Cardiomyopathies produced by Toxoplasma gondii

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Toxoplasma gondii, a parasitic agent, can produce lesions in the brain, eyes, uterus, myocardium, lymph glands, etc. in adults, children, and fetus.[1-6] Toxoplasmic etiology of cardiomyopathies has not been investigated as thoroughly as other causes of cardiac involvement. We and others have been studying this parasitic etiology of cardiomyopathies during the last 6 years.[7-11] This report includes 11 patients in which Toxoplasma gondii seems to be the most probable etiology. In 3 of these patients, there were evidences of severe myocardium involvement as shown by necropsy and in one of them a parasite was found in the myocardium.

Material and method

Since March, 1960, through April, 1966, every patient suffering from a myocardiopathy was investigated as follows: history and physical examination, nutritional habits, alcoholic ingestion, electrocardiogram (ECG), chest x-rays with heart volume calculated by Rohrer and Kahlstorf method,[12] phonocardiogram, serologic test for syphilis, toxoplasmic infection and Chagas' disease, electrophoresis of plasma proteins, antistreptolysins titer, investigation of lupus erythematosus disseminatus cells, and all the routine laboratory tests (blood cell count, urine, glycemia, and uremia). Furthermore, vectorcardiograms (VCG) according to Grishmann's cubic system was performed in 10 patients and heart catheterization in 5. Cardiomyopathy diagnosis was made whenever any manifestation of heart disease with or without cardiac enlargement or heart failure was found in patients in which atherosclerosis, hypertension, syphilis, rheumatic heart disease, cor pulmonale, congenital heart disease, or other known etiologies were ruled out.[13] Toxoplasmic etiology was accepted only when titers of 1/64 of Sabin and Feldman and/or hemagglutination (HAT) reactions increased, and complement fixation test (C.F.T.) was positive in any moment during the course of the illness.[6,14-16] Sabin and Feldman and HAT reaction within a range of 1/64, with negative C.F.T., are considered normal in our country.[14-16] Serologic tests are considered highly specific for toxoplasmic infection according to Thiermann and Knierim,[14-17] and to our own experience as described below.

Our case material comprises 2 groups of patients; the first group with heart failure and the second group without. In the first group, we had 3 men and 2 women with an

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age distribution ranging from 30 to 49 years. In the second group, there were 3 men and 3 women whose ages ranged from 14 to 49 (only 1 woman was 49, the other patients ranged from 14 to 25).

Specific treatment was performed 13 times in 11 patients, with 50 mg. of pyrimethamine (Daraprim), 1 gram of sulfamethoxypyridazine, and 1 mg. per kilogram of weight of prednisone during the first 10 days; in the following 10 days, half of the doses of pyrimethamine and sulfamethoxypyridazine were used, and prednisone was given in progressively decreasing doses. Case 4 received a second treatment when she showed a serologic reactivation. The same was done with Case 6 when a choroiditis appeared coincident with serologic reactivation 3 years after the first treatment. In a pregnant woman (Case 1), no prednisone was given and a mixture of sulfadiazine, sulfamerazine, and sulfamethazine was administered in doses of 3 grams for the first 10 days and 2 grams for the second 10 days. In the patients with heart failure, we did not administer digitalis or diuretic in order to assess the effectiveness of the treatment described.

An epidemiologic investigation was performed in all patients. This included a serologic study of the persons living with the patient and a history of contacts with domestic animals such as chickens, cats, and dogs. In Case 5, an experimental inoculation of a macerate of an axillary gland was performed in mice. Necropsies were carried out in the cases of the 3 patients who died. Histologic study was thoroughly done. Multiple blocks were obtained and studied in serial sections. In 2 of

Table I. *Patients without heart failure*

Case	*Age*	*Sex*	*Symptoms before admission*	*Complications*	*Results*
1	19	F	3 mo.; precordial pains, palpitations, obstetrical problems; 1 child with congenital disease died at delivery	None	Good; clinical improvement; cardiac complaints disappeared; she had 2 pregnancies without complications; RBBB persisted
2	17	M	5 mo.; palpitations and precordial oppression	Multiple pulmonary emboli	Bad; died 50 days after admission; ECG showed progressive myocardial damage; Toxoplasma recovered from myocardium by experimental innoculation
3	23	F	1 mo.; palpitations and precordial pains; sister of Case 2	None	Excellent; complaints disappeared; ECG became normal; heart size became normal; no limitations 3 years after admission
4	49	F	1 yr.; palpitations and shortness of breath	None	Excellent; symptoms disappeared; ECG became normal; heart size decreased; symptom-free 3 years after treatment; serologic reactivation treated
5	14	M	1 mo.; palpitations and dyspnea on great efforts	Generalized toxoplasmosis; maculopapular exanthema, lymphadenopathy, fever; innoculation of a macerate of an axillary gland in mice gave positive reactions but parasite not recovered	Excellent; symptom-free 3 years after treatment; ECG without alterations; heart size became normal; no limitations on efforts
6	25	M	4 mo.; palpitations and precordial pains; dyspnea on effort	Gastrointestinal bleeding; bilateral choroiditis 3 years after heart involvement with serologic reactivation	Good; shortness of breath persisted; palpitations disappeared; ECG normal after 5 months of treatment; serologic reactivation and choroiditis treated with excellent results

these patients, experimental innoculations of a macerate of cardiac tissues in mice were done. In Case 2, innoculation with macerate of a mediastinal gland and spleen was also performed. Mice were observed for periods ranging from 40 to 120 days during which time serologic reactions were repeatedly performed (Sabin and Feldmann and C.F.T.).

Results

Clinical picture. The clinical picture, electrocardiographic and radiologic findings are summarized in Tables I, II, III, and IV. Five patients were admitted with symptoms of heart failure. Palpitations and/or precordial pain were the only symptoms in 6 patients; in all of these patients there were arrhythmias or alterations of the repolarization in the ECG and enlargement of one or more cavities as shown by x-rays. The symptoms were present 1 month to 3 years before admission. It is interesting to note that patients with heart failure, in general, had symptoms for a longer period of time than those without heart failure. In patients without heart failure, complaints had been present for periods of less than 6 months, except in the case of one patient in whom symptoms had appeared 1 year before admission. The shortest symptomatic period in the patients with heart failure was 8 months (Case 11), but the other 4 had symptoms for at least 1 year before admission.

The physical examination only showed signs related to heart failure or arrhythmias. In one patient, there was gland enlargement as a manifestation of a generalized toxoplasmosis (Case 5). Hepatomegaly was only present in patients with congestive heart failure. A short systolic murmur in different areas was the most common finding in auscultation and phonocardiography. In Case 8, a holosystolic murmur of the mitral area was heard and inscribed, but it disappeared after treatment (Fig. 1). In another case, an early diastolic murmur

Table II. *Electrocardiographic* and radiologic findings in patients without heart failure*

Case	*Electrocardiogram*	*Radiology*
1	A-V block 2:1; complete RBBB	Heart volume+† LA + LV + RV + PA dilated
2	Ventricular premature beats; A-V block (P-R 0, 24″); subendocardiac damage; incomplete LBBB	Heart volume + LA + to ++ RV ++ PA dilated Ao. dilated
3	ST-T changes; inverted T waves in D_3 and aV_F	Heart volume 0 to + LA ++
4	Bigeminy ST-T changes	Heart volume ++ LV +++
5	A-V block 2:1; incomplete LBBB; ventricular premature beats; left ventricle anterior wall ischemia	Heart volume + LA + LV ++ RV +++
6	ST-T changes LVH	Heart volume + RA ++ RV normal LV ++

*Abbreviations: RBBB, right bundle branch block; LBBB, left bundle branch block; RVH, right ventricular hypertrophy; LVH, left ventricular hypertrophy; BVH, biventricular hypertrophy; LA, left atrium; LV, left ventricle; RV, right ventricle; RA, right atrium; PA, pulmonary artery; and Ao., aorta.

†Size of cavities between 1 and 4 + : +, slight (means double heart volume as expected for body weight and height); ++, moderate (means triple heart volume as expected for body weight and height); +++, marked; and ++++, very marked.

Table III. *Patients with heart failure*

Case	*Age*	*Sex*	*Symptoms before admission*	*Complications*	*Results*
7	49	M	2 yr.; symptoms of left ventricular failure	None	Good; symptoms disappeared; ischemic T waves and ventricular premature beats disappeared; heart size reduced 50% without digitalis for 5 years after discharge
8	30	M	1 yr.; symptoms of left ventricular failure	None	Excellent; symptom-free 2 years after treatment; ECG normal; heart size decreased
9	44	F	3 yr.; congestive heart failure	None	Fair; transient clinical improvement; under control for 2 years with diuretics; no digitalis; heart size unchanged
10	44	F	3 yr.; congestive heart failure	None	Bad; transient clinical improvement; premature beats disappeared; heart size augmented; died suddenly 6 months after treatment
11	43	M	8 mo.; congestive heart failure	None	Bad; progressive deterioration; ECG showed progressive left bundle block; died 1 month after admission

Table IV. *Electrocardiographic* and radiologic findings in patients with heart failure*

Case	*Electrocardiogram*	*Radiology*
7	Ventricular premature beats; incomplete LBB; left ventricle lateral ischemia; LVH	Heart volume +++ RA + RV ++ LA ++ to +++ LV +++
8	A-V block (P-R 0, 24″); ST-T changes; left atrium hypertrophy; BVH	Heart volume +++ RA ++ RV normal LV ++
9	Bigeminy; A-V block (P-R 0, 26″); incomplete LBBB; LAH; BVH	Heart volume +++ RA ++ RV +++ LA +++ to ++++ LV +++ PA dilated Ao. dilated
10	Electric alternance; multiple ventricular and supraventricular premature beats; LVH; P waves alterations	Heart volume +++ RA +++ RV ++ LA + LV +++
11	Atrial fibrillation; complete LBBB	Heart volume ++++ RA ++ LA +++ to ++++ PA dilated Ao. dilated

*Abbreviations as in Table II.

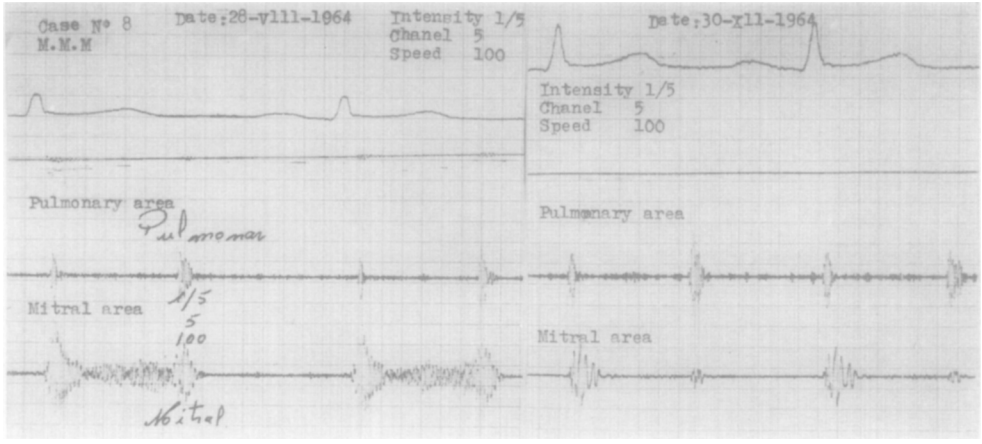

Fig. *1.* Phonocardiograms recorded before and after treatment. Pansystolic murmur of the mitral area disappeared. Both tracings were registered with the same technique (Case 8).

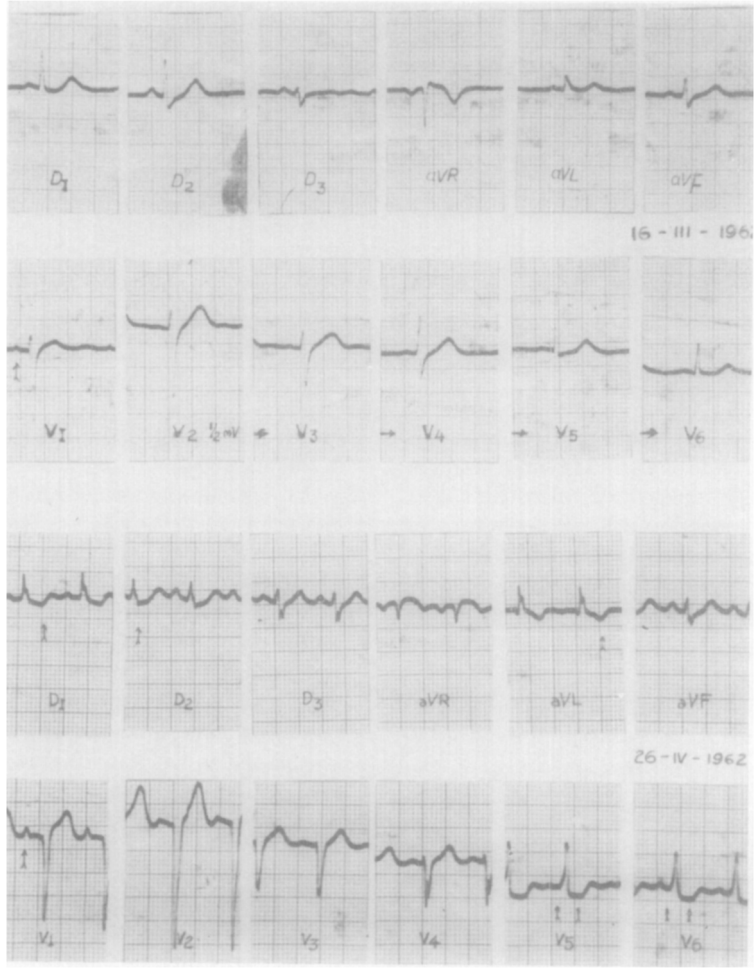

Fig. *2.* First tracing when admitted, shows slight alterations of ST-T segment in D_1, D_2, and V_5. Second tracing shows alterations of ST-T segment suggestive of left ventricle subendocardial injury, retarded A-V conduction, changes in P waves (arrow in V_1), and disappearance of R in V_1 and V_2 (Case 2).

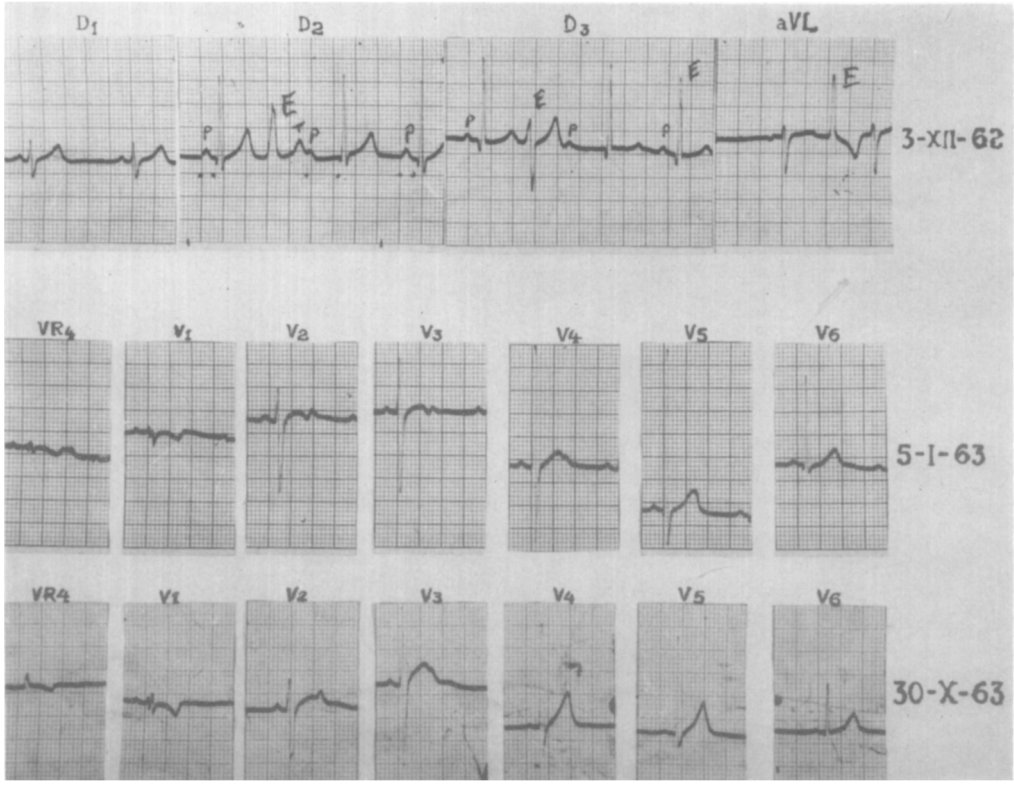

Fig. *3.* First tracing before treatment shows A-V block of 2:1 type. Second tracing, after treatment, shows normalization of A-V block, but alterations of T, of ischemic type in V_{2-3}, which became normal in third tracing (Case 5).

along the left parasternal border was inscribed (Case 2). This is an unusual finding in patients with primary myocardial disease.[18] In this case, Toxoplasma gondii was recovered from myocardium and necrotic lesions were found in the ascending aorta. In 9 patients, there were arrhythmias: 1 had atrial fibrillation, 6, supraventricular premature beats, 1, atrioventricular (A-V) block 2:1 associated to ventricular premature beats, and 1, A-V block 2:1. A prolonged P-R interval was present in 3 patients; in 2 of them, it was associated with ventricular premature beats. There was a bundle branch block of the right side in 1, and of the left side in 5 patients (Cases 2, 5, 7, 9, and 11). In 6 patients, there were electrocardiographic tracings suggestive of myocardial damage or ischemias (Cases 2, 3, 4, 5, 6, and 8); 4 of them were young patients 14-, 17-, 23-, and 25-years-old (Figs. 2 and 3) and in 1 who died (17-years-old, Case 2) necropsy did not show coronary artery disease.

VCG's in 10 patients showed no differences with ECG tracings except in 1 case (Case 6) in which the VCG showed an incomplete right bundle branch block (RBBB) that the ECG failed to show.

The x-rays showed enlargement in all patients. In 2, there was enlargement of only 1cavity; the left atrium in one (Case 3) and the left ventricle in the other (Case 4). Even the patients without heart failure had moderate to important cardiac enlargement. In Cases 3, 4, and 5, without heart failure, heart size became normal after treatment, and in Cases 7 and 8, with heart failure, a significant reduction of heart size was observed.

In 5 patients, a right heart catheterization was performed. In 3 of the patients in whom the procedure was performed when there was no clinical failure (Cases 3, 5, and

Table V. *Range of titers of serologic reactions before and after treatment*

Case	*Sabin and Feldmann*	*Hemagglutination*	*Complement fixation test*
1	B 1/64-1/1,024	1/64-1/512	(−)-1/5
	A 1/1,000-1/64	1/512-1/64	1/5-(−)
2	B 1/256	1/512	(−)-1/5
	A 1/256	1/512	1/5
3	B 1/64-1/256	1/64-1/512	(−)-1/5
	A 1/256-1/64	1/512-1/64	1/5-(−)
4	B 1/64-1/256	1/64-1/512	(−)-1/5
	A 1/256	1/512	(−)-1/5-(−)
5	B 1/512	1/512-1/2,000	1/20-1/80
	A 1/512-1/256	1/2,000-1/64	1/80-(−)
6	B 1/256-1/512	1/256-1/512	1/10-1/80
	A 1/512-1/256	1/512-1/256	1/80-1/5
7	B 1/16-1/256	1/64-1/512	(−)-1/5
	A 1/256	1/512-1/64	1/5-(−)
8	B 1/16-1/64	1/256	(−)-1/5
	A 1/64-1/16	1/256-1/64	1/5-(−)
9	B 1/4,000	1/8,000	1/20
	A 1/5,000	1/8,000-1/256	1/20-(−)
10	B 1/16-1/256	1/64-1/512	(−)-1/5
	A 1/256-1/64	1/512-1/256	1/5-(−)
11	B 1/64	1/64-1/256	(−)-1/5
	A 1/64	1/256	1/5

8), cardiac index and pulmonary resistances were normal. In Case 3, in which a left atrial enlargement by x-rays was found, a transseptal catheterization of the left atrium revealed a normal pressure and the calculated mitral area according to Gorlin's formula was normal (4 sq. cm.). In 1 patient with clinical failure (Case 7), there was a low cardiac index, high vascular resistance, and an increase in arteriovenous oxygen difference. In all of the patients, there was a slight elevation of right atrial pressure (mean 5 to 12 mm. Hg).

The serologic study is shown in Table V. All the patients had titers which were considered significant for diagnosing toxoplasmic infection, and all of them also presented a positive complement fixation test which indicated actual activity of the disease. The epidemiologic investigation demonstrated direct contact with domestic animals such as dogs, cats, and chickens in 10 patients. A total of 12 relatives were studied. There was active serologic infection in 1 brother and a sister of Case 2, who died, and from which Toxoplasma gondii was recovered from the myocardium. The sister is included in this report (Case 3). The brother refused further studies, even though he had cardiac enlargement, dyspnea on effort, and palpitations.

Results of treatment. Details are given in Tables I and III. Among the 6 patients who were admitted without heart failure, one died as a result of pulmonary emboli and acute cor pulmonale (Case 2). In the other 5, the results of treatment were excellent because symptoms disappeared in all but 1 patient (Case 6), heart size became normal or decreased significantly, and the arrhythmias or electrocardiographic pattern of ischemia improved or disappeared. One of these 5 patients was followed-up for 2 years, and the other 4 for periods of 3 years. Two of them (Cases 4 and 6) had a serologic reactivation without signs of new cardiac involvement. In Case 6, this serologic reactivation coincided with bilateral choroiditis. This complication subsided after a second treatment. None of them showed recurring symptoms. Case 5 presented signs of generalized acute toxoplasmosis at the time when he was admitted; maculopapular exanthema, adenopathy, fever, and general malaise. Experimental innoculation of an axillary gland macerate in mice gave positive serologic reactions but the parasite was not recovered. Symptoms disappeared after treatment.

Two of the 5 patients with heart failure died (Cases 10 and 11). In one of them (Case 10), in spite of clinical improvement, x-rays showed an increase of heart size and she died suddenly 6 months after treatment was finished. The other patient died in refractory insufficiency 1 month after treatment. The ECG showed progressive left bundle branch block (LBBB). Three patients with heart failure (Cases 7, 8, and 9) showed a marked clinical improvement without the use of digitalis, and they have been compensated for periods of 2 to 5 years.

Only 1 patient (Case 6) showed secondary reaction to treatment. He had a gastrointestinal bleeding which subsided with the interruption of prednisone.

Pathology. The 2 patients who died in cardiac insufficiency showed marked enlargement of all cavities. One patient (Case 11) had a cardiac weight of 650 grams with marked hypertrophy and dilatation of all

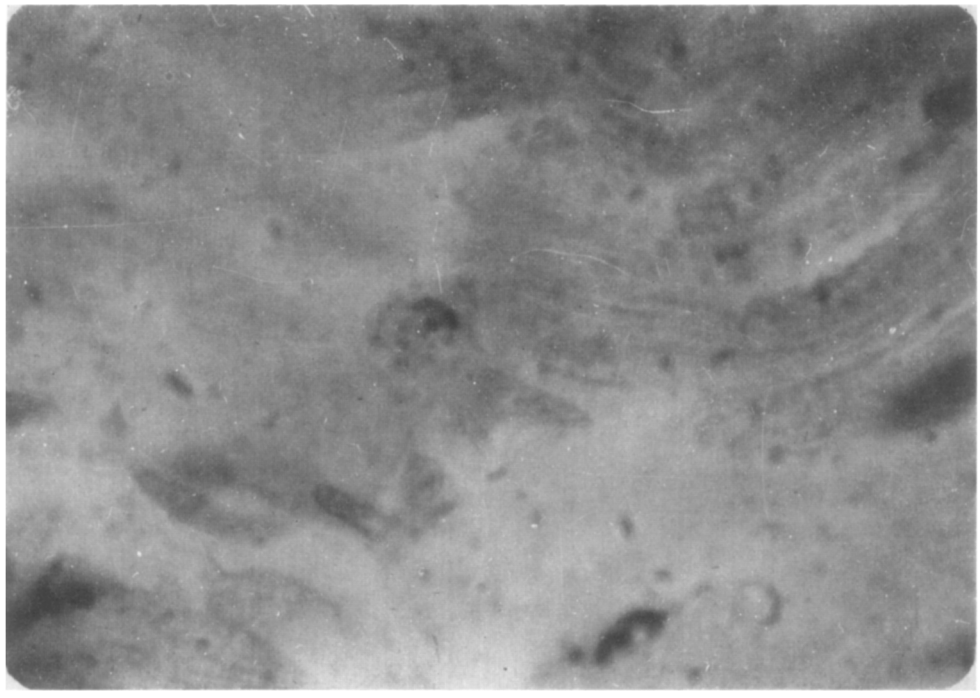

Fig. 4. Histologic section of myocardium showing a pseudocyst of Toxoplasma gondii. Microphotograph taken with immersion lens (100/1, 30; Case 2).

Fig. 5. Histologic section of ascending aorta taken with minor magnification (10/0, 25) to show the 3 layers. There are 2 necrotic focuses surrounded by polynuclear infiltrate. There is marked destruction of the media but also of the other 2 layers. Toxoplasma was not recovered from this part but necrotic lesions are similar to those produced by the parasite (Case 2).

cavities, especially of the left ventricle. Microscopic study in this patient revealed extensive fibrosis in both ventricles mainly in the interventricular septum. Inflammatory infiltration was not found. The coronary arteries were thoroughly studied, but did not show signs of atherosclerosis. There was valvular indemnity. Experimental inoculation of myocardial tissue in mice was performed but Toxoplasma was not recovered after 120 days of observation.

One patient (Case 10) died in the street and an autopsy was performed at the city morgue. As in Case 11, there was a marked enlargement and hypertrophy of myocardium with extensive fibrotic scars but coronary atheroma or valvular damage were not found.

In Case 2, Toxoplasma gondii was recovered from the myocardium. A complete report of this case has already been made.[10] The parasite was found in the form of pseudocysts in the myocardium (Fig. 4). The ascending aorta showed inflammation involving the 3 layers (Fig. 5). Experimental innoculation in mice was successful. Toxoplasma gondii was recovered after 51 days. Mice which were innoculated with a macerate of the spleen showed positive Sabin and Feldman reaction with titers of 1/2,000 and C.F.T. of 1/4,000. Those innoculated with macerate of a mediastinal lymph node showed no reaction.

Discussion

There is little doubt that in these patients Toxoplasma gondii infection was almost certainly the etiology of heart disease. We have demonstrated the presence of the parasite in the myocardium in 1 of the patients (Case 2). A second patient had a bilateral choroiditis 3 years after heart involvement (Case 6). This patient had prolonged fever of unknown etiology at the age of 14 with adenopathy which subsided spontaneously. In a third patient (Case 5), mice innoculated with a macerate of an axillary gland showed positive serologic reactions. Although it is impossible to rule out other etiologies of cardiac involvement in the rest of the patients, the most common causes of heart disease were not present and the serologic study was diagnostic of Toxoplasma.[6,14,16,17] In our patients, the titers were higher than those of the general population, which were found to be no higher than 1/64.[15,19] Furthermore, serologic reactions were performed in 112 patients with heart disease of different etiologies. We found only 2 patients in which the titers were higher than 1/64. One of these patients had constrictive pericarditis and the other a rheumatic mitral regurgitation. The titers for HAT were 1/1,024 and 1/4,000, respectively, with positive C.F.T. We believe this patient had active toxoplasmosis. In the other 110 patients, the titers were negative or their maximal value was not higher than 1/64. We considered rising titers and positive C.F.T. which showed activity of the disease to be significant.[3,4,14,16] As has been observed by others,[14,16] C.F.T. became negative shortly after treatment. The epidemiologic study was highly important because it demonstrated a very high incidence of contact with animals which have been considered as carriers of Toxoplasma gondii[20] and permitted us to discover a cardiac compromise in a very early stage in a relative of 1 of the patients (Case 2). The serologic study and the electrocardiographic alterations were the most important diagnostic elements in all the patients. It is important to note that the ECG fluctuates and must, therefore, be repeated periodically.

It is noteworthy that most of the patients were under 40 years of age, an age group in which atherosclerotic heart disease is very uncommon in Chile. This is important if we consider the electrocardiographic tracings showing patterns of ischemia or subendocardiac damage even in patients who were well under 30 years of age.

It seems reasonable to separate patients into 2 distinct groups; one without heart failure which had the shortest history before admission and a second one which presented cardiac failure and had the longest history of complaints. The first group showed a marked improvement after treatment not only of the clinical picture but also of the ECG and heart size. We considered the results of treatment in this group as good or excellent in most of them. Although the complaints were vague and nonspecific, cardiac involvement was conclusively demonstrated by alterations of ECG and x-rays. All the patients showed enlargement of one or more cavities from slight to moderate.

This coincides with Paulley and co-workers[3,4] findings.

Treatment was more effective in the group of patients with left ventricular failure than in those with congestive heart failure. This group showed the greatest cardiac enlargement at x-rays.

It has been thought that a specific strain of Toxoplasma might be responsible for the cardiac involvement,[2] Case 5, however, would suggest the opposite because he presented myocardial involvement simultaneously with fever, maculopapular exanthema, and lymphadenopathy which have been described in acute toxoplasmosis in adults.[2] We would consider this case as a miliary form according to Theologides' classification.[21] Experimental innoculation of a lymph node from this boy gave highly suspicious results because mice presented very high titers of HAT although Toxoplasma was not recovered. Case 6 is another example of different localization of the parasite in the same patient. These facts lead us to think that in some patients cardiac compromise could be the only or the most prominent manifestation of a generalized disease. This was analyzed by Bengtsson.[22]

Hemodynamic findings in 5 of our patients showed no remarkable or specific feature and the procedure was of no risk at all.

We have not seen Stokes-Adams crisis in our patients as found by Shee,[23] although in 2 patients there was A-V block of the 2:1 type. The most frequent arrhythmia was the supraventricular premature beats.

Treatment was made with an association of prednisone with the drugs commonly used (pyrimethamine and sulfadrugs).[2,6] Results were satisfactory in those patients without heart failure and only fair or poor in those with heart failure. We used prednisone because it has been effective in bundle branch and A-V blocks[23] and because the necrotic lesion of Toxoplasma is most probably an autoimmune phenomenon[6] and corticosteroids might control it and prevent later fibrosis. It might be of great value to initiate treatment early in the evolution of the disease. This is exemplified by Case 3. She was a sister of Case 2 and when she came for a routine epidemiologic checkup, she had a Sabin and Feldman reaction of 1/64, but C.F.T. was negative. She had no cardiac limitations or complaints and the ECG and chest x-rays were normal. After a period of 2 months, she complained of palpitations and precordial pains. The ECG showed alterations of repolarization and there appeared to be left atrial enlargement on the x-rays. The serologic study showed Sabin and Feldmann reaction of 1/256, HAT 1/512, and positive C.F.T. 1/5. Symptoms disappeared immediately after treatment was started and ECG and x-rays went back to normal. The serologic evolution showed slow regression to normal as in other cases. Her case was followed-up for a period of 3 years during which she had no further complaints.

Pathologic findings in the myocardium have been described as focal necrosis[2,16,17] with lymphocytes, plasma cells, and histiocytic infiltration leading to fibrosis. In one of our patients (Case 2), we found focal necrosis of the 3 layers of the ascending aorta and Toxoplasma was recovered from the myocardium. This focal necrosis of the aorta is most likely of Toxoplasma origin. In the other patients there was only fibrosis. One of them (Case 11) had marked septal fibrosis which would explain the ECG findings of progressive LBBB.

Summary

Eleven cases of cardiomyopathy are presented in which the toxoplasmic infection was ascertained by serologic study. The parasite was recovered from the heart in one of them. All other common etiologies were ruled out by clinical and laboratory procedures.

Results showed 2 different groups of patients: one without and one with cardiac failure. One patient of the first group died as a consequence of pulmonary embolism, and in another, cardiac involvement was part of a generalized acute toxoplasmosis. Two patients of the second group died in refractory insufficiency.

Treatment results were generally good. This study suggests that failure might be due to a late complication of the toxoplasmic infection of the heart and that it is most important that proper diagnosis be made as early as possible.

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