Pulmonary Arterial Hypertension and Connective Tissue Disorders

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75.1 Clinical History

A 40-year-old female was brought to the emergency services of our hospital with nonrecordable pulse and blood pressure, feeble heart sounds, and no response to deep pain. Accompanying relatives provided a history of rapidly progressive shortness of breath with chest pain on and off and multiple joint pains for the past 15 days. She had been diagnosed as a case of systemic lupus erythematosus (SLE) 3 years ago, but had not followed up in the last 2 years. She died within 2 h of admission.

The patient's personal medical file contained some records of previous assessment and investigations. A history of hair loss, photosensitivity, Raynaud's phenomenon, and dysphagia had been recorded. It was also mentioned that the patient had no skin changes of SLE or scleroderma. The hematological and biochemical investigations were as follows: Hemoglobin 12.5 g/dL, total leukocyte count 6000/cmm (differential count—neutrophils 68%, lymphocytes 30%, and eosinophils 2%), platelet count 2 lakhs/cmm, serum cholesterol 149 mg/dL, triglycerides 84 mg/dL, high density lipoproteins 24 mg/dL, and low density lipoproteins 103 mg/dL. Serological parameters revealed positive antinuclear antibodies and anti-double-stranded DNA antibodies at 1:160 and 1:80 titers, respectively, with serum complement C_3 129 mg/dL and C_4 41 mg/dL. An additional investigation retrieved was the ANA immunofluorescence test that had been recorded as showing a centromeric pattern. ECG was normal, while a high-resolution computed tomography had shown cardiomegaly, severe pulmonary hypertension (pulmonary artery diameter of 30 mm), and stigmata of old tuberculosis (scarring of bilateral upper lobes and calcified hilar lymph nodes). At that time, her records showed that she had been advised digoxin, sildenafil, atorvastatin, fruselac, low-molecular weight heparin, and aspirin.

75.2 Autopsy Findings

At autopsy, remarkable features were seen in the lungs. Both the lungs were of normal size and shape with patchy visceral pleural thickening and opacification. The cut surfaces showed very marked prominence of the pulmonary arteries with extensive thickening of the walls and near total luminal obliteration (Fig. 75.1). Some of the plaques had a distinct pale-yellow color (Fig. 75.1b). On histology, there was extreme

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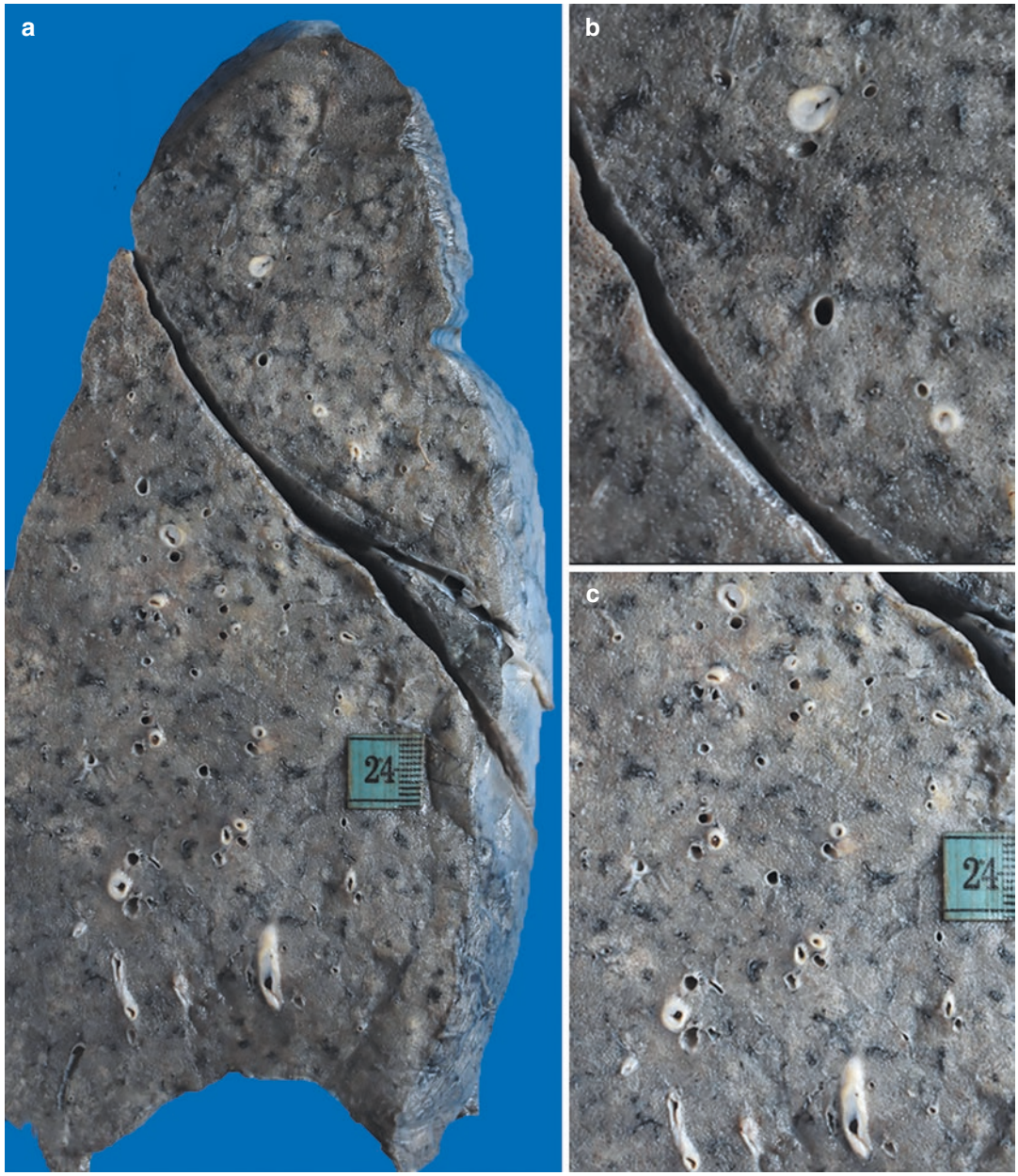

Fig. 75.1 (**a**) The cut surface of the left lung and the close-up of (**b**) left upper and (**c**) lower lobes show extreme narrowing of the pulmonary arteries of all sizes. The larger arteries show a pale hue

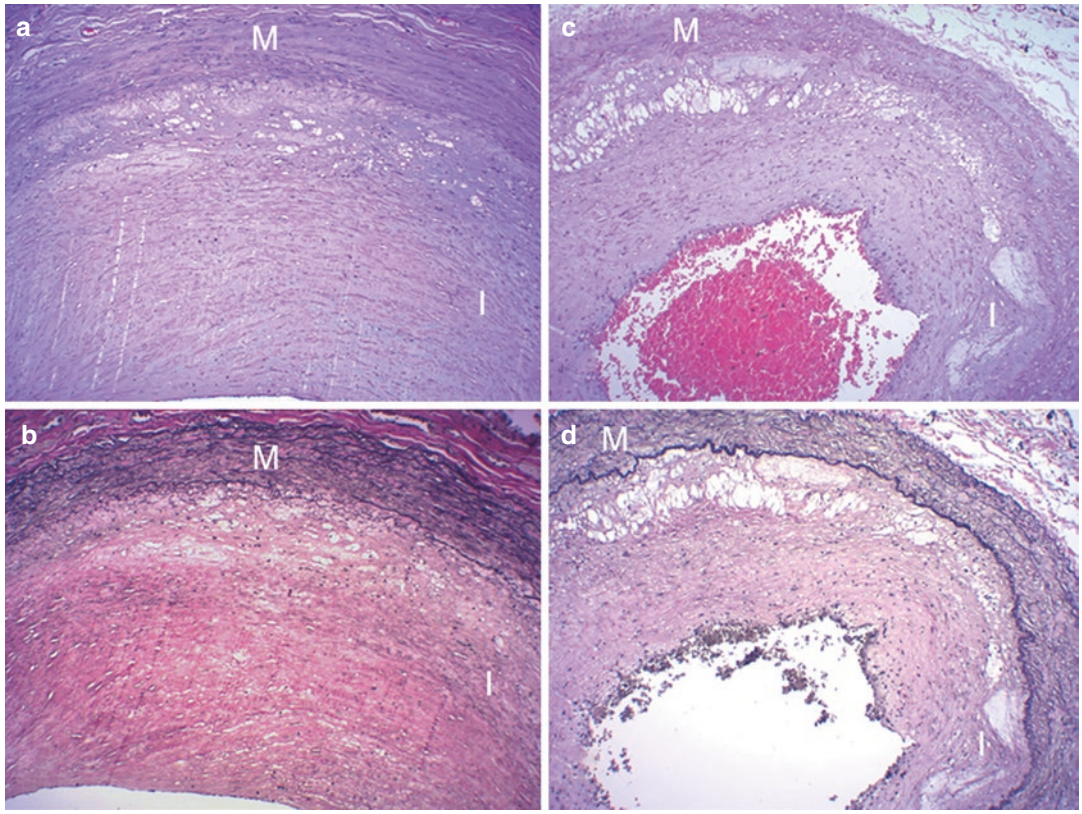

Fig. 75.2 Elastic pulmonary artery ((**a**) H&E × 100, (**b**) Elastic van Gieson × 100) and muscular pulmonary (**c**) H&E × 100, (**d**) Elastic van Gieson × 100) showing remarkable narrowing of their lumina by eccentric intimal proliferation with foamy macrophages at the basal aspects. The internal elastic lamina is intact (*I* intima, *M* media)

narrowing of the elastic and muscular arteries (Fig. 75.2) by exuberant intimal proliferation. The internal elastic lamina was largely intact. The intimal thickening was largely fibro-myxoid (Fig. 75.3a) and towards the basal aspects, there were small to large collections of foamy macrophages (Fig. 75.3b). These changes were seen in the muscular arteries of all sizes, including the arterioles; some of the arteries also showed mild medial hypertrophy (Fig. 75.3c, d). Veins and venules were normal. There was acute bronchiolitis with neutrophilic infiltration; features of interstitial lung disease were not present. The heart (250 g) showed moderate right ventricular hypertrophy with a fresh thrombus in the right atrial appendage. The pulmonary trunk was as large as the ascending aorta with intimal thickening and few atherosclerotic plaques. Renal vascular changes (Fig. 75.4) appeared to be consistent with that seen in scleroderma. Chronic passive venous congestion was present in the liver with focal hemorrhagic necroses.

Cause of Death: Right heart failure due to pulmonary arterial hypertension (PAH).

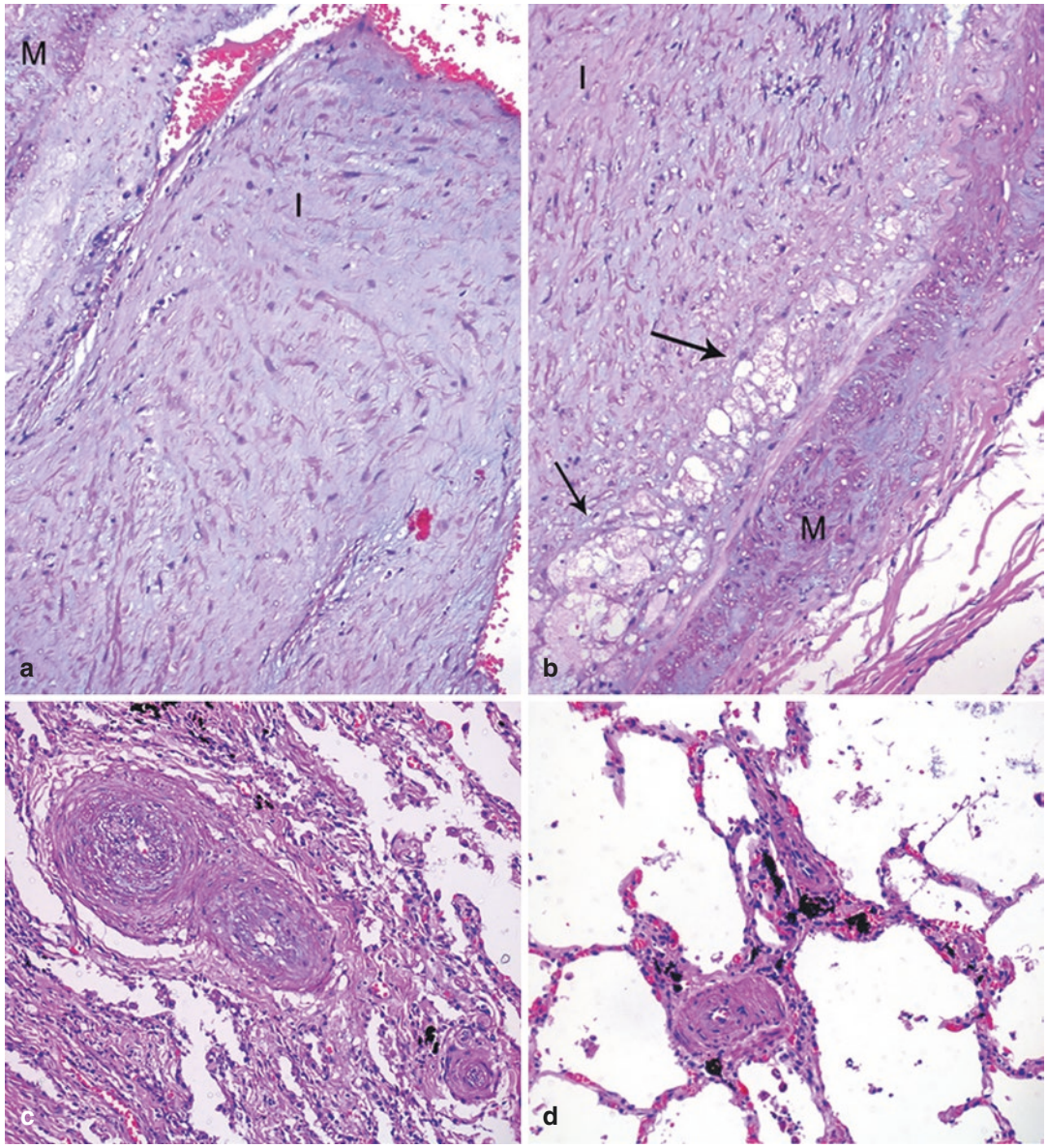

Fig. 75.3 (**a**) The intima I shows paucicellular fibromyxoid proliferation (H&E × 400); (**b**) Collections of foamy macrophages (arrows) are seen at the interface between the thickened intima I and the media M. Increased ground substances are also seen to intersect the smooth muscle bundles of the media (H&E × 400); (**c**) and (**d**) Show muscular arteries with medial hypertrophy and fibro-intimal thickening with muscularization of the arterioles (H&E × 400)

75.3 Discussion

Autopsy histopathological findings in the present case revealed features of well-established pulmonary hypertension (PH) in a setting of an autoimmune connective tissue disorder (CTD). PH, defined as an increase in the resting mean pulmonary arterial pressure of more than 25 mmHg, is classified on the basis of the hemodynamics and clinical settings. Utilizing additional parameters of pulmonary arterial wedge pressure and pulmonary vascular resistance, the PH is divided into 3

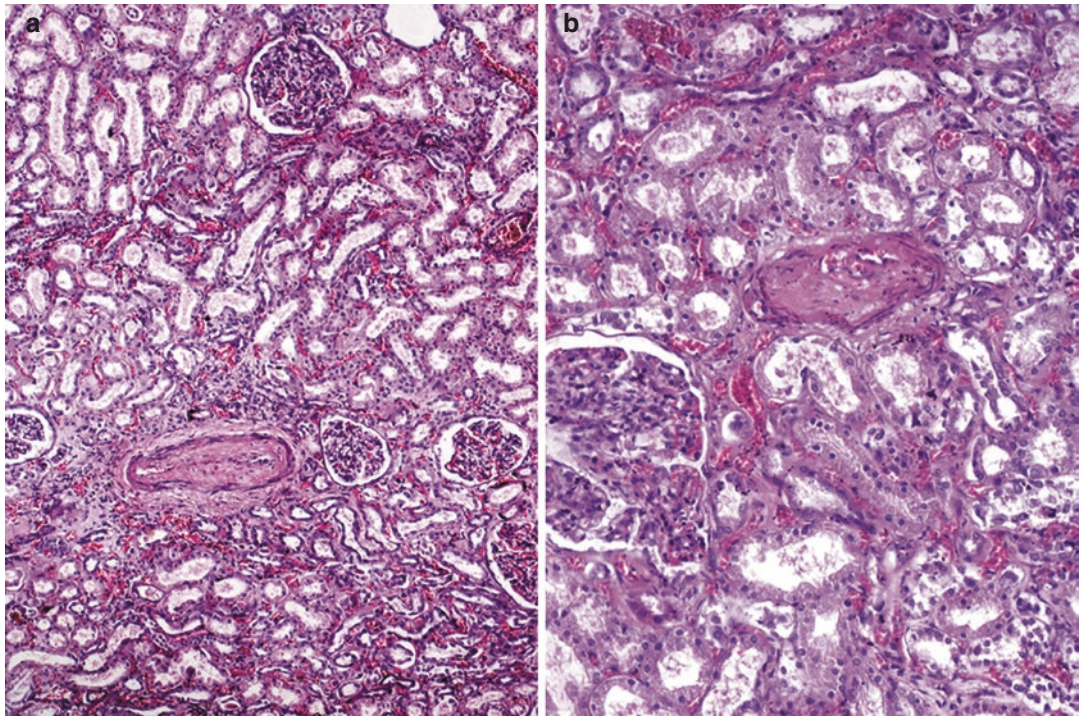

Fig. 75.4 Renal parenchyma showing intimal proliferation of the renal arteries (**a**) H&E × 200 and (**b**) H&E × 400

groups—precapillary, isolated postcapillary, and combined pre−/postcapillary PH. Five categories of PH are based on the etiopathogenetic mechanisms and therapeutic management, and they include Category 1—PAH, Category 2—PH associated with impaired left heart function, Category 3—PH secondary to underlying lung disease, Category 4—PH due to thromboembolism, and Category 5—PH arising from multifactorial causes. Though all of these can occur to a lesser or greater extent, PAH remains the most common and dreaded complication in CTD patients with reported estimates ranging from 2.8 to 32%. The proliferative remodeling of the small pulmonary arteries in PAH with CTDs is mediated by endothelial dysfunction induced by dysregulation of endothelin I, nitric oxide, and prostacyclin and elevated pro-inflammatory cytokines in a setting of autoantibodies and immune complexes. Among the CTDs, systemic sclerosis (SSc) accounts for up to 60–80% of PH, followed by mixed connective tissue disease and SLE; in other CTDs, it is estimated to be less than 1%.

SSc or scleroderma is an autoimmune disease that is characterized by a triad of small-vessel noninflammatory vasculopathy, excessive and progressive fibrosis, and a variable inflammatory infiltrate that can involve virtually any organ system. It shows a female preponderance (male-to-female ratio of 1:4–1:14) and a mean age of presentation of 50 years. Apart from the presence of ANAs, SSc patients have a host of other antibodies. Based on the degree of skin involvement, SSc is usually classified into limited (LcSSc) and diffuse (DcSSc) cutaneous forms. Earlier and frequent multiorgan involvement is seen with the diffuse subtype. Furthermore, LcSSc has an elevated titer of anticentromere antibodies, while DcSSc is associated with a predominance of anti-topoisomerase 1 (Scl-70) and anti-RNA polymerase III, antibodies. Apart from skin, the organ systems which are affected are the lungs, heart, gastrointestinal tract, kidneys, and musculoskeletal system. There is also a rare subset, SSc-sine scleroderma, where visceral involvement occurs in the absence of typical skin changes of SSc.

Despite an earlier diagnosis of SLE in our patient, there had been subsequent documentation of Raynaud's phenomenon and dysphagia and a centromeric ANA pattern had been noted; skin changes were absent. Furthermore, the available clinical information did not fulfil the classification criteria for SLE. The examination of the gastrointestinal system (including the esophagus) at autopsy did not reveal any abnormality. But primary involvement of the lungs and kidneys in this case suggested the diagnosis of the rarer variant of SSc-sine scleroderma. Unfortunately, the patient did not have thorough examination, investigations, and follow-up.

Systemic manifestations of SSc are very often seen in the lungs, as compared to the other organs. They occur in the form of interstitial lung disease (seen in 25–50% of patients) and PH, often associated with antitopoisomerase 1 antibody and anticentromere antibody positivity, respectively. Together, they are leading causes of morbidity and mortality in SSc patients. The cause of PH in these patients is extremely variable. About 8–12% of the patients with SSc have PAH (group 1), the most common pattern, seen in both subsets of SSc and associated with late onset of the disease and postmenopausal status. The arteries show prominent intimal fibrosis and medial hypertrophy; plexiform lesions are infrequent. Some patients can also show pulmonary venoocclusive like changes. PH can also develop as a complication of ILD (Group 3 PH), or left ventricular myocardial dysfunction (Group 2 PH) or as a consequence to antiphospholipid antibody (APLA)-related chronic thromboembolism (Group 4). Alarmingly, an overlap of different forms of PH can occur within the same patient. The present case revealed advanced PAH without significant interstitial lung involvement. Apart from right ventricular hypertrophy, there was no fibrosis in the left ventricular myocardium. The presence of an atrial appendage thrombus was noted in our index case. While the patient in the present case had been advised low-molecular weight heparin, there was no documentation of any test for APLA in the records retrieved. We presume that the thrombus could have been related to relative stasis in a dilated chamber in response to the severe PH. Hence, in this patient, PAH was the sole and extremely severe pulmonary manifestation and affected arteries of all sizes. As with other causes of PAH (See Chaps. 71 and 72), significant signs and symptoms occur late in the disease and hence it would be imperative to have periodic screening of these patients so that appropriate therapy targeting the vasoconstrictive/vasodilatatory mediators can be promptly instituted.

Further Reading

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