Pulmonary hypertension and filariasis

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Two cases of 'primary' pulmonary hypertension with hypereosinophilia, in whom adult filarial worms were found, are described from Ceylon. The significance of the association between filariasis, tropical pulmonary eosinophilia, and pulmonary hypertension is discussed. It is postulated that pulmonary hypertension followed the chronic destruction of microfilariae in the lungs and their embolization in the lung capillaries and that pulmonary hypertension was secondary to filariasis.

Filariasis due to *W. bancrofti* infection is endemic along the south west coastal border of Ceylon. Tropical pulmonary eosinophilia is also common. 'Primary' pulmonary hypertension has been reported to be relatively more common in Ceylon than in Western countries (Obeyesekere and De Soysa, 1970). The frequent occurrence of high eosinophil counts—levels exceeding 3000/mm³ which is the range commonly associated with tropical pulmonary eosinophilia, positive complement-fixation tests for filariasis in many patients, and the strikingly similar geographical incidence of 'primary' pulmonary hypertension and filariasis suggested a cause-and-effect relation. The purpose of this report is to document two patients with 'primary' pulmonary hypertension and hypereosinophilia with symptoms and signs of tropical pulmonary eosinophilia in whom adult filarial worms were found. The role of filariasis as a probable cause of pulmonary hypertension is discussed.

Case reports

Case 1

A married female schoolteacher, aged 30 years, was admitted to the Cardiology Unit, General Hospital, Colombo, on 12 July 1970, complaining of increasing shortness of breath, fatigue, intermittent pyrexia, and loss of weight of one year's duration. The cough was worse at night and early morning and often accompanied by wheezing. She became breathless when walking half a mile on the flat. Dyspnoea was accompanied by tightness in the chest and dizzy spells. She had lived for many years in a suburb of Colombo where filariasis due to *W. bancrofti* was endemic. On examination, she was underweight but not cyanosed or orthopnoeic. Pulse was small

and regular. Jugular venous pressure was raised 4 cm with a prominent 'a' wave. Blood pressure was 110/90 mmHg. Cardiac impulse was right ventricular in type with a systolic lift over the right ventricular outflow tract. Pulmonary second sound was narrowly split and moved normally with respiration, with a loud second component. An ejection click and soft, grade 2/6 ejection systolic murmur were heard over the pulmonary area. A prominent fourth heart sound was heard over the lower left sternal edge. There were widespread crepitations and sibilant rhonchi all over the chest. The liver was palpable 3 cm. No ankle oedema was present. Blood count showed a haemoglobin level of 12.8 g/100 ml. The total white blood cell count was 18,800/mm³, and the absolute eosinophil count (by Dunger's method) was 11,525/mm³. Erythrocyte sedimentation rate (Westergren) was 30 mm in the first hour. Urinalysis and stools examination were negative. The serum protein level was 7.2 g/100 ml, globulin 3.4 g/100 ml. No microfilariae were seen in thick films prepared from capillary blood collected during the day and night, venous blood collected during the day and night, and pulmonary artery blood collected during cardiac catheterization. The fluorescent antibody test was strongly positive as was an intradermal skin test with filaria antigen. Chest x-ray showed considerable dilatation of the pulmonary artery and main branches with pruning of the peripheral vessels and cardiomegaly (cardiothoracic ratio 0.54) with enlargement of the right ventricle. There were increased reticular markings throughout both lung fields. Electrocardiogram recorded sinus rhythm with an electrical axis of +110°, normal P waves, PR interval 0.16 sec, and right ventricular hypertrophy grade 2 (Hollister and Goodwin, 1963). Cardiac catheterization confirmed the diagnosis of 'primary' pulmonary hypertension. Pulmonary artery pressure 120/56 mmHg. There was no intracardiac shunt. An enlarged right inguinal lymph node detected during cardiac catheterization was excised and sent for histological examination. Paraffin sections stained with haematoxylin and eosin showed a lymph node containing fragments of adult filarial *W. bancrofti*

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FIG. 1 Microscopical section of lymph node showing sections of adult filarial worm *W. bancrofti*. (H. & E. $\times 150$.)

worms (Fig. 1), surrounded by an area of round cell infiltration, mainly eosinophils and polymorphs (eosinophilic pseudoabscess). There was hyperplasia of the lymphoid follicles with pericapsular fibrosis and eosinophilic infiltration in the capsule. The appearances were those of filarial lymphadenitis.

Lung biopsy on 2 September showed diffuse and small focal collections of eosinophils especially around the bronchioles. There were a few focal areas of collapsed lung tissue with thickening of the intima of smaller vessels and medial muscle hypertrophy of the larger vessels—changes compatible with pulmonary hypertension.

Course and diagnosis The patient had typical features of 'primary' pulmonary hypertension, hypereosinophilia, respiratory symptoms, and signs of tropical pulmonary eosinophilia and filarial lymphadenitis confirmed by biopsy. She was treated with diethyl carbamazepine (100 mg thrice daily for 10 days). This was followed by a decrease in her cough and wheezing and a pronounced drop in her absolute eosinophil count from 11,525 to 2019/mm³. However, there was no improvement in her effort dyspnoea, chest discomfort, and dizzy spells. The chest x-ray showed no alteration in the cardiac shadow, the lung fields cleared, highlighting even more the pruning of the proximal pulmonary arteries. The electrocardiogram remained unchanged.

Case 2

A man, aged 35 years, came from a village along the southern coast of Ceylon where filariasis is endemic. He

was admitted to the Cardiology Unit, General Hospital, Colombo, on 23 November 1971, complaining of dyspnoea on exertion and angina of 5 years' duration, syncopal attacks of one month's duration, and haemoptysis. His illness started in 1967 when he noticed increasing breathlessness on exertion accompanied by discomfort in his chest, an irritating cough, and paroxysmal wheezing at night. He was admitted to the local hospital where, after a blood test and chest x-ray, a diagnosis of tropical pulmonary eosinophilia was made and treated with diethyl carbamazepine. He was discharged symptom free and remained so until 1969 when the same symptoms developed. Towards the latter part of 1971, he continued to have a non-productive, irritative cough and wheezing. On 5 November 1971 after recurrent severe haemoptysis, he was admitted to hospital and given a blood transfusion. The dyspnoea on exertion became progressively worse. During the month before admission he had several attacks of syncope after exertion. At the time of his admission to the cardiology unit, he could barely walk 50 yards on the flat.

On examination, the patient was underweight (312.5 kg) and pale. The pulse was regular, jugular venous pressure was raised 6 cm with a prominent 'a' wave, and blood pressure was 110/90 mmHg. The apex beat was in the fifth space in the midclavicular line, the cardiac impulse was right ventricular in type with a prominent systolic lift over the right ventricular outflow tract and left pulmonary artery. On auscultation there was a loud systolic click heard over the pulmonary area, the second sound split narrowly with inspiration, with pronounced accentuation of the second component. There was a prominent fourth heart sound heard over

FIG. 2 *a*) Microscopical section of nodule on epididymis showing sections of mature female filarial worms *W. bancrofti* with microfilariae in the uterus. (H. & E. $\times 150$.) *b*) (H. & E. $\times 750$.)

the lower left sternal edge. There were widespread sibilant rhonchi and fine crepitations heard all over his chest. The liver was palpable 3 cm and the spleen 3 cm below the costal margin. There were two thin fibrous cords about 2 mm in thickness palpable over both medial aspects of the thighs in the region of the long saphenous vein, and a nodule in the head of the left epididymis.

The leucocytes numbered $18,000/\text{mm}^3$ of which 28 per cent were neutrophils, 26 per cent lymphocytes, and 46 per cent eosinophils. The absolute eosinophil count was $6075/\text{mm}^3$. The erythrocyte sedimentation rate was 42 mm in 1 hour. The total serum protein was 6.9 g/100 ml, albumin 2.8 g/100 ml and globulin 4.1 g/100 ml. The haemoglobin level was 10.7 g/100 ml, mean corpuscular haemoglobin concentration was 30 per cent, reticulocytes 4.5 per cent. The red cells were normocytic with mild anisocytosis.

No microfilariae were seen in capillary, venous, or pulmonary artery blood. The fluorescent antibody test for filariasis was strongly positive. Serum alkaline phosphatase was 9 King-Armstrong units, serum aspartate aminotransferase (SGOT) was 15 international units, serum glutamic pyruvic transaminase was 5 international units, serum lactic dehydrogenase was 161 international units (normal 50–170), serum bilirubin 0.6 mg/100 ml, zinc sulphate turbidity 18 units, thymol turbidity 1 unit. Coombs' test, both direct and indirect, was negative. There were no lupus erythematosus cells in the blood. Urinalysis was normal with no bile and normal urobilin. Microscopical examination of faeces showed hookworm ova.

Radiology of chest showed cardiomegaly (CTRO.6) with right ventricular enlargement, prominent right atrium, considerable dilatation of the pulmonary artery and main branches, with pruning of the peripheral vessels. The peripheral lung fields showed increased reticular markings throughout both lung fields.

Electrocardiogram showed sinus rhythm, electrical axis of $+120^\circ$, normal P waves, and right ventricular hypertrophy grade 3. Histological examination of the 'fibrous' cord revealed a lymph node showing some proliferation of reticulum cells with focal collections of melanin pigment. The changes were compatible with dermatotropic lymphadenitis, commonly seen after filarial lymphangitis. Histological examination of the nodule on the epididymis showed a granulomatous reaction around portions of adult female filarial worms (most probably *W. bancrofti*) (Fig. 2) which appeared dead and hyalinized. There was pronounced eosinophilic infiltration in the surrounding tissue. Elsewhere in the section were several scattered fragments of adult filarial worms showing microfilariae in the uterus and nuclear details suggesting recent death of the worm. The appearance was that of a filarial granuloma.

Cardiac catheterization confirmed pulmonary hypertension with pulmonary artery pressure 115/65 mmHg, femoral artery oxygen saturation 92 per cent. There was no intracardiac shunt.

Course, diagnosis, and treatment This patient had all the clinical features of 'primary' pulmonary hypertension (Obeyesekere and De Soysa, 1970). He had a filarial

granuloma on the epididymis confirmed by biopsy. He had features of tropical pulmonary eosinophilia, cough and wheezing, hypereosinophilia, a strongly positive fluorescent antibody test, and hepatosplenomegaly. In addition, he had ankylostomiasis which together with the recent history of haemoptysis was the probable cause of his anaemia. The laboratory investigations excluded a haemolytic anaemia. The anaemia was treated and rapidly corrected with oral ferrous sulphate and ankylostomiasis eradicated with tetrachlorethylene. In view of obvious filarial infection and evidence of tropical pulmonary eosinophilia, he was treated with diethyl carbamazine (150 mg thrice daily for 10 days). His cough and wheezing disappeared, there was a pronounced improvement in his exercise tolerance and other symptoms. There was an immediate drop in his absolute eosinophil count from 6075 to $895/\text{mm}^3$. There was a gradual decrease in the size of the liver and spleen. However, the signs of pulmonary hypertension remained, and the electrocardiographic changes and radiological evidence of cardiomegaly persisted.

Discussion

A study of the biopsy material examined at the Department of Pathology of the Colombo General Hospital between 1966 and 1972 revealed that filarial worms were detected in only 9 out of 22,727 consecutive surgical biopsies, giving a frequency of only 0.039 per cent.

Worms were detected in 5 out of a total of 1357 lymph nodes examined, 2 in 2797 specimens of

FIG. 3 Significant reduction of 'absolute' eosinophil counts in 8 patients with 'primary' pulmonary hypertension and hypereosinophilia after treatment with diethyl carbamazine.

FIG. 4 Map of Ceylon showing areas where *W. bancrofti* is endemic.

breast tissue, 2 in 85 specimens of testicular tissue, and none in 18,486 specimens from other sites. In spite of filariasis being endemic in Ceylon the demonstration of filarial worms in human tissues is extremely rare. There were no recorded cases of adult filarial worms ever being detected in any patients suffering from tropical pulmonary eosinophilia.

Obeyesekere and De Soysa (1970) and Obeyesekere (1972) have previously commented on the higher prevalence of 'primary' pulmonary hypertension in Ceylon when compared with the U.K. In five years (between 1967 and 1972) 65 patients were diagnosed in the Cardiology Unit of the Colombo General Hospital in a consecutive series of 2500 patients investigated with cardiovascular disease, a frequency of 2.6 per cent. Wood (1956) collected only 17 instances in 10 years in a series of 10,000 patients, a frequency of only 0.17 per cent. The following unusual features in Ceylon were also reported: the large number of men affected in a disease which has been previously described predominantly in women, the severity of the pulmonary hypertension, the frequent association with eosinophilia, and a significant fall in the eosinophil counts when the patients were treated with diethyl carba-

mazine (Obeyesekere, 1972). This was strikingly demonstrated in 8 patients with 'primary' pulmonary hypertension who had hypereosinophilia (absolute counts over $4000/\text{mm}^3$) all of whom showed a significant reduction of the eosinophil counts following treatment with diethyl carbamazine (Fig. 3) (Obeyesekere, 1973). The demonstration of filarial worms in the lymph node and the testes of these 2 patients suffering from 'primary' pulmonary hypertension, therefore, appears to corroborate further the view that a true causal relation with filariasis exists.

When considering the pathological lesions caused by *W. bancrofti*, it is well to remember the 3 developmental stages of the parasites in the human host: developing the larvae, adult worms, and microfilariae. Developing larvae and adult worms bring about changes in the adjacent tissues producing the characteristic lesions of classical filariasis: lymphangitis, lymphadenitis, funiculitis, and elephantiasis. Microfilariae are invariably found in the blood but seldom cause lesions. Hypereosinophilia is absent, with an average eosinophil count of $850/\text{mm}^3$ (Lie and Sandosham, 1968). In tropical pulmonary eosinophilia the lesions are not confined to the lymphatic system, and are found in the lung, liver, and spleen associated with hypereosinophilia, pulmonary symptoms—chronic cough and wheezing—and enlargement of lymph glands (Webb Job, and Gault, 1960). Hypereosinophilia is a constant feature with counts varying from 2000 to $4000/\text{mm}^3$. Microfilariae are rarely present in the peripheral blood (D'Abrera, 1958), though continually produced by the adult worms (Meyers and Kouwenaar, 1939). It is now believed that any person hypersensitive to a specific filarial antigen can develop tropical pulmonary eosinophilia (Kouwenaar, 1948; Reisel and Groen, 1951; D'Abrera, 1959; Lie, 1962). As a result microfilariae are destroyed, while adult worms may continue to produce microfilariae for a long time. Meyers and Kouwenaar (1939) described a case where the disease lasted more than three-and-a-half years.

In the 2 patients reported, the improvement of the respiratory symptoms and striking response of the eosinophil counts after treatment with diethyl carbamazine are strongly indicative of tropical pulmonary eosinophilia. The presence of adult filarial worms in the 2 patients further supports the contention that tropical pulmonary eosinophilia is an allergic reaction towards microfilariae which were being continuously destroyed while the adult worms continued to produce them. Their continued destruction in the lung could have led to embolization of the pulmonary capillaries and production of pulmonary hypertension.

These unusual manifestations of filariasis and the demonstration of adult filarial worms (*W. bancrofti*) in two patients suffering from another rare disorder 'primary' pulmonary hypertension, suggest very strongly a causal relation. This is further reinforced by the fact that the majority of patients suffering from 'primary' pulmonary hypertension lived in the very same geographical area where filariasis is endemic (Fig. 4). It is therefore postulated that while the symptoms and signs of tropical pulmonary eosinophilia result from an allergic reaction directed towards microfilariae which are being destroyed, pulmonary hypertension may follow destruction of the microfilariae and their continued embolization in the lung capillaries. This may explain why patients with 'primary' pulmonary hypertension in Ceylon had many features not previously described in Western countries. The pulmonary hypertension is probably not 'primary' but secondary to filariasis.

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