Chronic Idiopathic Pericardial Effusion

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Chronic idiopathic pericardial effusion is an uncommon condition, and few cases have been reported from Great Britain. Wood (1956) has drawn attention to 6 cases associated with hypertension and Bedford (1964) has reported 7 with 'chronic effusive pericarditis'. Similar instances, in which the pericardial fluid has contained numerous cholesterol crystals, have been described recently by Griffin and Swan (1963) and Livesley and Jack (1965).

The purpose of this paper is to report 2 patients with chronic pericardial effusion in whom investigations failed to reveal the aetiology. Both of them demonstrate points of special interest, and lipid studies on the serum and pericardial fluid from a patient with 'cholesterol pericarditis' are reported for the first time.

Earlier reports of chronic pericardial effusions of unknown aetiology are reviewed, and diagnostic and therapeutic measures are discussed. The value of a radioactive scanning technique for demonstrating large collections of pericardial fluid is emphasized. In addition, some possible aetiological factors are discussed.

CASE REPORTS

Case 1. A.R., a lady aged 63, was first seen in June 1964, because of dyspnoea and hypertension. She had been referred to a medical unit in May 1960, following a mass radiography film which had shown a large heart shadow. Positive clinical findings at that time were a blood pressure of 210/110 mm.Hg and a grade 1 hypertensive retinopathy. Chest radiograph showed an increase in the transverse cardiac diameter, and an electrocardiogram showed a low voltage pattern.

In January 1963 she sustained an injury to the left side of the chest, with fractured ribs, and subsequently she noticed dyspnoea on climbing hills. The breathlessness increased and was interfering with her house-

work, when she was referred for further investigation in 1964.

Examination revealed a well-looking woman with a blood pressure of 210/130 mm.Hg and a regular pulse with no paradoxus. There was no clinical evidence of hypothyroidism. The jugular venous pressure was raised to 12 cm., and there was a considerable increase in cardiac dullness with an audible atrial sound in the fourth left interspace. The liver was enlarged to two finger breadths, and there was a trace of sacral oedema. No crepitations were heard in the lung fields and there was no ascites. The optic fundi showed arteriovenous nipping.

Investigations. Hæmoglobin was 11.9 g./100 ml.; white cell count 5,600/c.mm.; sedimentation rate 7 mm. in 1 hour (Westergren); serum proteins 7 g./100 ml. (albumin 4 g., globulin 3 g.); serum electrolytes normal; serum cholesterol 250 mg./100 ml. A latex test for rheumatoid factor and a test for antinuclear factor were negative, and LE cells were not found. A Mantoux test was positive 1:1,000.

Chest radiograph revealed a cardiothoracic ratio of 85 per cent, and the electrocardiogram showed low voltage complexes with flattened T waves in the præcordial leads (see Fig. 1 and 3). The presence of a pericardial effusion was suggested by radioactive scanning and confirmed by aspiration of 600 ml. of rust-coloured fluid from the pericardial sac on June 26, 1964. The fluid contained 6 g. protein, and microscopy and culture failed to show any evidence of tuberculosis. After the paracentesis the patient had a spontaneous diuresis and her blood pressure fell to 150/100 mm.Hg. She was treated with chlorthalidone 100 mg. daily, and improved considerably. The jugular venous pressure became normal; the blood pressure stayed around 130/100 mm.Hg; chest radiography indicated a reduction in transverse cardiac diameter, and the electrocardiogram showed increased voltage and upright T waves. The patient was discharged from hospital on August 4, but by October 1964, in spite of lack of symptoms, the electrocardiogram and chest radiograph suggested re-accumulation of the pericardial effusion and she was readmitted for operation.

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FIG. 1.—Case 1. Electrocardiogram immediately before operation and 6 months later.

FIG. 2.—Case 2. Postero-anterior radiograph. (A) Showing large cardiac silhouette. (B) After pericardial aspiration and air replacement. (C) Five months after operation.

FIG. 3.—Case 1. Postero-anterior radiograph. (A) Before operation. (B) Two months after operation.

Operation (November 6). Pleuropericardial fenestration was performed. The pericardium was slightly thickened but no tumour was found. 1,500 ml. fluid were removed from the pericardial sac. Histology of a biopsy specimen of pericardium showed non-specific chronic inflammation and fibrosis.

Progress. The immediate post-operative course was uneventful, and the blood pressure was 150/90 mm.Hg. Subsequent blood pressure readings rose to 210/100 mm.Hg, and treatment with rauwolfia alkaloids was begun. There was no clinical or radiological evidence of recurrence of the effusion and the patient was free from symptoms 10 months after the operation.

Case 2. L.O., a lady aged 46, was first seen in January 1965. She had chorea at the age of 15 years, and a mass radiography film was considered to show cardiac enlargement when she was 26 years, though she was reassured subsequently. In August 1964 she was referred to hospital following a mass miniature x-ray examination. Investigations at that time showed a haemoglobin of 82 per cent, with a normal white cell count; a blood urea of 30 mg./100 ml.; sedimentation rate 16 mm. in 1 hour; and normal electrophoresis of the serum proteins. Chest radiograph revealed a considerable increase in the transverse cardiac diameter.

The patient complained that for the past 9 months she had felt tiredness and dyspnoea on climbing hills. Physical examination revealed a blood pressure of 140/80 mm.Hg, and she was in sinus rhythm with no pulsus paradoxus. There was considerable increase in cardiac dullness and the heart sounds were normal. The jugular venous pressure was normal, the liver could not be felt, and there was no peripheral oedema. No clinical evidence of hypothyroidism was found.

Investigations. Haemoglobin 13.2 g./100 ml.; white cell count 4,500/c.mm.; serum electrolytes normal; serum proteins 7.2 g./100 ml. (albumin 5 g., globulin 2.2 g.) with a normal electrophoretic pattern; serum cholesterol 283 mg./100 ml. A test for antinuclear factor was negative, no LE cells were detected, and the latex test for rheumatoid factor was negative. Gum biopsy showed no evidence of amyloidosis and the Wassermann reaction was negative. The toxoplasma dye test was positive in a titre of 1/128 with a negative complement fixation test. ¹³¹I studies showed that the patient was euthyroid.

Chest radiograph showed a cardiothoracic ratio of 75 per cent and a radioactive scan demonstrated a pericardial effusion. The electrocardiogram showed a low voltage pattern with flattening of the T waves. Cardiac catheterization demonstrated that the catheter tip was well within the outer margin of the heart shadow and a biplane angiogram, with injection of dye into the right ventricle, confirmed the diagnosis. At pericardial aspiration on February 3, 600 ml. pale yellow fluid containing cholesterol crystals was withdrawn and replaced by air (see Fig. 2). The pericardial fluid contained 8 g. protein, and microscopy and cultures showed no evidence of tuberculosis. The lipid content of the pericardial fluid was identical to the lipid content of serum taken after an overnight fast (see Table I).

TABLE I

LIPID COMPOSITION OF FASTING SERUM
AND PERICARDIAL EFFUSION (CASE 2)

Lipid	Total lipid extract	
	Serum	Pericardial effusion
Total cholesterol (mg./100 ml.)	283	291
Free cholesterol (mg./100 ml.)	75	76
Cholesteryl esters (mg./100 ml.)	208	215
Glycerides (mg./100 ml.)	167	162
Phospholipids (mEq/l.)	3.50	3.50
Free fatty acids (mEq/l.)	1.14	1.10

Note: Total lipid extracts of fasting serum and of pericardial fluid were prepared by shaking each with 20 vol. ethanol-ether (3:1) and filtering. Free fatty acids, cholesteryl esters, glycerides, and phospholipids were separated by silicic acid chromatography.

Operation (February 23). Pleuropericardial fenestration was performed. There was no evidence of pericardial neoplasia and histology of a pericardial biopsy specimen showed fibrosis and a chronic inflammatory cellular reaction of a non-specific type.

Progress. Apart from a left-sided pleural effusion, the post-operative course was satisfactory and there had been no recurrence of the pericardial effusion 8 months later.

DISCUSSION

The features of chronic large pericardial effusions have been reviewed by Bedford (1964), and a comprehensive bibliography has been published in his paper. Congestive heart failure is a common mode of presentation, but cases with a prolonged course and few symptoms have been described frequently. Both the present cases were originally referred to hospital after mass miniature radiography, and Case 1 showed evidence of congestive cardiac failure.

Diagnosis and Management. Various techniques have been used to demonstrate the presence of pericardial effusions, including cardiac catheterization (Wood, 1951), angiocardigraphy (Williams and Steinberg, 1949), angiopneumography (Phillips, Burch, and Hellinger, 1961), and pericardial paracentesis. A radioactive scanning technique to determine the presence of pericardial effusion has been described and appears to have the advantage of being simple to perform and is probably less hazardous to the patient than other methods (Rejali, MacIntyre, and Friedell, 1958). Radioactive ¹³¹I-labelled human serum albumin is injected intravenously, and the size of the cardiac blood pool on a scintiscan is matched with the size of the cardiac silhouette on the postero-anterior view of the chest radiograph. In both the present cases this technique suggested the presence of a pericardial

effusion, and the diagnosis was confirmed by pericardial aspiration and at operation. Cardiac catheterization and angiocardigraphy may be hazardous when the alternative diagnosis is severe cardiac failure, and the wider use of the radioactive scanning technique seems justifiable in patients with unexplained enlargement of the heart shadow on x-ray examination.

Bedford (1964) has summarized the causes of chronic pericardial effusion. Neither of the present cases was anæmic and careful clinical and laboratory investigation failed to reveal any evidence of scleroderma or systemic lupus erythematosus. Case 1 had a chest injury 18 months before investigation, but a chest film taken before the accident had shown enlargement of the heart shadow, and it is doubtful whether traumatic hæmopericardium was responsible for the pericardial effusion. It is important to exclude pericardial neoplasm and tuberculosis as causes of the effusion. Chest radiography after pericardial paracentesis with air replacement may demonstrate a pericardial tumour, though visualization at operation is preferable. A biopsy specimen from the pericardium can be taken at thoracotomy and definitive operative treatment can be performed at the same time. The value of pericardial biopsy has been stressed by Proudfit and Effler (1956), and Evans (1961), in the introduction to a symposium on pericardium, has stated that 'pericardial biopsies should be used more frequently'. Antituberculous therapy has often been used for patients with pericardial effusion despite inability to prove a tuberculous ætiology. However, negative findings on microscopy and culture of a pericardial biopsy specimen and the pericardial fluid probably exclude tuberculosis, and antituberculous drugs can be omitted (Souders, 1963; Schwartz, Nay, and Fitzpatrick, 1963). Early operation has been recommended for pericardial effusion whenever conservative treatment has failed to produce a prompt remission in symptoms (Mannix and Dennis, 1955). Thoracotomy was performed, therefore, in both the present cases in order to combine direct inspection of the pericardium, pericardial biopsy, and surgical treatment.

The choice of operation lies between the creation of a pericardial window and pericardectomy with removal of the major part of the pericardium. Pleuropericardial fenestration has been shown to give effective relief of pericardial effusion (Silverstone, 1955; Proudfit and Effler, 1956), though Storey, Stanford, and Maggio (1960) have advocated pericardectomy on the grounds that the pericardial window may close and that it is unlikely to prevent the later development of constrictive pericarditis. Pleuropericardial fenestration operations relieved

the pericardial effusions in both the present patients and there has been no recurrence of the fluid and no evidence of constriction so far.

Ætiology. Viral infection may be responsible for some cases of chronic idiopathic pericardial effusion, but proof of this is lacking. Constrictive pericarditis may follow hæmopericardium (Schaffer, 1961), but persistent pericardial effusion after traumatic hæmopericardium is associated with pyrexia and præcordial pain (Tabatznik and Isaacs, 1961), unlike the type of case under discussion. Case 1 had a chest injury before the discovery of the pericardial effusion, but a chest radiograph taken before the accident had shown an enlarged cardiac silhouette, and it is likely that the effusion was present then.

The report of two brothers with asymptomatic pericardial effusions (Genecin, 1959) raises the possibility of a metabolic defect in some cases. The younger brother had cholesterol crystals in the pericardial fluid, which contained cholesterol 85 mg./100ml. The total fat, cholesterol, phospholipid, and fatty acid content of pericardial fluid has been estimated in a case of isolated chylopericardium (Madison and Logue, 1957), but lipid studies have not been reported previously in patients with chronic idiopathic pericardial effusion. The serum lipids in Case 2 are within normal limits and the same lipids are found in the pericardial fluid, which suggests that serous exudation is an adequate explanation for the lipid content of the pericardial fluid and that it is not necessary to invoke a metabolic defect in this patient. Spodick (1964) has suggested that intrapericardial bleeding is the common denominator in cholesterol-rich effusions, but it is not necessary to postulate pericardial hæmorrhage as the cause of the lipid composition of the fluid in Case 2.

Bedford (1964) has suggested that auto-immune pathology may be involved in the pathogenesis of chronic effusive pericarditis. Positive antinuclear factor tests were found in 3 of his 7 cases, one of which had scleroderma; and Szatkowski and Inoue (1963) have reported a case of "cholesterol pericarditis" with an abnormal latex test for rheumatoid arthritis, though they considered tuberculosis to be the cause of the effusion despite negative smears and cultures of the fluid from the pericardial and pleural cavities. No evidence of auto-antibody production has been found in the present cases. Both had normal erythrocyte sedimentation rates and paper electrophoresis of the serum proteins was normal; LE cells were not found and latex tests for rheumatoid arthritis and systemic lupus erythematosus and an antinuclear factor test were negative.

TABLE II
HYPERTENSION IN PATIENTS WITH CHRONIC IDIOPATHIC PERICARDIAL EFFUSION

Reference	No. of cases	Patient's age and sex	Blood pressure (mm.Hg)	Comment
Levy <i>et al.</i> (1952)	1	44 F	176/112	Hypertension recognized 5 years before pericardial aspiration
Mannix and Dennis (1955)	1	43 F	150/120	"Cholesterol pericarditis"; hypertension persisted after pericardectomy Lower blood pressure readings recorded also Previous operation for "thymoma"; mediastinal scarring suggested as aetiological factor Patient had polycythæmia Hypertension diagnosed 5 years before recognition of pericardial effusion Long history of hypertension, mitral disease, and alcoholism, possible auto-immune pathology Acromegalic
Shumacker and Harris (1956)	1	53 M	210/120	
Genecin (1959)	1	24 M	190/100	
Connolly <i>et al.</i> (1959)	2	64 F	170/100	
Scheuer (1960)	1	43 F	160/120	
Bedford (1964)	2	49 F	180/115	
		41 M	200/120	
		60 F	190/130	

The association of obscure pericardial effusions with hypertension was first noted by Wood in 1956, and it is of interest that several of the cases reported elsewhere have demonstrated the association, though this aspect has not been stressed. Excluding the 6 cases cited by Wood, there have been 9 with chronic pericardial effusion of unknown aetiology and hypertension out of 40 reported cases with adequate investigation and blood pressure records (see Table II). The first patient (Case 1) had been shown to have hypertension 4 years before the diagnosis of pericardial effusion was confirmed. Her blood pressure was reduced after pleuropericardial fenestration, but has since risen again and she has been started on hypotensive medication. The significance of hypertension in cases of chronic idiopathic pericardial effusion is unknown, but an underlying cardiovascular abnormality may be a factor in the production of excess pericardial fluid.

Histology of the pericardium in cases of chronic idiopathic pericardial effusion normally shows fibrosis and an infiltration with chronic inflammatory cells. This thickened pericardium limits reabsorption, and the high colloid osmotic pressure of the pericardial fluid increases the tendency to fluid accumulation. A single causative factor may be responsible for both the exudate and the pericardial thickening, or, alternatively, two separate events may occur. Impaired pericardial absorption may result from damage to the pericardium caused by rheumatic fever (Winters and Soloff, 1961), and Camp and White (1932), in a necropsy study of patients dying in congestive cardiac failure, noted a raised incidence of pericardial effusion in patients with rheumatic heart disease compared with patients with other cardiac disorders. It is interesting that one of the present patients (Case 2) gave a history of chorea in childhood, and other authors have reported patients with chronic idiopathic pericardial effusion and a preceding history of chorea (Connolly

et al., 1959), "migratory arthritis" (Storey *et al.*, 1960), and rheumatic fever (Bedford, 1964). Thus the sequence of events in some chronic effusions of unknown aetiology may be:

Stage 1 Rheumatic fever/chorea → pericarditis → chronic pericardial fibrosis with impaired absorptive surface.

Stage 2 Separate factor at a later date causing exudation into the pericardial sac, e.g. viral infection, auto-immune illness.

Stage 3 Chronic effusion owing to limited reabsorption of fluid by the thickened pericardium with further accumulation of fluid secondary to the high colloid osmotic pressure of the pericardial exudate.

SUMMARY

Two patients with chronic idiopathic pericardial effusion have been described. A radioactive scanning technique has been used to show the pericardial fluid in both cases, and the technique is recommended as a safe, reliable method for the demonstration of large pericardial effusions. Pleuropericardial fenestrations have relieved the symptoms of both patients, and there has been no recurrence of the pericardial fluid. A pericardial biopsy specimen has been taken at operation in both cases, and chronic non-specific pericarditis has been found.

Possible factors in the aetiology of chronic idiopathic pericardial effusion have been discussed. No evidence of auto-immune pathology could be demonstrated in the present cases. The first patient has hypertension and the association of hypertension with chronic pericardial effusion of unknown aetiology has been reported by previous authors, though this aspect has been stressed in few series. The nature of the relationship remains obscure. The second patient is an example of "cholesterol pericarditis" of unknown aetiology, and extensive lipid studies on the serum and the pericardial fluid are reported. This patient has a

previous history of chorea and a possible mechanism by which the chorea may be involved in the pathogenesis of the chronic effusion is suggested.

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