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Nobukata Kazawa
Department of Radiology &
Hematology, Kansai Medical
University, Fumino 10-15
Moriguchi City, Osaka
Prefecture, Japan

Kazuyoshi Ishii
Department of Radiology &
Hematology, Kansai Medical
University, Fumino 10-15
Moriguchi City, Osaka
Prefecture, Japan

Haruka Shimazu
Department of Radiology &
Hematology, Kansai Medical
University, Fumino 10-15
Moriguchi City, Osaka
Prefecture, Japan

Noboru Tanigawa
Department of Radiology &
Hematology, Kansai Medical
University, Fumino 10-15
Moriguchi City, Osaka
Prefecture, Japan

Bin Sawada
Department of Radiology &
Hematology, Kansai Medical
University, Fumino 10-15
Moriguchi City, Osaka
Prefecture, Japan

Corresponding Author:
Nobukata Kazawa
Department of Radiology &
Hematology, Kansai Medical
University, Fumino 10-15
Moriguchi City, Osaka
Prefecture, Japan

A case of the pulmonary nodular amyloidosis: Multiple calcified nodules exhibiting interval growth

**Nobukata Kazawa, Kazuyoshi Ishii, Haruka Shimazu, Noboru Tanigawa
and Bin Sawada**

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Abstract

In a 71-year-old woman, 2 years and 10 months ago, several nodular shadows with calcification were pointed out in both lung fields on the chest X-ray (CXR). After 1 year and 3 months, abnormal shadows were increased in size on CXR, then, she visited our hospital for detailed examination and treatment. On computed tomography (CT), several nodular shadows with partial calcification were observed in both lung fields. CT after 1 year and 1 month (6 months before), showed several circular to slightly lobulated mass ranging in diameter of 6-24 mm around the bronchovascular bundles of both lungs and the peri-lobular area such as subpleural peripheral zone and punctate to dendritic calcification also progressed compared to the previous CT.

The thoracoscopic partial left lung resection revealed 2 relatively well-defined nodular lesions with a yellow to brown cut surface. Histologically, the deposition of amorphous eosinophilic substance was found around/in the bronchi and blood vessel's wall of the lesions with partial calcification and/or ossification. A diagnosis of AL-type amyloidosis was made by the immunohistochemical findings. Pulmonary amyloidosis is radiologically classified into (1) nodular, (2) tracheobronchial, and (3) lung parenchymal type (diffuse alveolar septal type) according to the deposition patterns. Dendrite irregular calcification, irregular contours, different sizes 0.5-5 cm mean diameter, are characteristic radiological finding of the pulmonary nodular amyloidosis, and it is important to know that it occasionally shows the significant growth simulating malignant diseases.

Keywords: pulmonary amyloidosis, multiple calcified nodules, interval growth

Introduction

Usually, amyloid which histologically shows green birefringence on Congo-red stain and are visible under polarized light is deposited in an interstitial distribution with thickening of alveolar walls and blood vessels, interstitial tissues such as fat or bone marrow, rectal mucosa, pulmonary & renal interstitium, and ureter.

Literally, ultrastructural studies showed that early deposits occur as focal thickening of the basement membrane. Larger deposits formed small nodules. Organ parenchyma such as the respiratory system may be replaced by amyloid materials in severe forms. Hemorrhage such as purpura (particularly facial area), bleeding from increased fragility of blood vessels, peripheral neuropathy, carpal tunnel syndrome, congestive heart failure, nephrotic syndrome, malabsorption, and bone pain are relatively common clinical manifestations. Amyloid related cardiac disease, cerebral hemorrhage, and renal insufficiency lead to be occasionally fatal.

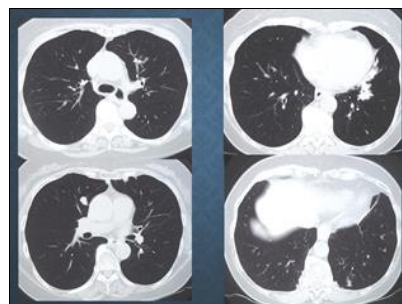


Fig 1

Case presentation

In October 2017, a 71-year-old woman firstly visited the primary care doctor because of the CXR abnormal shadows on annual medical check-up. A chest radiograph showed multiple lung nodular opacities bilaterally. She had a history of splenectomy for lymphoproliferative disorder (pathological diagnosis was unknown). On CT several nodular shadows with partial calcification were observed in both lung fields, which were firstly considered to be chronic/old inflammation (Fig.1 a, b). Gradual increase of the size and number of nodule and calcification were demonstrated after one year and 3 months on CXR (Fig. 2) and HRCT (Fig.3a, b), then she was referred to the respiratory medicine of our hospital for the purpose of detailed examination and treatment. The attempt of bronchoscopy with bronchoalveolar lavage was not sufficient to allow diagnosis. Pulmonary function test at that time indicated almost normal with a total lung vital capacity of 2.42 (105% of predicted), FVC 2.44 l (113.5% of predicted) FEV1.0 2.05l (119.9 of predicted), and a diffusing capacity of 12.37ml /mm per mm Hg (121.8% of predicted).

Nodular shadows with partial calcification were observed in both lung fields, which were considered to be chronic inflammation. On sequential CT, both shadows gradually increased in size and number after one and a half years.

In January 2020 after the imaging follow-up (2 years and 3 months), she referred the department of thoracic surgery for histopathological evaluation of multiple growing nodules. She had medical history of osteoporosis, hyperlipidemia, and surgical splenectomy for lymphoproliferative disease (pathological diagnosis was unknown). She had no habit of drinking nor smoking. Whole-body CT with IV contrast material revealed old vertebral compression fracture, adenomyomatosis of the gallbladder, several renal cysts, and mild wall thickening of the urinary bladder. Mild lymphadenopathy in the mediastinum and right supraclavicular fossa were observed. However, cardiac enlargement, hepatomegaly, renal swelling were not observed. No apparent pleural nor pericardial effusion were observed.

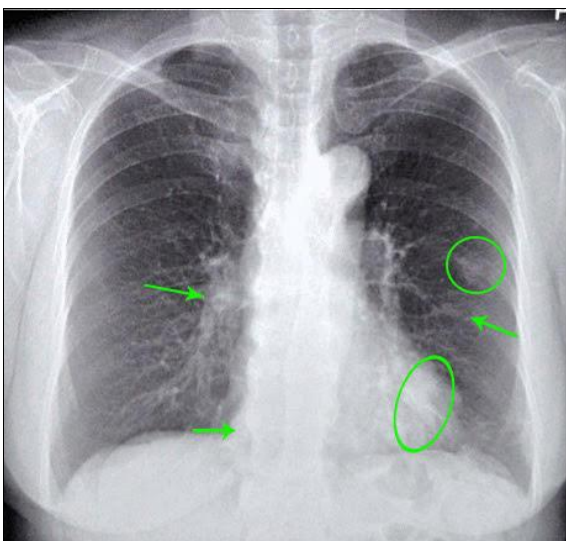


Fig 2

Her laboratory data were as follows. RBC 423x10⁴/ul Hb 12.9g/dl Plt 33.2x10⁴/ul WBC 6600/ul (Neu 54.7, Lymph 9.7, Eosino 9%), GLU 99mg/dl Na 141mEq/l K 4.1mEq/l

Cl 105mEq/l BUN 12mg/dl CRE 0.58mg/dl GFR Creat 77ml/min↓, UA 4.3mg/dl Alb corrected Ca 9.1mg/dl TP 7.3g/dl Alb 4.0g/dl A/G 1.21↓AST(GOT) 20U/l ALT(GPT) 14U/l ChE 524↑U/l T-Bil 0.6mg/dl ALP 210U/l γ-GTP 19U/l LDH 162U/l CK 75U/l TG 89mg/dl CRP 0.334mg/dl BNP 6.9pg/ml KL-6 504u/ml CEA 1.9ng/dl CYFRA 3.0ng/dl SCC 0.7ng/dl SLX 32ng/dl Pro-GRP 42.6pg/dl HCV (-) STS (-) TP (-) HIV (-) Serum AA amyloid (SAA) 21(>8) ug/ml.

On high-resolution computer tomography (HRCT), peri-bronchovascular, and peri-lobular (such as subpleural, peri-septal) oriented nodules and branching shadows were observed in both lung fields, most of which were accompanied by dendrite calcification. Granulomatous inflammation such as fungi or mycobacteria, granulomatosis with polyangiitis (GPA), pulmonary plasmacytoma, hamartoma, amyloidosis, and metastatic lung tumor, bronchogenic calcified carcinoma with lymphangitic spread, pulmonary hyalinizing granuloma, and inflammatory myofibroblastic tumors, etc. were suspected by these radiological findings. Thoracoscopic partial lung resection revealed 2 nodules of amyloid depositions in the left lung, exhibiting slight yellow to brown on the cut surface. Histologically, 2 relatively well-defined eosinophilic nodular lesions were found in the lung parenchyma partially accompanied by calcification and/or ossification. Eosinophilic substances were also found around the bronchi and in the walls of blood vessels. Cell atypia and necrosis suggestive of neoplastic growth were not found. DFS staining was also positive for eosinophilic materials. These findings were consistent with amyloidosis. AA amyloid was negative at the immunochemical histological evaluation. No chromosome abnormality, nor specific monoclonality of bone marrow specimens were found in a tumor-like lesion or an infiltrative process.

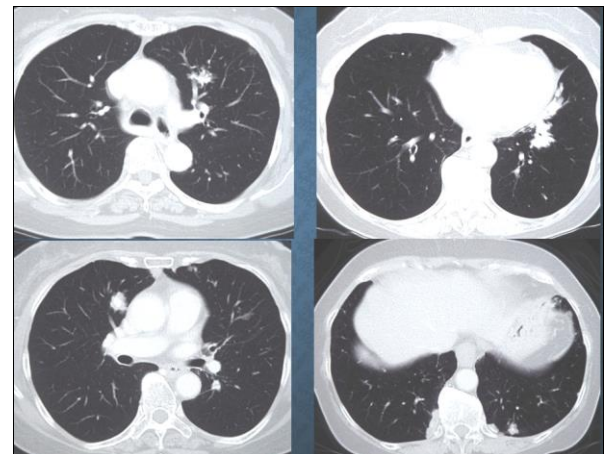


Fig 3

Discussion

Amyloidosis is a collection of disease entities that produce considerable morbidity and mortality and are increasing in prevalence. The imaging findings are diverse. Amyloidosis can involve any organ in the form of a focal, tumor-like lesion or an infiltrative process¹). About 20 different proteins can form amyloid fibrils but the two main types are AL amyloid, derived from the variable region of immunoglobulin light chains, and amyloid A (AA), derived from an acute-phase serum protein (SAA). In all types of amyloid, about 10% of the deposited material consists of a

glycoprotein, amyloid P, also derived from a serum protein. Other types of amyloid include transthyretin-derived (ATTR) amyloidosis, which affects mainly the heart and lung as senile systemic amyloidosis and is also involved in several familial forms of the disease; and hemodialysis-associated amyloidosis in which the deposits are formed mainly from β 2-microglobulin.

Systemic amyloidosis

Depending on the extent of the organism affected, there are systemic (amyloid is deposited in the interstitial space of multiple tissues and organs) and localized (amyloid is deposited in one or a few solitary lesions) form of amyloidosis. Localized form of amyloidosis has a significantly better prognosis than systemic ones 1, 2, 3). Lungs are often involved by localized one, AL type is 1/3 with multiple myeloma, macroglobulinemia, and B-cell lymphoma. It may also occur with lymphoplasmacytic and other forms of malignant lymphoma, particularly low-grade mantle zone lymphoma. Almost 90% of patients with AL amyloidosis are over 50, with an average age of 65 years, and there is a slight male predominance. In most patients, cardiac involvement which is often symptomatic and may be the cause of death occurs. Deposition in the kidney impairs renal function, bowel involvement may produce impaired motility, malabsorption, perforation, obstruction, or hemorrhage. Other organs affected include the tongue with macroglossia, sensory and autonomic nerves with neuropathy, and the skin. Even though it may not be apparent clinically, there is microscopic evidence of pulmonary involvement in about 75% of patients with AL amyloidosis [4].

Systemic amyloidosis (AA type) might be a reaction to several disease processes (rheumatoid arthritis (RA), inflammatory disease (Crohn disease), Reiter syndrome, ankylosing spondylitis, familial Mediterranean fever, Sjögren syndrome, systemic lupus erythematosus, dermatomyositis, vasculitis, chronic osteomyelitis, leprosy, cystic fibrosis, bronchiectasis, and it can be familial form [5]). Some tumors, particularly renal cell carcinoma and Hodgkin lymphoma, can also be associated with AA amyloidosis. For most patients, renal deposition and eventually renal failure is the significant effect, and AA amyloid is deposited in many tissues, in particular the liver and spleen, causing hepato-splenomegaly. In the lung, it usually results in diffuse interstitial infiltration.

In long-term dialysis patient, amyloid fibrils, principally composed of β 2 microglobulins (β 2-M), in the osteoarticular structures and viscera. Other subtypes such as gene mutation ATTR and senile TTR are also known.

Pathologically, amyloidosis was first described by Karl Rokitansky in 1842 consisting of the accumulation of pathological protein (amyloid) within both cells and extracellular space. It usually develops in the course of chronic inflammation or some neoplasms.

Leser (1877), Wild (1886) [1, 3, 4].

Small deposits of amyloid are mostly found in tissues associated with capillaries and arterioles in the lungs and brain [5, 6].

Hui *et al.* reported 48 patients with localized respiratory amyloidosis, of which 14 had tracheobronchial amyloidosis, 28 showed either solitary or multiple pulmonary nodules and six had a diffuse interstitial parenchymal pattern. Most of the patients with nodular amyloidosis were

asymptomatic, while those with tracheobronchial or diffuse interstitial amyloidosis had respiratory symptoms [7].

1. Nodular type: Nodule measuring 0.4 to 5 cm in diameter is formed (amyloidoma) in the periphery of the lung field or subpleural area. It is often identifiable in the alveolar interstitium at the periphery of the nodule. They may be single or multiple, occasionally significantly larger, the largest reported example being 15 cm. The mean age was 65 years old with no gender prevalence. They are often an incidental finding on chest X-ray and appear as well-defined, occasionally irregular nodule. On CT, they are depicted as a round to slightly lobulated mass with a clear boundary with slightly lobular contours. A non-calcified spiculated nodule resembling cancer may be observed. Cavitation is not accompanied in most cases. Most of the nodules were in the mid lung zone, with 80% (4/5 patients) being predominantly peripheral lung or subpleural area. Nodular amyloidosis can present as multiple lesions or, less commonly, as a single lesion with lower lobe and subpleural predominance. The amyloid nodules are usually well-defined with lobulated contours; they can vary in size from 0.5–15 cm and may gradually grow over time without regression. Nodular amyloidosis is usually localized to the respiratory system. Affected patients are generally asymptomatic and the amyloid nodules detected incidentally. Nodular pulmonary amyloidosis in association with bullous disease has been described in patients with Sjögren syndrome.

The diagnosis is usually established by percutaneous, transthoracic needle-core biopsy, but inaccessible nodules may require a thoracoscopic or open biopsy. However, hemorrhagic complications and air embolism have been described following transbronchial biopsy. It has been reported in XP that the subpleural space and the base of the lung are dominant, but there is no character in the regional distribution of nodules on CT such as the left and right, or upper and lower lungs.

Most of them have clear boundaries, but if they are irregular, it is difficult to distinguish them from adenocarcinoma.

The nodules are firm or hard in consistency with irregular and well-defined borders. The cut surface is gray or tan with a typical waxy consistency. Microscopically they consist of amorphous eosinophilic material producing structure-less aggregates. There is deposition in vessel walls and along alveolar septa, where these persist within the nodules. Focal calcification and ossification may be present. Mature plasma cells and lymphocytes may be present both within the amyloid and around the margins, together with histiocytic giant cells. Nodular parenchymal amyloidosis is relatively common form. These nodules are smoothly marginated and usually are slow growing. Although cavitation may occur, the cavitory lesion often shows disappearance and shrank [6]. As with the tracheobronchial form, calcification within the nodules is fairly common and is well depicted on HRCT. In these patients, HRCT can be helpful in assessing the nodules, as well as other manifestations such as randomly scattered cysts, bronchial wall thickening and bronchiectasis. Rarely, cystic lung disease can be seen in the absence of Sjögren syndrome. Immunohistochemically, the detection of amyloid material which appears inert, proteinaceous, homogeneous, acellular and eosinophilic; with Congo red staining, the amyloid proteins display green

birefringence under polarized light. Nodular form causes spherical or irregular lesions in the pulmonary parenchyma, indistinguishable from pulmonary metastases.

We described a two-year follow-up case with a nodular form of pulmonary amyloidosis.

Nodular pulmonary amyloidosis usually mimic other nodular pulmonary disorders, such as neoplastic and granulomatous processes [Table1].

Table 1: Multiple nodules (no cavities)

Metastatic tumor
Infection: Mycosis, Cryptococcosis, Actinomycosis, Parasite)
Sarcoidosis
Lymphoma
Silicosis
Pneumoconiosis
Amyloidosis COP (cryptogenic organized pneumonia)
Eosinophilic granuloma

On MRI, it usually showed low to iso signal on T1WI, and moderate to low signal intensity on T2WI, On DWI (Diffusion-Weighted Image), it demonstrated iso to low signal.

2. Tracheobronchial type: Thickening and calcification of the larynx and trachea and proximal bronchi, forms plaques or nodules in the epithelium of the respiratory tissue. narrowing the lumen 1-3) were observed. Therefore, obstructive symptoms such as dyspnea, stridor, hemoptysis, cough, atelectasis, and infection are accompanied related to airway stenosis or obstruction. Stent replacement, conservative excision, carbon dioxide laser ablation, and Nd: YAG (neodymiumyttrium-aluminum-garnet) laser therapy might be required for obstructive symptoms. In localized AL type, it is common in the trachea and larynx (60%: vocal cords 43.8%) calcification 65%). It also occurs in the sinuses, pharynx, oral cavity (submucosa), and lips. Systemic, non-airway lesions such as macroglossia are also seen.

Computed tomography shows slightly higher attenuation than muscle, calcification, and bone erosion.

The contrast effect is usually poor 8) like our cases.

The diagnosis is usually readily established by bronchoscopic biopsy and the main differential diagnosis are relapsing polychondritis, tracheomalacia, tracheobronchopathia osteochondroplastica sarcoidosis, and GPA. An association between amyloidosis and tracheobronchopathia osteochondroplastica has been proposed, Calcification and/or ossification occurring in amyloid deposits can produce appearances simulating tracheobronchopathia, and it may require careful examination in order to identify the residual amyloid [9])

The mean age of patients with tracheobronchial amyloidosis is 56.6-57.8 years old. The deposits of amyloid may be localized, diffuse, or multifocal and take the form of submucosal plaques or polypoid nodules that may be mistaken for neoplasms. Calcified amyloid deposition, which can be mural or endobronchial, resulting in sub-segmental collapse.

3. Diffuse interstitial form (diffuse alveolar septal type)

Diffuse parenchymal or alveolar septal amyloidosis is the least common form of this disease, but it is the most significant clinically. Broadly defined interstitial thickening

such as a lobular spacing wall, pleura, and the perivascular area is observed, and many granular and fine ((2-5 mm) nodules like sarcoidosis and agglutinated tuberculosis are involved. Traction bronchiectasis may be found (Cryptococcus). Consolidation is also possible representing an increase in reticular opacities, interlobular septal thickening, Pathologically, amyloid was found surrounds bronchi, arterioles, and lymph node

Infiltration into the heart, kidney, and liver is a prognostic factor, The median survival after diagnosis was 16 months in 1980-the 90s10). The differential diagnosis; lymphoproliferative disease, interstitial pneumonia such as RB-ILD, LCH, IgG4-related disease, etc. 7.9)

Table 2: Differential diagnosis of diffuse interstitial pattern

Lymphoproliferative disorder
Sarcoidosis
Pneumoconiosis
Primary lung cancer with metastasis
GPA, EGPA
RB-ILD
LCH
IgG4-related disease
LYG

The average age was 55 years old. With no gender prevalence. It progresses slowly in the clinic and causes little damage but in surgically resected cases, It may recur in a few years [8])

In diffuse interstitial disease, amyloid is present in the media of small blood vessels and the parenchymal interstitium. In the alveolar septum, its first deposits in the alveolar capillaries and basement membrane epithelium and then spreads to fill most of the stromal space of the alveolar wall.

Secondary types are found in LIP, Sjogren's syndrome, multiple myeloma, and plasma cell granulomas. Radiologically, amyloid deposits exhibit both inflammatory and neoplastic features including non-specific interstitial and alveolar opacities, predominantly basal and peripheral, well-defined nodules and confluent subpleural opacities.

Morphologically, amorphous irregular calcification is a characteristic finding of amyloid deposits. Mediastinal / hilar lymphadenopathy (calcification ++) can be seen, but there is almost no pleural effusion.

In alveolar wall and capillary damage, leading to impaired gas exchange. As with tracheobronchial amyloidosis, patients usually present with a cough, dyspnea and hemoptysis, or a combination of these symptoms.

In most systemic amyloidosis, diffuse deposition of amyloid occurs in the interstitium of the lung. Primary systemic disease may also be associated with pleural amyloidosis. There may be an associated giant cell reaction, causing a misdiagnosis of tuberculosis or another granulomatous disease even pathologically. Extensive deposition of amyloid in vessel walls is occasionally responsible for pulmonary hypertension and cor pulmonale. In diffuse parenchymal amyloidosis, typically identified in patients with primary systemic amyloidosis, reticular opacities, interlobular septal thickening, and small, well-defined nodules of 2 to 4-mm in diameter were observed predominantly in the subpleural regions [11]). Although, hemorrhagic diathesis is rarely a complication of pulmonary amyloidosis, instances of alveolar hemorrhage were

recorded, occasionally with fatal consequences. In senile systemic amyloidosis, the lungs are invariably involved together with the myocardium, due to deposition of the ATTR form of the amyloid fibril.

It occurs frequently, and the distribution is peri-bronchial, sub-pleural, lung parenchymal, interlobular wall thickening, and bronchial wall thickening. Unusually, it predominantly deposited in a lymph node ^[12] or pleural tissues ^[13].

Miscellaneous findings: Mediastinal and hilar lymph node enlargement can occur in isolation or as a component of systemic amyloidosis. Pleural involvement has also been reported, the appearance is similar to that of lymphoid interstitial pneumonia, and the two processes may coexist in the setting of Sjögren syndrome. 779 manifesting as pleural thickening and persistent pleural effusions ^[14]. At necropsy, about 20% have lymph node infiltration, but CT rarely shows lymphadenopathy. Differentiation from sarcoidosis, silicosis, granulomatous disease, after treatment state of lymphoma are needed.

Definitive diagnosis: The reference standard for diagnosing amyloidosis is histopathological confirmation of amyloid with Congo red staining under cross-polarized light; with this staining, amyloid demonstrates apple-green birefringence or positivity of DFS staining]. Ment and prognosis depend on the type and distribution of the disease, with localized forms usually managed conservatively and systemic forms treated with chemotherapy and anti-inflammatory agents. Patients with tracheobronchial disease may be treated with debulking or excision of the lesion(s). The broad differential diagnosis includes primary and metastatic malignancy and other benign lesions. The radiological differential diagnosis of bilateral multiple nodules, slowly gradual growing mass, progressive calcified lesions are listed up in table ^[3].

There is insufficient data on pulmonary localized amyloidosis that can take a good course with no treatment; in one report, the nodule gradually became enlarged over 14 years, finally occupying all lung fields ^[6]. Slow continual growth of more than 20 years on chest radiograph and asymptomatic cases has been reported ^[7]. As for the characteristic of pulmonary localized amyloidosis ^[15, 16, 17]

Table 3: Gradual growing tumor

Fungal infection (Cryptococcosis)
Hamartoma
Hyalinizing granuloma
Lung cancer (well-differentiated adenocarcinoma)
Low-grade lymphoma
Amyloidosis
Organizing pneumonia
Round atelectasis

Calcification

Calcification/ossification which is a characteristic finding of pulmonary amyloidosis was reported in 30 to 60% of cases. Dystrophic calcifications form in damaged areas of lung as a result of inflammation or infection, such as tuberculosis, or in areas of previous hemorrhage or infarct. Calcification can also form in neoplasms such as chondrosarcoma or osteosarcoma. Metastatic pulmonary calcification develops in areas of normal lung in patients with altered calcium and

phosphate metabolism, leading to calcium deposition in the lungs and other organs such as bones and kidneys. Hypercalcaemia secondary to chronic renal failure is the most common cause of metastatic pulmonary calcification. Other causes include primary hyperparathyroidism, skeletal metastases and multiple myeloma). Diffuse pulmonary ossification has been increasingly recognized since the advent of CT. Ashkenazi Jews Reticulonodular markings or ground-glass opacity and interlobular septal thickening in the lower lungs gaucher disease which is an autosomal recessive lysosomal storage disorder with deficiency of glucocerebrosidase. Deposition of lipid laden macrophages occurs in Gaucher cells in various organs. Diffuse reticular markings Interlobular septal thickening and DIP-like reaction are observed. CT images show mass like foci of calcified lung (arrows) ^[14]. Pathologically, pulmonary ossification can be classified as either nodular (NPO) or dendriform (DPO) based on the respective morphological appearances. Of the two entities, NPO is more common ^[15]. Nodular pulmonary ossification classically described with long-standing severe mitral stenosis, NPO can occur with any condition, leading to chronic pulmonary edema and pulmonary venous hypertension. Histologically, NPO is characterized by calcified or ossified intra-alveolar masses that are usually devoid of marrow elements or fat. On radiography HRCT, small, discrete, round calcified nodules 1–5 mm in diameter are present in the mid to lower lungs ^[15]. The differential diagnosis in these patients includes healed varicella infection or remote disseminated granulomatous infections such as histoplasmosis. Dendriform pulmonary ossification is postulated to be a reaction to chronic lung insult, resulting in metaplasia of pulmonary fibroblasts into bone. In contrast to NPO, DPO predominantly affects the alveolar interstitium and usually contains marrow or fat elements. DPO commonly develops in the setting of chronic inflammation, including interstitial fibrosis, and may also be seen in patients with a history of amyloidosis, cystic fibrosis, asbestos exposure or treatment with busulfan). DPO is most common in men in their fifth and sixth decades of life. The clinical course is usually indolent or slowly progressive. The chest radiographic findings of DPO include delicate branching linear opacities and small distinct nodules. The differential diagnosis includes fibrosis, bronchiectasis and lymphangitic spread of tumor.

Ground-glass opacifications represent an initial finding related to microscopic calcifications that were later followed by macroscopic calcific depositions.

Non-neoplastic—most common cause of calculi is hypercalcaemia in the setting of chronic renal failure. Other causes are conditions causing primary hyperparathyroidism, iatrogenic (following calcium therapy), Paget’s disease. 2. Neoplastic—parathyroid carcinoma, multiple myeloma, lymphoma/leukemia and metastases such as chondrosarcoma. Pulmonary ossification 1. Nodular type—in chronic venous congestion. 2. Dendriform type—in chronic lung insult with resultant fibrosis. 3. Bone forming neoplasms such as osteosarcoma. punctate and serpentine calcifications often located in areas of co-existing lung disease such as fibrosis. Both NPO and DPO can show uptake of bone scanning agent (e.g. technetium-99m methylene diphosphonate). Pulmonary alveolar microlithiasis Introduction and clinical features Pulmonary alveolar microlithiasis is a rare disease characterized by

intra-alveolar deposition of microliths, which consist primarily of calcium and phosphorous. The etiology is unknown, although recent studies have found an autosomal recessive trait caused by mutations of the SLC34A2 gene in affected patients 19). Pulmonary alveolar microlithiasis occurs in all age groups. Most patients are asymptomatic, and the diagnosis is established during imaging studies for other conditions. On radiography, diffuse calcified micronodules are present in both lungs, leading to a “sandstorm” appearance 20). These nodules are most prevalent in the mid to lower lungs, likely because of the increased surface area and blood supply. Interstitial thickening can also present, although this finding is clearer on HRCT. Radiography may also show a lucent sub-pleural line reflecting extra-pleural fat between the ribs and the calcified lung, described as “the black pleura sign” 20). HRCT shows discrete calcified micronodules scattered throughout the lungs. Apparent interlobular septal thickening and calcification may also be present, presumably the result of increased concentration of microliths in the periphery of the secondary pulmonary lobule. Pleural and pericardial calcification has also been described. The differential diagnosis includes PAP, sarcoidosis, pneumoconiosis, idiopathic pulmonary haemosiderosis, amyloidosis and metastatic calcification. Magnetic resonance imaging (MRI) can show increased signal intensity of the lesions on T1-weighted image. Microlithiasis can be definitively diagnosed through bronchoalveolar lavage or lung biopsy. Dendriform pulmonary ossification. HRCT image shows branching and punctate calcifications
 We supposed that the tumor wall became thinner and was crushed by pressure.

4. Calcification

Table 4: Tuberculosis (mycobacterium)

Tuberculosis (mycobacterium)
Histoplasma
Chickenpox(healed)
Parasite (Paragonimiasis pentastomiasis cysticercosis) primary and secondary hyperparathyroidism
Hypervitaminosis D
Sarcoidosis
Rheumatoid nodule
Hyalinzing granuloma
Silicosis
Pneumoconiosis Metastasis (e.g. Mucinous adenocarcinoma Osteosarcoma Chondrosarcoma Breast)
Mitral valve stenosis
Amyloidosis
Alveolar microlithiasis
Tumoral calcinosis/hyperostosis-hyperphosphatemia syndrome
Diffuse pulmonary ossification (DPO)
Prior hemorrhage or infarction
Pulmonary hypertension
Arterio-venous malformation.
Post-treatment such as radiation therapy

HRCT revealed that the black pleural line on a chest radiograph was caused by a fat-dense layer between ribs and the calcified parenchyma. MRI showed both lower zones with diffusely increased signal intensity on T1-weighted images caused by the accumulation of calculi. Calcification is also found in osteosarcoma, chondrosarcoma, mucin-producing gastrointestinal cancer, and metastasis of ovarian

tumor, but is characterized by fine punctate and dendritic calcification. Osseous metaplasia within the areas of calcification may be also present pathologically in pulmonary alveolar microlithiasis. The calcific particles of nodules were positive for bone scintigraphy. Functional imaging with fluorodeoxy glucose-positron emission tomography (FDG-PET) and amyloid scintigraphy with technetium-aprotinin have been shown to be high signal in the area of amyloid deposition) [21].
 The PET-CT is also a useful tool in decision making on the treatment of a localized nodular form of pulmonary AL-amyloidosis) [23, 24].

Gastrointestinal System

In both primary and secondary amyloidosis, the most commonly involved organ system is the gastrointestinal system, with the colon being the most frequent. Esophageal and gastric involvement usually manifests as dysmotility, wall thickening, and gastroesophageal reflux disease. These result from amyloid infiltration of the muscular and/or destruction of the Auerbach plexus. When the small intestine is involved, the most common finding is diffuse or nodular wall thickening. Abdominal pain, malabsorption, and hemorrhage are rare complications. Colonic biopsy specimens are positive in 80% of patients with systemic amyloidosis. but wall thickening (17%) and lumen dilation (15%) due to submucosal infiltration mainly in the colon, gastroduodenal. multiple cystic submucosal masses of the stomach, amyloidosis of the gallbladder, and soft tissue infiltration of the subcutaneous fat,
 Esophageal and gastric involvement usually manifests as dysmotility, wall thickening, and gastroesophageal reflux disease. These result from amyloid infiltration of the muscularis and/or destruction of the Auerbach plexus. Malabsorption syndrome and diarrhea occur when deposited in the small and large intestines with occasional gastrointestinal bleeding) [25].
 Contrary to the high pathologic specificity, radiologic findings are rare and nonspecific. The most common finding is colonic dilatation owing to a dynamic ileus and more rarely bowel wall thickening. Even more rarely, intramural bowel hemorrhage or perforation can occur.
 Splenomegaly is the finding associated with splenic involvement. This causes increased fragility, and spontaneous rupture can ensue with life-threatening consequences. The liver is also commonly involved, but radiologic signs are diffuse infiltration is the rule, which causes decreased attenuation at CT and hepatomegaly. Abnormal liver function is rare but is a poor prognostic sign, being associated with a less than 6-month life expectancy. Amyloid deposits in the liver parenchyma along the sinusoids or on the walls of blood vessels. There are few abnormalities in liver function, and hepatomegaly is also caused by the effects of congestive heart failure (50%). Heterogeneous focal or diffuse low absorption areas) [25], persistent contrast enhancement areas [26]), liver rupture due to rapid deposition (extremely rare) [27], and marked calcification. The portal vein or hepatic vein tends to narrow, and the bile duct may also show multiple stenosis. Splenomegaly is about 10%.Nodules and tumors in the spleen are rare
 Gallbladder wall infiltration can be difficult to diagnose, and the patient may receive the false diagnosis of low-grade chronic acalculous cholecystitis. Macroglossia can also

result from amyloid infiltration of the intrinsic muscles.

Cardiac System

In the chest, the heart is the most commonly involved organ. Amyloid infiltration is initially clinically silent. It can progress to a systolic dysfunction with wall thickening and low voltages at electrocardiography. Cardiac involvement is more common in primary amyloidosis and can remain silent until it manifests as heart failure. Congestive heart failure is the most common cause of death associated with one-third of primary amyloidosis and myeloma. Amyloid infiltrates the interstitium of the heart and causes heart failure, arrhythmia, and myocardial infarction^[12]. Te-99m pyrophosphate and prolonged delayed contrast enhancement MRI study^[26] are useful diagnostic methods. In cases where heart failure is indeed the presenting symptom, the average life expectancy is less than 1 year. The diffuse thickening of the left ventricular wall leads to decreased ejection fraction. The amyloid infiltration is often revealed by cardiac biopsy. The chest wall, paraspinal regions, and even the breast parenchyma can show mass like amyloidosis.

Genitourinary System

Renal involvement in pathologic specimens is quite common. However, renal function compromise is rare, usually manifesting as nephrotic syndrome. Focal lesions are rare and may calcify, mimicking a caliceal calculus. On US, amyloidosis is one of the rare causes of increased echogenicity and enlarged kidneys. Proteinuria, decreased renal function, cortical atrophy Small kidneys—amyloid contracted kidney-50%^[27].

Early stage is pyelonephritis-like heterogeneous renal swelling. Progression to end-stage renal disease is also rare.

Musculoskeletal System

Muscular infiltration can cause hypertrophy, chronic pain, and weakness and preferentially involves the shoulder girdle. When patients present, they usually appear to have well-developed shoulder musculature, which is counterintuitive given their usually advanced age and symptoms. This appearance is termed the shoulder-pad sign. Most commonly, however, musculoskeletal involvement manifests as synovial thickening that resembles pigmented villo-nodular synovitis but lacks the MR imaging findings of chronic hemorrhage and hemosiderin deposition. Late findings include cartilage erosion.

Other Regions

Involvement of the hematopoietic system and peripheral neuropathy do not have any radiologic findings, but their clinical complements can be corroborative evidence in support of the diagnosis. Finally, it is important to remember that amyloidosis can manifest as a focal mass-mimicking lesion and involve any part of the body, such as the mesentery, retroperitoneum, and supporting ligaments. It can infiltrate exocrine glands as well as lymph nodes and complicate the differential diagnosis. These mass lesions are not infrequently found to be calcified. The process is gradual; however, the molecular process and significance of calcification are unknown.

Localized or diffuse invasion of bone marrow, osteolytic/erosive lesions (may or may not have calcification), "blow-out" lesions, diffuse osteoporosis, bone

cortex thinning, trabecula. Amyloidosis around blood vessels (wall to lumen) causes infarction^[28].

Bilaterally symmetric lesions of the shoulder, wrist, hip, and elbow joints, near the joint trabecular bone lowering area, A large subchondral cyst with swelling of soft tissue Marginal erosion and osteosclerosis occur, but osteophyte formation is low.

In long-term dialysis patients, due to accumulation and inflammation of β_2 -microglobulin in the synovium

Osteochondrosis near the joint without calcification occurs (around the hip joint), and destructive spondylo-arthritis is observed in the cervical spine^[29].

In addition to muscle hypertrophy, it can also be deposited on tendons, ligaments, and tendon sheaths (carpal tunnel syndrome).

In conclusion, we experienced a case of multiple nodular pulmonary amyloidosis (AL type) in which an interval growth was observed in 2 years and 3 months.

The margin was slightly irregular, and calcification gradually progressed, and lung metastasis of mucinous adenocarcinoma were supposed in the differentiation, making preoperative diagnosis difficult. Although pulmonary amyloidosis is a very rare disease, it should be kept in mind as one of the differential diagnoses of multiple pulmonary nodules showing gradual growth. The most common findings in the HRCT are lobulated contours, calcifications, different sizes 0.5-15 cm, and slowly growing of lesions; cavitation is very rare.

Abbreviations

AA: serum amyloid A related Amyloidosis

AL: Light chain related Amyloidosis

ATTR : Amyloid include transthyretin-derived

CT: Computed Tomography

CXR: chest X-ray

DFS: Direct Fast Scarlet

EGPA: Eosinophilic Granulomatosis with Polyangiitis:

FDG : Fluorodeoxyglucose

FVC: Forced vital capacity

FEV1.0%: Percent Predicted Forced Expiratory Volume in One Second

GPA: Granulomatosis with polyangitis

HRCT: High Resolution Computer Tomography

IgG4 : Immunoglobulin G4

IV: Intra Venous

LYG: **Lymphomatoid Granulomatosis**

LCH: Langerhans Cell Histiocytosis

PET-CT: Positron Emission Tomography-CT

RB-ILD: Respiratory Bronchiolitis-Associated, Interstitial Lung Disease

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