Southwest Journal of Pulmonary, Critical Care & Sleep

Journal of the Arizona, New Mexico, Colorado and California Thoracic Societies www.swjpcc.com

November 2023 Imaging Case of the Month: A Crazy Association

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HPI: A 55-year-old man presents with a history of cough, poor appetite, low energy, and weight loss over the previous 6-10 months following COVID-19 infection 2 months earlier.

PMH, SH, FH: The patient's past medical history was positive for CVOID-19 infection 2 months earlier as well as pneumonia, not specified, in the previous year.

The patient's past medical history was also remarkable for a 7-unit gastrointestinal hemorrhage approximately one year earlier following polypectomy for benign lesions in the transverse colon. During that hospital admission a complete blood count showed 1% blasts which prompted hematology consultation. The consulting oncologist felt the peripheral blasts were the result of a leukemoid reaction secondary to increased bone marrow stimulation owing to the patient's acute anemia caused by the gastrointestinal hemorrhage. Macrocytosis and reticulocytosis was also noted and attributed to the same. Repeat complete blood count showed no blasts although some myelocytes, metamyelocytes, and polychromasia was noted for which follow up assessment was recommended. Serum B12 and folate levels were normal.

The patient had no prior surgeries.

The patient was not taking any prescription medications.

The patient is a non-smoker. He has no known allergies and drinks alcohol only socially and denied illicit drug use.

There was no significant family history.

Physical Examination: The patient's physical examination showed his temperature to be 96.7°F with borderline elevated pulse rate of 95/min, a normal respiratory rate, and blood pressure of 118/67 mmHg. Room air oxygen saturation was 98%.

Initial Laboratory: A complete blood count showed a normal white blood cell count at 5.6 $x10^9$/L (normal, 3.4 – 9.6 $x10^9$/L), with 75% bands (normal, 50-75%). His hemoglobin and hematocrit values were 10.1 gm/dL (normal, 13.2 – 16.6 gm/dL) and 31.6% (normal, 38.3 – 48.6%). The platelet count was normal at 225 x 10^9/L (normal, 135 – 317 x 10^9/L). The patient's serum chemistries and liver function studies were normal aside from mildly decreased total protein at 5.7 gm/dL (normal, 6.3-.9 gm/dL). The patient had an elevated anti-nuclear antibody titer at 1:320. SARS-CoV-2 PCR testing was positive.

Radiography: Frontal chest radiography (Figure 1) was performed.

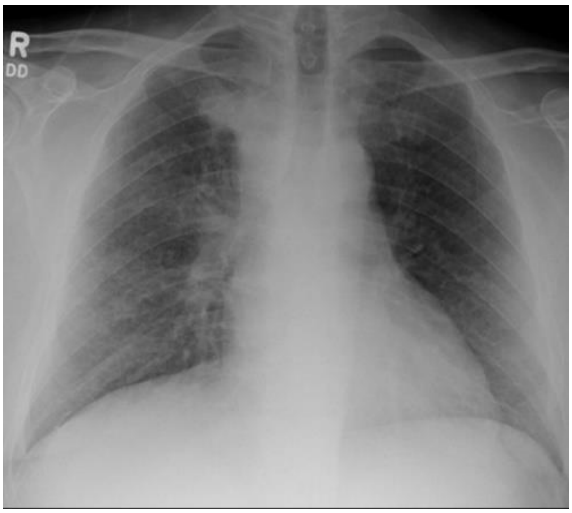

Figure 1. Frontal chest radiography at presentation. Click here to open Figure 1 in a new, enlarged window.

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

1. Frontal chest radiography shows normal findings
2. Frontal chest radiography shows marked cardiomegaly
3. Frontal chest radiography shows mediastinal lymphadenopathy
4. Frontal chest radiography shows pleural effusion
5. Frontal chest radiography shows multifocal consolidation

Correct!

3. Frontal chest radiography shows mediastinal lymphadenopathy

Frontal chest radiography shows a normal heart size. Patchy areas of ground-glass opacity are present in the right lung, and a nodule is present in the medial right upper lobe. The right hilum appears enlarged and the right paratracheal region is thickened, suggesting lymph node enlargement in both locations. No pleural effusion is seen.

Based on the chest radiographic findings, which of the following ***is accurate***?

1. Frontal chest radiographic findings most likely represent COVID-19 infection
2. Frontal chest radiographic findings most likely represent fungal infection
3. Frontal chest radiographic findings most likely represent sarcoidosis
4. Frontal chest radiographic findings most likely represent viral infection other than COVID-19
5. Frontal chest radiographic findings most likely represent bacterial pneumonia

Correct!

2. Frontal chest radiographic findings most likely represent fungal infection

The frontal chest radiograph shows right peribronchial and mediastinal lymph node enlargement associated with a medial apical right upper lobe nodule- such findings are not typical of viral infections, including COVID-19. While non-specific, these imaging abnormalities could be seen with fungal infection. Although sarcoidosis may produce both nodules and mediastinal and peribronchial lymph node enlargement, the lung nodules in sarcoidosis are typically much smaller- often less than 1 cm- and not solitary in nature, and the peribronchial lymphadenopathy is commonly symmetric, unlike the appearance in this case. Bacterial infection more commonly presents as consolidation, which is lacking in this case, and lymphadenopathy is not commonly seen at chest radiography.

Upon further questioning, the patient admitted to some shortness of breath, which lead to the ER staff obtaining a D-dimer level, which was elevated at 3341 ng/mL (normal, <500 ng/mL) which prompted CT pulmonary angiography (Figure 2).

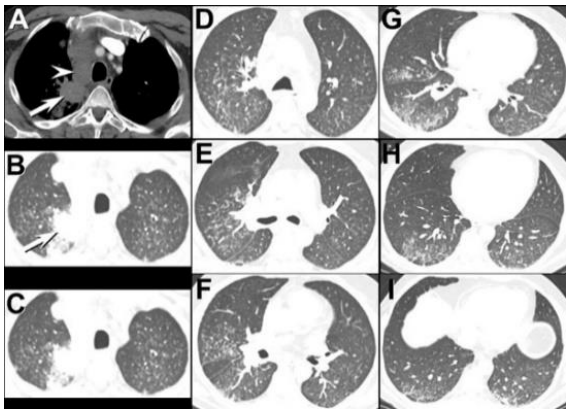

Figure 2. Axial enhanced CT pulmonary angiography in the upper (A-C), Mid (D-F), and lower (G-I) lungs. Click here to open Figure 2 in a new, enlarged window. Click here to open a video of Figure 2.

Which of the following represents ***an appropriate interpretation*** for this examination?

1. CT pulmonary angiography shows right peribronchial and mediastinal lymphadenopathy as well as interstitial abnormalities
2. CT pulmonary angiography shows acute pulmonary embolism
3. CT pulmonary angiography shows multifocal ground-glass opacity
4. CT pulmonary angiography shows loculated pleural effusion
5. CT pulmonary angiography features of fibrotic lung disease

Correct!

1. CT pulmonary angiography shows right peribronchial and mediastinal lymphadenopathy as well as interstitial abnormalities

Enhanced CT pulmonary angiography confirms the presence of right paratracheal and peribronchial lymph node enlargement as well as the presence of a medial right apical lung nodule. Interstitial abnormalities, at least in part consisting of interlobular septal thickening, are present, but these abnormalities are not fibrotic in appearance- no honeycombing, traction bronchiectasis, or significant architectural distortion is seen. No pleural effusion is present and ground-glass opacity is absent. No evidence of pulmonary embolism is seen.

Based on available information this far, which of the following is the ***best working diagnosis***?

1. Bacterial pneumonia
2. Post-acute COVID-19
3. Multifocal adenocarcinoma
4. Pulmonary lymphoma
5. Fungal infection

Correct!

5. Fungal infection

The lack of fever and the imaging findings argue against bacterial pneumonia. The lung nodule and lymph node enlargement as well as the appearance of the lung opacities are not suggestive of either acute COVID-19 or post-acute sequelae of COVID-19. Pulmonary lymphoma is a possibility, but often when lymphoma is present in the lungs, it is the result of direct invasion from affected lymph nodes or presents as multiple lung nodules without mediastinal or peribronchial lymphadenopathy- neither is the case in this circumstance. Multifocal adenocarcinoma in the lungs commonly presents as multiple small nodules which may be non-solid in appearance or as multifocal areas of consolidation, with or without cystic change. The imaging findings were regarded as suspicious for possible bronchogenic malignancy and the patient underwent ^{18}FDG – PET scan (Figure 3).

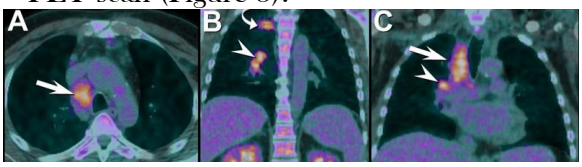

Figure 3. Axial (A) and coronal (B and C) FDG-PET images. Click here to open Figure 3 in a new, enlarged window.

Which of the following represents ***an appropriate interpretation*** for this examination?

1. ^{18}FDG – PET shows widespread hypermetabolic activity beyond the hypermetabolism in the lung nodule and right peribronchial and mediastinal lymph node enlargement
2. ^{18}FDG – PET shows hypermetabolic activity in the right upper lobe nodule ***but not*** in the peribronchial or mediastinal lymph node enlargement
3. ^{18}FDG – PET is non-diagnostic, probably owing to improper fasting
4. ^{18}FDG – PET shows hypermetabolic activity in interstitial lung abnormalities
5. ^{18}FDG – PET shows hypermetabolic activity in the right upper lobe nodule ***as well as*** in the peribronchial or mediastinal lymph node enlargement

Correct!

5. ^{18}FDG – PET shows hypermetabolic activity in the right upper lobe nodule as well as in the peribronchial or mediastinal lymph node enlargement

^{18}FDG – PET shows that the medial right apical nodule and the right peribronchial and mediastinal lymphadenopathy are hypermetabolic, but no other sites of hypermetabolism are seen.

Based on the information thus far, which of the following represents ***the most appropriate next step*** for the patient's management?

1. ^{68}Ga-PET Dotatate PET scan
2. Pulmonary function testing
3. Bronchoscopy with biopsy
4. Percutaneous transthoracic biopsy
5. More than one of the above

Correct!

5. More than one of the above

Bronchoscopy with biopsy may be the optimal approach to obtain a tissue diagnosis for the patient's thoracic abnormalities, although transthoracic needle biopsy could also be performed. Pulmonary function testing may prove valuable at some point in the course of this patient's care, but at this point efforts must be directed towards obtaining a diagnosis for the lung and mediastinal abnormalities. ^{68}Ga-PET Dotatate PET scan may prove useful if the patient is subsequently diagnosed with neuroendocrine malignancy, but is premature at this point; the chest CT findings are consistent with possible neuroendocrine malignancy, but are certainly not specific for this diagnosis.
The patient underwent percutaneous transthoracic needle mediastinal lymph node biopsy (Figure 4).

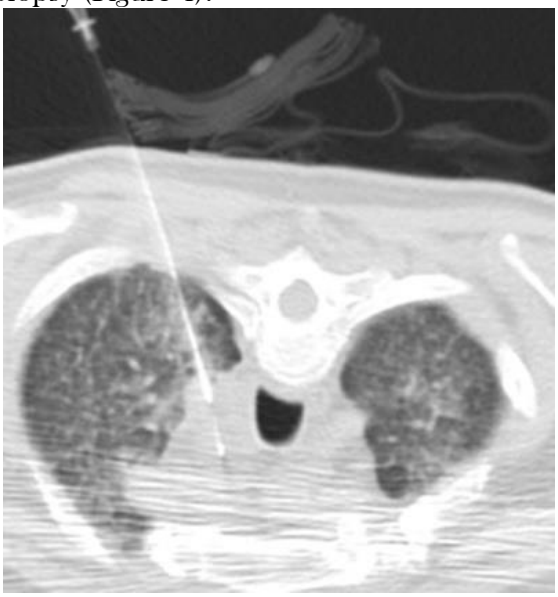

Figure 4. Prone CT during percutaneous needle biopsy of the right paratracheal lymphadenopathy. Click here to open Figure 4 in a new, enlarged window.

The biopsy showed non-necrotizing granulomatous inflammation but no evidence of malignancy. Bronchoscopy with endobronchial ultrasound and biopsy of the right paratracheal lymphadenopathy was also performed and showed similar histologic findings; no coccidioidomycosis spherules were identified. The patient then underwent testing for coccidiomycosis, which showed

immunodiffusion testing positive for IgM antibodies, suggesting acute infection. Coccidioidomycosis complement fixation was positive at 1:32. The patient was started on fluconazole.

The patient was continued on antifungal therapy which was switched from fluconazole to itraconazole due to the lack of appropriate decrease in complement fixation titers assessed at follow up. The patient continued to complain of inability to gain the weight he lost (approximately 45 lbs. over a number of months) as well as fatigue. Repeat complete blood count showed a normal white blood cell count at 4.5 $x10^9$/L (normal, 3.4 – 9.6 $x10^9$/L). The absolute neutrophil count was 1.08 $x10^9$/L (normal, 1.56 – 6.45 $x10^9$/L). His hemoglobin and hematocrit values were 8.1 gm/dL (normal, 13.2 – 16.6 gm/dL) and 23.5% (normal, 38.3 – 48.6%). 6% blasts were noted. The platelet count was normal at 166 x 10^9/L (normal, 135 – 317 x 10^9/L).

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

1. Continue present management on antifungals
2. Switch antifungal therapy to amphotericin
3. Serum protein electrophoresis
4. Bone marrow aspiration / biopsy
5. Brain MRI

Correct!

4. Bone marrow aspiration / biopsy

The persistent, even worsening over the previous months, macrocytic anemia, in the context of the patient's symptoms, raises the possibility of a bone marrow abnormality. Bone marrow biopsy was performed and showed hypercellular bone marrow with atypical megakaryocytic hyperplasia, occasional granulocytic hypogranularity, mild basophilia, and 1-2% blasts. Dyserythropoiesis with multinucleation and internuclear bridges and nuclear fragmentation was noted. Cytogenic analysis showed 47XY, +8[20] karyotype and a Tier 1 mutation in U2AF1. Fluorescence in situ hybridization (FISH) showed trisomy 8. No evidence of plasma cell dyscrasia or lymphoma was seen, but the bone marrow biopsy findings were interpreted as suggestive of myeloid dysplasia, specifically myelodysplasia with multilineage dysplasia (MDS-MLD). Therapy with venetoclax and azacitidine was begun and stem cell transplant was discussed. Several months later the patient underwent repeat chest CT (Figure 5) for assessment of the effectiveness of antifungal therapy.

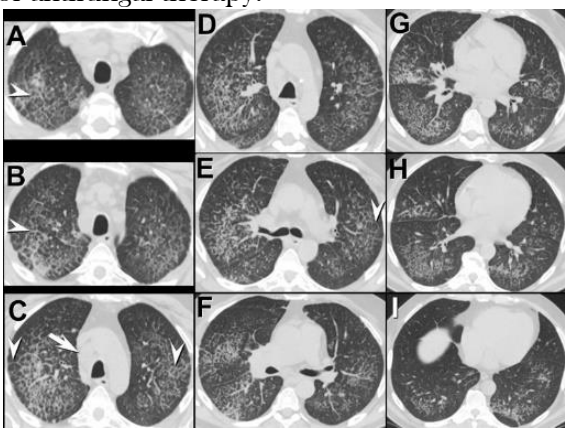

Figure 5. Axial unenhanced CT obtained 7 months after initial presentation. Click here to open Figure 5 in a new, enlarged window. Click here to open a video of Figure 5.

Which of the following represents ***an appropriate interpretation*** for this examination?

1. Unenhanced chest CT shows worsening right peribronchial and mediastinal lymph node enlargement
2. Unenhanced chest CT shows worsening linear and interstitial abnormalities
3. Unenhanced chest CT shows new small symmetric pleural effusions
4. Unenhanced chest CT shows new multifocal consolidation

5. Unenhanced chest CT features suggesting developing fibrotic lung disease

Correct!

2. Unenhanced chest CT shows worsening linear and interstitial abnormalities

Unenhanced chest CT shows persistent, but decreased right paratracheal lymph node enlargement and the previously seen medial right apical nodule [Figure 2] has largely resolved. No new pleural effusion is seen. Significant progression in right-greater-than-left, multifocal, bilateral small interlobular septal thickening associated with some ground-glass opacity is noted. Only minimal lobular right upper lobe consolidation is present.

Which of the following represents ***the most appropriate description*** of the CT scan pattern?

1. Reverse ground-glass halo sign
2. Finger-in-glove sign
3. CT angiogram sign
4. Crazy-paving pattern
5. Atoll sign

Correct!

4. Crazy-paving pattern

The appearance of smooth interlobular septal thickening and intralobular lines superimposed on a background ground-glass opacity, often with a geographic appearance of abnormal lung sharply demarcated from uninvolved lung, has been referred to as the "crazy-paving" pattern. The "finger-in-glove' sign, a term often applied at chest radiography, represents a tubular opacity resulting from bronchial impaction, often in the context of allergic bronchopulmonary aspergillosis. The CT angiogram sign represents the appearance of enhancing vessels within low attenuation consolidation at CT. Initially thought to suggest the presence of malignancy, particularly mucinous bronchogenic malignancy, this sign is very non-specific and can be seen in a wide variety of conditions. The "reverse ground-glass halo" [or "reverse halo"] sign and "atoll" sign refer to the same CT finding- a focal rounded area of ground-glass opacity surrounded by a complete or incomplete ring of consolidation. Initially thought to be specific for the presence of organizing pneumonia, this sign is still suggestive of that entity but can be seen in a number of other conditions, including infections and vascular insults.

Which of the following represents ***the most appropriate differential diagnostic consideration*** for the appearance at CT?

1. Worsening fungal infection
2. Worsening pulmonary COVID-19 infection
3. Pulmonary alveolar proteinosis
4. Development of a drug-related hypersensitivity reaction
5. Development of increased pressure edema

Correct!

3. Pulmonary alveolar proteinosis

The resolution of the medial right apical nodule and the decrease in mediastinal lymphadenopathy suggests a positive response to antifungal therapy, not worsening of infection. Increased pressure edema can certainly manifest as worsening smooth interlobular septal thickening, but often such pulmonary parenchymal findings are associated with other features of increased pressure edema, such as cardiac enlargement, small pleural effusion, fat infiltration, and other findings of third-spacing, but these latter findings are lacking in this case. COVID-19 infection can rarely present with ground-glass opacity and interlobular septal thickening, but this pattern is uncommon and typically associated with significant respiratory symptoms as well as physiologic abnormalities, and this CT pattern occurs in the acute phase of the infection, not typically

months later. Pulmonary parenchymal lymphoma is rare in general, and, as noted previously, often presents as multiple non-solid or part-solid nodules or direct extension of peribronchial or mediastinal lymph node involvement. However, intrathoracic lymphoproliferative disorders may manifest in numerous different ways, including interlobular septal thickening, given the presence of lymph tissue within the interlobular septae. Nevertheless, this presentation of intrathoracic lymphoproliferative disorder is very rare, and the patient's underlying diagnosis of MDS-MLD is more associated with development of acute myeloid leukemia rather than lymphoma. Medication-induced pulmonary injury, or drug reactions, may be classified using the American Thoracic Society idiopathic interstitial pneumonia classification system- many drug reactions present with these patterns. Other patterns of parenchymal injury related to medication include lymphadenopathy and sarcoid-like reactions, pleural effusion, nodules, and an acute eosinophilic pneumonia-like pattern. The latter may somewhat resemble this patient's CT scan, but this reaction pattern is quite rare and, based on the CT performed 7 months earlier, appears to be developing over time rather than acutely. The pattern at CT is consistent with the "crazy-paving" pattern which is suggestive of pulmonary alveolar proteinosis.

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

1. Granulocyte-monocyte – colony – stimulating factor (GM-CSF) titer evaluation
2. Paxlovid (nirmatrelvir/ritonavir) therapy
3. Bronchoscopy
4. Surgical lung biopsy
5. More than one of the above

Correct!

5. More than one of the above

The chest CT findings are very unlikely to be related to COVID-19, and therefore Paxlovid (nirmatrelvir/ritonavir) therapy is not necessary. Surgical lung biopsy could certainly achieve a diagnosis for the lung parenchymal abnormalities but is needlessly invasive. Rather, bronchoscopy would provide the ability to determine if pulmonary alveolar proteinosis is present with risks substantially less than surgical lung biopsy. Similarly, given the suspicion for pulmonary alveolar proteinosis, granulocyte-monocyte – colony – stimulating factor [GM-CSF] titer assessment would be appropriate.

During the course of evaluation, the patient presented to the ER with complaints of worsening shortness of breath and non-neutropenic fever, with D-dimer again elevated at 6475 ng/mL (normal, <500 ng/mL), which prompted CT pulmonary angiography (Figure 6).

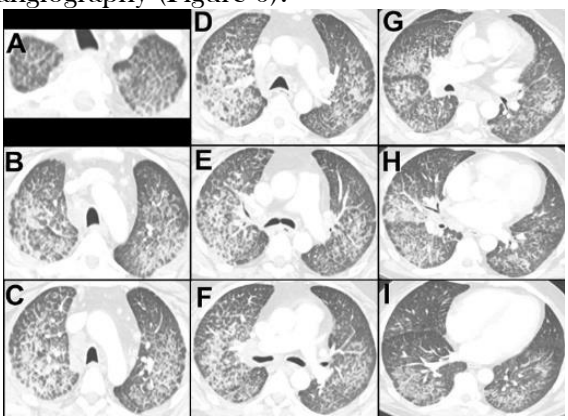

Figure 6. Axial unenhanced CT obtained 9 months after initial presentation. Click here to open Figure 6 in a new, enlarged window. Click here to open a video of Figure 6.

Which of the following represents ***an appropriate interpretation*** for this examination?

1. Repeat CT pulmonary angiography shows *worsening* of the previously seen crazy-paving pattern

2. Repeat CT pulmonary angiography shows recurrence of the peribronchial and mediastinal lymphadenopathy
3. Repeat CT pulmonary angiography shows *regression* of the previously seen crazy-paving pattern
4. Repeat CT pulmonary angiography shows *stability* of the previously seen crazy-paving pattern
5. Repeat CT pulmonary angiography shows new disseminated small nodules

Correct!

1. Repeat CT pulmonary angiography shows worsening of the previously seen crazy-paving pattern

Repeat CT pulmonary angiography shows interval worsening of multifocal, bilateral smooth interlobular septal thickening associated with intralobular lines and ground-glass opacity, consistent with worsening of the previously noted "crazy paving" pattern. Mild mediastinal lymphadenopathy remains.

A viral panel was negative (including for SARS-CoV-2), and echocardiography showed normal left ventricular function. GM-CSF testing showed an antibody level <15 pg/mL (normal, <15 pg/mL). Given all the information presented thus far, which of the following represents ***the most appropriate next step*** for the patient's management?

1. Expectant management with follow up in 3 months
2. Bronchoscopy with bronchoalveolar lavage and transbronchial biopsy
3. Thoracoscopic lung biopsy
4. Institute corticosteroid therapy dose
5. Change itraconazole anti-fungal therapy to amphotericin

Correct!

2. Bronchoscopy with bronchoalveolar lavage and transbronchial biopsy

The CT abnormalities are clearly worsening and therefore expectant management is not appropriate, particularly given the patient's worsening symptoms. Thoracoscopic lung biopsy could obtain an accurate diagnosis for the lung parenchymal abnormalities but is unnecessarily invasive given that fiberoptic bronchoscopy may also be capable of establishing the diagnosis. The findings at CT are not suggestive of a steroid-responsive condition, and hence presumptive corticosteroid therapy is not advisable. The patient's anti-fungal therapy appears effective given the improvement in nodular lung disease in the medial right upper lobe as well as the initial regression, and now stability of, mediastinal lymphadenopathy.

Given the presence of fever and the patient's chemotherapy regimen, broad-spectrum antibiotic therapy was begun. The patient underwent flexible fiberoptic bronchoscopy with bronchoalveolar lavage and transbronchial biopsy in the right upper lobe as well as endobronchial ultrasound-guided biopsy of the right paratracheal lymph nodes. The bronchoalveolar lavage fluid appeared cloudy and showed 44% lymphocytes, 22% neutrophils, 14% macrophages, and 20% eosinophils. The transbronchial biopsy material stained strongly with periodic acid-Schiff (PAS). The diagnosis of secondary pulmonary alveolar proteinosis in the context of myelodysplastic syndrome was established. Pulmonary medicine felt that the lack of significant milky return at fiberoptic bronchoscopy indicated that whole-lung lavage would not be necessary and instead treatment of the underlying myelodysplastic syndrome would be more appropriate.

Diagnosis: Secondary pulmonary alveolar proteinosis in the context of myelodysplasia with multilineage dysplasia.

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