CASE SERIES

COMPARING APPLES WITH APPLES. CLINICO-RADIOLOGICAL DIAGNOSIS OF MULTIPLE CYSTIC LUNG DISEASES.

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ABSTRACT

The presence of multiple cystic lung lesions in chest radiology entertains a long list of differentials including infections like tuberculosis, staphylococcal pneumonia & pneumocystis jirovecci pneumonia; non infectious causes e.g pulmonary Langerhan's cell histiocytosis, and diseases which mimic cysts including cystic bronchiectasis & emphysema. Multiple cystic lung disease requires a careful evaluation and can sometimes create a diagnostic dilemma both for pulmonologists and the radiologists. A case series of six different cystic lung diseases is presented with emphasis on characteristic radiological features, which in the presence of some clinical and biochemical parameters can help in making accurate diagnosis and may obviate the need for invasive lung biopsy. HRCT chest is now recognized as a benchmark in many diagnostic areas of respirology and the aim to present this series is to highlight the important diagnostic radiological features which should be recognized by the physicians working in respiratory medicine.

Key words: Diagnosis, high resolution computed tomography, multiple cystic lung disease.

INTRODUCTION:

A cyst is any round circumscribed space that is surrounded by an epithelial or fibrous wall of variable thickness and radiologically appears as a round parenchymal lucency having a well defined interface with the normal lung[1]. Multiple cystic lung disease (MCLD) is characterized by the presence of multiple cystic lesions on conventional or high resolution computerised tomography (HRCT). In comparison, other radiolucent lesions include cavities, pnematoceles, bullae and honey combing. A cavity is a gas-filled space, seen as a lucency within pulmonary consolidation, a mass or a nodule and a bulla is an enlarged emphysematous space, defined as a rounded focal lucency or area of decreased attenuation, >1 cm in diameter, bounded by a thin wall1. A pneumatocele is an approximately round thin-walled airspace in the lung most frequently caused by acute pneumonia, trauma, or aspiration of hydrocarbon fluid.[1]Sub-pleural location of cystic airspaces having comparable diameter characterized by well defined walls defines the presence of honeycombing[1,2]. Several mechanisms of cyst formation (bronchiolar check-valve mechanism, dilation of the bronchioles and vascular occlusion or ischemic necrosis) have been proposed; however, most remain speculative and only partially explain how very dissimilar disorders share MCLD as a common denominator.[3]MCLD may be suspected on plain chest radiographs; however HRCT imaging allows appropriate analyses of the precise diagnostic features of the multiple cysts and other possible accompanying abnormalities if present, with a minority requiring lung biopsy[4].

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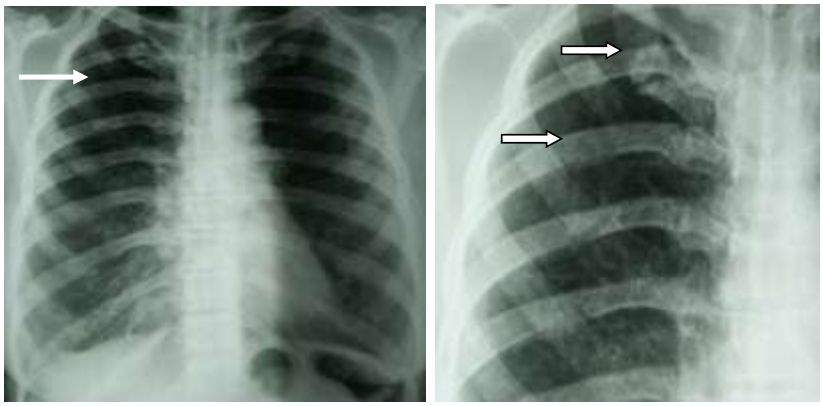
CASE 1: ***A Middle Aged Female Having Bilateral Multiple Diffuse Cystic Lung Disease with Prior History of Chylo-pneumothorax. Lymphangioleiomyomatosis.***

A 48 years old non smoker house wife, resident of Jhang presented with a five years history of gradually progressive dyspnea and chest pain. She was also suffering from allergic rhinitis & intermittent seasonal bronchial asthma and had history of right sided spontaneous chylo-pneumothorax requiring tetracycline pleurodesis 3 years ago. Her mother was asthmatic & she had two healthy children while her gynecological, drug & socioeconomic history were insignificant. On examination, she was alert, afebrile having a pulse of 90/m, BP 115/75 mmHg & respirations were regular 20/m with SpO_2 92% on room air (post exertion 85%). Chest examination revealed bilateral normal vesicular breathing with equal breath sounds intensity and polyphonic wheezes. Remaining general and systemic examination was normal.

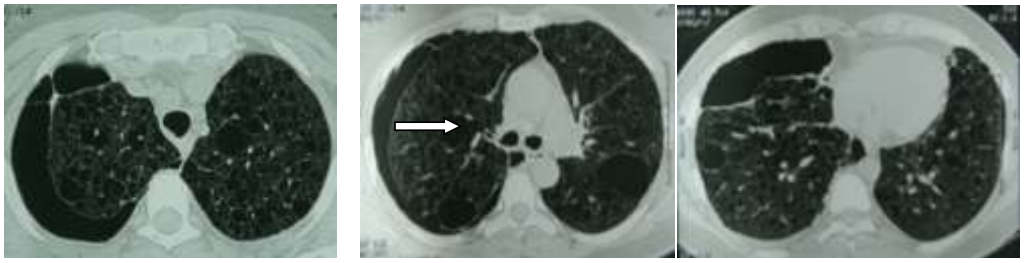
Initial chest radiograph (figure I-A and I-B) showed hyper inflated lungs, partial right sided pneumothorax, bilateral lower zone reticulation and shaggy right heart border. Arterial blood gas analysis showed ph 7.48, PCO_2 48 mm Hg, PO_2 66 mm Hg, HCO_3 42 mmol/L and O_2 saturation 92%. Office spirometric values included: FVC 1.02 L (41% predicted), FEV_1 0.88 L (42% predicted), FEV_1/FVC 86.3, PEF 3.34 L/s (56% predicted) and FEF_{25-75} 0.87 L/s (27% predicted) with good post bronchodilatation reversibility. Complete blood counts and serum biochemistry were unremarkable. Allergy panel showed raised serum IgE level to 261 iu/ml, peripheral blood eosinophils 6% and absolute eosinophils 468/cmm (normal 40-440). Ultrasonography of abdomen showed a hyperechoic cystic fatty nodular lesion most likely an angiomyolipoma (was also present in a 3 years old report). HRCT chest (figure II A, B, C and III) showed multiple variable sized thin walled cysts distributed uniformly throughout lung fields from apices to bases with intervening normal lung parenchyma and a right sided loculated pneumothorax. There were bilateral increased lung volumes without honey combing or any ground glass opacification (GGO).

In the light of her asthmatic symptoms, history of a chylo-pneumothorax, hepatic angiomyolipoma and characteristic thin wall diffuse cystic lesions having uniform distribution throughout lung parenchyma; she was diagnosed as having lymphangioleiomyomatosis. Her management included montelukast, inhaled long acting beta agonist (LABA) & inhaled corticosteroid (ICS) and was advised to arrange and take sirolimus (Rapamune) 2mg daily (not available in Pakistan). She received flu and pneumonia vaccine shots, was advised to avoid lifting heavy weights and to follow in pulmonary clinic with CBC & liver function tests (LFTs) every month and spirometry every 6 months.



A **B**

Figure I: (**A**) CXR-PA showing hyper inflated lungs, shallow right sided pneumothorax (arrow), bilateral lower zone coarse reticulations and shaggy right heart border and (**B**) closer view of right upper lung field revealing pneumothorax (arrows).



A **B** **C**

Figure II: HRCT chest axial images above the level of aortic arch (**A**) at the level of carina (**B**) and the basal regions (**C**) showing multiple rounded varying sized thin walled (barely visible to 2mm in thickness) cysts distributed uniformly throughout lung fields with intervening normal lung parenchyma and a right sided pneumothorax with internal septations.

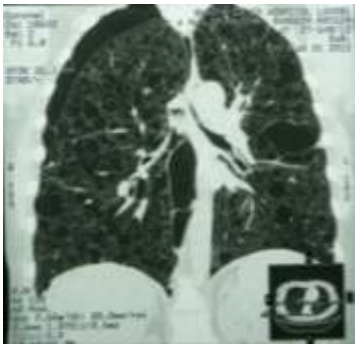


Figure III: HRCT chest coronal image showing bilateral multiple cystic air spaces of varying sizes distributed uniformly throughout lung fields and right sided pneumothorax with internal septations.

CASE 2: ***An Elderly Male having Bilateral Multiple Temporally Heterogenous Honey Comb Cysts of Peripheral Predominance. Idiopathic Pulmonary Fibrosis.***

A 70 years old male retired office worker from education department, ex-cigarette smoker (30 pack years) resident of Lahore, presented in emergency room (ER) with worsening of progressive exertional dyspnea and dry cough accompanied by generalized body weakness of two months duration. Two years ago, he was diagnosed as having idiopathic pulmonary fibrosis (IPF) and was given prednisolone and azathioprine. He was compliant to his treatment for 2 years and felt moderate relief in dry cough but noticed weight loss and gradually progressive decline in his exercise tolerance due to worsening in his dyspnea (MRC grade 4). Ten years ago he suffered from pulmonary tuberculosis for which he took complete treatment. He kept no pets or birds at home and his family, travel, drug & socioeconomic history were insignificant.

On examination, he was malnourished, apparently dyspneic but oriented and cooperative. He was lying in bed having a pulse of 100/min, temperature 38^{o}C, blood pressure 110/65 mm Hg, regular respirations of 42/min and SpO_2 84% on room air. Flapping tremors, palmer erythema and clubbing of fingers and toes were also present. Chest examination was consistent with right

sided tracheal shift, bilaterally reduced movements and vesicular breathing with coarse velcro rales from middle to lower parts of chest posteriorly with no change after coughing. Systemic examination was unremarkable except for reduced power of 4/5 in proximal muscles of upper and lower limbs. Chest radiograph showed bilateral reticular shadowing involving pericardiac regions and peripheral lung fields with loss of volume and tracheal shift towards right (figure IV). Arterial blood gas analysis values were: pH 7.35, PO_2 50, PCO_2 43, HCO_3 29, SO_2 86%. Further investigations included: CBC: Hb 13.8 g/dL, WBC 8.2 /cmm, platelets 350,000/mic.L, Hct 44%, serum biochemistry was unremarkable including: ALT 23u/L, AST 24 u/L, alkaline phosphatase 80 u/L and bilirubin 0.6 mg/dL, BUN 15 mg/dL and creatinine 1.2 mg/dL. HRCT chest was consistent with temporally heterogenous linear infiltrates of fibrotic foci and honey comb cysts of variable sizes located predominantly in peripheral lung regions especially in lower lobes (figures V, VI & VII).

He was hospitalized in pulmonology ward for five days with a diagnosis of respiratory failure due to idiopathic pulmonary fibrosis and malnutrition with proximal myopathy because of chronic steroids use. He received oxygen at 3 L/m via face mask (SpO_2 92%), paracetamol for pain relief and calcium and vitamin D supplementation. His previous treatment regimen including prednisolone and azathioprine were stopped and he was given pneumococcal and influenza vaccines. He was counseled regarding IPF having no definite remedy and was discharged on domiciliary oxygen along with advice on high protein nutrition to improve his weight and light rehabilitative exercises to the tolerable levels while breathing oxygen to help desensitize him for dyspnea.

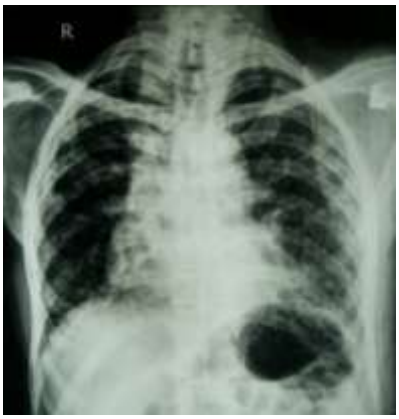


Figure IV: Bilateral coarse reticulo-nodular shadowing with bibasilar honey comb cysts and loss of volume (suggestive of IPF) and tracheal shift towards right (attributable to healed tuberculosis).

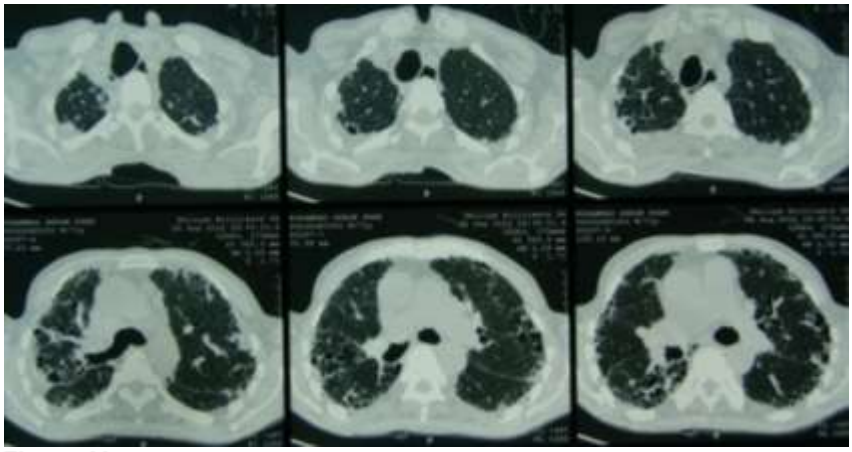


Figure V:.HRCT axial images showing irregular interlobular septal thickening and honey comb cysts located predominantly in peripheral lung regions especially in lower lobes with relative sparing of central lung regions.

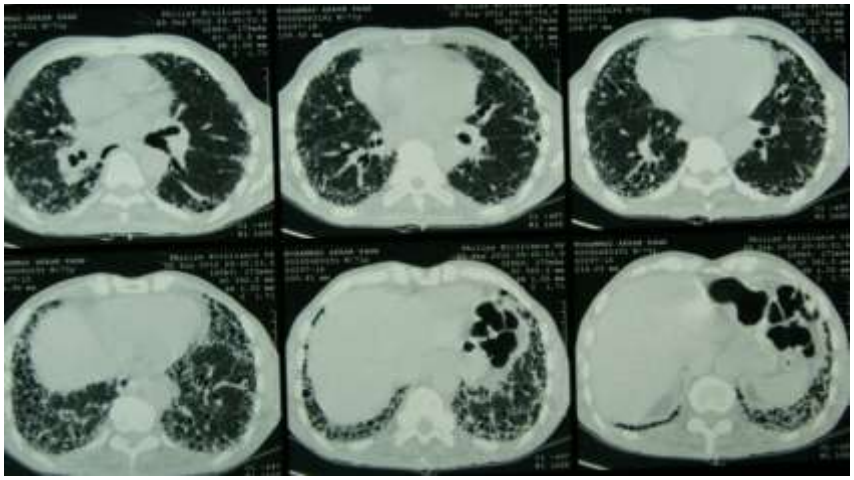
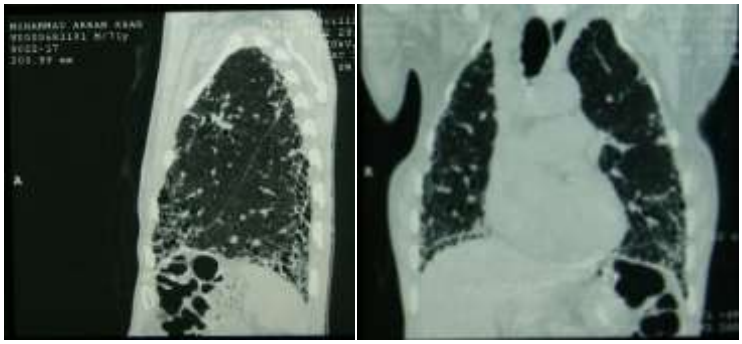


Figure VI:. HRCT chest axial images showing peripheral honey comb cysts with apico-basal gradient.



A **B**

Figure VII: HRCT chest (**A**) sagittal images (**B**) coronal images showing interlobular septal thickening and honey combing with peripheral distribution & relatively sparing of central lung fields.

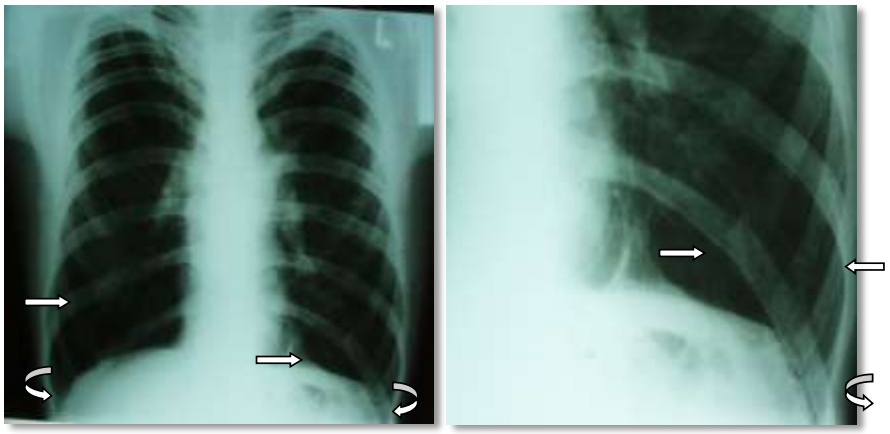
CASE 3: ***A Young Non smoker Male with Bilateral Multiple Pulmonary Parenchymal Lucencies having Invisible Walls. Alpha-1 Antitrypsin Deficiency Emphysema.***

A 35 years old non smoker male, landlord, resident of Bahawalpur, was seen in the pulmonary clinic, with a history of progressive exertional dyspnea and occasional wheezing of six years duration. In the past, he was never hospitalized for any medical or surgical ailment. He was taking treatment for asthma but experienced minimal symptomatic relief. He was married, with one male healthy child of 2 years age and the family history for any chronic lung or liver disorder was negative. On general physical examination, he was alert & cooperative, afebrile with pulse 88/m, blood pressure 112/75 mm of Hg & respiratory rate was 18/min with SpO_2 95%. Chest examination was consistent with signs of hyperinflation including fullness of supraclavicular fossae; anterior bulging with prominent sternal angle, widened costal margins and poor excursion of diaphragm, bilateral wheezes & occasional basilar inspiratory rales. Remaining general and systemic examination was unremarkable. Laboratory evaluation showed a normal CBC, BUN, creatinine & normal electrolytes. Chest radiographic findings included hyper inflated lung fields, & increase lucencies in the lower zones (figure VIII A and B). His office spirometry was carried out that showed very severe obstruction without any significant reversibility post BD. and the values included: FEV_1 1.14 L (30% pred), FVC 4.37 L (96% pred), FEV_1/FVC ratio 26.1%, PEF 3.36 L/s (36 % pred), FEF_{2575}0.40 L/s (9% pred), SVC 4.51 L (99% pred).

His further investigations showed very low serum alpha-1 antitrypsin level 0.04 g/dl = 6 µmol/L (normal level 0.1- 0.33 g/dl) and normal serum IgE level 30 ng/ml. Repeated alpha-1 antitrypsin level was again low (0.03 g/dl = 5 µmol/L). LFTs, ECG and ultrasonography of the abdomen, especially the hepatobiliary system were normal. ABG analysis revealed pH 7.39, PO_2 92 mmHg, PCO_2 36 mmHg and HCO_3 24 mmol/L. He covered 350 meters distance without any breaks in his six minute walk test and was maintaining $SpO_2$90-94% on room air without any desaturation post exertion. HRCT chest was consistent with pan lobular emphysema mostly involving the lower lobes (figure IX, X-A and X-B). His diffusion capacity for carbon monoxide (DLCO) was reduced to 40.3% of its predicted value, again suggestive of loss of gas exchange tissue/lung parenchyma due to advanced emphysema. His serum for genetic testing was sent to a German volunteer centre and was found to be negative for the three common mutations M, S and Z (kits available) and it was concluded that he had some rare unidentified mutation. In the light of the above investigations, he was finally diagnosed as suffering from pan lobular emphysema due to severe alpha-1 antitrypsin deficiency leading to very severe COPD.

He was given supportive treatment for COPD and was started with weekly intravenous augmentation therapy with alpha-1 antitrypsin (imported from Germany) and received his first

weekly dose of 3g (60 mg/Kg body weight; Prolastin®) infusion. After he received 4 weekly doses, his alpha-1 antitrypsin level was performed that was well within the protective threshold. Besides, he was further advised to consider contacting a regional lung transplant center in the near future.



A **B**

Figure VIII: (**A**).CXR-PA: Hyperinflation, prominent central pulmonary vessels with peripheral pruning, vertical cardiac shadow, lower zone lucencies (straight arrows), diaphragmatic depression and scalloping/prominence of its muscular strips causing pseudo-blunting of costophrenic angles (curved arrows); (**B**) closer view of left lower hemithorax.

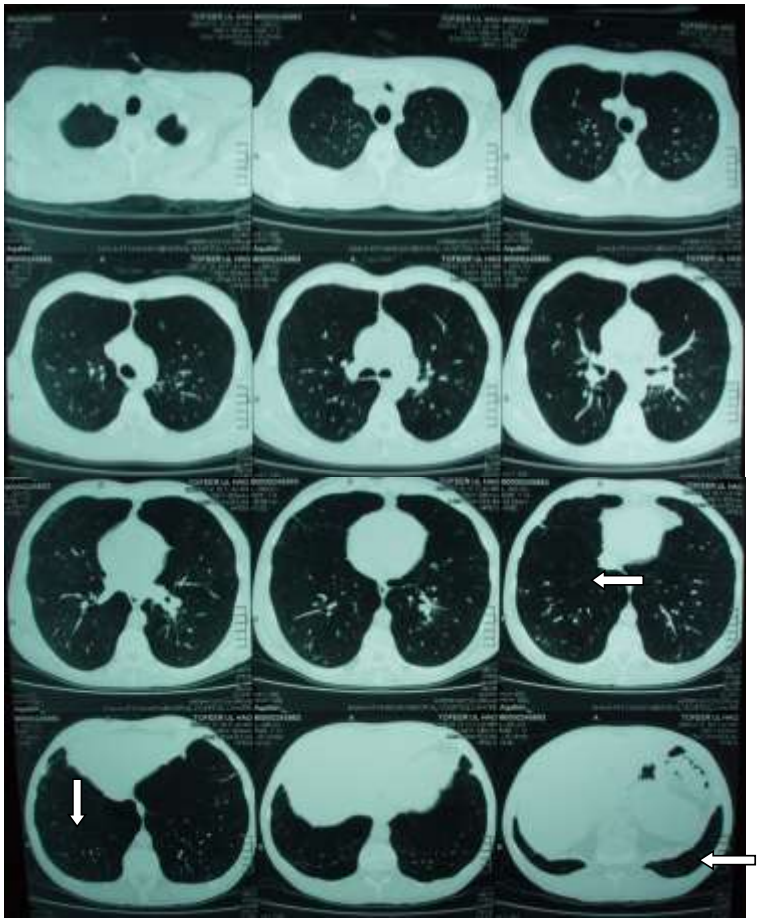


Figure IX: HRCT axial images showing pan lobular emphysema: widespread hypo attenuating spaces with very thin/barely visible walls (especially in lower lobes; white arrows) due to loss of lung parenchyma and decreased vascularity with apparently preserved upper lobes attenuation.

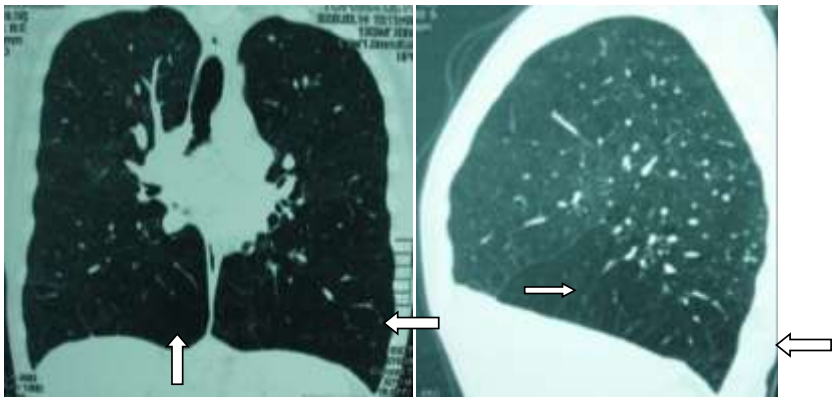


Figure III: HRCT chest (**A**) coronal image and (**B**) sagittal image showing pan lobular emphysema with lower lobes predilection (low attenuation lesions with paucity of blood vessels; white arrows) and low lying flat diaphragm.

CASE 4: ***A Middle Aged Male Cigarette Smoker with Bilateral Multiple Thin Walled Pulmonary Parenchymal Cysts. Emphysema due to Tobacco Smoking.***

A 59 years old male shop keeper, active cigarette smoker (40 pack years) resident of Lahore presented in pulmonology OPD after being referred from the cardiology department due to dyspnea that was out of proportion to his coronary heart disease. He revealed history of long standing cough with mucoid sputum production, and gradually progressive exertional dyspnea (MRC grade 3) of three years duration but no orthopnea or paroxysmal nocturnal dyspnea. His family, drug, travelling & socioeconomic history were not contributory. On examination, he was oriented and cooperative and had no respiratory distress at rest. He was sitting upright and had a pulse of 88/min, temperature 38^{o}C, blood pressure 125/78 mm Hg, regular respirations of 24/m and SpO_2 90% on room air. Chest examination was consistent with centrally placed trachea, reduced movements and breath sounds intensity on both sides and vesicular breathing with sibilant wheezes all over. Systemic examination revealed no abnormality except soft heart sounds.

CXR-PA view (figure XI) demonstrated upper and middle zones being more lucent compared to the lower zones, left lung apex showing lucent lesions with linear markings and bilateral generalized prominent bronchovascular markings. His recently obtained laboratory investigations including CBC, BUN, creatinine, lipid profile, liver function tests and urine routine examination were within the normal limits. ABG values included: pH 7.36, PO_2 82, PCO_2 36, HCO_3 24, SO_2 94 %. His post bronchodilator office spirometry (FEV_1/FVC 66, FEV_1 44% pred) was consistent with the diagnosis of severe COPD. HRCT chest (figures XII, XIII, and XIV) revealed centrilobular lesions of low attenuation of variable sizes with very thin walls having predominant location in upper lobes consistent with centrilobular emphysema. He was counseled for smoking cessation with verenicline and ICS+LABA aerosol inhaler and low dose oral theophylline & was advised for yearly influenza and pneumococcal vaccination (PCV 13 once followed by PPV 23 after 8 weeks and was advised booster of PPV 23 after 5 years).

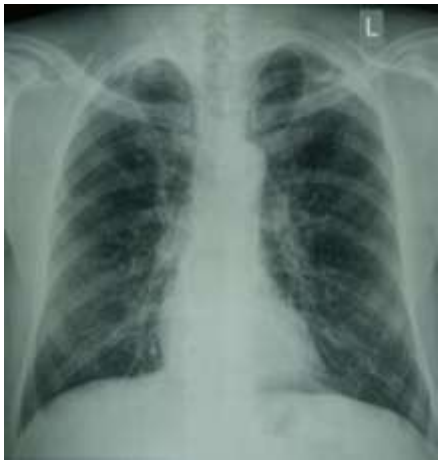


Figure XI: Chest radiograph demonstrating upper and middle zones being more lucent compared to the lower zones with accentuation of peripheral lung markings as a consequence to chronic bronchitis.

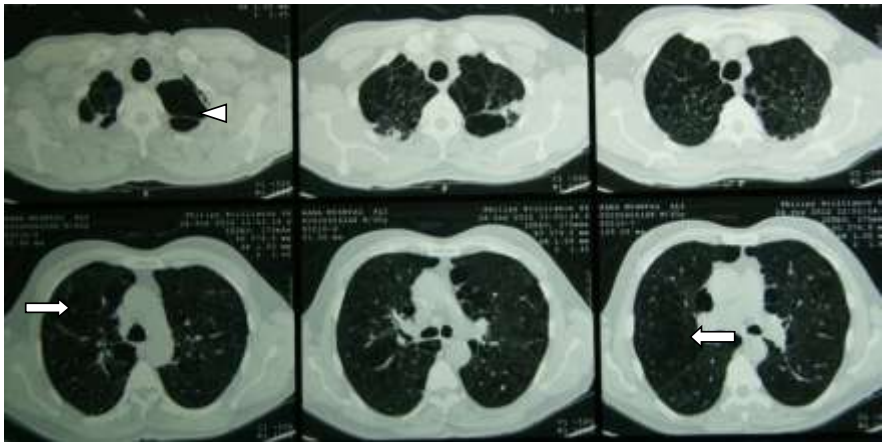


Figure XII: HRCT axial images of centrilobular emphysema showing centrilobular areas of low attenuation having variable sizes (>1cm are bullae; arrow head) with imperceptible walls. Sub-pleural emphysematous areas are paraseptal emphysema (white arrows).

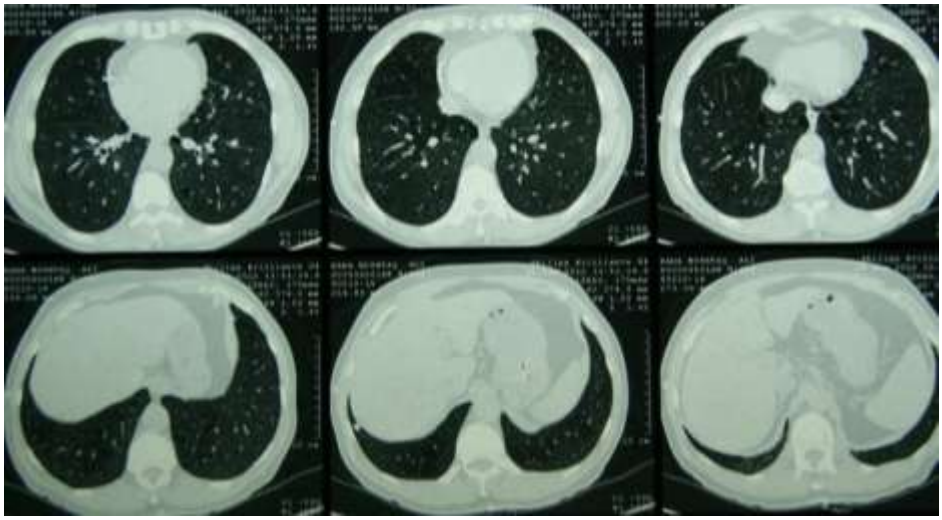
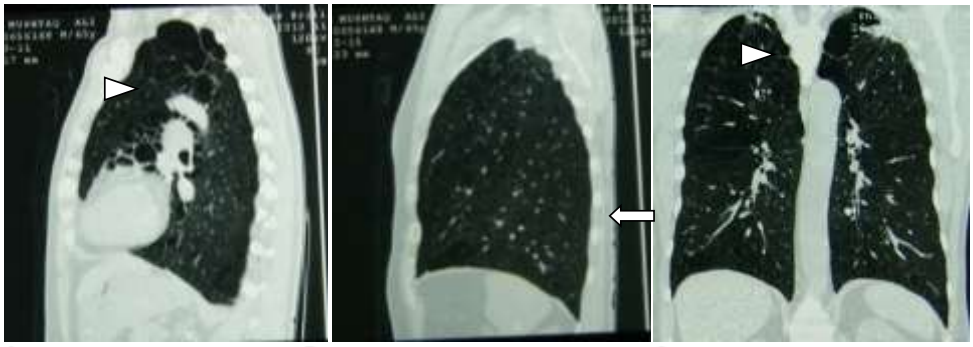


Figure XIII: HRCT axial images showing centrilobular emphysema relatively sparing the lower lobes (compared to the figure XI) with intervening normal lung parenchyma.



A **B** **C**

Figure XIV: HRCT chest sagittal images (**A** and **B**) and (**C**) coronal image showing centrilobular areas of low attenuation lacking visible walls (centrilobular emphysema) with predominant upper lobes distribution (arrow heads). There is relative preservation of lower lobes showing normal lung parenchyma (arrows).

CASE 5: ***A Middle Age Male with Sjögren's Syndrome having Bilateral Thick Walled Cysts having Random Distribution. Lymphoid Interstitial Pneumonia.***

A 45 years old male tailor by profession, ex-cigarette smoker, resident of Burewala presented in ER with one week history of worsening exertional dyspnea, cough with sputum and fever. Two years ago, he was diagnosed as having Sjögren's syndrome (anti SS-A/Ro positive; having dry mouth & eyes, fatigue, exertional dyspnea of MRC grade 1-2 and joint pains) and was on prednisolone, hydroxychloroquin and azathioprine as advised by his rheumatologist. There was also history of gradually progressive exertional dyspnea for the last one year which was now of

MRC grade 4 for the last two weeks. On examination, he was obviously dyspneic having a pulse of 100/m, temperature 39°C, BP 130/80 mm Hg, regular shallow respirations of 38/m and bed side SpO_2 82% (on room air). He was centrally cyanosed and clubbed. Respiratory system examination was consistent with bilateral vesicular breathing, wheezes and coarse crackles throughout the chest. Systemic examination revealed loud P2, mild epigastric tenderness and weakness (4/5) of proximal muscles of lower limbs. Chest radiograph showed cystic lesions with bilateral loss of lung volumes and enlarged cardiac silhouette (figure XV). Arterial blood gas analysis was consistent with type I respiratory failure & values included: pH 7.36, PO_2 58, PCO_2 42, HCO_3 20, BE 4.1, SO_2 84 %.

He was hospitalized in pulmonology unit and was managed with oxygen inhalation at 2 L/m (SpO_2 92%), salbutamol nebulization& ceftazidime while continuing his previous treatment. Further diagnostic work up included CBC: Hb 12.8 g/dl, WBC 16.5/cmm, platelets 358,000/mic.L and Hct 40.2%. Serum biochemistry included: ALT 34u/L, AST 35 u/L, alkaline phosphatase 80 u/L and bilirubin 0.5 mg/dl, BUN 14 mg/dl and creatinine 1.1 mg/dl. Serology for hepatitis B and C were negative as was HIV screening. Echocardiography revealed dilated right sided chambers, mild tricuspid regurgitation with normal left atrium and ventricle. BAL from right upper lobe showed 80% lymphocytes and 20% polymorphs with negative staining for Langerhan's cells, no atypical cells and negative fungal smear, Gram and ZN staining with no growth on pyogenic culture.

HRCT chest showed cysts with well defined walls having random distribution with predominant involvement of central portions of lungs mostly involving upper lobes especially on the right side with interspersed normal lung parenchyma. Lower lobes were relatively spared and peripheral areas of Ground glass opacification (GGO) and reticulonodular opacities were also seen (figures XVI and XVII). Final diagnosis in the light of above investigations was cor pulmonale due to chronic respiratory failure secondary to bilateral cystic lung disease most likely lymphoid interstitial pneumonia based on BAL lymphocytosis in the presence of typical cystic radiological shadowing, unlike other patterns of interstitial lung disease found in patients with Sjögren's syndrome. He was discharged on supportive treatment along with domiciliary oxygen after two weeks of treatment and was advised regular follow ups in pulmonary outdoor department.

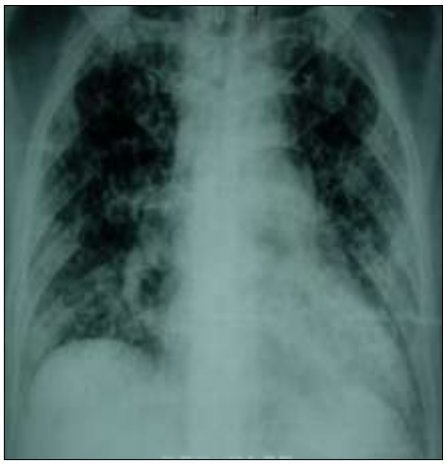
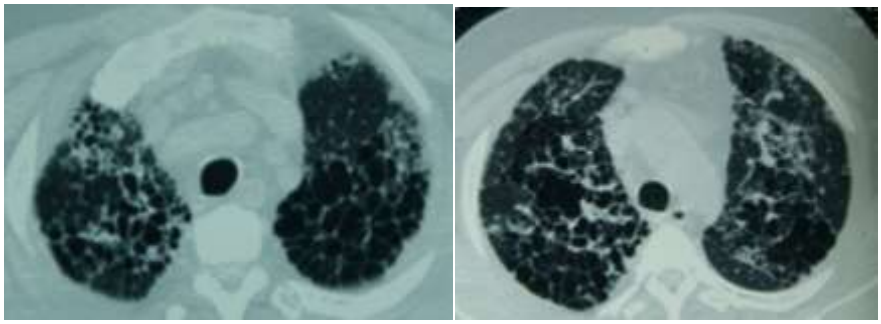
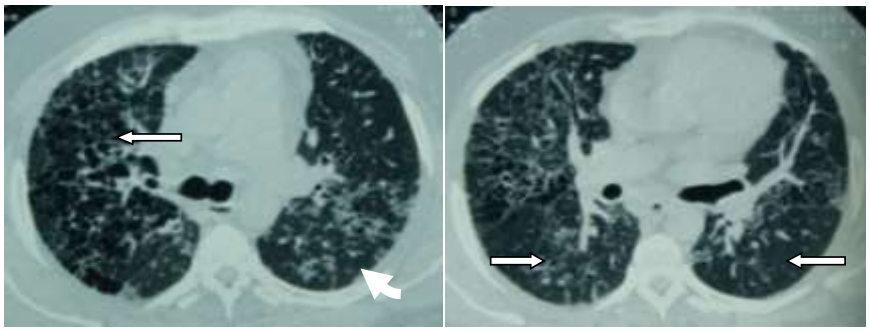


Figure XV: Chest radiograph showing nonspecific mild diffuse interstitial thickening predominantly basal with bilateral cystic lesions and some loss of lung volume with cardiomegaly.



A **B**

Figure XVI: HRCT axial images (**A**) at the level of trachea above aortic arch showing randomly distributed multiple variable size cysts with well defined walls and (**B**) at the level of aortic arch showing bilateral variable size cysts, septal thickening, patchy GGOs and centrilobular and subpleural nodules.



A **B**

Figure XVII: HRCT axial images (**A**) at the level of pulmonary trunk showing variable size thin walled cysts particularly more marked on the right side (arrow) with interspersed normal lung parenchyma on left side. Peripheral areas of GGO and reticulonodular opacities are also seen (curved arrow); (**B**) at the level of heart showing thin walled cysts, patches of GGO and centrilobular and subpleural nodules in peri-lymphatic distribution in lower lobes (arrows).

CASE 6: ***A Young Asthmatic Male with Bilateral Extensive Thick Walled Pulmonary Parenchymal Cystic Lesions of Central predominance. Advanced Cystic Bronchiectasis.***

A 36 years old never smoker male office clerk, resident of Lahore presented in ER with worsening of exertional dyspnea, cough with sputum and fever of 2 weeks duration. He revealed history of bronchial asthma since childhood having multiple environmental triggers. On examination, he was a young dyspneic person having difficulty completing a sentence & was sitting upright having a pulse 110/m, temperature 39^{o}C, BP 110/70 mmHg regular respirations of 34/m and SpO_2 88%. Chest examination was consistent with bilateral vesicular breathing and polyphonic wheezes all over & coarse crackles in middle to lower chest posteriorly. Systemic examination was unremarkable; chest radiograph showed hyper inflated lung fields with bilateral perihilar cystic changes (figure XVIII) and blood gas analysis was consistent with type I respiratory failure.

He was hospitalized with a diagnosis of acute exacerbation of bronchial asthma having suspicion of allergic bronchopulmonary aspergillosis with central bronchiectasis and was given

supportive treatment. His CBC and serum biochemistry was unremarkable. Sputum analysis showed no growth on pyogenic culture and negative Gram & ZN staining while fungal hyphae were seen in two specimens. Allergy panel showed serum IgE level 6500 IU/ml, positive skin prick test for Aspergillus & positive serum anti-Aspergillus antibodies (IgG). Spirometry was consistent with severe obstruction and mild restriction.

HRCT chest (figures XIX-A, B and C) was consistent with extensive cylindrical, varicose and cystic bronchiectasis involving all lobes and scattered areas of minimal ground glass opacification & minimal fibrosis. Final diagnosis in the light of above investigations was respiratory failure due to bilateral extensive bronchiectasis secondary to allergic bronchopulmonary aspergillosis and repeated chest infections. After one week of hospitalization, he was discharged on inhaled and oral steroids, montelukast & itraconazole with advice for regular follow up in OPD.

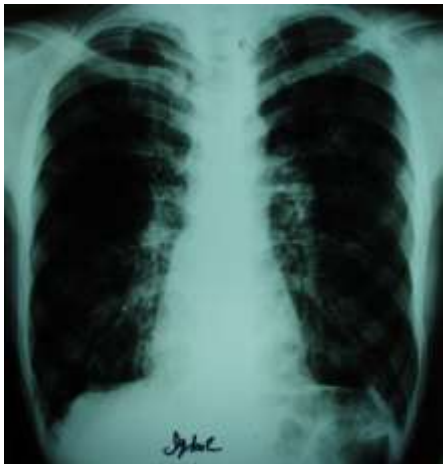


Figure XVIII: CXR-PA showing hyper inflated lung fields with low lying flat diaphragms, linear fibrotic shadows in left apex and bilateral perihilar, pericardiac and lower zones cystic lesions.

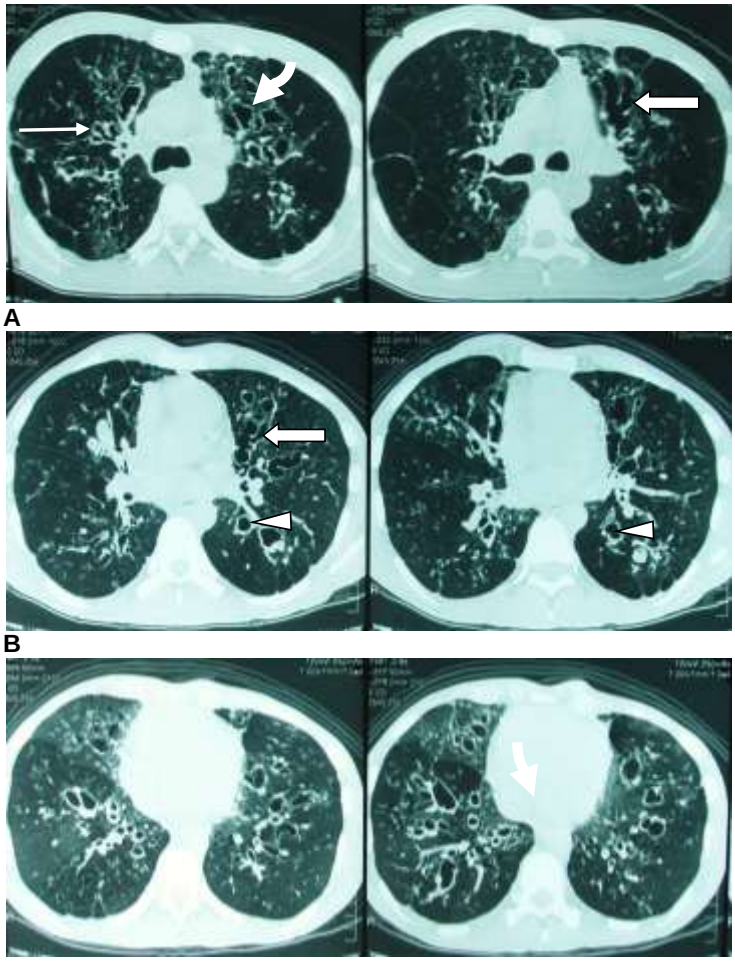


Figure XIX: HRCT chest axial images showing (**A**) cylindrical bronchiectasis (thin arrow), varicose bronchiectasis (white thick arrow) and thick walled cystic bronchiectasis (curved arrow);(**B**)varicose bronchiectasis (white thick arrow) extending to the peripheries and signet ring shadows/dilated airways having diameter greater than accompanying blood vessels (arrow heads),and (**C**) bilateral thick walled cystic bronchiectasis.

Table I: Clinico-Radiological Features of Multiple Cystic Lung Diseases.

Patient's Features	Lymphangioleiomyomatosis	Idiopathic Pulmonary Fibrosis	Alpha-1 Antitrypsin Deficiency Emphysema	Smoking Induced Emphysema	Lymphoid Interstitial Pneumonia	Bronchiectasis
Age (years)	48	70	35	59	45	36
Gender	FM	M	M	M	M	M
Illness Duration (years)	5	2	6	3	2	5
Co-morbid States	Allergic rhinitis Seasonal asthma	Proximal myopathy	Bronchial asthma	Coronary heart disease	Sjögren's syndrome	Allergic broncho-pulmonary aspergillosis
Predominant Symptoms	Gradually progressive dyspnea	Dry cough & gradually progressive dyspnea	Gradually progressive dyspnea	Cough with sputum & gradually progressive dyspnea	Gradually progressive dyspnea	Cough with sputum & gradually progressive dyspnea
Predominant Signs	Wheezes	Crackles	Wheezes	Wheezes	Wheezes & Crackles	Wheezes & Crackles
Blood Gas Analysis	Type II respiratory failure	Type I respiratory failure	Normal	Hypoxemia	Type I respiratory failure	Type I respiratory failure
Spirometry	Obstructive	Restrictive	Obstructive	Obstructive	Combined	Obstructive
Supportive Test	Liver angiomyolipoma	None	Low AAT level (0.04g/dL)	None	Anti SS-A/Ro positive	High IgE (6500u/L)
Chest Radiographic Findings	Hyperinflation, partial right pneumothorax, bilateral lower zone reticulation	Hypoinflation & bilateral peripheral reticulation	Hyperinflation, lower zone lucencies, diaphragmatic depression	Prominent bronchovascular markings & lucent upper and middle zones	Hypoinflation & bilateral cystic lesions	Hyperinflated lung fields with bilateral perihilar cysts
HRCT Chest Findings	Thin wall cysts distributed uniformly throughout lung fields from apices to bases	Temporally heterogenous linear infiltrates & predominantly peripheral lower lobe honey comb cysts	Widespread hypoattenuating spaces with very thin/barely visible walls predominantly in lower lobes	Centrilobular lesions of low attenuation of variable sizes with very thin walls having predominance in upper lobes	Randomly distributed cysts having well defined walls with predominant involvement of central lungs	Extensive cylindrical, varicose and cystic bronchiectasis involving all lobes

DISCUSSION:

MCLD is a rare computed tomography imaging syndrome often associated with pneumothorax resulting mostly from rare orphan disorders, the three major being lymphangioleiomyomatosis, Langerhan's cell histiocytosis and Birt–Hogg–Dube´ syndrome (associated with mutations of the folliculin gene).[1,5]Other important causes of multiple cystic lung diseases include cystic bronchiectasis, lymphoid Interstitial pneumonia (especially in Sjögren's syndrome), hypersensitivity pneumonitis, idiopathic pulmonary fibrosis, centrilobular and panlobular emphysema, with a few further recent descriptions[5,6]. The multiplication and increase in size of

the pulmonary cysts may lead to the progressive destruction of the lung, and eventually to respiratory failure[5].

The initial imaging tool for the lung parenchyma remains the chest radiograph having a number of limitations with an overall sensitivity of 80% and a specificity of 82% for the detection of diffuse parenchymal lung disease[7]. HRCT in lung diseases provides more detail than either chest radiography or conventional CT scanning, with an overall sensitivity of 95% & a specificity approaching 100%and can more accurately assess the pattern and distribution of disease including linear and reticular opacities, nodular opacities, large confluent opacities (eg, ground-glass, consolidation), and decreased parenchymal opacification (eg, emphysema, cystic lesions, mosaic attenuation, air trapping); these patterns may be accompanied by parenchymal bands and architectural distortion[8]. Further discussion will be focused on predominant patterns of common cystic lung diseases in the context of their HRCT imaging patterns.

Lymphangioleiomyomatosis (LAM) is a rare disorder characterized by hamartomatous proliferation of atypical smooth muscle along lymphatics in the lung, thorax, abdomen, and pelvis which presents with MCLD on HRCT imaging[9]. Pulmonary lesions identical to LAM may occur in patients with tuberous sclerosis complex (TSC), an autosomal dominant familial disorder associated with neurologic and cutaneous manifestations, which are not seen in sporadic LAM[10]. Diagnosis of LAM is often delayed for 3 to 5 years after the onset of symptoms which may be erroneously ascribed to: chronic bronchitis, asthma, emphysema, pulmonary Langerhan's cell histiocytosis (PLCH), or chronic interstitial lung disease (ILD) [11]. Plain chest radiographs are nonspecific but may demonstrate pneumothoraces (occurs in approximately 80% of patients during the course of the disease), cystic or reticulonodular shadows, pleural effusions, or hyperinflation[12]. On HRCT, there are numerous thin-walled cysts, ranging in size from a few mm to 6 cm, throughout both lungs without predilection for specific regions or lobes; the intervening lung parenchyma is normal (figures I, II & III)[13,14]. Cysts are usually round, but may assume polygonal or bizarre shapes as multiple cysts coalesce & can rupture and result in pneumothoraces (30-40%)[13]. In contradistinction to other chronic ILDs, cavitation, nodules & interstitial fibrosis foci are absent or a minor feature in LAM as is mediastinal or intrathoracic lymphadenopathy[13]. Ground glass opacification (GGO) seen rarely, are reflective of foci of alveolar hemorrhage, pulmonary hemosiderosis, or diffuse proliferation of smooth muscle cells in the parenchyma[12,13].

Pulmonary Langerhan's cell histiocytosis (PLCH), also called pulmonary histiocytosis X, eosinophilic granuloma of the lung or pulmonary Langerhan's cell granulomatosis, is an uncommon interstitial lung disease that primarily affects young adults having a history of current or prior cigarette smoking[14]. Langerhan's cells are normally found in the dermis, the reticulo-endothelial system, the lung, and the pleura and in PLCH, there is infiltration of these cells in lung parenchyma leading to formation of nodules which break up into small cysts with progressive destruction of lungs[15]. On HRCT there are bilateral cysts which in contrast to LAM, predominantly involve upper and middle lung zones and are mostly accompanied by peri-bronchial nodules and interstitial thickening in the initial stages while advanced stages are characterized by predominantly cysts[16]. Serial chest CT scanning suggests a sequence of progression from nodules to cavitating nodules to cystic lesions[17].

Idiopathic pulmonary fibrosis (IPF) also called cryptogenic fibrosing alveolitis (CFA) is specific form of chronic, progressive, fibrosing interstitial pneumonia of unknown etiology, occurring in adults and is limited to the lungs[18]. Disease progression is usually insidious, at least initially but some patients may develop an acute deterioration after a period of apparent stability[18,19]. HRCT may be adequate to establish the diagnosis with a high degree of certainty in patients with a compatible clinical presentation and no evidence of another contributing process (eg, hypersensitivity pneumonitis, systemic sclerosis, rheumatoid arthritis) but when the results of HRCT are not ideal for IPF, a video-assisted thoracoscopic or open lung biopsy is indicated[18].

The characteristic radiographic changes in IPF (pathologically defined by the presence of usual interstitial pneumonia or UIP pattern) is characterized by peripheral/subpleural reticular opacities (fibrotic foci) often sparing the central portions of lungs (see figures in section of IPF case) often associated with traction bronchiectasis called the UIP pattern on HRCT, accompanied by honey combing (defined as subpleural, clustered cystic air spaces with well-defined walls) is common and is critical for making a definitive diagnosis of IPF[18]. The cystic spaces are typically 3 to 10 mm in diameter, but occasionally may be as large as 2.5 cm [19]. Temporal (lesions appearing in different timings/having different ages) and spatial (different regions/non symmetrical) heterogeneity are characteristic of IPF[20]. In contrast to PLCH having combination of both cysts and nodules with upper and middle zones predominance and LAM having thin wall cysts involving all regions of lung parenchyma, cysts in IPF are thick walled (honey combing) and are peripheral with sparing of central regions of lungs[12,16,18]. Advanced stage IPF may be characterized by large honey comb cysts, which can be differentiated from PLCH and LAM on the basis of lung volumes: IPF has decreased lung volumes and PLCH & LAM tends to have slightly increased lung volumes[5,24].

Emphysema, besides being related to alpha-1 antitrypsin deficiency (AATD), is mostly caused by exposure to tobacco smoke and is defined pathologically as abnormal and permanent destruction and enlargement of airspaces distal to the terminal bronchioles, without obvious fibrosis[21]. These dilated air spaces appear as thin wall (<2mm) lucent cysts (without the well-defined walls one would expect to see with PLCH, LAM cysts or thick wall honey combing with IPF) on HRCT which when become >1 cm are called bullae/bullous emphysema[22]. HRCT can determine whether the emphysema is centriacinar or panacinar (AATD), irregular, or para septal (peripheral sub-pleural) [23]. Centriacinar emphysema (tobacco smoke related) occurs preferentially in the upper lobes and produces holes (lucent/black lesions with thin walls) in the center of secondary pulmonary lobules (centrilobular lucencies)[22,23]. In contrast, panacinar emphysema due to AATD more commonly involves the lung bases and involves the entire secondary pulmonary lobule; the whole acinus is destroyed and thus dilated[24]. As pulmonary tissue is lost, pulmonary vessels appear smaller, fewer in number (destruction), and spread farther apart; AATD emphysema on HRCT (see figures of case 3 and 4) therefore appears as 'large lucent lesions devoid of vascular markings having barely visible walls' [22,24].

Lymphoid interstitial pneumonia (LIP) is an uncommon form of interstitial lung disease that is characterized histopathologically by infiltration of the interstitium and alveolar spaces of the lung by lymphocytes, plasma cells, and other lymphoreticular elements which can rarely progress to low-grade lymphoma[26]. LIP is associated with immune function disturbances – most commonly AIDS as well as connective tissues disorders, especially Sjögren's syndrome and many autoimmune processes including pernicious anemia, rheumatoid arthritis, systemic lupus erythematosus, chronic active hepatitis, and biliary cirrhosis[27]. LIP has a varied radiographic appearance & can appear as basilar reticular opacities or as a nodular process on CXR; as the infiltrative process continues, alveolar spaces become involved, and a mixed pattern of interstitial and alveolar opacities appears[28]. HRCT is useful to establish the extent of disease, define the hilar anatomy, and identify any pleural involvement; GGO, centrilobular nodules, and interstitial thickening are more frequent while well defined lung cysts having perivascular distribution without any zonal predilection are more common among patients with Sjögren's syndrome associated LIP, whereas they are rare in those with pulmonary lymphoma[29]. In one study, the number of cysts ranged from one to 105 (mean n 514), with their size ranging from 3 to 52 mm (mean 16 mm), predominating in the lower and outer one-third zones[30]. Pleural thickening and effusions are rare in LIP, as are hilar and mediastinal lymphadenopathy, which suggest an underlying malignant process[31].

Comment [I1]: Is it 514?

Bronchiectasis is the destruction and dilatation of bronchi which is diagnosed clinically on the basis of chronic daily cough with viscid sputum production (for months or years), and radio graphically by the presence of bronchial wall thickening and luminal dilatation on chest CT

scanning[32]. HRCT scanning has become the imaging modality of choice (sensitivity 97%; specificity up to 99%) for demonstrating or ruling out bronchiectasis and its extent (Figures XVIII and XIX) & helps clinicians to evaluate the status of the surrounding lung parenchyma and exclude other lesions such as neoplasms[33]. Initially dilated bronchi have straight and usually regular outlines; bronchi extend to the periphery of the lung and do not taper (tram-track lines representing thickened dilated bronchial walls) and is called 'cylindrical bronchiectasis' which with further damage develop beaded/varicose appearance (alternating areas of constriction and dilatation similar in appearance to saphenous varicosities) called 'varicose bronchiectasis' whose further progress leads to cystic dilatation with a honeycomb appearance (cystic bronchiectasis); their walls being thicker than bullae of emphysema and cysts of LAM [34].

Cystic, cylindrical, and varicose forms may coexist in the same patient[34]. Varicose and cystic bronchiectasis may appear as multiple, thick-walled, irregular cysts; however, cystic bronchiectasis can be differentiated from true cystic lung disease by the continuous relationship (connection) of the cystic structure to bronchial tree (bronchi can be seen extending to the lung periphery that should not be visible within 1 cm of the pleura in normal lung) [35]. The most specific criteria for bronchiectasis on HRCT are an internal bronchus diameter that is wider than its adjacent pulmonary arteries (which normally have similar or larger diameter), known as 'signet ring sign', with the "stone" of the ring representing the pulmonary artery; the failure of the bronchi to taper as they move toward the periphery of the lung parenchyma, and bronchi visualized in the outer 1 to 2 cm of the lung fields[34,35]. Secondary criteria include excessive bronchial wall thickening, impacted mucus, and crowding of the bronchi[36]. Cystic (saccular) ectatic lesions may contain air-fluid levels and are representative of bronchiectasis presence in fourth and higher-order bronchi[1].

Other than the common disorders described above, there are many more causes of multiple cystic lung diseases which are beyond the scope of this article. Some of other conditions include lymphomas, amyloidosis, non amyloid light chain déposition disease, infections, malignancies especially metastases of sarcomas, desquamative interstitial pneumonia, hypersensitivity pneumonitis, and a variety of other disorders[1].

REFERENCES:

1. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Müller NL, Remy J. Fleischner Society: Glossary of terms for thoracic imaging. Radiology 2008;246:697-722.
2. Sumikawa H, Johkoh T, Ichikado K, et al. Usual interstitial pneumonia and chronic idiopathic interstitial pneumonia: analysis of CT appearance in 92 patients. Radiology 2006; 241: 258–66.
3. Lee KN, Yoon SK, Choi SJ, Goo JM, Nam KJ. Cystic lung disease: a comparison of cystic size, as seen on expiratory and inspiratory HRCT scans. Korean J Radiol 2000; 1: 84–90.
4. King TE Jr. Smoking and subclinical interstitial lung disease. N Engl J Med 2011; 364:968-970.
5. Cordier JF, Johnson SR. Multiple cystic lung disease. Eur Respir Mon 2011; 54: 46–83
6. Hartman TE. CT of cystic diseases of the lung. Radiologic Clinics of North America. 2001;39:1231-43.
7. Mathieson JR, Mayo JR, Staples CA, Müller NL. Chronic diffuse infiltrative lung disease: comparison of diagnostic accuracy of CT and chest radiography. Radiology 1989; 171:111-116.
8. Müller NL. Clinical value of high-resolution CT in chronic diffuse lung disease. AJR Am J Roentgenol 1991; 157:1163-1170.
9. Johnson SR, Cordier JF, Lazor R, Cottin V, Costabel U, Harari S, et al. European Respiratory Society guidelines for the diagnosis and management of lymphangioleiomyomatosis. EurRespir J. 2010;35:14–26.
10. Staley BA, Vail EA, Thiele EA. Tuberous sclerosis complex: diagnostic challenges, presenting symptoms, and commonly missed signs. Pediatrics. 2011;127:117–125.
11. Taveira-DaSilva AM, Pacheco-Rodriguez G, Moss J. The natural history of lymphangioleiomyomatosis: markers of severity, rate of progression and prognosis. Lymphat Res Biol. 2011;8:9–19.
12. Chu SC, Horiba K, Usuki J, Avila NA, Chen CC, Travis WD, et al. Comprehensive evaluation of 35 patients with lymphangioleiomyomatosis. Chest. 1999;115:1041–52.

13. Avila NA, Dwyer AJ, Rabel A, Moss J. Sporadic lymphangioleiomyomatosis and tuberous sclerosis complex with lymphangioleiomyomatosis: comparison of CT features. Radiology 2007; 242: 277–285.
14. Tazi A. Adult pulmonary Langerhans' cell histiocytosis. EurRespir J 2006; 27:1272.
15. Basset F, Corrin B, Spencer H, Lacronique J, Roth C, Soler P, et al. Pulmonary histiocytosis X. Am Rev Respir Dis 1978; 118:811.
16. Kulwiec EL, Lynch DA, Aguayo SM, Schwarz MI, King TE Jr. Imaging of pulmonary histiocytosis X. Radiographics 1992; 12:515.
17. Canuet M, Kessler R, Jeung MY, Métivier AC, Chaouat A, Weitzenblum E. Correlation between high-resolution computed tomography findings and lung function in pulmonary Langerhan's cell histiocytosis. Respiration 2007; 74:640-646.
18. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J RespirCrit Care Med 2011; 183:788.
19. Martinez FJ, Safrin S, Weycker D, Starko KM, Bradford WZ, King TE Jr, et al. The clinical course of patients with idiopathic pulmonary fibrosis. Ann Intern Med 2005; 142:963-967.
20. Wells A. Clinical usefulness of high resolution computed tomography in cryptogenic fibrosing alveolitis. Thorax 1998; 53:1080-1087
21. Rennard SI. COPD: overview of definitions, epidemiology, and factors influencing its development. Chest 1998; 113:235S-241S.
22. Mair G, Miller JJ, McAllister D, Maclay J, Connell M, Murchison JT, et al. Computed tomographic emphysema distribution: relationship to clinical features in a cohort of smokers. EurRespir J 2009; 33:536-542.
23. Grydeland TB, Dirksen A, Coxson HO, Pillai SG, Sharma S, Eide GE, et al. Quantitative computed tomography: emphysema and airway wall thickness by sex, age and smoking. EurRespir J 2009; 34:858-865.
24. Parr DG; Stoel BC; Stolk J; Stockley RA. Pattern of emphysema distribution in alpha1-antitrypsin deficiency influences lung function impairment. Am J RespirCrit Care Med. 2004 Dec 1;170:1172-8.
25. Brauner MW, Grenier P, Tijani K. Pulmonary Langerhans' cell histiocytosis: Evolution of lesions on CT scan. Radiology 1997;204:497-502.
26. Swigris JJ, Berry GJ, Raffin TA, Kuschner WG. Lymphoid interstitial pneumonia: a narrative review. Chest 2002; 122:2150-2164.
27. Rajagopala S, Swamy S, Kumar A, Rout P. Ace in the hole! Respiration 2011; 82:212-216.
28. Cosgrove GP, Fessler ME, Schwartz MI. Lymphocytoplasmic infiltrations of the lung. In: Interstitial Lung Disease, 4th ed, Schwarz MI, King TE Jr (Eds), BC Decker Inc, Hamilton 2003:825.
29. Johkoh T, Müller NL, Pickford HA, Hartman TE, Ichikado K, Akira M, et al. Lymphocytic interstitial pneumonia: thin-section CT findings in 22 patients. Radiology 1999; 212:567-572.
30. Watanabe M, Naniwa T, Hara M,Arakawa T, Maeda T. Pulmonary manifestations in Sjogren's syndrome: correlation analysis between chest computed tomographic findings and clinical subsets with poor prognosis in 80 patients. J Rheumatol 2010; 37: 365–73.
31. Lynch DA, Travis WD, Müller NL, Idiopathic interstitial pneumonias: CT features. Radiology 2005;236:10-21.
32. Barker AF. Bronchiectasis. N Engl J Med 2002; 346:1383-1393.
33. Failo R, Wielopolski PA, Tiddens HA, Hop WC, PozziMucelli R, Lequin MH. Lung morphology assessment using MRI: A robust ultra-short TR/TE 2D steady state free precession sequence used in cystic fibrosis patients. MagnReson Med. 2009;61:299-306.
34. King P, Holdsworth S, Freezer N, Holmes P. Bronchiectasis. Intern Med J. 2006;36:729–37.
35. Feldman C. Bronchiectasis: new approaches to diagnosis and management. Clin Chest Med. 2011;32:535–46.