November 2020 Imaging Case of the Month: Cause and Effect?

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Clinical History: A 36 -year-old woman with Crohn's disease and ulcerative colitis diagnosed approximately 1 year earlier, was initially treated with adalimumab, but later switched to prednisone and budesonide when subcutaneous nodules and migraines were attributed to this medication. Subsequently a flare of gastrointestinal symptoms prompted hospitalization with colonoscopy which showed severe pancolitis consistent with ulcerative colitis. One month following hospital discharge, the patient then presented to the Emergency Department with continued complaints of nausea, diarrhea, abdominal pain, intermittent fever (self-measured to 101º F), joint pain, and a pruritic rash all over her body. These symptoms had occurred following her hospitalization 2 months earlier. She also complained of 25 lbs. weight loss over the previous year.

In addition to prednisone and budesonide, the patient's medications included hydroxyzine, famotidine, vitamin C, and hydrocodone-acetaminophen. The patient denies allergies and did not smoke nor use drugs.

Physical examination showed the patient to be afebrile with normal heart and respiratory rates and blood pressure = 112/75 mmHg. Her room air oxygen saturation was 99%. Her examination was remarkable for tenderness to palpation over the left > right lower quadrants with rebound tenderness and positive fecal occult blood testing. Her skin examination also showed a diffuse, pinpoint, maculopapular rash affecting her trunk as well as both the upper and lower extremities.

The patient's complete blood count and serum chemistries showed hypokalemia=3.0 mmol/L (normal, 3.6-5.2 mmol/L), mild anemia (hemoglobin / hematocrit = 11.2 gm/dL / 34.3% [normal, 12.3-15.7 gm/dL / 37-46%]), and a minimally elevated lipase of 63 U/L (normal, 13-60 U/L). Liver and renal function testing were within normal limits.

Which of the following represents ***an appropriate next*** step for the patient's management?

1. Obtain gastrointestinal consult
2. Obtain a travel history
3. Obtain abdominal CT
4. All of the above
5. None of the above

Correct!
4. All of the above

All of the above considerations are appropriate. In particular, CT of the abdomen and pelvis is indicated urgently to exclude abscess, bowel obstruction, and other complications related to inflammatory bowel disease.

The patient did not have a recent travel history, but did live in the Philippines 11 years ago. She was referred for CT examination of the abdomen and pelvis (Figure 1), which showed colitis extending from the distal transverse colon through the rectum.

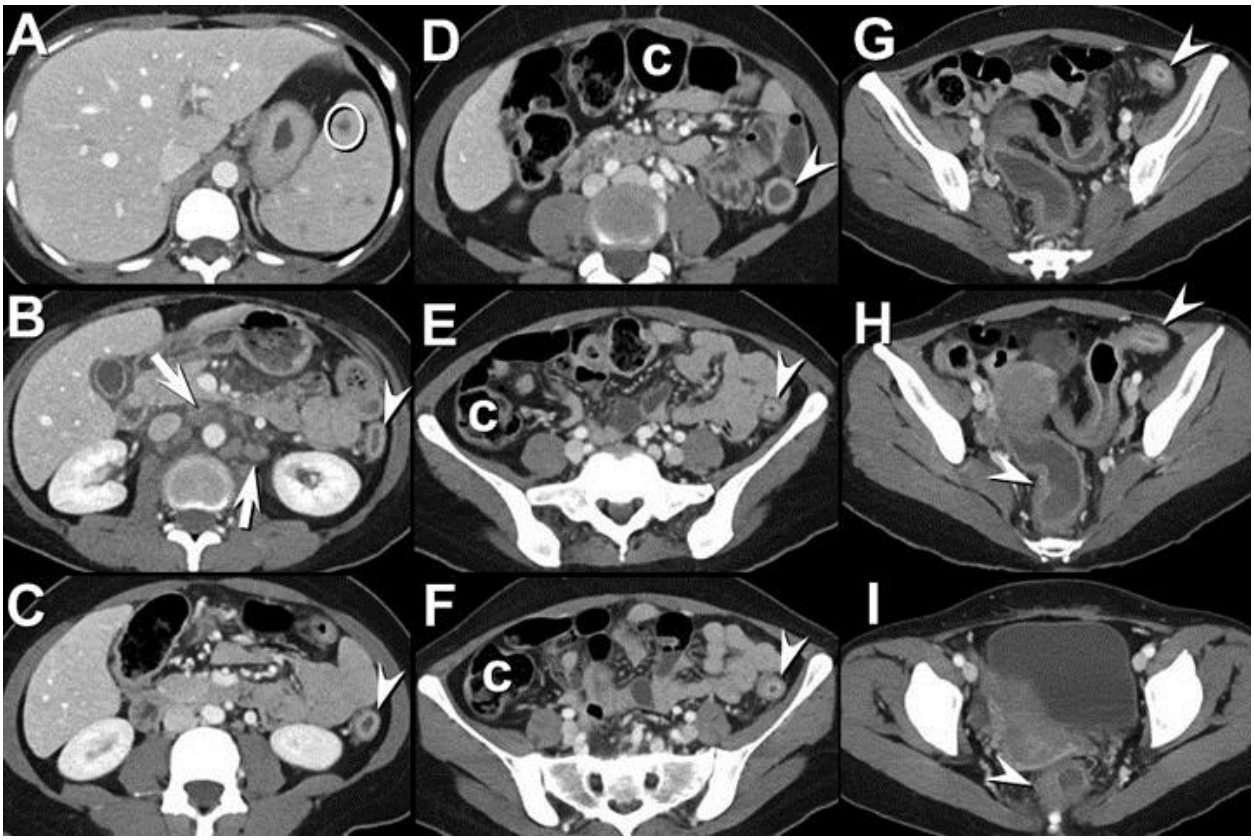

Figure 1. Figure 1A-I: Axial enhanced abdominal CT shows diffuse colonic thickening extending from the distal transverse colon through the rectum (arrowheads) as well as retroperitoneal lymphadenopathy (arrows). Small non-specific hypoattenuating splenic lesions (circle) and nonspecific gallbladder wall thickening are also present. c = normal right and transverse colon; note thin wall.

Additionally, this examination revealed abnormal soft tissue in the porta hepatis and retroperitoneal lymphadenopathy as well as non-specific low attenuation splenic lesions. Gastroenterology (GI) was consulted and recommended testing to exclude gastrointestinal pathogens prior to initiation of intravenous corticosteroids as well as testing for possible SARS-CoV-2 infection. The presence of the lymph node enlargement at CT raised concern for a second, superimposed process, including

potential malignancy; GI recommended MR enterography for evaluation of these lymph nodes as well as soft tissue in the porta hepatis and the splenic lesions. Small bilateral basal pulmonary nodules (Figure 2) were incidentally noted as well.

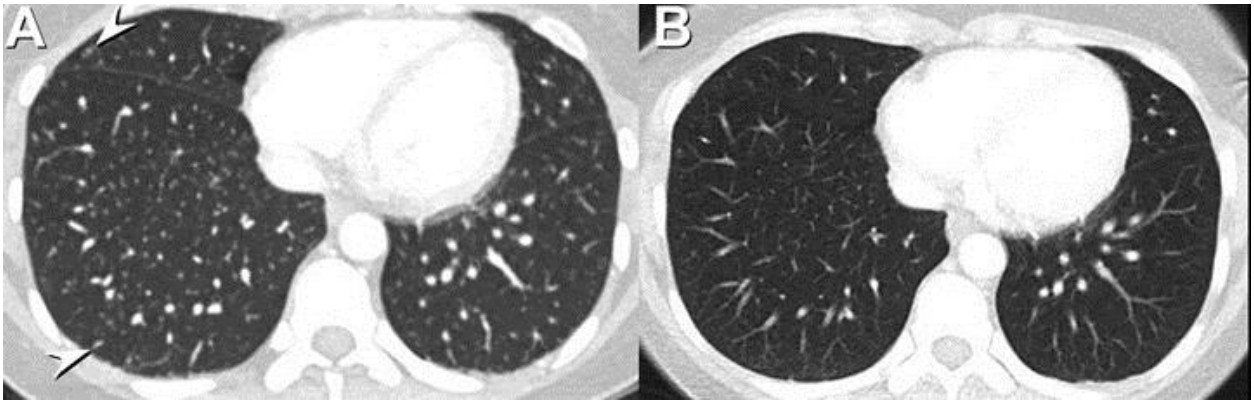

Figure 2. Comparison of lung bases from CT abdomen and pelvis at presentation (A) and 1 month earlier while the patient was hospitalized at an outside institution. Note that numerous, small, circumscribed nodules at presentation (arrowheads, A) have developed over the previous month (B).

The MR enterography study showed the large bowel inflammation, focal splenic lesions, and lymphadenopathy, but nothing of significance in addition to what was already known at CT. Testing for GI pathogens and SARS-CoV-2 was negative, and intravenous corticosteroid therapy was begun. Three sputum acid fast bacillus tests were negative.

Which of the following represents ***an appropriate next*** step for the patient's management?

1. Perform ^{18}FDG-PET scan
2. Perform an upper gastrointestinal series
3. Perform chest MRI
4. Perform percutaneous biopsy of a retroperitoneal lymph node
5. Perform upper endoscopy

Correct!
4. Perform percutaneous biopsy of a retroperitoneal lymph node

Among the choices listed, percutaneous biopsy of one of the enlarged lymph nodes in the retroperitoneum is the most direct approach to answer the question of whether or not there is a second process superimposed on the patient's ulcerative colitis. Neither an upper gastrointestinal series nor upper endoscopy is indicated at this point because the patient does not have complaints referable to the upper gastrointestinal system. Chest MRI would offer no particular value for the evaluation of this patient. ^{18}FDG-PET scan could be of benefit to determine if there are other sites of potential involvement by a second process, but there is already a target for such an evaluation- the retroperitoneal lymph nodes- and hence ^{18}FDG-PET scan is premature at this point.

The retroperitoneal lymph node biopsy showed scant lymphoid tissue with histiocytic aggregates. The sample was insufficient for flow cytometry. Acid-fast bacilli staining and GMS staining for fungi on the biopsy sample were both negative. The patient underwent flexible sigmoidoscopy, which showed severe inflammation of the distal colon and rectum.

Which of the following represents ***an appropriate next*** step for the patient's management?

1. Initiate infliximab therapy
2. Maintain the patient on corticosteroid therapy only
3. Perform ^{18}FDG-PET scan
4. Perform enteroclysis
5. Re-start adalimumab therapy

Correct!
1. Initiate infliximab therapy

Treatment with infliximab may be beneficial for the patient's active inflammation for ulcerative colitis, which should prove superior compared to corticosteroid therapy alone. There is a question of failure on previous adalimumab therapy, making this choice of therapy less appealing. ^{18}FDG-PET scan again could be of benefit to determine if there are other sites of potential involvement by a second process given the suggestion of such at the interpretation of the abdominal CT, but it is unclear if ^{18}FDG-PET would provide management-altering data at this point. Enteroclysis is a technique whereby a nasogastric tube is placed into the proximal small bowel and a solution is pumped into the small bowel to distend small bowel and allow visualization of the small bowel mucosa to assess for inflammatory disease. This study has now largely been abandoned in favor of either CT or MR enterography.

Antifungal therapy with liposomal amphotericin B was empirically started. Infliximab therapy was planned, and as part of this new therapy, Infectious Disease was consulted. The patient was referred for chest radiography (Figure 3).

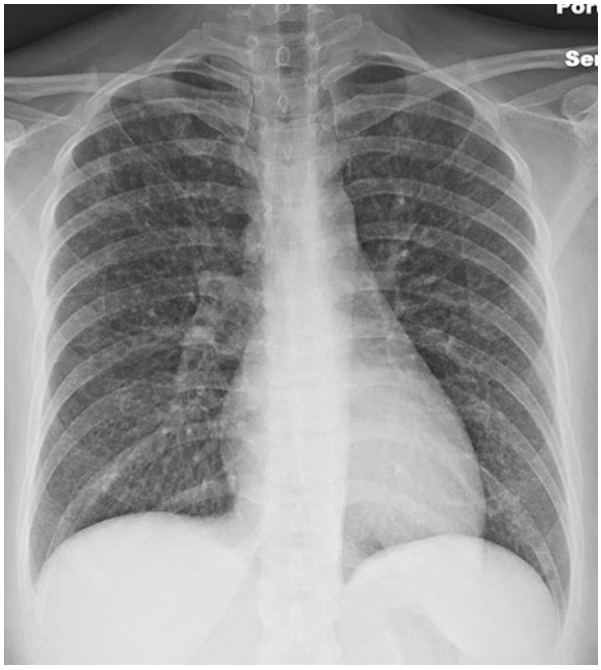

Figure 3. Frontal chest radiography.

Which of the following statements regarding the chest radiograph is ***most accurate***?

1. The chest radiograph shows a mediastinal mass
2. The chest radiograph shows a pneumothorax
3. The chest radiograph shows lymphadenopathy
4. The chest radiograph shows multifocal hazy lung opacity
5. The chest radiograph shows multiple small nodules

Correct!
5. The chest radiograph shows multiple small nodules

The frontal chest radiograph shows faintly visualized small, bilateral circumscribed nodules in the lung parenchyma bilaterally best seen best appreciated in the magnified inset image shown in Figure 4.

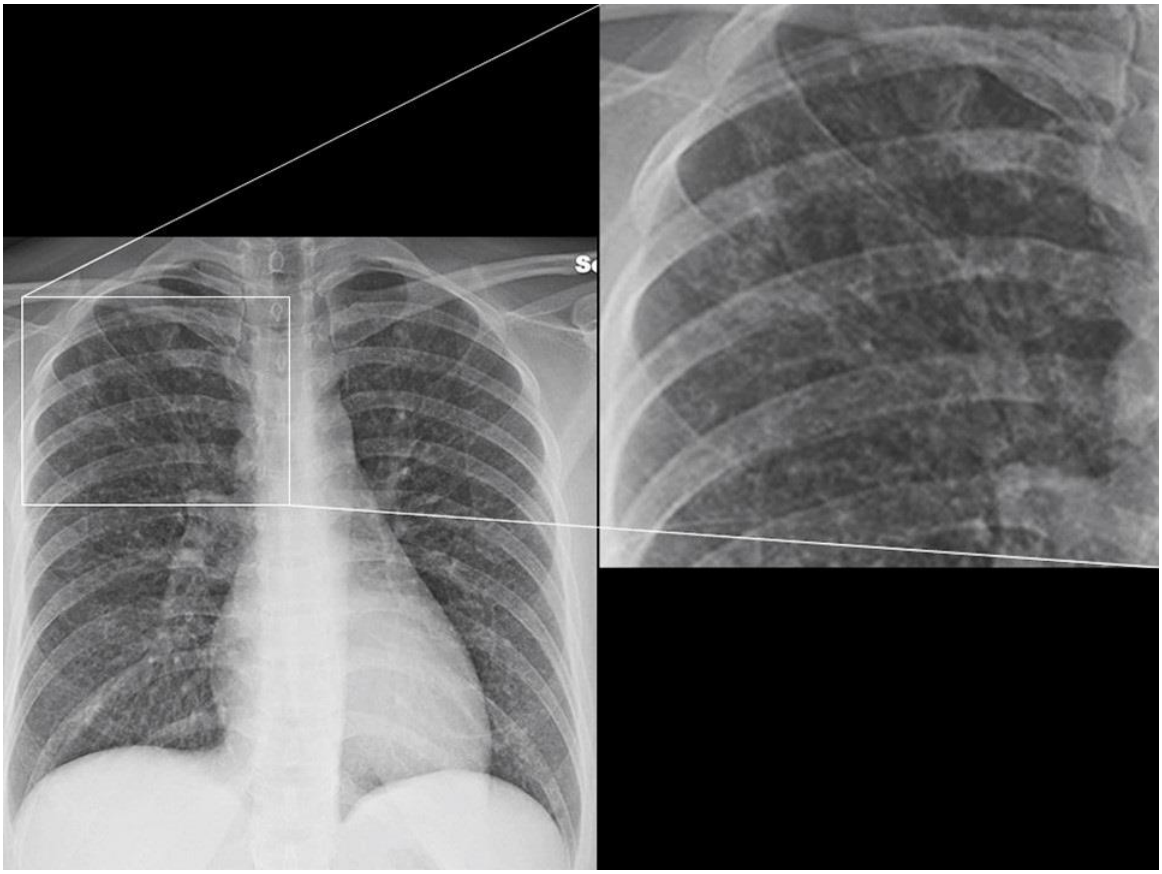

Figure 4. Magnified inset image from frontal chest radiography.

No clear mediastinal or peribronchial lymph node enlargement is seen. The cardiomediastinal contours appear normal, and no pulmonary parenchymal infiltrative abnormalities, such as ground-glass opacity, consolidation, or fibrotic disease, is present. No evidence of pneumothorax is seen.

Which of the following represents an ***appropriate differential diagnostic consideration*** for the patient's chest radiographic findings?

1. A histiocytic disorder
2. A lymphoproliferative disorder
3. A thoracic manifestation of inflammatory bowel disease
4. Disseminated infection
5. Pulmonary hemorrhage

Correct!
4. Disseminated infection

Pulmonary hemorrhage typically appears as multifocal or diffuse lung opacity, not small circumscribed nodules. Lymphoproliferative disorders within the thorax may present in numerous ways, most commonly lymphadenopathy and/or mediastinal mass. The solitary pulmonary nodule or multiple pulmonary nodules (the latter particularly in the context of immunocompromise) are less common intrathoracic manifestations of lymphoproliferative disorders. Lymphoproliferative disease can also manifest as pleural abnormalities or osseous lesions. Lymphoproliferative disease can manifest as small pulmonary nodules, but this manifestation is rare, whereas disseminated infection commonly presents in this manner. Pulmonary manifestations of inflammatory bowel disease are numerous, but most commonly manifest as airway disorders (bronchiectasis and small airway obstruction, uncommonly tracheal inflammation or airway stenoses) or organizing pneumonia. Fibrotic disease and/or alveolitis may also be a thoracic manifestation of inflammatory bowel disease or the medications used to treat the disorder. Rare necrobiotic nodules may be a presentation of inflammatory bowel disease within the thorax, but usually such nodules are larger and less numerous than those present at chest radiography in this patient. Finally, histiocytic disorders, such as Langerhans cell histiocytosis, commonly present with upper small nodules with lobe cystic abnormalities, although rarely Langerhans cell histiocytosis may manifest with small nodules, typically upper lobe predominant, without accompanying cysts. Other histiocytic disorders are very rare, such as Rosai-Dorfman disease, and are more commonly associated with lymph node enlargement. Some histiocytic disorders can present with small nodules that may resemble sarcoidosis, but such a manifestation is exceedingly rare and far less common than disseminated infection presenting with small nodules.

The rash the patient presented with was improving with the use of topical steroid cream. General surgery was consulted for possible repeat retroperitoneal lymph node biopsy, but deferred, advising cardiothoracic surgery consult for mediastinoscopy. Testing for coccidioidomycosis was negative. Hematology / Oncology was consulted regarding the possibility of a second superimposed process in addition to the ulcerative colitis, namely potential malignancy. The consult team could not identify a palpable lymph node to target for another biopsy, and they recommended against a bone marrow biopsy given the normal white blood cell count, normal white blood cell differential count, and normal platelet count and anemia attributable to chronic disease. The consultant advised ^{18}FDG-PET scan (Figure 5) for selecting a target for additional tissue sampling.

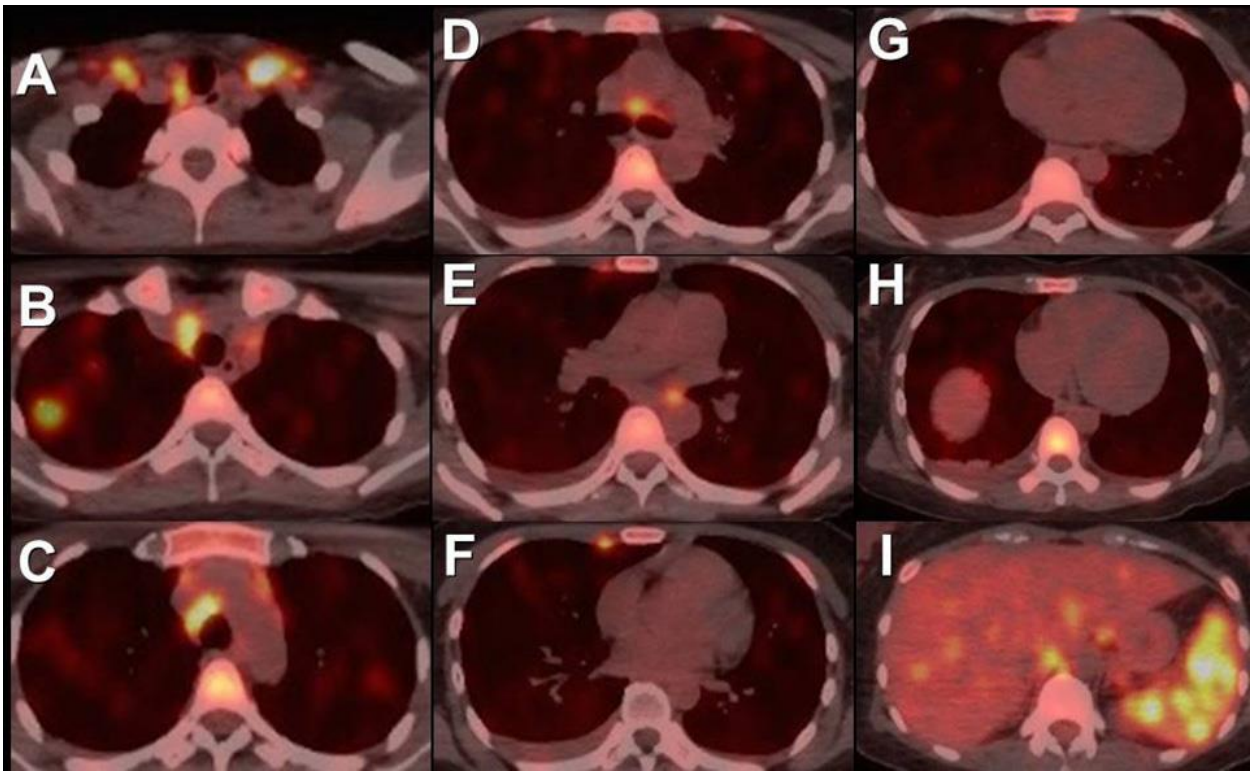

Figure 5. ^{18}FDG-PET scan shows multifocal mediastinal and supraclavicular metabolically active lymphadenopathy as well as metabolically active lesions within the thoracic spine and spleen. A small right and trace left pleural effusions show no metabolic activity. Hypermetabolism is also seen in the right upper lobe laterally.

Which of the following statements regarding the chest radiograph is ***most accurate***?

1. The ^{18}FDG-PET does not add any information to that already known with chest radiography
2. The ^{18}FDG-PET scan does not show metabolically active lymphadenopathy
3. The ^{18}FDG-PET scan is of limited quality owing to technical limitations
4. The ^{18}FDG-PET scan shows metabolically active pleural disease
5. The ^{18}FDG-PET scan shows suitable targets for additional intervention

Correct!

5. The ^{18}FDG-PET scan shows suitable targets for additional intervention

The ^{18}FDG-PET scan shows numerous metabolically active mediastinal and supraclavicular lymph nodes, splenic lesions, and osseous lesions. The ^{18}FDG-PET scan shows that these lymph nodes may harbor pathology and thus represent targets for intervention. The pleural effusions are not metabolically active and thus are less attractive for intervention. While the ^{18}FDG-PET scan shows metabolically active osseous findings, bone lesions are typically less attractive for intervention because processing material for molecular testing to identify the biomarkers in the context of cancer staging is suboptimal when such material is obtained from bone biopsies. Also, although percutaneous interventions on the spleen are possible, owing to the highly vascular nature of this organ, such interventions are commonly a last resort.

Infectious Disease was consulted. Which of their following represents the ***most appropriate*** recommendations for the patient's management?

1. Blood, urine, and stool culture for acid-fast bacilli
2. Fungal testing (blastomycosis serology, histoplasmosis serology, histoplasmosis urine antigen, Fungitell testing for invasive fungal infection, serum *Aspergillus* antigen, fungal blood culture, urine cocci antigen)
3. Perform chest CT
4. Perform Quantiferon testing
5. All of the above

Correct!
5. All of the above

All of the above suggestions are reasonable recommendations from the Infectious Disease consultant. Additionally, the Infectious Disease consultant also recommended *Strongyloides* serologic testing, HIV testing stool for ova and parasites.

Fungal testing was unrevealing and the patient was HIV negative. All tests for parasitic infections were negative. The patient underwent chest CT (Figure 6) to evaluate the abnormal findings seen at chest radiography.

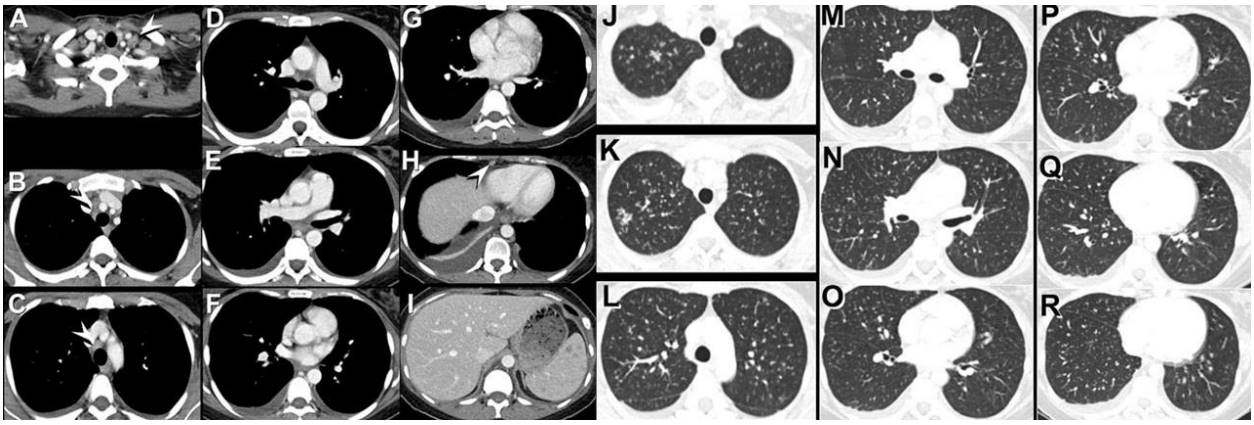

Figure 6. Axial enhanced chest CT displayed in soft tissue (A-I) and lung (J-R) windows.

Which of the following statements regarding the chest radiograph is ***most accurate***?

1. The chest CT shows basal and peripheral ground-glass opacity and consolidation
2. The chest CT shows features of fibrotic lung disease
3. The chest CT shows features suggestive of pulmonary artery hypertension
4. The chest CT shows numerous small, circumscribed pulmonary nodules
5. The chest CT shows pleural effusion and thickening

Correct!

4. The chest CT shows numerous small, circumscribed pulmonary nodules

The axial enhanced chest CT shows mildly enlarged lymph nodes, particularly in the left supraclavicular zone, corresponding to the metabolically active lymph nodes seen at ^{18}FDG-PET scan as well as numerous bilateral, small, circumscribed pulmonary nodules. No features to such fibrotic disease, such as honeycombing, traction bronchiectasis, and architectural distortion, are present. While small right-greater-than-left pleural effusions are present, no pleural thickening is evident. Small circumscribed pulmonary nodules are present, but no significant ground-glass opacity or consolidation is seen right basal passive atelectasis adjacent to the right pleural liquid is noted]. The main pulmonary artery is normal in size, so there is no CT evidence of pulmonary hypertension.

Pulmonary Medicine was consulted and performed bronchoscopy. Visual inspection at bronchoscopy was unrevealing and testing for bronchoalveolar lavage fluid for various respiratory pathogens, including acid-fast bacilli, was negative. The patient's Quantiferon test returned positive, and was repeated, and was positive a second time. Outside medical records were obtained that revealed that the patient's Quantiferon test was negative about one year earlier, performed prior to initiation of adalimumab therapy.

Which of the following represents the ***most appropriate*** recommendations for the patient's management?

1. Consult general surgery for biopsy of a metabolically active lymph node
2. Initiate infliximab therapy
3. Perform mediastinoscopy
4. Repeat the retroperitoneal lymph node biopsy
5. Re-start adalimumab therapy

Correct!
1. Consult general surgery for biopsy of a metabolically active lymph node

Starting or re-starting immunosuppressive biologic therapy would be inappropriate given the lingering question of undiagnosed infection. Mediastinoscopy could access one of the metabolically active right paratracheal lymph nodes, but may be needlessly invasive given that other more superficially located metabolically active lymph nodes are present. While repeating the retroperitoneal lymph node biopsy could potentially retrieve material for diagnostic testing, a technically adequate retroperitoneal lymph node biopsy has already been performed and did not successfully establish a diagnosis; therefore, a different target for repeat intervention may stand a better chance of obtaining the material needed to establish the correct diagnosis.

The liposomal amphotericin therapy was stopped. Cardiothoracic surgery was consulted for mediastinoscopy but deferred, noting that the ^{18}FDG-PET scan showed abnormalities for intervention that could be targeted in a less invasive fashion. General surgery declined repeat biopsy of a retroperitoneal lymph node, citing that a diagnosis was unlikely for such a procedure as the interventional radiology procedure properly sampled an enlarged retroperitoneal lymph node yet failed to retrieve material harboring a diagnosis. However, general surgery did agree to biopsy one of the enlarged, metabolically active supraclavicular lymph nodes, and hematology / oncology continue to recommend obtaining tissue to establish the etiology of the imaging findings. Tissue obtained during the flexible sigmoidoscopy showed cytomegalovirus, and ganciclovir therapy was initiated. Multidrug anti-tuberculous therapy with ethambutol, rifampin, pyrazinamide, and INH was initiated.

General surgery performed an excisional biopsy of an enlarged left supraclavicular lymph node approximately 6 days following bronchoscopy. The histopathology of this lymph node showed granulomatous inflammation with necrosis. The acid-fast smear was negative, but two days later the acid-fast stain was positive for *Mycobacterium tuberculosis*.

Diagnosis: Disseminated *Mycobacterium tuberculosis* as result of biologic treatment with a tumor necrosis factor therapy

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