Autoimmune myocarditis: a clinical entity

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In a case of myocarditis electron microscopic and immunofluorescent studies of a transmural myocardial biopsy specimen indicated an autoimmune process. Extensive inflammatory cell infiltration, immunoglobulin and complement deposition along the sarcolemma and in the interstitium, and capillary endothelial injury were found. After a short course of immunosuppressive therapy the inflammatory process was replaced by collagenous scarring and lymphocytic depletion; the blood vessels were then normal. Earlier therapy in such cases may be lifesaving.

Des études au microscope électronique et par immunofluorescence ont été faites sur un prélèvement de tissu myocardique obtenu par biopsie transmurale dans un cas de myocardite. Ces études ont démontré la présence d'un processus autoimmun. Une infiltration étendue par des cellules inflammatoires, des dépôts d'immunoglobulines et de complément le long du sarcolemme myocardique et dans l'espace interstitiel, et des lésions de la paroi capillaire ont été mises en évidence. Après un court traitement d'immunosuppression le processus inflammatoire a été remplacé par une cicatrice fibreuse. De plus, l'immunosuppression a provoqué une déplétion lymphocytaire et une normalisation des vaisseaux sanguins. Un traitement au tout début pourrait signifier la survie du patient.

The role of autoimmunity in myocarditis has been the subject of speculation and experimentation;[1,2] however, no well documented case of autoimmune myocarditis in a human has been reported. It seemed important to us, therefore, to document a case of myocarditis in which evidence indicated that such a mechanism was involved, and in which immunosuppressive therapy was followed by clinical and histologic evidence of remission.

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Case report

Clinical course and findings

A 28-year-old man was admitted to hospital because of chest discomfort and palpitations. He had been well until 3 months prior to admission, when he began to experience episodes of palpitations two to three times a week. Each episode lasted 30 to 60 minutes and was unrelated to activity. During these episodes he noted some precordial tightness and shortness of breath. The palpitations recurred 12 hours prior to admission and continued until his arrival at the emergency ward. He had been exposed to chickenpox approximately 4 months previously, but clinical disease had not developed. He had not had a recognizable illness in the recent past.

Apart from a pulse of low volume, with a rate of 95 beats/min, the physical findings at the time of admission were normal, and the heart and lungs appeared normal roentgenographically. However, spontaneous attacks of ventricular tachycardia that resolved spontaneously into sinus rhythm occurred in the next 24 hours. The electrocardiogram during these attacks showed bizarre QRS complexes and ventricular rates of 130 to 200 beats/min.

From the second hospital day onwards the attacks continued but failed to remit. Lidocaine, procainamide, quinidine, propranolol, digoxin and bretylium tosylate were used alone and in various combinations in an attempt to control the tachycardia. Because of the persistence of the arrhythmia cardioversion was performed on the 14th hospital day and sinus rhythm was obtained. The next day an apical midsystolic click was heard and an echocardiogram indicated holosystolic prolapse of the posterior mitral leaflet.

Investigations were carried out during this admission to rule out a variety of possible causes of myocarditis, and the presumptive diagnosis was mitral valve prolapse (Barlow's syndrome). The patient was discharged taking a combination of propranolol and quinidine, which seemed to control the arrhythmia.

Brief attacks of palpitations continued, and dyspnea with effort increased. Three weeks after discharge the man was readmitted with pulmonary edema. Again the electrocardiogram showed ventricular tachycardia (rate 175 beats/min), but the chest roentgenogram now indicated cardiomegaly with diffuse air-space disease. Propranolol and quinidine were discontinued and treatment with diuretics was instituted. Because the episodes of arrhythmia recurred, repeated cardioversion with continuous intravenous administration of lidocaine was required.

The titre of serum antibodies to rubella virus increased from 32 to 256 over 4 weeks. Laboratory findings were normal except for persistent lymphocytopenia, with lymphocyte counts varying between 0.4 and 1.3×10^9/L.

On the 13th hospital day a transmural biopsy of the left ventricle was performed. The biopsy specimen was processed for light and electron microscopy and immunofluorescent study.

Biopsy findings

Light microscopic examination demonstrated a core of ventricular myocardium including both the epicardial and the endocardial surfaces. The epicardium and the outer two thirds of the myocardium appeared normal. The inner third of the myocardium, however, was replaced by an extensive inflammatory infiltrate

made up of lymphocytes and histiocytes (Fig. 1). The histiocytes formed occasional giant cells, and necrotic and degenerated cardiac muscle cells could be visualized in these heavily inflamed areas. Special staining for acid-fast bacteria and fungi was unproductive. The histologic findings were interpreted as representing idiopathic interstitial (Fiedler's) myocarditis.[3]

Electron microscopy carried out on samples selected from the inner third of the myocardium revealed extensive cardiac muscle injury. Some cardiac muscle cells showed ultrastructural signs of irreversible damage such as granular calcium phosphate densities in mitochondria, homogenized and fragmented myofilaments and sarcoplasmic membrane discontinuities. In other cardiac muscle cells, intracellular edema and dilatation of sarcoplasmic reticulum were the dominant alterations, while the myofilaments and mitochondria were relatively well preserved. Adjacent to damaged cardiac muscle cells, widened intercellular spaces were packed with inflammatory cells, mostly histiocytes and lymphocytes, with an occasional plasma cell (Fig. 2). Histiocytes were found focally in groups; interdigitation of the cytoplasmic boundaries resulted in the multinucleated cell forms appearing with light microscopy as giant cells. A conspicuous finding was finely granular electron-dense material on the sarcolemmal surface of some cardiac muscle cells, loosely distributed in the interstitium around capillaries, and within membrane-bound bodies of histiocytes (Fig. 3). The

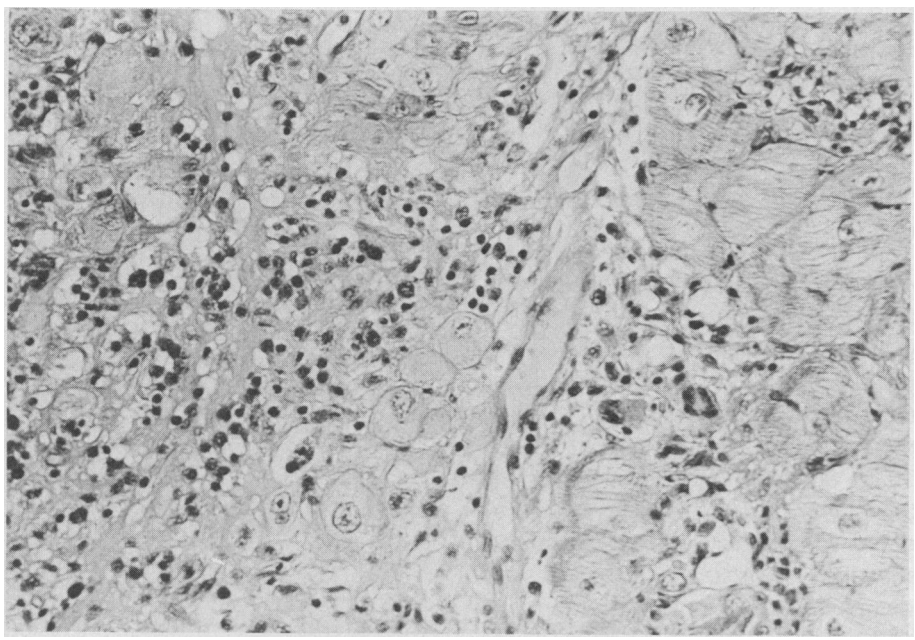

FIG. 1—Extensive inflammatory infiltrate composed of lymphocytes, histiocytes and occasional giant cells in inner third of left ventricular myocardium (hematoxylin–eosin [H–E]; × 300).

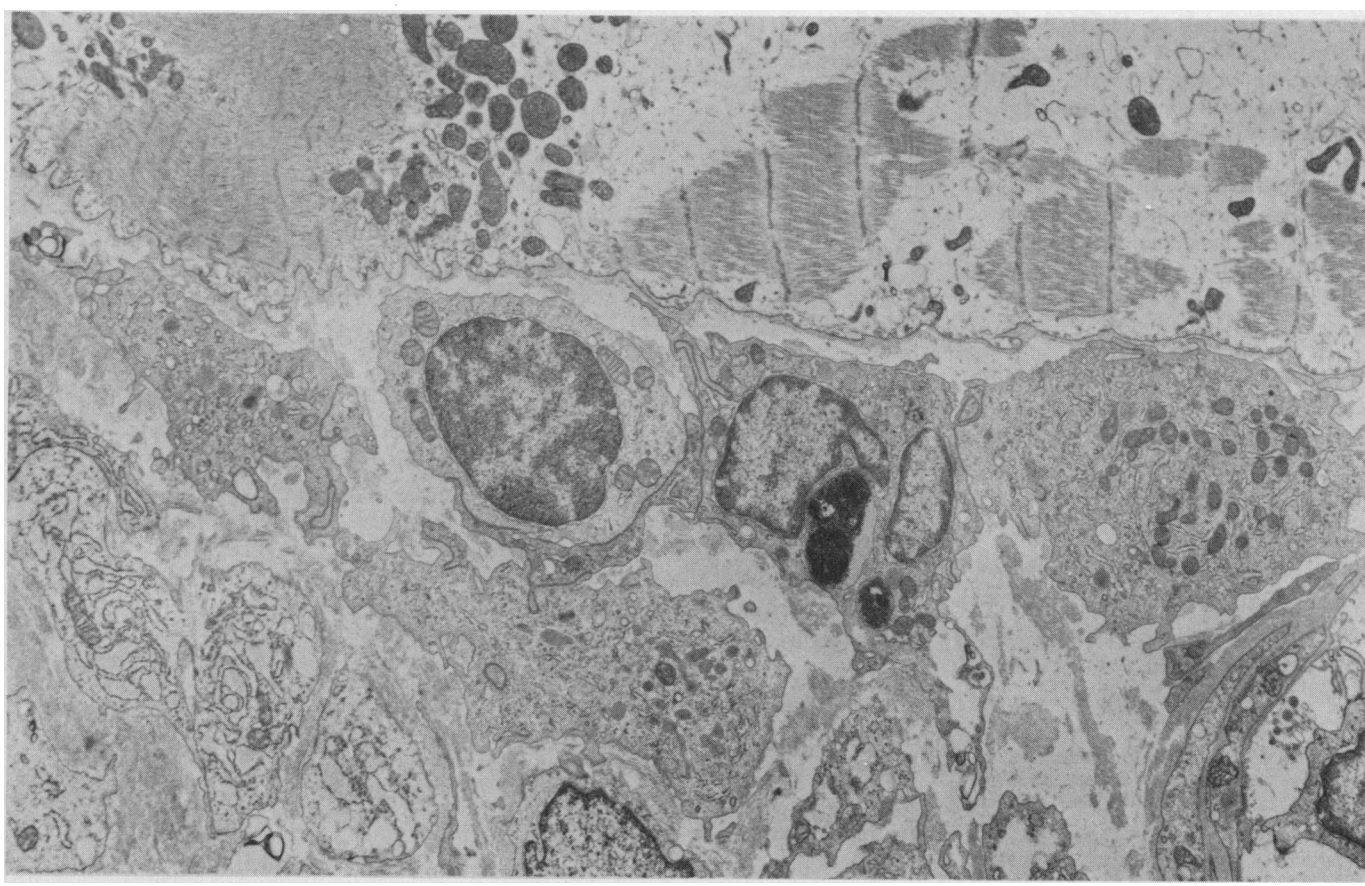

FIG. 2—Lymphocytes and histiocytes adjacent to swollen cardiac muscle cell (uranyl acetate and lead citrate; ×6900).

coronary capillaries showed marked swelling of either individual endothelial cells or the entire circumference of the endothelium; the latter resulted in almost complete occlusion of the capillary lumen. The endocardial endothelial cells were relatively well preserved in the examined samples.

Immunohistopathologic studies of the biopsy specimen revealed linear staining for IgG in focal areas along the sarcolemma of the myocardial fibres (Fig. 4). In addition, there were small granular deposits in the interstitium, principally along blood vessels, which stained for IgG, IgM and the C3 component of complement. To verify the specificity of these findings we tested the patient's serum by means of the indirect immunofluorescence test for IgG antibodies using tissue from the patient's heart and other normal human hearts. In all instances linear staining was noted along the sarcolemma and subsarcolemma. In the rat heart that

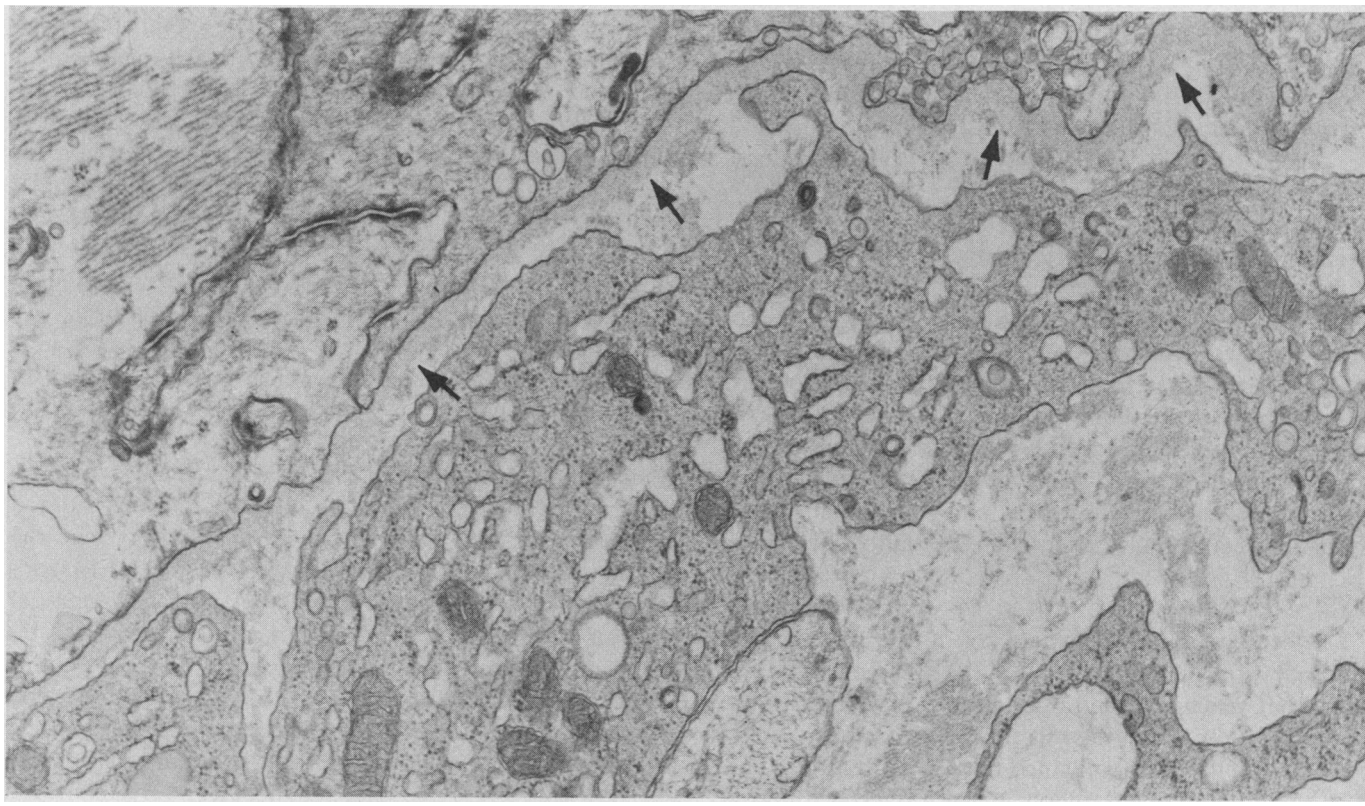

FIG. 3—Thick layer of finely granular electron-dense material on sarcolemma of cardiac muscle cell (arrows) (uranyl acetate and lead citrate; ×27 000).

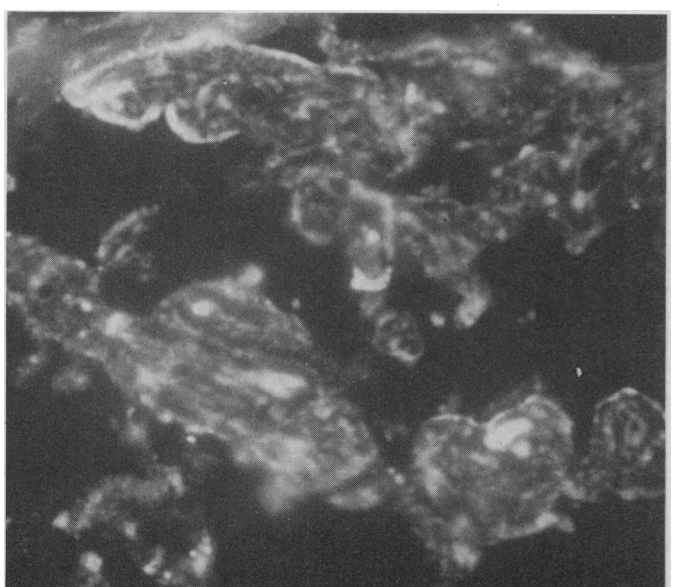

FIG. 4—Immunofluorescent pattern of cardiac biopsy: linear deposition of IgG on cardiac muscle sarcolemma (×500).

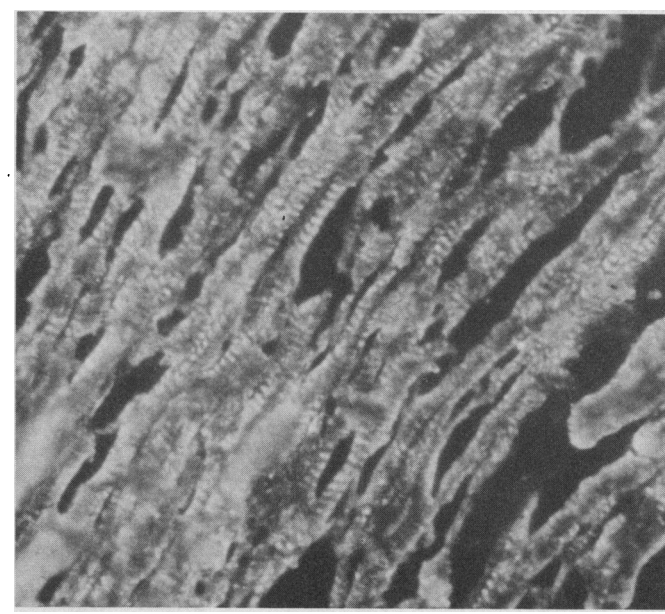

FIG. 5—Extensive staining of rat myocardium for IgG by indirect immunofluorescence with use of patient's serum (×500).

was tested with serum collected on numerous occasions following the onset of immunosuppressive therapy, pronounced staining of the sarcoplasmic cross-striation was seen (Fig. 5). The titre of the IgG antibodies was 320 on day 18, 160 on day 23 and 80 on day 29 of the second admission.

Subsequent clinical course

Because of the biopsy findings therapy with azathioprine, 100 mg, and dexamethasone, 16 mg daily, was started on the 16th hospital day. The cardiovascular status gradually stabilized and there was no recurrence of the arrhythmias. On the 24th day the patient suddenly showed hemiparesis compatible with embolism to the territory of the left middle cerebral artery. On the 34th day an acute abdominal condition developed and a perforated duodenal ulcer was found at laparotomy. Cardiac arrest occurred during the procedure and the patient could not be resuscitated.

Autopsy findings

The heart weighed 320 g and contained several small thrombi in the dilated left ventricular and right atrial chambers; these were most likely the source of multiple emboli since there were small areas of infarction in the brain and the lungs. The perforated duodenal ulcer with extensive peritonitis probably resulted in the death of the patient.

Histologic examination of specimens from the heart showed focal necrotic areas in both left and right ventricular myocardium. However, these areas were characterized by myocytolysis and cellular resorption rather than an acute inflammatory infiltrate. In addition, the subendocardial layers that previously had been most affected by the disease process showed extensive fibrosis consistent with healing of the interstitial myocarditis (Fig. 6).

Electron microscopic examination of myocardial tissue samples from the subendocardial layers of the left ventricle showed that the cardiac muscle cells were separated from each other by large masses of collagen fibres. Inflammatory cells were rare, and the capillaries appeared structurally normal. The capillary, venular and arteriolar endothelial cells showed well preserved fine structure and were interconnected by particularly well developed junctional complexes. The cardiac muscle cells embedded in the massively collagenized interstitial areas showed degenerative changes and signs of attempted cellular regeneration, such as formation of leptofibrils.

Immunofluorescent study of the cardiac tissue taken at autopsy revealed findings similar to those in the biopsy.

Discussion

The histologic features of myocarditis and the ultrastructural changes found in the cardiac biopsy specimen were consistent with those of an immune myocardial injury. The presence of IgG, IgM and C3 along the sarcolemma and subsarcolemma of the myocardial fibres, circulating autoantibodies with similar reactivity, an extensive mononuclear cell infiltrate in the subendocardial layers of the heart, electron-dense deposits on sarcolemmal surfaces and in the cardiac interstitium, and changes of the coronary capillary endothelium supported this. The extent of myocardial damage, however, was probably aggravated by ischemia secondary to occlusions of small coronary vessels.

The deposits of immunoglobulins and complement, and the corresponding electron-dense deposits in the interstitium and along the sarcolemma, were probably locally formed antigen–antibody complexes. Such a pathogenetic mechanism has been seen in other organs.[4] Whether it was primary or merely an epiphenomenon was not determined. Although others have also found deposition of γ-globulin in the ventricular myocardium in cases of idiopathic cardiomyopathy[5] and experimental myocarditis,[2,6] autoimmunity was not widely accepted as the cause because of the low frequency of circulating antiheart antibodies in this disease.[1,7] However, the cytotoxic effect of antibodies has clearly been shown in vitro in experimental allografts and myocardial explants.[8,9]

The morphologic features of the cardiac muscle post mortem differed strikingly from those observed in the cardiac biopsy specimen. Electron-dense sarcolemmal and interstitial deposits, marked lymphocytic and histiocytic reaction and conspicuous capillary endothelial injury associated with extensive recent cardiac muscle damage were the dominant lesions in the biopsy specimen. By contrast,

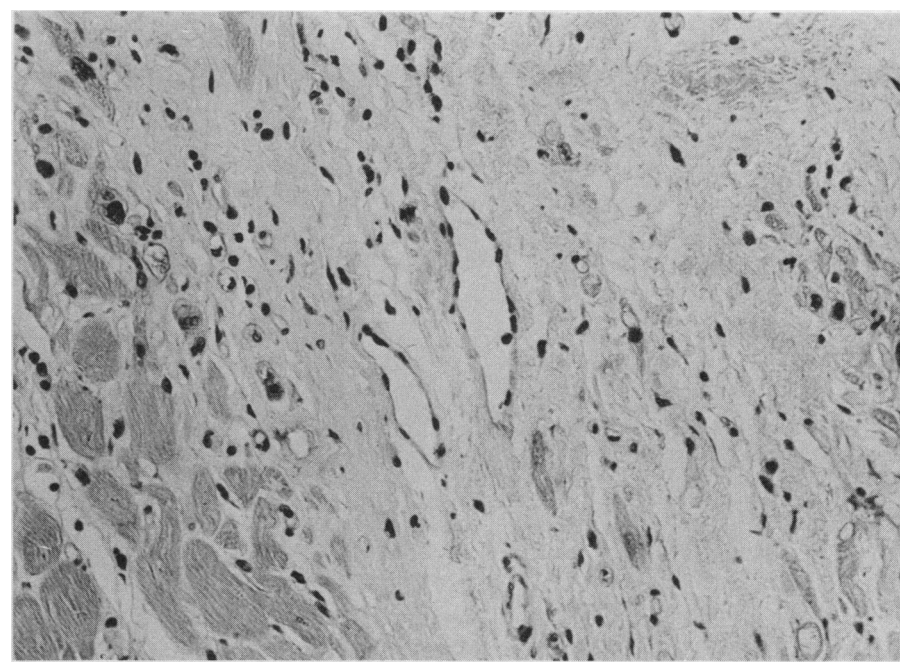

FIG. 6—Extensive scarring and minimal inflammatory cellular infiltrate in myocardium post mortem, 3 weeks after start of immunosuppressive therapy (H–E; ×300).

lymphocytic depletion, re-established capillary structure and massive collagenous scarring characterized the postmortem specimen. Although histologic examination of the myocardium still revealed focal necrotic areas, light and electron microscopy of the primarily affected subendocardial layers clearly indicated that healing had taken place.

The triggering event for such an immune response remains obscure, but, as with the postcardiotomy syndrome and rheumatic heart disease, tissue injury, caused, for example, by a viral infection, may play a role.[10,11] The rise of the titre of serum antibodies to rubella in our case may be important. The localization of the lesion in the subendocardial areas of the ventricles may be dictated by hemodynamic factors.

The clinical improvement and the significant decrease in the antibody titres in this patient after initiation of therapy with azathioprine and dexamethasone, together with the absence of an inflammatory cell infiltrate in the autopsy specimen, also suggest that immunologic mechanisms may have been of pathogenetic importance. However, this form of therapy was probably instituted too late in the course of the illness to have a satisfactory effect upon it. Obviously in such cases if a beneficial effect is to be achieved from immunosuppressive or anti-inflammatory therapy, or both, such therapy must be instituted in the early stages of the disease, before massive necrosis of the tissue has occurred.

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References

1. Fowler NO: Autoimmune heart disease. *Circulation* 44: 159, 1971
2. Laufer A: Human and experimental myocarditis. The possible role of immune processes in pathogenesis. *Isr J Med Sci* 11: 37, 1975
3. Covey GW: Acute isolated myocarditis (Fiedler's myocarditis); case report. *Am J Clin Pathol* 12: 160, 1942
4. Stiller CR, Russell AS, Dossetor JB: Autoimmunity: present concepts. *Ann Intern Med* 82: 405, 1975
5. Sanders V, Ritts RE jr: Bound gamma globulin in idiopathic disease of the myocardium. *JAMA* 194: 59, 1965
6. Kaplan MH, Frengley JD: Autoimmunity to the heart in cardiac disease. Current concepts of the relation of autoimmunity to rheumatic fever, postcardiotomy and postinfarction syndromes and cardiomyopathies. *Am J Cardiol* 24: 459, 1969
7. Camp TF, Hess EV, Conway G, et al: Immunologic findings in idiopathic cardiomyopathy. *Am Heart J* 77: 610, 1968
8. Carpenter CB, Soulillou JP, D'Apice AJ, et al: The role of antibodies in the rejection and enhancement of organ allografts: non-Ag-B (Ia) antigens. *Adv Immunol* 22: 1, 1976
9. Ghose T, Mammen M: Interaction in vitro between myocardial cells and autologous lymphocytes and sera from patients with rheumatic carditis. *Chest* 71: 730, 1977
10. Sanders V: Viral myocarditis. *Am Heart J* 66: 707, 1963
11. Smith WG: Coxsackie heart disease in adults. *Am Heart J* 73: 439, 1967