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May 2021 Imaging Case of the Month: A Growing Indeterminate Solitary Nodule

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A 58-year-old woman with a history of orthotopic heart transplant, performed for Adriamycin-induced cardiomyopathy, treated with mycophenolate and tacrolimus, presented for routine interval follow up. The patient's past medical history was significant for follicular thyroid carcinoma treated with total thyroidectomy and bilateral breast carcinoma in remission as well as hypothyroidism and type II diabetes mellitus. In addition to tacrolimus and mycophenolate, the patient's medications included aspirin, insulin, itraconazole (for anti-fungal prophylaxis), levothyroxine, prednisone (tapering since transplant), and valganciclovir. The patient recently complained of rhinorrhea and cough productive of brown-tinged sputum, improving over the previous 2 weeks; she denied fever, chills, shortness of breath, night sweats chest pain, or gastrointestinal symptoms.

Physical examination showed the patient to be afebrile with normal heart and respiratory rates and blood pressure. Her room air oxygen saturation was 99%.

The patient's complete blood count and serum chemistries showed largely normal values, with the white blood cell count at the upper normal at 9.7 x 10^9 /L (normal, 4-10 x 10^9/L). Her liver function testing and renal function testing parameters were also within normal limits. Echocardiography showed normal left ventricular systolic function. The patient underwent frontal chest radiography (Figure 1).

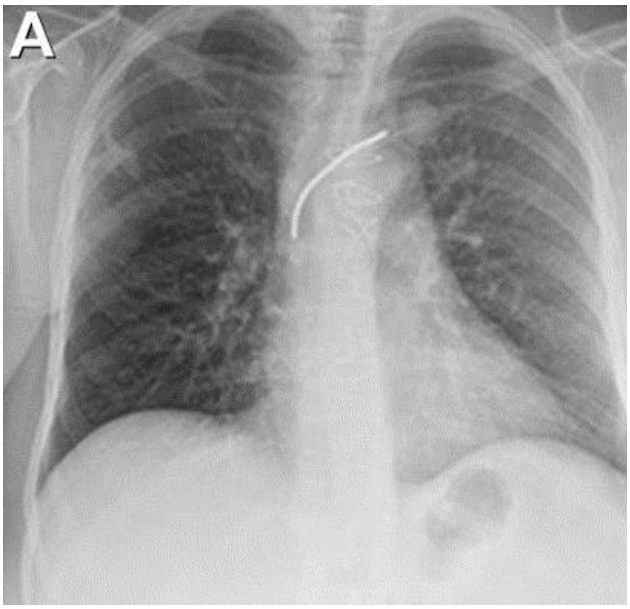

Figure 1: Frontal chest radiography.

Key Words: malakoplakia, lung nodule, nodule, pulmonary nodule, immunocompromised host, lung biopsy, solitary nodule, cardiac transplantation, heart transplant, Michaelis-Gutmann bodies

Which of the following represents ***an appropriate interpretation*** of her frontal chest radiograph?

1. Frontal chest radiography shows a right pleural effusion
2. Frontal chest radiograph shows a left apical nodule
3. Frontal chest radiography shows multifocal consolidation
4. Frontal chest radiography shows peribronchial and mediastinal lymphadenopathy
5. Frontal chest radiography shows cardiomegaly

Correct!
2. Frontal chest radiography shows a left apical nodule

The frontal chest radiograph (Figure 1) shows a normal heart size. No evidence of pleural effusion is present. There is no evidence of consolidation and the hilar and mediastinal contours appear normal, but a circumscribed medial left upper lobe nodule is present.

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

1. Comparison to prior chest radiography
2. Chest MRI
3. Lateral decubitus chest radiography
4. ^{18}FDG-PET scan
5. More than one of the above

Correct!
1. Comparison to prior chest radiography

Whenever a lesion is discovered at chest imaging, comparison to older chest imaging studies is of paramount importance. If a chest lesion can be shown to be stable for a significant length of time, the evaluation of a chest lesion may be tempered, saving expense, potential radiation exposure, patient anxiety, and possibly even complications. Further evaluation with cross sectional imaging or ^{18}FDGPET may occasionally be averted with this approach, the latter typically employed after a nodule at chest radiography has been evaluated with chest CT and found to be indeterminate. Lateral decubitus chest radiography is usually reserved for assessment of layering pleural effusion [with the affected side dependent] or pneumothorax [with the affected side non-dependent].).

A chest radiograph performed one year earlier, prior to the patient's cardiac transplantation, was located for comparison (Figure 2).

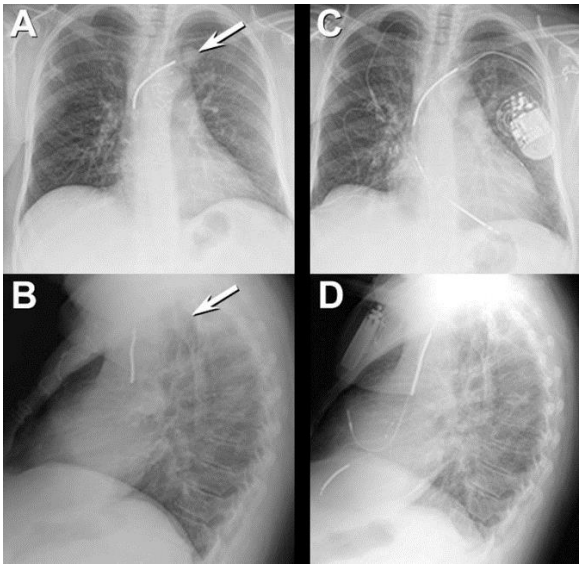

Figure 2: The current frontal and lateral chest radiograph (A and B) is compared with a prior frontal and lateral chest radiograph just 12 months earlier (C and D), and shows that the left upper lobe nodule (arrow) is new. The patient's heart transplant had been performed in the interval between the two examinations- note the abandoned defibrillator lead remaining in the native superior vena cava.

Given this comparison, which of the following represents an ***appropriate differential diagnostic consideration*** for the patient's presentation chest radiographic findings?

1. Bronchogenic malignancy
2. Coccidioidomycosis
3. Hamartoma
4. Post-transplant lymphoproliferative disorder
5. More than one of the above

Correct!

1. Bronchogenic malignancy
2. Coccidioidomycosis
4. Post-transplant lymphoproliferative disorder
5. More than one of the above

Given the patient's cardiac transplantation and immunosuppression, malignancy- both bronchogenic malignancy and post-transplant lymphoproliferative disorder- is a consideration when a new nodule is encountered at chest radiography. Clearly infectious etiologies for a new nodule, including fungal infections, are considerations as well, even given that the patient is on chronic anti-fungal therapy. Among the differential diagnostic considerations listed, hamartoma is unlikely to account for the new nodule as such lesions grow slowly, and the nodule would probably be visible on the chest radiograph performed one year earlier.

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

1. Perform unenhanced chest CT
2. Perform lateral decubitus chest radiography
3. Perform ^{68}Ga-Dotatate scan
4. Perform ^{18}FDG-PET scan
5. Perform contrast enhanced thoracic MR

Correct!
1. Perform unenhanced chest CT

Unenhanced chest CT is typically the diagnostic study of choice when a new indeterminate nodule is encountered in an adult patient. As noted previously, lateral decubitus chest radiography is reserved for assessment of layering pleural effusion [with the affected side dependent] or pneumothorax [with the affected side non-dependent]. PET scanning with ^{68}Ga-Dotatate is typically used for the evaluation of neuroendocrine malignancies, and could play a role for this patient if that diagnosis is subsequently confirmed, but is as yet premature. Thoracic MR is not commonly employed for the assessment of new pulmonary nodules; chest CT is generally more rewarding for that application).

The patient underwent unenhanced chest CT (Figure 3).

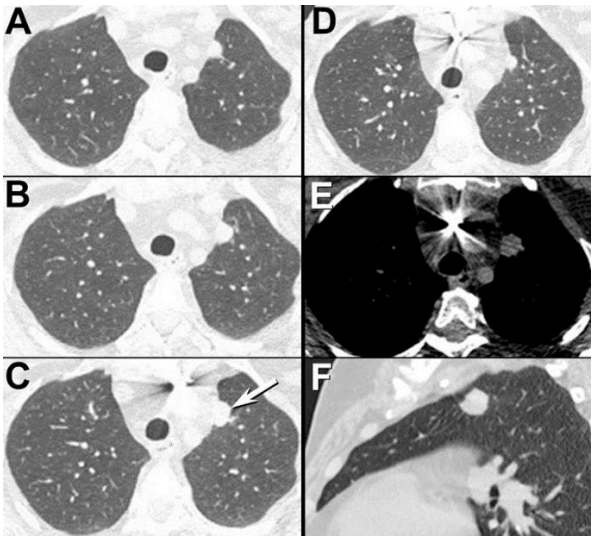

Figure 3: Axial (A-D) and sagittal (F) unenhanced chest CT displayed in lung (A-D, F) and soft tissue (E) windows shows a non-calcified mildly lobulated 16 mm left upper lobe nodule in contact with the left superior mediastinum (arrow, C), accounting for the chest radiographic abnormality. The patient has undergone previous right mastectomy with associated right apical reticulation representing previous radiation therapy. Lung parenchymal attenuation is heterogeneous.

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

1. Chest CT shows an indeterminate subpleural left upper lobe nodule
2. Chest CT shows widespread pulmonary nodules
3. Chest CT shows extensive interlobular septal thickening
4. Chest CT radiography shows peribronchial and mediastinal lymphadenopathy
5. Chest CT radiography shows multifocal ground-glass opacity and consolidation

Correct!
1. Chest CT shows an indeterminate subpleural left upper lobe nodule

The unenhanced chest CT shows a lobulated, non-calcified left upper lobe nodule corresponding to the chest radiographic abnormality. No other nodules are present. While the lung parenchymal attenuation in general is somewhat inhomogeneous, no interlobular septal thickening, ground-glass opacity, or consolidation is evident. No definitely peribronchial or mediastinal lymph node enlargement is seen.).

Testing for coccidioidomycosis infection and tuberculosis was negative. A urine analysis and culture disclosed the presence of *Escherichia coli* urinary tract infection, but the patient's white blood cell count and other laboratory parameters remained within normal limits. The patient underwent short-term follow up CT, approximately 5 weeks later, for reassessment of the left upper lobe pulmonary nodule (Figure 4).

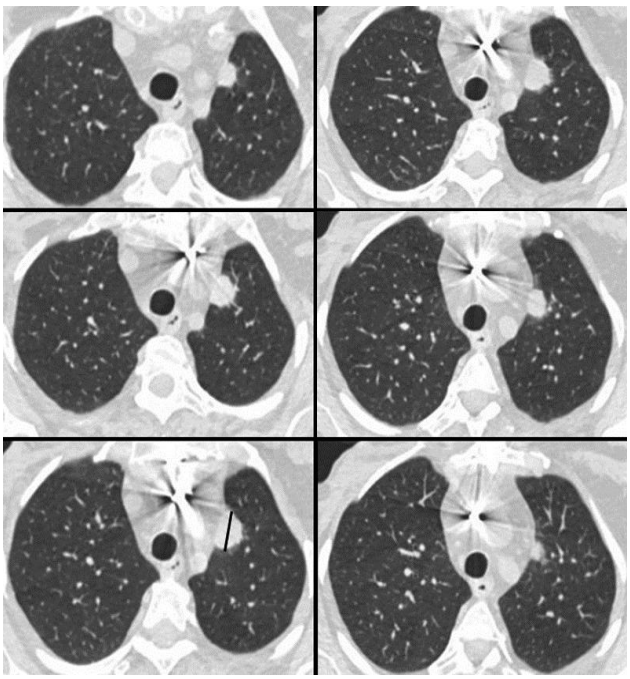

Figure 4: Axial unenhanced chest CT performed 5 weeks after Figure 3 shows the left upper lobe nodule (black line), previously measuring 16 mm, has enlarged slightly, now measuring 20 mm. A slight ground-glass halo is now faintly visible.

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

1. Chest CT shows the nodule has *decreased* in size
2. Chest CT shows the nodule remains unchanged
3. Chest CT shows the nodule has *increased* in size
4. Chest CT shows that new nodules have developed
5. Chest CT shows that the nodule has developed cavitation

Correct!
3. Chest CT shows the nodule has increased in size

The left upper lobe nodule has enlarged somewhat, previously 16 mm maximal dimension, now 20 mm, consistent with a doubling time of 43 days. A faint ground-glass halo has developed around the margins of the lesion, but no new nodules or areas of consolidation are present. There is no evidence of cavitation.

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

1. Perform ^{18}FDG-PET scan
2. Perform percutaneous transthoracic lung biopsy
3. Perform robotic assisted bronchoscopy
4. Perform surgical lung biopsy
5. More than one of the above

Correct!
2. Perform percutaneous transthoracic lung biopsy
3. Perform robotic assisted bronchoscopy
5. More than one of the above

Given the lack of a definitive diagnosis and the broad differential diagnostic considerations for an enlarging, indeterminate pulmonary nodule in an immunosuppressed patient, tissue sampling is appropriate. There are a number of options for tissue sampling for this lesion, including percutaneous transthoracic needle biopsy, bronchoscopic techniques, and even surgical lung biopsy, possibly using a video-assisted approach. A surgical biopsy may be needlessly invasive at this point, given that other less invasive measures may obtain the diagnosis and are commonly attempted first when feasible. The lesion is amenable to percutaneous transthoracic needle biopsy, although the access route may be limited- an anterior approach may be favored given the long intrapulmonary needle course mandated by a posterior approach, but the anterior approach window is limited by the osseous structures of the chest wall. Robotic-assisted bronchoscopy is an alternative method that may be able to access the nodule.

The patient underwent robotic assisted bronchoscopic biopsy and bronchioloalveolar lavage of the left apical nodule (Figure 5).

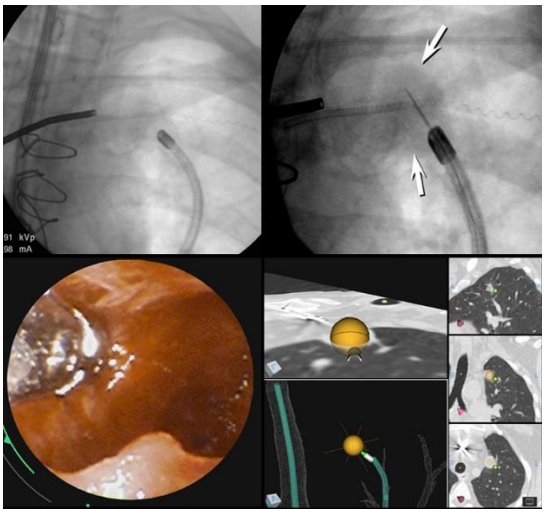

Figure 5: Robotic-assisted navigational bronchoscopy. Fluoroscopic image shows the robotically-guided needle within the nodule (arrows). The image at the lower left shows direct bronchoscopic visualization of the nodule, and the lower right image shows the robotic guiding system.

The results of this procedure revealed *Escherichia coli*, identical to the organism discovered in the patient's urinary culture, sensitive to Augmentin. Histopathological analysis showed sheets of oval- to spindle-shaped histiocytes with the presence of Michaelis-Gutmann bodies (Figure 6).

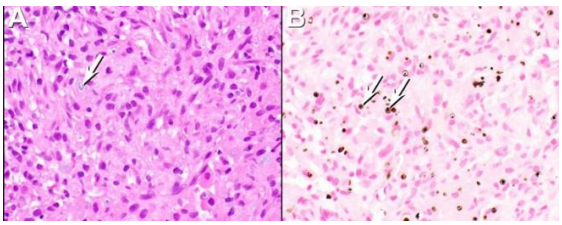

Figure 6: Robotic-assisted bronchoscopic biopsy specimen from the left upper lobe nodule. (A) Transbronchial biopsy specimen (hematoxylin & eosin, 400X) shows sheets of oval- to spindle-shaped histiocytes, some of which had light purple cytoplasmic inclusions (arrow). (B) Von Kossa staining highlights the inclusions to be positive for calcium (arrow), indicating the presence of Michaelis-Gutmann bodies.

Based on this information, which of the following represents ***the most likely diagnosis*** for this patient?

1. Post-transplant lymphoproliferative disorder
2. Bronchogenic malignancy
3. *Aspergillus* infection
4. Malakoplakia
5. Sclerosing pneumocytoma

Correct!
4. Malakoplakia

The histopathologic features do not indicate the presence of malignancy, either related to bronchogenic carcinoma or a lymphoproliferative disorder. Histopathological features of sclerosing pneumocytoma include surface and round cells, the latter with abundant eosinophilic cytoplasm with indistinct cell borders and nucleoli, oval nuclei, possibly even chromatin, and indistinct nucleoli; vacuolization, hyperchromasia, pleomorphism may be present. A sclerotic stroma may be seen. However, none of these features were mentioned in the biopsy specimen, making sclerosing pneumocytoma an unlikely diagnosis. Furthermore, sclerosing pneumocytoma- a benign neoplasm- would be expected to grow slowly, rather than the rapid interval enlargement seen with this lesion. No evidence of fungal hyphae to suggest *Aspergillus* infection was seen after biopsy; rather bacteria were recovered. Michaelis-Gutmann bodies were present histopathologically in the biopsy specimen; these structures represent concentrically layered basophilic inclusions, thought to reflect the remains of incompletely digested bacterial remnants that have undergone mineralized by calcium or iron. While most commonly encountered in the urinary tract, Michaelis-Gutmann bodies are typical of malakoplakia.

Clinical Course: The patient had been started on ciprofloxacin, but her *Escherichia coli* urinary tract infection was found to be resistant to this drug and she was switched to Augmentin. She completed this therapy and chest CT was repeated 4 months after diagnosis (Figure 7), showing that the nodule had decreased in size from its largest measurement of 20 mm to 12 mm.

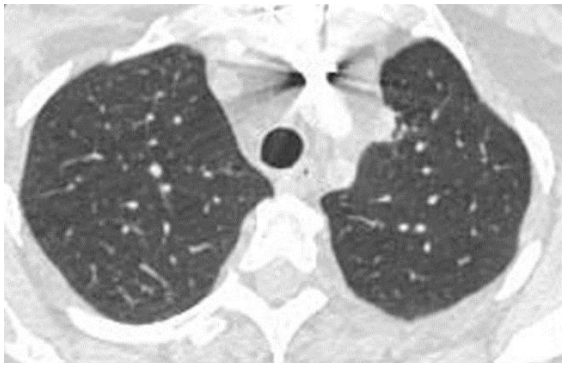

Figure 7: Unenhanced chest CT performed 4 months after the diagnosis of malakoplakia was made and following prolonged antibiotic therapy shows decreased size of the left upper lobe nodule, now 12 mm, previously 20 mm.

One year after diagnosis the patient is doing well.

Diagnosis: Malakoplakia presenting as a growing solitary pulmonary nodule

Discussion: Malakoplakia is a rare, often chronic, multisystem granulomatous inflammatory condition that typically presents as single or multiple soft plaques affecting various organs, most commonly the genitourinary system. The mean age of diagnosis is approximately 50 years, although malakoplakia may present at any age. While whites are more commonly affected than other races, sources differ regarding the sex predilection of malakoplakia. A history of immunosuppression, such as diabetes mellitus, malignancy, organ transplantation, alcoholism, lymphoproliferative disorder, or chronic corticosteroid therapy is a common predisposing factor.

Although the urinary tract is the most commonly affected site, malakoplakia has been reported in a number of other organ systems, such as the gastrointestinal tract, skin, neck, lungs, and central nervous system. When presenting in the urinary tract, patients often complain of dysuria, hesitancy, and

urgency, often in the context of a urinary tract infection. The presentation of malakoplakia in other organ systems results in symptoms referable to those systems, with a pulmonary presentation typically manifesting as one or more pulmonary nodules that may be detected asymptomatically.

The pathogenesis of malakoplakia is thought to be related to a defective response to bacterial infection, particularly impaired phagolysosomal activity by monocytes and macrophages- these cells are able to *ingest* bacteria but cannot *digest* them, and the partially digested bacteria accumulate in the cytoplasm of phagocytic cells, leading to an immune-mediated granulomatous response. The residual bacterial glycolipid provides a substrate for iron and calcium deposition within the phagocytic cells, leading to the formation of the histopathologically pathognomonic feature of malakoplakia- the basophilic inclusion body known as the Michaelis-Gutmann body. The most commonly associated infection in patients with malakoplakia is *Escherichia coli*; *Klebsiella* and *Proteus* species are less commonly associated.

Treatment of malakoplakia may consist of surgical resection for amenable lesions, particularly when the presentation of the disorder resembles malignancy. Antibiotic therapy directed at *Escherichia coli* is commonly employed. Reduction in immunosuppression may be required induce malakoplakia regression.

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