D. L. Brown,[1] *M.D.; C. V. Wetli,*[2] *M.D.; and J. H. Davis,*[3] *M.D.*

Sudden Unexpected Death from Primary Pulmonary Hypertension

REFERENCE: Brown, D. L., Wetli, C. V., and Davis, J. H., **"Sudden Unexpected Death from Primary Pulmonary Hypertension,"** *Journal of Forensic Sciences*, JFSCA, Vol. 26, No. 2, April 1981, pp. 381-386.

ABSTRACT: Five cases of sudden unexpected death from primary pulmonary hypertension (PPH) are reviewed. Right ventricular myocardial hypertrophy and a dilated pulmonary conus may be the only findings at the initial gross examination. Characteristic microscopic changes in the lungs are primarily those of plexiform vascular lesions. The pathophysiology and morphologic alterations of PPH are discussed, and the association of this entity with collagen vascular diseases and mixed connective tissue disease is emphasized. It is concluded that PPH is an unusual cause of sudden unexpected death and its diagnosis may be difficult because prior signs or symptoms may be absent. The increased familial incidence of PPH underscores the necessity of considering this entity in cases of sudden unexpected death of obscure cause.

KEYWORDS: pathology and biology, death, hypertension

Primary pulmonary hypertension (PPH) is an unusual disease with distinctive abnormalities of the pulmonary arterial system. The commonly recognized clinical course is episodic dizziness, syncope, and dyspnea. The average survival after diagnosis is less than four years. Recent reviews have provided excellent clinical and pathological discussions of this entity [*1-4*].

This communication describes five cases of PPH characterized by sudden and unexpected death. In four cases there were no prior clinical diagnoses of the disease. Attention is focused on the morphologic diagnosis of PPH, its occasional familial incidence, occasional association with mixed connective tissue and collagen-vascular disease, and association with hereditary hemorrhagic telangiectasia.

Case Summaries

Case 1

A three-year old white boy was engaged in a friendly pillow fight with his brother when he suddenly collapsed and died. Medical reports indicated his mother had had a normal

Received for publication 5 June 1980; revised manuscript received 21 July 1980; accepted for publication 14 Aug. 1980.

[1] Associate medical examiner, Dade County, Fla.

[2] Associate medical examiner, Dade County, Fla., and assistant professor of pathology, University of Miami School of Medicine, Miami, Fla.

[3] Chief medical examiner, Dade County, Fla., and professor of pathology, University of Miami School of Medicine, Miami, Fla.

Copyright © 1981 by ASTM International

pregnancy and delivery. A systolic murmur at the cardiac apex and aortic region, audible only with the patient leaning forward, was once noted. A week before his death he was treated for a common cold.

At autopsy the lungs were normal except for pronounced telangiectasia beneath the visceral pleura. The right cardiac ventricle was thicker than the left and the pulmonary conus was dilated compared to the aorta. Microscopically an obliterative endothelial proliferation of pulmonary capillaries, arterioles, and small arteries was striking. Occasional plexiform groups of capillaries were associated with dilated venous structures (Fig. 1). Intraluminal and perivascular fibrinoid deposits were infrequent.

Case 2

A 32-year-old female was the mother of the boy in Case 1. Her son's death lead to a medical evaluation that showed she had right ventricular myocardial hypertrophy. Two months later cor pulmonale and polycythemia developed. The following month she died suddenly while hanging clothes.

At autopsy telangiectatic areas were scattered over the skin, visceral pleura, and mesentery. The liver was markedly congested, and the right ventricle wall was 0.5 cm thick. The pulmonary valve was 13 cm in circumference, and the pulmonary artery contained scattered atheromatous plaques. Microscopically the pulmonary arterioles and capillaries had changes similar to those in Case 1. Many arterioles also had hypertrophied muscular walls. Larger pulmonary arteries had a markedly thickened intima infiltrated by lymphocytes and large foamy cells. Pulmonary arteritis was present but rare (Fig. 2).

Case 3

A 27-year-old white female entered a local emergency room complaining of chest pains, dizziness, and syncope. An electrocardiogram disclosed complete atrioventricular block. She was considered to have an anxiety reaction and discharged. Three months later a pregnancy test was positive. One month later she awoke with dyspnea and suddenly collapsed and died.

Postmortem examination revealed alopecia and profuse scaling of the scalp. Pitted scars covering the dorsal aspects of both arms suggested a factitious dermatitis. Approximately 150 mL of yellow serous fluid filled but did not distend the pericardial sac. The 320-g heart was mildly hypertrophied and dilated. The lungs were dusky and edematous. No atherosclerotic plaques were seen in the pulmonary arteries, and there were no telangiectatic areas. There was generalized visceral congestion and the uterus contained a normal conceptus of about three months' gestation.

Microscopic examination revealed splenic arterioles with prominent concentric rings of young collagen infiltrated by lymphocytes and plasma cells. The scalp had the histopathologic changes characteristic of systemic lupus erythematosus [*5*]. A sample of fluoride-preserved blood was positive for antinuclear antibodies (ANA) in a speckled pattern at a dilution of 1:2560. Blood was not tested for extractable nuclear antigen (ENA) [*6*].

Sections of lung showed plexiform groups of capillaries with endothelial proliferation associated with dilated veins and occasional fibrinoid deposits (Fig. 3). The bone marrow was completely hyperplastic, and extramedullary hematopoiesis was seen in splenic red pulp. Axillary lymph nodes were hyperplastic, but other lymph nodes and the thymus appeared normal.

Case 4

A 44-year-old white female was evaluated for exertional dyspnea and Raynaud's phenomenon. She had an ENA titer of 1:1 000 000, an ANA titer of 1:320, false positive

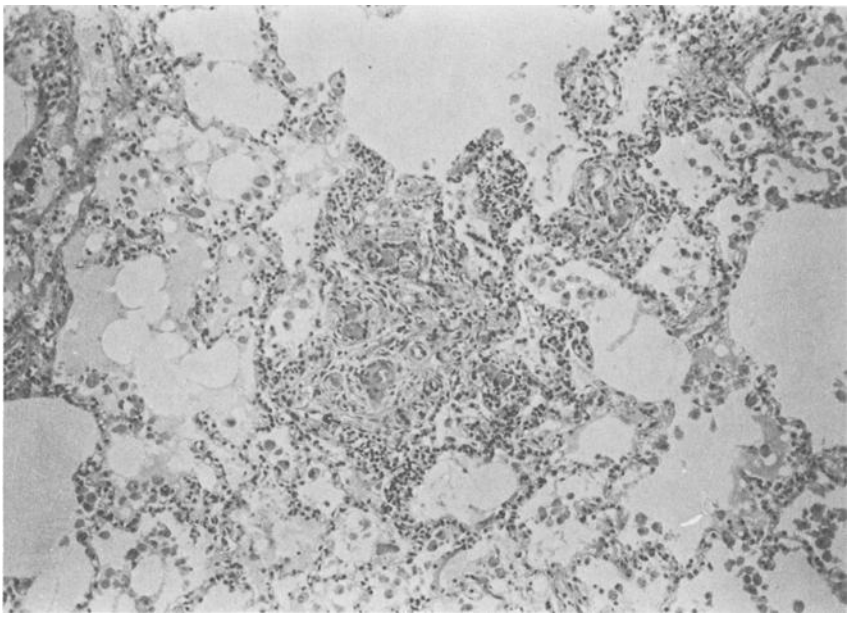

FIG. 1—*Obliterative endothelial proliferation and dilated venous structures create plexiform vascular lesions; Case 1 (hematoxylin and eosin stain).*

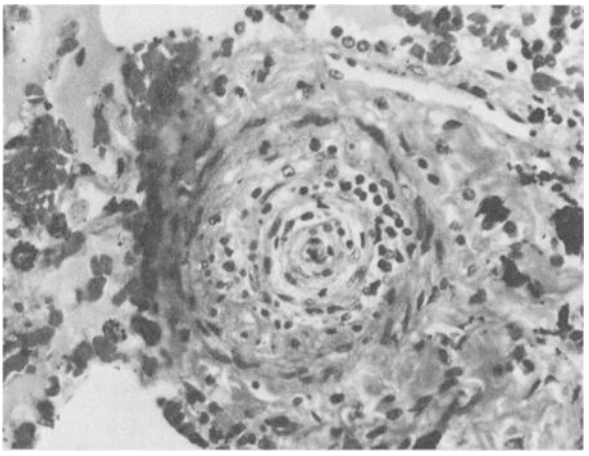

FIG. 2—*Concentrically laminated intimal fibrosis with medial hypertrophy; Case 2 (hematoxylin and eosin stain).*

serologic tests, polyclonal hypergammaglobulinemia, and a positive lupus erythematosus cell preparation. A diagnosis of mixed connective tissue disease [6, 7] was made. She was treated with corticosteroids, but this treatment was subsequently discontinued by the patient. Six months later she was admitted to the hospital for an elective hysterectomy. Postoperatively she was ambulatory, afebrile, and taking soft food. On the second postoperative evening she suddenly developed dyspnea and sinus tachycardia and died an hour later.

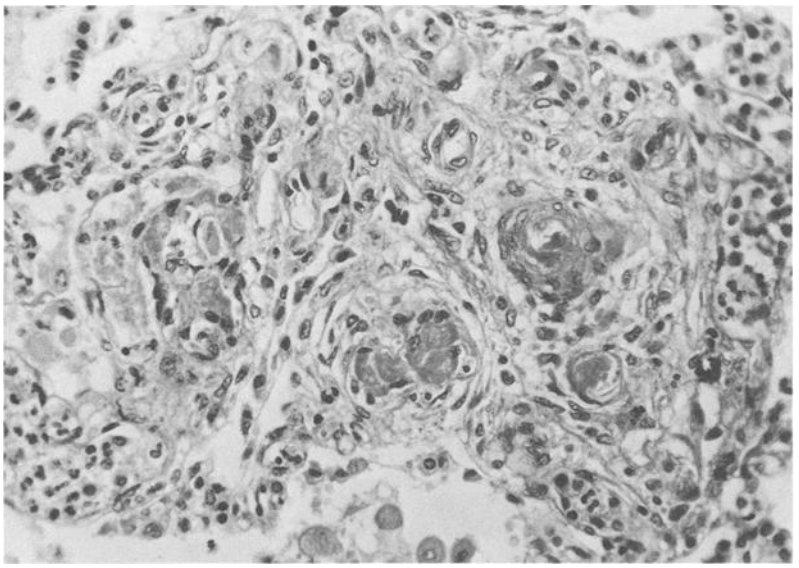

FIG. 3—*Plexiform groups of capillaries, endothelial proliferation, and fibrinoid deposits; Case 3 (hematoxylin and eosin stain).*

Postmortem examination revealed alopecia and pitted dermal hyperpigmentation of the upper chest and dorsal aspects of the arms. The edematous lungs had slight pleural thickening. Prominent right ventricular hypertrophy and marked atherosclerosis of the pulmonary artery were noted. Microscopically there was endothelial obliteration of pulmonary arterioles and capillaries.

Case 5

A two-year-old black female experienced progressive dyspnea, cough, and peripheral edema for 17 months. A definitive diagnosis was never obtained. Cardiac catheterization disclosed increased pulmonary artery pressure, and right ventricular hypertrophy was radiologically evident. Digitalis and diuretics controlled congestive heart failure. She died unexpectedly four days after elective admission to a hospital for further diagnostic studies.

At autopsy the pulmonary trunk was markedly dilated, and the right atrium and right ventricle were prominent. Microscopically the pulmonary arterioles and capillaries were obliterated with endothelial proliferation (Fig. 4).

It is noteworthy that the mother of this child had died 13 months earlier with intractable congestive heart failure resulting from primary pulmonary hypertension.

Discussion

Primary pulmonary hypertension is a rare disease predominantly of children and young adult females [*2*]. More than half its victims die within four years of onset with progressively worsening symptoms of dizziness, dyspnea, syncope, and congestive heart failure [*4*]. A few survive for two decades or more [*1,8*], while even fewer die suddenly and unexpectedly [*9*] with virtually no prior symptoms of the abnormality. It has been associated with or aggravated by pregnancy, parturition, certain drugs (namely oral contraceptives [*2*], aminorex

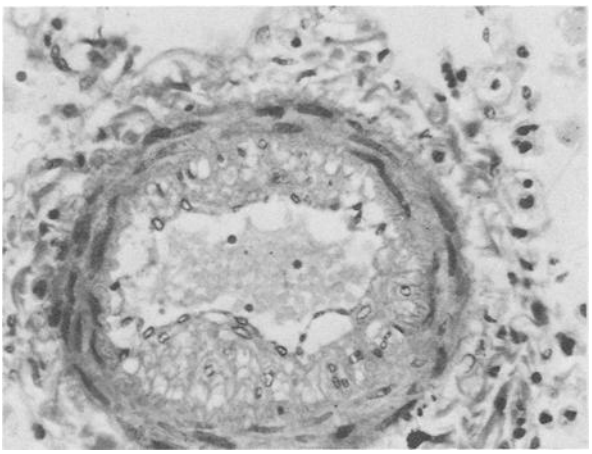

FIG. 4—*Endothelial proliferation and medial hypertrophy seen in a two-year-old victim of PPH; Case 5 (hematoxylin and eosin stain).*

fumarate [*2*], and amitriptyline [*10*]), and autoimmune disorders [*2,4,11-14*]. A familial transmission of PPH as an autosomal dominant gene with variable penetrance [*2,14,15*] has been reported.

The Waagenvoorts [*1*] describe two main varieties of PPH. The vasoconstrictive form is more common and is characterized by medial hypertrophy of pulmonary arteries with concentrically laminated intimal fibrosis and, occasionally, fibrinoid vascular lesions. These lesions are complicated intertwining groups of small vessels with prominent endothelial cells associated with a pulmonary artery and dilated vascular structures ("dilatation lesions"). The morphologic features suggest they result from intermittent pulmonary vasoconstriction [*1*]. Some drugs associated with PPH (aminorex fumarate and amitriptyline) are pharmacodynamically related to adrenergic innervations [*10*]. Microscopic pulmonary vascular lesions in those people who inject drugs designed to be taken orally appear plexiform. However, intermittent vasoconstriction is not thought to play a role in the development of these changes associated with intravenous drug abuse [*16*].

The second variety of PPH is thought to result from recurrent pulmonary thromboemboli [*1,2,17*]. Microscopically one sees hypertrophy of pulmonary arteries, thrombi in various stages of organization, eccentric patches of intimal fibrosis with narrowing or obliteration of the vascular lumina, and recanalization with formation of intraarterial fibrous septa [*1*]. Increased levels of antiplasmin [*17*] were found in one relative of a patient with this variant of PPH. The cases presented here had the vasoconstrictive variety of PPH.

The relevance of these cases to the practice of forensic pathology is threefold. First, PPH may be a cause of sudden unexpected death with few, if any, prior signs or symptoms. The only hope of diagnosis rests with a carefully performed autopsy. Right ventricular hypertrophy and dilatation will usually be the first clues. However, grossly evident telangiectasia and nonspecific skin lesions may also been seen. Careful scrutiny of several histologic preparations of lung with particular attention to vascular structures is necessary. Abnormal features, especially early plexiform lesions, may be obscured by pulmonary edema and congestion and will be missed if there is only a cursory review of the material. Second, PPH may be the cause of sudden unexpected death in individuals with a history of Raynaud's phenomenon, systemic lupus erythematosus, mixed connective tissue disease, or other collagen vascular disease. Such disease was evident in two of our cases. Third, once the autopsy diagnosis of PPH is established as a cause of the sudden unexpected death, the pathologist

must be aware that the entity may be familial. The family physician or surviving relatives should be informed.

Acknowledgments

Dr. Ned Kuivenen, St. Joseph's Hospital, Phoenix, Ariz., assisted in the investigation of Case 4; Dr. Rita Fojaco, associate professor of pathology at the University of Miami School of Medicine, assisted in the investigation of Case 5; and Ms. Beverly Knoll assisted in manuscript preparation.

References

[1] Waagenvoort, C. and Waagenvoort, N., "Primary Pulmonary Hypertension: A Pathologic Study of Lung Vessels in 156 Clinically Diagnosed Cases," *Circulation*, Vol. 42, 1970, pp. 1163-1184.

[2] Trell, E., "Primary and Chronic Thromboembolic Pulmonary Hypertension," *Angiology*, Vol. 23, 1972, pp. 550-574.

[3] Waagenvoort, C., "Vaso-Constrictive Primary Pulmonary Hypertension and Pulmonary Veno-Occlusive Disease," *Cardiovascular Clinics*, Vol. 4, 1971, pp. 97-113.

[4] Walcott, G., Burchell, H. B., and Brown, A. L., "Primary Pulmonary Hypertension," *American Journal of Medicine*, Vol. 49, July 1970, pp. 70-78.

[5] Clark, W. H., Reed, P. J., and Mihm, M. D., "Lupus Erythematosus—Histopathology of Cutaneous Lesions," *Human Pathology*, Vol. 4, No. 2, June 1973, pp. 157-163.

[6] Sharp, G. C., Irvin, W. A., Tan, E. M., Gould, R. G., and Holman, H. R., "Mixed Connective Tissue Disease—An Apparently Distinct Rheumatic Disease Syndrome Associated with a Specific Antibody to an Extractable Nuclear Antigen (ENA)," *American Journal of Medicine*, Vol. 52, Feb. 1972, pp. 148-159.

[7] Sharp, G. C., "Mixed Connective Tissue Disease," *Bulletin on the Rheumatic Diseases*, Vol. 25, No. 9, 1974-1975, pp. 828-831.

[8] Charters, A. D. and Baker, W. de C., "Primary Pulmonary Hypertension of Unusually Long Duration," *British Heart Journal*, Vol. 32, 1970, pp. 130-133.

[9] Robertson, B., "Idiopathic Pulmonary Hypertension in Infancy and Childhood," *Acta Pathologica et Microbiologica Scandinavica*, Vol. 79, 1971, pp. 217-227.

[10] Tiesberg, P. and Hognestad, J., "Primary Pulmonary Hypertension in Infancy," *Acta Paediatrica Scandinavica*, Vol. 62, 1973, pp. 69-72.

[11] "Case Records of the Massachusetts General Hospital," *New England Journal of Medicine*, Vol. 288, No. 4, Jan. 1973, pp. 204-210.

[12] Sergent, J. S., Lackshin, M. D., and Cummings, P., "Primary Pulmonary Hypertension and SLE," *New England Journal of Medicine*, Vol. 288, May 1973, pp. 1078-1079 (letters to the editor).

[13] Mack, J. W., Jr., Fry, M. B., and McIntosh, O. A., "Pulmonary Hypertension in Systemic Lupus Erythematosus (Cont.)," *New England Journal of Medicine*, Vol. 289, 1973, pp. 157-158 (letters to the editor).

[14] Trell, E., Johansson, B. W., Linell, T., and Ripa, J., "Familial Pulmonary Hypertension and Multiple Abnormalities of Large Systemic Arteries in Osler's Disease," *American Journal of Medicine*, Vol. 53, July 1972 pp. 50-63.

[15] Melmon, K. L. and Braunwald, E., "Familial Pulmonary Hypertension," *New England Journal of Medicine*, Vol. 269, No. 15, Oct. 1963, pp. 770-775.

[16] Tomashefski, J. F. and Hirsch, C. S., "The Pulmonary Vascular Lesions of Intravenous Drug Abuse," *Human Pathology*, Vol. 11, No. 2, March 1980, pp. 133-145.

[17] Inglesby, T. V., Singer, J. W., and Gordon, D. S., "Abnormal Fibrinolysis in Familial Pulmonary Hypertension," *American Journal of Medicine*, Vol. 55, July 1973, pp. 5-14.

Address requests for reprints or additional information to
Dr. Donna Brown
Medical Examiner's Office
1050 N.W. 19 St.
Miami, Fla. 33136