

# Nephrotic syndrome, mediastinal mass, and pulmonary embolus

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## CASE PRESENTATION

KEVIN P. THELEMAN, MD: A previously healthy 17-year-old white man in East Texas developed fever, cough, and malaise and was treated by his primary care physician for a presumed "walking pneumonia" that failed to resolve after treatment with azithromycin. Approximately 2 weeks after the onset of symptoms, edema appeared and progressed to anasarca. The patient was referred to a nephrologist. A kidney biopsy was recommended, but the patient's parents opted for an empiric trial of prednisone. A 24-hour urine collection yielded 17.9 g of protein. The edema worsened despite furosemide and metolazone therapy. The edema lessened, however, with intravenous torsemide, but within 24 hours of this therapy, the patient had acute pleuritic chest pain. His PO<sub>2</sub> level was 67 mm Hg, and a ventilation/perfusion scan was interpreted as high probability for pulmonary embolism. Chest radiography disclosed a probable mediastinal mass. He had been taking prednisone, 25 mg twice daily, for approximately 2 weeks; omeprazole and heparin were added. He was referred to Baylor University Medical Center (BUMC) for further evaluation.

The patient denied using tobacco, alcohol, or illicit drugs and was not sexually active. Both parents were healthy. There was no family history of kidney disease, a hypercoagulable state, or a clotting disorder.

On physical examination at BUMC, the patient was breathing oxygen but was in no acute distress. No edema was apparent. He had no thyromegaly, venous distention, or palpable lymph nodes. The chest was clear. No precordial murmurs or abnormal heart sounds were heard. No abdominal abnormalities were noted, and no testicular masses were found. Neurologic examination disclosed no abnormalities. The skin was normal.

The laboratory findings are summarized in the *Table*. The serum total protein, albumin, globulin, and calcium levels were low, and the serum total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels were high. The 24-hour urine protein was 15.4 g. Creatinine clearance results were normal. There were 0 to 1 leukocytes and erythrocytes per high-power field in the urine. The partial thromboplastin time was increased, but the patient was receiving heparin. The fibrinogen level was normal. Tests for HIV, hepatitis B surface antigen, and hepatitis C antibody were negative; the rapid plasma reagin test was nonreactive.

**Table. Laboratory values after admission to Baylor University Medical Center**

Sodium	130 mEq/L	Aspartate aminotransferase	39 U/L
Potassium	3.8 mEq/L	Alanine aminotransferase	55 U/L
Chloride	97 mEq/L	Lactate dehydrogenase	1051 U/L
Bicarbonate	26 mEq/L	Cholesterol	588 mg/dL
Blood urea nitrogen	21 mg/dL	High-density lipoprotein	88 mg/dL
Creatinine	0.9 mg/dL	Low-density lipoprotein	446 mg/dL
Calcium	7.1 mg/dL	Triglycerides	252 mg/dL
Albumin	1.5 g/dL	White blood cell count	10.0 × 10 <sup>3</sup> /μL
Total bilirubin	0.4 mg/dL	Hematocrit	48%
Alkaline phosphatase	96 U/L	Platelet count	194 × 10 <sup>3</sup> /μL
		Erythrocyte sedimentation rate	7 mm/h

## DIFFERENTIAL DIAGNOSIS

ANDREW G. HICKL, MD: This 17-year-old patient had no significant past medical history and no personal or family history of kidney disease. He had no tuberculosis exposure. He presented with fever, malaise, and cough but no night sweats or weight loss. He was treated for a "walking pneumonia" with azithromycin but did not respond. He then developed nephrotic syndrome with anasarca; a 24-hour urine test at that time confirmed significant proteinuria but normal renal function. He subsequently had a pulmonary embolus, and during his examination a chest radiograph revealed a possible lung mass, so he was transferred to BUMC for further evaluation.

On examination here, he was afebrile and normotensive. He had no peripheral lymphadenopathy, hepatosplenomegaly, rash, or testicular masses or swelling, and he was not edematous. He had been on prednisone for 2 weeks and was recently treated with intravenous diuretics. A chest radiograph here revealed a possible mediastinal mass and a pleural effusion. Significant proteinuria, 15 g per 24 hours, with normal renal function was confirmed. He had an inactive urinary sediment, his serum albumin level was low, and his lipids were high, all consistent with the nephrotic syndrome. His calcium level was low, but it corrected to normal when the low albumin level was considered. He

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had an elevated lactate dehydrogenase level and a normal blood count. The sedimentation rate was normal, and tests for hepatitis B and C, HIV, and rapid plasma reagin were all negative.

Three key features need addressing: the nephrotic syndrome, the mediastinal mass, and the pulmonary embolus. The nephrotic syndrome is defined as heavy proteinuria (generally >3 g/day) along with hypoalbuminuria (due to urinary loss), hyperlipidemia, lipiduria, and edema. This syndrome can produce a hypercoagulable state, and it is associated with an inactive urinary sediment. In contrast, the nephritic syndrome is associated with an active urinary sediment characterized by hematuria, red cell casts, and a variable amount of proteinuria. In a more diffuse glomerulonephritis, varying degrees of renal insufficiency, systemic hypertension, and edema may be present. This patient had a pure nephrotic syndrome.

Specific glomerular diseases tend to produce particular syndromes of renal dysfunction that can manifest varying degrees of both nephrotic and nephritic features. The ones most likely to be associated with the nephrotic syndrome are *minimal change disease*, *membranous nephropathy*, *diabetic nephropathy*, *amyloidosis*, and *focal segmental glomerulosclerosis (FSGS)*. If we consider the patient's age and the specific glomerular syndrome with which he presents, the differential can be narrowed to the following glomerular diseases: minimal change disease, membranous nephropathy, FSGS, amyloidosis, diabetic nephropathy, and IgA nephropathy. The first 2 diseases in this list are the most likely.

*Minimal change disease* is the most common cause of idiopathic nephrotic syndrome in children and accounts for roughly 10% to 15% of nephrotic syndrome cases in adults. Secondary causes include several drugs, toxins, infections, malignancies, and allergies. Important secondary causes to consider in this patient would include HIV, mononucleosis, chronic nonsteroidal anti-inflammatory drug (NSAID) use, Hodgkin's disease, non-Hodgkin's lymphoma, and leukemia. The patient is HIV negative, he gave no history of NSAID use, and leukemia is ruled out by his normal blood count. Minimal change disease manifests with an abrupt onset of proteinuria and the development of nephrotic syndrome with heavy proteinuria. Nephritic features are unusual, renal function is typically normal, and microscopic hematuria is infrequent.

*Membranous nephropathy* is the most common cause of idiopathic nephrotic syndrome in adults, accounting for roughly 25% of cases. It most frequently occurs in the fifth and sixth decades of life, and 80% to 90% of patients are >30 years of age at diagnosis. Secondary causes include several autoimmune disorders, neoplasms, infections, and drugs. Important secondary causes to consider in our patient include sarcoidosis, non-Hodgkin's lymphoma, Hodgkin's disease, leukemia, lung and testicular cancer, and a few infections such as tuberculosis, secondary syphilis, and hepatitis B and C. Some secondary causes can be excluded. Leukemia is unlikely given the normal blood count. He is unlikely to have lung cancer given his young age and the fact that he doesn't smoke. Testicular cancer is important but unlikely given his normal examination results, and negative test results for hepatitis B, hepatitis C, and syphilis exclude these infections. Membranous nephropathy causes heavy proteinuria in >80% of patients, often with the full-blown nephrotic syndrome. The remaining patients have asymptomatic proteinuria. A few present

with hematuria, and most present with either a normal or slightly decreased renal function. Hypertension is typically not present at diagnosis.

The last 4 diagnoses in the list are less likely to be the cause of this patient's illness. Patients with FSGS most commonly present with proteinuria, and the majority present with the nephrotic syndrome. Hematuria is present in >50% patients with FSGS, diminished glomerular filtration rate occurs in 20% to 30%, and systemic hypertension occurs in about 33%. HIV and heroin nephropathy are important secondary causes. FSGS can be ruled out because the patient has normal renal function and blood pressure, he lacks hematuria, he is HIV negative, and he gives no history of intravenous drug abuse.

*Amyloidosis* is characterized by the extracellular deposition of a variety of normal serum proteins. Primary amyloidosis typically occurs in patients >50 years of age. Patients present with proteinuria, and about 50% have the nephrotic syndrome. Most patients present with renal insufficiency. Because primary amyloidosis is a systemic disease, other organs are involved. Amyloidosis is unlikely in this patient: he is young, he has normal renal function, he gives no history of chronic inflammatory illnesses that could lead to secondary amyloidosis, and he has no evidence of systemic organ involvement.

*Diabetic nephropathy* is an important cause of a pure nephrotic syndrome, but it can be ruled out in this instance. The patient has a normal glucose and gives no history of diabetes.

*IgA nephropathy* most often manifests as macroscopic hematuria following an upper respiratory infection or as intermittent microscopic hematuria. The nephrotic syndrome is far less common, and proteinuria is typically <1 g per day. For these reasons, I rule out IgA nephropathy.

The most likely diagnosis for this patient's glomerular disease is *minimal change disease*, with membranous nephropathy being a close second.

The first step in evaluating a *mediastinal mass* is to place it in one of 3 anatomic compartments: the anterior, middle, or posterior mediastinum. The most common lesions seen in the anterior mediastinum are thymomas, teratomas, lymphomas, and thyroid masses. The most common masses seen in the middle mediastinum are lymphomas, including non-Hodgkin's lymphoma and Hodgkin's disease; carcinomas such as lung cancer; granulomatous lesions such as tuberculosis, sarcoid, and histoplasmosis; and vascular masses such as aortic root dilatation. In the posterior mediastinum, neurogenic tumors, meningoceles, and esophageal diverticuli are most commonly found. Other diseases that can cause a mediastinal mass include testicular cancer with metastatic lung involvement, acute or chronic lymphocytic leukemias, and infections such as brucellosis, mononucleosis, and toxoplasmosis. We can narrow the differential by considering only the diseases that can cause a nephrotic syndrome and a mediastinal mass and then correlating those diagnoses with this patient's clinical scenario.

*Mononucleosis* can cause fever, malaise, mediastinal lymphadenopathy, and the nephrotic syndrome due to minimal change disease, but the patient lacks several typical signs and symptoms such as a sore throat, pharyngitis, posterior cervical lymphadenopathy, and splenomegaly. Although mediastinal lymphadenopa-

thy and the nephrotic syndrome can occur with mononucleosis, each is uncommon.

Patients with *toxoplasmosis* can present with fever and malaise, which this patient has, but the most common presentation is nontender cervical lymphadenopathy, which he lacks. Mediastinal adenopathy can occur with toxoplasmosis, but this is an uncommon manifestation. Toxoplasmosis is occasionally associated with the nephrotic syndrome or glomerulonephritis, but the specific glomerular lesions typically seen in toxoplasmosis, i.e., IgA nephropathy, most often produce a nephritic picture.

Patients with *primary tuberculosis* can present with fever, cough, malaise, and hilar adenopathy and later develop a pleural effusion that results in pleuritic chest pain and dyspnea. Membranous nephropathy has been associated with tuberculosis and thus could explain the patient's nephrotic syndrome. Nevertheless, he lacks several other typical symptoms such as hemoptysis, night sweats, and weight loss. His presentation is more subacute than chronic, which we would expect with tuberculosis, and the acute onset of his pleuritic chest pain and dyspnea is more consistent with a pulmonary embolus. Lastly, he volunteers no history of tuberculosis exposure or other risk factors.

*Lung cancer* is highly unlikely given the patient's young age and the fact that he doesn't smoke.

*Testicular cancer* is important to consider. He could have a testicular seminoma with metastasis to the mediastinal lymph nodes, or he could have an extragonadal germ cell tumor arising from the mediastinum. Both of these malignancies are associated with membranous nephropathy; however, testicular cancer can be excluded based on his normal examination and on the premise that extragonadal germ cell tumors are uncommon.

*Lymphocytic leukemia*, either acute or chronic, is another consideration. This patient's mediastinal mass may be caused by acute lymphocytic leukemia, as typically seen with the T-cell leukemias, or he could have hilar adenopathy caused by chronic lymphocytic leukemia. Both leukemias are associated with the nephrotic syndrome, typically minimal change disease, but both are unlikely. The patient has a normal blood count and peripheral smear, and he has no peripheral lymphadenopathy or hepatosplenomegaly.

*Sarcoidosis* is a possibility. The patient has constitutional symptoms (fever, malaise, and cough) and a mediastinal mass, all of which occur in most patients with sarcoid. Also, sarcoid can cause the nephrotic syndrome. The patient, however, lacks peripheral lymphadenopathy and skin, eye, or joint involvement, all of which are common with sarcoid. In addition, his calcium level and sedimentation rate are normal. Renal glomerular disease is uncommon with sarcoid.

The last 2 diagnoses, *Hodgkin's disease* and *non-Hodgkin's lymphoma*, are the most likely in this patient. Hodgkin's disease involves a malignant proliferation of tumor cells arising from the lymphoreticular system. There are 4 histologic subtypes; nodular sclerosis is the most common. The bimodal age distribution peaks at ages 15 to 34 and again after age 50, and the disease is more prevalent in men. It initially is localized and then spreads to contiguous lymphoid structures. Fifty percent of patients present with a neck or supraclavicular adenopathy, and 60% present with mediastinal adenopathy. Nodes involved tend to be

centripetal or axial. About 25% of patients have constitutional symptoms, such as weight loss, night sweats, fever, malaise, and fatigue. The nephrotic syndrome has been associated with Hodgkin's disease, and minimal change disease is the most common lesion. The diagnosis is made when a biopsy of involved tissue reveals Reed-Sternberg cells.

Based on his age and clinical presentation, this patient most likely has Hodgkin's disease. He has typical symptoms (fever, malaise, and cough) and presents with a mediastinal mass and the nephrotic syndrome, both of which are associated with Hodgkin's disease. However, the second illness, non-Hodgkin's lymphoma, is a close second. About 70% of patients with non-Hodgkin's lymphoma present with persistent, painless peripheral lymphadenopathy, and approximately 20% present with a mediastinal mass. Fewer than 20% have systemic complaints. An elevated lactate dehydrogenase level can be seen, as in this patient, and is generally a poor prognostic indicator. The nephrotic syndrome has been associated with non-Hodgkin's lymphoma, and membranous nephropathy is the most common lesion seen. Diagnosis is made by biopsy. Non-Hodgkin's lymphoma is less likely in this patient given that he lacks peripheral lymphadenopathy on examination. Patients with Hodgkin's disease present more commonly with a mediastinal mass and constitutional symptoms. Thus, Hodgkin's disease is the more likely diagnosis.

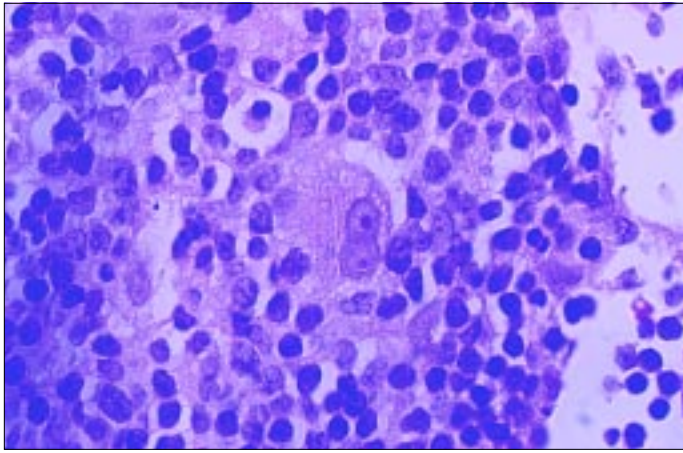
The third key feature of this patient's case is the *pulmonary embolus*. The nephrotic syndrome causes an acquired hypercoagulable state that can predispose patients to various thromboembolic complications. Abnormalities in the coagulation system include an increase in several coagulation factors and increased fibrinogen levels. In addition, antithrombin III levels are decreased due to urinary loss.

In conclusion, I think this patient has *Hodgkin's disease*, causing *mediastinal adenopathy*, and an associated *nephrotic syndrome* due to *minimal change disease*. The nephrotic syndrome produced an acquired hypercoagulable state that led to the *pulmonary embolus*. The alternative diagnosis is non-Hodgkin's lymphoma, which is more commonly associated with membranous nephropathy that could lead to a renal vein thrombosis and cause the patient's pulmonary embolus.

Additional tests would include chest computed tomography and a biopsy of the mediastinal mass. A kidney biopsy would be helpful but purely academic. Lastly, if the patient has Hodgkin's disease, a staging workup might include abdominal pelvic computed tomography and a bone marrow biopsy.

## **PATHOLOGY REPORT**

STEPHEN A. MAY, MD: We received multiple fragments of pink-gray, fleshy, soft tissue, measuring together approximately 1 cm in greatest dimension, labeled "right paratracheal mass." Histologic sections with hematoxylin and eosin stain showed diffuse effacement of lymph node architecture with a cellular infiltrate characterized by a vague nodularity and no fibrosis. The infiltrate was composed of small lymphocytes, scattered eosinophils, plasma cells, and many paler areas composed of atypical mononuclear cells. These cells tended to be relatively large (20 to 50  $\mu$  in diameter) compared with the background leukocytes. Some also displayed rims of weakly acidophilic cytoplasm and single or multilobed nuclei with thick membranes and vesicular



**Figure 1.** Bilobed Reed-Sternberg cell in a mixed inflammatory background. Note the acidophilic macronucleoli. Hematoxylin and eosin stain,  $\times 1000$ .

chromatin patterns. Acidophilic macronucleoli with clear halos were also a prominent feature. A few of these atypical cells had bilobed nuclei, a classic feature of Reed-Sternberg cells of Hodgkin's lymphoma (Figure 1). Additionally, some cells were surrounded by lacunar spaces. The clear spaces are processing retraction artifacts that disrupt the cytoplasm. The initial diagnosis was *Hodgkin's lymphoma, mixed cellularity type*, due to the presence of classic Reed-Sternberg cells. Although lacunar-type atypical cells are classic for nodular sclerosing Hodgkin's lymphoma, they are not pathognomonic for it and can be found in all subtypes.

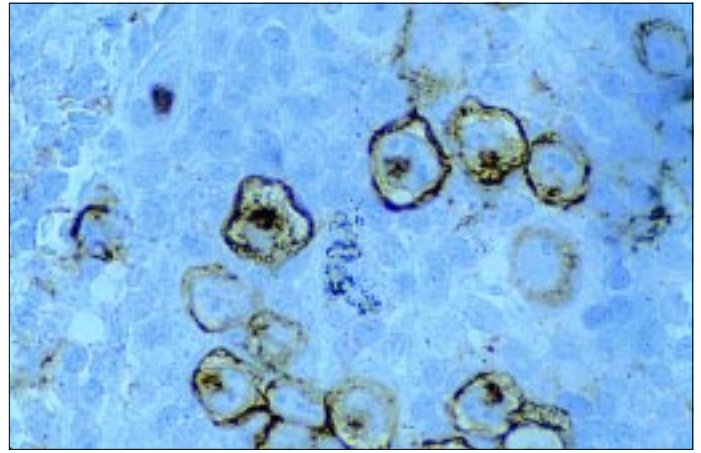
A battery of immunohistochemical stains showed a strong positive reaction for CD15 in the tumor cells, with cytoplasmic membrane and Golgi staining (Figure 2). About 80% of mixed cellularity cases stain positively for CD15. Antibody to CD15 also marks monocytes and granulocytes. The Reed-Sternberg cells also stained positively for CD30, a feature seen in about 90% of cases. Activated lymphocytes can also be stained with this antibody. Antibody reaction to CD20, a pan-B-cell marker, was negative in the atypical cells as expected. The cells were also stained for leukocyte common antigen (CD45) and the pan-T markers CD3 and CD5, and the results were negative as expected.

A bone marrow biopsy specimen showed 85% cellularity, no lymphoid aggregates or atypical cells, and a trilinear representation of hematopoietic cells with orderly maturation. The myeloid:erythroid precursor ratio was within normal limits, 3:1.

In summary, the patient's paratracheal soft tissue mass was diagnosed as Hodgkin's lymphoma, mixed cellularity type. The bone marrow biopsy specimen was normal.

## DISCUSSION

KEVIN P. THELEMAN, MD: The patient had stage IA Hodgkin's disease as determined by biopsy of the paratracheal mass, computed tomography, positron emission tomography (PET) utilizing 2-[F-18]fluoro-2-deoxy-D-glucose (FDG), and bone marrow biopsy. He probably had minimal change disease, although this was not confirmed by kidney biopsy and an argument could be made for membranous nephropathy. The pulmonary emboli were secondary to a hypercoagulable state resulting from the nephrotic syndrome and possibly the lymphoma.



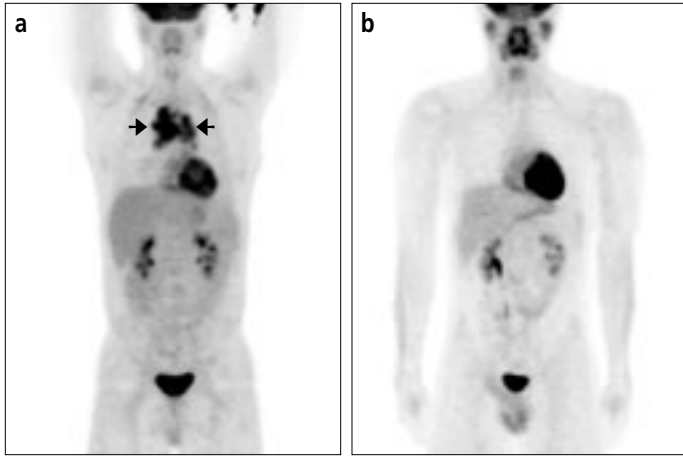
**Figure 2.** Cytoplasmic membrane and Golgi staining with CD15 antibody in Reed-Sternberg cells,  $\times 1000$ .

The development of glomerular injury with neoplasia is well established in the literature. As early as 1966, Lee et al described 10 patients with various malignancies and the nephrotic syndrome (1). The most prominent associations are with Hodgkin's lymphoma and carcinoma. When the nephrotic syndrome occurs in patients with Hodgkin's disease, minimal change is the most common pathologic lesion (2). Carcinomas, on the other hand, produce glomerulonephritis 80% to 90% of the time (3). The association of the nephrotic syndrome with Hodgkin's disease is well established. Dabbs et al cited 61 cases throughout the literature in a 1986 review (4); however, the incidence of nephrotic syndrome in a combined study of >1700 cases of Hodgkin's disease was only 0.4% (5). The nephrotic syndrome is also reported in non-Hodgkin's lymphoma, but this is even less common (4).

Symptoms of Hodgkin's disease and the nephrotic syndrome typically appear at the same time. On occasion, the nephrotic syndrome is the initial presenting symptom, which spurs the debate regarding whether a search for occult malignancy should be performed in cases of idiopathic nephrotic syndrome. Treatment of the lymphoma, including radiation alone, is associated with reversal of the nephrotic syndrome. This suggests that resolution is based on loss of tumor rather than a direct effect on the kidney. Likewise, the Hodgkin's disease and the nephrotic syndrome tend to relapse concomitantly (4, 5).

The pathogenesis of the minimal change lesion is unclear but is believed to be a disorder of the T lymphocytes via a lymphokine-mediated process (4). The pathogenesis of membranous glomerulopathy is most likely mediated by immune complexes composed, at least in part, of tumor-associated antigens that cause subepithelial deposits in the glomeruli (4).

The patient's hypercoagulable state and resultant pulmonary emboli are mainly a result of the nephrotic syndrome. In the nephrotic syndrome, the level of the anticoagulant antithrombin III, which has a molecular weight very close to that of albumin, is markedly decreased due to renal wasting. Urinary loss of protein C, protein S, and plasminogen may also contribute. In the nephrotic syndrome, levels of factors V and VII and the procoagulant fibrinogen are increased (6). Thrombotic phenomena are much more common in patients with membranous or membranoproliferative nephropathy yet are also described in



**Figure 3.** Three-dimensional whole-body PET images in the anterior projection. **(a)** Pretreatment scan shows the hypermetabolic mediastinal mass (arrows). **(b)** In the most recent scan, the mass is no longer visible.

minimal change disease. Hodgkin's disease may also contribute to increased coagulation, as malignancy is commonly associated with a hypercoagulable state. However, this link is more often related to adenocarcinomas such as colon, breast, and lung cancers.

This patient's disease had a complicated course, and he was hospitalized repeatedly. After tests to stage the Hodgkin's disease, he was given chemotherapy. Shortly thereafter, he had another pulmonary embolus and a lower lobe pulmonary infarct. Doppler

studies were unable to determine the source of the emboli. Other problems included a spontaneous pneumothorax and a recurrent pneumothorax. He eventually received 2 additional rounds of chemotherapy but then developed an exudative pleural effusion and *Klebsiella* pneumonia. Open thoracotomy was required.

Pulmonary function tests indicated that further bleomycin would not be appropriate. Ultimately, the patient was treated with 4000 cGy of radiation therapy. He is now receiving warfarin and has a negative PET scan and no proteinuria. He is considered cured. The initial whole-body PET scan, showing the hypermetabolic mediastinal mass, is seen in *Figure 3a*. In the most recent scan (*Figure 3b*), the mass is no longer visible on FDG-PET.

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