Endomyocardial fibrosis in Egypt: an illustrated review

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Abstract

The detailed features of right sided endomyocardial fibrosis are described in 15 out of 10 000 consecutive patients who all had infection with *Schistosoma mansoni* and came from rural Egypt. Laboratory investigations, 12 lead electrocardiography, chest radiography, and Doppler echocardiography were performed in all patients. Cardiac catheterisation and angiography were performed in eight. Endomyocardial biopsy specimens were obtained from the right ventricles of two patients and pericardial biopsy specimens from two. Pericardiocentesis was performed in all patients. All patients were infected with *S. mansoni* and had schistosomal hepatic fibrosis and ascites. Eleven had splenomegaly. All patients had raised cervical venous pressure with prominent Y descent and atrial fibrillation. Eosinophilia was notably absent. Echocardiography showed apical fibrosis in the right ventricle, obliteration of the ventricle, and moderate to massive exudative pericardial effusion in all patients. Calcification and fibrosis extended into the right ventricular outflow tracts in two patients. Huge right atrial thrombi occurred in five patients. Tricuspid regurgitation (grades I-II) was detected in 11 patients by Doppler ultrasonography. Haemodynamic and angiographic data confirmed the pure right sided restrictive pathophysiology. Pericardial biopsy specimens showed perivascular inflammatory infiltrates in two patients and a schistosomal granuloma in one. Endocardial biopsy specimens showed dense fibrosis with many fibroblasts. Endomyocardial fibrosis in Egypt is unique in several aspects. It always affected only the right side of the heart. Calcification and fibrosis extended to the right ventricular outflow tract. Pericardial inflammatory reaction was present. The relation to schistosomiasis and the link to periportal hepatic fibrosis in these patients is intriguing.

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Endomyocardial fibrosis is a common disease in the humid zones of tropical Africa. It

accounts for 10-20% of deaths due to heart disease in equatorial Africa.¹ The disease is equally frequent in both sexes and affects children and young adults.² Cases of endomyocardial fibrosis are also found throughout the equatorial belt, including India, Brazil, Colombia, and Sri Lanka.³ Recognition of cases outside the tropical zone has been reported with increasing interest, particularly in patients who have never visited tropical regions.⁴⁻⁶

Endomyocardial fibrosis is a form of restrictive cardiomyopathy distinguished by intense endocardial fibrosis of the apical and subvalvar regions of one or both ventricles that results in ventricular inflow obstruction.⁷ Combined right and left ventricular fibrosis occurs in about half the patients, with the left ventricle alone being affected in 40% and the right ventricle alone in only 10%.⁸

We report our experience with 15 Egyptian patients presenting with typical features of right sided endomyocardial fibrosis.

Patients and methods

From September 1991 to April 1993, endomyocardial fibrosis was diagnosed in 15 out of 10 000 consecutive patients in whom echocardiography had been performed at this cardiology unit. The male to female ratio was 2.75:1. The mean age was 35 (9) years, with a range of 16 to 50 years. All of them came from AlBeheira district in the Nile Delta, where schistosomiasis is endemic. They were either agricultural labourers (Fellaheen) or housewives who had had contact with water in canals and drains. Their socioeconomic status was modest. The selection process was not biased so as to include only those with right sided endomyocardial fibrosis.

The clinical presentation and routine laboratory profile, including differential white blood cell count, were recorded in all patients. Standard 12 lead electrocardiography and chest radiography were performed in all patients.

DIAGNOSTIC TECHNIQUES

Cross sectional echocardiography with Doppler ultrasonography was performed in all patients using transducers (2.5 MHz) of either mechanical annular array (OTE SIM 5000) or phased array (HP SONOS 500). Multiple views were obtained using standard techniques. The volume of cardiac chambers was measured using the area-length method. Cardiac catheterisation and ventriculography

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were performed in eight patients (cases 8–15) using a single plane Philip's angiographic system with digital cardiac imaging facility. Pressure recordings were obtained by two transducers of equal sensitivity for simultaneous recording of right and left sided pressures. Endomyocardial biopsy specimens were obtained from the right ventricles of two patients (cases 10 and 11) using a Cordis long sheath and biptome. Pericardiocentesis was performed in all patients through a subxiphoid percutaneous approach under fluoroscopic guidance. Pericardial biopsy specimens were obtained by subxiphoid pericardiostomy in two patients (cases 9 and 10) who had recurrent massive pericardial effusion.

Results

CLINICAL PRESENTATION

All patients had a history of infection with *Schistosoma mansoni*. The duration of illness ranged from one to six years (mean 2.9 (1.4) years). All patients presented with progressive abdominal distension and oedema of both legs followed by exertional dyspnoea. Clinical examination showed that all patients had noticeable distension of the neck veins without inspiratory emptying and a prominent Y descent. There was no pulsus paradoxus in any of the patients. All patients had bilateral leg oedema and ascites. All patients had atrial fibrillation. Right ventricular S3 gallop was heard in 10 patients and tricuspid regurgitation murmur (not exceeding grade 2/6) was detected in eight. No patient had signs of pulmonary hypertension, mitral regurgitation, or left ventricular gallop. Abdominal ultrasound examination showed characteristic periportal fibrosis in all patients. Eleven patients had splenomegaly without generalised lymphadenopathy. One patient (case 14) had bilateral pleural effusion.

RESULTS OF INVESTIGATIONS

None of the patients had eosinophilia. The absolute count of eosinophils ranged from 45 to 180 cells/mm³ with a mean of 87 (39) cells/mm³. Four patients had mild microcytic hypochromic anaemia (cases 4, 8, 9, and 14).

All patients had atrial fibrillation. Low voltage QRS complexes were detected in six patients (cases 2, 4, 9–11, and 14). Otherwise the electrocardiographic findings were non-specific.

A chest x ray film showed that all patients had strikingly enlarged hearts. The mean cardiothoracic ratio was 0.83 (range 0.6–0.9). There was no evidence of pulmonary venous congestion.

ECHOCARDIOGRAPHY (TABLES 1 AND 2)

Cross sectional echocardiography showed that all patients had pericardial effusion, which was moderate in five patients (cases 5, 6, 8, 12, and 14) and massive in the rest. Echocardiographic criteria for cardiac tamponade (right or left ventricular or atrial collapse) were not detected in any patient. All patients had right ventricular apical obliteration and fibrosis (figs 1 and 2), which was so extreme in some patients that the right ventricle looked like a diminutive rudimentary pouch. The right ventricular outflow tract was dilated in eight patients (cases 1, 3, 9–13, and 15). All patients had giant right atria with a volume ranging from 200–1350 ml (mean = 802 (330) ml). Five patients (cases 3, 9, 13–15) had right ventricular apical calcification. Two patients (cases 8 and 11) had dense fibrosis and calcification of the endocardium of the right ventricular outflow tract (fig 3).

None of the patients had left ventricular apical obliteration or endocardial thickening, or both. The size of the left atrium as well as the left ventricle was within normal range. All

Table 1 Cross sectional echocardiographic and Doppler findings in 15 patients with endomyocardial fibrosis and schistosomiasis

Case no	Pericardial effusion	Right ventricular		Tricuspid regurgitation	Mitral valve		Calcification	Thrombi
		Apical obliteration	Outflow dilatation		Prolapse	Regurgitation		
1	Massive	Yes	Yes	Moderate	Mild			
2	Massive	Yes	No	Mild	Mild	Mild		Right atrium
3	Massive	Yes	Yes	Mild	Mild		Right ventricular apex	
4	Massive	Yes	No	Mild	Mild			
5	Moderate	Yes	No	Moderate				
6	Moderate	Yes	No	Mild				Right atrium
7	Massive	Yes	No	Mild				Right atrium
8	Moderate	Yes	No	Mild		Mild	Right ventricular outflow tract Right ventricular apex	Right atrium
9	Massive	Yes	Yes	Mild	Mild			
10	Massive	Yes	Yes	Mild	Mild	Mild	Right ventricular outflow tract	Right atrium
11	Massive	Yes	Yes	Mild	Mild			
12	Moderate	Yes	Yes	Moderate				
13	Massive	Yes	Yes	Mild			Right ventricular apex Right ventricular apex	
14	Moderate	Yes	No	Mild			Right ventricular apex Right ventricular apex	
15	Massive	Yes	Yes	Mild	Mild	Mild	Right ventricular apex	

Table 2 Echocardiographic measurements in 15 patients with endomyocardial fibrosis and schistosomiasis

Case no	Right atrium (ml)	Left atrium (ml)	Left ventricular:		Ejection fraction (%)
			End diastolic volume	End systolic volume	
1	410	42	127	54	57
2	1180	26	80	35	56
3	1049	53	160	65	59
4	990	42	126	50	60
5	520	60	182	89	51
6	1350	28	74	35	53
7	200	25	60	25	58
8	946	32	90	49	45
9	750	35	80	42	48
10	980	25	75	35	53
11	1056	35	80	40	50
12	1011	70	921	99	53
13	495	31	95	35	63
14	482	26	62	30	52
15	619	63	190	70	63
Mean (SD)	802 (330)	39 (15)	112 (50)	50 (21)	55 (5)

Figure 1 Cross sectional echocardiogram of apical four chamber view in patient in case 3 showing right ventricular apical obliteration (RV), dilated right atrium (RA), and pericardial effusion (PE), (LV, left ventricle; LA, left atrium).

Figure 2 Cross sectional echocardiogram of subcostal long axis view in patient in case 10 showing dilated right atrium (RA), right atrial thrombus (TH), right ventricular obliteration, normal left ventricular (LV) endocardial surface, and massive pericardial effusion (PE) (AO, aorta).

Figure 3 Cross sectional echocardiogram of parasternal short axis view in patient in case 11 showing endocardial thickening and calcification (arrow) of the right ventricular outflow tract (RVOT), (RA, right atrium; PA, pulmonary artery; AO, aorta; PE, pericardial effusion).

Figure 4 Cross sectional echocardiographic parasternal short axis view (more rightward than view in figure 3) in patient in case 11 showing a huge right atrial thrombus (T) which fills more than half of the dilated right atrial cavity. (RA, right atrium; RVOT, right ventricular outflow tract; AO, aorta).

right atrial wall. No right ventricular or left ventricular thrombi could be detected in any patient. Mild mitral valve prolapse was detected in nine patients (cases 1–4, 9–11, and 15). No valvar thickening or calcification could be seen at the mitral, pulmonary or aortic valves. It was extremely difficult to judge the state of the tricuspid valve in multiple echocardiographic views because of the huge dilatation of the right atrium and the small right ventricular residual cavity.

Doppler studies detected grade one mitral regurgitation in four patients (cases 2, 8, 10, and 15), grade one tricuspid regurgitation in eight (cases 2–4, 6, 7, 9, and 13), and grade two tricuspid regurgitation in three (cases 1, 5, and 12).

HAEMODYNAMICS

Patients who had cardiac catheterisation (cases 9–15) had raised mean right atrial pressure (range 16–25 mm Hg, mean 20 (4) mm Hg) (table 3). All of them showed a deep Y descent of the right atrial pressure curves (fig 5) and a dip and plateau pattern in the right ventricular pressure tracing. The nadir of the right ventricular diastolic pressure (the dip) ranged from 6 mm Hg to 26 mm Hg with a mean of 12 (6) mm Hg. The plateau of right ventricular diastolic pressure ranged from 15 mm Hg to 28 mm Hg with a mean of 20 (4) mm Hg. The ratio of right ventricular diastolic to systolic pressure in the right

patients had good global left ventricular systolic function (ejection fraction ranged from 45% to 63%, mean 54 (5%)). The right ventricular outflow tract showed increased contractility. Right atrial thrombi were detected in five patients (cases 2, 6–8, and 11). Thrombi were large enough to fill from a third to a half of the dilated right atrium (fig 4), and they looked like they were attached to the

Table 3 Haemodynamic data in eight patients with endomyocardial fibrosis and schistosomiasis who underwent cardiac catheterisation

Pressure (mm Hg)	Case no								Mean (SD)
	8	9	10	11	12	13	14	15	
Right atrial mean	23	25	18	18	16	16	18	25	20 (4)
Right ventricular:									
Diastolic									
Dip	18	26	8	12	8	6	10	10	12 (6)
Plateau	25	28	16	19	15	17	20	20	20 (4)
Systolic	35	46	28	24	25	35	28	35	32 (7)
Diastolic/systolic	0.7	0.6	0.6	0.8	0.6	0.5	0.7	0.7	0.6 (0.1)
Pulmonary artery:									
Systolic	34	45	26	25	25	35	28	32	31 (7)
Diastolic	17	15	12	12	9	11	15	12	13 (3)
Mean	21	22	15	15	13	14	18	17	16 (5)
Mean pulmonary capillary	6	2	8	5	9	8	9	9	7 (2.5)
Left ventricular:									
Systolic	100	90	75	125	110	100	130	90	102 (18)
End diastolic	12	4	7	8	7	10	9	10	8 (2)
Difference between right and left ventricle*	13	24	9	11	8	7	11	10	11 (5)

*Right ventricular diastolic plateau pressure minus left ventricular end diastolic pressure.

ventricle was high, with a mean of 0.6 (0.1) (range 0.5–0.8). All patients had normal pulmonary artery pressure at rest except one patient (case 9) who had had a slightly raised systolic pulmonary artery pressure. Left ventricular pressures and pulmonary capillary wedge pressures were normal. The right ventricular diastolic pressure was evidently higher

than left ventricular diastolic pressure in all patients (pressure difference ranged from 7 mm Hg to 24 mm Hg with a mean of 11 (5) mm Hg). None of the patients showed a dip and plateau pattern in the traces of left ventricular pressure.

ANGIOGRAPHY

In all patients who had ventricular angiography there was obliteration of the right ventricular apex with dilatation of the right ventricular outflow tract. None of these patients had left ventricular apical obliteration. Tricuspid regurgitation was severe in two patients (cases 9 and 11) and moderate in four (cases 10, 12, 13, and 15). No patient had either mitral regurgitation or impairment in left ventricular contractility. A right atrial filling defect was seen in two patients (cases 8 and 11).

PERICARDIOCENTESIS

Pericardiocentesis yielded from 1 l to 3 l of straw coloured pericardial fluid, which proved to be exudate. The protein content ranged from 30–40 g/l. There were few red blood cells and many monocytes. In patients in whom haemodynamic studies had been performed the right sided pressures remained raised after pericardiocentesis.

Figure 5 Top: Right atrial pressure tracing in patient in case 10 showing prominent Y descent (Y) followed by rapid rise and plateau (P) pattern which is more evident with long cycles due to atrial fibrillation. Bottom: Simultaneous traces of right and left ventricular pressure showing the difference between the two ventricles and the raised pressure in the right ventricle.

HISTOPATHOLOGICAL STUDY

Endomyocardial biopsy

Sections of the endomyocardial biopsy specimens showed only endocardial tissue. These sections showed marked fibrosis on trichrome staining. Haematoxylin and eosin showed unexpected hypercellularity of the fibrosis. Cells were mostly fibroblasts.

Pericardial biopsy

Sections of the two pericardial specimens showed mild to moderate pericardial fibrosis and perivascular inflammatory infiltration with lymphocytes and macrophages. There was a schistosome surrounded by granulomatous reaction in a perivascular location in one patient (case 11).

Discussion

Although first reported from tropical Africa,^{9,10} endomyocardial fibrosis has been recognised in other areas outside and within the equatorial belt around the world (France,⁴ Saudi Arabia,⁵ United States,⁶ Brazil,¹¹ and India¹²). The cause of tropical endomyocardial fibrosis is unknown. It seems to be related to the tropical environment, primarily dietary deficiency, and eosinophilia, and different immunological patterns. Previous theories relating endomyocardial fibrosis to magnesium deficiency and increased cerium and thorium¹³⁻¹⁵ have not proved tenable. Although minor degrees of eosinophilia are common in tropical Africa, as a result of helminthic infestation, profuse eosinophilia is seldom seen in tropical endomyocardial fibrosis.^{16,17} High concentrations of malarial immunoglobulin and IgM circulating autoantibodies to thyroid and gastric parietal cell mucosa have been reported in patients with endomyocardial fibrosis.¹⁸

To our knowledge, ours is the first report of endomyocardial fibrosis in patients with schistosomiasis. We studied 15 consecutive patients presenting with right sided endomyocardial fibrosis. Cross sectional echocardiography confirmed the pure right sided nature of the disease in all our patients. Similar clinical¹⁹ and cross sectional echocardiographic findings have been described in patients with right sided endomyocardial fibrosis.^{5,7,20-22} However, the extension of fibrosis and calcification to the right ventricular outflow tract were not features. The haemodynamic^{7,23-25} and angiographic^{1,8,26} features of endomyocardial fibrosis have been reported, but most series have described a mixed form of the disease with both ventricles being affected. Our haemodynamic and angiographic study also confirmed the pure right sided nature of the disease in all patients undergoing catheterisation. Histologically endomyocardial fibrosis is characterised by thickening and fibrosis (acellular collagen tissue) of the endocardium and subjacent myocardium.^{27,28} However, the presence of many cells, mostly fibroblasts, in our patients suggests an ongoing active fibroblastic process.²⁹ Also, the presence of a schistosomal granulomatous reaction in the pericardial biopsy specimen from one of our patients is

unique. To our knowledge, schistosomal granuloma has been reported in only one case of constrictive pericarditis.³⁰

SCHISTOSOMIASIS AND THE HEART

Schistosomal cor pulmonale is the principal cardiac manifestation of schistosomiasis. It is a chronic vascular cor pulmonale caused by widespread damage of the small pulmonary arteries.³¹ Most cases occur in patients with the hepatosplenomegaly form of schistosomiasis. It has not been reported at necropsy in the absence of Symmers' periportal fibrosis.³² In 1953 Girgis and Baragani reviewed 1000 Egyptian patients with heart disease and found that schistosomal cor pulmonale accounted for 2% of all the patients studied.³³ In this hospital, we often see patients with schistosomal cor pulmonale as it is a big referral centre. They present with symptoms of low fixed cardiac output. The results of clinical examination, chest radiography, and 12 lead electrocardiography are diagnostic and indicate severe pulmonary hypertension.³⁴ Atrial fibrillation is a rare finding. Schistosomiasis does not commonly affect the myocardium.^{35,36} Gazayerli found adult schistosomal worms in the coronary vessels at necropsy.³⁷ In 1938 Shaw and Ghareeb studied at necropsy 282 Egyptian patients infected with schistosomiasis.³⁸ They described schistosomal cor pulmonale in 2.1% of cases, but they did not report any case of endomyocardial fibrosis. Cheever *et al* reviewed 400 consecutive and unselected necropsies from Kasr El Ainy Hospital in Cairo in 1978.³⁹ They found 225 cases of infection with *S haematobium* and *S mansoni*. Schistosomal pulmonary arteritis and schistosomal cor pulmonale were present in two of the 11 cases with Symmers' fibrosis. Again, endomyocardial fibrosis was not mentioned.

CHANGING PATTERN OF SCHISTOSOMIASIS IN EGYPT

Abdel Wahab *et al* have described a reversal in the relative frequencies of the two common schistosomal infections in Egypt.⁴⁰ The prevalence of infection with *S mansoni* increased from 3.2% to 73%, whereas infection with *S haematobium*, which had been very common in 1935 (74%), had almost disappeared (2.2%) in 1979. This reversal in the pattern of the two schistosomal infections was also reported by El-Alamy and Cline in the Qalyub region of the Nile Delta.⁴¹ The construction of the Aswan High Dam in upper Egypt may have changed ecological conditions favouring the survival of the snail vector for *S mansoni* (Biomphalaria). Such a reversal of the pattern of schistosomiasis in Egypt would be of great importance because an increase in *S mansoni* infection will increase the morbidity of and mortality from hepatosplenic disease and its sequelae.⁴⁰ Antischistosomal treatment has also undergone a dramatic change in the past 10-15 years in Egypt. Praziquantel has practically replaced antimony compounds. It has been given widely in all rural health units throughout the country.

RELATION OF ENDOMYOCARDIAL FIBROSIS TO SCHISTOSOMIASIS

Fibrosis plays a pivotal role in the pathogenesis of many lesions of chronic schistosomiasis. Symmers' clay pipestem periportal fibrosis was visualised by ultrasonography in all our patients. Ultrasonography is at least as sensitive as wedge biopsy in diagnosing Symmers' fibrosis.⁴² The unknown factors causing fibrosis in the liver may also cause fibrosis in the heart. Dunn *et al* determined the rate of collagen synthesis in slices from schistosomal livers and found it to be 4–25 times greater than normal.⁴³

Restriction of disease to the venous side of the heart suggests that toxins coming from the liver are poured directly through the hepatic veins and inferior vena cava into the right atrium and ventricle, where they inflict their damage. The source of these presumed toxins may be schistosomal granulomas in the liver and the gut, where they may bypass the liver through portosystemic collaterals. Passing through the pulmonary capillary bed seems to neutralise these toxins, thus sparing the left side of the heart.

CONCLUSIONS

We believe that the coexistence of *S. mansoni* and endomyocardial fibrosis in our patients was not merely a coincidence. Why some patients with Symmers' periportal fibrosis develop endomyocardial fibrosis and others do not remains an unanswered question. It bears resemblance to another equally important question: why do some of these same patients develop pulmonary arteritis and cor pulmonale while others do not? A further perplexing issue is: why has endomyocardial fibrosis, not been recognised before in either clinical or postmortem studies in patients with schistosomiasis? The reversal of the relative frequencies of the two schistosomal infections in Egypt may have played a part. The relation of the radical change in treatment to the prevalences of the two types of infection is unknown. We emphasise, however, that today's high technology gave us the opportunity to examine thousands of patients by high resolution cross sectional echocardiography and see what we had not seen or conceived before.

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