Raynaud’s Disease and Primary Pulmonary Hypertension

By Guillermo C. Celoria, M.D., Gilbert H. Friedell, M.D., and Sheldon C. Sommers, M.D.

PARTICULARLY since the advent of cardiac catheterization, primary pulmonary hypertension has been of increasing interest to clinicians and pathologists alike. To some it represents a pulmonary vasospastic disease, presumably of neurohumoral type, analogous to systemic essential hypertension. The occasional association of primary pulmonary hypertension with Raynaud’s disease is thought to support this theory.

Seven case reports are available in which Raynaud’s disease was associated with what was considered to be primary pulmonary hypertension.1-4 The detailed findings in the case of Taft and Mallory1 and that of Wade and Ball2 are of particular interest because of the scarcity of pathologic investigations in cases of Raynaud’s disease with or without pulmonary hypertension.

Pulmonary hypertension was confirmed by cardiac catheterization in 3 of the 7 cases, but without autopsy confirmation. One of these 3 catheterized patients (case 2 of Smith and Kroop3) has since died, and an autopsy was performed.

Report of Case

N. C., (A58-159). A 41-year-old white married telephone operator was in generally good health until 1951, when she noticed numbness, tingling, and blanching of all fingers up to the palm when exposed to the cold. During the previous several years she had had a cholecystectomy, a breast biopsy, and a total hysterectomy, but no history of Raynaud’s phenomenon. Her symptoms gradually progressed so that constant warmth was necessary to prevent pain. Atrophic changes of the fingertips became evident later. In 1953 bilateral thoracic sympathectomies resulted in disappearance of symptoms except for continued blanching of her fingers on exposure to cold. Six months later, during the winter, she developed Raynaud’s phenomenon in her toes and subsequently bilateral lumbar sympathectomies were performed in 1954 with good results.

Shortly after the final sympathectomy she began to experience episodes of dyspnea, weakness, and dizziness. These occurred only while she was standing, especially after exertion. She had numbness and tingling of the body during some of these episodes and fainted on several occasions. Blurring of vision was noted at times and scotomata were seen with some of the attacks.

The exertional dyspnea became progressively more severe and in April 1956 she was first admitted to this hospital. The essential clinical feature included (1) a loud and “split” pulmonic second sound, (2) a blood pressure of 135/100 mm. Hg with no appreciable positional change, (3) an enlarged right ventricle and pulmonary artery with normal-size left ventricle and left atrium seen on the roentgenogram, (4) electrocardiographic evidence of right ventricular hypertrophy, and (5) reproduction of some of her symptoms by hyperventilation. Three months later, ankle edema was present. Studies of pulmonary function at this time were indicative of primary pulmonary hypertension.

She was rehospitalized for treatment and further study in October 1956. At that time both right and left ventricular failure were found. Over the upper part of the body there were numerous telangiectases which blanched on pressure. Cardiac catheterization confirmed the diagnosis of marked pulmonary hypertension with advanced right heart failure.

The cardiac catheterization data included cardiac output, 3.8 L. per minute; cardiac index, 2.08 L. per minute per M.2; and arteriovenous oxygen diffusion, 7.2 vol. per cent. Oxygen saturations of the pulmonary artery, 52.3 per cent; right ventricle, 53.9 per cent (paired sample); right ventricle, 47.3 per cent; right atrium, 45.6 per cent (paired sample); superior vena cava, 40.4 per cent; and brachial artery, 93.3 per cent. Pressures recorded in mm. Hg were right atrium 20; right ventricle 105/20; pulmonary artery, 105/40; pulmonary “capillary” 10; and systemic blood pressure, 130/80.

These changes were interpreted by the catheterization team as showing advanced right-sided heart failure from marked pulmonary hypertension. Elevated pulmonary artery pressure and normal pulmonary “capillary” pressure were considered to indicate narrowing of pulmonary arterioles, rather than an element of left-sided heart failure. A detailed analysis of these findings will be reported elsewhere by Chobanian et al.5

From the Department of Pathology, Massachusetts Memorial Hospitals, Boston, Mass.
Skin and muscle biopsies were reported to show no evidence of seleroderma or other collagen disease. No clinical or radiologic evidence of seleroderma developed later in her course. She was digitalized, given mercurial diuretics, and discharged with the clinical diagnoses of primary pulmonary hypertension and Raynaud’s disease.

The patient was subsequently hospitalized on 3 occasions for treatment of cardiac failure. During the last of these, in December 1958, she died after a prolonged period of hypotension. An autopsy was performed 6 hours after death.

On gross examination there was cyanosis of the face and of the fingertips. Over the face and chest multiple small dark red-blue areas resembling telangiectases were seen. The skin on all fingers was smooth and shiny, and the fingernails on both hands were short and rough. There was slight peripheral edema.

In the right pleural cavity 300 ml. of yellow-pink watery fluid were found, and the lung appeared collapsed. A few fibrous adhesions were also noted between the lower lobe and the posterior parietal pleura. The left pleural cavity was obliterated by dense fibrous adhesions that somewhat constricted the lung.

There were an estimated 400 ml. of thin, straw-colored fluid in the pericardial cavity. The heart weighed 410 Gm. and was enlarged, due primarily to dilatation and some hypertrophy of the right atrium and ventricle. The ventricle measured 0.7 cm. in thickness, compared to normal thickness of 0.4 cm. The pulmonary artery was dilated and showed some atherosclerosis.

The right lung weighed 210 Gm. and the left 190 Gm. They appeared negative, except for a small amount of pink mucoid material in some of the bronchi. There was moderate dilatation of the pulmonary arterial branches and the largest showed thickening of their walls and scattered yellowish intimal plaques.

The other organs appeared negative, except for an apparent telangiectasis of the jejunum.

Microscopic sections of both lungs showed slight septal fibrosis in some regions, dilatation of a few alveoli with rupture of some of the septa, and mild subpleural fibrosis, but no primary parenchymal disease. In the lung, the primary disease process
appeared to be vascular, affecting all branches of the arterial, and to a lesser extent the venous, pulmonary tree.

There was marked atherosclerosis of the larger arteries, with eccentric narrowing of the lumens in the vicinity of subintimal plaques. Oil-red-O stains for fat showed abundant lipid in these plaques and elsewhere in the subintimal tissue. No proliferation of endothelial cells was apparent. There was slight hypertrophy of the muscular media, and elastic fibers were wrinkled and fragmented in some arteries.

The muscular arteries, ranging from 100 to 1,000 microns in diameter, also showed marked change, but of a different type. Below 250 to 300 microns in diameter, the most prominent finding was a marked cellular intimal proliferation with extreme narrowing or occlusion of the lumens (figs. 1 to 3). These hyperplastic cells stained with the Verhoeff-Van Gieson stain like smooth muscle. Slight intimal fibrosis was associated in some instances, but the proliferative change predominated.

In the muscular arteries that exceeded 300 microns in diameter, some hyperplasia of endothelial cells was also seen, and moderate edema of many of these cells was noted. The most characteristic intimal change, however, was an eccentric fibrosis of slight to moderate degree (fig. 4).

The media of muscular arteries of all sizes was generally thickened, primarily by an increase in smooth muscle but to some extent by fibrosis. The elastic laminae of medium and small arteries was often wrinkled, thickened, and occasionally fragmented. Edema of the adventitia was evident in most of the muscular arteries of small and medium size.

Acute arteritis was noted in several muscular arteries that ranged from 250 to 500 microns in diameter. These arterial walls showed focal necrosis with neutrophils infiltrating all layers of the wall and the adjacent connective tissue. In some of these vessels thrombi were present, a few of which showed early peripheral organization (fig. 5). A thrombus, possibly of embolic origin, was also noted in one section in a small muscular artery of about 100 microns in diameter, but here there was no apparent arteritis.

In the arterioles the marked intimal cellular proliferation (fig. 6) was also present and the arteriolar lumens were either markedly narrowed or occluded. In some arterioles, particularly those near the parent arteries, smooth muscle persisted in the media while in others the wall contained an increased amount of relatively acellular tissue that stained like fibrous tissue with the Verhoeff-Van Gieson stain.

Elsewhere dilated arterioles with thinned walls were noted. Small veins showed moderate to marked subintimal acellular fibrous thickening, but in contrast to arterioles had no endothelial proliferation (fig. 7). Larger veins also had fibrous thickening of their walls and in addition some atherosclerotic changes.

Slight to moderate hyaline coronary arteriolosclerosis and slight interstitial myocardial edema and fibrosis were present. In the spleen, pancreas, and liver there was slight to moderate hyaline thickening of arterioles with narrowing of their
lumens. In larger arterioles and small muscular arteries there were, in addition, slight hyperplasia of endothelial cells and of medial smooth muscle cells and fraying of adventitial collagen.

Only minimal intimal proliferation and hyaline arteriolosclerosis existed in the kidneys and other organs, except for the skin. Here there was moderate hyaline arteriolar thickening as well as both cellular endothelial hyperplasia and medial hypertrophy of small muscular arteries. Sections could not be obtained from digital vessels.

Discussion

Smith and Kroop in their cases 1 and 3, noted marked pulmonary arteriolar sclerosis. From their photomicrographs there would also appear to have been extensive involvement of small muscular arteries. The sub-intimal thickenings of the arterial and arteriolar walls appeared to be relatively acellular in character. Taft and Mallory also placed the lesion primarily in the arterioles and drew a parallel between the changes in these vessels and those in "rapidly progressive nephrosclerosis." The thickened arterioles were relatively acellular, and no areas of necrosis were noted.

In their autopsied case, Wade and Ball found the major change to be in the smaller muscular arteries, ranging from 80 to 250 microns in diameter. The lumens of these vessels were reduced by a concentric intimal fibrosis or fibroelastosis characteristically un-

accompanied by inflammatory infiltration or degeneration of the media or adventitia. Rare recent but no remote thrombi were noted. An atrial septal defect 2 by 1.5 cm. in greatest dimensions was present in this case and although it was considered by the authors merely as an incidental finding, it could have altered pulmonary dynamics enough to account for the morphologic findings. Similar vascular changes were noted in the digital arteries, pancreas, and kidneys, whereas a focal fibrinoid arteritis was noted in the adrenal glands and a mild cellular arteritis was seen in the liver. Some of the prominent arterial lesions in their case were thought to resemble the changes in scleroderma, whereas other lesions simulated polyarteritis.

The main pulmonary lesion in the present case was vascular also, involving chiefly the small muscular arteries and arterioles. In contrast to the previously reported cases, however, these vessels were occluded by the proliferation of endothelial cells, a change not observed elsewhere in the body. In previous cases the thickening of pulmonary vascular walls was due to an increase in relatively acellular fibrous or fibroelastic tissue. If the same underlying disease process is present in our case as in those of Taft and Mallory, Smith and Kroop, and Wade and

Figure 6

Marked narrowing of small arteriolar lumen by cellular proliferation is seen in this high-power photomicrograph. Verhoeff-van Gieson.

Figure 7

Two small veins with cellular fibrosis of their walls are seen in the center of the field. Marked congestion of alveolar septa is also noted. Masson trichrome.
Ball, and if cellular proliferation precedes fibrosis as in other vascular disorders, then in our case the cellular endothelial proliferation in the small muscular arteries and arterioles would represent earlier changes than previously described.

The necrotizing arteritis restricted to the muscular pulmonary arteries from 250 to 500 microns in diameter is interpreted as an acute response to a high degree of pulmonary hypertension proximal to the major point of obstruction to pulmonary arterial blood flow, namely in the distal arteries and proximal arterioles. Thrombosis in these vessels is thought to be secondary to the arteritis. Arteritis was not found in other organs.

This patient suffered basically from a widespread disorder of the arteries and arterioles with marked exacerbation of vascular disease in the lungs. The morphologic findings are in part compatible with the hypothesis of Smith and Kroop that the pulmonary hypertension is secondary to a recurrent arterial spasm similar to that causing the peripheral manifestations of Raynaud’s disease. The muscular hypertrophy of the media, the occasionally observed concentric arrangement of smooth muscle nuclei, and the wrinkling of the elastic membranes of the small muscular arteries furnish morphologic evidence of vasospasm. These findings, however, may to some degree also represent compensatory changes in response to increased intravascular pressure. Complete resolution of the etiology of the pulmonary vascular changes in these cases, therefore, must await further studies.

**Summary**

A case of Raynaud’s disease with autopsy is reported in which the clinical picture was dominated by pulmonary hypertension apparently unassociated with any significant pulmonary parenchymal disease. Microscopically cellular intimal proliferation of small pulmonary muscular arteries and arterioles was the most characteristic lesion. In several proximal medium-sized muscular arteries there was necrotizing arteritis with thrombus formation. Similar vascular lesions were not found in other organs, although generalized arteriosclerosis and arteriolosclerosis were present. The pulmonary vascular changes are thought to represent a local exacerbation of generalized vascular disease, but a specific etiology was not apparent.

**Summario in Interlingua**

Es reportate un caso de morbo de Raynau con necropsia, in que le tableau clinic esseva dominate per hypertension pulmonar apparentemente non-associate con significative morbo pulmo-parenchymal. Microscopicamente, le proliferation cellular del intima in le arterias e le arteriolas del musculo pulmonar esseva le lesion le plus characteristique. In pleure arterias muscular proximal de dimensiones intermediari, arteritis necrotisante con formation de thrombos esseva constatate. In altere organos nulle simile lesions vascular esseva trovate, ben que arterio- e arteriolosclerosis generalisate esseva presente. Es opinate que le alterationes pulmo-vascular representa un exacerbation local de generalisate morbo vascular, sed nulle etiologia specific esseva apparente.

**References**

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