COXSACKIE B5 MYOPERICARDITIS IN A YOUNG ADULT

— Clinical Course and Endomyocardial Biopsy Findings —

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An 18-year-old student with recent gastrointestinal symptoms was found to have Stokes-Adams syndrome. A transvenous pacemaker was successfully inserted with clinical improvement. Subsequent viral titer studies and serum enzyme changes supported the diagnosis of coxsackie B5 myopericarditis. The first cardiac catheterization and endomyocardial biopsy of the right ventricle were performed on the 14th hospital day; the former revealed no hemodynamic abnormalities, but the latter showed marked necrosis of the myofibers, disarray of the remaining ones, mononuclear cell infiltration and the appearance of fibroblasts with fine collagen fiber proliferation in the interstitium. A second biopsy of both ventricles, carried out on the 46th hospital day, showed no necrosis of the myofibers or inflammatory cell infiltration but increasing collagen fiber proliferation in the interstitium and disarray of the surviving myofibers. These pathological findings suggest the healing process of the myopericarditis. To the best of our knowledge, reports of viral myopericarditis with serial endomyocardial biopsies have been few.

SINCE Saphir and Gore¹ demonstrated that viral myocarditis was not rare in autopsy material, increasing attention has been paid to the heart in viral infection. A large variety of viruses may involve the heart, but the coxsackie viruses, especially group B, seem to be the most common agents responsible for viral myocarditis even in adults²⁻⁶. Cardiac arrhythmia or conduction disturbance is probably the most frequent manner of viral myocarditis. If Stokes-Adams syndrome due to complete heart block in young adults occur, its diagnosis is highly suspicious. As far as we know, there have been few reports of a clinical surviving case of acute viral myocarditis in which serial endomyocardial biopsies

were performed.⁷ We recently had the opportunity to follow the clinical course of a patient with acute coxsackie B5 virus myopericarditis associated with complete A-V block and ventricular standstill. This report describes the clinical course and histopathological findings of the myocardium obtained by an endomyocardial biopsies during the process of recovery.

CASE REPORT

An 18-year-old male student had been healthy until May 19, 1981, when he developed malaise and headache. The next day he had epigastralgia and non-pleuritic substernal chest pain. On the following day his temperature was 38.0°C. On May 22, he had soft stools and vomited coagulated blood after drinking water. Two hours later he noted palpitation associated with vom-

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Fig.1. Serial of electrocardiographic changes produced by acute myopericarditis. On May 22, ventricular standstill and drift of baseline due to external cardiac massage. On May 23, pacemaker rhythm. On May 24 ectopic atrial rhythm and complete right bundle branch block (QRS duration of 0.16 sec) with QRS frontal plane axis of -100° . Small Q waves in leads V_1 and V_2 . On May 25, convex elevation of ST segment, flattening of T wave and reduction of R wave voltage in lead V_2 . Thereafter, the mean QRS frontal plane axis is deviated to the right gradually, R wave voltage is increased and QRS duration shortened in the chest leads.

iting. Loss of consciousness with convulsive seizures of short duration appeared and recurred several time during the next few hours. He was admitted to a near-by emergency hospital. An electrocardiogram revealed complete A-V block which progressed to ventricular standstill (Fig. 1). Consciousness returned, with idioventricular rhythm, after an intravenous infusion of isoproterenol. He was transferred to our hospital for further examination and management.

Immediately after admission, a transvenous temporary pacemaker was inserted into the right ventricle, because isoproterenol is considered to be a possible cause of myocardial damage and ventricular tachycardia. The pacing rate was set at 60/min. Temperature was 37.4°C , blood pressure 96/74 mmHg. The pharynx was moderately injected. The chest was clear according to auscultation and percussion. The heart was enlarged without murmur or friction rub. Heart

sounds varied in intensity. The liver was not palpable. There was no edema of the extremities. Neurological examination was normal.

The urine gave a 1+ test for protein; the sediment contained 2 red cells per high-power field. Throat culture yielded normal flora; blood culture was sterile. The hemoglobin value was 15.0 g/dl, peripheral white blood cell (WBC) count, $11800/\text{mm}^3$ with 61% neutrophils, 6% monocytes and 33% lymphocytes, and the erythrocyte sedimentation rate (ESR) was 8 mm (one hour). The serum glutamic oxaloacetic transaminase (SGOT) was 2700 mU/ml (normal 5–40), the glutamic pyruvate transaminase (SGPT) 1335 mU/ml (normal 5–40), the lactate dehydrogenase (LDH) 1980 mU/ml (normal 100–225), γ -glutamyl transpeptidase (γ -GTP) 53 U/L (normal < 35), the uric acid 11.2 mg/dl, the urea nitrogen 26 mg/dl, the phosphorus 3.1 mg/dl, the calcium 8.9 mg/dl, the serum amylase

Fig.2. Chest roentgenogram obtained during hospitalization. A: On the 2nd hospital day (May 23), cardiac enlargement with a CTR of 0.58 and no pulmonary vein congestion. Swan-Ganz pacing catheter is inserted into the apex of the right ventricle. B: On the 8th hospital day (May 29), CTR has decreased to 0.45.

Fig.3. Mitral valve echocardiogram taken on the 2nd hospital day with pacemaker in place. LVDd is 4.3 cm, LVDs is 3.6 cm, mean Vcf is 0.56 circ/sec and EF is 35% (by Teichholz). When the pulse generator is turned off, a mitral valve A wave follows each electrocardiographic P wave.

1220 U/L (normal 30–400), the creatine kinase (CK) 599 U/L (normal <100), the aldolase 184.8 U/L (normal 1.2–7.6) and the serum protein 7.0 g/dl (the albumin 4.6 g/dl and the

globulin 2.4 g/dl). The sodium was 137 mEq, the potassium 4.8 mEq, the chloride 105 mEq and the carbon dioxide 24.3 mEq per liter. A cold agglutinin test was negative. Tests for

Fig.4. A: Light microscopy of the first endomyocardial biopsy specimens from the right ventricle, which was carried out on the 14th day of hospitalization, reveals severe myocardial damage and disarray of the remaining myofibers. Note absence of calcification in the necrotic area. Mononuclear cells and fibroblasts with fine collagen fiber proliferation are present. Hematoxylin and eosin stain. B: Light microscopy of the second right ventricular endomyocardial biopsy specimens, taken on the 46th hospital day, shows the surviving myocardial fibers are atrophic and myofiber disarray remains. Collagen fibers are increasing in numbers in the interstitium. Note absence of necrosis of myofibers and inflammatory cell response. Hematoxylin and eosin stain.

TABLE I CHANGES OF ANTIVIRAL ANTIBODY TITERS IN SERUM

	5/23/81	6/2/81	6/16/81	7/2/81	8/31/81
<i>Mumps</i> (CF)	× 4	< × 4			
<i>Adeno</i> (CF)	× 8	× 16			
<i>Echo3</i> (HI)	< × 8	< × 8			
<i>Echo7</i> (HI)	< × 8	< × 8			
<i>Echo11</i> (HI)	< × 8	< × 8			
<i>Echo12</i> (HI)	< × 8	< × 8			
<i>CoxsackieA7</i> (NT)	× 16	× 32			
<i>CoxsackieA9</i> (NT)	< × 4	× 4			
<i>CoxsackieA16</i> (NT)	× 4	× 8			
<i>CoxsackieB1</i> (NT)	× 8	× 8	× 16	× 8	
<i>CoxsackieB2</i> (NT)	< × 4	< × 4	< × 4	< × 4	
<i>CoxsackieB3</i> (NT)	× 32	× 16	× 16	× 16	
<i>CoxsackieB4</i> (NT)	× 8	× 16	× 16	× 16	
<i>CoxsackieB5</i> (NT)	× 16	× 64	× 64	× 64	× 32
<i>CoxsackieB6</i> (NT)	< × 4	< × 4			

CF = complement fixation; HI = hemagglutination inhibition; NT = neutralizing titer

antistreptolysin-O (ASO), syphilis, rheumatoid factor and antinuclear antibodies were all negative. C-reactive protein (CRP) was positive (4+). An X-ray film of the chest showed cardiac enlargement with a cardiothoracic ratio (CTR) of 0.58; there was no pulmonary vein congestion (Fig. 2). An echocardiogram showed no pericardial effusion, but low cardiac function was revealed: the left ventricular end-diastolic dimension (LVDd) was 4.3 cm, the left ventricular end-systolic dimension (LVDs) was 3.6 cm, the mean velocity of circumferential shortening (mean Vcf) was 0.56 circ/sec, and the ejection fraction (EF) was 35% (Fig. 3).

The patient was treated with 1,200,000 of penicillin G-K units by intravenous drip infusion daily and aspirin 3.0g t.i.d. orally, although infection with some viral disease was considered to be the most likely clinical diagnosis. When the pulse generator was temporarily turned off on the 2nd hospital day, only P waves were seen without any escaped beats (Fig. 3). On the 3rd hospital day, the pacemaker rhythm competed abruptly with his own heart beats. An electrocardiogram revealed ectopic atrial rhythm at a rate of 75/min with complete right bundle branch block and left anterior hemiblock (mean QRS frontal plane axis of -100°); small Q waves appeared in leads V_1 and V_2 . The temporary pacemaker was removed. On the 4th hospital day a pericardial friction rub was heard in the

4th intercostal space at the left sternal border, which disappeared by the next morning. Thereafter, he showed progressive improvement without complaints. The drugs were discontinued by the 7th day of hospitalization. Repeated electrocardiograms indicated persistence of ectopic atrial or normal sinus rhythm with complete right bundle branch block (Fig. 1).

On the 12th hospital day, an echocardiogram revealed that the LVDd was 4.2 cm, the LVDs was 2.8 cm, the mean Vcf was 1.19 circ/sec and the EF was 62%.

On the 14th hospital day, the first cardiac catheterization and endomyocardial biopsies of the right ventricle were performed. The cardiac index was 3.5 L/min/m², and the mean pulmonary wedge pressure was 7 mmHg. The light microscopic findings of the specimens showed marked myocytolysis with focal myofiber necrosis and disarray of the remaining myocardial fibers. No definite calcification was seen in the necrotic area. In addition to edema and widening of the interstitium, there was much myocardial cell debris and a few infiltrating mononuclear cells and fibroblasts with the early phase of fine collagen fiber proliferation in the interstitium (Fig. 4A).

On the 25th hospital day, all laboratory tests became normal.

On the 35th hospital day, a thallium-201 myocardial scintigram was obtained after an

injection of 2 mCi of thallium-201. The pattern of uptake was fairly uniform except for an area of definite perfusion defect in the apical region in the anterior view.

The second cardiac catheterization and endomyocardial biopsies of both ventricles were performed on the 46th hospital day. Normal left ventricular volume and no evidence of left ventricular dyskinesia were revealed. The cardiac index was 3.0 L/min/m², and left ventricular end-diastolic pressure was 10 mmHg. The light microscopic findings of the right ventricular endomyocardial biopsy materials revealed almost no necrotic myofibers or inflammatory cell reaction. The remaining myofibers were atrophic and in disarray. The collagen fibers in the interstitium or replacement fibrosis were abundant (Fig. 4B). In the left ventricle, damaged myocardial fibers and fibrosis in the interstitium were much less prominent than in the right.

Viral cultures from the initial throat swab and feces were negative. Serologic studies, however, showed acute (the 2nd hospital day) and convalescent (the 42nd hospital day) neutralization titers of 1:16 and 1:64, respectively, to the coxsackie B5 serotype (Table I).

DISCUSSION

The clinical manifestations of coxsackie B virus myocarditis in the adult are usually, but not invariably, preceded or accompanied by systemic manifestations of viral disease. Frequent among these are fever, symptoms of an upper respiratory tract infection, and abdominal symptoms, including nausea and emesis. Myalgia, pleurodynia and arthralgia are common.⁸ The electrocardiographic changes observed most frequently are elevation of ST segments and flattening to inversion of T waves. Transient Q waves, premature ventricular contraction, transient second- or third-degree heart block, as well as bundle branch block, have been described.⁸ There have been some reports that Stokes-Adams attacks due to complete heart block may occur in viral or non-specific myocarditis, and temporary pacing is necessary to overcome this manifestation.^{4,9}

In the case described here the diagnosis of coxsackie B5 virus myopericarditis was established by abnormal levels of serum enzymes, positive signs of inflammation, electrocardiographic and radionuclide and viral studies, as well as radiographic and endomyocardial biopsy

findings. A myocardial scintigram demonstrated myocardial damage in the apical region, where tissue specimens are usually obtained by endomyocardial biptome. The first endomyocardial biopsy of the right ventricle revealed marked myocytolysis and necrosis associated with mononuclear cell infiltration and fine collagen fiber proliferation in the interstitium. The biopsy missed the early stage of the acute illness. Increasing collagen fiber proliferation and absence of abundant inflammatory cell infiltrations, however, seemed to signify the beginning of the healing process of the acute myopericarditis.¹⁰ The second biopsy showed neither necrosis of the myofibers nor inflammatory cell infiltration but abundant collagen fibers in the interstitium and disarray of the surviving myofibers. Myocardial fiber disarray is frequently seen in hypertrophic cardiomyopathy.¹¹ The disarray of myofibers in this case may have been secondary to the fibrosis, perhaps a result of the mechanical effect of the fibrotic tissue on the immediately adjacent surviving myocardial fibers.¹² Cardiac catheterization showed, however, that myocardial function was not impaired, because the necrotic lesions may be focal in both the subendocardial and epicardial regions.

The serial electrocardiographic changes were also of great interest. The pathological process was diffuse and presumably involved the 3 fascicles of the conduction system because only P waves were present when the pacemaker stopped. It seemed that the necrotic lesion was limited to the right bundle branch in view of the complete right bundle branch block when A-V conduction was restored. According to the clinicopathological analysis by Harris and his associates, active non-specific myocarditis involved both bundle branches but the A-V node was intact.¹³ The biopsy materials in this case showed that myocardial damage was more severe in the right than in the left ventricle. Thus, complete right bundle branch block may persist. Transient small Q waves in leads V₁ and V₂ concurred with the appearance of a pericardial friction rub. The emergence of Q waves may imply transient focal transmural myocardial damage because the inflammatory process in the subendocardium spread to the epicardium and the pericardium.

Viral myocarditis in adults is generally benign, and fatal cases are rare, if management is appropriate.⁸ In this case there was progressive clinical improvement confirmed by the findings of the

repeated biopsy. The histopathological findings of the myocardium obtained by serial endomyocardial biopsy in this case appeared to agree with the experimental study of viral myocarditis in hamsters. That is, many necrotic foci decreased rapidly in size, and fine moderate fibrotic replacement was observed on the 9th to the 22nd day after virus inoculation. Thereafter, areas of replacement fibrosis gradually decreased in size in most animals, but a few animals developed congestive cardiomyopathy.¹⁰

The relation of coxsackie virus to chronic heart disease is not yet clear. It may be that some cases of idiopathic cardiomyopathy are late sequelae of viral myocarditis. Obviously, a continuing, long-term follow-up will be required to evaluate late cardiac function. Endomyocardial biopsy is useful in exploring the relationship between viral myocarditis and idiopathic cardiomyopathy.

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