PH GRAND ROUNDS

Persistent Pulmonary Artery Filling Defects: Looking Beyond Anticoagulation Failure

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Presentation: A 63-year-old previously healthy woman presented to the emergency department (ED) with a 7-day history of acute dyspnea on exertion and substernal chest pressure. She had recently returned from a vacation that included air travel. On evaluation, she was found to have mild hypoxia, requiring 1 liter per minute of oxygen to maintain SpO_2 saturation of 92%. Her vital signs and physical examination were otherwise unremarkable. Computed tomography pulmonary angiogram (CTPA) demonstrated a large filling defect within the main pulmonary artery with extension into the right-sided segmental and subsegmental branches (Figures 1A-1D). Cardiac biomarkers were within normal limits. A transthoracic echocardiogram (TTE) showed mild right ventricular (RV) dilation with preserved systolic function (Figures 2A and 2B). A diagnosis of pulmonary embolism (PE) was made and she was admitted for initiation of anticoagulation. She was discharged home 2 days later in stable condition on enoxaparin and warfarin therapy.

One month later, she returned to the ED with progressive dyspnea, new right-sided pleuritic pain, and nonproductive cough. She had a heart rate of 126 beats per minute, and required supplemental oxygen at 3 liters per minute. A prominent S2 was noted without associated murmurs or gallops. There was no jugular venous distention or lower-extremity edema. Lung fields were clear to auscultation bilaterally. Laboratory studies were notable for a pro-brain natriuretic peptide level of 1138 pg/mL; international normalized ratio was within the therapeutic range. Repeat TTE showed interval development of dilated right-sided heart chambers, increased RV filling pressure, abnormal RV relaxation, and moderate tricuspid valve regurgitation (Figures 2C and 2D). CTPA showed enlargement of the filling defect within the main pulmonary artery and right-sided segmental branches, as well as new filling defects within the left superior lobar artery. There were also peripheral airspace consolidations within the right lower lobe (Figures 3A-3D). Right heart catheterization showed mildly elevated pulmonary artery pressures (Table 1). A gadolinium-enhanced chest magnetic resonance imaging (MRI) study showed no enhancement within the intraluminal lesion, suggesting a large bland thrombus (Figures 4A and 4B).

Management: The patient underwent percutaneous catheter-directed throm-

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bolysis and suction thrombectomy, which provided partial recanalization within the main pulmonary and right superior lobar arteries. Forceps biopsies were taken from the intraluminal lesion at the time of suction thrombectomy and were consistent with bland thrombus. However, she did not respond to this therapy, and her cardiopulmonary status deteriorated. She underwent surgical pulmonary thromboendarterectomy at our institution, because she was too unstable for transport to a referral center.

Diagnosis: Intraoperatively, a large mass-like structure was excised from the pulmonary trunk and right pulmonary artery. Pathologic analysis of an intraoperative frozen specimen yielded a preliminary diagnosis of an osteogenic sarcoma. The tumor was noted to be invading through

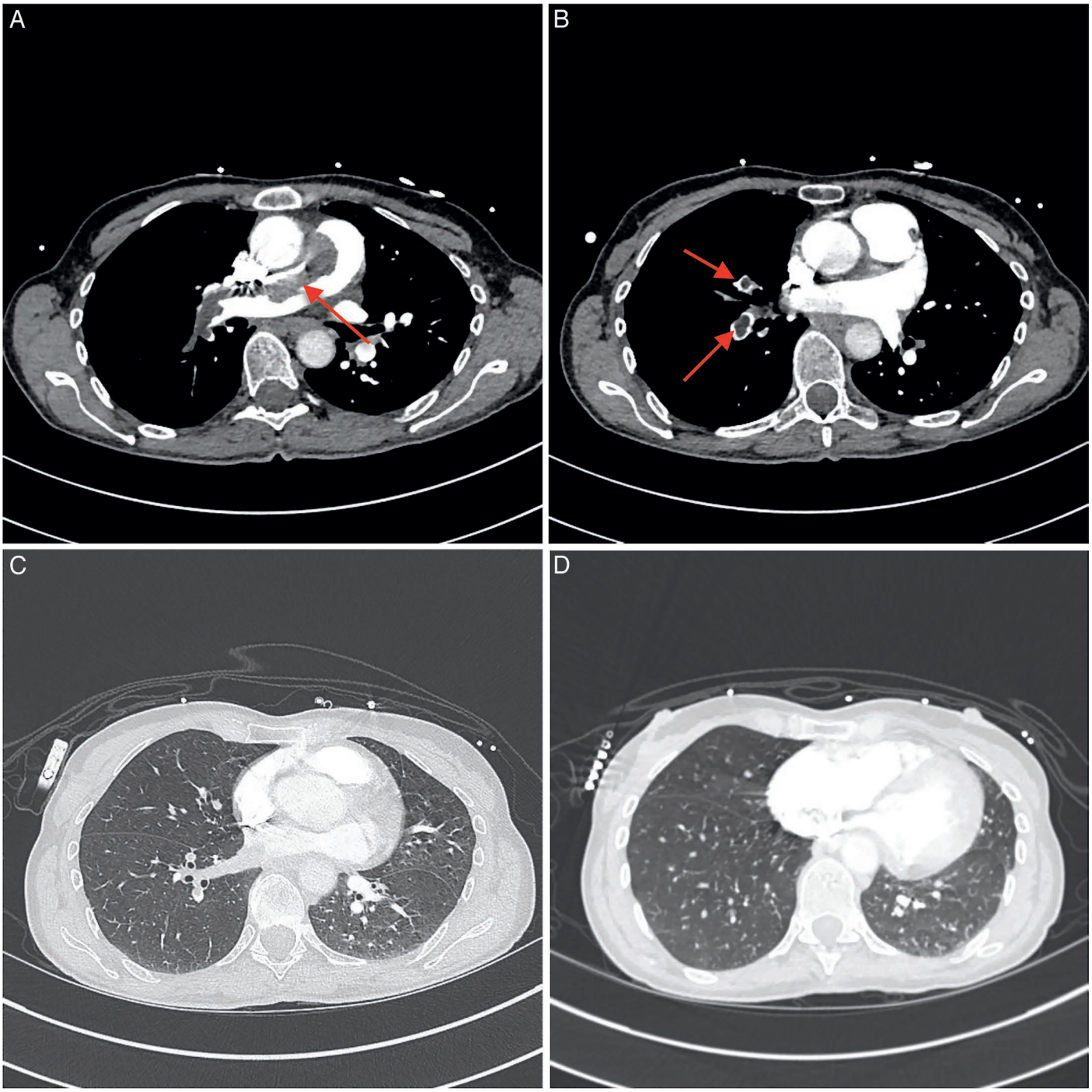


Figure 1A: CTPA representative selection demonstrating a large filling defect within the right pulmonary artery and middle and inferior lobar arteries (red arrow).
Figure 1B: CTPA representative selection demonstrating filling defects within the right segmental pulmonary arteries (red arrows).
Figure 1C: CTPA representative selection of the lung parenchyma.
Figure 1D: CTPA representative selection demonstrating mild flattening of the interventricular septum without significant RV enlargement. No significant parenchymal disease is noted.

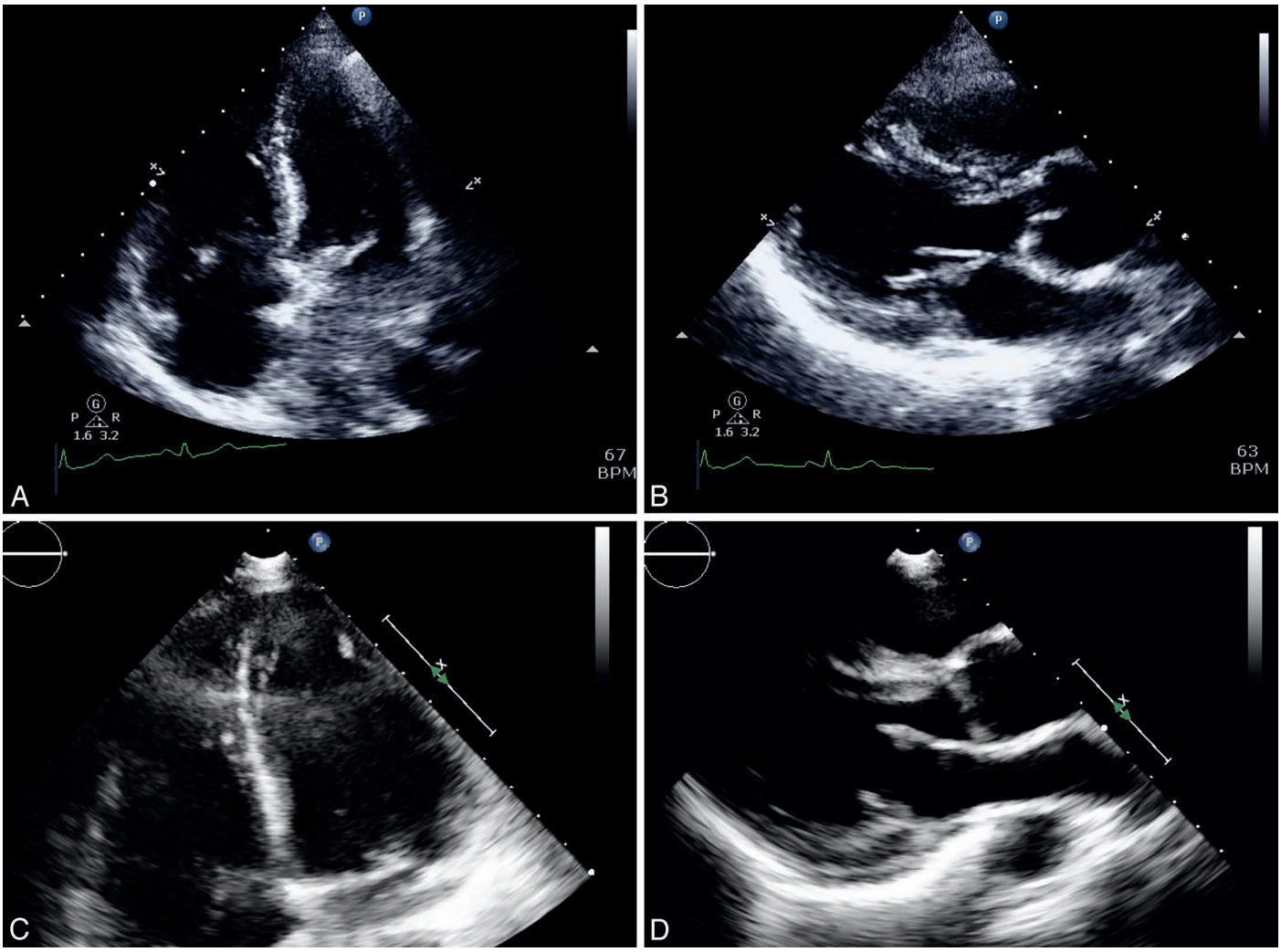


Figure 2A: TTE apical 4-chamber view showing mild RV dilation.
Figure 2B: TTE parasternal long axis view showing mild RV dilation.
Figure 2C: Repeat TTE apical 4-chamber view showing worsened RV enlargement, septal bowing, and severely decreased RV systolic function.
Figure 2D: Repeat TTE parasternal long axis view showing RV enlargement and septal bowing.

the walls of the right pulmonary artery into the adjacent lung parenchyma, necessitating right pneumonectomy (Figures 5A and 5B). A complete debulking procedure was not possible because of gross evidence of involvement of left pulmonary artery and its distal branches. A diagnosis of metastatic intravascular chondroblastic osteosarcoma was confirmed, complicated by foci of undifferentiated pleomorphic sarcoma (Figures 6A and 6B). The postoperative course was complicated by sepsis and multisystem organ failure. Based on poor prognosis and rapid deterioration, she elected for comfort measures only and died two days later.

Discussion: Pulmonary artery sarcomas (PAS) were first described by Mandelstamm in 1923.[1] Fewer than 300 cases have been reported in the literature since that time. The World Health Organization categorizes PAS into 3 main subtypes: angiosarcoma, leiomyosarcoma, and intimal sarcoma.[2] Clinical presentation is similar regardless of the tumor subtype, and symptoms may include dyspnea, chest pain, coughing, and hemoptysis. Consequently, many of these cases are initially misdiagnosed as acute or chronic thromboembolic disease.

There is no consensus diagnostic algorithm for the evaluation of suspected PAS. In general, laboratory testing is of little utility. Echocardiography may show evidence of pulmonary hypertension (PH) and RV dysfunction, nonspecific findings. Similarly, ventilation/perfusion scans are generally unable to differentiate between thrombus and tumor, as both conditions appear as discrete perfusion defects.[3] CTPA may be a more useful imaging modality, demonstrating large obstructive filling defects in the proximal pulmonary arteries. Nonmalignant thromboembolic disease rarely presents with lesions that occupy the entire vascular lumen.[3] This phenomenon has been referred to as the "wall eclipsing sign," and is felt to be pathognomonic for pulmonary artery tumors.[4] Gadolinium-enhanced chest MRI has also been proposed as a diagnostic imaging study that can distinguish PAS from PE.[5,6] Contrast enhancement of the intraluminal lesion

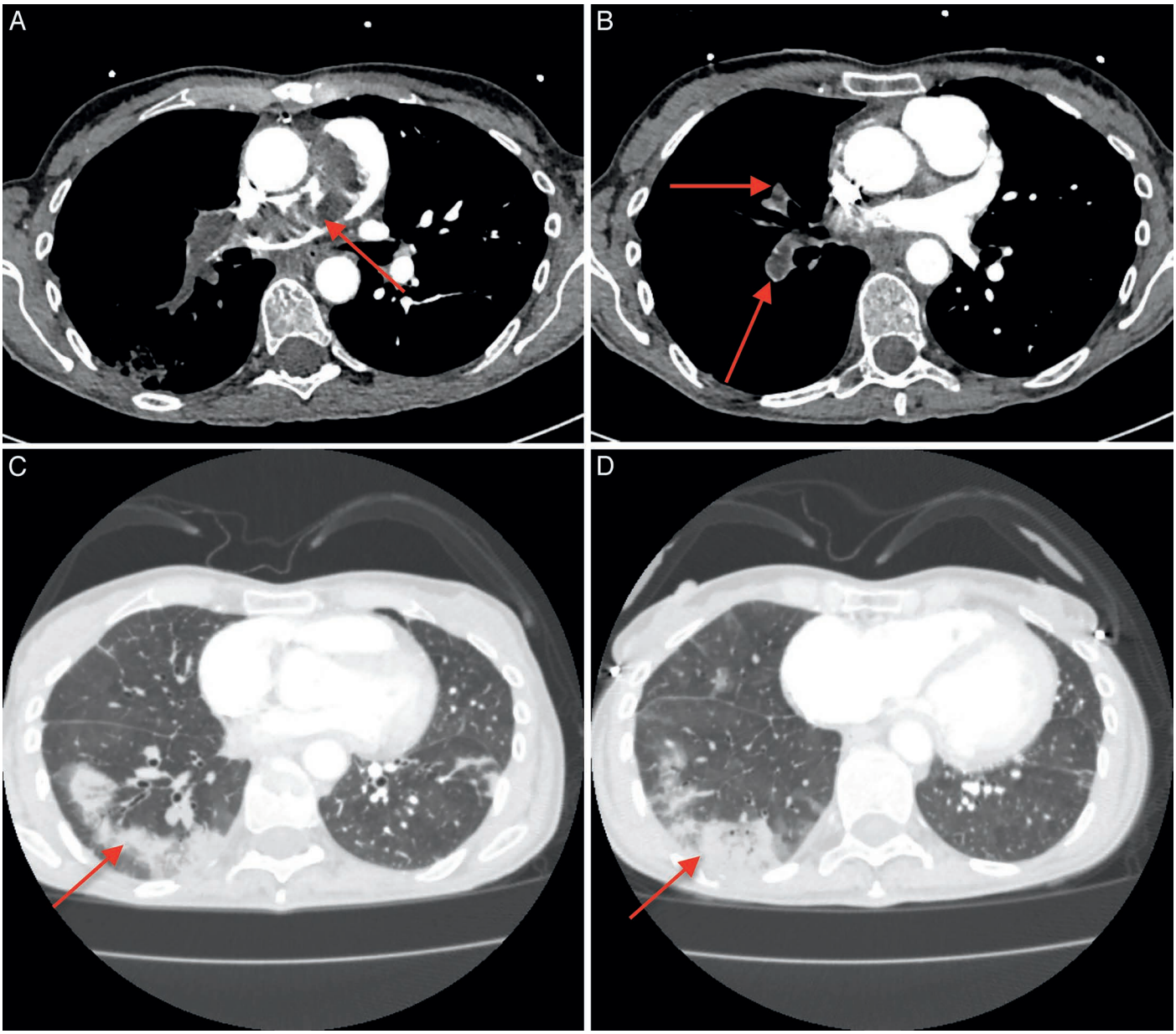
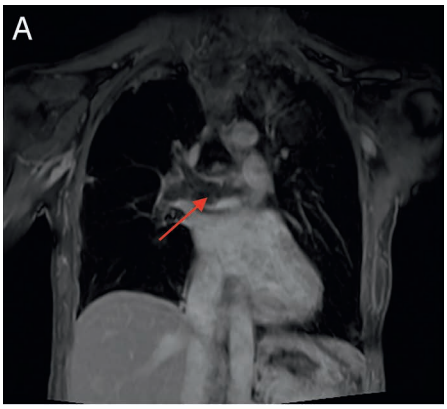


Figure 3A: CTPA representative selection demonstrating a large, obstructing filling defect within the pulmonary artery trunk, right pulmonary artery, and right segmental branches (red arrow).
Figure 3B: CTPA representative selection demonstrating a large, obstructing filling defect within the pulmonary artery trunk, right pulmonary artery, and right segmental branches (red arrows).
Figure 3C: CTPA representative selection demonstrating a multiple peripheral ground-glass opacities and areas of consolidation (red arrow).
Figure 3D: CTPA representative selection demonstrating a multiple peripheral ground-glass opacities and areas of consolidation (red arrow).

suggests the presence of an intravascular tumor. However, as our case illustrates, the absence of contrast enhancement is not sufficient to exclude intravascular tumors. Another radiographic modality, fluorodeoxyglucose (FDG) positron emission tomography (PET), may be helpful in distinguishing between thrombi and malignant lesions. The degree of FDG uptake tends to be significantly higher in the latter group.[6,7]

The mainstay of therapy for these tumors is surgical resection, which may prolong tumor-free survival.[7,8] The role of chemotherapy is unclear, and there are no consensus recommendations for specific therapeutic regimens.[9] Overall, prognosis is poor with mean survival rates between 1 and 2 years in most case series.[3,7-9] This is likely due in part to delay in diagnosis. A strong index of suspicion is necessary in patients with presumed thromboembolic disease who fail to respond to appropriate anticoagulation therapy. PAS should also be considered in patients undergoing evaluation for chronic thromboembolic pulmonary hypertension (CTEPH) who have large proximal filling defects. Given that no single imaging study can rule out an intravascular sarcoma, a multimodality approach, including CTPA, chest MRI, and PET imaging, may be necessary to improve diagnostic accuracy. In addition, early referral to a surgical



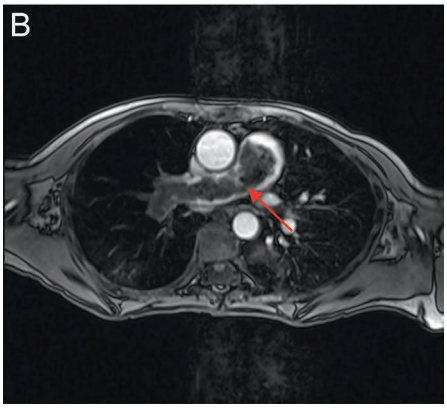


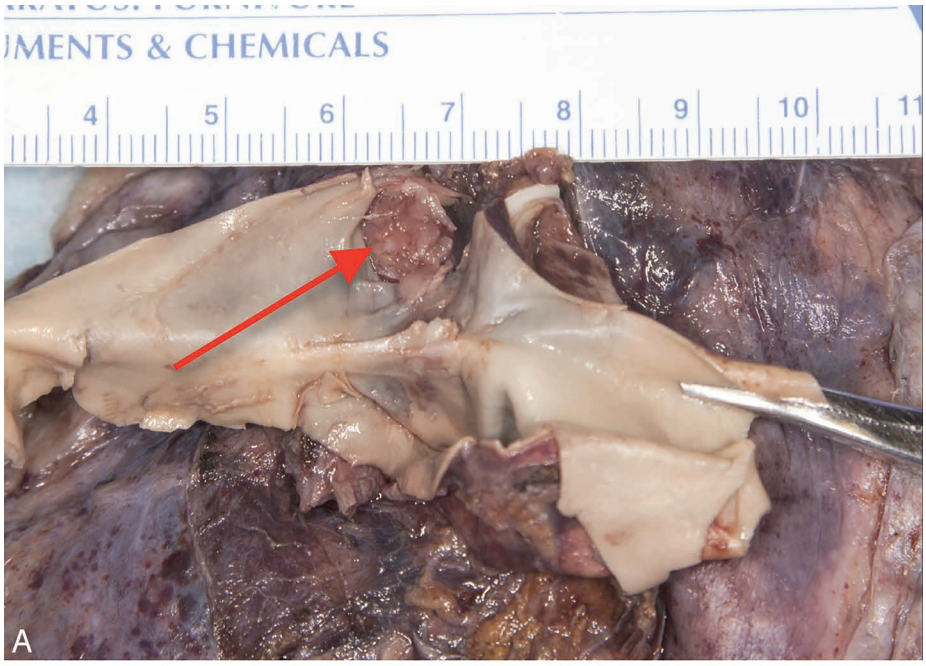
Figure 4A: Contrast-enhanced chest MRI representative selection demonstrating a large filling defect within the main pulmonary artery and right-sided pulmonary artery branches (red arrow).
Figure 4B: Contrast-enhanced chest MRI axial T1 representative image demonstrating a large filling defect within the main pulmonary artery and right-sided pulmonary artery branches. No significant contrast enhancement is noted within the lesion (red arrow).

center of excellence should be strongly considered.

Expert Commentary*: Pulmonary vascular neoplasms are one of the notorious mimics of acute and chronic pulmonary thromboembolic disease. As illustrated by this case, the initial clinical presentation and even computed tomography (CT) angiographic imaging are often indistinguishable from that associated with an acute pulmonary embolic event. At the onset, there was little to suggest an alternative diagnosis in this patient, given the abrupt onset of cardiopulmonary symptoms, the predisposition to an acute thromboembolic event (recent air travel), and the presence of intraluminal filling defects by CT angiography. However, a moment of diagnostic pause

Table 1. Right Heart Catheterization.

Right atrial pressure, mm Hg	6/4 (4)
Right atrial oxygen saturation, %	52
RV pressure, mm Hg	43/3 (16)
Pulmonary artery pressure, mm Hg	42/17 (25)
Pulmonary artery oxygen saturation, %	51
Pulmonary artery occlusion pressure, mm Hg	4
Cardiac output, L/min (thermodilution)	4.4
Cardiac output, L/min/m2	2.75
Pulmonary vascular resistance, Wood units	3.8



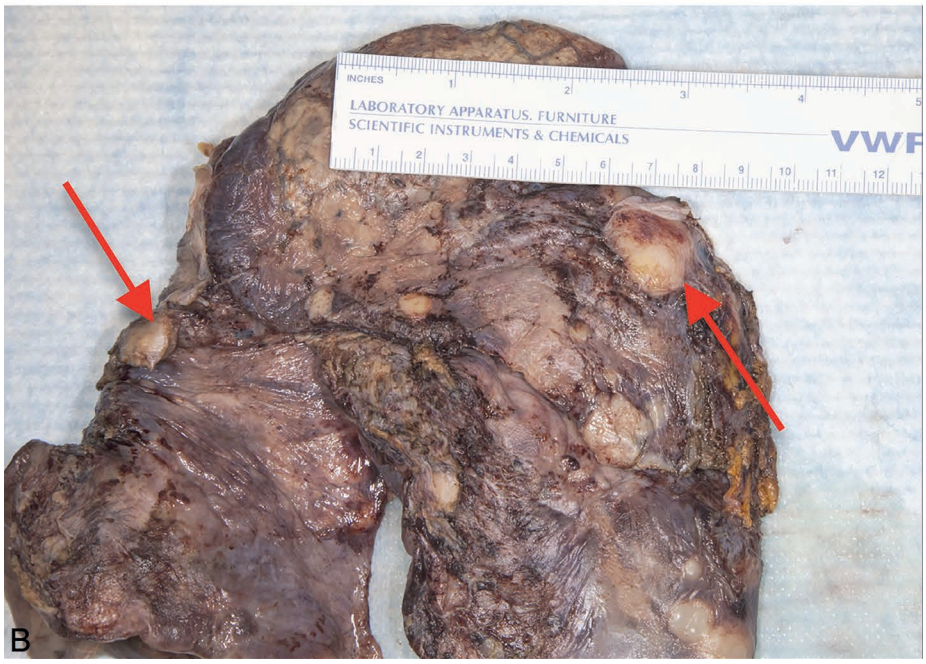
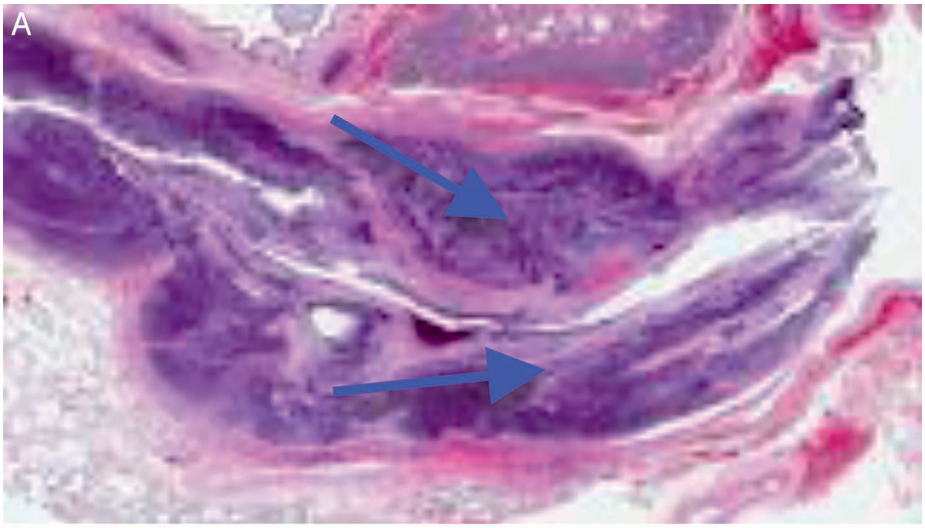


Figure 5A: Gross specimen of the right lung showing a cartilaginous tumor obstructing the pulmonary artery (red arrow).
Figure 5B: Gross specimen of the right lung showing multiple cartilaginous tumor nodules throughout the lung parenchyma (red arrows).



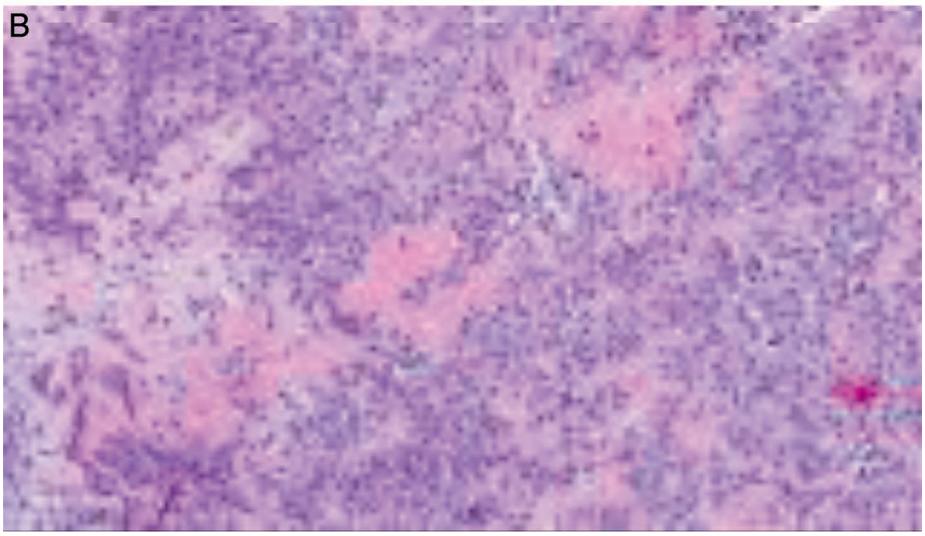


Figure 6A: A large-caliber artery is filled and distorted with lobulated, cartilage-predominant tumor (blue arrows). Normal lung (lower left), bronchus (upper left), and lymph node (top center) are also present. (10x hematoxylin and eosin stain)
Figure 6B: Areas of tumor from the peripherally located nodules show osteoid production by sheets of high-grade cells with large nuclei, prominent nucleoli, and conspicuous mitotic activity. (200x hematoxylin and eosin stain)

is generally warranted when the "thrombus" appears to disrupt the vascular tissue plane (as seemingly is the case in Figure 1A where there is "thrombus adherent" to the main pulmonary artery). And given the mesenchymal origins of these vascular tumors, lesions involving the right ventricle and traversing the pulmonic valve, irregular thickening of the RV outflow tract, a "bulging" of a main pulmonary artery lesion into the outflow tract,[4] and adherent lesions in the most proximal aspects of the pulmonary vasculature … especially without accompanying emboli in the more distal vessels … should raise suspicions of a more malignant etiology. These are not typical clinical or radiographic features observed with acute pulmonary emboli. Isolated, unilateral lesions, the presence of parenchymal nodules, and the absence of a deep vein thrombosis or a venous thrombus source should also alert the physician to the possibility of an alternative diagnosis. Another hint that a neoplasm may be present is "growth of the clot" during what is considered appropriate anticoagulation. Often considered an "anticoagulant failure," the specific enlargement of the previously imaged clot without new emboli, and the involvement of the very proximal pulmonary vasculature should again raise concerns that thrombus is not the issue. Unusual in this case was the rapidity with which the lesions enlarged, suggesting a very malignant process. This patient's presentation a month after her initial diagnosis with evidence of right heart failure was simply a manifestation of progressive encroachment on the pulmonary vessels with tumor.

The confirmation of a pulmonary vascular neoplasm prior to surgical resection can be difficult. This was again well illustrated by this case. Gadolinium-enhanced chest MRI can be helpful in the distinction between pulmonary artery neoplasms and thrombus, though intravascular tumors can result in false-negative studies. FDG-PET imaging seems more reliable based on clinical experience and the limited data available.[7] The variable performance of these modalities may simply reflect the degree of malignancy within the spectrum of pulmonary artery tumors. And the success of catheter-based biopsy will logically be influenced by the extent of material obtained. Personal experience with this approach has been limited; furthermore, there has not been a report describing the usefulness of this technique in establishing the diagnosis of pulmonary artery tumors.

In most cases, the presurgical diagnosis is presumptive and generally based on the clinical presentation, radiographic features, and the response to anticoagulants if the initial diagnosis was a pulmonary embolus. And from a practical perspective, unless a patient refuses, surgical exploration and resection is warranted even without a presurgical diagnosis, as typically the differential diagnosis involves CTEPH, and most of these patients have signs and symptoms of PH and right heart failure as they present late in the course of their disease. It is therefore advisable, if the clinical situation allows, that a center with expertise in the performance of endarterectomy surgery should be consulted and a referral initiated. The immediate goals for surgery are similar to those for patients with CTEPH: to relieve PH and right heart dysfunction. This underscores the importance of performing as complete an endarterectomy as possible; simply removing visible tumor may not provide adequate RV afterload. In addition to the possibility of pulmonary hemodynamic improvement,

a pulmonary vascular tumor endarterectomy will result in tissue acquisition for diagnostic purposes, tumor debulking, and some survival benefit, albeit variably dependent on the extent of resection and the type of tumor present.[5] Rarely is the tissue type such that a cure is obtained with surgery. Often surgical resection is simply the first step in the management of this rare and clinically challenging neoplasm. Consultation with radiation and medical oncology is required to provide the essential multidisciplinary treatment plan to achieve the best possible outcome.

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Teaching Points

1. Pulmonary artery sarcomas are relatively rare intravascular tumors that may present with signs and symptoms that mimic acute or chronic thromboembolic disease.
2. Pulmonary artery sarcomas should be considered in patients who fail to respond to appropriate anticoagulation therapy.
3. The diagnosis is primarily based on imaging studies to include CTPA, chest MRI, and PET scans.
4. No single imaging study is sufficiently sensitive to exclude the presence of a pulmonary artery sarcoma.
5. Surgical debulking is the mainstay of therapy and may provide a survival advantage in this patient population. Consequently, early referral to a center of excellence should be strongly considered.

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ERRATUM

The Volume 15, No 1 issue of *Advances in Pulmonary Hypertension* contained an error in the PH Grand Rounds column, "Pulmonary Arterial Hypertension: 'A Journey to Lung Transplant." The PVR values in Tables 2 and 3 reflect an incorrect calculation from the original outside medical records. The editors thank Michael Slack, MD, Professor, Department of Pediatrics, University of Maryland School of Medicine; Director, Pediatric and Adult Congenital Interventional Cardiac Catheterization Laboratory, University of Maryland Medical Center, Baltimore, for pointing out this oversight . Dr Slack reinforces that PVR is the basis for many critical clinical decisions and provides the following 3 different ways to express PVR:

	Reference Range		
Measurement	**dyn·s/cm^5**	**MPa·s/m^3**	**mmHg·min/l or HRU/Wood units**
Pulmonary vascular resistance (PVR)	20-130	2-13	0.25-1.6

In cardiac ICUs, the units of dyn.s/cm5 are often used and the conversion factor between this value and Wood units is, conveniently, 80. During cardiac catheterization, the convention is to use the Cardiac Index (not cardiac output) and express the PVR in Wood units, which are indexed to body surface area.