A Highly Suspected Case of Chronic Chagas' Heart Disease Diagnosed in Japan

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A 50-year-old South American Indian woman, a native of Brazil and now a resident of Shiga Prefecture, was admitted to our hospital because of dyspnea on exertion. We initially suspected dilated cardiomyopathy due to an enlarged and diffusely hypokinetic left ventricle (LV) on echocardiogram. Coronary arteriograms were normal, and histological examination of right ventricular endomyocardial biopsy specimens showed findings compatible with chronic myocarditis. Magnetic resonance imaging revealed localized thinning and a small apical aneurysm at the LV. Since she had previously lived in a high-risk region for Chagas' disease, two immunological examinations for *Trypanosoma cruzi* were performed. The results of both tests were compatible with the disease. Recently, an increasing number of patients with Chagas' disease have been found in the United States among immigrants from South American countries, and the risk of transmission of the disease through contaminated blood transfusion is becoming a national problem. We report this case with reference to the present state of the problem in the United States and the potential problems it presents in Japan because of the marked increase in the number of immigrants from the affected area.
(*Jpn Circ J* 1995; **59**: 219–223)

CHAGAS' disease is an endemic zoonosis caused by the protozoan parasite *Trypanosoma cruzi*. About 16 to 18 million persons are thought to be infected with the parasite and another 100 million individuals are at risk of acquiring the infection. It is a major cause of morbidity and mortality, and the greatest public health problem in all Latin American countries¹. Since it is an endemic disease, little is known of it in Japan. In fact, there has been only one case of chronic Chagas' disease reported in Japan to date². Recently, large numbers of immigrants from high-risk regions for Chagas'

disease have entered the United States, and it has been reported that many of them are infected with *Trypanosoma cruzi*³. Future economic changes and subsequent dynamic changes in the world's population, may produce an increase in the number of immigrants to Japan with this public health problem, as is currently seen in the United States.

CASE REPORT

A 50-year-old South American Indian woman was admitted to the hospital because of dyspnea on exertion. The patient was born in Brazil and raised in an agricultural area about 100 km upstream from Belem, a city at the mouth of the Amazon. She

Key words:

Chagas' disease
Trypanosoma cruzi
Magnetic resonance imaging

(Received May 18, 1994; accepted November 25, 1994)

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Fig. 1. Electrocardiogram showed normal sinus rhythm at a rate of 81 per min, a tendency for low voltage in limb leads and intraventricular conduction delay.

Fig. 2. Echocardiogram revealed dilatation of the left ventricle (LV) and right ventricle (RV). The LV end-diastolic dimension was 62 mm, and the LV end-systolic dimension was 54 mm. LV wall motion was diffusely hypokinetic with an estimated LV ejection fraction of 0.27. The RV diastolic dimension was 27 mm, and RV wall motion was also diffusely hypokinetic. The left atrium was dilated with an internal dimension of 45 mm.

married an immigrant from Japan at the age of 25. She was well until her marriage, but began to feel dyspnea when climbing up stairs. In May, 1991, she came to Japan with her husband who was employed in Shiga Prefecture. In March, 1992, she returned to Brazil because of dyspnea and leg edema. She was admitted to a hospital in Belém and the symptoms diminished after medical treatment. The diagnosis of Chagas' disease was not made at that time. In January, 1993, she returned to Japan, but was admitted to the hospital in May, 1993, due to reappearance

of dyspnea after a common cold. She never smoked or consumed any alcohol. She and her husband do not have a child. Her family history was not remarkable and she denied any severe febrile illness or other symptoms suggestive of acute Chagas' disease. On admission, her temperature was 36.7 °C, her pulse was 72 beats per minute, and her respiration rate was 18 beats per minute. Her blood pressure was 110/60 mmHg. On physical examination, the patient had no lymphadenopathy, but her neck vein was distended while she was sitting. A grade II/VI high-

Fig.3. Magnetic resonance imaging revealed localized thinning and a small apical aneurysm with a narrow neck at the LV, which are characteristic features of Chagas' heart disease. No thrombus was detected in the LV.

pitched apical pansystolic murmur which radiated to the axilla was heard. The third heart sound was heard, but the fourth was not. The abdomen and extremities were normal without peripheral edema, and neurological examination was negative. The hematological values were normal except for eosinophilia (17.1%), and the blood chemical values were within normal limits. Urine and stool tests were negative. An electrocardiogram showed normal sinus rhythm at a rate of 81 per min, with intraventricular conduction delay and a mean QRS-wave axis of 67 degrees (Fig. 1). A chest X-ray revealed pulmonary congestion and cardiac enlargement with a cardio-thoracic ratio of 64%. Among a total of 113,359 QRS complexes during a 24-h Holter ECG recording, there were 26 isolated supraventricular ectopic beats, 979 ventricular ectopic beats, of which 83 were in bigeminy and 3 were paired, and multiple short runs of accelerated idioventricular rhythm and a 5-beat run of ventricular tachycardia at a rate of 150 beats per min. Her heart rate was from 42 to 105, with a mean of 68 beats per min. An echocardiogram revealed dilatation of the left ventricle (LV) and right ventricle (RV) (Fig. 2). The LV end-diastolic dimension was 62 mm, and the LV end-systolic dimension was 54 mm. LV wall motion was diffusely hypokinetic

Fig.4. In Western blotting for *Trypanosoma cruzi*, the patient's serum (C) was compared with that of two positive controls (A, B) and two negative controls (D, E). As shown, the patient's serum (C) showed the same bands as that of the positive controls (A, B).

with an estimated LV ejection fraction of 0.27. The RV diastolic dimension was 27 mm, and RV wall motion was also diffusely hypokinetic. The left atrium was dilated with an internal dimension of 45 mm. Doppler color flow imaging revealed moderate to severe mitral and tricuspid regurgitation. At cardiac catheterization, the mean right atrial pressure was 2 mmHg, the right ventricular (RV) pressure was 45/5 mmHg, the pulmonary artery pressure was 45/16 mmHg, with a mean of 30 mmHg, the mean pulmonary-capillary wedge pressure was 14 mmHg, the cardiac index was 2.26 L/min/m², the LV pressure was 125/24 mmHg, and the aortic pressure was 125/75 mmHg. Coronary arteriograms showed normal coronary arteries. A biplane left ventriculogram showed severe hypokinesis of the anterobasal, anterolateral, septal, posterolateral segments, and akinesis of the apical, diaphragmatic, and posterobasal segments. The LV ejection fraction was 0.23. Histological examination

of RV endomyocardial biopsy specimens showed mild fibrosis, thickening of endomyocardium and infiltration of inflammatory cells, which consisted mostly of mononuclear leucocytes. Magnetic resonance imaging revealed localized thinning and a small apical aneurysm with a narrow neck at the LV, which are characteristic features of Chagas' heart disease^{4,5}. No thrombus was detected in the LV (Fig. 3). Abdominal echocardiogram showed dilatation of the inferior vena cava and a slightly enlarged spleen. Immunological examination for *Trypanosoma cruzi* was performed using two methods: indirect immunofluorescence and the Western blotting method. In indirect immunofluorescence, the patient's serum was compared with that of two Brazilian positive controls, as well as that of two Japanese negative controls. The patient's serum showed a positive titer of 256. In Western blotting, the patient's serum (C) was compared with that of two positive controls (A, B) and two negative controls (D, E). As seen in Fig. 4, the patient's serum (C) showed the same bands as that of the positive controls (A, B). We made the diagnosis of Chagas' disease in this patient based on the fact that she had lived in a high-risk region for Chagas' disease, the shape of her heart was characteristic of the disease, and the two methods of serum examination were positive for *Trypanosoma cruzi*.

DISCUSSION

Chagas' disease has an acute and a chronic phase, with an indeterminate phase of two or three decades between the two. The acute phase is characterized by high parasitemia, while only a few parasites are sequestered in tissues in the indeterminate phase⁶. The acute phase can be recognized by unilateral purple palpebral edema (Romaña's sign). However, most cases are undiagnosed because of slight or no symptoms, as in our case. Chronic progressive Chagas' disease develops in 10% to 20% of infected persons and is manifested by a chronic fibrosing myocarditis involving myocardium and the atrioventricular conduction system. It leads to cardiac failure, arrhythmias, thromboembolic phenomena and sudden death⁷. However, these conditions are non-specific

for Chagas' disease and it has been reported that Chagas' disease is mostly undiagnosed or misdiagnosed as either dilated cardiomyopathy or coronary artery disease in the United States. One report showed that 18 of 25 patients had been treated for dilated cardiomyopathy or coronary artery disease before a diagnosis of Chagas' disease was made⁸.

Although the precise pathologic mechanism of Chagas' heart disease is not yet known, some kind of autoimmunity is believed to participate in the pathogenesis⁹. Reactivation of the disease in the chronic phase and transmission among immunosuppressed and immunocompromised patients are now possible problems!^{10,11}

In our case, the histological findings of the endomyocardial biopsy specimens were non-specific. It has been reported that in a histological examination of an endomyocardial biopsy specimen, intracellular parasites in cardiac myocytes are frequently found only in the acute phases, although there is almost no specific change for Chagas' disease in the chronic phase⁶. Therefore, the diagnosis of chronic Chagas' heart disease can not be made on the basis of histological examination alone. Indirect immunofluorescence and Western blotting for *Trypanosoma cruzi* in the present case are widely used in Latin America!¹² Since these two methods are highly sensitive, but lack specificity, it is generally recommended that a serum examination should be positive by at least two different assay methods to make the diagnosis. Recently, to improve the specificity, the polymerase chain reaction has been used to detect nuclear DNA of *Trypanosoma cruzi*!¹³

Localized thinning and a small apical aneurysm with a narrow neck at the left ventricle in the present case are important features in this disease. This relatively specific finding is detected at the apex in more than 50% of Chagas' hearts and is predominant (83%) in the left ventricle. The diameter of the aneurysm usually does not exceed 5 cm!¹⁴

In our present case, no direct demonstration of *Trypanosoma cruzi* in the histological specimen nor immunohistological examination of the specimen were done. Therefore, the definitive diagnosis of Chagas' disease cannot be made. However, the patient's long-term presence in the high-risk area,

positive results of both indirect immunofluorescence and the Western blotting method, and characteristic finding of left ventricular aneurysm, the possibility for the patient having Chagas's heart disease is thought to be very high.

In the United States, Chagas' disease has become an important public health problem. According to the Immigration and Naturalization Service, almost 5 million immigrants from Latin America settled in the United States from 1961 to 1987. It is presumed that about 370,000 Latin American immigrants in the United States are infected with *Trypanosoma cruzi*, and 74,000 are in the chronic phase of Chagas' disease.¹⁵ In one study performed in Washington, DC, a positive seroreactivity was found in 5% of 205 voluntary blood donors who had immigrated from El Salvador and Nicaragua.¹⁶ It has been reported that the attack rate after transfusion of seropositive blood products ranges from 12% to 50%.¹⁵ Transmission of the parasite by transfusion of contaminated blood and transplantation of contaminated organs has become a serious problem because the screening test is not yet performed in blood banks. In Japan, since the Immigration Law was revised in 1992, the number of immigrants from endemic areas (especially Brazil) has increased rapidly due to historical and economic conditions. There were 147,803 immigrants from Brazil to Japan in 1992 (11.5% of all immigrants).¹⁷ This represents a remarkable increase from just 4,150 (0.4% of all immigrants) in 1988.¹⁶ Since the total number of immigrants from Latin America in 1992 was 187,140,¹⁵ it is estimated that there are now about 13,800 infected persons and 2,800 persons with progressive chronic Chagas' disease in Japan. Therefore, the risk of transfusion-associated transmission is not negligible. Since Chagas' disease is not common in Japan, there is a good chance of misdiagnosis or undiagnosis, as in the United States. In addition, the screening test is not performed in blood banks in Japan, as in the United States. Due to the changing international economic environment, the number of immigrants who move from developing countries to developed countries should continue to remain high.

Thus, we can expect that endemic diseases, such as Chagas' disease, may be seen more often in Japan.

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