August 2020 Imaging Case of the Month: Piecing Together a Cause for Multisystem Abnormalities

Prasad M. Panse MD
Clinton E. Jokerst MD
Michael B. Gotway MD

Department of Radiology
Mayo Clinic Arizona
Scottsdale, AZ USA

Clinical History: A 65-year-old woman with chronic hoarseness and dyspnea now presents with complaints of diarrhea and bloating. The patient indicated her dyspnea had developed over the previous year, now occurring after one flight of stairs. The patient also complains of some substernal burning after waling 2-3 blocks. Her past medical history was largely unremarkable, and her past surgical history included only a cesarean section and carpal tunnel surgery. She has no allergies and her medications included thyroxine, fluoxetine, and a steroid inhaler. She was a previous smoker for 8 years, quitting 30 years ago. Upon directed questioning, the patient also complains of generalized weakness and 13-14 lbs. weight loss in the previous year.

Physical examination showed normal vital signs and was remarkable only for atrophy of the patient's right calf muscles, which the patient claimed she knew about and had occurred over the previous year and a half. The neurologic examination was entirely normal. The examining physician noted that the patient's tongue appeared somewhat enlarged and reddened, but was not coated and midline upon protrusion.

The patient's complete blood count and serum chemistries showed all values within the normal range except for a serum albumin level of 2.9 gm/dL (normal, 3.5-5 gm/dL). Her erythrocyte sedimentation rate was mildly elevated at 55 mm/h (normal, 0-29 mm/hr). The patient was referred for chest radiography (Figure 1).

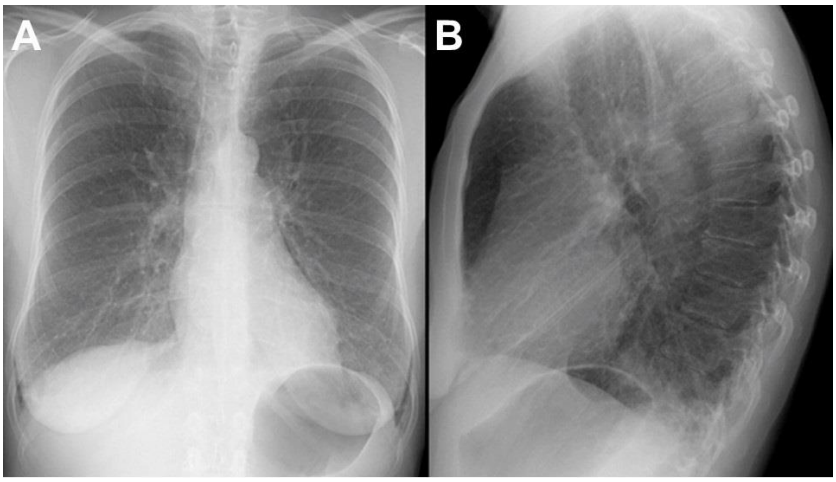

Figure 1. Frontal (A) and lateral (B) chest radiography.

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

1. The chest radiograph shows mediastinal and peribronchial lymph node enlargement
2. The chest radiograph shows multifocal basal consolidation
3. The chest radiograph shows normal findings
4. The chest radiograph shows numerous small nodules
5. The chest radiograph shows small bilateral pleural effusions

Correct!
2. The chest radiograph shows multifocal basal consolidation

The frontal and lateral chest radiographs show right base consolidation evidenced by obscuration of the right hemidiaphragm (Figure 2).

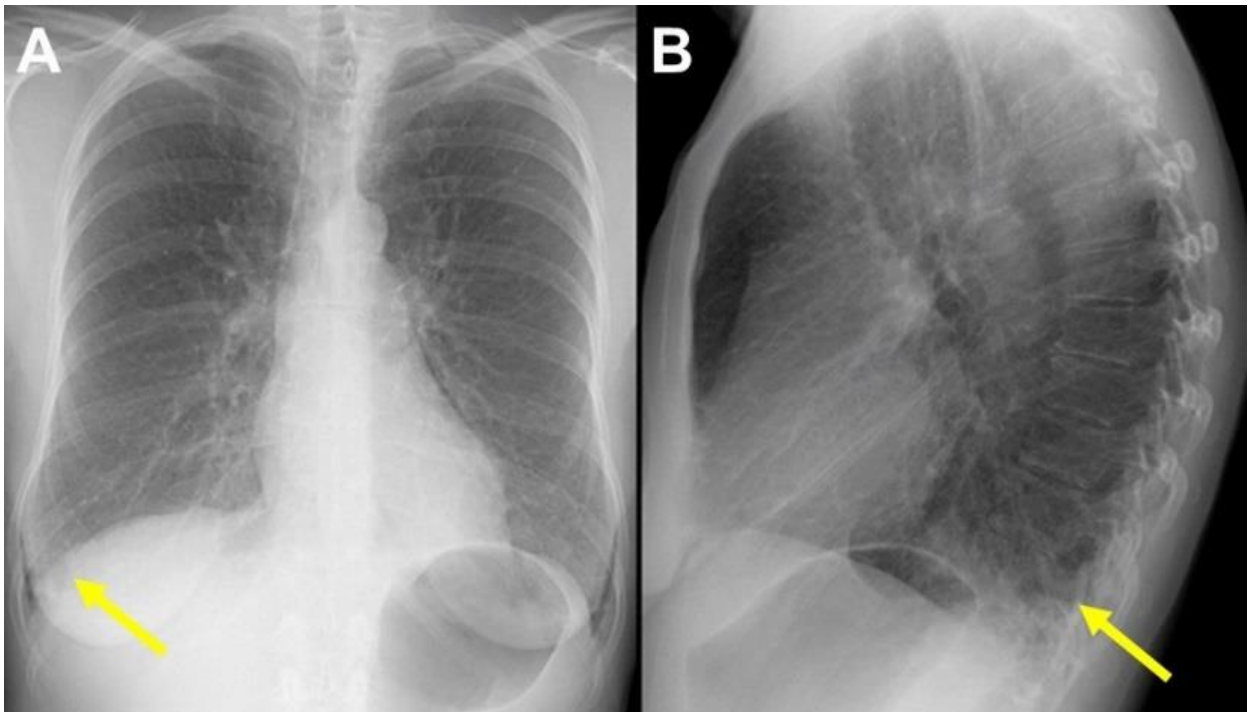

Figure 2. Frontal (A) and lateral (B) chest radiography shows right base consolidation (arrow) evidenced by obscuration of the right hemidiaphragm. Mild indistinctness at the left lung base is also evident (arrow).

Mild indistinctness at the left lung base is also evident, suggesting bilateral basilar consolidation No definite pleural effusion is seen. The heart size and lung volumes appear normal. No mediastinal or peribronchial lymph node enlargement is present and no nodules are seen.

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

1. Obtain a travel history
2. Obtain chest MRI
3. Obtain gastrointestinal consult
4. Perform ^{18}FDG-PET scan
5. Perform bronchoscopy

Correct!
3. Obtain gastrointestinal consult

The patient's substernal chest burning and the bilateral basal lung opacities, while non-specific, raise the possibility of recurrent aspiration, for which gastrointestinal medical consultation is appropriate. The patient's symptoms are very non-specific and, while a dedicated travel history is always a good idea, nothing in the patient's history suggests the presence of an unusual infection such as a parasite. Chest MRI would not be of value for this patient. If cross sectional imaging were desired to further evaluate the basal lung findings seen at chest radiography, chest CT, not MR, would be more useful. Similarly, bronchoscopy is not an unreasonable test to obtain in the setting of an unknown cause of pulmonary opacities at imaging, but is premature at this point. Finally, typically, results from ^{18}FDG-PET scanning are interpreted in the context of the imaging findings at chest CT and the latter has yet to be performed. Furthermore, ^{18}FDG-PET scanning is typically employed for staging known or suspected malignancies or for characterization of indeterminate lung nodules, and neither situation is the case here.

The patient underwent gastrointestinal medicine consultation. The gastrointestinal physician recommended a paraneoplastic antibody panel to evaluate what was regarded as a "muscular dystrophy-like" process involving the right calf, CT enterography to evaluate the complaint of weight loss and diarrhea, manometry to evaluate for possible esophageal motility disorder, speech therapy consultation and barium swallow to assess for an oropharyngeal source of dysphagia, and upper endoscopy and colonoscopy. Stool studies to exclude an infectious etiology for the patient's complaints were also recommended.

Testing for coccidioidomycosis and tuberculosis and a serum anti-nuclear antibody test were negative. Sleep studies suggested sleep-disordered breathing, with her oxygen saturation less than 90% for 71% of the night. Esophageal manometry suggested distal esophageal spasm, and the patient's swallowing study indicated the presence of oropharyngeal dysphagia, but no evidence of pulmonary aspiration. Stool studies were unremarkable and none of the paraneoplastic antibodies returned abnormal. Upper endoscopy and colonoscopy showed no specific abnormalities, and the CT enterography study was unremarkable. Otorhinolaryngology consultation was obtained and disclosed the presence of laryngopharyngeal reflux as well as "glottic insufficiency" and "supraglottic muscle tension". No vocal cord abnormalities were noted.

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

1. Obtain a neurology consult
2. Perform chest CT to evaluate the abnormal chest radiographic findings
3. Perform stress testing for possible coronary artery disease
4. 1 and 3
5. All of the above

Correct!
5. All of the above

It is certainly sensible to obtain chest CT to evaluate the chest radiographic findings further, particularly given that the evaluation of the working diagnosis- aspiration- is thus far unconvincing. A neurology consult is reasonable, given that the right calf atrophy raises the possibility of an underlying neuromuscular disorder. Given the patient's age and as yet unexplained substernal chest discomfort and dyspnea with exertion, testing for physiologically significant coronary artery disease is also reasonable.

The patient underwent chest CT (Figure 3) to evaluate the abnormal findings seen at chest radiography.

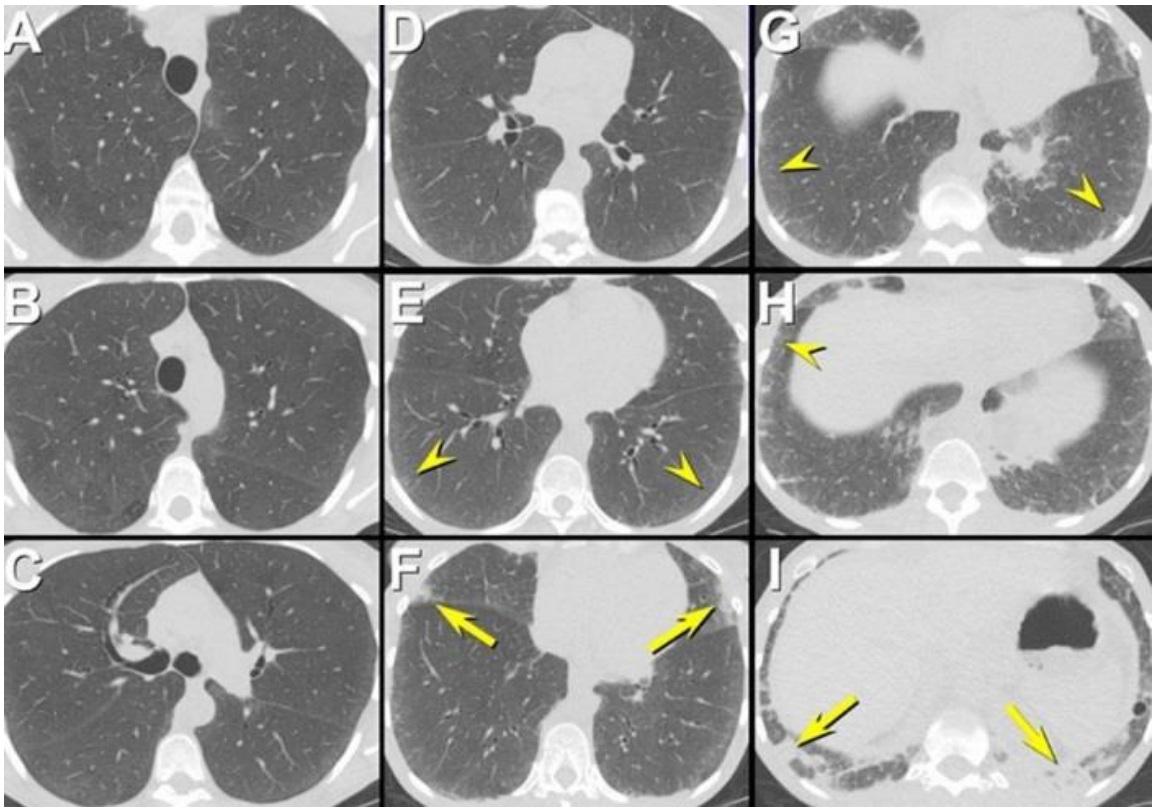

Figure 3. Axial unenhanced chest CT through the upper (A and B), mid (C and D), and lower (E-I) lungs.

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 bronchiectasis
3. The chest CT shows features of fibrotic lung disease
4. The chest CT shows features suggestive of pulmonary artery hypertension
5. The chest CT shows pleural effusion and thickening

Correct!
1. The chest CT shows basal and peripheral ground-glass opacity and consolidation

The axial unenhanced chest CT through the upper (A and B), mid (C and D), and lower (E-I) lungs shows multifocal, bilateral peripherally predominant faint ground-glass opacity (arrowheads) transitioning to lobular consolidation (arrows) more inferiorly. No features of fibrosis, such as architectural distortion, traction bronchiectasis, and honeycombing, are present. There is no evidence of pleural abnormality, either thickening or effusion. No CT features of pulmonary hypertension, particularly enlargement of the central pulmonary arteries, is seen.

Which of the following is ***an appropriate consideration*** for the chest CT findings?

1. Aspiration pneumonia
2. Chronic eosinophilic pneumonia
3. Non-specific interstitial pneumonia
4. Organizing pneumonia
5. More than one of the above

Correct!
5. More than one of the above

The axial unenhanced chest CT shows basal, peripheral predominant ground-glass opacity and consolidation, and all of the listed diagnostic possibilities can, or characteristically, show a peripheral predominance of findings at CT. Aspiration often shows a dependent distribution, and some of the opacities are located in a dependent distribution. Non-specific interstitial pneumonia often presents with peripheral ground-glass opacity, which is present in this case; consolidation may be seen less frequently, but may occur. The lack of clearly fibrotic features at CT is less common in patients with non-specific interstitial pneumonia, but when the disorder shows a primarily cellular histopathological pattern, CT features of fibrosis may be quite inconspicuous. Both organizing pneumonia and chronic eosinophilic pneumonia often show areas of peripheral consolidation at CT. While chronic eosinophilic pneumonia may more commonly show more upper lobe predominant abnormalities, and the lack of peripheral eosinophilia is atypical for this diagnosis, the consideration of the possibility of chronic eosinophilic pneumonia remains appropriate.

A neurology consult was requested which disclosed possible submandibular gland enlargement as well as symmetric lower extremity reflexes but with absent ankle jerks bilaterally. Toe walking was abnormal bilaterally and vibratory sense in the great toes was absent bilaterally as well. Lower extremity muscular weakness was found, and relative atrophy of the right calf was confirmed. The patient also underwent a stress echocardiogram which did not show features suggesting flow-limiting coronary atherosclerosis, although the study was suboptimal given that the workload was insufficient. The echocardiogram (Figure 4) also showed moderate left ventricular muscular hypertrophy and grade 2/4 diastolic dysfunction, and longitudinal strain was reported at =14% (normal, <-18%).

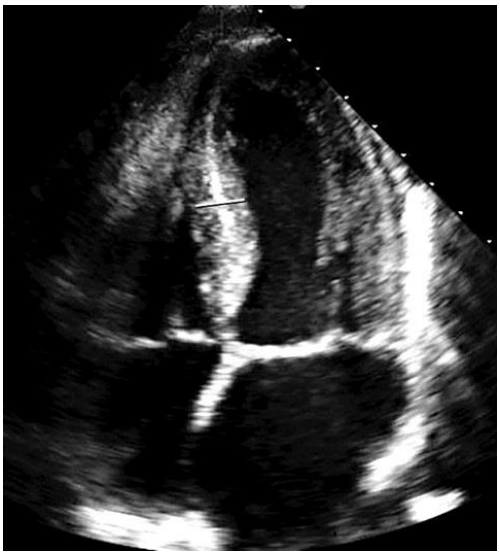

Figure 4. 4-chamber echocardiogram shows left ventricular muscular thickening (line shows thickened interventricular septum.

Which of the following represents ***<u>an appropriate test</u>*** for this patient given the information so far?

1. Bronchoscopy
2. Cardiac MRI
3. Enhanced neck CT
4. Nerve conduction studies
5. All of the above

Correct!
5. All of the above

All of the above studies are appropriate. Bronchoscopy with bronchioloalveolar lavage, possibly transbronchial biopsy, is a reasonable procedure to perform given the lower lobe pulmonary infiltrative abnormalities. An enhanced neck CT is a reasonable study to obtain given the bilateral submandibular gland enlargement. Cardiac MRI is often performed for evaluation of abnormalities detected at echocardiography, particularly when left ventricular hypertrophy is present, raising the possibility of an infiltrative cardiomyopathy. Nerve conduction studies are reasonable to purse given the lower extremity weakness and abnormal reflexes detected at clinical examination.

The patient underwent enhanced neck CT which showed bilateral submandibular gland enlargement and mild tongue enlargement but no lymphadenopathy. Nerve conduction studies showed paraspinal thoracolumbar and florid distal lower extremity fibrillation potentials suggesting a radicular process. Cardiac MRI (Figure 5) was performed and showed findings characteristic of an infiltrative, restrictive cardiomyopathy.

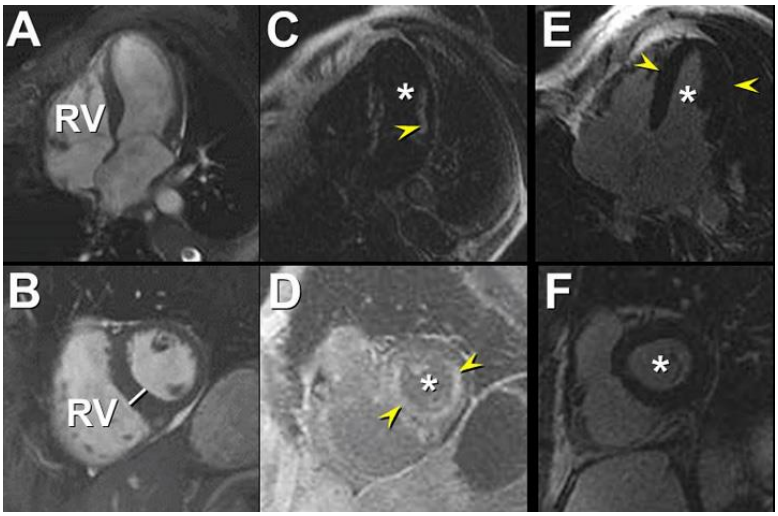

Figure 5. 4-chamber (A) and short axis (B) steady-state free precession cardiac MR images (a “white blood sequence that allows visualization of flowing blood without the use of intravenous contrast) show left ventricular muscular hypertrophy evidenced by thickening of the inferior base-to-mid-cavity interventricular septum (line, B). 4-chamber (C) and short axis (D) late gadolinium enhancement cardiac MR images (a sequence performed 8 – 10 minutes following intravenous contrast administration) shows very poor enhancement of the cardiac blood pool (*) as well as intense subendocardial delayed enhancement (arrowheads). The thickened left ventricular muscle and subendocardial delayed enhancement suggests an infiltrative, restrictive cardiomyopathy. Normal 4-chamber (E) and short axis (F) late gadolinium enhancement cardiac MR images presented for comparison. Note how the myocardium is properly “nulled,” appearing black (arrowheads), and there is substantial contrast in the blood pool (*)- this appearance is normal for this sequence. No delayed enhancement is present. RV= right ventricle.

Which of the following represents ***appropriate confirmatory testing*** for the diagnosis in this patient?

1. ^{18}FDG-PET scanning
2. Abdominal fat aspirate
3. CT sialography
4. Endomyocardial biopsy
5. Video-assisted Thoracoscopy lung biopsy

Correct!
2. Abdominal fat aspirate

An endomyocardial biopsy could be performed to obtain a definitive diagnosis from the thickened left ventricle, but is needlessly invasive given the information known so far as well as the fact that less invasive sampling may be capable of establishing the correct diagnosis. Similarly, video-assisted thoracoscopic lung biopsy could effectively sample the lung parenchymal abnormalities but is also needlessly invasive. ^{18}FDG-PET scanning can neither confirm nor exclude a particular histopathologic diagnosis; rather, ^{18}FDG-PET scanning may disclose sites of metabolically active potential disease, which may be useful for prioritizing interventions. However, there are several organs that have already been shown to be abnormal and there are biochemical data pointing to a diagnosis, and therefore ^{18}FDG-PET scanning is not needed to search for additional sites of disease for intervention. Furthermore, a number of disorders may not show metabolic activity at ^{18}FDG-PET scan, and therefore the presence of absence of PET scan abnormalities would not be management-altering for this patient. CT sialography can be useful for assessing salivary duct calculi and other abnormalities affecting the salivary duct system. While the patient was reported to have submandibular gland enlargement, this finding reflects involvement of her systemic disorder and not the result of salivary duct obstruction.

The patient underwent serum protein electrophoresis showed an “M” spike measured at 1.9 gm/dL and immunofixation confirmed the presence of a monoclonal IgG lambda protein. A fat pad aspirate stained positive for Congo red. A radiographic skeletal survey showed no lytic or osteoblastic lesions.

Which of the following diagnoses is ***most likely to be the correct diagnosis*** for this patient?

1. Chronic lymphocytic leukemia
2. IgG- sclerosing disease
3. Multiple myeloma
4. Rosai-Dorman disease
5. Systemic amyloidosis

Correct!
5. Systemic amyloidosis

While multiple myeloma can result in the presence of amyloid proteins that are responsible for the patient's multisystem abnormalities, the lack of osteolytic lesions at radiographic skeletal survey argues for primary systemic amyloidosis rather than multiple myeloma. Chronic lymphocytic leukemia would not explain the patient's serum biochemical abnormalities and also typically presents with multi-station lymphadenopathy at imaging; the latter is conspicuously absent in this patient. IgG-4 disease is a reasonable thought whenever unusual multisystem abnormalities are present, but the data obtained thus far do not point towards that diagnosis. Rosai-Dorfman disease, also known as sinus histiocytosis with massive lymphadenopathy, is a rare, non-Langerhans cell reactive histiocytic disorder which typically presents as lymphadenopathy in the neck in younger patients, and is typically self-limited. The clinical, imaging, and biochemical data obtained are not consistent with this disorder. Rosai-Dorfman disease can resent as extranodal abnormalities in older patients, but is quite rare and the pattern of lung involvement is one of nodular abnormalities or septal thickening, rather than the ground-glass opacity and consolidation seen in this patient. Furthermore, Rosai-Dorman disease does not explain the patient's nervous system abnormalities are cardiomyopathy.

The abdominal fat aspirate subtyping analysis by mass spectroscopy revealed AL lambda light chain amyloidosis. Bone marrow biopsy showed 38% plasma cells expressing monotypic lambda cytoplasmic immunoglobulin light chains, CD 38, and CD138. Free lambda light chain analysis showed a level of 2443 mg/L (normal, 5.71 to 26.3 mg/L.

Diagnosis: Systemic amyloidosis, AL immunoglobulin light chain, with systemic involvement

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