Clinical aspects of virus/immune myocarditis*

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Summary. Although a cause-and-effect relationship between viral infection and myocarditis remains inferential, two distinct clinical syndromes can be identified. During the early viral phase, the cardiac manifestations emerge while the symptoms of active viral infection are also present. During the chronic phase, symptoms of the viral infection may be remote or nonexistent, and identification of active myocarditis is contingent upon an aggressive diagnostic approach with endomyocardial biopsy and gallium 67 imaging. The exact incidence of myocarditis in patients with heart failure of unknown cause is unclear due to lack of standardization of histologic parameters. There are no other clinical clues to the presence of myocarditis in those patients presenting with cardiomyopathy or ventricular arrhythmia. For further clarification of the incidence and various presentations of myocarditis a large multi-center trial is necessary.

Although several viruses have been implicated as the cause of myocarditis in man, some of Koch's postulates have yet to be fulfilled because isolation of a virus from the human myocardium has been demonstrated only in rare instances [1–3]. Studies of the clinical presentation of myocarditis are therefore based only on indirect evidence of viral causation. Insights into the pathogenesis of human disease may be obtained, however, by observations in animal models of myocarditis [4]. When Coxsackie virus B3 (CVB3) is inoculated into mice a biphasic disease results [5]. During the acute (virus-mediated) phase, self-limited myocardial viral replication occurs. The virus is cleared by interferon, monocytes, and humoral immune responses within 10 days of the initial infection. Histologically, foci of myocardial necrosis and a sparse inflammatory infiltrate are present. In spite of viral clearance from the myocardium, a lymphocytic inflammatory infiltration develops, marking the beginning of the chronic (immune-mediated) phase. This phase develops as a result of cell-mediated immune responses to a neoantigen that develops during the acute phase [6]. Six months following infection, the animals remain clinically normal but histologically show evidence of fibrosis and myocyte hypertrophy with persistent inflammatory infiltration [7]. By 12–15 months following infection, the inflammatory infiltration subsides; however, there is chamber dilatation with mural thrombus formation and histologic evidence of myocyte hypertrophy and fibrosis similar to that seen in dilated cardiomyopathy [8]. It is at this phase that the animal first develops signs of congestive heart failure. In this model, therefore, the clinical signs of myocarditis manifested as congestive heart failure develop long after the initial viral infection. If this model reflects a similar pathophysiology occurring in man, it is easy to understand the difficulty in demonstrating a direct link between a viral infection and signs of myocarditis, since it is likely that the cardiac manifestations develop long after the initial viral infection which initiated the complex immune responses, culminating in the development of chronic cardiac failure.

Acute viral myocarditis

Numerous viruses and prokaryotes have been postulated as causing myocarditis in man. Several of the more prominent of these are listed in Table 1 [9–32]. Absolute proof of the

| Table 1. Causative agents in myocarditis |
| --- |
| **Viruses** | **Prokaryotes** |
| Arbovirus | Chlamydia |
| Arenavirus | Mycoplasma |
| Junin virus | Rickettsia |
| Coronavirus | |
| Enterovirus | |
| Coxsackie a and b | |
| Echo | |
| Polio | |
| Herpes virus | |
| Cytomegalovirus | |
| Ebstein-Barr virus | |
| Herpes simplex | |
| Varicella/Zoster | |
| Influenza | |
| Mumps | |
| Rubella | |
| Rubeola | |

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The diagnosis of viral myocarditis is contingent upon the identification of replicating virus in the myocardium. This has only been possible in isolated patients with overwhelming viral infection of the myocardium [1–3]. Moderate associations of viral infection with myocarditis may be documented by rising viral antibody titers at the time of clinical presentation of an acute cardiac syndrome [33]. Using this criterion, errors can be made when a patient with latent nonviral heart disease develops clinical manifestations only during increased metabolic demands associated with an acute febrile syndrome of any cause.

Several reports have documented electrocardiographic ST segment, T wave, and QT interval changes following screening of large populations during viral epidemics [34–37]. This implies that acute viral myocarditis is a very common disease and the vast majority of patients remain totally asymptomatic. Initial clinical clues, therefore, to the presence of acute viral myocarditis relate to the identification of the noncardiac manifestations common to the viral syndromes: fever, myalgias, pharyngitis, lymphadenopathy, diarrhea, hepatitis, nephritis, orchitis, and encephalitis. Since entervoiral and Mycoplasma pneumoniae infections may result in myocarditis, a febrile syndrome with associated myalgias should alert the clinician to possible myocardial involvement [30]. Other nonspecific manifestations of the viral infections include gastrointestinal complaints, hepatitis, lymphadenopathy, orchitis, nephritis, and encephalitis [12, 19, 38–40]. Nonspecific laboratory abnormalities include elevation of the erythrocyte sedimentation rate, transaminases, and creatinine phosphokinase, and atypical lymphocytes in the peripheral blood [12].

The most common cardiac presentation during the acute phase of viral myocarditis, summarized in Table 2, is pericardial pain [41, 42]. All enteroviruses causing myocarditis result in myopericarditis, and suspicion of myocardial involvement only develops when chest pain leads to noninvasive cardiac studies, such as echocardiography or radio-nuclide ventriculography, which identify myocardial dysfunction. When careful echocardiographic studies are performed in patients with suspected viral myocarditis, findings compatible with concentric left ventricular hypertrophy, but thought to be secondary to myocardial edema, are identified [43, 44]. Furthermore, segmental wall motion abnormalities or decreased ejection fraction on radionuclide ventriculography may also be seen [45]. When the evaluation includes invasive cardiac studies, a restrictive hemodynamic pattern is identified [46]. If the patient has cardiac symptoms shortly after the onset of the viral syndrome, congestive heart failure, ischemic cardiac pain, and syncope are reported [42, 47]. Although the incidence is quite low, evidence of left ventricular dysfunction, ranging from mild abnormalities to cardiogenic shock, may be present at the time of presentation. Recently, several investigators have reported ischemic cardiac pain and apparent myocardial infarction as a manifestation of acute viral myocarditis [48–53]. Akinetic segments have been identified on echocardiography [53]. Although coronary arteritis has been postulated as an etiology of this ischemic syndrome [54], transmural myocardial necrosis with resultant aneurysm formation has been shown in the murine Coxsackie virus B4 model, suggesting that a vasculopathy need not be present [55]. We have identified myocarditis by biopsy obtained from segments remote from the myocardial infarction [56].

| Table 2. Cardiac manifestations of acute viral myocarditis |
|----------------------------------------------------------|
| Electrocardiographic ST-T changes or prolonged QT interval |
| Pericardial pain/effusion |
| Congestive heart failure |
| Syncope/sudden death due to: Ventricular arrhythmia |
| Complete heart block |
| Left ventricular hypertrophy |
| Restriction |
| Myocardial infarction |

Syncope and complete AV block have been reported in one-third of patients presenting with acute viral myocarditis [47]. Electrocardiography has also documented ventricular arrhythmia as the etiology of the syncopal attack and may explain the 17% incidence of myocarditis seen at autopsy in children who die suddenly [57]. Although the cardiac symptoms that develop during acute myocarditis may be severe, the vast majority of patients spontaneously recover or only present to the physician during the chronic phase of the illness.

Chronic myocarditis

Before the development of safe techniques of endomyocardial biopsy, the identification of myocarditis during the chronic phase was not possible unless a clear-cut progression from an acute viral myocarditis to a chronic dilated cardiomyopathy could be established. In patients presenting with ventricular arrhythmia or left ventricular dysfunction of recent onset, no clinical clues can aid in the diagnosis of myocarditis. Since the introduction of routine use of endomyocardial biopsy, an accurate diagnosis of chronic myocarditis has been possible histologically [58]. Following the report of Mason and others at Stanford, several centers have reported their incidence of biopsy-proven myocarditis [59]. The incidence of biopsy-proven myocarditis shown in Table 3 varies from 1% to 63% [60–72]. In updating our series of patients referred to our center with congestive heart failure of unknown cause, we verified a diagnosis of myocarditis in...
Table 4. Clinical and hemodynamic comparison of patients with and without biopsy-proven myocarditis

|          | Bx+  | Bx−  |
|----------|------|------|
| n        | 14   | 109  |
| Age [years] | 38.9 ± 16.8* | 46.4 ± 14.5 |
| Sex (M/F) | 11/3 | 74/35 |
| CI III-IV CHF | 11 (78%) | 81 (74%) |
| CI [l/min/m²] | 2.3 ± 0.7 | 2.6 ± 0.7 |
| PAW [mmHg] | 17.4 ± 8.8 | 19.1 ± 10.0 |
| PAsys [mmHg] | 37.1 ± 15.8 | 42.4 ± 15.4 |
| LVEDD [cm] | 6.2 ± 0.8* | 6.9 ± 1.0 |
| EF [%]     | 17.5 ± 8.0 | 17.8 ± 8.4 |

*Bx+ Biopsy-proven myocarditis, CI III-IV CHF symptomatic heart failure, NYHA class III or IV, CI cardiac index, PAW, mean pulmonary arterial wedge pressure, PAsys, pulmonary arterial systolic pressure, LVEDD left ventricular end-diastolic dimension, EF ejection fraction

* mean ± SD
* P < 0.01

14 of 123 (11%). Clinical and hemodynamic parameters comparing patients with and without biopsy-proven myocarditis are presented in Table 4. The only finding of interest is that the left ventricular end-diastolic dimension on echocardiography was smaller in those patients with biopsy-proven myocarditis. Furthermore, all patients with biopsy-proven myocarditis presented to our center within 12 months of onset of symptoms, suggesting that the smaller end-diastolic diameter may be related to chronicity of disease.

Difficulty in ascertaining the true biopsy incidence of myocarditis from Table 3 is a result of the variability in histologic interpretation of the biopsies. It is likely that those centers with the highest incidence of myocarditis are most liberal in the histologic criteria for the condition. Once histologic criteria are standardized, the technique of endomyocardial biopsy, the standard against which all techniques for identification of active myocarditis are compared, will become highly specific; it may, however, still lack sensitivity due to sampling error, since myocarditis can be focal in distribution. In autopsy studies of patients dying of varicella pneumonia, myocarditis was thought to be uncommon when sought by routine sectioning; however, when careful sequential sectioning of the myocardium was done, the incidence of myocarditis rose strikingly [22]. In preliminary reports, the discrepancy between right and left ventricular histologic incidence of inflammatory infiltration was shown to be significant [73, 74].

The recent observation that gallium 67, an inflammation-avid radioisotope, can identify myocarditis may potentially obviate this underestimation of the incidence of myocarditis by endomyocardial biopsy. Following our initial description of three patients with gallium 67 myocardial uptake in patients with dilated cardiomyopathy of recent onset [75], we performed gallium 67 scans on a larger series of patients with dilated cardiomyopathy and demonstrated myocardial uptake in 19 [76]. When 15 of these patients were treated with immunosuppressive agents, six showed a dramatic clinical and hemodynamic response to therapy, suggesting that in these patients myocarditis was in fact the mechanism of gallium uptake. When parallel endomyocardial biopsies and gallium 67 scans were performed on a series of patients with dilated cardiomyopathy [70], gallium was avid for the myocardium in five of six patients with biopsy-proven myocarditis (Fig. 1). In the isolated patient in whom the gallium 67 scan was negative, dense uptake of the isotope was found in the posterior mediastinal lymph nodes, decreasing the possibility of visual identification of uptake over the myocardium. The overall incidence of myocarditis on biopsy in the latter series was 7%. If the gallium scan was positive, the incidence rose dramatically to 36%. When the gallium scan was negative, only 1 of 57 patients (2%) had myocarditis on biopsy.

We have also studied subgroups of patients with dilated cardiomyopathy and have reported the presence of a familial predisposition to myocarditis with documentation of biopsy-proven myocarditis in many members of two separate families [77]. Further supportive evidence was provided when a suppressor cell defect was identified in the proband of the first family. Another subset of patients with congestive heart failure of recent onset with a high incidence of histologic myocarditis is peripartal heart disease. Melvin
and co-workers first described myocarditis in three patients with peripartal heart disease and suggested immunosuppression would be a rational therapeutic modality [78]. In our series of 14 patients with peripartal heart disease, histologic myocarditis was identified in five (35%), which is a threefold higher incidence of myocarditis than in our general cardiomyopathic population [79]. In patients with life-threatening ventricular arrhythmias with otherwise normal myocardial function, the incidence of active myocarditis on biopsy has been reported as 50% [80]. Clinical, hemodynamic or electrophysiologic parameters could not differentiate those with active myocarditis from those with other myocardial histology.

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Discussion

**Discussants:** Fowles, O'Connell,Billingham, Maisch, Edwards, Ruzytillo

The question of the applicability of isotope analogues in detecting allograft rejection was raised. The 72-h delay with gallium imaging was considered to be undesirable in this situation, and a shorter imaging agent is desirable, particularly for monitoring therapy in myocarditis.

Reference to studies on indium in experimental animals was made, and good correlation between these studies and the morphologic changes has been observed. A newer technique assessing changes echocardiographically has been devised with a 100% correlation between echocardiographic changes and morphology on tissue obtained by biopsy.

It was, however, emphasized that examination of biopsies is reliable for acute rejection myocarditis and adriomy- cin toxicity, particularly when five to ten samples from each ventricle have been obtained. Agreement between the presenter and another discussant on the reduction of IgM antibodies in the late phase of myocarditis was also reached.

It was finally agreed that myocarditis may mimic myocardial infarction, causing transmural myocyte necrosis. Biopsy and coronary arteriograms which are normal in these cases should assist in making an accurate diagnosis.