WWW — White · Wash · Well

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Mr Chui first presented in Dec 2007 when he was 67 years old. He presented with one week history of cough, yellowish sputum and fever. He had no hemoptysis or chest pain. He reported travel history to mainland China two weeks ago and he enjoyed hot spring for four days there. The symptoms started a few days after his hot spring. On physical examination, he had stable vital signs, SaO2 was 96% on room air, he had no cervical node or finger clubbing. There was bilateral fine crepitation on chest auscultation. His chest X-ray showed bilateral hazziness **(Figure 1)**. His neutrophil count was slightly elevated, his eosinophil and hemoglobin level were normal. His sputum grew only commensals and AFB smear was negative. His fever subsided and chest symptoms improved after taking augmentin and klacid.

However, despite symptomatic improvement and prolonged courses of antibiotic, his chest X-ray showed persistent diffuse hazziness. Further investigations showed no evidence of diabetes, immune mar kers and serum IgE level were all negative, CRP was <0.35, anti HIV was negative and MT2 was 8mm at 48 hours. His FEV_1 was 3.16 liters(L)(109%), FVC was 3.80L(102%), FEV /FVC ratio was 83%, TLC was 5.47L(92%), corrected DLCO was 94%. HRCT was done **(Figure 2)**. Flexible bronchoscopy reviewed no endobronchial lesions and there was scanty mucoid secretion bilaterally. Bronchoalveolar lavage (BAL) and transbronchial biopsy (TBBx) were done at right middle lobe and right lower lobe. BAL reported no malignant cells and TBBx reported no inflammation, granuloma or malignancy. Patient remained asymptomatic, his SaO2 was 93-96% on RA. In view of the persistent hazziness on chest x-ray, surgical lung biopsy was discussed and agreed by patient. During the right thoracotomy lung biopsy, there were multiple degassing and re-inflation required due to desaturation after each lung stapling. The

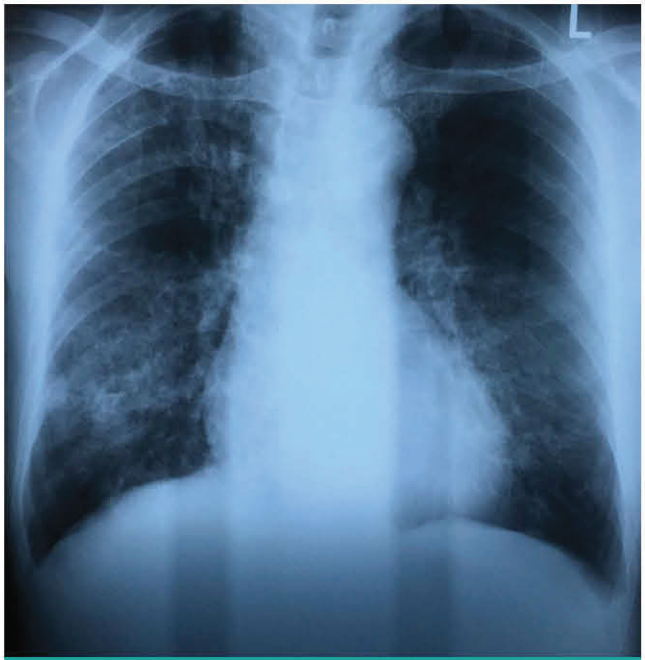

Figure 1: Chest X-ray at presentation

surgical lung biopsy was performed at right lower lobe and biopsy was reported hemorrhage only on pathological examination, while the PAS stain was negative. After discussion with pathologist, it was believed that the hemorrhage was probably related to the repeated inflation and deflation of lung during sampling. As there was no definite diagnosis made and the patient was asymptomatic, he was kept under observation.

In Sep 2008, patient remained minimal symptomatic but there was mild decline of lung function (FEV_1 109% → 103%, FVC 102% → 98%, TLC 92% → 86%, DLCO 94% → 84%), trial of oral prednisolone 30mg daily was started. Two months after systemic steroid was initiated, his lung function and HRCT deteriorated **(Figure 3)**. In view of the non-responsiveness to steroid and crazy-paving pattern on HRCT, pulmonary alveolar proteinosis (PAP) was highly suspected. Bronchoscopy was repeated. During bronchoscopy, the returned fluid was clear, but PAP was finally confirmed by both BAL and TBBx with PAS staining. Scanty Nocardia was also isolated from BAL.

At the time the diagnosis of PAP was made, the patient reported some dry cough, his SaO2 was 90% on RA and his lung function further deteriorated (FEV_1: 90%, FVC 81%, TLC 80%, DLCO 54%). Therefore the patient underwent whole lung lavage (WLL) at bilateral lungs (sequentially at three weeks apart) in Jan 2009. In view of the isolation of nocardia from BAL, a course of tienam was initiated prior to WLL and followed by oral septrin. After WLL, there were significant improvement in his symptoms, lung functions (FEV_1: 109%, FVC 103%, TLC 93%, DLCO 94%), CXR and HRCT **(Figure 4)**.

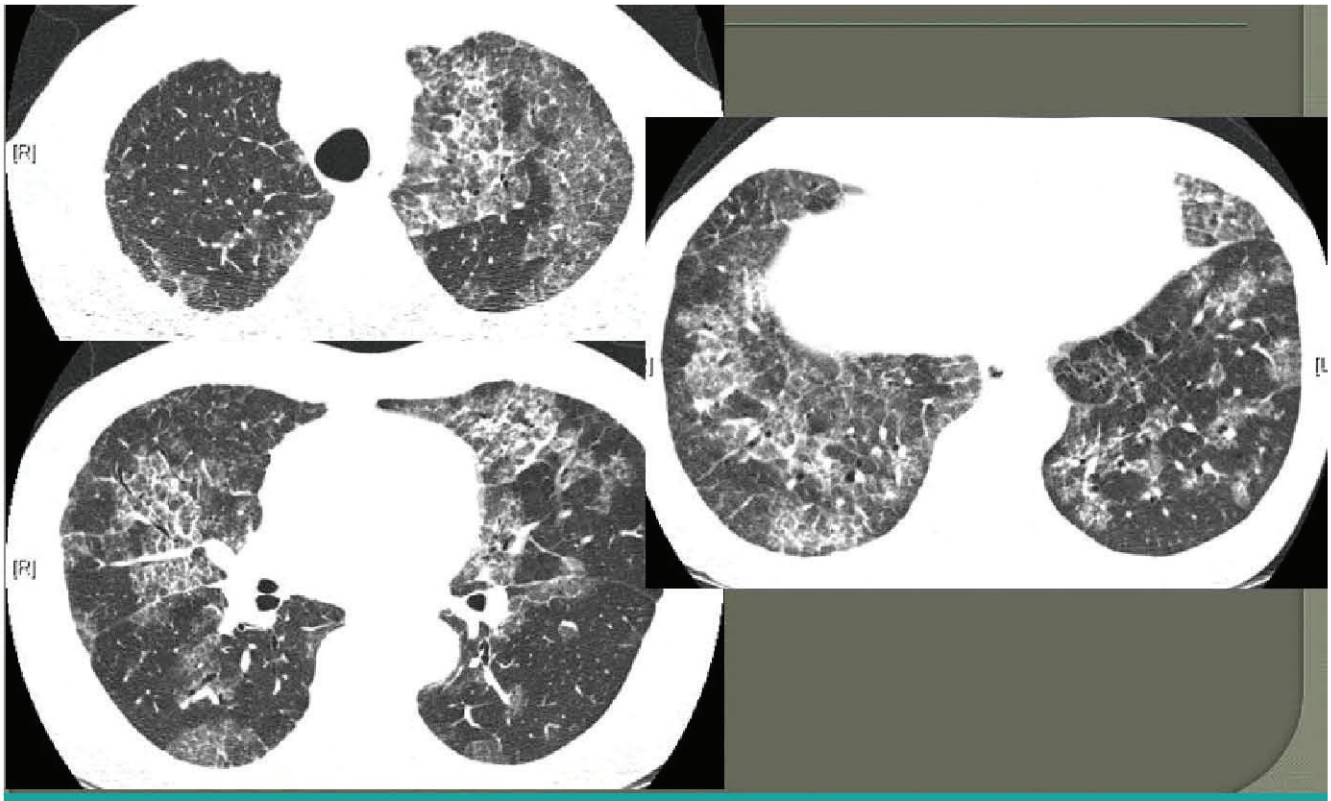

Figure 2: HRCT at presentation

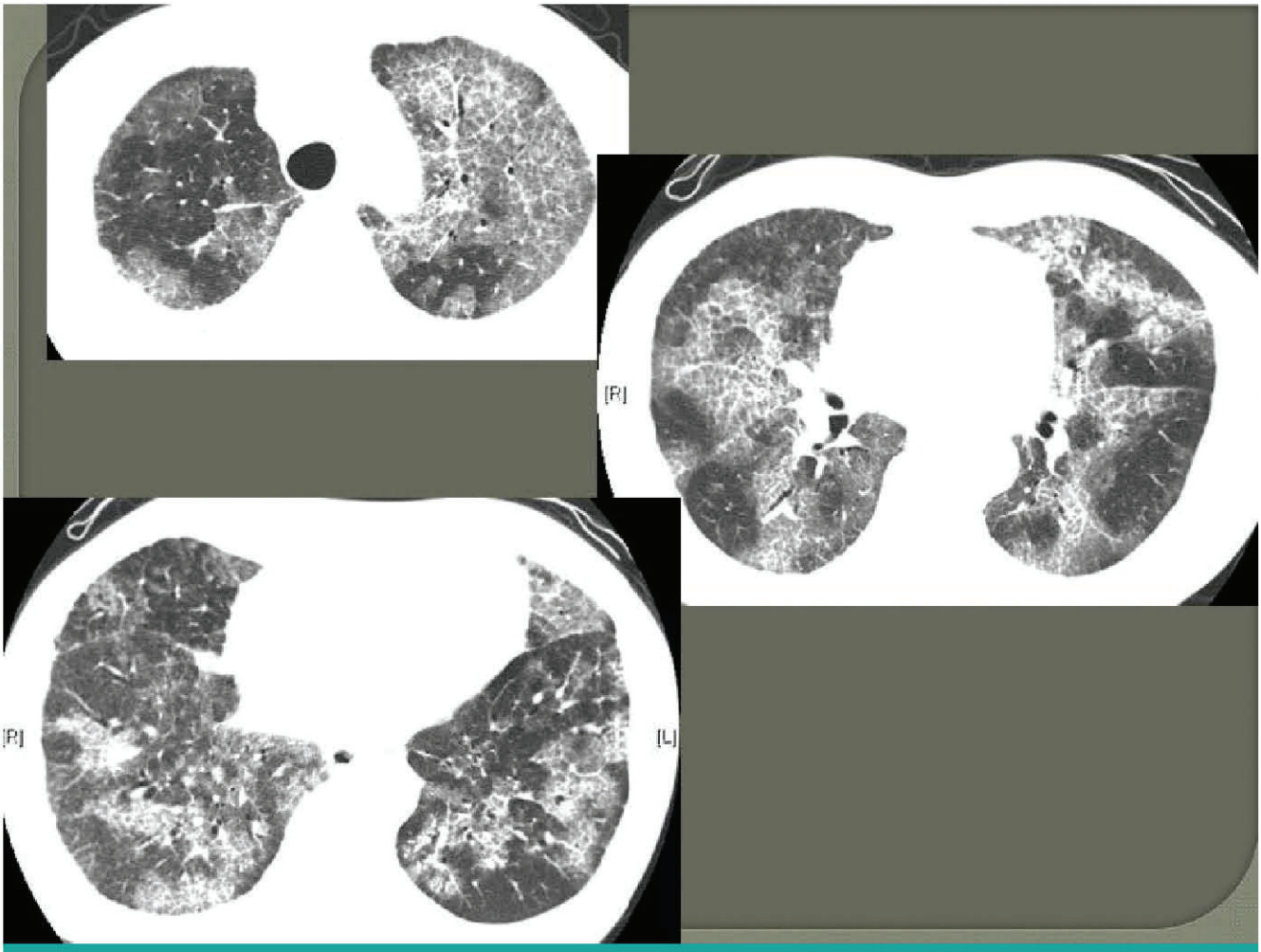

Figure 3: HRCT progressed after 2 months of systemic steroid

After the first bilateral WLL, his symptoms, lung functions, chest x-ray and HRCT slowly progressed **(Figure 5)** and finally at 18 months after his first WLL, he required another bilateral (sequential) WLL in Sep 2010. Patient improved again after his second bilateral WLL **(Figure 6)**. Unfortunately, lung fibrosis developed slowly over the next five years **(Figure 7a&b)**, patient eventually required long term oxygen in Jan 2016. Bronchoscopy with BAL and TBBx was repeated and found pathological changes of PAP only without alternative causes identified. In view of his age (76 years old in 2016) and his poor lung function (FEV_1: 56%, FVC 50%, TLC 51%, DLCO 41%), the option of bronchoscopic lobar lavage as an alternative to WLL were discussed. Patient agreed trials of bronchoscopic lobar lavage and three sessions of bronchoscopic lobar lavage were performed at left lower lobe in mid 2016. Each session was 3 weeks apart and around 250ml normal saline was instilled to the left lower lobe at each session. There was no significant subjective or objective improvement after the three sessions of mini-lavage. Patient finally succumbed due to respiratory failure in 2016.

Pulmonary alveolar proteinosis (PAP) syndrome is a rare disorder first described in 1958, and reported an incidence of 6 to 7 per million populations. The etiology was abnormal surfactant

homeostasis. Defective cellular receptors or signaling pathways in surfactant production and its clearance lead to PAP syndrome. GM-CSF also plays an important role in surfactant homeostasis through signaling macrophages, which are responsible for surfactant catabolism; hence, abnormal GM-CSF signaling could lead to PAP as well.

PAP syndrome could be congential, primary or secondary **(Figure 8)**. Autoimmune PAP contributes to 90% of all PAP syndromes and is characterized by a high level of Anti-GM CSF antibodies. Anti-GM CSF Ab is an IgG which could occasionally been seen at low level in healthy subjects, while a high level is of almost 100% sensitivity and 98% specificity for diagnosis of autoimmune PAP[2]. Autoimmune PAP has predominance in male (male: female = 2:1 by Inoue Y et al[1]) and the median of onset age was 35-55years old. Autoimmune PAP often presents with dyspnea in progressive onset, or it could present with symptoms of infection as a complication of PAP. However, one third of autoimmune PAP patients could remain asymptomatic despite overt radiological abnormalities[1].

Secondary PAP accounts for around 9% of all PAP. Secondary PAP was most commonly described in hematological conditions with myeloid cell lines abnormalities e.g. CML, MDS. It was reported 5.3% patients with hematological malignancy (AML, CML, ALL) and 8.8% in those with neutropenia[3,4]. Other medical conditions also reported association with PAP, for example non-hematological malignancy such as adenocarcinoma, chronic

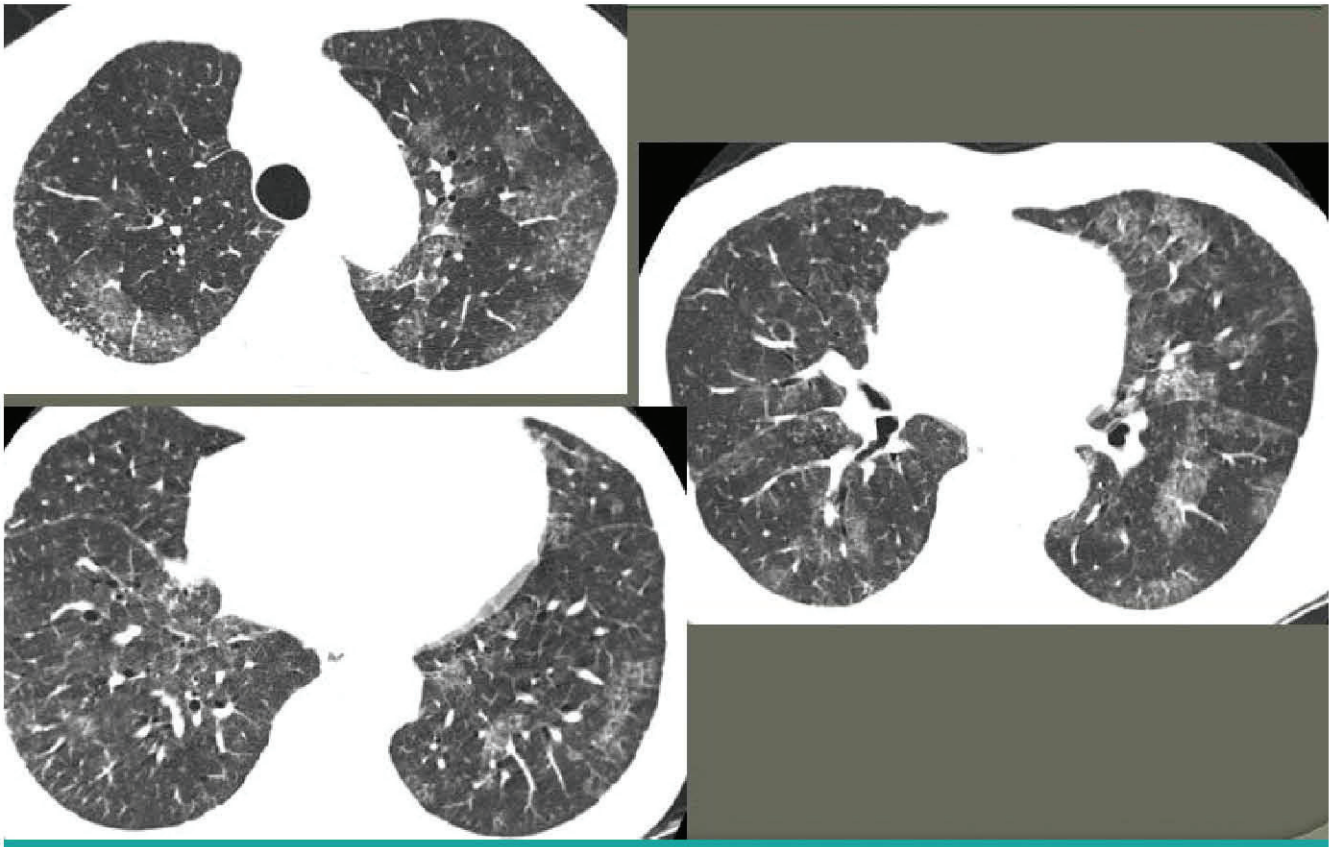

Figure 4: HRCT after first bilateral WLL

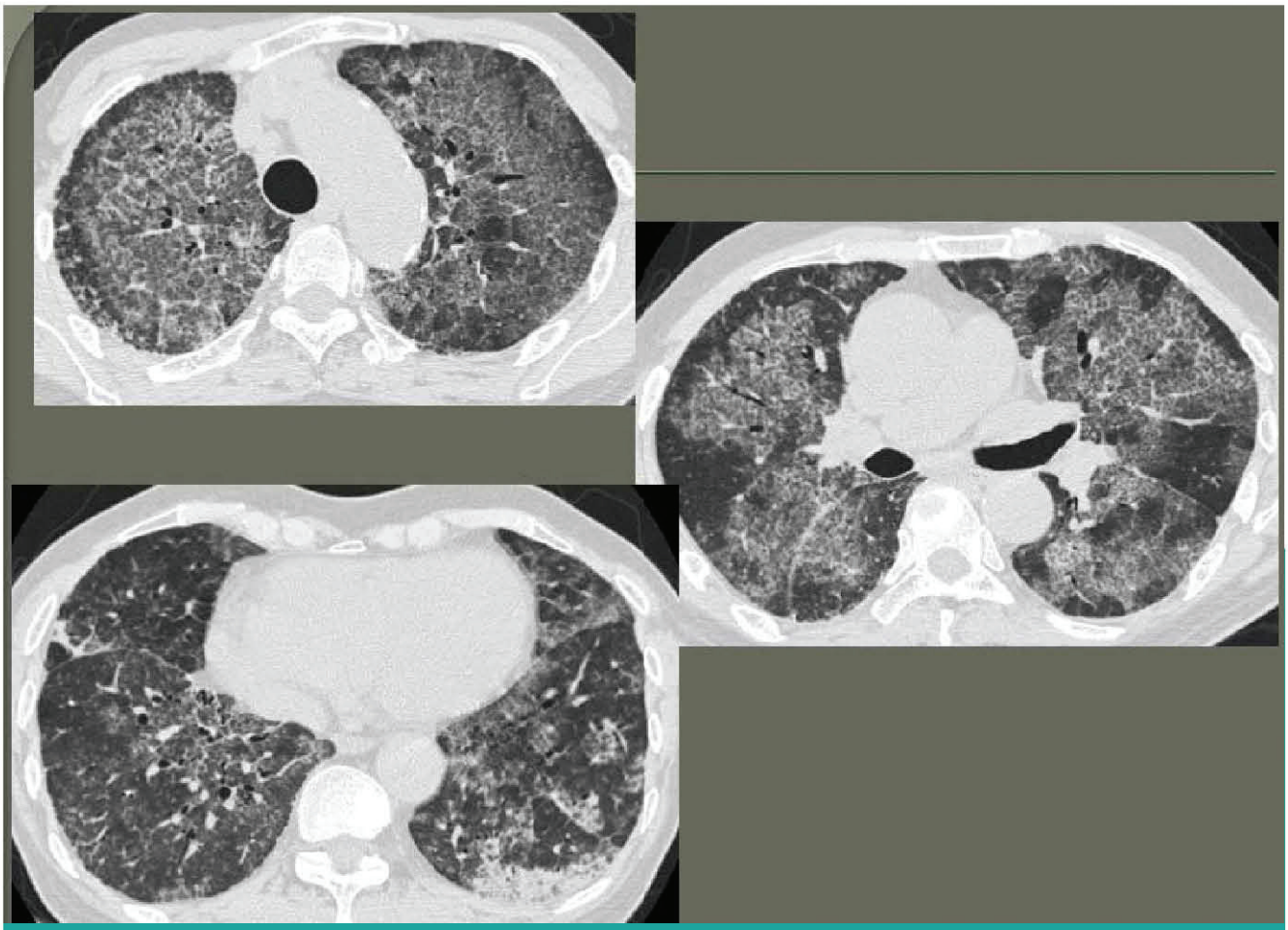

Figure 5: HRCT at 18 months after first bilateral WLL

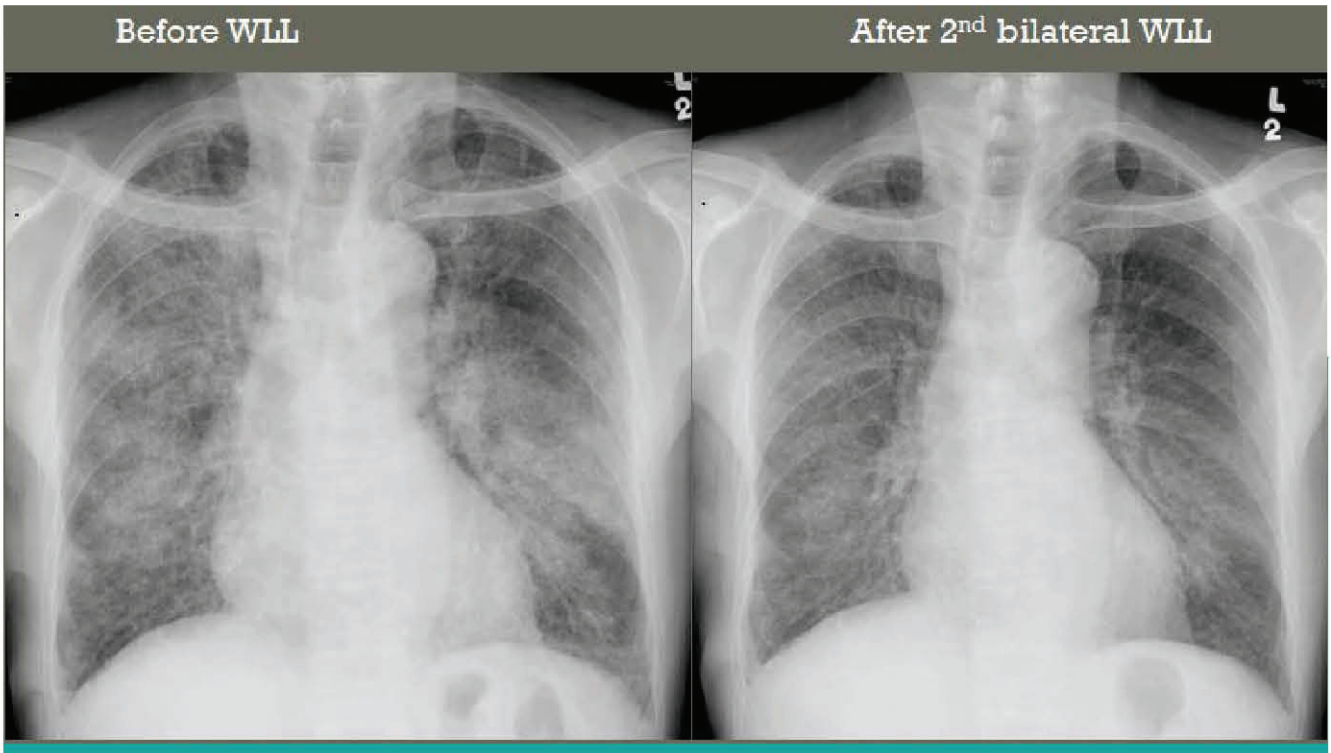

Figure 6: CXRs before & after 2nd bilateral WLL

inflammatory syndromes and immunodeficient conditions e.g. amyloidosis, severe combined immunodeficiency disease, AIDS. Inorganic and organic environmental exposure leads to secondary PAP in some cases. Among all exposure, silica exposure is the commonest substance to cause PAP[5], it is believed that silica disrupts the surfactant homeostasis. Secondary PAP should be considered in an individual with known associating medical conditions. Anti-GM CSF Ab is absent in secondary PAP.

Serological tests other than Anti-GM CSF Ab in autoimmune PAP, include non-specifically elevated serum LDH level, serum surfactant protein A (SP-A), SP-B, SP-C level etc. PAP typically showed mild hypoxia at arterial blood gas analysis. Lung function test usually revealed mild restriction with a disproportionately severely reduced DLCO[6].

HRCT classically describe bilateral patchy air space shadows resembling pulmonary edema. Occasionally mixed alveolar and interstitial infiltrates, nodular shadows, asymmetrical or even focal abnormalities are reported. For the classical ground glass opacity (GGO) patterns, crazy paving pattern referring to GGO with thickened interlobular septa is characteristic but not pathognomonic of PAP. “Geographic GGOs” refers to GGO with relatively well demarcated, straight or angulated margins which reflect the underlying lobar and lobular boundaries.

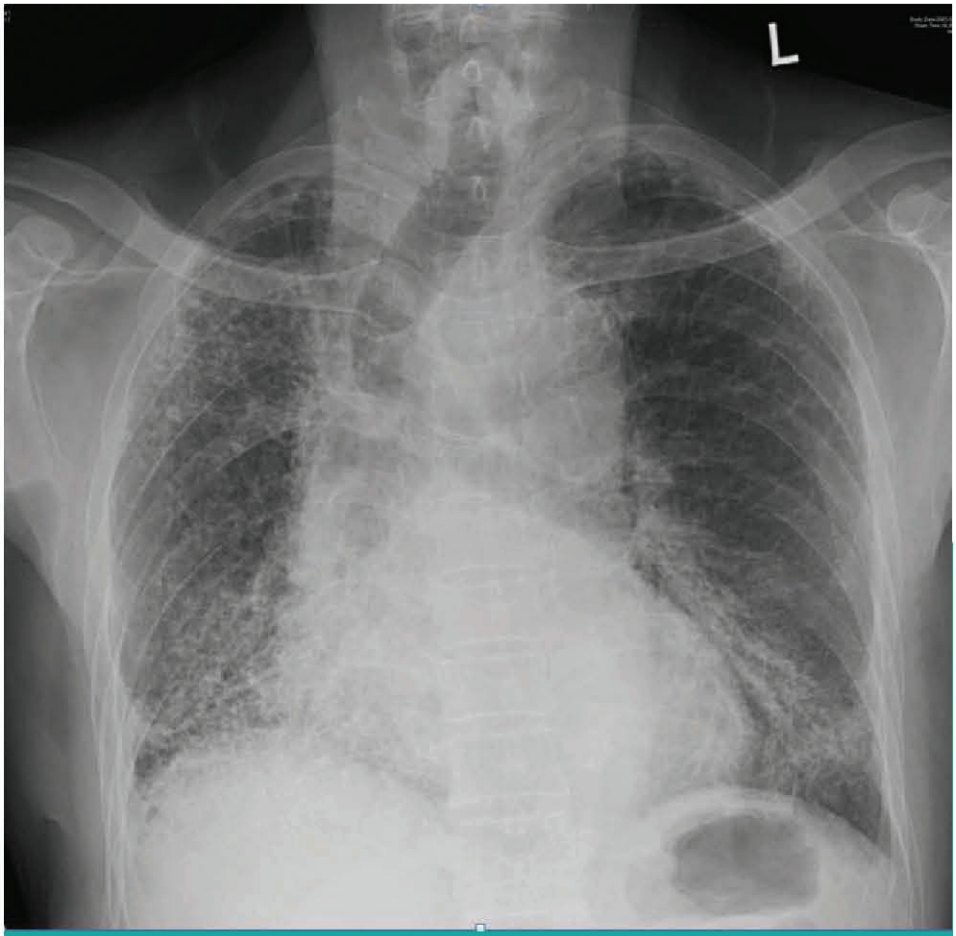

Figure 7a: CXR at 4 years after second bilateral WLL

Crazy paving pattern and geographic GGO are more commonly seen in autoimmune PAP. For secondary PAP, the GGOs tend to be more homogenous and less geographic[7].

Bronchoscopic examination could elicit the diagnosis if high level of suspicion given prior to procedure. The gross appearance of returned BAL would be milky, waxy and forming sediment upon standing. Cytopathological examinations of BAL should reveal normal or increased lymphocytes, increased absolute amount of phospholipid and protein content but their relative compositions remain the same as normal subjects. Granular, acellular, eosinophilic lipoproteinaceous material would be observed. Further analysis by cell blocks of BAL would show alveolar macrophages engorged with lipid material and a foamy and vacuolated appearance. Sediment composited of tubular myelin, lamella bodies and fused membranous structures would be seen under electronic microscopy. The GM-CSF level in BAL would be elevated in case of GM-CSF receptor dysfunction.If it remains non-diagnostic with the above investigations, surgical lung biopsy would demonstrate eosinophilic lipoproteinaceous material filling alveoli and terminal airways, and stained strongly positive by periodic acid Schiff (PAS) reagent. The alveolar wall, interstitium and vasculature would be normal.

With appropriate clinical suspicion, PAP could be diagnosed by HRCT together with BAL alone in 59% patients and with the addition of TBBx

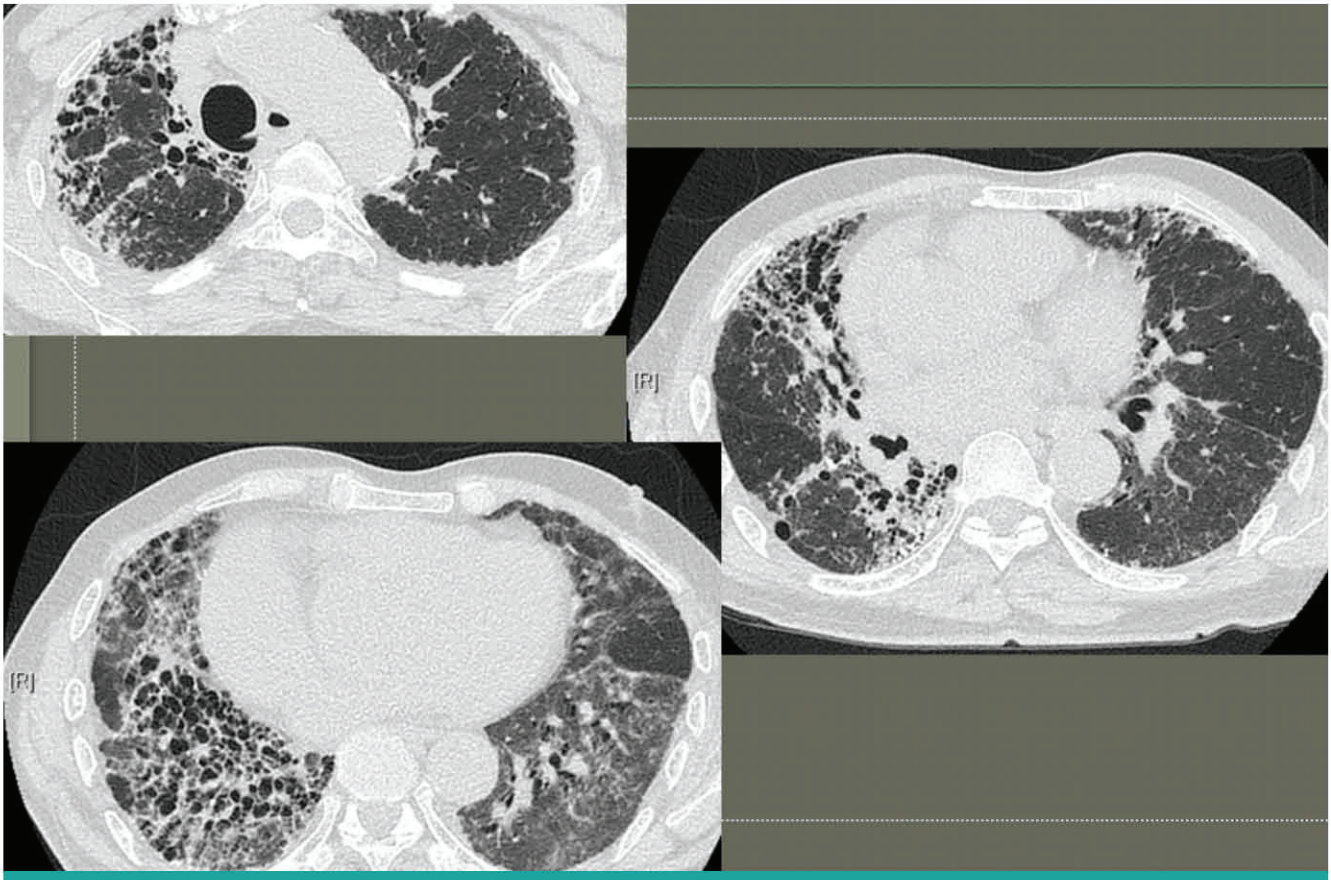

Figure 7b: HRCT at 4 years after second bilateral WLL

in another 34%. Only 7% patients required surgical lung biopsy to diagnose PAP[6]. A possible diagnostic algorithm was summarized on **(Figure 9)**.

As majority of PAP was autoimmune PAP, data of clinical course and specific treatment is mainly derived from the experience in autoimmune PAP. For autoimmune PAP, it was reported in a large series that 45% patients run a stable course, 30% spontaneously improve, and 25% progressively deteriorate[8]. Survival at 2years, 5years and 10years were 78±8%, 75±8%, and 68 ±9% respectively. Respiratory failure accounts for 72% mortality, infection in 20% and unrelated causes in 8% of patients. Secondary infection of intrathoracic and/or extrathoracic sources, community-acquired, hospital-acquired or opportunistic infection are all known complications of PAP. It is believed the underlying dysfunctional neutrophils and macrophages render PAP patients vulnerable to infection. End stage pulmonary fibrosis due to irreversible scarring is rarely seen in PAP.

Whole lung lavage (WLL) has been the most established treatment in primary and secondary PAP over 5 decades, although many aspects including its indications, setup of procedures etc remained non-standardized. WLL was generally performed under general anesthesia with double lumen endotracheal intubation. Supine, prone, or lateral position with the targeted side up, can be used. Normal saline at 37 degree celcius of 1-1.5 litres per cycle was infused to patient through the double lumen endotracheal tube to the targeted lung. The lavage fluid will be drained by gravity and the removal of fluid was facilitated by chest percussion by physiotherapist. The lavage fluid returned would be milky at the beginning and WLL is continued until the returned fluid is clear. A total of at least 10-15 cycles is generally needed. Although there is no standardized indications for WLL, in practice, WLL is considered in patients with reduced exercise tolerance, dyspnea on activity of daily living, PaO2 <60mmHg on room air, or a shunt fraction >10-12%. Complications reported include hypoxemia, hydropneumothorax, ARDS, pneumonia and sepsis. Bilateral sequential WLL in a single treatment session, and also bronchoscopic segmental or lobar lavage under local anesthesia had been performed in literatures[9].

95% patients respond to WLL within hours. Improvement in PaO2 by 20mmHg, A-a gradient by -30mmHg, FEV_1 by 0.26L, VC by 0.50L and DLCO by 4.4mL/mmHg/min were observed. 5-year survival also increases from 85±5% without WLL to 94±2% after WLL. Patients undergo a median number of two WLL per patient, and 70% patients received one WLL within 5years of diagnosis[8].

Besides considering WLL, underlying conditions should be treated in secondary PAP. Alternative treatment for the minority of autoimmune PAP patients who do not respond to WLL includes inhalational or subcutaneous GM-CSF, rituximab and plasmapharesis. Lung transplant had been performed in a patient with autoimmune PAP but unfortunately the disease recurred several years later[10]. Exogenous surfactant and bone marrow transplant had been tried in congenital and hereditary PAP.

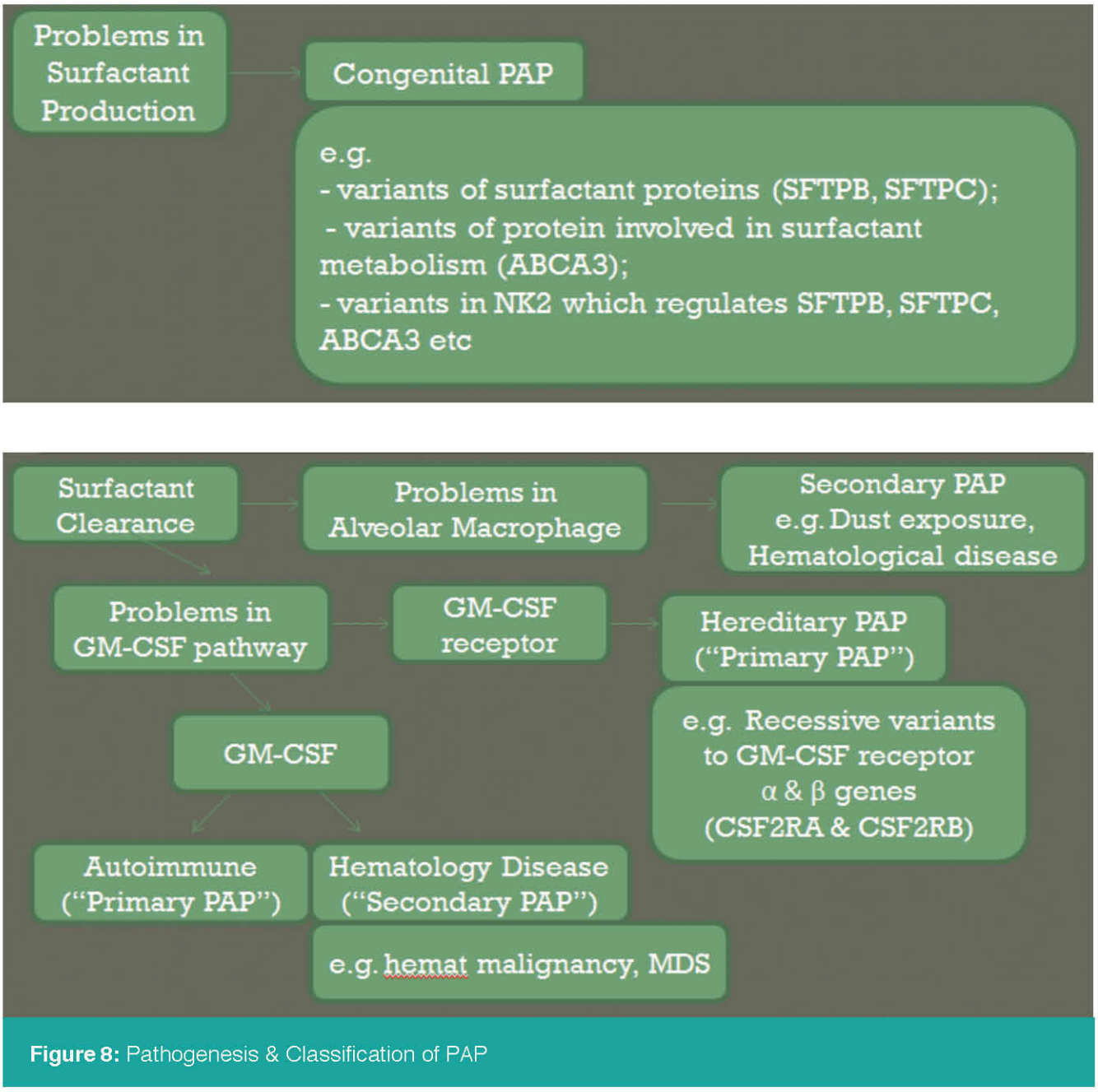

Figure 8: Pathogenesis & Classification of PAP

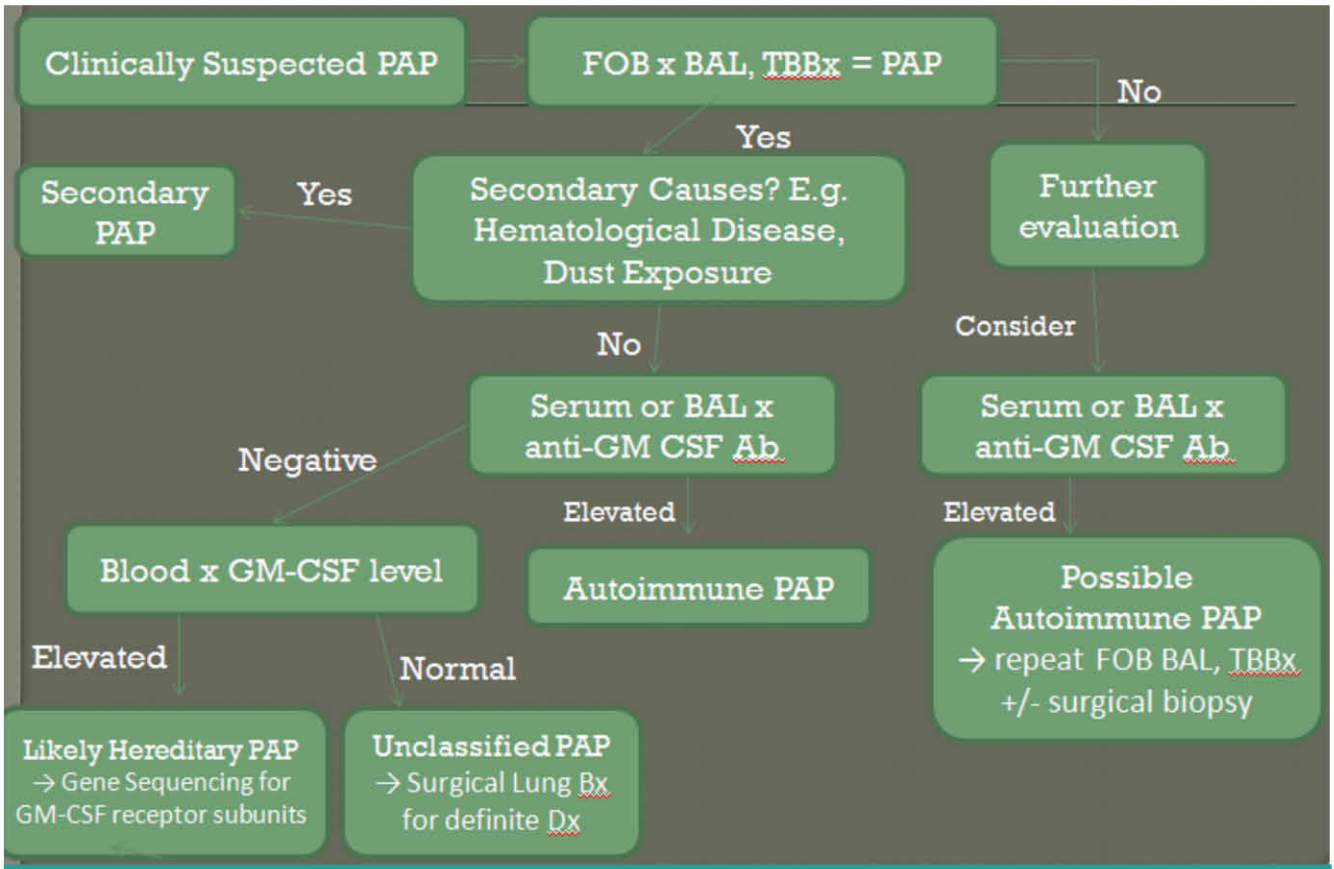

Figure 9: Possible diagnostic algorithm for PAP

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