Death in a Young Adult With Sickle Cell Disease

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A 27-year-old African-American female with known sickle cell disease was admitted for sickle cell crisis and presumed sepsis. The patient’s past medical history was complicated by multiple sickle cell-related complications, including seizures and multiple prior blood transfusions. Her hospital course included Staphylococcus epidermidis bacteremia, for which broad spectrum antibiotics were prescribed. On hospital day nine, the patient was found unresponsive and declared dead after unsuccessful efforts at resuscitation. An unlimited autopsy examination was conducted under authorization of the coroner. Findings included numerous pathologic features ascribed to sickle cell disease, including systemic siderosis and splenic atrophy [weight 10gm (140±78)], fibrosis, and Gamma Gandy nodules. Additional autopsy findings included cardiomegaly with a heart weight of 450gm (312±78), right atrial and right ventricular chamber dilatation, and hepatomegaly with a liver weight of 2650gm (1475±362). The image below demonstrates microscopic examination of the lung parenchyma.

Figure 1: Histologic section from lung parenchyma demonstrating a small caliber pulmonary artery with an intraluminal plexus of capillary-like channels separated by proliferating intimal cells and resulting in luminal stenosis and superimposed thrombotic material (40x, Hematoxylin and Eosin stain).

What is the name of this hallmark arterial lesion? What clinical disorder does it represent?
plexiform arterial lesion (Grade IV) indicative of pulmonary hypertension

Pulmonary hypertension (PH) is a complex clinical diagnosis that has a variety of causes and encompasses multiple subtypes that, over the course of time, have been sub-classified, defined, and then reclassified again. Previously subdivided into two main categories, the revised consensus schema now details five clinical groupings of disorders that cause PH. An overview of these five clinical groupings can be seen in Table 1. The microscopic features ascribed to PH can broadly be called plexogenic arteriopathy (PA). However, details regarding the spectrum of distinct histopathologic features have also been subject to a variety of grading systems that have undergone subsequent revisions and subdivisions. The more widely accepted schema for describing the histopathologic lesions of PA was detailed by Katzenstein et al. and yields six graded lesions (Grade I–VI), with each successive grade meant to reflect increasing severity of the clinical disease. A modified grading system for histologic lesions can be seen in Table 2. The Grade V lesion, otherwise known as the plexiform lesion, remains the pathologic hallmark of clinical PH, and a variety of hypotheses have been offered to explain its pathogenesis.

Sickle cell disease (SCD) is an autosomal recessive inherited genetic disorder caused by a single point mutation in the gene for the B-globin chain of hemoglobin that results in chronic, severe hemolytic anemia. It is one of the most common heritable hematologic diseases, with more than 200 million worldwide mutation carriers and nearly 1 in 600 African-Americans homozygous for the SCD mutation. While the median age of survival in SCD has risen to roughly 45 years of age, lung manifestations remain the leading cause of both morbidity and mortality, despite the fact they remain underdiagnosed by physicians. Pulmonary complications in SCD vary widely and include acute chest syndrome, restrictive lung disease, thromboembolism, and PH. SCD as a cause of PH has gained only recent acceptance despite being initially described in 1936 by Yater and Hansman. As a cause of PH, SCD is now recognized within the new clinical classification scheme, falling clearly into Group 5: PH with unclear multifactorial mechanisms, subgroup 5.1: those due to hematologic disorders such as chronic hemolytic anemia. It is associated with impaired exertional tolerance, progressive heart failure, and a higher relative mortality largely due to right heart failure, thromboembolism, or cardiac arrhythmia. Right heart catheterization remains the gold standard test for the diagnosis of PH, defined as a

Table 1: Current Clinical Classification Scheme for Pulmonary Hypertension (PH) [adapted from Simmoneau et al.]

<table>
<thead>
<tr>
<th>Clinical Group Number</th>
<th>Major Category</th>
<th>Subcategories</th>
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<tbody>
<tr>
<td>Group 1</td>
<td>Pulmonary Arterial Hypertension (PAH)</td>
<td>1.1 Idiopathic, 1.2 Heritable [1.2.1 BMPR2, 1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3, 1.2.3 Unknown Gene] 1.3 Drug- and Toxin-Induced, 1.4 Associated with [1.4.1 Connective tissue disease, 1.4.2 HIV, 1.4.3 Portal hypertension, 1.4.4 Congenital heart disease, 1.4.5 Schistosomiasis] 1’ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis 1” Persistent PH of newborn (PPHN)</td>
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<tr>
<td>Group 2</td>
<td>PH Due to Left Heart Disease</td>
<td>2.1 LV Systolic dysfunction, 2.2 LV Diastolic dysfunction, 2.3 Valvular disease, 2.4 Congenital/Acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies</td>
</tr>
<tr>
<td>Group 3</td>
<td>PH Due to Lung Disease</td>
<td>3.1 COPD, 3.2 ILD, 3.3 Mixed restrictive/obstructive pattern disease, 3.4 Sleep disordered breathing, 3.5 Alveolar hypoventilation disorders, 3.6 Chronic exposure to high altitude, 3.7 Developmental lung disease</td>
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<tr>
<td>Group 4</td>
<td>Chronic Thromboembolic PH (CTEPH)</td>
<td>5.1 Hematologic disorders: chronic hemolytic anemia, MPO disorders, splenectomy; 5.2 Systemic disorders: sarcoidosis, histiocytosis, lymphangioleiomyomatosis; 5.3 GSD, gaucher, thyroid disorders; 5.4 Other: tumoral obstruction, fibrosing mediastinitis, CRF, segmental PH</td>
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<tr>
<td>Group 5</td>
<td>PH Due to Unclear Multifactorial Mechanisms</td>
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BMPR2 = bone morphogenic protein receptor type II, ALK-1; ENG = endoglin, SMAD9; CAV1 = caveolin-1; HIV = human immunodeficiency virus; LV = left ventricle; COPD = chronic obstructive pulmonary disease; ILD = interstitial lung disease; MPO = myeloproliferative; GSD = glycogen storage disease; CRF = chronic renal failure.
mean pulmonary arterial pressure (PAP) >25 mmHg. Using PAP pressures, the estimated prevalence of PH in SCD has been reported to be approximately 10%. Autopsy studies in patients with SCD, however, have yielded rather different information. In one study, changes of PH were found in 100% (20 of 20) of the autopsied individuals with SCD; while in another, more recent study conducted by Graham et al., PH changes were found in only one-third of its 21 SCD decedents who underwent autopsy. The histopathologic severity of vascular lesions associated with PH in SCD has also been debated in the autopsy literature, with the hallmark Grade V plexiform lesion being recognized by one series in 12 of 20 patients (60%) but in only 1 of 21 patients (0.05%) in the more recent study.

Aside from SCD as a cause of PH, extensive research and ample literature over the last 50 years have greatly expanded the number of clinical disorders known to cause PH, including pulmonary capillary hemangiomatosis, veno-occlusive disease, interstitial lung disease, sarcoidosis, chronic obstructive lung disease, left heart dysfunction, and individuals harboring a bone morphogenic protein receptor type 2 (BMPR2) mutation. The vast majority and diversity of these causes was considered in the development of the newest consensus clinical subcategories of PH.

The autopsy case depicted here of a young adult with SCD demonstrates the hallmark plexiform lesion (Grade IV) seen in plexogenic arteriopathy (PA) of PH. Greater awareness is needed of the fact that lung manifestations of SCD remain the main contributors to morbidity and mortality. With the nonspecific clinical presentation of PH in SCD, a higher index of clinical suspicion for PA and right heart failure is needed. Further signs of right heart failure in the current case include the right-sided cardiac dilatation, cardiomegaly, and hepatomegaly. As previously mentioned, autopsy studies depicting the morphologic changes seen in SCD lungs have provided valuable insights into SCD as a cause of PH. Further studies are warranted, as our understanding of the processes underlying PA continues to evolve and our efforts turn to therapies targeted at each of the clinical subgroups or perhaps each of the histopathologic grades of lesions.

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REFERENCES


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