Pulmonary Calcifications: 
Seeing Beyond the Granuloma

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Learning Objectives

• Understand the pathogenesis of pulmonary calcifications
• Recognize different patterns of pulmonary calcification
• Identify the common causes of pulmonary calcifications

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Outline

• Pathology and pathogenesis of pulmonary calcification and ossification

• Benign calcifications
  – Nodules
  – Interstitial disease
  – Metastatic calcification

• Malignant calcifications
  – Calcified nodules
  – Ossified nodules

• Calcification mimics
Pathology of Pulmonary Calcification & Ossification

• Calcification represents deposition of insoluble calcium phosphate or calcium carbonate crystals in soft tissue.
• Ossification refers to calcium deposition within bone (collagen) matrix, forming mature trabecular bone with or without marrow formation.
• Calcification and ossification can involve the chest wall, pleura, lung parenchyma, hilum, mediastinum and vasculature. Here, we focus on the lung parenchyma.
Dystrophic Calcification

- *Dystrophic calcification* occurs in dying and dead tissue.
- Injured and dying cells are unable to maintain normal calcium homeostasis, resulting in elevation of intracellular calcium levels and calcium deposition.
- Serum calcium levels are typically normal.
- Dystrophic calcification typically results in a localized deposit and can occur in malignancy, granulomatous infection, inflammation and fat necrosis.
- The exact etiology of calcification in mucin-producing adenocarcinomas is unclear but is likely dystrophic calcification.
Metastatic Calcification

- Metastatic calcification is characterized by the deposition of calcium salts in previously healthy tissue and is associated with serum hypercalcemia.
- It is influenced by serum calcium and phosphate concentrations, alkaline phosphate activity, and local physiological conditions, especially pH.
- Excess serum calcium salts (calcium phosphate/calcium carbonate) derived from bone are required.
- These calcium salts can precipitate in tissues with a favorable local environment, such as alkaline pH.
- Stomach, kidneys, and heart can all be affected, but the lungs are most susceptible
  - The lung apices are the most common site due to the relative alkaline environment (decreased blood flow, better ventilation -> decreased CO₂).
Pulmonary Ossification

- Pulmonary ossification is a rare condition characterized by bone formation in alveoli and the interstitium.

- Exact etiology is unknown – serum calcium and phosphate levels are usually normal.
  - Unlike heterotopic ossification, serum alkaline phosphatase is usually normal.

- Two described patterns:
  - Nodular circumscribed form – characterized by lamellar bone deposits in alveoli. Commonly idiopathic, but may be associated with chronic pulmonary venous congestion.
  - Dendritic form – characterized by interstitial branching bony spicules. Associated with chronic interstitial fibrosis.
Benign Calcifications - Granulomatous Disease

- Granuloma is a focal inflammatory response characterized by an organized collection of macrophages
  - May have central caseous necrosis
  - Granulomas may calcify due to necrosis.
- Calcification is common after granulomatous infections, including
  - Mycobacteria (particularly tuberculosis)
  - Histoplasmosis
  - Other endemic fungi
  - Rarely, *Pneumocystis jiroveci*
- Calcification in granulomas can be central, punctate or lamellated.

Ancillary findings that suggest granulomatous disease include calcified mediastinal and hilar lymph nodes
  - Splenic calcifications are common in histoplasmosis.

*Right:* 73F with right lower lobe calcified granuloma (arrow) and calcified mediastinal lymph nodes (arrow).
Broncholith

• A broncholith represents a calcification within an airway.
• Broncholiths commonly occur when a calcified lymph node erodes into a bronchus
  • These are usually associated with prior tuberculosis or histoplasmosis.
• They can also result from aspiration of a previously calcified fragment, like bone.
• CT will demonstrate an endobronchial calcified nodule
  • May be associated with distal bronchiectasis, mucoid impaction or atelectasis.
• These are dangerous to remove as they may result in hemorrhage from bronchial arteries

70F with a small calcification within a right middle lobe bronchus. Note the distal bronchiectasis as well as a calcified right hilar lymph node.
Broncholith

- Potential complications of broncholiths include
  - Hemoptysis from vascular erosion
  - Bronchial obstruction with post-obstructive atelectasis or pneumonia
  - Rarely, bronchoesophageal fistula

Right: 60M with right lower lobe post-obstructive pneumonia after a calcified subcarinal lymph node ruptured into the right mainstem bronchus.
Varicella pneumonia

• Diffuse micronodular pulmonary calcifications can occur after severe varicella zoster pneumonia.
• Caused by dystrophic calcification of necrotic parenchymal foci.
• Manifests on imaging as numerous 1-5mm calcified pulmonary nodules.
  – Can simulate a miliary pattern
• Calcified nodules from varicella pneumonia are not associated with calcified lymph nodes.
Hamartoma

- Hamartomas are benign neoplasms composed of mesenchymal tissues such as cartilage, fat, connective tissue, smooth muscle and calcification.
  - Also known as pulmonary chondroma
- Typical CT findings are of a smooth, round nodule or mass.
  - Fat density is present on CT in about 60% of cases
  - Popcorn-like calcification (arrow) or central calcification is present in 25% of cases.
- Hamartomas with little fat and no calcification can be difficult to distinguish on CT from a primary lung malignancy or metastasis and may require tissue sampling.
- Carney’s triad is a rare syndrome characterized by the presence of:
  - Extra-adrenal paragangliomas
  - Gastrointestinal stromal tumors (GIST)
  - Pulmonary chondromas

Above: 50 year old man with a left lower lobe nodule containing popcorn calcifications, consistent with hamartoma.
Sarcoidosis

- Sarcoidosis can cause dystrophic pulmonary calcification due to pulmonary fibrosis and scarring, along with nodal calcification.
- Pulmonary features include perilymphatic nodules or peribronchial fibrosis with an upper lung predominance
  - With fibrosis, upper lobe volume loss is common
- Confluent fibrosis may form mass-like opacities surrounding the hila, referred to as progressive massive fibrosis (PMF)
  - These may calcify
- Lymphadenopathy is common in sarcoidosis and may calcify
  - Central, amorphous mediastinal and hilar nodal calcification ("icing sugar" nodes) are the most common pattern of nodal calcification in sarcoid.
    - A peripheral, "egg-shell" nodal calcification pattern can also occur.
- Silicosis is caused by inhalation of airborne crystalline silicon dioxide and appears very similar to sarcoidosis. PMF in silicosis is referred to as ‘complicated silicosis’.

63M with sarcoidosis and progressive massive fibrosis, which has calcified. Also note the calcified mediastinal lymph nodes.
Dendriform Pulmonary Ossification

- Dendriform pulmonary ossification (DPO) represents tiny foci of branching ossification within the lung
  - Generally seen in the lung periphery at the bases
- It may be seen sporadically or in association with pulmonary fibrosis
  - The strongest association is with idiopathic pulmonary fibrosis (seen in up to 29% of patients)
  - It has also been described in pneumoconiosis caused by exposure to rare earth metals
- CT appearance is peripheral reticulation with punctate or linear calcifications
- DPO may be detected on technetium-99m MDP bone scan as focal pulmonary uptake.

66M with a possible usual interstitial pneumonia-pattern fibrosis. CT at the lung bases demonstrates multifocal punctate peripheral calcified foci (arrows), representing dendriform ossification.
Amyloidosis

Amyloidosis is a group of diseases caused by deposition of an abnormal fibrillary form of a protein. There are several types:

- Amyloid light chain (AL) deposition – may be localized or systemic (associated with plasma cell dyscrasia)
- Serum amyloid A (AA) – caused by chronic systemic inflammation
- ATTR amyloid - seen either in hereditary amyloidosis (from a mutation in the TTR gene) or in senile amyloidosis (elderly patients).
- Almost all pulmonary amyloidosis is from AL disease.

Localized pulmonary amyloidosis is more common and typically manifests as solitary/multiple pulmonary nodules

- These calcify in approximately 50% of patients.
- Cysts may form, particularly cysts associated with nodules, thought to be related to airway obstruction
- The nodular form is typically not associated with systemic disease.

*Right: 77F with multiple calcified and non-calcified pulmonary nodules, biopsy-proven to represent amyloidosis.*
Systemic amyloidosis with pulmonary involvement is less common than the localized nodular form but is more commonly symptomatic, causing pulmonary hypertension and respiratory failure.

It is caused by interstitial and alveolar amyloid deposition, typically AL amyloid.

Imaging often shows septal thickening, sometimes with groundglass or consolidation

- Calcifications may develop within the affected lung
- Nodules are uncommon in systemic amyloidosis

Right: 41-year-old woman who presented with dyspnea and was found to have diffuse groundglass, septal thickening, and lower lobe consolidation, which calcified. Surgical lung biopsy demonstrated amyloid deposition, and the patient was found to have systemic AL amyloidosis.
Metastatic Calcification

- As described previously, metastatic calcification occurs in patients with abnormal serum calcium-phosphate product.
- This is most commonly seen in end-stage renal disease patients, who develop tertiary hyperparathyroidism.
- Much less commonly, metastatic calcification has been described after liver transplantation
  - Mechanism is believed to be metabolic alkalosis from citrate included in blood products – these patients receive large volume transfusions
- Metastatic calcification is typically asymptomatic, but severe, symptomatic cases have been described.

- Several different imaging appearances have been described.
- The most commonly seen form is **centrilobular opacities** at the lung apices
  - These range from ground glass to frank calcium density
Metastatic Calcification

- Alternatively, diffuse ground glass may be seen throughout the lungs
  - When atelectatic, the lung appears high density
  
- Localized forms may demonstrate dense calcification or focal ground glass

*Top right:* 51F with end-stage renal disease and chronic diffuse ground glass. Note the high density atelectasis on this non-contrast CT.

*Bottom right:* 67F status post liver transplantation, who developed this right lower lobe calcification after the transplant.
Metastatic Calcification

- 99mTc-MDP bone scans can confirm the presence of metastatic calcification.

- In this case on the right, a patient with end-stage renal disease developed a ground glass opacity in the left lower lobe. SPECT Tc-MDP bone scan shows corresponding focal uptake.
Pulmonary Alveolar Microlithiasis

- Rare disorder of unknown etiology characterized by intra-alveolar accumulation of calcifications (“microliths”)
  - Familial in approximately 50% of cases
  - Associated with a mutation in sodium-phosphate cotransporter SLC34A2. Phosphate accumulates in alveoli, with resulting calcium deposits.
- Serum calcium and phosphate are normal.
- It causes a progressive interstitial lung disease. There is no effective treatment, and patients may require lung transplantation.
- Imaging (radiographs and CT) demonstrate diffuse, lower lobe predominant calcified micronodules
  - Septal thickening may be seen at CT as well
Pulmonary Hemosiderosis

• Represents iron deposition in the lung secondary to recurrent episodes of pulmonary hemorrhage.

• Two types:
  – Primary – may be idiopathic or associated with vasculitis
    • Appearance: that of pulmonary hemorrhage, with diffuse groundglass and often septal thickening. May progress to pulmonary fibrosis.
    • Generally does not calcify/ossify.
  – Secondary – most commonly due to mitral stenosis
    • Micronodules or reticulation with a lower lung predominance
    • May lead to pulmonary ossification, with calcific-density nodules that may become confluent at the lung bases.
Malignant Calcification

• Calcification in pulmonary malignancy can occur in both primary lung cancer and metastases.

• Primary
  – Adenocarcinoma, typically mucinous
  – Squamous cell carcinoma
  – Large cell neuroendocrine carcinoma
  – Carcinoid

• Metastases
  – Mucinous adenocarcinomas, particularly of gastrointestinal origin
  – Thyroid carcinoma (papillary & medullary)
  – Osteosarcoma & Chondrosarcoma (true bone or cartilage formation)
  – Synovial sarcoma
  – Others
Mucinous Lung Adenocarcinoma

• Pathology specimens exhibit calcifications in 16% of lung cancers.
• Calcifications are present on CT in approximately 10% of primary lung cancers.
• They can be punctate or amorphous in appearance.
  – Be aware that eccentric punctate calcification is not a benign appearance.

Top right: 70M with multifocal mucinous lung adenocarcinoma manifesting as peripheral consolidations containing punctate calcification.
Bottom right: 60M with metastatic mucinous lung adenocarcinoma. Note the necrotic, partially calcified mediastinal lymph node conglomerate as well as partially calcified pulmonary metastases.
Metastatic Carcinoma

- Metastatic adenocarcinomas may display dystrophic calcification
  - This is particularly associated with mucinous adenocarcinomas of gastrointestinal origin
  - Other adenocarcinomas include breast and ovary (particularly serous)
- Papillary and medullary thyroid carcinoma metastases may calcify as well
  - Medullary thyroid cancer produces calcitonin, which raises serum calcium levels.

*Top right:* 58M with rectal adenocarcinoma and speckled calcifications in a right upper lobe metastasis as well as right paratracheal lymph node.

*Bottom right:* 38M with miliary metastases from medullary thyroid cancer, many of which are calcified. Also note calcified hilar lymphadenopathy.
Metastatic Sarcoma

- Sarcomas with osseous differentiation may produce bone-forming – ossified – lung metastases
- This is most commonly seen in osteosarcoma
  - Calcified nodules in these patients are not necessarily granulomas!

*Top right: 19F with osteosarcoma of the right humerus and calcified pulmonary metastases.*

*BOTTOM right: 81F with a myoepithelioma involving a right rib, which was resected. Over the next several years, the patient developed multiple calcifying nodules, presumed metastases.*
Metastatic Germ Cell Tumors

- Malignant germ cell tumors most commonly originate in the testes or ovaries, less commonly in the mediastinum.
- These tumors are unusual in that the primary and metastases may *differentiate* from primitive cells into more mature elements.
- The most common manifestation of this is growing teratoma syndrome, where the metastases of a non-seminomatous germ cell tumor differentiate into mature teratomas after chemotherapy.
  - These teratomas may then grow (they are not susceptible to chemotherapy) but demonstrate purely benign elements at pathology.
- The patient on the right has a germ cell tumor of the mediastinum and developed growing, calcifying pulmonary nodules.
  - Lung resection demonstrated ossification – presumably osseous elements from differentiating metastases.
Mimics of Pulmonary Calcification

• Not all high-density material in the lungs is calcification!
• Important mimics include:
  – Aspirated barium
  – Lymphangiographic contrast
  – Foreign bodies and embolized material
• Clinical history and distribution will help to differentiate these possibilities
Aspirated Barium

- Barium is commonly used as a contrast agent in video swallow examinations and GI fluoroscopy.
- Aspirated barium may appear as punctate or endobronchial foci of high attenuation, which may mimic calcified pulmonary nodules.
- Aspirated barium may persist for months or years after the aspiration event.
- This may mimic calcified granulomas or dendriform pulmonary ossification.
  - Features of acute or chronic aspiration in the lungs suggest aspirated barium.
  - Asymmetry, dependent distribution, and endobronchial foci may also assist with the diagnosis.

50M with lymphoma. CT of the lung bases demonstrates peribronchial consolidation in the left lower lobe, consistent with aspiration pneumonia. This study was performed soon after a swallow study and shows high-density foci in the left lower lobe, consistent with aspirated barium.
Lymphangiographic Contrast

- Lymphangiography is performed in patients with suspected (or known) chyle leaks or lymphatic malformations
  - Most commonly, this is a thoracic duct injury after surgery
- Lymphatic channels in the pleura may communicate with the lung
  - Lymphangiographic contrast may intravasate into lung tissue, particularly if normal lymphatics have been disrupted
- This may mimic dendriform pulmonary ossification or aspirated barium
  - History of lymphangiogram and tubular densities leading to the retroperitoneum are key to distinguishing these possibilities

Left: 77F status post left pleurectomy with chyloous left pleural effusion. Top image demonstrates extravasation of contrast during a lymphangiogram. Subsequent chest CT (bottom) shows contrast within the pleura and lung parenchyma.
Foreign bodies may be aspirated into bronchi or lung parenchyma

Catheter fragments, vertebroplasty cement, and embolization agents may embolize into the pulmonary arterial system

They key to distinguishing these from pulmonary calcifications is their location within bronchi or vascular structures

Top right: Embolized catheter fragment in a left upper lobe pulmonary artery.  
Bottom right: Embolized glue from thoracic duct embolization procedure in right upper lobe pulmonary artery branches.
Summary

- Calcifications in the lung may occur from benign and malignant causes. These may represent local processes or reflect an underlying systemic disease.
- Dystrophic calcification occurs in healed infections (e.g. granuloma), tumors (e.g. mucinous adenocarcinoma), and interstitial disease (e.g. amyloidosis)
- Ossification/chondroid matrix may be seen in benign processes (e.g. hamartoma) or malignancies (e.g. metastatic osteosarcoma)
- Metastatic calcification represents calcium deposition in tissues from an abnormal serum calcium-phosphate product
- Other dense materials such as barium and other contrast agents may mimic calcification
Summary – Patterns of Calcification

• Nodules
  – Granuloma, Varicella
  – Hamartoma
  – Amyloidosis
  – Primary lung cancer
  – Metastases – mucinous adenocarcinoma, thyroid cancer, osteosarcoma

•Interstitial thickening or fibrosis
  – Amyloidosis (systemic)
  – Dendriform pulmonary ossification
  – Sarcoidosis
  – Pulmonary hemosiderosis

•Ground glass
  – Metastatic calcification
  – Amyloidosis (systemic)
References

1. Pulmonary Calcifications: A Pictorial Review and Approach to Formulating a Differential Diagnosis. SB Amin, R Slate, T Lucien, H Mohammed. Current problems in Diagnostic Radiology 2010
3. Amyloidosis and the respiratory tract. JD Gillmore, PN Hawkins. Thorax 1999
7. Dendriform pulmonary ossification in patient with rare earth pneumoconiosis. HK Yoon, HS Moon, SH Park, JS Song, Y Lim, N Kohyama. Thorax 2005

Thank you!

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