May 2013 Pulmonary Case of the Month: the Cure Can be Worse than the Disease

Lewis J. Wesselius, MD¹
Thomas V. Colby, MD²

Departments of Pulmonary Medicine¹ and Laboratory Medicine and Pathology²
Mayo Clinic Arizona
Scottsdale, AZ

History of Present Illness
A 65 year old man from Colorado presented for evaluation of “lung masses.” He had a prior diagnosis of dermatomyositis made in 2010 and had been with intravenous immunoglobulin (IVIG), prednisone and methotrexate. He had been previously seen in January, 2011 with a 5 mm left lower lobe nodule on thoracic CT which was unchanged compared to August, 2010. A thoracic CT scan done in July, 2011 in Colorado was interpreted as stable.

Over the prior month had been having chest discomfort. He had a history of pulmonary embolism (PE) and felt the pain was similar in quality to his prior PE. This prompted a chest x-ray and he was told of “lung masses”. He had also experienced 20 pound weight loss.

His current medications included methotrexate 25 mg weekly, prednisone 3 mg every other day and warfarin 7 mg daily.

PMH, SH, FH
In addition to dermatomyositis, he has a history of a left lower extremity deep venous thrombosis with PE. At that time protein S deficiency, activated protein C resistance and factor V Leiden mutation were diagnosed and an inferior vena cava filter were placed. He also has a history of paroxysmal atrial fibrillation and the prior lung nodule noted above.

He was a prior smoker, quitting in 1991, but briefly resuming in 2010. The patient had social alcohol use but no drug use.

The patient’s father died at age 75 from prostate cancer; his mother died at age 89 with heart disease; and he had a sister living with throat cancer.

Physical Examination
Vital signs: Afebrile; Blood pressure 114/65 mm/Hg; Pulse 80 regular; Oxygen Saturation 97% on room air at rest
HEENT: limited ability to open mouth
Chest: few late exp wheezes
CV: Regular rhythm, no murmur
Skin: diffuse erythema, particularly on face.
Neuro: muscle strength normal

**Radiography**
His thoracic CT is shown in Figure 1.

![CT images](image1.png)

Figure 1. Representative images from the thoracic CT scan showing lung windows (Panels A-C) and mediastinal windows (Panels D-F).

Which of the following are pulmonary manifestations of dermatomyositis?
1. Lung cancer
2. Aspiration pneumonia
3. Interstitial lung disease
4. Metastatic cancer particularly from the cervix, pancreas, breasts, ovaries, gastrointestinal tract and lymph nodes
5. All of the above
Pulmonary complications are frequent in dermatomyositis (1). Dysphagia due to involvement of the oropharyngeal striated muscles and upper esophagus leads to aspiration pneumonia. Interstitial lung disease is also a frequent pulmonary complication. Cancers occur in up to 15% of dermatomyositis patients particularly of the lungs, cervix, pancreas, breasts, ovaries, gastrointestinal tract and non-Hodgkin’s lymphoma.

Which of the following statements are true?

1. The doubling time of lung cancers averages about 30 days
2. Thoracic PET scan can dependably separate lung cancers from noncancerous thoracic lesions
3. Biopsy of a pulmonary nodule is required to make a diagnosis of lung cancer
4. Multiple lung nodules are inconsistent with a diagnosis of aspiration pneumonia
5. A negative cocci serology excludes a diagnosis of coccidiomycosis
Correct!

3. Biopsy of a pulmonary nodule is required to make a diagnosis of lung cancer

This patient has several abnormalities on his CT scan done on February 28, 2013 including multiple lung masses, enlarged bilateral hilar and subcarinal lymphadenopathy and a small left pleural effusion. The largest mass in the left lower lobe measures 4.1 X 3.6 cm. Neither the masses nor the lymphadenopathy were apparent on the previous CT scan done in July, 2011. The mean doubling time of lung cancer is about 100 days although the range can be as broad as 30-500 days (2).

A cocci serology, either an antigen or antibody test, should be done in areas such as Arizona where coccidiomycosis is prevalent. However, negative cocci serologies do not exclude the disease. Our patient's cocci serology was negative.

Aspiration pneumonia can present as multiple lung nodules, especially when present in the lower lobes.

This patient’s doubling time for his largest lung mass was less than 30 days suggesting that this was not a lung cancer and might be from an inflammatory cause. PET scanning may be useful in the assessment of solitary pulmonary lung nodules. Several studies indicate that PET scanning appears to be valuable in deciding whether a nodule is benign or malignant, as well as in staging local regional and distant metastatic disease. In some centers, PET/CT scanners are available to allow more precise anatomic localization.

The short doubling time of the patient’s mass and his reluctance to undergo an invasive procedure prompted a PET scan (Figure 2).
Figure 2. Static images from a color-enhanced PET-CT scan (Panels A-F) and a black and white PET scan (Panel G) showing increased radiotracer uptake in the lung nodules and mediastinal lymph nodes.

A fine needle aspiration biopsy was performed but was nondiagnostic. Which of the following procedures is most likely to reveal a diagnosis?

1. Repeat cocci serology
2. Repeat CT scan in 3 months for enlargement of the masses
3. Bronchoscopy with Wang needle biopsy of the mediastinum and transbronchial biopsy of the lung mass
4. Repeat needle aspiration biopsy
5. Video-assisted thorascopic biopsy
Correct!

5. Video-assisted thorascopic biopsy

As of yet a diagnosis has not been made. It is not likely that a repeat cocci serology or repeat CT scan in 3 months will be particularly helpful. Repeat needle biopsies when the fist biopsy showed adequate tissue is unlikely to be revealing the diagnosis. Bronchoscopy is a possibility but for peripheral lesions needle biopsy usually has a higher diagnostic yield. Therefore, the best answer is a video-assisted thorascopic (VATS) biopsy.

The surgical pathology is shown in figures 3-5.

![Figure 3](image1.png)

**Figure 3.** H&E stains of low power view of wedge resection of lung nodules (Panels A-C) and in situ hybridization for Epstein-Barr virus (EBV) RNS (Panel D).

![Figure 4](image2.png)

**Figure 4.** High power view H&E stains of lung nodules.
Figure 5. Special stains for CD3 (Panel A, T lymphocytes), CD 20 (Panel B, B lymphocytes), CD 15 (Panel C, neutrophils) and CD 30 (Panel D, activated T and B cells).

What is the pathologic diagnosis?
1. Lymphoma
2. Small cell lung cancer
3. Non-small cell lung cancer
4. Metastatic colon cancer
5. Viral pneumonia
Correct!

1. Lymphoma

The low power views show irregular fibroinflammatory nodules with central necrosis and an associated polymorphous cellular infiltrate consisting of small lymphocytes, histiocytes and plasma cells. Figure 3, panel D also shows some cells are Epstein-Barr virus positive.

Higher power views show large atypical cells including Reed-Sternberg cells against a background of lymphocytes. Reed–Sternberg cells are large and are either multinucleated or have a bilobed nucleus (thus resembling an "owl's eye" appearance) with prominent eosinophilic inclusion-like nucleoli. Reed–Sternberg cells are CD30 and CD15 positive.

The final pathology diagnosis was an atypical lymphohistiocytic infiltrate with necrosis best classified as EBV-positive immunodeficiency-associated lymphoproliferative disorder with Hodgkin lymphoma-like features.

What is the treatment for this type of lymphoma?

1. Mechlorethamine plus vincristine plus procarbazine plus prednisone (MOPP)
2. Doxorubicin plus bleomycin plus vinblastine plus dacarbazine (ABVD)
3. Radiation therapy with 25 Gy to 30 Gy to clinically uninvolved sites and 35 Gy to 44 Gy to regions of initial nodal involvement
4. Both MOPP and radiation therapy
5. Stop methotrexate
Correct!
5. Stop methotrexate

Immunodeficiency-related lymphoproliferative disease (LPD) include post-transplant LPD, HIV/AIDS-associated LPD, senile EBV-associated LPD and methotrexate-associated LPD. The usual risk of Hodgkin’s lymphoma is about 0.26% in males and 0.21% in females (4). This increases 5-15 fold in HIV/AIDS, 2 to 20 fold in rheumatoid arthritis and 50 to 100 fold post-transplant.

Methotrexate-associated LPD is most often reported in patients with rheumatoid arthritis treated with methotrexate (4,5). The disease is often extranodal. We are unaware of any other cases limited to the chest. This must be differentiated from classic Hodgkin’s disease as rheumatoid arthritis has a 2-fold to 20-fold increased risk of Hodgkin’s disease even in the absence of methotrexate. The mean duration of methotrexate therapy in patients with methotrexate-induced LPD is 3 years.

Methotrexate-associated LPD (or HL-like proliferation) may regress with withdrawal of MTX with 75% survival reported at 5 years (5-7). Classic Hodgkin’s lymphoma in this setting has a worse prognosis with 50% survival and only 30% regress with chemotherapy. EBV is almost always found with LPD with HL-like features. Methotrexate-associated LPD may regress with discontinuation of methotrexate, although it can redevelop and require chemotherapy.

The methotrexate in our patient was withdrawn, and at his last follow up, his lesions are resolving.

References