Does Endomyocardial Biopsy Aid in the Diagnosis of Active Rheumatic Carditis?

Jagat Narula, MD; Prem Chopra, MD; Kewal K. Talwar, MD; K. Srinath Reddy, MD; Ramachandran S. Vasan, MD; Rajendra Tandon, MD; Madan L. Bhatia, MD; James F. Southern, MD, PhD

Background. Carditis is the only component of rheumatic fever that leads to permanent disability. The diagnosis of carditis is presently made by using composite clinical criteria based on the revised Jones' criteria. Since myocardial involvement is an important component of rheumatic carditis, right ventricular endomyocardial biopsies were performed in 54 patients with clinical acute rheumatic fever and quiescent rheumatic heart disease to evaluate the role of biopsy for the diagnosis of rheumatic carditis.

Methods and Results. In 11 of the 54 patients, clinical consensus was certain about rheumatic fever and carditis based on the revised Jones' criteria (group 1). Histomorphological abnormalities in these patients were scarce. The diagnostic features of rheumatic myocarditis including Aschoff nodules or histiocytic aggregates were encountered in 3 patients (27%). Lymphocytic infiltration was sparse. A majority of patients demonstrated myocyte degeneration, interstitial degeneration, or occasional interstitial mononuclear cell infiltration, but since these histopathological lesions may occur in other conditions also, they were considered nondiagnostic. In 33 of the 54 patients with preexisting rheumatic heart disease, the diagnosis of carditis was suspected based on varied clinical presentations. Since previous cardiac findings were not available in these patients, the clinical diagnosis of carditis could not be made without equivocation (group 2). Twenty-three patients presented with unexplained acute onset of congestive heart failure and evidence of recent streptococcal infection (group 2A). While 13 of them had one or more other major manifestations, 10 patients had only minor manifestations. Mimetic carditis was suspected in the remaining 10 of 33 patients based on carditis having occurred in previous episodes of rheumatic fever (group 2B). The endomyocardial biopsy provided confirmatory evidence of rheumatic myocarditis in 9 patients of group 2A but in none of the 10 patients with suspected mimetic carditis. Nondiagnostic myocyte or interstitial alterations were frequently observed in group 2. Ten of the 54 patients had no clinical evidence of active carditis (group 3). No histological alterations diagnostic of rheumatic carditis were noted in these patients. Twenty-two follow-up biopsies were performed in the first 10 consecutive patients. Diagnostic histiocytic aggregates or Aschoff nodules were observed in initial biopsies in 4 of 10 patients, and nonspecific myocyte or interstitial alterations were observed in 9. All patients with diagnostic changes in initial biopsy demonstrated fibrohistiocytic nodules in 6-12-week biopsy samples. Nondiagnostic alterations, similar to those seen in acute cases, were present in 5 of 8 patients at 6 weeks, 5 of 8 patients at 12 weeks, and 3 of the 6 patients at 24 weeks despite the presumed adequate immunosuppressive therapy. No complications related to biopsy were encountered.

Conclusions. The present study highlights the low frequency of diagnostic features in the biopsy specimens of patients with definite clinical rheumatic carditis. Although such alterations are not observed in patients with chronic rheumatic heart disease, endomyocardial biopsy does not appear to provide additional diagnostic information where clinical consensus is certain about diagnosis of rheumatic carditis. Our study, however, substantiates the concept of carditis underlying unexplained congestive heart failure of acute onset in patients with preexisting rheumatic heart disease and elevated antistreptolysin-O titers. (Circulation. 1993;88[part 1]:2198-2205.)

KEY WORDS - rheumatic heart disease - rheumatic fever - pharyngitis

Rheumatic fever continues to be a major cardiovascular health problem in the developing countries and has recently shown resurgence in North America. Carditis is the only component of rheumatic fever that leads to permanent disability, and accurate recognition of carditis has significant therapeutic and prognostic implications. The diagnosis of rheumatic carditis is currently made by using a composite clinical standard based on the Jones' criteria (Table 1). Nevertheless, there are clinical situations where the Jones' criteria are not satisfied, and clinical consensus is equivocal. Myocardial involvement is an important component of the spectrum of rheumatic fever. There are several anecdotal reports of endomyocardial biopsies in patients with rheumatic carditis.
Table 1. The Revised Jones' Criteria*

<table>
<thead>
<tr>
<th>Major Criteria</th>
<th>Minor Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carditis</td>
<td>Fever</td>
</tr>
<tr>
<td>Polyarthritis</td>
<td>Arthralgia</td>
</tr>
<tr>
<td>Chorea</td>
<td>History of previous definite RF/RHD</td>
</tr>
<tr>
<td>Subcutaneous nodules</td>
<td>Increased ESR, presence of CRP or leukocytosis</td>
</tr>
<tr>
<td>Erythema marginatum</td>
<td>Prolonged PR interval</td>
</tr>
</tbody>
</table>

Plus supporting evidence of preceding streptococcal infection: history of recent scarlet fever, positive sore throat culture for group A Streptococcus; increased antistreptolysin-O, or other streptococcal antibody titers.

Clinical Diagnosis of Carditis by the Revised Jones' Criteria

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Patients With No Previous History of RF/RHD</th>
<th>Patients With Previous RF/RHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valvulitis†</td>
<td>A significant apical systolic murmur of mitral regurgitation, apical mid-diastolic (Carey-Coombes) murmur, basal early diastolic murmur</td>
<td>A definite change in the character of any preexisting murmur or appearance of a new significant murmur</td>
</tr>
<tr>
<td>Cardiomegaly</td>
<td>Unequivocal cardiac enlargement</td>
<td>An obvious increase in cardiac size</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>Friction rub, pericardial effusion, ECG or echocardiographic evidence</td>
<td>Friction rub, pericardial effusion, ECG or echocardiographic evidence</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>In a child or young adult in absence of other discernible causes</td>
<td>?</td>
</tr>
</tbody>
</table>

RF indicates rheumatic fever; RHD, rheumatic heart disease; ESR, erythrocyte sedimentation rate; and CRP, C-reactive protein.
*Diagnosis of rheumatic fever by Jones' criteria = 1 major + 2 minor manifestations + essential evidence of recent streptococcal infection or 2 major manifestations + essential evidence of recent streptococcal infection.10,11
†Recent AHA recommendations do not insist on major manifestations in patients with preexisting RHD who present with minor manifestations and evidence of preceding streptococcal infection.31
‡Characteristics of the murmurs indicating carditis have been described by the AHA.11

...but the role of endomyocardial biopsy for evaluation of rheumatic carditis has not been assessed. The present study prospectively examines the histological features seen in endomyocardial biopsies of early rheumatic carditis to evaluate the role of biopsy for diagnosis of carditis, especially where clinical consensus fails to clearly indicate the presence or absence of carditis.

Methods

Patients

Fifty-four patients with either acute rheumatic fever or clinically inactive rheumatic heart disease form the basis of this study (Table 2). The age of the patients ranged from 7.5 to 47 years, and the male-to-female ratio was 38:16. These patients were grouped into the following categories.

Group 1: Patients with 'certain' carditis. In group 1 (n=11), the diagnosis of acute rheumatic fever as well as rheumatic carditis, based on the revised Jones' criteria,10,11 was considered "certain" by three cardiologists. Carditis was diagnosed in all patients as one of the major manifestations. In addition, all patients had minor manifestations and elevated antistreptolysin-O titers. Seven of the 11 patients had probable first attack of rheumatic fever (group 1A).10,11 Diagnosis of carditis was based on the presence of mitral incompetence with or without aortic involvement in all cases. In addition to valvulitis, pericarditis was observed in 1 and congestive failure in 3 cases. Six patients had at least one more major manifestation of rheumatic fever.

The remaining 4 of the 11 patients of group 1, had documented rheumatic heart disease and presented to the hospital with definite recurrence of rheumatic activity.10,11 Presence of pericarditis in all patients in the setting of rheumatic fever provided the evidence of rheumatic carditis.10,11 All 4 patients had recent occurrence of congestive heart failure. Since precise information regarding previous cardiac status was not available in this group, a definite change in previous murmurs or cardiac size could not be documented. Two of the 4 patients had at least one other major manifestation.

Group 2: Patients with 'suspected' carditis. All patients of this group (n=33) had preexisting rheumatic heart disease. Carditis in the current admission was "suspected" due to varied clinical presentations but not deemed "certain" in the consensus judgment of the three cardiologists. Previous cardiac findings were not available, and a documentation of interval change in previous murmurs or cardiac size was not possible. None of the patients had evidence of pericarditis.

In 23 of the 33 patients (group 2A), the diagnosis of acute rheumatic carditis was clinically suspected due to recent unexplained occurrence or worsening of congestive heart failure. Of the 23 patients, 13 demonstrated at least one other major manifestation of rheumatic fever confirming the diagnosis of rheumatic activity by the revised Jones' criteria (subgroup 2A1). The remaining 10 of the 23 patients with unexplained congestive heart failure did not have any other major manifestation (subgroup 2A2). One of the 10 patients developed subcutaneous nodules, and another patient suffered from chorea during the hospital stay. All 33 cases had minor manifestations and an evidence of recent streptococcal infection.

In group 2B, the remaining 10 of the 33 patients of group 2, the diagnosis of acute rheumatic fever was
considered unequivocal on the basis of revised Jones’
criteria.10,11 The diagnosis of carditis could not be
ascertained due to lack of availability of previous car-
diac findings and absence of pericarditis. None of
the patients had congestive heart failure. Carditis in
the present episode was suspected on the basis of carditis
having occurred in previous episode(s) of rheumatic
fever (mimetic carditis10,21), even if no other clinical
feature suggestive of carditis was observed.

Group 3: Patients with ‘no evidence’ of carditis. Group
3A patients (n=2) had rheumatic polyarthritis but no
evidence of carditis. Group 3B patients (n=8) with
quiescent rheumatic heart disease underwent biopsy
during preoperative cardiac catheterization. There was
no evidence of recent streptococcal pharyngitis or rheu-
matic activity in any of the patients.

Endomyocardial Biopsies

Seventy-six right ventricular endomyocardial biopsies
were performed in 54 patients after informed consent
was obtained from patients or parents prior to each
biopsy. All patients tolerated the procedure well. No
complications related to biopsy occurred in any of
the patients. After the initial biopsy, all patients of groups 1
and 2A were treated with tapering doses of prednisone
for 12 weeks.22 Patients with congestive heart failure
also received digoxin and diuretics. Patients of groups
2B and 3A were treated with aspirin.22 Penicillin pro-
phylaxis was started or regularized in all patients at
the admission. Twenty-two follow-up biopsies were per-
formed at 6, 12, and 24 weeks in the first 10 consecutive
patients.

Percutaneous right ventricular endomyocardial biopsy
was performed using a Cordis bioptome passed through
the right femoral vein. Three to five pieces of endomyo-
cardial tissue measuring 1 to 2 mm in diameter were
obtained for paraffin embedding at each biopsy from the
right ventricular septum. Biopsy fragments were fixed by
immersion in 10% buffered formalin and processed
conventionally. Paraffin sections were stained with hema-
toxylin-eosin and Masson’s trichrome and analyzed for
the presence of Aschoff nodules and histiocytic aggre-
gates,14,15 for borderline myocarditis and myocarditis as
per recommendations of Dallas criteria,23 as well as for
myocytolysis, interstitial alterations, myocyte hypertro-
phy, and fibrosis. In 30 instances, including most of the
follow-up biopsies, one to two additional biopsy frag-
ments were obtained and snap-frozen in liquid nitrogen
isopentane bath for frozen section hematoxylin-eosin
examination and subsequent immunohistochemical
studies (data not presented).

The biopsy specimens obtained and processed at All
India Institute of Medical Sciences were interpreted in the
Department of Pathology at Massachusetts General
Hospital by the pathologist (J.F.S.) who had no clinical
information about the patients.

Results

Histological findings of initial biopsies are listed in
Table 3, and examples are shown in the Figure. Histological
abnormalities were scarce in biopsies from patients
with definite clinical acute rheumatic carditis (group 1).
The cardiac myocytes were focally degenerated and occa-
sionally necrotic or rarely myofibrillolytic. The degenera-
tive foci often lacked cellular infiltrates. Only one biopsy
fragment demonstrated a probable myocarditic focus
based on the Dallas criteria.23 Rare nuclei appeared
hypertrophic. Fibrin and other granular eosinophilic
material deposition (interstitial degeneration) with spreading
apart of histological components occurred focally about
blood vessels and was interpreted as interstitial edema.
Occasionally mononuclear cells, predominantly histio-
cytes, and rarely lymphocytes were present interstitially
and perivascularly. Perivascular histiocytic aggregates
resembling Aschoff nodules were identified in three biopsy
specimens. In one patient, an aggregate appeared to be in

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TABLE 2. Major Manifestations of Jones’ Criteria in Patients Included in Present Study

<table>
<thead>
<tr>
<th>Feature</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preexisting rheumatic heart disease or previous history of rheumatic fever*</td>
<td>1A</td>
</tr>
<tr>
<td>New murmur in primary episode</td>
<td>7/7</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>1/7</td>
</tr>
<tr>
<td>Recent-onset congestive heart failure</td>
<td>3/7</td>
</tr>
<tr>
<td>Definite change in previous murmurs or cardiac size</td>
<td>NA</td>
</tr>
<tr>
<td>Carditis by revised Jones’ criteria</td>
<td>7/7</td>
</tr>
<tr>
<td>Additional arthritis and subcutaneous nodules</td>
<td>1/7</td>
</tr>
<tr>
<td>Additional arthritis</td>
<td>5/7</td>
</tr>
<tr>
<td>Additional subcutaneous nodules</td>
<td>0/7</td>
</tr>
<tr>
<td>Rheumatic fever by revised Jones’ criteria</td>
<td>7/7</td>
</tr>
</tbody>
</table>

*Definite previous history of rheumatic fever or heart disease was considered a major manifestation in the original Jones’ criteria.22
†Diagnosis of carditis cannot be made since previous cardiac findings were not known.
‡One patient developed chorea during hospital stay.
§One patient developed chorea and another developed subcutaneous nodules in the hospital, confirming the diagnosis of rheumatic
fever.

All patients had requisite number of minor criteria. Elevated ASLO titers were present in all but one patient. This patient had high
ADNaseB titer. NA indicates not applicable.
TABLE 3. Histological Findings in Patients With Rheumatic Fever and Rheumatic Heart Disease

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Patients</th>
<th>HA/AN</th>
<th>Cells</th>
<th>Myocyte Degeneration</th>
<th>Interstitial Degeneration</th>
<th>Focal Fibrosis</th>
<th>Interstitial Edema</th>
<th>Interstitial Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>7</td>
<td>3</td>
<td>5</td>
<td>2</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1B</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>11</td>
<td>3</td>
<td>5</td>
<td>3</td>
<td>6</td>
<td>5</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>2A1</td>
<td>13</td>
<td>5</td>
<td>5</td>
<td>7</td>
<td>6</td>
<td>6</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>2A2</td>
<td>10</td>
<td>4</td>
<td>5</td>
<td>1</td>
<td>6</td>
<td>6</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>2A</td>
<td>23</td>
<td>9</td>
<td>10</td>
<td>8</td>
<td>12</td>
<td>12</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>2B</td>
<td>10</td>
<td>0</td>
<td>5</td>
<td>1</td>
<td>3</td>
<td>7</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>33</td>
<td>9</td>
<td>15</td>
<td>9</td>
<td>15</td>
<td>19</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>3A</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3B</td>
<td>8</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

HA indicates histiocytic aggregates and AN, Aschoff nodules.

a healing stage. The histiocytic aggregates or Aschoff nodules were interpreted as diagnostic for rheumatic carditis. Presence of myocyte and/or interstitial degenerative lesions with or without interstitial mononuclear infiltration were considered nondiagnostic alterations. Two patients (both of group 1B) did not demonstrate any diagnostic or nondiagnostic alterations suggestive of active carditis in their biopsy fragments. The histiocytic aggregates, myocyte degeneration, and interstitial degeneration were not noted in patients with chronic inactive rheumatic heart disease (group 3B) or in patients with noncarditic presentation of rheumatic fever (group 3A). Three patients of group 3, however, had rare interstitial mononuclear cells in the biopsy specimens.

Aschoff nodules or histiocytic aggregates were present in biopsies of 9 of 23 patients (39%) presenting with unexplained congestive heart failure (group 2A); two patients demonstrated fibrohistiocytic aggregates suggestive of a healing stage of the Aschoff nodule. The Aschoff nodules or histiocytic aggregates were not found in any patient suspected to have mimetic carditis (group 2B). DEFINITIVE diagnosis of rheumatic carditis, therefore, could be made in nine patients of group 2A but none of the patients in group 2B. Interstitial granular debris and occasional interstitial or periadventitial mononuclear cells were frequent in group 2 patients. Myocyte degenerative changes were commonly observed only in group 2A. One patient in group 2A and two patients in group 2B had no diagnostic or nondiagnostic features of myocardial injury in their biopsy specimens.

Follow-up biopsies were performed in the first 10 consecutive patients after initiation of immunosuppressive therapy (Table 4).22 The antistreptolysin-O titers and acute phase reactants normalized before cessation of immunosuppression at 12 weeks. Twenty-two biopsies were obtained at 6, 12, and 24 weeks after the initial presentation in 8, 8, and 6 patients, respectively. Four patients had diagnostic Aschoff nodules or histiocytic aggregates in their initial biopsy. Nine of 10 patients had one or more abnormalities—either myocyte or interstitial alterations. All patients with Aschoff nodules or histiocytic aggregates in their initial biopsy demonstrated fibrohistiocytic nodules at 6 or 12 weeks. One patient with no diagnostic lesion in initial biopsy also demonstrated a fibrohistiocytic lesion at 12 and 24 weeks after the initial biopsy. Interstitial alterations or myocyte degeneration were noted in 5 of 8 cases at 6, 5 of 8 cases at 12, and 3 of 6 cases at 24 weeks.

Discussion

Biopsy Findings in Acute Rheumatic Carditis

Numerous autopsy reports have confirmed that the Aschoff nodule is the hallmark of active rheumatic carditis. In the present study, Aschoff nodules were infrequently seen in the biopsy specimens. This may reflect the actual sparse occurrence of these lesions or the inability of the biopsy to detect focal lesions. There appears to be a greater tendency for these lesions to be observed in more severe disease. All of our patients demonstrating Aschoff nodules or histiocytic aggregates had overt clinical congestive heart failure. Four other case reports of endomyocardial biopsy are available from patients of rheumatic fever; all four biopsies contained Aschoff bodies and all four cases had congestive heart failure.16-19 This is also consistent with higher prevalence of Aschoff nodules in autopsy material that represents carditis severe enough to account for mortality. The paucity of classic Aschoff nodules in acute rheumatic fever also suggests that the Aschoff nodule may be a relatively mature lesion occurring later in the course of rheumatic carditis. However, sequential biopsies in the present study do not support this explanation.
Aschoff nodule with multinucleated giant cells and fibrin deposition (a); such characteristic lesions are infrequently observed and are confined to patients with congestive heart failure. Interstitial histiocytic aggregate (b) and interstitial histiocytic aggregates with fibrin degeneration (c); more common than Aschoff nodules, these lesions lack characteristic Anitschkow or Aschoff cells and may represent an immature Aschoff body. Fibrohistiocytic nodules (d and e) probably represent healing foci with gradually increasing fibrosis and scarce cellular component; these lesions were common in follow-up biopsies from patients with Aschoff nodules, and the ultimate fate of these lesions probably is nondescript perivascular fibrosis. Three cases demonstrated fibrohistiocytic nodules in their initial biopsy suggesting a subacute stage of the disease. Occasional interstitial mononuclear cell infiltration with interstitial degeneration (f, thin arrows) and myocyte degeneration were the commonest histopathological alterations. Only one case demonstrated a definite myocarditic focus (myocyte necrosis surrounded by mononuclear cells; f, thick arrow). All micrographs hematoxylin-eosin ×100.
TABLE 4. Characteristics of Follow-up Biopsies in Patients With Rheumatic Carditis

<table>
<thead>
<tr>
<th>Biopsy Group</th>
<th>Week</th>
<th>Patient 0</th>
<th>Patient 6</th>
<th>Patient 12</th>
<th>Patient 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>1B Edema</td>
<td>PV-cells, IH, edema, PV-fib</td>
<td>NA (lost to follow-up)</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>2A1 Myo deg, int cells, edema, int deg</td>
<td>NA</td>
<td>Dense PV+IF, edema</td>
<td>IF</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>2A1 HA, myo deg</td>
<td>Int cells, myo deg, IF</td>
<td>FHN, int deg, int cells</td>
<td>MH, int cells</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>2A1 AN, edema, IH, PV-fib</td>
<td>Myo necr, int cells, IF</td>
<td>FHN</td>
<td>Myo deg, int deg</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>2A1 Int deg, int cells</td>
<td>IF</td>
<td>Myo deg, int cells, IF</td>
<td>FHN, IF</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>2A1 HA, myo deg</td>
<td>FHN</td>
<td>Int deg, IF</td>
<td>IF</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>2A1 AN, int deg, IF</td>
<td>FHN, edema, int cells</td>
<td>NA (refused biopsy)</td>
<td>NA</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>2B Int deg, int cells</td>
<td>Int cells, edema, IH, PV-fib</td>
<td>FHN, int cells</td>
<td>FHN, Int deg</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>2A1 Myo deg, IF</td>
<td>NA (refused biopsy)</td>
<td>Myo deg, IF</td>
<td>NA (lost to follow-up)</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>2A1 Myo deg, int deg, edema</td>
<td>NDAR</td>
<td>NDAR</td>
<td>Not done</td>
</tr>
</tbody>
</table>

Abbreviations: AN indicates Aschoff node; HA, histiocytic aggregate; FHN, fibrohistiocytic nodule; IF, interstitial fibrosis; IH, interstitial hemorrhage; Deg, degeneration; Necr, necrosis; Int, interstitial; Myo, myocyte; PV, perivascular; and NA, not available.

In our series, the Aschoff nodules or histiocytic aggregates observed in the initial biopsies were replaced by fibrohistiocytic lesions over time. The ultimate fate of the Aschoff nodules appears to be foci of nondescript perivascular fibrosis.

Another explanation of the low prevalence of Aschoff nodules may be the inability of biopsy to detect focal lesions in the right ventricular endocardium. Gross and Ehrlich24 listed the interventricular septum as the most common site to find Aschoff nodules. The pulmonary conus also was a frequently involved location. Clawson35 stated that Aschoff nodules were located in the apex as frequently as in other portions of the myocardium. Also, in two cases of fatal rheumatic carditis examined by us at autopsy, endocardial as well as intramural perivascular Aschoff nodules were equally likely. This concurs with the conclusions of both Gross and Ehrlich, and Clawson. Our biopsies from the right ventricular apical and outflow septum should be representative of cardiac involvement in rheumatic fever.

Nondiagnostic interstitial and myocyte alterations were more frequently observed than the Aschoff or histiocytic aggregates. The muscle fibers were separated with or without occasional mononuclear cells, interstitial debris, and interstitial hemorrhage. Degenerative myocyte changes were common, but these foci generally lacked a cellular infiltrate. Lymphocytes were frequently seen in our biopsy series. This observation is in agreement with a recent immunohistochemical study26 but at variance to previous autopsy reports emphasizing perivascular and interstitial lymphocytic infiltration in the myocardium.14,15 In terms of semantics, the absence of distinctive findings of myocyte necrosis associated with lymphocytic infiltration argues against the use of the term myocarditis with reference to rheumatic fever, at least when the Dallas criteria are applied.23

Role of Biopsy in Diagnosis of Rheumatic Myocarditis

Because only Aschoff nodules or histiocytic aggregates are considered diagnostic of rheumatic myocarditis, the sensitivity of endomyocardial biopsy is 27%. Nonspecific myocyte or interstitial alterations occurred in the majority of the patients with definite rheumatic carditis (group 1) and not in the patients with chronic inactive rheumatic heart disease (group 3B). These changes have been observed in many different conditions and lack specificity, thus not allowing their use as diagnostic criteria. A positive endomyocardial biopsy based on histiocytic aggregates of Aschoff nodules confirms the presence of active carditis. However, a negative biopsy does not exclude rheumatic carditis. Since treatment of clinically diagnosed active rheumatic carditis has been shown to result in significant reduction in both morbidity and mortality,27 all patients with rheumatic carditis based on the revised Jones’ criteria should be treated regardless of biopsy results. Therefore, no additional diagnostic information is obtained in this group of patients by performing endomyocardial biopsy. In group 2A, the clinical consensus regarding the presence of carditis was unclear. The importance of unexplained congestive heart failure as an isolated manifestation of carditis, especially with recurrence of rheumatic activity, has been debated.14,15 The revised Jones’ criteria require additional presence of a new murmur or an obvious increase in cardiac size for congestive heart failure to qualify as a major manifestation. These features are difficult to demonstrate, especially if previous cardiac status is not known. Biopsy provided confirmatory evidence of rheumatic myocarditis in nearly 40% of our patients, while nondiagnostic changes were observed in a majority of remaining cases consistent with some form of myocardial injury. The present study therefore suggests that recent-onset, unexplained congestive heart failure with underlying rheumatic heart disease indicates a high probability of rheumatic carditis that can often be confirmed by endomyocardial biopsy in the presence of raised anti-streptolysin-O titers and minor manifestations of rheumatic fever, even if the other major stigmata of rheumatic fever are absent. The 40% positive biopsy rate is greater than the rate of positive endomyocardial biopsy (5% to 10%) in suspected lymphocytic myocarditis.28

Given the demonstrated insensitivity of endomyocardial biopsy to detect active carditis in focal myocardial inflammation,29,30 we believe that it is likely the majority of
patients with unexplained congestive heart failure and elevated antistreptolysin-O titers have active rheumatic carditis and probably should be treated even in the face of negative endomyocardial biopsy. This assumption is in agreement with the recent American Heart Association recommendations and the original Jones’ criteria. Presence of additional major manifestations of revised Jones’ criteria would not be required for the diagnosis of rheumatic fever in this group of patients by original Jones’ criteria where definite previous history of rheumatic fever or rheumatic heart disease was considered a major criterion by itself. Recent American Heart Association recommendations also do not insist on the major manifestations in patients with preexisting rheumatic heart disease who present in the recurrent attack with several minor manifestations and evidence of recent streptococcal infection. However, further studies to evaluate the efficacy of treatment versus observation in this clinical scenario are needed.

In group 2B, the previous cardiac findings were not known, and mimetic carditis was suspected even in the absence of congestive heart failure. The concept of mimetic recurrences in rheumatic fever was proposed by Feinstein and Spagnuolo, who reported that all of their patients with carditis in antecedent episode(s) subsequently had some form of cardiac involvement in recurrences. Kuttner and Mayer found that 75% of second attacks of rheumatic fever were similarly mimetic. In both the reports, the presence or absence of carditis was determined by interval clinical examination. In the present study, endomyocardial biopsy did not demonstrate the specific lesions of rheumatic myocarditis in patient group 2B, but interstitial alterations were commonly observed in these patients. However, the diagnostic accuracy of these features is unclear, and clinical use uncertain.

**Sequential Endomyocardial Biopsies in Rheumatic Carditis**

Typical Aschoff nodules have been shown in autopsy studies up to 3 months after the onset of rheumatic fever in the absence of steroid therapy. In our study of sequential biopsies in 10 patients receiving immunosuppression, there was evidence of healing with Aschoff nodules or histiocytic aggregates being replaced by fibrohistiocytic foci. Nondiagnostic alterations, similar to those seen in acute cases, were present in a large proportion of biopsies at 6, 12, and 24 weeks. Presence of myocyte degenerative changes at 12 or 24 weeks in three patients is disconcerting and suggests delayed resolution despite presumed adequate therapy and clinical improvement. In the absence of focal cellular infiltrates, the nonspecific degenerative changes in sequential endomyocardial biopsies probably would not contribute to monitoring of the disease activity or response to therapy.

**Conclusions**

The biopsy in patients presenting with active rheumatic carditis demonstrates myocyte degeneration usually without lymphocytic infiltration and frequently without Aschoff nodules. Endomyocardial biopsy does not provide additional diagnostic information where clinical consensus is certain about diagnosis of carditis, and we cannot recommend endomyocardial biopsy as a routine diagnostic or prognostic tool in these patients. Our study has demonstrated histological support to the concept of carditis underlying unexplained recent congestive heart failure. The case for treating the patients with suspected mimetic carditis without congestive heart failure is not persuasive but merits further study.

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**References**

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