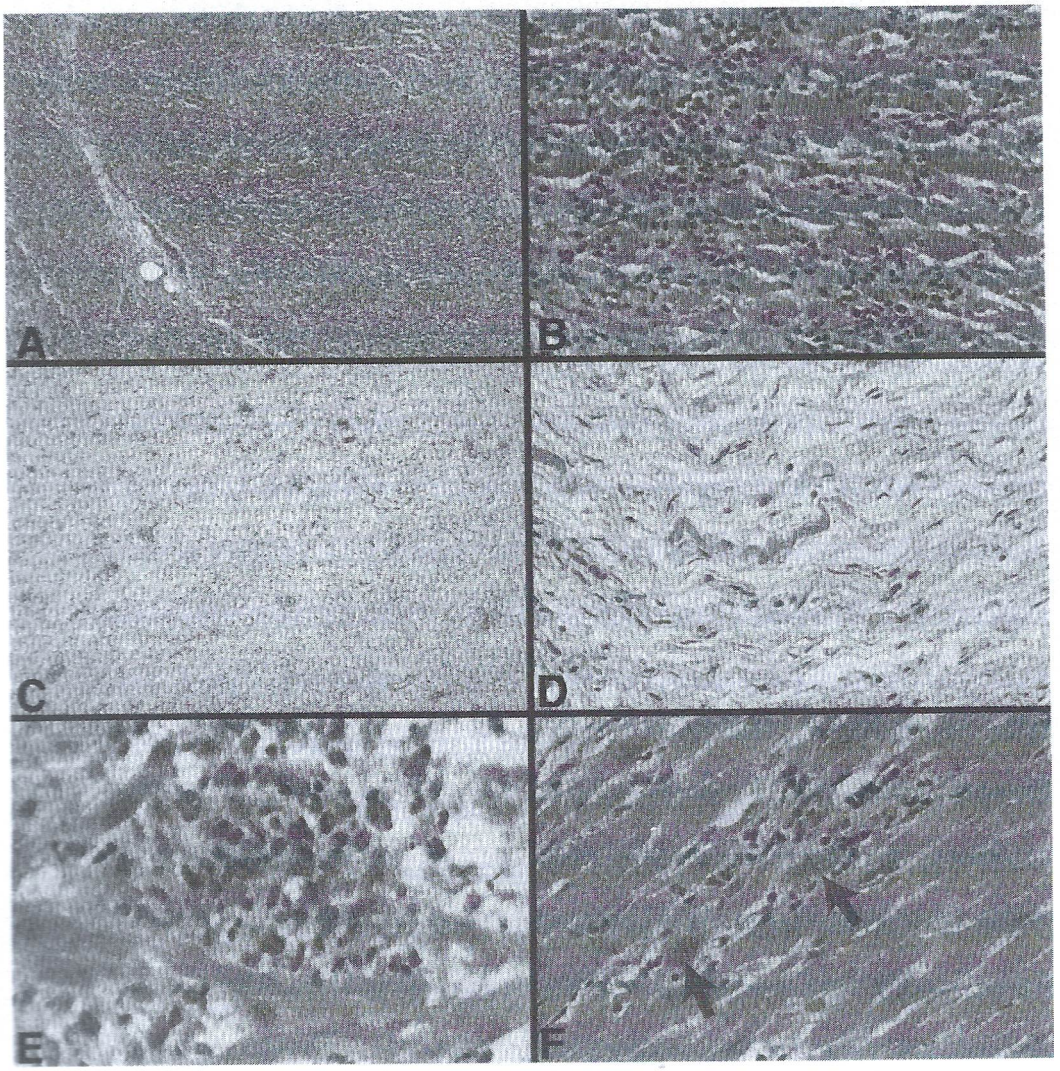

Fig. 14-2. Idiopathic lymphocytic myocarditis. See color plate 22.

Immunologic studies have expanded our understanding of the pathogenesis of this disease process. Immunofluorescence studies of cases of active myocarditis showed the presence of the third component of complement (C3) in 50% of cases; this diminished with resolution of the inflammatory lesions.[36] Indirect immunofluorescence studies also identified increased staining for antibodies directed against sarcolemmal antigens and myofibrillar components in biopsy samples showing resolving myocarditis. Different investigators reported immunophenotypic profiles of the infiltrating cells[37,38] (Gopal S, Achalu R, Day JD, Huang M, Narasimhan U, Day MT, Kasper EK, Trichon BH, Chen CL, Cina SJ, Berry GJ, Robertson AL, Hruban RH, unpublished data). The majority of lymphocytes are $CD3^+$ T cells with helper and suppressor subtypes. Macrophages and natural killer cells are also present, but B cells are infrequent or absent (Fig. 14-3; see color plate 23). Up to 25% of lymphocytes stain for Bcl-2, and 27% of the myocytes express p53.

Programmed cell death (apoptosis) is detectable by in situ hybridization end labeling. Early myocyte necrosis is shown by myosin light chain staining in most cases of lymphocytic myocarditis (Gopal S, Achalu R, Day JD, Huang M, Narasimhan U, Day MT, Kasper EK, Trichon BH, Chen CL, Cina SJ, Berry GJ, Robertson AL, Hruban RH, unpublished data). Other markers of immunologically mediated cell injury include the persistent expression of intercellular adhesion molecule 1 and vascular cell adhesion molecule 1 in myocardial biopsy samples.[39] Increased numbers of interstitial dendritic cells have been shown in active myocarditis, suggesting an important pathogenetic role.[40]

The role of viral infection in human myocarditis was strengthened by the identification of enterovirus genome by in situ hybridization, polymerase chain reaction (PCR), and PCR–single-strand conformation polymorphism techniques in the heart samples of patients with myocarditis and dilated cardiomyopathy.[41-44] Interestingly, enteroviral RNA sequences have been found by PCR methodologies in other conditions not related to myocarditis or dilated cardiomyopathy. These include coronary artery disease, cardiac allograft rejection, normal donor heart tissue, and cardiac fibroelastosis.[45]

Morphologic Mimics of Idiopathic Myocarditis

The common histopathologic lesions that can be mistaken for idiopathic myocarditis are presented in Table 14-5. The issue of how many lymphocytes are normally within the myocardium has been addressed. This is particularly important in assessing the possibility of lymphocytic myocarditis. Edwards et al.[46] determined that the mean number of lymphocytes within normal myocardial tissue is fewer than 5.0 per high-power field. This figure was derived from 170 endomyocardial biopsies of patients with clinical evidence of heart disease. Tazelaar and Billingham[47] examined endomyocardial biopsy specimens from 86 young disease-free cardiac transplant donors at the time of transplantation. Foci composed of at least 5 mononuclear inflammatory cells were found in 9.3% of cases.

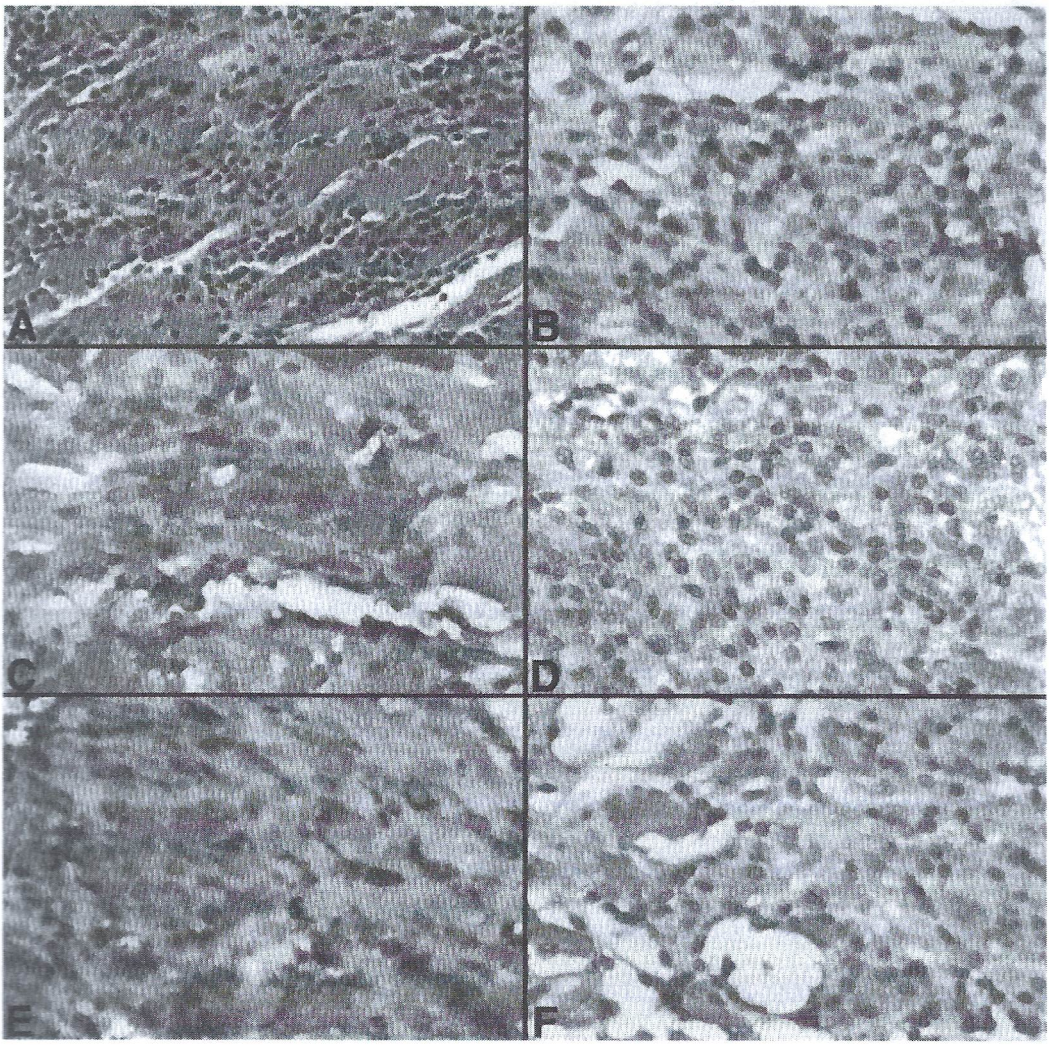

Fig. 14-3. Immunophenotype of lymphocytic myocarditis. See color plate 23.

Table 14-5
Morphologic Mimics of Idiopathic (Lymphocytic) Myocarditis

1) Lymphocytes and interstitial cells in normal myocardium
2) Lymphocytes in dilated cardiomyopathy
3) Ischemic necrosis and pressor or catecholamine effects
4) Biopsy-site changes
5) Hematolymphoid and nonhematolymphoid malignancies
6) Other types of myocarditis (eg, infectious, toxic, giant cell types)
7) Extramedullary hematopoiesis in myocardial scars

Other types of interstitial cells found within the normal myocardium that can be confused with inflammatory cells include endothelial cells, smooth muscle cells, pericytes, fibroblasts, and mast cells. Hill and Swanson[48] reported the presence of extramedullary hematopoietic cells, including immature erythroid and myeloid precursors within healing infarcts of ischemic and cardiomyopathic hearts, and areas of fibrosis in congenital defects. Interestingly, they also included 1 case of viral myocarditis within this study.

The issue of chronic myocarditis and idiopathic dilated cardiomyopathy has been mentioned. This remains a continuing source of confusion for pathologists. Our practice is to avoid the term "chronic myocarditis." Mononuclear leukocytic infiltrates are commonly found in dilated cardiomyopathy. Tazelaar and Billingham[49] examined random myocardial samples from 108 recipient hearts with end-stage idiopathic dilated cardiomyopathy and found inflammatory cells in 87% of cases. These were localized to the interstitial tissues and within fine or coarse interstitial fibrosis (Fig. 14-4 *A*; see color plate 24). The presence of myocyte hypertrophy characterized by large, irregular, hyperchromatic, and often bizarre-shaped nuclei and collagenous eosinophilic interstitial fibrosis are cardinal features of idiopathic dilated cardiomyopathy.[50] Distinguishing features are summarized in Table 14-6.

Another morphologic mimic of myocarditis is vasopressor or catecholamine effect and ischemic necrosis. Large doses of vasopressive agents may be required to support the patient hemodynamically. These can produce direct myocyte toxicity or "microinfarcts" by constriction of small "end vessels." The affected myocytes appear fragmented and hypereosinophilic and are surrounded by a minimal mixed inflammatory cell infiltrate (Fig. 14-4 *B*; see color plate 24). The distribution of the lesions near or around small intramyocardial arteries and the mixed nature of the infiltrate prevent confusion with acute myocarditis. The trichrome stain highlights the necrotic myocytes by their blue-gray tinctorial appearance. The damaged myocytes may undergo punctate calcification and mimic infectious myocarditis such as toxoplasmosis.

Ischemic necrosis can occur because of prolonged hypotension, particularly in patients with underlying coronary heart disease. Patterns include discrete subendocardial foci of necrosis characterized by hypereosinophilic myocytes with pyknotic smudged nuclei and loss of cytoplasmic striations and fine detail. This zonal injury pattern is sharply delineated by Masson trichrome stain. The normal red-orange myocytes are easily distinguished from the gray-blue necrotic fibers. In the setting of ischemia with reperfusion injury, fragmented myocytes may be found associated with foci of interstitial hemorrhage. These are caused by endothelial injury progressing to rupture of the microvasculature. In healing ischemic lesions, granulation tissue replaces the necrotic region, and histiocytes and pigment-laden macrophages are evident (Fig. 14-4 *B*). Over weeks to months, this lesion is infiltrated by mature scar tissue.

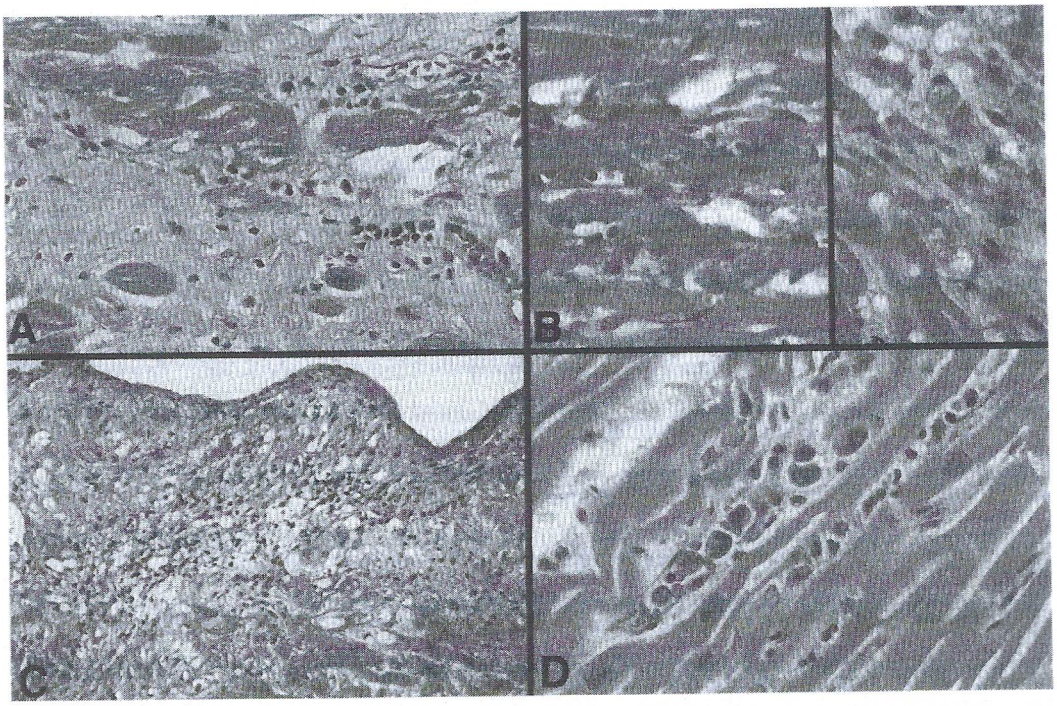

Fig. 14-4. Differential diagnosis of lymphocytic myocarditis. See color plate 24.

Table 14-6
Histopathologic Features of Lymphocytic Myocarditis (LM) and Idiopathic Dilated Cardiomyopathy (IDCM)

Finding	LM	IDCM
Focal/diffuse/cellular infiltrates	+	+
Polymorphous cell infiltrates	+	–
Endocarditis/pericarditis	+	–
Vasculitis	+	–
Global myocyte hypertrophy	–	+
Bizarre nuclear morphology	–	+
Myofibrillar loss	–	+
Myocyte damage/necrosis	+	–
Interstitial fibrosis		
Focal	+	+
Diffuse	–	+
Mature eosinophilic collagen	–	+

On occasion, we have observed changes related to previous biopsy sampling in follow-up biopsies. Two patterns are seen in biopsy-site changes. Within the first 2 weeks an endothelial-lined craterlike lesion is observed in the subendocardial tissues. Surrounding aggregates of fibrin are variable amounts of granulation tissue admixed with scattered acute and chronic inflammatory cells. Coagulative necrosis of adjacent myocytes can be seen. Progressive organization leads to replacement by cicatricial collagenous tissue with distortion of adjacent myocytes in a disarray pattern. It is not uncommon to find collections of lymphocytes and occasional hemosiderin-laden macrophages within the hyalinized tissue, including cases of dense cellular aggregates (Fig. 14-4 *C*; see color plate 24). The latter can be confused with myocarditis, but the presence of fibrous scar tissue is the key discriminator. A trichrome stain is useful in these cases. We have also seen cases of foreign material with an associated giant cell reaction in previous biopsy sites (Fig. 14-5 *A*; see color plate 25).

Neoplastic infiltrates are uncommon findings on endomyocardial biopsies. Hematolymphoid malignancies such as leukemias and lymphomas are characterized by their atypical cytologic features and the absence of necrosis and fibrosis (Fig. 14-5 *C* and 5 *D*; see color plate 25). Immunophenotypic and molecular studies are helpful to confirm the clonality of these processes and to distinguish them from myocarditis. We observed a case of

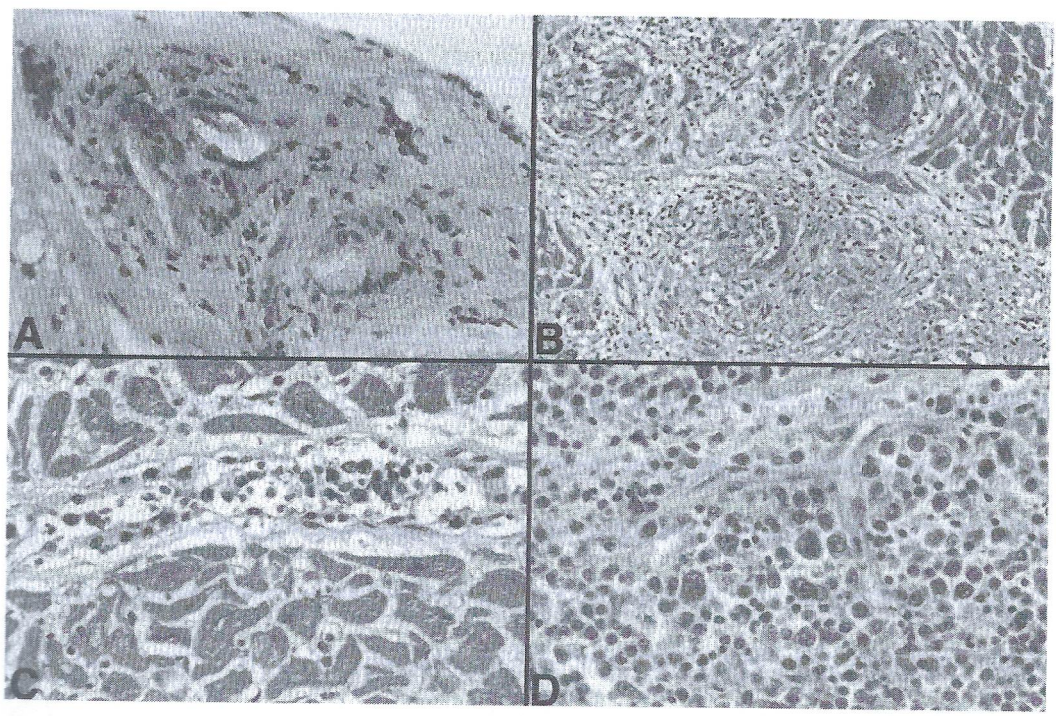

Fig. 14-5. Differential diagnosis of idiopathic giant cell myocarditis. See color plate 25.

metastatic malignant melanoma presenting as diffuse interstitial infiltrates within the myocardium in association with sparse myocyte damage (Fig. 14-4 D; see color plate 24).

INFECTIOUS MYOCARDITIS

In developed countries infectious causes of heart muscle inflammation are uncommon in immunocompetent individuals. Patients with acquired immunodeficiency syndrome (AIDS), transplant-associated immunosuppression to prevent allograft rejection, and advanced stages of malignancy are susceptible to bacterial, viral, fungal, protozoan, and rickettsial infections. In many developing countries these remain a significant cause of morbidity and mortality, and cardiac involvement is observed frequently. Some specific forms of infectious myocarditis are discussed.

Bacterial Myocarditis

The causes of bacterial myocarditis are listed in Table 14-7. Four basic morphologic patterns can be enumerated: 1) suppurative, 2) toxin-related, 3) granulomatous, and 4) nonspecific lymphocytic myocarditis. Suppurative or pyogenic myocarditis is the most common type and is usually caused by staphylococcal, streptococcal, pneumococcal, or meningococcal infections. The classic mechanisms of myocardial dissemination include septicemia or localized infection from a contiguous source such as infected lung. Infective endocarditis is the most common pattern underlying septic myocarditis in our experience.[51,52] Bacterial infections complicating myocardial infarction and coronary stent placement have been reported.[53,54]

The morphologic findings range from focal neutrophilic collections within the myocardium to microabscess formation (Fig. 14-6 *A* and 6 *B*; see color plate 26). In some

Table 14-7
Bacterial and Spirochetal Causes of Myocarditis

Bacterial	Actinomycosis	Mycoplasma
	Brucellosis	Pneumococcal
	Cholera	Salmonellosis
	Diphtheria	Staphylococcal
	Gonococcal	Streptococcal
	Haemophilus	Tularemia
	Meningococcal	Whipple disease
	Mycobacterial	
Spirochetal	Leptospirosis	Relapsing fever
	Lyme disease	Syphilis

Modified from Feldman and McNamara.[30] By permission of the Massachusetts Medical Society.

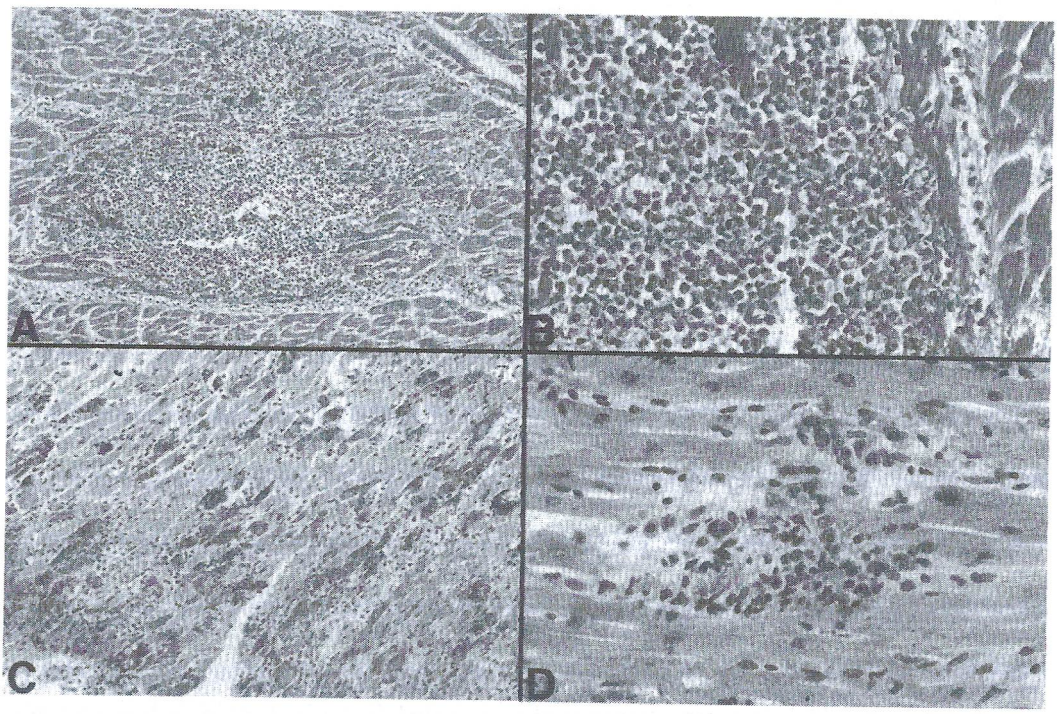

Fig. 14-6. Bacterial myocarditis. See color plate 26.

cases the collections of microorganisms are readily found on sections stained with hematoxylin and eosin, but we routinely prepare sections with Gram stain for confirmation.

Conduction abnormalities have been reported in cases of brucellosis,[55] *Mycoplasma* infection,[56] and *Legionella* infection.[57] Rare causes of bacterial myocarditis include human granulocytic ehrlichiosis,[58] psittacosis,[59] and salmonella.[60-62]

Diphtheric myocarditis occurs in up to a quarter of patients with diphtheria and remains the most frequent cause of death in patients with this disease. Myocardial dysfunction is affected by a potent exotoxin liberated by *Corynebacterium diphtheriae* that interferes with protein synthesis. Until recently, diphtheria was rare in western countries, but outbreaks have been reported in Scandinavia and the Baltic countries, particularly in alcoholics.[63] Romberg[64] described the pathologic features in the classic monograph in 1891. At postmortem examination the hearts are flabby and dilated and the myocardium exhibits a streaky appearance. Microscopic features include patchy hyaline and granular degeneration of myocytes associated with collections of mononuclear inflammation (Fig. 14-6 *C* and 6 *D*; see color plate 26). In the late or chronic stages of the disease, myocardial scarring is found. The conduction system is preferentially involved in this disease, and the development of complete atrioventricular block is regarded as a poor prognostic sign.

Tuberculosis is a rare but classic example of granulomatous bacterial myocarditis. Although uncommon in most western countries, it remains a differential diagnostic consideration in cases of myocarditis associated with giant cells. Routes of myocardial involvement include hematogenous, lymphatic, and direct contiguity. Morphologic patterns that have been described include nodular masses (tuberculoma), miliary nodules, and diffuse cellular infiltrates.[65-67] Caseating and noncaseating granulomas are found, and histochemical stains and bacteriologic studies are essential for establishing the diagnosis. Granulomatous bacterial infections have been reported in cases of Whipple disease, but the more common pattern is collections of foamy macrophages containing periodic acid-Schiff-positive granules.[68] Lymphohistiocytic infiltrates with multinucleated giant cells and liquefactive necrosis (gummatous lesions) are the hallmarks of syphilitic myocarditis in adults.[69,70] Predilection for the upper portions of the interventricular septum can result in conduction defects. In the congenital form of this disease, the histopathologic findings are mononuclear cell infiltrates without gummatous lesions.

Direct bacterial toxicity with or without a coexisting immune-mediated dysfunction is a suspected mechanism in Lyme carditis. Between 1% and 8% of patients infected by the tick-borne spirochete *Borrelia burgdorferi* develop cardiac involvement usually characterized by variable degrees of atrioventricular or interventricular block. Endomyocardial biopsy samples resemble idiopathic lymphocytic myocarditis, and in rare cases spirochetal organisms are identified by modified silver stains.[71-73] Cardiac involvement in leptospirosis (Weil syndrome) is also characterized by cellular infiltrates composed predominantly of mononuclear cells with sparse neutrophils and focal necrosis.

Viral Myocarditis

The role of viral agents in the pathogenesis of idiopathic myocarditis has been mentioned previously, and other chapters examine postviral autoimmunity mechanisms, direct viral cytopathic injury, and induction of viral-specific immune response through mediators such as interleukin -1, -2, and -6; tumor necrosis factor; interferon; and nitrous oxide.[74] In addition to the enteroviruses and echoviruses, numerous RNA and DNA viruses are linked to myocarditis (Table 14-8). Many of these viruses produce nonspecific lymphocytic myocarditis seen on histopathologic examination.[75-85] Others such as cytomegalovirus (CMV) and varicella have intranuclear inclusions that aid diagnosis.[86] The following discussion is limited to CMV myocarditis, EBV-associated lymphoproliferative disorders, and human immunodeficiency virus (HIV)-related myocardial lesions.

Cytomegalovirus Myocarditis — Human CMV is a ubiquitous virus belonging to the herpesvirus family that infects 50% to 90% of adults. Serious morbidity and mortality are limited to infections occurring in fetal development, in immunosuppressed patients receiving chemotherapy, transplant recipients, and AIDS patients.[87-91] Hepatitis, infectious

Table 14-8
Viral Causes of Myocarditis

Adenovirus	Junin virus
Arbovirus	Lymphocytic choriomeningitis
Arenavirus (Lassa fever)	Measles
Coxsackievirus	Mumps
Cytomegalovirus	Parvovirus
Dengue virus	Poliovirus
Echovirus	Rabies virus
Encephalomyocarditis virus	Respiratory syncytial virus
Epstein-Barr virus	Rubella
Hepatitis virus (A and C)	Rubeola
Herpes simplex virus	Vaccinia virus
Herpes zoster	Varicella virus
Human immunodeficiency virus	Variola virus
Influenza virus (A and B)	Yellow fever virus

Modified from Feldman and McNamara.[30] By permission of the Massachusetts Medical Society.

mononucleosis-like syndrome, pneumonitis, myocarditis, gastroenteritis, and retinitis have been described in the setting of acute infections.[92] Chronic infection plays a significant role in the development of transplant-accelerated arteriosclerosis.[93]

The diagnosis of CMV myocarditis requires the demonstration of nuclear inclusions composed of large central basophilic nuclei surrounded by a pale artifactual halo within myocytes, fibroblasts, or endothelial cells (Fig. 14-7 *A*; see color plate 27). Less frequently, cytoplasmic inclusions arranged as eosinophilic globules may be found. The density and distribution of the inflammatory response vary, and the response may be sparse or absent in the region of the inclusions. The composition of the infiltrate is generally polymorphous, with lymphocytes, histiocytes, eosinophils, and neutrophils. The presence of pyknotic debris and the mixed cell types or numerous eosinophils should heighten suspicion for infection. Immunohistochemical and molecular studies are useful in cases where the findings are equivocal[94-96] (Fig. 14-7 *B*; see color plate 27). After initiation of antiviral therapy, the inclusions appear more eosinophilic, inhomogeneous, and globular.[97] The introduction of prophylactic or preemptive strategies for CMV has resulted in a dramatic reduction in cases of CMV myocarditis at our institution.

Epstein-Barr Virus-Associated Lymphoproliferative Disorders — EBV infection involving the heart is uncommon. Nonspecific electrocardiographic alterations in patients with infectious mononucleosis have been reported. There is 1 published report of lymphocytic myocarditis on endomyocardial biopsy in a young woman with a clinical presentation simulating myocardial infarction with cardiogenic shock.[98] Immunocompromised patients

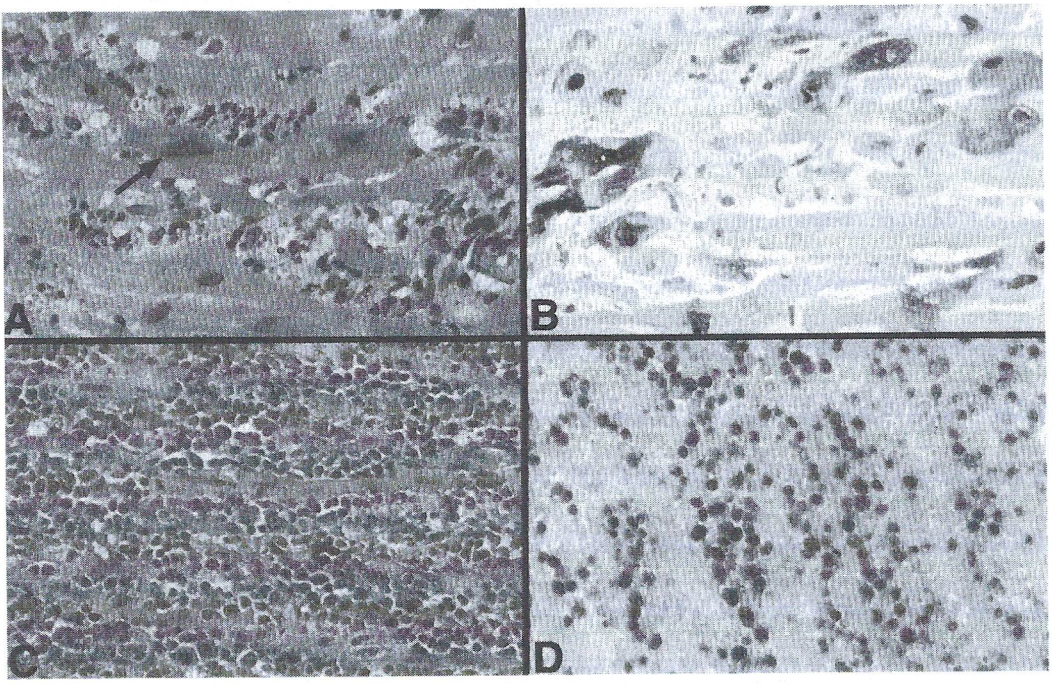

Fig. 14-7. Cytomegalovirus (CMV) myocarditis. See color plate 27.

such as transplant recipients and AIDS patients can develop EBV-driven lymphoid proliferations within the myocardium ranging from mononucleosis-like lesions to malignant lymphoma. We have encountered only 2 cases of post-transplant lymphoproliferative disease involving the allograft in endomyocardial biopsy samples. Useful morphologic clues include the presence of atypical lymphoid or lymphoplasmacytoid cells, atypical immunoblasts, brisk mitotic activity, and cellular necrosis (Fig. 14-7 *C*; see color plate 27). Polymorphic infiltrates may be difficult to distinguish from myocarditis and immunohistochemical and molecular studies are helpful (Fig. 14-7 *D*; see color plate 27). The majority of post-transplant lymphoproliferative disorders involve B cells and are EBV-associated in contrast to T-cell-mediated lesions of idiopathic myocarditis.

AIDS-Related Myocardial Lesions — Patients infected with HIV are at risk of development of various cardiac lesions (Table 14-9). These include endocardial valvular disease caused by marantic or infective endocarditis, pericardial effusions (sterile or infective), fibrinous or constrictive pericarditis, and myocardial lesions such as infectious myocarditis, neoplastic infiltration by Kaposi sarcoma or lymphoma, right ventricular hypertrophy with pulmonary hypertension, and drug toxicity.[99] Cases of dilated cardiomyopathy and non-infectious myocardial inflammation have also been reported. The changes range from borderline to active myocarditis according to the Dallas criteria and are reported in 11 of 16 HIV^+ patients (69%) undergoing endomyocardial biopsy for myocardial dysfunction.[100]

Table 14-9
Cardiac Lesions in AIDS Patients

I. Endocardial disorders
  Marantic endocarditis
  Infective endocarditis (bacterial, fungal)

II. Myocardial disorders
  Opportunistic infections
    Bacterial (tuberculosis, mycobacterium avium intracellulare)
    Fungal (cryptococcosis, aspergillosis, candidiasis, histoplasmosis, coccidioidomycosis)
    Protozoan (toxoplasmosis)
    Viral (cytomegalovirus, herpes simplex, human immunodeficiency virus)
  Noninfectious myocardial necrosis
    Catecholamine effect
    Drug toxicity
    Vascular spasm
  Pulmonary hypertension with right ventricular hypertrophy
  Neoplastic processes
    Kaposi sarcoma
    Malignant lymphoma

III. Pericardial disorders
  Infectious pericarditis (opportunistic infections)
  Neoplastic infiltration (Kaposi sarcoma, non-Hodgkin lymphoma)
  Uremic/noninfectious pericarditis

Modified from Kaul et al.[99] By permission of Mosby-Year Book.

These are mediated by $CD3^+$ T cells with a suppressor/cytotoxic $CD8^+$ phenotype.[101] Possible etiologies include direct HIV viropathic effect, coinfection with another cardiotrophic virus, postviral autoimmune mechanism, and drug toxicity. In our experience, the diagnosis of HIV-associated myocarditis and cardiomyopathy is one of exclusion, and common infectious causes such as toxoplasmosis, CMV, and mycobacterial and fungal infections should be sought by histochemical, immunohistochemical, molecular, and bacteriologic methods.

Fungal Myocarditis

Fungal myocarditis is another type of opportunistic infection that occurs in iatrogenically immunosuppressed patients, AIDS patients, intravenous drug abusers, and rarely after open heart surgery.[102-104] The fungal organisms that are reported are listed in Table 14-10. In our experience, most cases occur in the setting of advanced disseminated infections. The histopathologic findings include zonal myocardial infarcts because of hematogenous spread within intramyocardial vessels. Neutrophilic microabscesses and abundant tissue necrosis

are seen and warrant appropriate histochemical stains (Fig. 14-8; see color plate 28). Granulomatous formation and the presence of multinucleated giant cells are uncommon in our experience with solid organ and bone marrow transplant recipients. The presence of mixed infiltrates predominated by neutrophils and abundant pyknotic cellular debris are important clues to distinguish fungal myocarditis from idiopathic myocarditis. The number of fungal infections after thoracic transplantation at Stanford University has diminished since the introduction of aerosolized antifungal prophylaxis.[105]

Table 14-10
Fungal Causes of Myocarditis

Aspergillosis	Cryptococcosis
Blastomycosis	Histoplasmosis
Candidiasis	Mucormycosis
Coccidioidomycosis	

Modified from Feldman and McNamara.[30] By permission of the Massachusetts Medical Society.

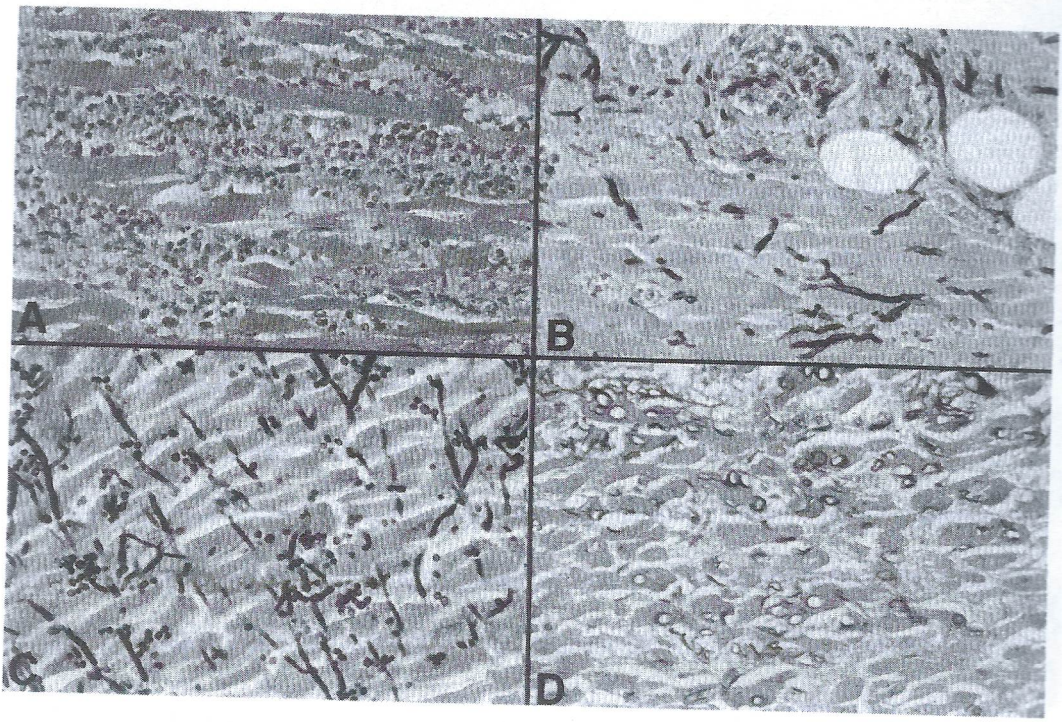

Fig. 14-8. Fungal myocarditis. See color plate 28.

Protozoan/Helminthic Myocarditis

Parasites that can cause myocarditis in humans are listed in Table 14-11. Of the protozoan causes, toxoplasmic myocarditis and Chagas disease are the most common. The helminthic infections represent tapeworm, flat-worm, and round-worm infestations and are rarely encountered in the United States. Trichinosis is the sole exception in this group, and infestation occurs after the consumption of raw or uncooked animal meat containing larval cysts.[106] Nonencysted larvae incite a brisk lymphohistiocytic response within the myocardium, and myocardial damage may be conspicuous in the early stages of the illness. Eosinophils may also be present within the inflammatory cell infiltrates.

Toxoplasmic Myocarditis — Infections by the obligate intracellular parasite, *Toxoplasma gondii*, occur clinically in congenital or acquired forms. Myocarditis is uncommon in immunocompetent adults, although rare cases are reported.[107] Three patterns of disease are recognized: acute or miliary infectious form, glandular form involving lymph nodes, and a localized form involving 1 or 2 organ systems.

We have observed cases of acquired cardiac toxoplasmosis in AIDS patients and in cardiac allograft recipients. In transplant patients, toxoplasmic myocarditis is now infrequently encountered in endomyocardial biopsy specimens because antibiotic prophylaxis is given to seronegative recipients receiving grafts from seropositive donors.[108] Like CMV, the inflammatory response may be variable and may resemble lymphocytic myocarditis or cardiac rejection. Lymphocytes and histiocytes often admixed with eosinophils are centered on necrotic, pyknotic myocytes. In some cases, toxoplasmic cysts may have sparse inflammation (Fig. 14-9 *A*; see color plate 29). Trophozoites may be difficult to identify in the biopsy samples, and immunohistochemical or molecular studies may be helpful[109] (Fig. 14-9 *B*; see color plate 29). At the ultrastructural level, encysted bradyzoites are found within myocytes. The organism is ovoid, measuring 4- to 6-microns long and 2- to 3-microns wide. The double-layered pellicle and anteriorly placed conoid are characteristic (Fig. 14-9 *C* and 9 *D*). An important diagnostic distinction must be made between bradyzoites of toxoplasmosis and the fine dystrophic calcifications within individual myocytes.[110,111] These represent encrustation of mitochondria and are usually seen in the setting of ischemic injury.

Chagas Disease — Myocarditis caused by the hemoflagellate, *Trypanosoma cruzi*, is the most common form of inflammatory heart muscle disease in Central and South America. Clinically, it is characterized by an acute phase followed by a latent phase and then the chronic phase. The acute phase develops after a short incubation period, and infection of myocytes by organisms occurs. Myocarditis occurs in a third of patients; most recover within 3 to 4 months. Death due to cardiac or neurologic complications is reported in 5% to 10% of cases, and at postmortem study the heart is enlarged, flabby, and mottled.[112] Microscopic sections reveal intact pseudocysts and a dense mixed inflammatory infiltrate of

Table 14-11
Protozoan/Helminthic Causes of Myocarditis

Toxoplasmosis	Paragonimiasis
Sarcocystosis	Trichinosis
Trypanosomiasis	Visceral larva migrans
Ascariasis	Echinococcosis
Cysticercosis	Filariasis
Schistosomiasis	

Modified from Feldman and McNamara.[30] By permission of the Massachusetts Medical Society.

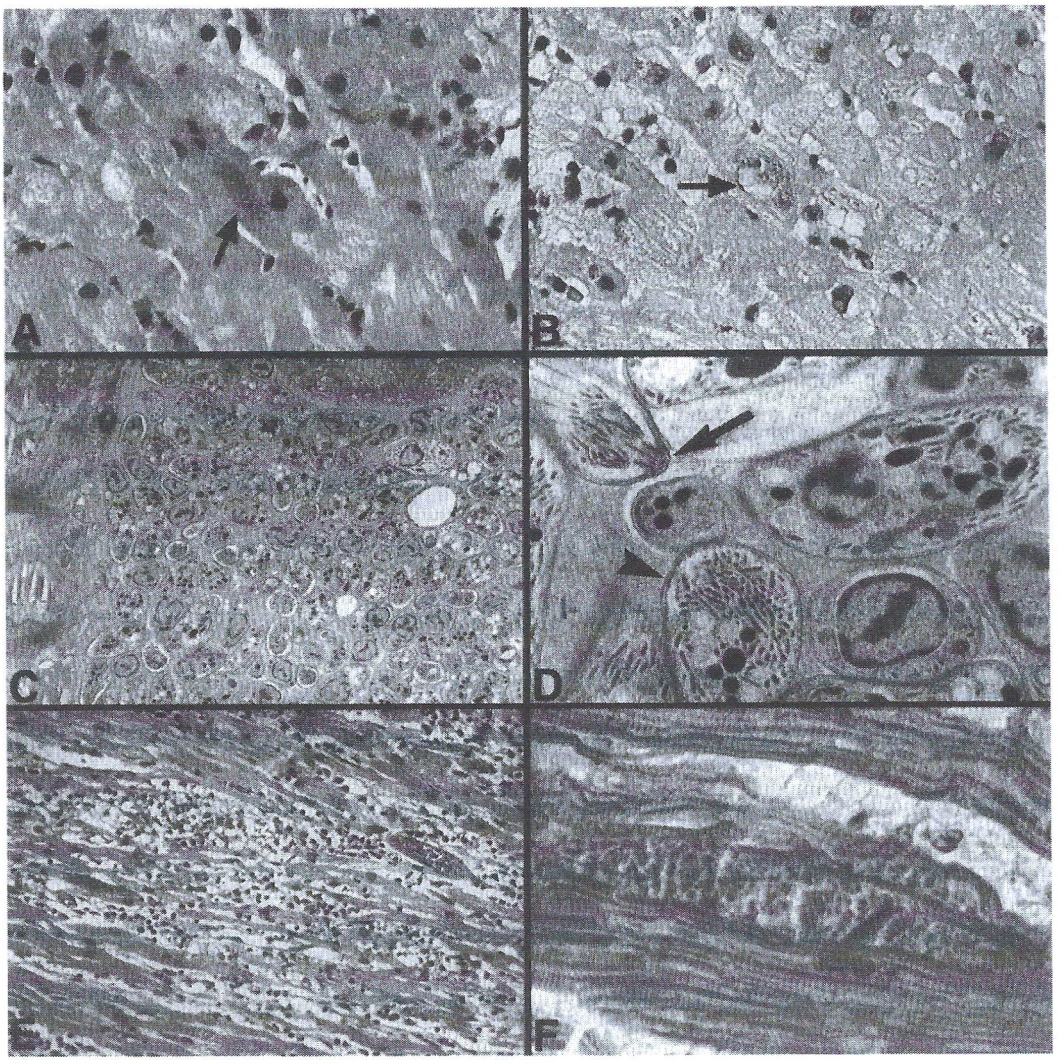

Fig. 14-9. Parasitic myocarditis. See color plate 29.

lymphocytes, plasma cells, histiocytes, and polymorphonuclear leukocytes associated with myocyte necrosis (Fig. 14-9 *E* and 9 *F*; see color plate 29). Both cell-mediated and antibody-mediated mechanisms are thought to be involved in the pathogenesis of the lesions in response to antigens released by infected cells becoming adsorbed onto surfaces of infected and noninfected host cells.[113]

The chronic phase of Chagas disease occurs years to decades after the acute infection. The morphologic findings consist of dilated cardiomyopathy. Patients can present with arrhythmias, congestive heart failure, or thromboembolic lesions.[114] Identification of parasites within the myocardium is uncommon at this time, but foci of residual myocarditis and fibrosis are reported. The role of postinfectious immunity and autoimmune-mediated myocardial disease in Chagas disease remains unresolved.

Rickettsial Myocarditis

Cardiac involvement in the rickettsial diseases is usually subclinical and consists of abnormalities in the electrocardiogram. The 3 causes–Rocky Mountain spotted fever, scrub typhus, and Q fever–are each characterized by nonsuppurative vasculitic lesions of small vessels, including capillaries, venules and arterioles, and small arteries. Endothelial and medial smooth muscle cell invasion by microorganisms results in endothelial cell injury, thrombus formation, and necrosis. An accompanying lymphocytic myocarditis is seen more frequently in Rocky Mountain spotted fever than in scrub typhus.[115-117] Organisms can be identified in tissue sections by a modified Giemsa stain. Immunofluorescence stains are also available. Endocarditis is the most common lesion in Q fever, but venous thrombosis and small vein vasculitis can occur.

DRUG-RELATED MYOCARDITIS

Drug-induced myocardial dysfunction remains a significant clinical problem and the list of drugs implicated continues to grow. Five patterns are recognized: 1) hypersensitivity myocarditis, 2) toxic myocarditis, 3) endocardial fibrosis (eg, ergotamine tartrate, methysergide, or phentermine or fenfluramine), 4) drug-induced cardiomyopathy (eg, anthracycline or chloroquine), and 5) giant cell myocarditis.[118,119] A partial list of the drugs associated with hypersensitivity and toxic myocarditis is presented in Table 14-12.

Hypersensitivity Myocarditis

Hypersensitivity myocarditis is the most common form of acute drug-related myocardial injury. More than 2 dozen drugs have been identified that cause hypersensitivity myocarditis, but the majority of cases are caused by sulfonamides, methyldopa, and penicillin and its derivatives.[120-122] It is also observed in patients undergoing cardiac transplantation and may be related to prolonged dobutamine infusion.[123-125] Clinical presentation can include rash,

Table 14-12
Drug-Induced Myocarditis

Hypersensitivity myocarditis		
Penicillin	Isoniazid	Tetanus toxoid
Sulfonamides	Amphotericin B	Indomethacin
Tetracycline	Ampicillin	Ephedra
Streptomycin	Chloramphenicol	Cefaclor
Phenylbutazone	Methyldopa	Diphtheria toxin
		Clozapine
Toxic myocarditis		
Anthracycline	Cocaine	
Cyclophosphamide	Catecholamines	
Arsenicals	Theophylline	
Fluorouracil	Quinidine	
Lithium	Barbiturates	
Amphetamines	Paraquat	

Data from Billingham,[118] La Grenade L, Graham D, Trontell A. Myocarditis and cardiomyopathy associated with clozapine use in the United States (letter to the editor). N Engl J Med 2001;345:224-225, and Kilian JG, Kerr K, Lawrence C, Celermajer DS. Myocarditis and cardiomyopathy associated with clozapine. Lancet 1999;354:1841-1845.

fever, peripheral eosinophilia, and occasionally arrhythmias, sudden death, and congestive heart failure. It is not dose-dependent and can occur at any time during drug administration.

The histopathologic features include temporally uniform lesions distributed in the subendocardial, perivascular, and interstitial tissues (Fig. 14-10 *A*; see color plate 30). The predominant inflammatory cells are eosinophils, but variable numbers of histiocytes and lymphocytes are also found (Fig. 14-10 *B*; see color plate 30). Myocyte necrosis is absent or focal and limited. Necrotizing vasculitis is not found, but infiltration of vessel walls by inflammatory cells is common.[126] Collections of histiocytes often centered on degenerated collagen bundles form ill-defined granulomas in up to 25% of cases, but fibrinoid necrosis, well-formed aggregates of epithelioid histiocytes ("hard granulomas"), multinucleated giant cells, interstitial fibrosis, and hemorrhage are absent in our experience (Fig. 14-10 *C*; see color plate 30). Immunohistochemical studies showed T-cell phenotypes of infiltrating lymphocytes and sparse or absent B cells.[126] Myocyte apoptosis was reported in 6 of 6 cases studied using in situ end-labeling techniques (Gopal S, Achalu R, Day JD, Huang M, Narasimhan U, Day MT, Kasper EK, Trichon BH, Chen CL, Cina SJ, Berry GJ, Robertson AL, Hruban RH, unpublished data). The absence of diffuse myocardial necrosis and giant cells distinguishes hypersensitivity myocarditis from drug-induced giant cell myocarditis.[119] Acute necrotizing eosinophilic myocarditis differs from hypersensitivity myocarditis by the presence of extensive necrosis and absence of systemic allergic symptoms (Fig. 14-10 *D*; see color plate 30).[127,128]

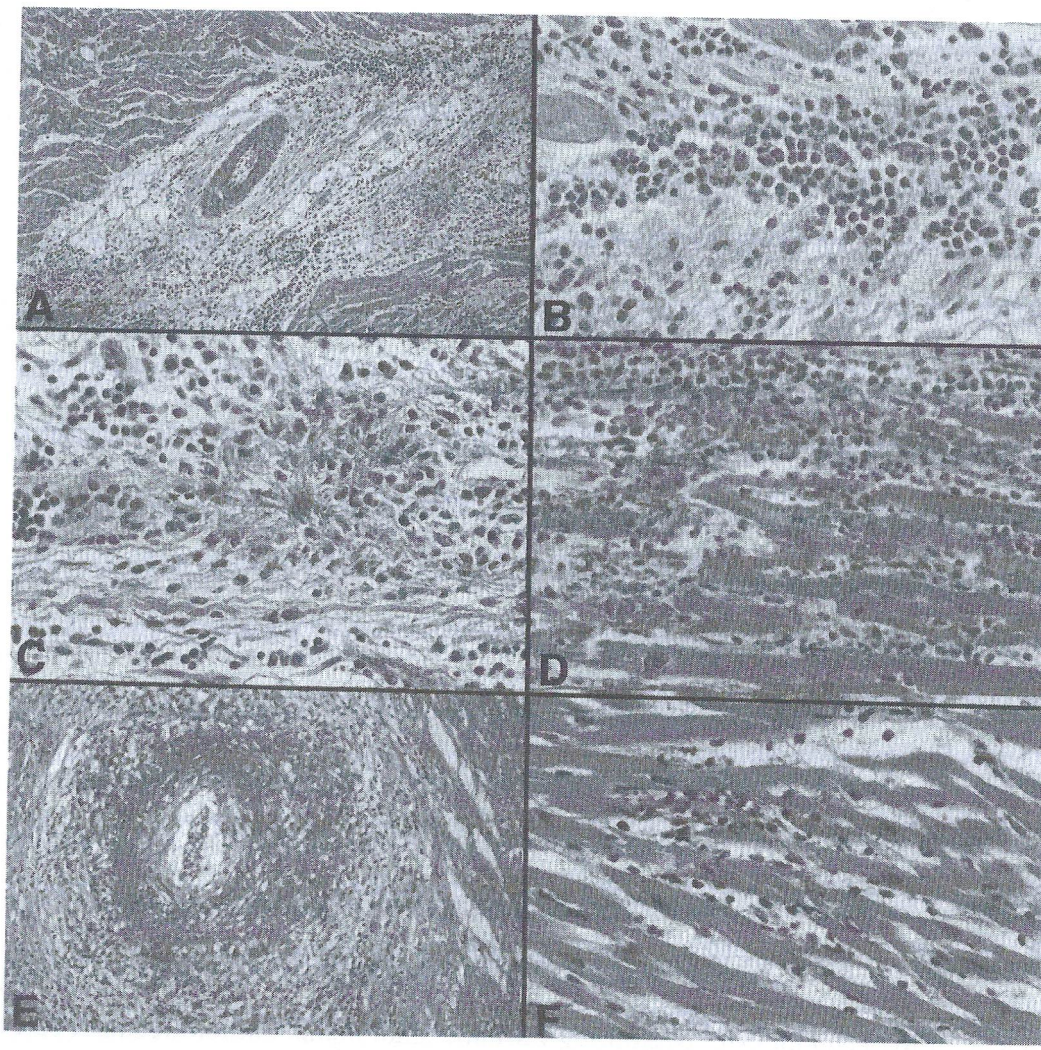

Fig. 14-10. Drug-related myocarditis. See color plate 30.

Toxic Myocarditis

Toxic myocarditis is an uncommon form of myocarditis and is characterized by direct myocyte cytotoxicity. Causative agents include antineoplastic agents such as cyclophosphamide and anthracyclines, catecholamines, cocaine, arsenicals, fluorouracil, lithium compounds, and antihypertensives. In contrast to hypersensitivity myocarditis, it is usually dose-dependent and the lesions may persist or progress after the cessation of the drug. The pathologic features reflect the cellular response to myocytopathic damage. The lesions are focal and temporally heterogeneous, reflecting the episodic or cumulative mechanism of injury. Some lesions in the biopsy sample may be acute, whereas others may be in the

reparative phases. Fibrosis is not uncommon. The inflammatory infiltrates are polymorphous (lymphocytes, plasma cells, and neutrophils), but eosinophils are rare or absent. Vasculitis with associated hemorrhage has been reported in cyclophosphamide cardiotoxicity (Fig. 14-10 *E*; see color plate 30). Bristow and colleagues[129] reported 4 cases of early anthracycline cardiotoxicity occurring within a few days or weeks after drug administration. These were characterized by acute pericarditis-myocarditis. The myocardial lesions were typical of toxic myocarditis (Fig. 14-10 *F*; see color plate 30).

MYOCARDITIS ASSOCIATED WITH SYSTEMIC PROCESSES

Myocarditis has been reported in nondisease processes such as peripartum myocarditis and systemic illnesses such as thrombotic thrombocytopenic purpura. Many of these are examples of immune-mediated myocarditis.

Collagen Vascular Diseases

Myocarditis is reported in many of the connective tissue diseases, including systemic lupus erythematosus (SLE), systemic sclerosis, polyarteritis nodosa, rheumatoid arthritis, polymyositis/dermatomyositis (PM/DM), thrombotic thrombocytopenic purpura, Wegener granulomatosis, and, rarely, in ankylosing spondylitis and mixed connective tissue disease.[130-135] SLE, rheumatoid arthritis, and PM/DM are most commonly associated with myocarditis. The morphologic features on endomyocardial biopsy or in postmortem material are nonspecific myocarditis similar to the idiopathic (postviral) type of myocarditis. This emphasizes the importance of adequate clinical information in the evaluation of these cases. In SLE, fibrinoid type of vasculitis may also be observed in the small intramyocardial arteries in the biopsy specimen. Immunofluorescence studies may demonstrate immunoglobulin, complement, and fibrinogen deposition suggesting a humorally mediated form of myocarditis.

Immunosuppressive therapy remains the mainstay of treatment. Drug-related toxic myocarditis should be considered in the differential diagnosis, particularly in SLE patients receiving quinidine-based therapy.

Acute Rheumatic Fever

Rheumatic fever remains a significant cause of cardiac morbidity and mortality in underdeveloped countries.[136] It is a sequela to group A streptococcal pharyngitis and arises as an autoimmune response to extracellular or somatic bacterial antigens that share similar epitopes in human tissues. Cardiac involvement occurs in up to 55% of patients and is characterized by a pancarditis (ie, inflammation of epicardial, myocardial, and pericardial tissues). The diagnosis of rheumatic myocarditis has been made at endomyocardial biopsy, at transplantation, and at autopsy.[137,138]

The myocardial lesions consist of nonspecific lymphocytic myocarditis and Aschoff nodules. The latter may be found within the endocardium, myocardium, pericardium, and conduction system and are pathognomonic of acute rheumatic fever. They represent oval collections of histiocytes, lymphocytes, plasma cells, and giant cells (Aschoff cells) located within the interstitium adjacent to small blood vessels (Fig. 14-11; see color plate 31). This "granulomatous stage" of Aschoff nodules arises 1 to 2 months after the onset of clinical symptoms and develops within or near foci of fibrinoid necrosis. They are eventually replaced by collagenous scar tissue.

Kawasaki Disease

Kawasaki disease (mucocutaneous lymph node syndrome) is currently the most frequent cause of acquired heart disease in children in the United States.[139,140] Coronary abnormalities develop in up to 20% of patients; other cardiac manifestations include pericardial effusion, valvular insufficiency, and nonspecific lymphocytic myocarditis. Four pathologic stages are observed. Stage I occurs between days 0 and 9 and is characterized by acute perivasculitis and vasculitis of arterioles, capillaries, venules, and small arteries. An endothelitis composed of mixed inflammatory cell types is found in the major epicardial coronary arteries. Myocarditis, pericarditis, and involvement of the conduction system may occur. In stage II (12-25 days), panarteritis with thrombosis of the epicardial arteries is present. A reparative phase is seen in stage III (28-31 days) and consists of organization of thrombi and intimal proliferation. The final stage (40 days to 4 years) shows recanalization of lumens, coronary aneurysms, and myocardial ischemic injury (Fig. 14-12 *A*, 12 *B*, and 12 *D*; see color plate 32). Residual foci of lymphocytic myocarditis may be found (Fig. 14-12 C; see color plate 32). The mainstay of therapy consists of supportive care, antiplatelet drugs, and immunoglobulin given intravenously.

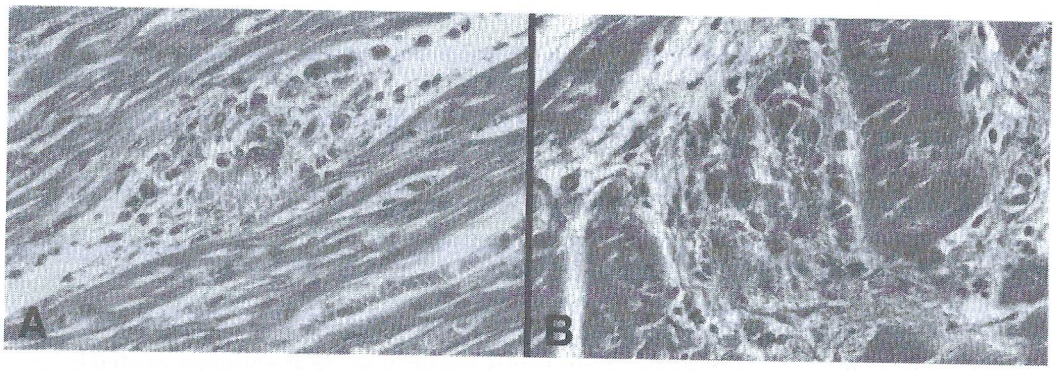

Fig. 14-11. Acute rheumatic myocarditis. See color plate 31.

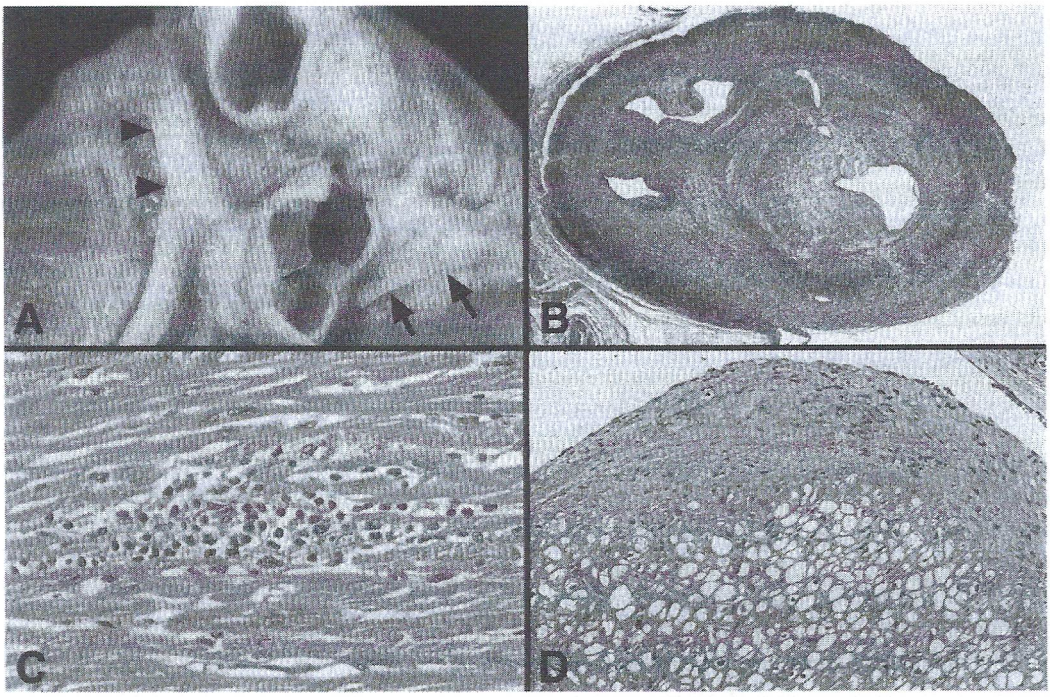

Fig. 14-12. Kawasaki disease. See color plate 32.

Peripartum Myocarditis

Peripartum myocarditis/cardiomyopathy is defined as myocardial dysfunction occurring during the third trimester of pregnancy or in the first 6 months postpartum.[141] Possible causes include viral infection, nutritional deficiencies, small vessel coronary disease, and immunologic interactions with fetal and myometrial antigens. Lymphocytic myocarditis is reported in 5% to 30% of cases. Rizeq and colleagues[141] reported an incidence of myocarditis of 8.8%, with all their cases occurring 1 to 8 weeks after onset of symptoms. All cases showed focal lymphocytic myocarditis according to the Dallas criteria. One of 3 cases had an associated cardiomyopathy. Whether postpartum myocarditis/cardiomyopathy is an entity distinct from idiopathic dilated cardiomyopathy remains unknown.

SARCOIDOSIS

Cardiac involvement in sarcoidosis occurs in 25% to 60% of patients but remains clinically silent in the vast majority of cases; isolated cardiac involvement in the absence of systemic disease is found in a minority of cases. Between 5% and 10% of patients present with cardiac dysfunction that includes: 1) arrhythmias, particularly ventricular types; 2) conduction disturbances, such as high degrees of atrioventricular block and complete bundle

branch block; 3) sudden death; 4) congestive heart failure; 5) papillary muscle dysfunction; 6) acute myocardial infarction-like syndrome; 7) ventricular aneurysm; and 8) recurring pericardial effusions.[142] In a study of cardiac sarcoidosis, left-sided heart failure and syncope were the most common symptoms at hospital presentation. Atrioventricular block and ventricular tachycardia accounted for more than 75% of arrhythmias, but sudden death occurred in 2% of cases (Okura Y, Dec GW, Hare JM, Kodama M, Berry GJ, Tazelaar HD, Bailey KR, Cooper LT, unpublished data). The sensitivity of the right ventricular endomyocardial biopsy ranges from 20% to 50% because of the patchy nature of the granulomatous lesions and preferential distribution in the cephalad portion of the interventricular septum, left ventricular free wall, and papillary muscles. A negative biopsy result does not exclude the diagnosis and some have advocated institution of immunosuppressive therapy even with a negative biopsy result.[143-146] Corticosteroid therapy is effective in many cases, and cardiac transplantation remains a therapeutic option for patients who fail to respond.[147,148] Recurrence in the allograft has been reported but is uncommon; augmented immunosuppressive therapy is efficacious.[149]

Macroscopic and Histopathologic Features

Various histopathologic patterns can be observed on endomyocardial biopsy specimens from patients with cardiac sarcoidosis. These include the classic noncaseating granulomatous inflammation, lymphocytic myocarditis, dilated cardiomyopathy, and in some cases normal myocardium (Fig. 14-13; see color plate 33). Diffuse myocardial involvement progresses to myocyte hypertrophy and interstitial fibrosis resembling dilated cardiomyopathy; in a minority of cases a restrictive profile is observed. The classic granulomatous pattern is characterized by firm white nodules forming discrete masses within the interventricular septum, left ventricular free wall, or papillary muscle (Fig. 14-14 *A*; see color plate 34). These may be confused with metastatic deposits or fibrous tumors. The histopathologic features are similar to extracardiac lesions and consist of noncaseating, well-formed (so-called hard) granulomas composed of epithelioid histiocytes and multinucleated giant cells arranged in round or oval aggregates. These can be found as isolated lesions or may coalesce to form larger zones within the myocardium. Endocardial and pericardial involvement are observed in some cases. Scattered around and within the granulomas are mature lymphocytes, but eosinophils are absent or sparse. Mature collagenous fibrosis is present and surrounds the granulomas (Fig. 14-13 *D*), but active myocyte necrosis is uncommon.

Ultrastructural, Immunohistochemical, and Molecular Findings

Transmission electron microscopy shows epithelioid histiocytes containing numerous cytoplasmic dense bodies and multilobulated nuclei. Multinucleated giant cells display convoluted cytoplasmic membranes with complex interdigitating folds, multiple nuclei, and moderate

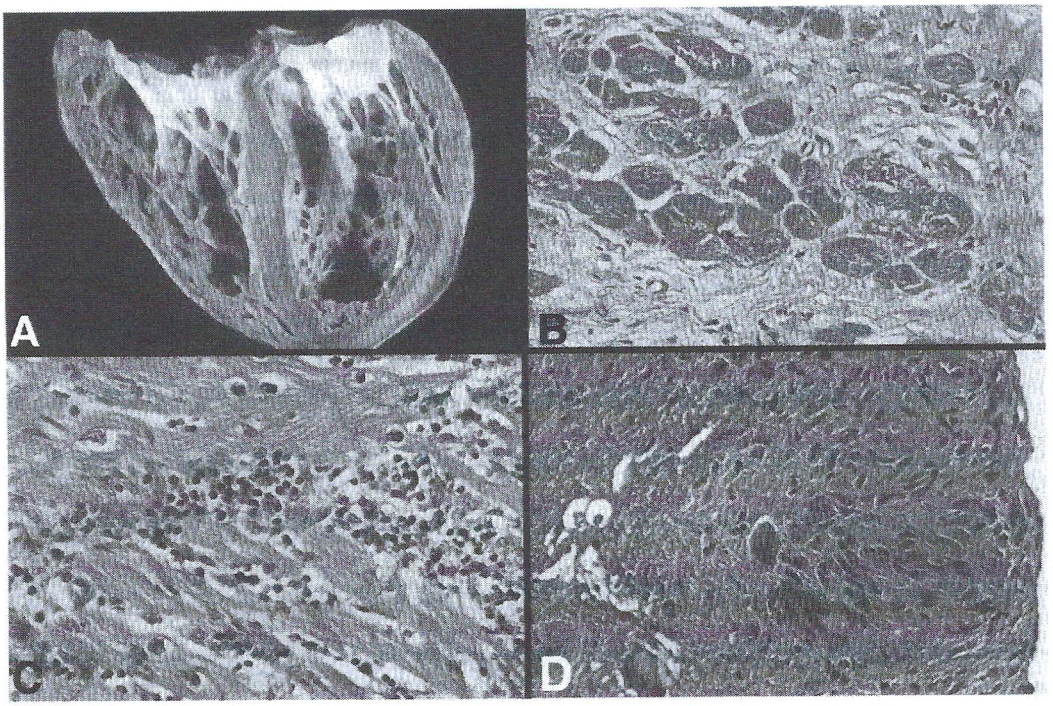

Fig. 14-13. Patterns in cardiac sarcoidosis. See color plate 33.

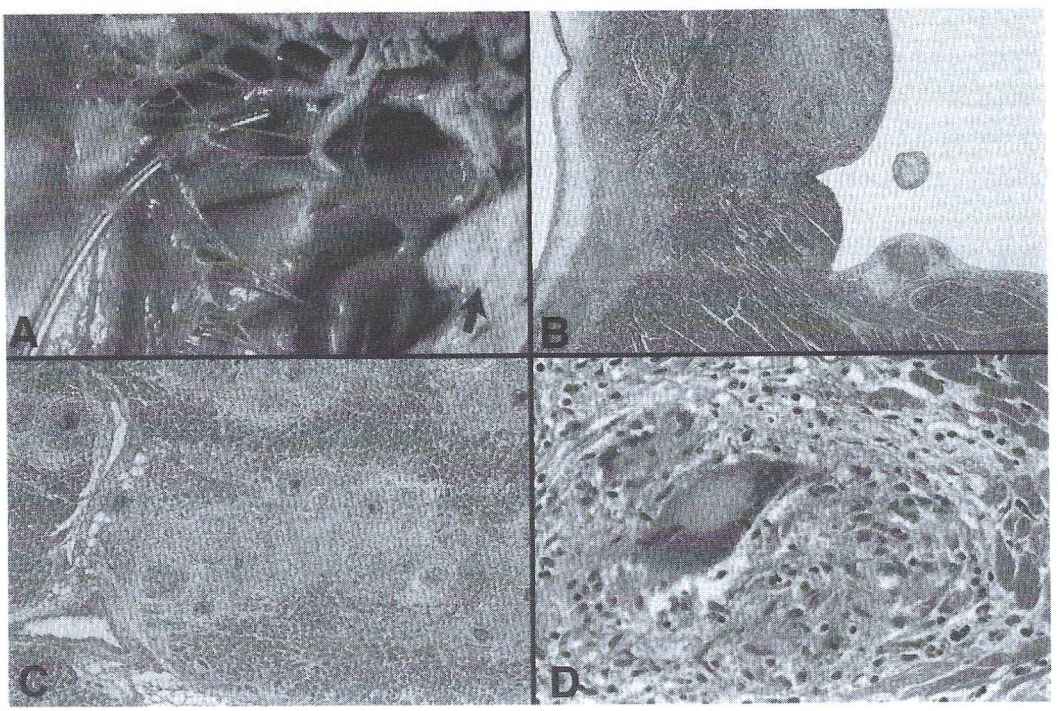

Fig. 14-14. Cardiac sarcoidosis. See color plate 34.

numbers of dense bodies, mitochondria, and endoplasmic reticulin.[142] The epithelioid histiocytes express CD68 and the infiltrating lymphocytes are almost exclusively $CD3^+$ T cells with a predominance of $CD4^+$ cells; B cells are rare.[150] Apoptotic nuclear changes and myocyte necrosis by reactivity for alpha-myosin are less intense than in lymphocytic and giant cell myocarditis (Gopal S, Achalu R, Day JD, Huang M, Narasimhan U, Day MT, Kasper EK, Trichon BH, Chen CL, Cina SJ, Berry GJ, Robertson AL, Hruban RH, unpublished data).

Differential Diagnosis in Cardiac Sarcoidosis

The differential diagnosis includes granulomatous and giant cell lesions of the heart. Granulomatous infections are uncommon in immunocompetent patients, but we routinely perform histochemical stains for fungal and mycobacterial microorganisms. In general, necrotizing granulomas are found in infectious lesions. Giant cell myocarditis is characterized by the presence of giant cells but, by definition, granulomas are absent. In hypersensitivity myocarditis, the histiocytic lesions are poorly formed and are centered on collagen fibers. Eosinophils are numerous, but multinucleated giant cells and fibrosis are not found. The granuloma-like lesions of acute rheumatic fever are poorly formed, and the giant cells are generally smaller and do not resemble Langerhans type. Foreign body-type giant cells surrounding catheter sheath fragments can be found in biopsy specimens of patients undergoing repeated biopsy procedures (Fig. 14-5 *A*). The edge of healing ischemic infarcts can contain giant cells of myogenic origin; lymphocytes and hemosiderin-laden macrophages are seen within the scar tissue. Granulomas are also reported in metabolic disorders such as lipogranulomatosis (Farber disease), oxalosis, and gout; in collagen vascular diseases such as rheumatoid nodules, Wegener granulomatosis, and Churg-Strauss syndrome; and in chronic granulomatous disease of childhood.[151]

IDIOPATHIC GIANT CELL MYOCARDITIS

Idiopathic giant cell myocarditis (IGCM) is a rare but frequently fatal form of myocarditis.[152] It often occurs in previously healthy young adults who present with the abrupt onset of heart failure or arrhythmias or both. Death occurs within weeks or months of onset of symptoms unless aggressive immunosuppression and cardiac transplantation are implemented.[153] Twenty percent of patients have an associated autoimmune disorder such as ulcerative colitis, cryofibrinogenemia, rheumatoid arthritis, myasthenia gravis, hyperthyroidism, or hypothyroidism. Other associations include drug hypersensitivity, Wegener granulomatosis, thymoma, sarcoidosis, and infections.[119,154] Patients receiving combination therapies such as corticosteroids plus cyclosporine or azathioprine survived for an average of 12 months compared with an average of 3 months for patients not receiving any immunosuppressive therapy.[153] In rare instances, after treatment some patients have prolonged survival before requiring cardiac transplantation.[155]

Morphologic Findings in IGCM

At postmortem examination or at transplantation, confluent or multifocal areas of necrosis are easily observed in the heart. The weight of the heart is usually normal or slightly increased. The 4 chambers of the heart are uniformly involved in most cases. In the late or healed stages of the disease, the ventricular wall may appear thin, but this reflects diffuse scarring and not aneurysmal changes because islands of myocytes are found within the collagenous scar tissue (Fig. 14-15 *C* and 15 *D*; see color plate 35). Endocardial and pericardial involvement have been described but the process is primarily centered on the myocardium.

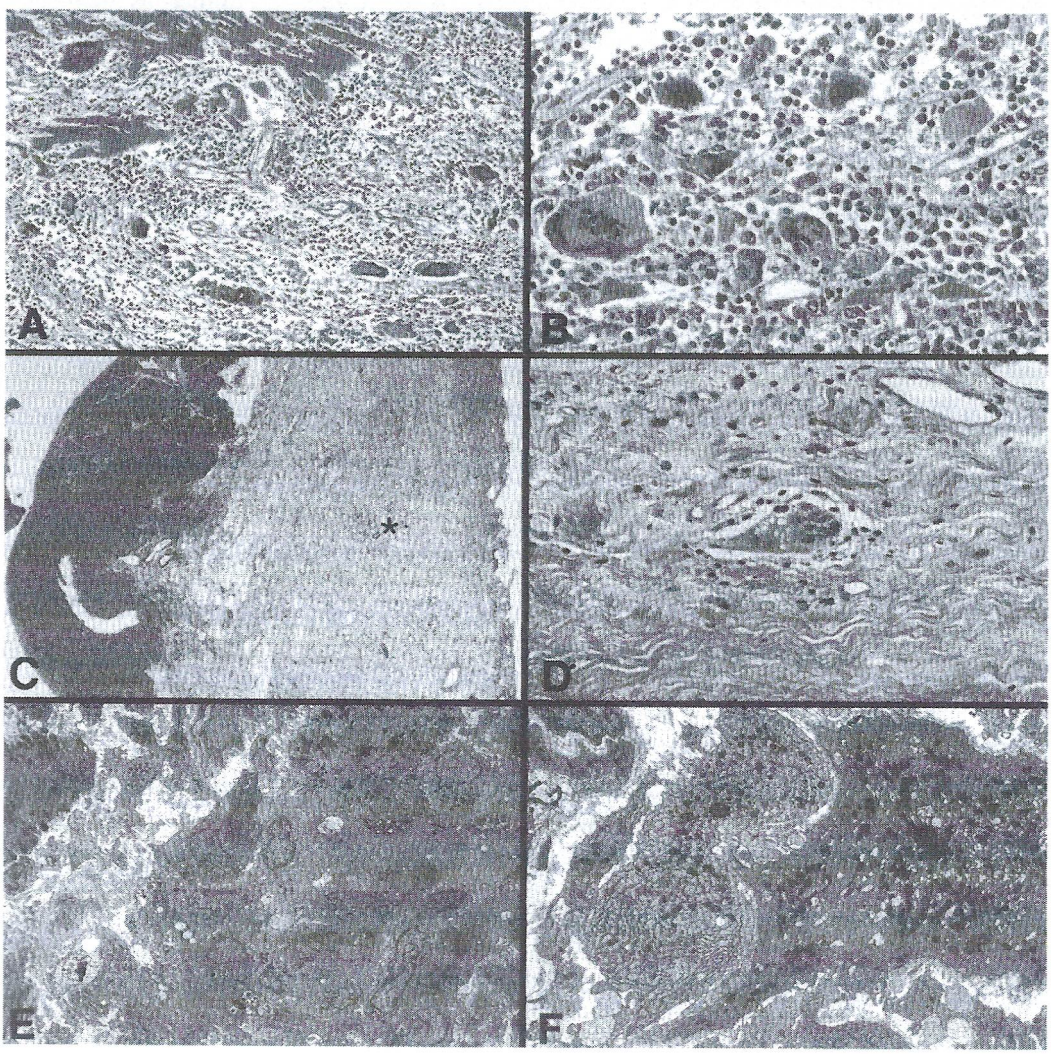

Fig. 14-15. Idiopathic giant cell myocarditis. See color plate 35.

The morphologic findings have been described.[150,153,156,157] These consist of regions of diffuse serpiginous necrosis containing multinucleated giant cells, lymphocytes, histiocytes, and eosinophils in the absence of sarcoidlike granulomas. The giant cells are distributed throughout the inflammatory infiltrates and in apposition to the sarcolemmal membranes of necrotic myocytes. They measure up to 90 x 20 microns and contain up to 20 nuclei in each cell (Fig. 14-15 *A* and 15 *B*; see color plate 35). The necrotic myocardium is replaced by edematous granulation tissue, and the border between viable and necrotic myocardium is not well delineated.

Litovsky and colleagues[150] proposed classification of IGCM into acute, healing, and healed phases. The acute or active phase is described above and is distinguished by the abundant inflammatory response, loose connective tissue stroma, and numerous giant cells of macrophage origin. In the healing or resolving stage, granulation tissue and immature fibrosis replace the myocardium, and the number of giant cells and inflammatory cells is diminished. In the healed or resolved phase, mature fibrosis is noted, with rare or absent giant cells and sparse inflammatory cells. Myocytes are found as islands of single cells or small clusters surrounded by scar tissue (Fig. 14-15 *C* and 15 *D*).

The distinction between active and resolving IGCM on endomyocardial biopsy specimen can be problematic in our experience, because the giant cells are not evenly distributed within the necrotic zones in either stage. Connective tissue stains such as Masson trichrome are helpful in identifying the quality and distribution of collagen. In explanted or postmortem heart specimens, some degree of overlap between the different stages is recognized, suggesting the temporal heterogeneity of this disease. This is an important caveat when examining endomyocardial biopsy specimens for the purpose of grading the response to immunosuppressive therapy.

Ultrastructural, Immunohistochemical, and Molecular Findings in IGCM

Until recently, the origin of the multinucleated giant cells in IGCM has been the subject of controversy. Derivation from myogenic and macrophagic cells was considered.[158,159] At the ultrastructural level, they contain large numbers of cytoplasmic vacuoles but not myofibrils, supporting macrophagic origin. Immunohistochemical studies provide further support because the giant cells stain strongly with the antibody KP1 that is raised to the macrophage-associated antigen CD68 and do not stain with muscle markers, actin, desmin, or myoglobin[150,160,161] (Fig. 14-16 *E* and 16 *F*; see color plate 36).

$CD3^+$ T cells are the predominant inflammatory cell type; B cells are rare or absent (Fig. 14-16 *A*; see color plate 36). In the active phase, CD8 cytotoxic or suppressor cells far outnumber CD4 cells (Fig. 14-16 *C* and 16 *D*; see color plate 36). In the healing stages, occasional actin-positive myogenic-type giant cells are found at the edge of inflamed and viable myocytes, suggesting the sequela of inflammatory injury to myocytes. $CD68^+$ giant

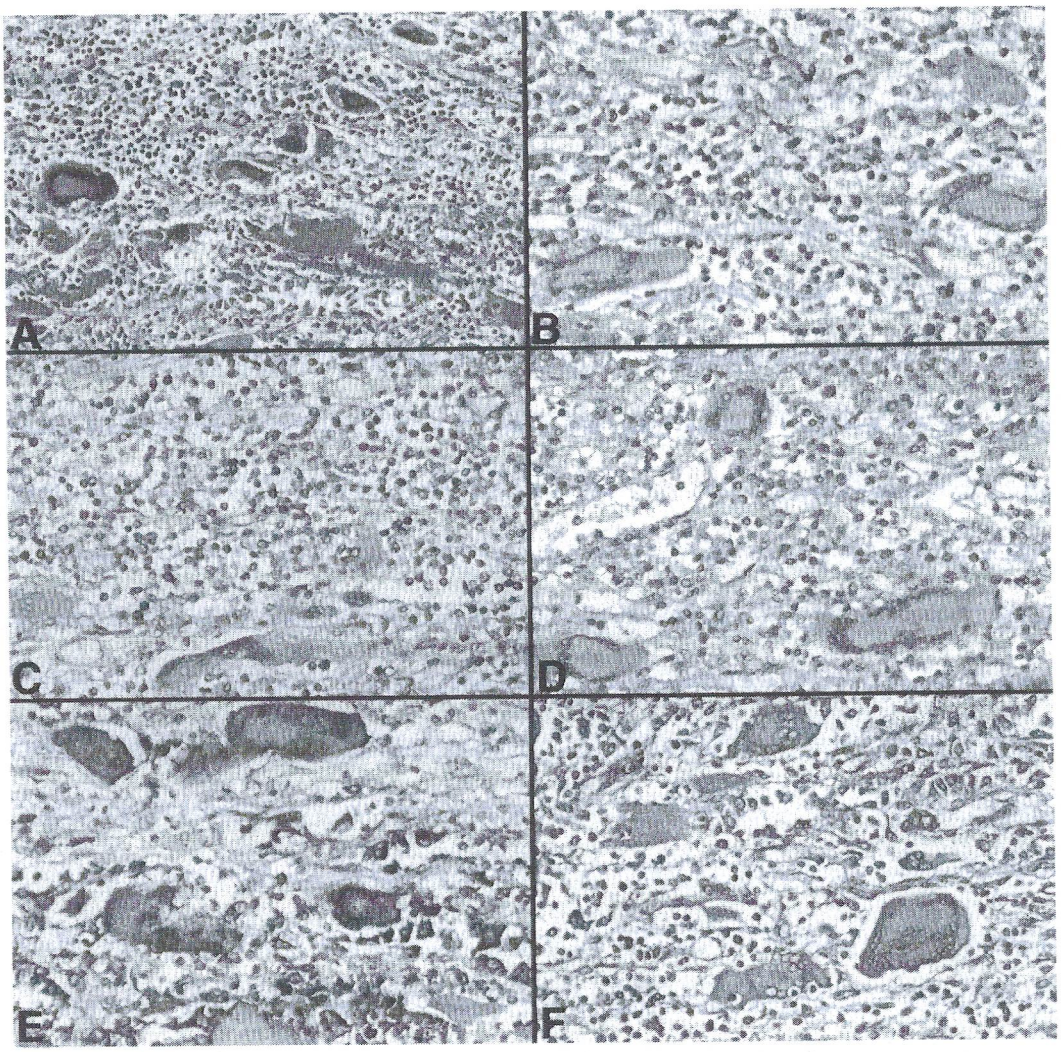

Fig. 14-16. Immunophenotype of idiopathic giant cell myocarditis. See color plate 36.

cells of macrophagic origin are more common than myogenic giant cells, but there are fewer of them than in the active phase. In one case, CD4 cells predominated over CD8 cells.[150] Apoptosis and necrosis are conspicuous by molecular techniques (Gopal S, Achalu R, Day JD, Huang M, Narasimhan U, Day MT, Kasper EK, Trichon BH, Chen CL, Cina SJ, Berry GJ, Robertson AL, Hruban RH, unpublished data).

Differential Diagnosis in IGCM

The diagnostic considerations are similar to those enumerated in the discussion of sarcoidosis. Foreign body granulomas are seen in biopsy samples of patients undergoing repetitive sampling (Fig. 14-5 *A*). The clinical and morphologic distinction between

cardiac sarcoidosis and idiopathic giant cell myocarditis can be problematic. Previously, some have claimed IGCM as a type of cardiac sarcoidosis. In our experience, some degree of overlap can exist, particularly on small endomyocardial biopsy samples. In general, however, close attention to the presence or absence of granulomas is the key discriminating feature. In addition, sarcoidosis has significantly more fibrosis and few or no eosinophils within the inflammatory infiltrate. Myocyte necrosis, particularly the broad zonal distribution, is a feature of IGCM, whereas the mass-like effect is seen in sarcoidosis (Okura Y, Dec GW, Hare JM, Kodama M, Berry GJ, Tazelaar HD, Bailey KR, Cooper LT, unpublished data). Hematolymphoid malignancies can be associated with architectural distortion and myocyte necrosis (Fig. 14-5 *C* and 5 *D*). In some cases, polymorphous cell infiltrates may be present, including eosinophils. Cytologic atypia of the neoplastic cells is the cardinal feature of these lesions. Immunohistochemical and molecular studies are useful, because the majority of these lesions are B cell. Histochemical stains and bacteriologic studies are required to distinguish infectious granulomatous lesions in the heart from IGCM. Eosinophils can be found in hypersensitivity myocarditis and in IGCM. The number of eosinophils is significantly more in hypersensitivity myocarditis, and myocyte necrosis is usually absent.

CONCLUSIONS

The diagnosis and classification of myocarditis are challenging. Use of the endomyocardial biopsy for the evaluation of patients with new-onset congestive heart failure or arrhythmias places the surgical pathologist in a critical role in the diagnosis and management of myocarditis. Direct and open communication with clinicians is essential for accurate clinical-pathologic assessment. Recognition of the architectural alterations in the myocardium and the predominant inflammatory cell type narrow the diagnostic possibilities. Lymphocytic infiltrates are found in lymphocytic myocarditis, some viral types, toxic myocarditis, sarcoidosis, hematopoietic malignancies, myocarditis associated with collagen vascular diseases, and postpartum myocarditis. Infiltrates composed predominantly of neutrophils suggest suppurative myocarditis, pressor effect, ischemic necrosis, and early viral and idiopathic myocarditis (particularly in children). Eosinophils may be a minor component of idiopathic and giant cell myocarditis but are predominant in hypersensitivity and parasitic myocarditis and in hypereosinophilic syndrome. Giant cells are seen in IGCM, sarcoidosis, rheumatic fever, and granulomatous infections and occasionally in idiopathic myocarditis (often of myogenic origin).[12] The treatment and prognosis for many of these types of myocarditis differ significantly, and therefore accurate classification is important.

The relationship of idiopathic myocarditis to the subsequent development of idiopathic dilated cardiomyopathy remains controversial. The application of molecular techniques has broadened our concepts about the pathogenesis of both disease processes. These clues should lead to therapeutic strategies for their treatment and prevention. The surgical pathologist will continue to play a central role in these efforts.

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