A Case of "False-Positive" High Probability Ventilation-Perfusion Lung Scan due to Tuberculous Mediastinal Adenopathy with a Discussion of Other Causes of "False-Positive" High Probability Ventilation-Perfusion Lung Scans

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From the case records of the Hospital of the University of Pennsylvania

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CLINICAL HISTORY

The patient was a 51-yr-old black female who had been in stable health until 1989. Her prior history was significant for Sheehan's syndrome of 28 years duration for which she took replacement therapy (prednisone 5 mg QAM + 2.5 mg QPM, synthroid 0.125 mg QAM). She also had a history of peptic ulcer disease, hyperlipidemia, and hypertension. In early 1989, she developed a positive PPD for which she took isoniazid for 9 mo. She remained in her usual state of health until November 1989, when she developed episodes of palpitations and right-sided chest pain. She was hospitalized for evaluation. Holter monitoring for 24 hr was negative. Cardiac catheterization demonstrated normal coronary arteries and normal left ventricular function. Despite these negative studies, over the next several months she gradually developed progressive dyspnea on exertion.

In March 1990, she experienced a syncopal episode while walking. She did not seek medical attention for this and remained stable until June 1990 when she noted progressive fatigue. In July 1990, she experienced a second syncopal episode, this time while walking upstairs. Several days later she had an episode of severe substernal chest pain, diaphoresis, and a sensation of heaviness in her legs. When this recurred she was admitted to a local hospital where acute myocardial infarction was ruled out. An echocardiogram done at that time demonstrated paradoxical septal motion, mild right atrial and right ventricular enlargement, and both tricuspid and pulmonic regurgitation. Pulmonary function tests were interpreted as demonstrating a mild restrictive pattern with normal airflows. During an exercise stress test she developed syncope with a heart rate of 30 bpm. Repeat cardiac catheterization revealed normal left atrial and left ventricular configurations and pressures. There was enlargement of the right atrium and right ventricle with right ventricular hypokinesis, moderate-to-severe tricuspid regurgitation, and pulmonary hypertension with pulmonary arterial pressures of 88/32 mmHg (mean pressure 50 mmHg). Ergonovine did not provoke coronary spasm. A ventilation/perfusion (V/P) lung scan was interpreted as indicating a high probability for pulmonary embolism with large mismatched perfusion defects, most notably in the right upper lobe (Fig. 1). She was started on i.v. heparin therapy. A repeat V/P lung scan, obtained approximately two weeks after the initial study, demonstrated no interval change. Doppler examinations of the lower extremities were normal. Venography could not be performed because of inability to obtain vascular access. Chest CT demonstrated calcified right hilar nodes and an enlarged calcified retrotracheal lymph node. The pulmonary arteries and right atrium were noted to be markedly enlarged. During the second week of heparin therapy, there was no improvement in the patient's condition. In fact, her arterial oxygenation worsened and her murmur of tricuspid regurgitation became more pronounced. Because of concern that this

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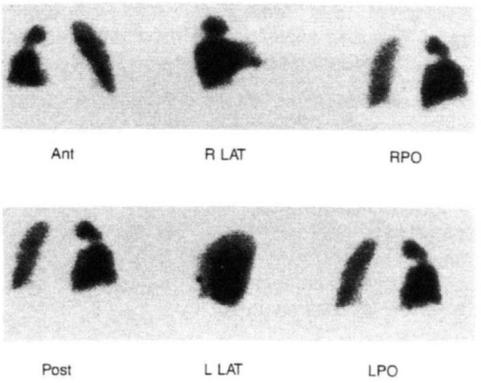

FIGURE 1
Repeat perfusion lung scan obtained after 2 wk of heparin therapy demonstrating multiple segmental defects in the right upper lung zone. The ventilation scan was unremarkable. This appearance was unchanged from the previous lung scan.

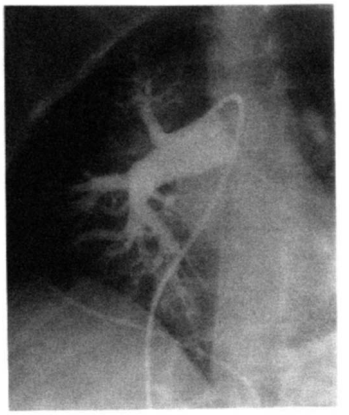

FIGURE 2
Pulmonary angiography of the right lung suggested decreased arborization of the vasculature in the right upper lobe without finding any evidence of embolization.

patient's disease and deterioration was a consequence of chronic pulmonary thromboembolism, the patient was transferred to our institution for further evaluation.

On arrival in our intensive care unit, she was noted to be a moderately obese, somewhat Cushingoid-appearing woman who was resting comfortably. Her blood pressure was 107/70, her respiratory rate was 18, her pulse was 64, and she was afebrile. Examination demonstrated clear lungs. Her cardiac exam demonstrated a normal S1, the pulmonic component of S2 was increased, and no S3 or S4 were appreciated. There was a holosystolic 3/6 murmur at the lower left sternal border radiating through the precordium and neck; the murmur augmented during expiration. A right ventricular heave was noted in the subxiphoid region. Her abdominal examination was benign. She had edema of the lower extremities and her neurologic examination was unremarkable. Her hemoglobin was 10.8. Her electrolytes were normal. A blood gas on 50% ventimask demonstrated a pH of 7.38, a PCO_2 of 33, a PO_2 of 128, and a bicarbonate of 19. Electrocardiogram revealed inverted T-waves in the precordial leads. Her chest X-ray was interpreted as showing moderate cardiomegaly with left atrial prominence; there was pulmonary vascular congestion noted and there was the suggestion of a mass in the subcarinal region.

On the morning after transfer, she underwent pulmonary angiography. No clot was noted on the right but there was an impression of diminished arborization of the pulmonary vasculature in the right upper lobe (Fig. 2). A nonocclusive thrombus in the pulmonary artery to one of the basal segments of the left lower lobe was demonstrated (Fig. 3). Pulmonary pressures were elevated and flow was diminished. No comment could be made about the venous phase of the angiogram. The patient was scheduled for MRI to evaluate her heart and pulmonary vessels as well as the subcarinal mass. Unfortunately, on the evening after the pulmonary angiogram, the patient developed a distended abdomen followed by emesis of coffee ground material. Some of this material was aspirated. The patient suffered respiratory arrest followed by bradycardia, which resulted in her demise. An autopsy was performed.

Pathologic Findings

At the time of autopsy, the most pertinent findings were seen in the mediastinum. There was a 4-cm diameter calcified caseated lymph node at the carina with apparent compression of the left atrium and narrowing of the pulmonary veins at their atrial insertions (Fig. 4). There was atherosclerosis of the pulmonary arteries and a large pericardial effusion. Microscopic examination showed changes of postcapillary pulmonary hypertension, with significant occlusion of the small pulmonary veins by sclerosis and fibrous tissue deposition. There was also arterialization of the pulmonary veins

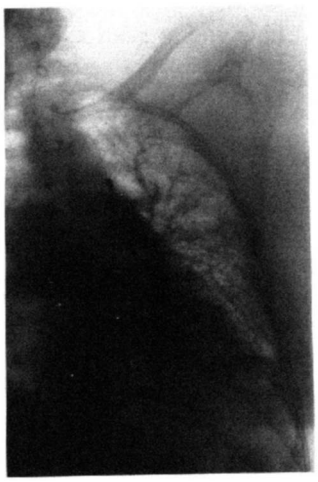

FIGURE 3
Subtraction image of the pulmonary angiography of the left lung showing a single distal clot in a basilar artery branch to a segment of the lower lobe.

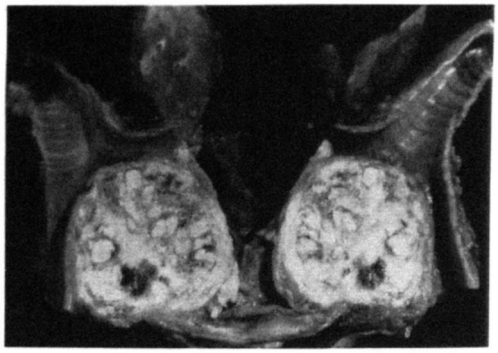

FIGURE 4
Gross autopsy specimen demonstrating a 4-cm calcified, caseated lymph node at the tracheal carina. This node was compressing the left atrium and narrowing the pulmonary veins at their atrial insertions. (Courtesy of G. Pietra, MD)

TABLE 1
Causes of "False-Positive" High Probability Ventilation-Perfusion Lung Scans

1. Prior PE (residual organized thrombotic material-not acute clot)
2. Compression or entrapment of pulmonary vasculature.
   1. Mass lesion (i.e., malignancy, especially lung cancer)
   2. Adenopathy (i.e., malignancy, sarcoid, TB, broncholithasis)
   3. Mediastinal fibrosis (i.e., idiopathic, post-radiation therapy)
   4. Compression by adjacent vascular structure (i.e., aortic aneurysm)
3. Intraluminal obstruction of pulmonary vasculature.
   A. Congenital vascular anomaly
      1. Agenexis
      2. Hypoplasia
      3. Coarctation
      4. Stenosis/branch stenosis
   B. Malignancy
      1. Metastatic (i.e., renal cell, myxoma, cardiac sarcoma)
      2. Primary tumor of pulmonary artery (i.e., sarcoma)
   C. Arteritis (i.e., Takayashu's disease, *Schistosomiasis*)

with intimal thickening. The pulmonary arterioles demonstrated secondary changes including intimal proliferation and recanalization. The alveolar septae were widened; there were severely dilated lymphatics and dilated bronchial vessels near the pleural surface. There was also additional evidence of prior pulmonary tuberculosis with a Ghon lesion in the right lower lobe. No acid-fast organisms were noted to be present. The final pathologic diagnosis was post-capillary pulmonary hypertension secondary to compression of the main pulmonary veins by the large calcified granulomatous mediastinal lymph node.

DISCUSSION

This patient appears to demonstrate an instance where a high probability lung scan represented neither acute pulmonary embolism (PE), which was initially suspected, nor chronic pulmonary thromboembolism, which was the subsequent diagnosis. In fact, the perfusion defects noted were most likely a consequence of sluggish blood flow due to obstruction of the central pulmonary veins and did not represent thromboembolic events at all.

Ventilation/Perfusion Lung Scans

Ventilation/perfusion lung scans are most often ordered for and interpreted in the context of evaluating for suspected PE. Lung scans are interpreted by pattern recognition correlating chest radiograph findings with those seen on the ventilation scan and the perfusion scan. Depending on the size of the perfusion defects and a comparison of the three imaging studies, the lung scans are assigned a probability of PE based on standard criteria (*1*). Despite the validation of these criteria, it is important to remember that there are causes of unmatched perfusion defects, even in the setting of an apparently normal chest X-ray, which are not due to PE. These conditions do give rise to unmatched perfusion defects; the interpretive problem arises when lung scans are considered solely as a diagnostic test for the presence of acute PE. We will call these "false-positive" high-probability lung scans. A listing of the more frequent causes of "false-positive" ventilation-perfusion lung scans is presented in Table 1.

Etiologies of False-Positive High Probability Lung Scan Pattern for Acute PE

Chronic, Unresolved Pulmonary Emboli. The most common reason for a V/P lung scan to be falsely interpreted as high probability for acute PE is the presence of chronic unresolved pulmonary thromboembolism (Fig. 5). Embolic material in the lungs may not dissolve completely even if treated with standard anticoagulation or thrombolytic therapy. Follow-up data from the NIH-sponsored UPET studies suggests that as many as 20% of perfusion lung scans do not return to normal after pulmonary embolic events (*2*). These persisting defects clearly lead to interpretation difficulties when a new embolic event is suspected.

The recently completed Prospective Investigation Of Pulmonary Embolism Diagnosis (PIOPED) study provides data supporting this (*3*). In the PIOPED study, 116 patients had their lung scans interpreted as high probability for PE. Of these patients 102 out of 116 had acute pulmonary emboli demonstrated at the time of angiography. This gives a positive predictive value for high probability V/P lung scans of 88%. If we analyze the data by excluding those patients who had a prior history of PE, we find that 97 patients in PIOPED had high probability V/P lung scans with no prior history of PE; 88 of these 97 patients had pulmonary emboli demonstrated at angiography. This gives a positive predictive value for high probability V/P lung scans in this population of 91%. However, this leaves us with 19 patients who had high probability lung scans and a history of prior pulmonary emboli; only 14 of these patients had acute pulmonary emboli demonstrated at

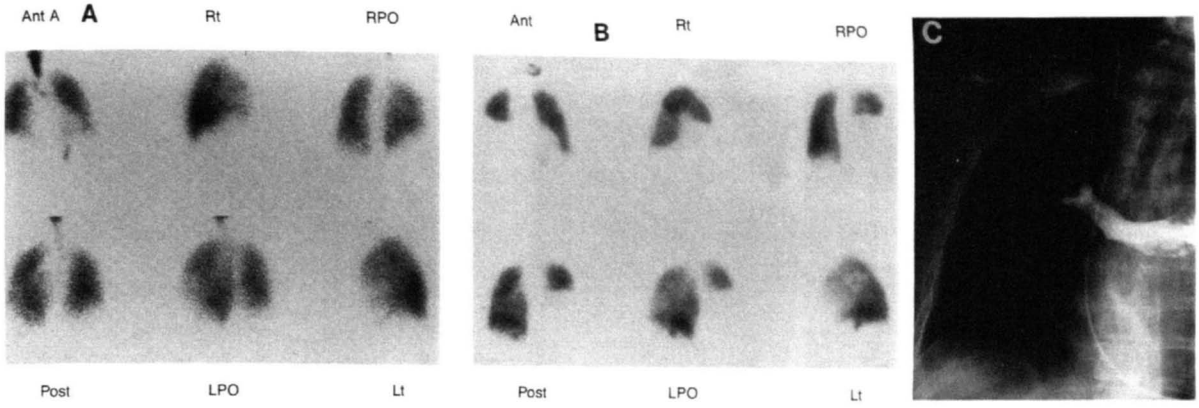

FIGURE 5
(A) Technetium-99m-DTPA aerosol ventilation lung scan from a patient who had a PE several years prior to this presentation. (B) Perfusion lung scan from this patient demonstrates large unmatched defect in right lower lobe. (C) Pulmonary angiogram from this patient demonstrates findings of chronic, organized thrombotic material; no acute pulmonary emboli were demonstrated.

pulmonary angiography. This gives a positive predictive value for high probability V/P lung scans of only 74% for patients with a prior history of PE.

Obviously, we can see that there is a significant clinical problem when failure of resolution of a substantial percentage of pulmonary emboli results in suboptimal predictive value on subsequent lung scans. We recommend that follow-up V/P lung scans be obtained soon after completion of the anticoagulation course in patients who have had large pulmonary emboli. This follow-up scan can serve as a baseline scan and, in part, may obviate the diagnostic confusion frequently resulting from suspected recurrent embolic events in this population.

Compression or Entrapment of Pulmonary Vasculature. Compression or entrapment of either pulmonary artery or pulmonary vein (as in the case of this patient) may be responsible for a mismatched perfusion defect on lung scan. Which vascular structure is compromised is a consequence of the location of the pathologic lesion. However, in many circumstances, it is the pulmonary vein that is compromised first, since it is a thinner-walled structure with a lower intraluminal pressure than the pulmonary artery and, therefore, it is more susceptible to compression. Often the cause of the vascular compromise is apparent on the chest radiograph but it is not appreciated whether it is responsible for the lung scan abnormalities. However, there are many cases when the plain chest radiograph does not lead one to suspect vascular compromise. This was true in this particular case. Pulmonary angiography may fail to clarify the diagnosis if the catheter is passed beyond the point of obstruction, or if the injection of contrast under pressure relieves the vascular compression. In those circumstances, further investigation with CT or MRI may be necessary to demonstrate the pathologic process. The following list detailing some of the causes of vascular compression is certainly not complete, and other processes may result in compression of the pulmonary arteries or veins with resultant abnormalities on perfusion lung scans (*4*):

1. Mass lesions in the mediastinum, the pulmonary hila, or more distally within the lung parenchyma may be responsible for compressing pulmonary arteries or veins. The most frequent cause of this is malignancy; most often primary carcinoma of the lung.
2. Adenopathy in either the mediastinum or in the pulmonary hila may cause compression of vascular structures. Most frequently, this is a consequence of neoplasia metastatic to the lymph nodes. Frequently, primary carcinoma of the lung is responsible for this finding, however, other metastatic malignancies or primary tumors involving the lymph node tissue (i.e., lymphoma) may also be responsible. Benign etiologies of nodal involvement may cause vascular obstruction. In this patient, we found that granulomatous enlargement of the lymph nodes due to prior tuberculosis caused compression of the central pulmonary veins, most likely at their insertions into the left atrium. In other instances, lymph node involvement due to sarcoidosis has been implicated in this process. Broncholithiasis has also been described as a cause of pulmonary vascular compression.
3. Entrapment of the vascular structures by fibrosis within the mediastinum can result in perfusion scan abnormalities. This has been described in patients with idiopathic mediastinal fibrosis, a progressive fibrotic process involving the mediastinum which is thought, in many cases, to be the

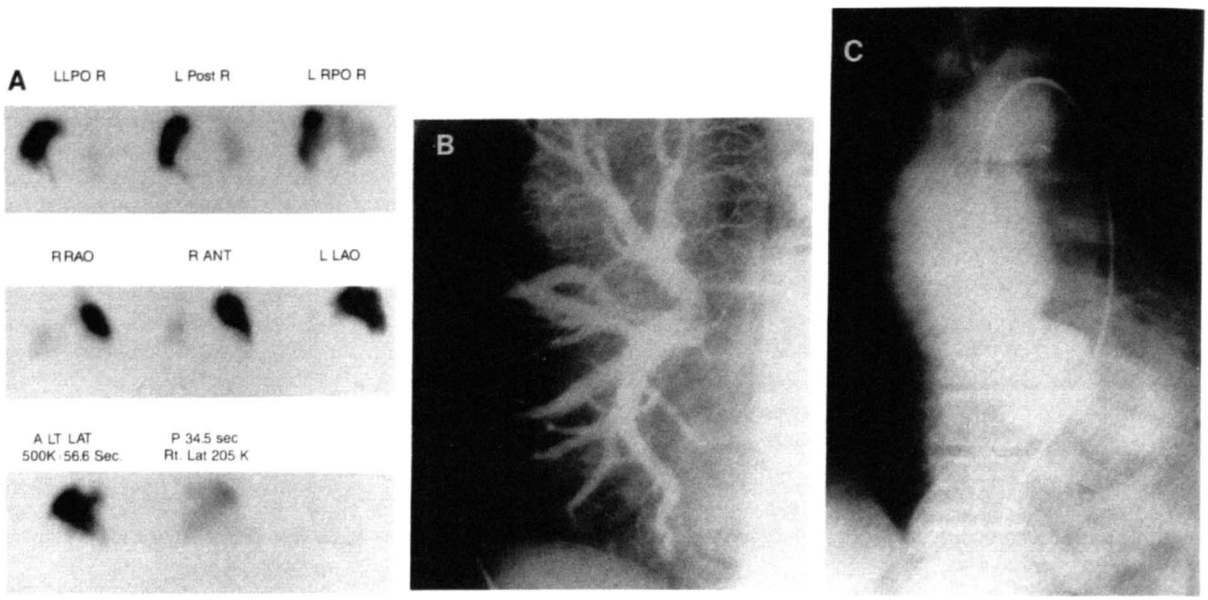

FIGURE 6
(A) Perfusion lung scan from an elderly male presenting with syncope, sharp right-sided chest pain, and widened A-a gradient. The scan shows significantly decreased perfusion to the entire right lung and the defects in the left upper and lower lobes. The ventilation lung scan was normal. (B) Pulmonary angiogram from this patient demonstrating normal vasculature. Note the absence of reflux of contrast into the main pulmonary artery; the angiography catheter has been passed beyond the area of vascular compression. (C) Aortogram from this patient demonstrating aneurysm of ascending aorta which was compressing the right main pulmonary artery and thereby creating the lung scan findings.

late consequence of infection with histoplasmosis. Scarring secondary to prior radiation therapy can also cause this process.

4. Pulmonary vascular structures may also be compressed by adjacent vascular structures. While this is infrequent, high probability lung scans, as the result of compression of a pulmonary artery by a thoracic aortic aneurysm, have been described (Fig. 6). In one such instance a patient treated with thrombolytic therapy on the basis of a high probability lung scan exsanguinated from a ruptured thoracic aortic aneurysm (*5*).

Intraluminal Obstruction of Pulmonary Vasculature. Intraluminal processes that affect the pulmonary artery or vein lumen can result in high probability lung scans. These processes may be quite difficult to diagnose, as they may not be associated with abnormalities detectable by chest radiography or other noninvasive diagnostic modalities (i.e., CT or MRI). An invasive study, such as pulmonary angiography or open biopsy, may be necessary to establish a diagnosis. Some causes for intraluminal obstruction include:

1. Congenital vascular anomalies. These anomalies, though infrequent, do occur and need to be considered in a list of diagnostic possibilities. Agenesis, hypoplasia, coarctation, or stenosis or branch stenosis may occur within the pulmonary tree. These abnormalities may be quite difficult to diagnose. In adults, it is important to exclude chronic thromboemboli before concluding that a vascular abnormality noted is congenital in origin. This is because chronic thromboemboli can cause progressive pulmonary hypertension and because chronic, organized thromboemboli can be treated successfully by surgical approach (*6*).
2. Malignancies. Intraluminal obstruction can occur by several different mechanisms. First, there may be malignancies which grow intravascularly and either extend directly or embolize to the pulmonary circulation. Renal cell carcinoma, myxoma, and intracardiac sarcomas all may result in obstruction of pulmonary arteries. The clinical syndrome resulting may be indistinguishable from that of an acute PE. Hematogenous dissemination of microscopic foci of carcinoma also occurs, although in this syndrome the tumor emboli are minute in size and tend to end up within the pulmonary microvasculature (*7*). Lymphangitic carcinomatosis has also been reported to occasionally cause abnormalities on perfusion scans. Primary tumors of the pulmonary artery may also cause vascular obstruction and a high probability lung scan (*8*). Most often, these tumors are sarcomas (Fig. 7). They are often quite difficult to diagnose and their presentations may range from that of an acute vascular obstruction to one of a more chronic process presenting in a manner similar to patients with unrecognized chronic pulmonary thromboemboli.

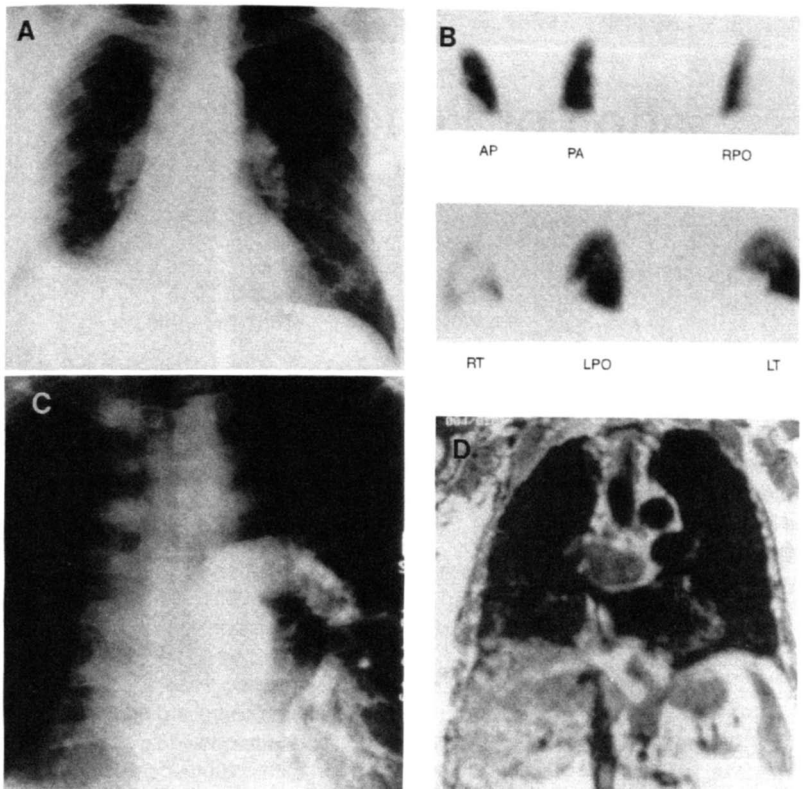

FIGURE 7
(A) Chest radiograph from a male presenting with several months of progressive dyspnea and pleuritic chest pain, which shows some pleural disease in the right and minor parenchymal abnormality in the left base. (B) Perfusion lung scan from this patient demonstrates almost complete absence of perfusion to the right lung. The ventilation lung scan was normal. (C) Pulmonary angiogram demonstrates absence of any flow to the right lung; the left lung proved to be normal without any evidence of thromboemboli. (D) MRI scan demonstrates a mass in the proximal right main pulmonary artery; this mass was found at surgery to be a primary sarcoma of the right pulmonary artery.

3. Vasculitis. While relatively uncommon in the United States, this is one manner by which *Schistosomiasis* eventually results in pulmonary hypertension. Systemic vasculitic processes, such as Takayasu's arteritis and systemic lupus erythematosus, may involve the pulmonary vasculature and result in obliterative lesions. It is quite uncommon for these vasculitidies to involve only the pulmonary circulation. However, pulmonary vascular involvement may not be suspected initially and a lung scan, if ordered, may be interpreted as representing thromboembolic disease unless large-vessel vasculitis is considered.

CONCLUSION

The V/P lung scan is an excellent screening test for detecting acute PE. It is quite sensitive and does not appear to miss clinically significant pulmonary emboli; however, it is not specific. There are etiologies of perfusion defects and of patterns interpreted as high probability for PE that are not due to acute thromboembolism. Consideration of all the information available, including that provided by chest X-ray and by clinical history, may help improve the accuracy of the lung scan for the diagnosis PE (*3*). However, there will continue to be cases where further investigation of the etiology of the high probability lung scan is warranted prior to the start of therapy.

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