

An Imaging Review Article on Pleura Pulmonary Calcification and its Impact

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ABSTRACT

The lungs as well as the pleura are common sites of calcification. Important causes of calcification of lung parenchymal are prior infections (like viral pneumonia, miliary Koch's), primary lung tumours and calcifying metastases to lung from carcinoma of breast, testes, thyroid and osteosarcoma. Lung parenchymal calcifications may also be seen in occupational lung diseases like coal workers pneumoconiosis.

Common causes of pleural calcification are tuberculosis, asbestosis, empyema and old hemothorax. Primary pleural

malignancy like mesothelioma and pleural metastases from carcinoma of breast, testes, thyroid and osteosarcoma can also calcify. While tiny calcifications are seen only on high resolution computed tomography [HRCT], larger calcifications are visible on routine chest radiographs as well. Ultrasound of the thorax does not demonstrate them satisfactorily.

As the calcifications involving the Lung and the Pleura can have grave significance especially in the setting of neoplastic conditions, it is important to know how they appear on some common imaging modalities.

Key Words: Tumoural calcinosis, Imaging, Radiology, MRI, X-Ray

INTRODUCTION

In quest of answers to find the cause of calcification processes involving the lung and the pleura, an approach based on the etiological factors appears rational, informative and satisfactory. The lung parenchymal shows calcifications as sequelae of prior infections. These infections could be due to viruses or due to bacteria like mycobacterium tuberculosis. Fungal infections too may manifest with calcifications. Primary tumors of the lungs like adenocarcinoma and small cell tumors too show calcifications. Lung metastases from primaries in breast, testes, thyroid and peripheral osteosarcoma too demonstrate calcifications. Lung parenchymal calcifications may also be seen in occupational lung diseases like coal workers pneumoconiosis. Commonest causes of pleural calcification are tuberculosis, asbestosis, empyema and old hemothorax. Primary pleural malignancy like mesothelioma and pleural metastases from carcinoma of breast, testes, thyroid and osteosarcoma can also calcify. Imaging modalities like plain radiographs and High Resolution Computed Tomography [HRCT], demonstrate the pulmonary as well as pleural calcifications satisfactorily.

THE PROCESSES AND DETERMINANTS OF PLEURO-PULMONARY CALCIFICATIONS

Pleural fibro-hyaline calcification and plaques are noted in about 1% of chest radiographs carried out as a routine in adults [1]. CT scan however demonstrates these calcifications in many more conditions like hamartoma [2], chondroma [3], carcinoid [4], lung carcinoma [5], metastatic calcifications following cardiac surgery in children [6], calcinosis following liver transplant [7], pulmonary alveolar microlithiasis [8], Amiodarone pulmonary toxicity [9] to name a few.

Pleural Calcification is commonly seen in Empyema, Tuberculosis, Hemothorax, Exudative pleural collections, Asbestos Exposure, Silicosis and Talc Exposure. Common causes of Empyema are Pneumonia, Septic emboli, Lung abscess, Bacterial Pneumonia like Staphylococcus aureus and Gram negative pneumonias. Pleural calcification is seen as radiopacity along the pleural contour [Table/Fig-1].

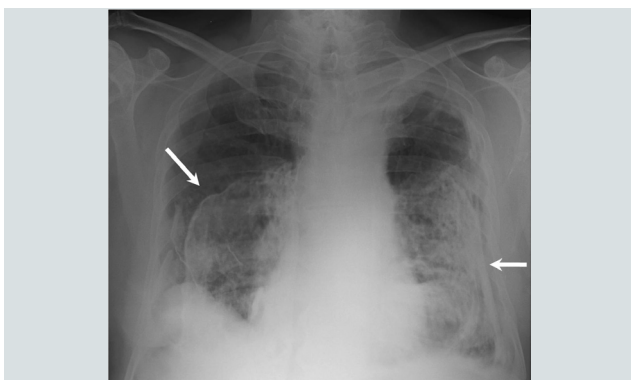
The stages in pleural calcifications in Para pneumonic Effusion are:

Stage 1 is an Exudative stage in which the capillary permeability is increased. Initially the accumulated pleural fluid is sterile. Most resolve with proper antibiotic therapy.

Stage 2 is characterised by fibro-purulent fluid containing bacteria and neutrophils. The fibrin deposition prevents resorption of fluid and leads to loculated collections.

Stage 3 occurs 2-3 weeks post initial effusion. There develops pleural fibrosis with entrapped lung. Dystrophic calcification finally develops after resolution of effusion.

In tuberculous effusion, there is rupture of sub-pleural caseating granulomas that gradually heal if adequately treated or if patient has good immunity; with fibrosis and ultimately develops dystrophic calcifications. As per newer research, it has been realized that lymphocytic alveolitis and pleural calcifications in non-occupational asbestos exposure confer protection against neoplasia [10]. Pulmonary calcifications are caused mainly by two mechanisms: the dystrophic form and the metastatic form [11, 12]. Despite the different aetiologies, it has been found that the pulmonary function and clinical manifestations are quite similar in both forms. It appears as well defined round or irregular radio-opacity within the confines of lung parenchyma [Table/Fig-2].



[Table/Fig-1]: Plain radiograph showing massive bilateral pleural calcification



[Table/Fig-2]: X-ray chest showing large right pulmonary and bilateral smaller nodal calcifications

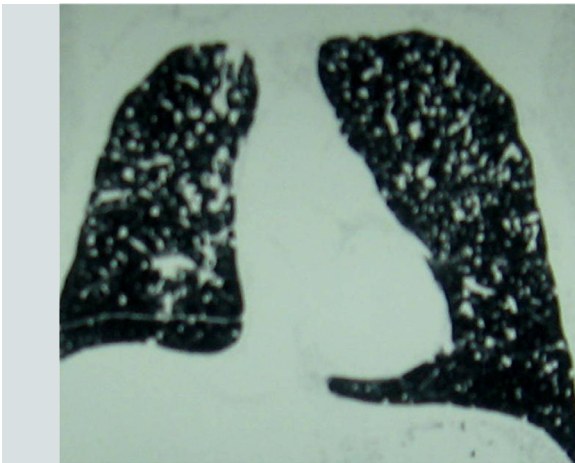
The term calcification refers to the deposition of calcium salts in tissues; whereas, the term ossification indicates calcium deposition in the collagen matrix or bone formation. These ectopic calcifications can involve the chest wall, pleura, lung parenchyma, hilum, mediastinum, and pulmonary vasculature. Calcium deposits may be limited or diffuse. Diffuse cal-

cification can be (a) metastatic, in which the calcium deposits occur in normal tissues, or (b) dystrophic, in which calcification occurs on injured lung tissue. The pathogenesis of these abnormalities is not fully understood, but hypercalcemia, hyperphosphatemia, alkalosis, and lung damage predispose to calcification and ossification. The physiological requirements for metastatic calcium deposition are the release of excessive calcium salts from bone and its transport through the circulation. Metastatic calcification may occur with normal or even low serum calcium levels; it is the elevated calcium-phosphate product that favors the process. In patients with metastatic calcification with a normal calcium-phosphate product, the presence of azotemia, an elevated parathyroid hormone, and exogenous vitamin D play a role. Metastatic calcification commonly occurs in chronic renal failure. Dystrophic classification frequently follows granulomatous infections (tuberculosis, histoplasmosis, coccidioidomycosis), viral infections (chicken pox and small pox), parasites (*Paragonimus westermanii* and *Pneumocystis jiroveci*), amyloidosis, coal and silica induced lung damage, pulmonary hypertension and vascular diseases. In sarcoidosis calcification can be either dystrophic or metastatic. Miliary mottling in Miliary Koch's is demonstrated in [Table/Fig-3] (CXR) and [Table/Fig-4] (HRCT). The pulmonary alveolar microlithiasis is well demonstrated in [Table/Fig-5] (CXR) and [Table/Fig-6] (HRCT). [Table/Fig-7] is an HRCT image showing calcific pulmonary metastases. At times pulmonary neoplastic masses can present with tiny calcifications within as shown in [Table/Fig-8].

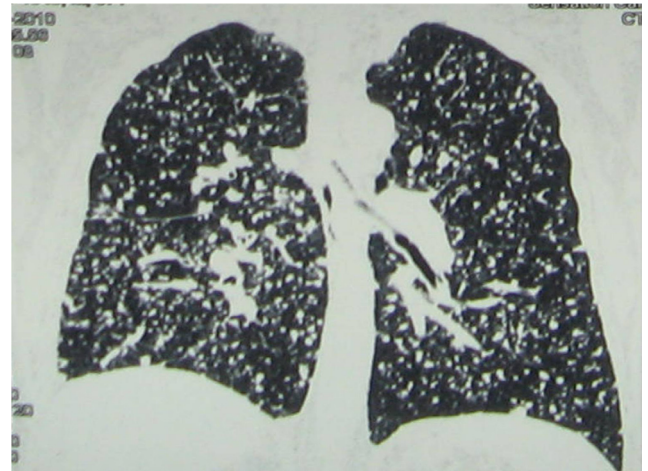
Metastases of carcinoma breast can be seen in lungs even after mastectomy [Table/Fig-9] and at times they too may calcify. Occasionally, calcified guinea worms can be seen in thoracic soft tissues as in [Table/Fig-10]. Masses involving thoracic wall like plasmocytoma [Table/Fig-11] and chondrosarcoma [Table/Fig-12] also show numerous calcifications. At times even the calcified hilar lymph node might be seen on routine screening [Table/Fig-13].



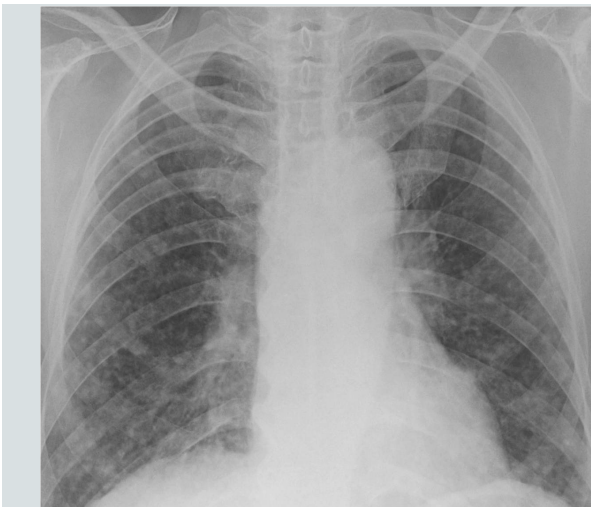
[Table/Fig-3]: X-ray showing miliary mottling in Miliary Koch's



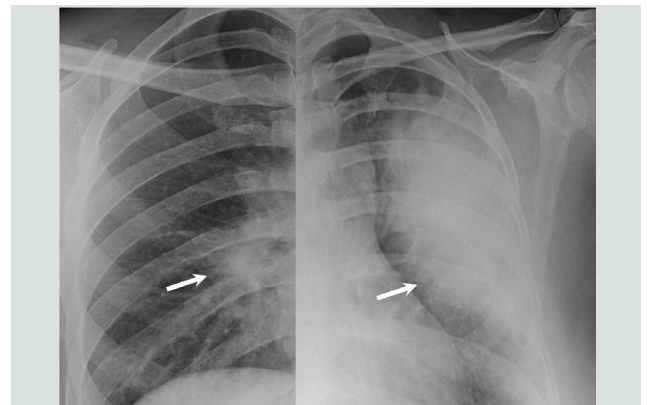
[Table/Fig-4]: HRCT showing miliary mottling in Miliary Koch's



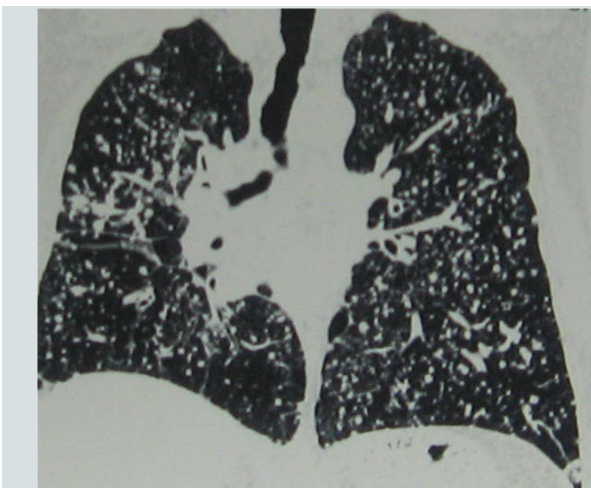
[Table/Fig-7]: HRCT showing pulmonary calcific metastases



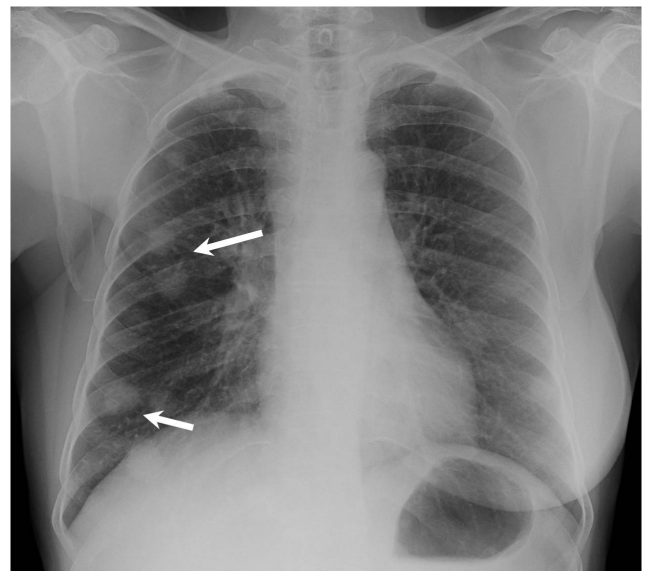
[Table/Fig-5]: X-ray showing pulmonary alveolar microlithiasis



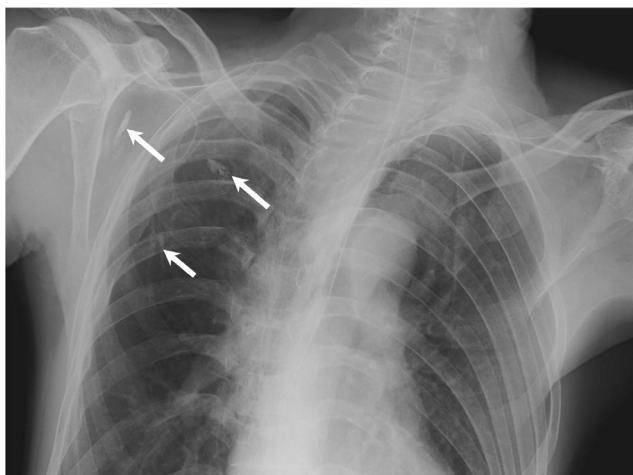
[Table/Fig-8]: CXR showing pulmonary neoplastic masses with tiny calcifications within



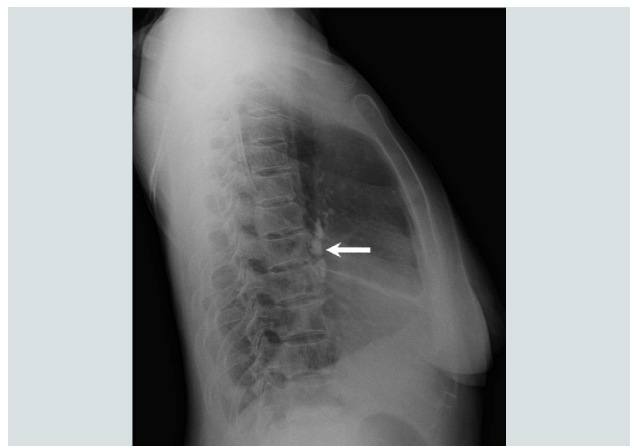
[Table/Fig-6]: HRCT showing pulmonary alveolar microlithiasis



[Table/Fig-9]: CXR showing pulmonary calcific metastases in a operated case of carcinoma breast



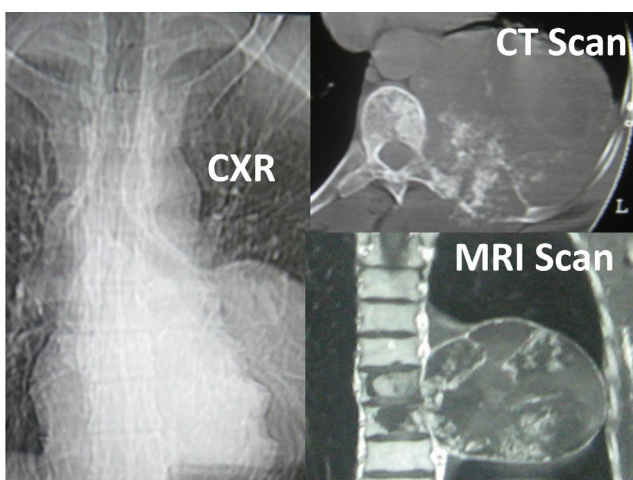
[Table/Fig-10]: CXR showing calcified guinea worms in thoracic soft tissues.



[Table/Fig-13]: CXR showing calcified hilar lymph node.



[Table/Fig-11]: Plain CT showing left solitary plasmocytoma with calcifications.



[Table/Fig-12]: CXR, CT & MRI showing calcifications in chondrosarcoma.

Morphological types of pleuro-pulmonary calcifications are:

1. Localized parenchymal calcifications e.g. Localized, usually benign, calcification in lung called 'popcorn' calcification that is seen in hamartoma. Calcified tuberculomas too have focal lesions.
2. Widespread calcified lesions in lung parenchyma are seen in infective conditions like tuberculosis and histoplasmosis. Occupational lung disorders may also show such presentations. Miliary Koch's and Pulmonary metastases too are the examples of this pattern.
3. Pentastomiasis occurs due to three arachnid parasites whose larva stages cause pulmonary pentastomiasis. i.e. *Linguatula serrata*, *Armillifer armillatus*, and *Porpcephalus moniliformis*. In pentastomiasis the chest x-ray shows numerous dense, discrete, crescentic or horse-shoe shaped opacities. Each opacity is about half a centimeter in diameter and represents a calcified nymph that adopts a semicircular posture when it dies. When seen end-on these shadows appear oval or linear and can easily be mistaken for cysticerci. Unlike cysticerci, they are only present in the lungs and not in the muscles. Calcified cysticerci are present in chest wall and in other muscles, and may resemble disseminated intra-thoracic calcification. Parenchymal and pleural calcifications also occur in *Paragonimus westermanii* pulmonary infections and are most likely related to calcified mummification of the parasites. Pulmonary and thoracic lymph node calcifications are seen in *Pneumocystis jiroveci* infections.
4. Pulmonary Alveolar Microlithiasis (PAM) is a genetic disease with an autosomal recessive trait caused by mutation of *SLC34A2* gene. The disease is found predominantly in Japan, Turkey and Italy and primarily af-

fects young people. The lower third of the lung fields are obscured by a granular sandstorm pattern of increased density caused by countless intra-alveolar microliths or calcospherites, which contain calcium and phosphorus. The appearance may be confused with alveolar proteinosis, but the sand-like granular opacity is diagnostic [12]. The long-term prognosis is poor even if the disease is diagnosed at the asymptomatic stage. No effective treatment exists.

5. Diffuse pulmonary ossification (DPO) is a rare disease characterized by diffuse small bone fragments in the lung tissue. It can be idiopathic or associated with chronic heart disease. The first case of this syndrome was described by Luschka in 1856. Now we recognize two types of DPO: dendritic and nodular [12]. Dendritic form is associated with history of pulmonary inflammation and fibrosis; whereas, nodular form is associated with chronic cardiac disease and pulmonary congestion. Once suspected the diagnosis can be confirmed by HRCT of the chest showing characteristic multiple punctuate and branching bone density lesions. Ossification can also be detected by using technetium-methylene diphosphate (Tc-MDP) bone scintigraphy. Bronchoalveolar lavage may reveal lymphocytes, eosinophils, macrophages, and giant cells. A lung biopsy showing characteristic interstitial branching bone spicules establishes the diagnosis of dendritic ossification. The nodular form usually displays intra-alveolar bone deposits without marrow elements. The pathogenesis is not known. Serum calcium, phosphorus, and alkaline phosphatase are normal. Transforming growth factor-B and bone morphogenic protein may play a role. Inter Leukin-4 and monocyte colony stimulating factor can transform human alveolar macrophage to osteoclasts, a cell important in bone remodeling. The disease mostly affects the elderly above the age of 60. Thus, it differs from alveolar microlithiasis which is a disease of the younger set. Regardless, most of the patients are asymptomatic; the diagnosis is suspected on routine chest radiography and confirmed by a lung biopsy. The disease is indolent and progresses slowly. There is no specific treatment. Early diagnosis will enable us to understand the disease and develop an appropriate treatment.
6. Calcification of hilar and mediastinal lymph nodes- It is usually irregular and amorphous. When caused by tuberculosis it is often associated with a small parenchymal nidus of calcium in the peripheral lung field; the combination is called Ghon complex. Rarely, only the rim of the hilar node calcifies; this is called eggshell calcification and is characteristic of silicosis, but may also occur in tuberculosis, sarcoidosis, and Hodgkin's disease after

radiation. It should not be confused with the crescentic calcium deposits seen in the dilated pulmonary arteries of chronic pulmonary hypertension. It may consist of a heavy central nidus with a lighter halo, giving rise to the characteristic target nodule. The calcified nodules that result from varicella pneumonia do not usually appear until two years after the infection, and are indistinguishable from histoplasmosis, pneumoconiosis and mitral stenosis. Pulmonary calcification from smallpox is now history and from herpes simplex virus a rarity. Occasionally, sarcoidosis may produce multiple nodular calcifications with or without hilar node calcification. The radiological picture may resemble alveolar microlithiasis. In sarcoidosis however, the calcification is confined to non-caseating granulomas, whereas, in pulmonary microlithiasis, the calcified stones are intra-alveolar.

HEALTH IMPACTS OF PLEURO-PULMONARY CALCIFICATIONS

The possible complications are functional disturbance, secondary infection, fistula formation and malignant change [1]. Medico-legally the calcified plaques of the parietal pleura represent an excellent sign of exposure to asbestos in a population [1]. In a study [10] conducted to see whether lymphocytic alveolitis and pleural calcifications in non-occupational asbestos exposure confers protection against neoplasia, it was found that none of those with neoplasia had alveolitis. The lymphocytes were mainly helper T-cells, and activation markers were more frequent among those with pleural calcifications. There was relative absence of pleural calcifications in cases with malignant pleural mesothelioma. This suggest that lymphocytic alveolitis correlates with pleural calcifications, whereas both are rarely present in patients with neoplasia.

Pleuro-Pulmonary Calcifications are thus mysterious strangers amongst us [12]. The availability of computerized tomography has expanded the differential diagnosis of calcifications involving the lung and pleural. Nevertheless, these still remain infrequent radiological oddities and are easily recognized during routine radiological examination. The conditions that cause thoracic calcification and ossification are usually asymptomatic and relatively benign. They are detected by chance on a routine chest x-ray examination or advanced imaging techniques. Bone scintigraphy and HRCT scan of with mediastinal images are superior in detecting calcification and ossification. A lung biopsy is needed to establish the diagnosis. Although, not much is known about their pathogenesis and treatment, they remain a source of clinical curiosity and stimulus to further research.

It must therefore be remembered that pleuro-pulmonary calcifications are a frequent finding in CT examinations of the

chest. In many cases, characteristic CT morphology and distribution of pulmonary and mediastinal calcifications may lead to a straightforward specific diagnosis of the underlying disease. In that respect, calcifications are often the residual finding of previous infections. Less often, they may be due to neoplasms, metabolic disorders, occupational exposure or previous therapy. Knowledge of the technical aspects of CT imaging is required to verify calcifications and avoid pitfalls [13]. The high attenuation on CT scan is most often caused by calcification, but may also be due to iodine, barium, or radiopaque foreign bodies [14].

Although, realms such as pathogenesis and correct management of this condition are still indistinct, they remain a source of clinical curiosity and stimulus to further research [15]. Traditional imaging modalities such as chest radiography and computed tomography are quite helpful in identifying as well as quantifying advanced calcification. Ultrasound can also demonstrate the superficial calcifications, but is of limited value for deeper lesions. Magnetic Resonance Imaging as well as Positron Emission Tomography is costly. But none of the imaging modalities can detect the early stages of this disorder and offer limited insight into the mechanisms of mineral dysregulation. Advances in optical molecular imaging are emerging as a promising tool that simultaneously detects pathobiological processes associated with inflammation and early stages of calcification in vivo at the (sub) cellular levels [16].

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