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A CONCISE OVERVIEW PULMONARY ALVEOLAR PROTEINOSIS (PAP)

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Abstract

Pulmonary alveolar proteinosis (PAP) is a kind of Lung disease that the alveoli is filled with the Periodic Acid Schiff (PAS) and it has a Positive Proteinaceous material in lips. It is auto immune disease mostly affected by 90% of people. PAP is mainly affected by the Type-II Alveolar cells and alveolar macrophage and causes the abnormalities of Pulmonary Surfactant clearness. The Surfactant (Essential element inside the lungs that prevent the tiny air sac-Alveoli) accumulates within the alveoli due to increase production rather than decrease clearance. It blocks air entering into the alveoli and difficult to pass the oxygen into the blood result in Dyspnea and Hypoxemia. PAP causes some symptoms like a dypnea, cough, chest pain, feeling tired, fever, etc… Lessen exhaustion, coughing, and dyspnea. Take care of hypoxemia, or low blood oxygen. Take the lipoproteinaceous material out of the alveoli physically. Use GM-CSF for autoimmune PAP (aPAP) or treat related disorders (secondary PAP). Prevent respiratory failure and control infections.

Methodology: PAP was diagnosed by the chest X-ray, CT scan and confirmed by using the staining of Broncho alveolar lavage fluid(BALF).It can be Evaluated at some conditions like Pulmonary function test, Radiological evaluation, GM-CSF(Granulocyte macrophage colony stimulating factor) signalling test etc.. It has no genetic test to diagnose the Autoimmune PAP.

Results: Therapeutic decisions are largely based on disease severity and type of PAP. Patients with mild symptoms monitored by pulmonary function testing, oxygenation, and chest radiography. Patient with the severity antibiotics will be given like Rituximab (Anti-CD20 monoclonal antibody)

Key Words: BALF, GM-CSF, Surfactant and Dyspnea.

Introduction:

Pulmonary Alveolar Proteinosis (PAP) is first discovered in the year of 1958. It was described as lung disease that alveolus is filled with Periodic Acid Schiff (PAS). Positive proteinaceous material is rich in lipids [1, 2]. The Type 2 alveolar cells and alveolar macrophage are the main causes the PAP abnormalities of pulmonary surfactant clearances. [3, 4]

PAP was mainly classified into four categories based on it causes. [5, 6, 7]

- ✓ Primary is a hereditary PAP and including autoimmune.
- ✓ Secondary
- ✓ Congenital
- ✓ Unclassified form

- ➢ Autoimmune PAP is mostly affected at overall 90 percentages of people.
- ➢ PAP is affect the children rarely.[7]
- ➢ It is occurring both congenital form, hereditary forms and it is mostly prevalent in child.
- ➢ It is an Autoimmune disease and it was medicated by the immunoglobulin (Ig G), Anti Granulocyte Macrophage-Colony Stimulation Factor (Anti GM-CSF) antibodies that cause decreases the alveolar macrophage function.[8]
- ➢ Diagnosis of PAP is done with blood test, Computed Tomography (CT) scan, X-ray than after confirmed by using staining of Bronchi Alveolar Lavage Fluid (BALF).[9]
- ➢ PAP is also known as Pulmonary Alveolar Lipoprotein (PAL) or phospholipids and it was first diagnosed at 1958.
- ➢ In this disease the surfactant has been accumulates within alveoli due to increase production and decrease clearance rather than. They blocks air from entering alveolar and oxygen from pass through in the body after result is cough, fatigue, weight loss, fever, dyspnea and hypoxemia.[10]
- ➢ Secondary PAP is that involve haematological disorder malignant and non- malignant that have chronic inhalation of toxic substance involved indium, aluminium, titanium silica or cellulose fibres with immune deficiencies.[11]
- ➢ Genetic PAP is affecting only children and involved MARSI-related, mutations in GM-CSF macrophage receptor gene etc… [12]

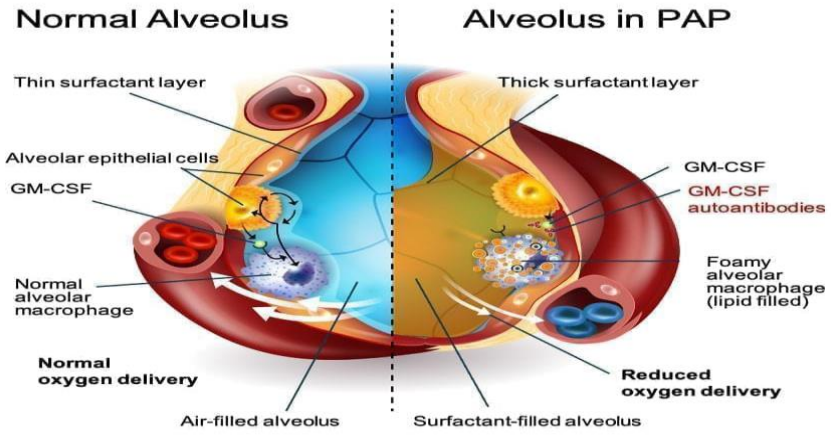

Fig. 1 Difference between Normal alveoli and PAP Alveoli

Causes of Pulmonary Alvelor Proteinosis

- ➢ Primary cause
- ➢ Secondary cause
- ➢ Genetic cause

A) Primary causes

IgG, anti GM-CSF, Deficiency in GM-CSF receptors.

B) **Secondary cause**

Kaolin, indium, titanium, talc, silica, aluminium, HIV infection, chemotherapy, organ transplantation, agammaglobulinemia, dermatomyositis, rheumatoid arthritis, Behcet's disease. [13, 14, 15]

C) Genetic causes

1. **SFTPB-Surfactant Protein B, (Pulmonary Surfactant-Associated Protein B)**

It is an essential, hydrophobic protein crucial for lung function, encoded by the *SFTPB* gene on human chromosome 2. It lowers surface tension in pulmonary alveoli, preventing lung collapse during breathing, and is vital for the proper spreading of surfactant. Deficiencies cause fatal respiratory distress, and it is a biomarker for lung cancer.

2. **SFTPC- Surfactant Protein C (or Surfactant Associated Protein C)**

SFTPC (Surfactant Protein C) is a gene encoding an extremely hydrophobic, lung-specific protein (SP-C) essential for reducing alveolar surface tension and preventing lung collapse. Produced by alveolar type II cells, it facilitates the spreading of pulmonary surfactant, which is critical for breathing and lung homeostasis

3. **Mutation/Loss of function in the NKX2-1 Gene,**
4. **ABCA3- ATP-Binding Cassette Subfamily A Member 3,**
5. **SLC7A7- SLC7A7 (Solute Carrier Family 7 Member 7)**

1. Toxic Exposures

- Aluminum dust → Lymphoid leukemias
- Cement dust → Myeloid leukemias
- Silica dust → Aplastic anemia
- Paint, Varnish, Petroleum → Hematological disorders
- Chlorine, Nitrogen dioxide → Immunodeficiencies

2. Infections

- AIDS → Immunodeficiency
- Pneumocystis jirovecii, Histoplasmosis, Cryptococcosis → Chronic infections
- Mycobacterium species → Immunodeficiencies
- Cytomegalovirus → Immunodeficiency

3. Immunodeficiencies

- Severe combined immunodeficiency → Increased risk of infections
- Immunoglobulin A deficiency → Increased risk of infections
- Thymic lymphoplasia → Immunodeficiency

4. Hematological Disorders

- Lymphoid leukemias, Myeloid leukemias, Non-Hodgkin's lymphoma → Cancer
- Myelodysplastic syndromes → Aplastic anemia
- Multiple myeloma, Waldenstrom's macroglobulinemia → Cancer
- Idiopathic thrombocytopenic purpura → Hematological disorder

- Amyloidosis → Chronic infections

Pathophysiology:

- Surfactant
- Surfactant homeostasis
- Primary
- Secondary
- Congenital

SURFACTANT:

- It is one of the essential elements lungs that present the tiny air sacs prevent from collapsing the alveoli. The decrease level of surfactant tension in the lungs can leads to the breathing easily. [16]
- They have 4 types' surfactant proteins A, B, C, D.
- These molecules is cross ponds to genes
  - SFTPA- Surfactant Associated Protein A,
  - SFTPB- Surfactant Associated Protein B,
  - SFTPC- Surfactant Associated Protein C,
  - SFTPD- Surfactant Associated Protein D.
- Eosinophilic material is included surfactant accumulation.
- It is one of the types of alveolar anti-infection defence.
- GM-CSF host cell include pulmonary bacterial, viral and fungi infection.

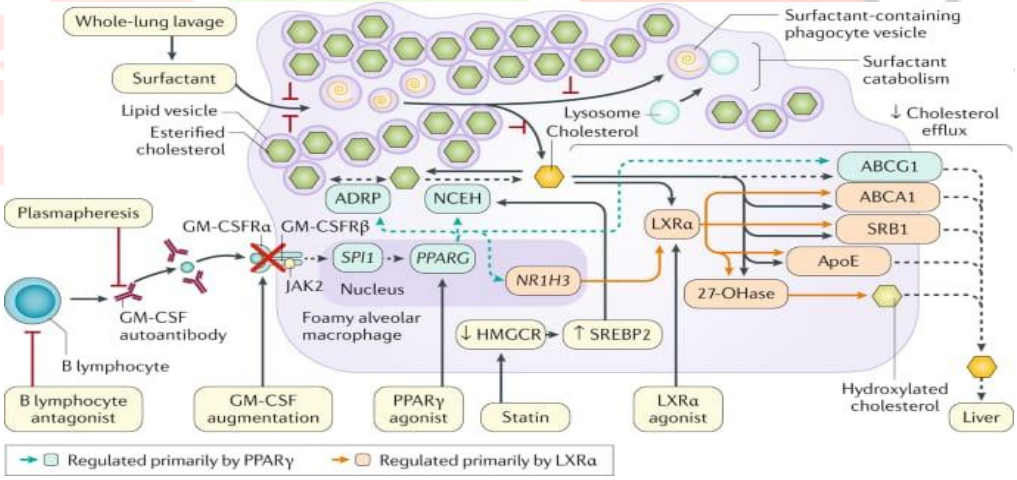

Fig.2 Mechanism of Surfactant

- Antibodies that interfere the cytokine leads to increase opportunistic infection.
- Lamellar bodies intracytoplasmic they stored at surfactant lipids.
- GM-CSF (Granulocyte macrophage-colony stimulating factors) that is one of major role in the pathophysiology of PAP. [17,18,19]

Surfactant Homeostasis:

- It is decreasing surface tension allow for low level gas exchange that also provides first line defence against microbial pathogens.
- Surfactant is Composed of
  - 80% - Polar phospholipids
  - 10 % - Cholesterol
  - 10 % - Surfactant protein[20,21]
- They are two forms,

1. Autoimmune PAP
2. Hereditary PAP

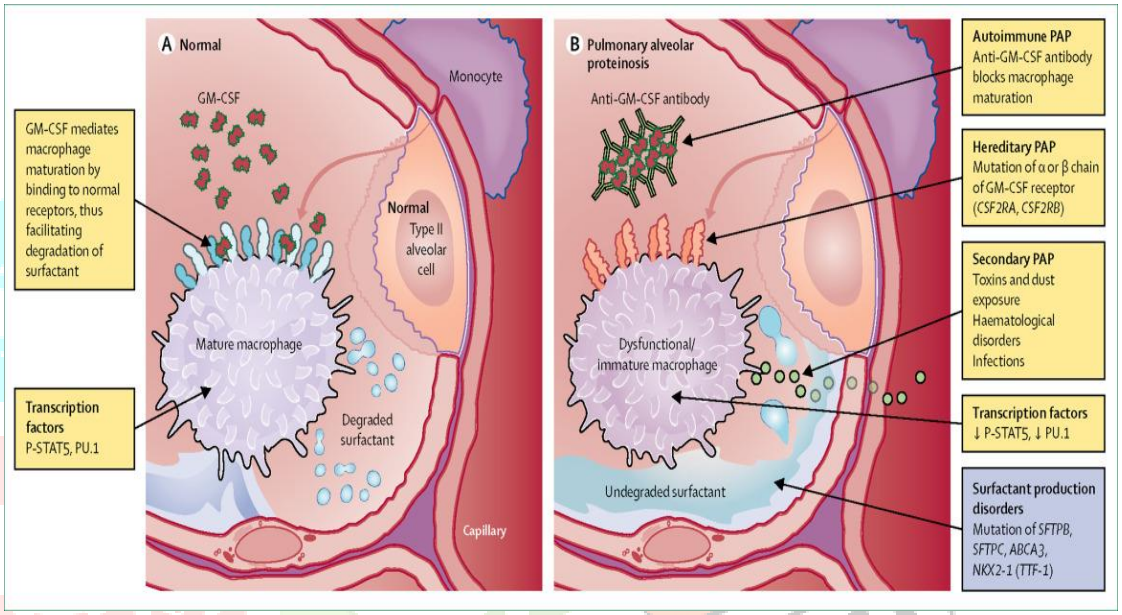

Fig.3 Mechanism of Pulmonary Alveolar Proteinosis.

Auto immune PAP (Primary):

GM-CSF is normal level in Broncho alveolar lavage fluid. If it is elevated (or) identified IgG, anti GM-CSF levels are observed in BALF and serum in autoimmune PAP patient. [22, 23]

Hereditary:

- It is caused by mutations in the gene that encode the alpha and beta sub units GM-CSF receptor include CSF2RA, CSF2RB.
- CSF2RA is gene on chromosome X and the beta chain enclosed by the CSF2RB gene chromosome.
- Signalling pathway involving transcription PU, PPAR α and PPAP
- Mostly affect girls with symptoms usually appearing with first few of life. [25,25]

Symptoms:

- The symptoms similar to the other lung disease.
- That may be indicating precancerous or cancerous changes.
- It is detected after an abnormal chest X- rays.
- Sometimes people have recurrent pneumonia, bronchitis, asthma or emphysema.
- PAP Symptoms include Shortness of breath, cough, chest pain, feeling tried, fever, weight loss, cyanosis and clubbing. [26]

Evaluation:

A) Pulmonary function test
B) Radiological evaluation
C) Bronchoscopy findings
D) GM- CSF Auto antibody test
E) GM-CSF signalling test
F) Genetic test
G) Lung biopsy
H) Diagnosis

A) Pulmonary function test:

- It is clinically acute in autoimmune PAP but in sometimes among the least well-defined manifestations of the disease.
- Autoimmune PAP is many patients have a normal spirometry result found.
- Lung volume should have be normal in patient with mild disease.
- Show may restrictive ventilatory pattern is impairment of disease severity.
- DLCO is one of that typically reduced in proportion of disease severity induced at mostly autoimmune PAP.
- After 6-minute walk that can be identify exercise induced decline in SPO2 (peripheral blood oxygen saturation), but hindered by variation in patient.
- Arterial blood gas analysis generally decrease in PO2, increase alveolar arterial (A-aDO2) increase arterial shunt fraction.
- Paco2 in unaffected unless respiration.
- Increase A-Ddo2 and exercise induced reduction in Pao2 correlate with decrease DLCO providing useful measure. [26,27,28,29]

B) Radiological evaluation:

- Radiographic is findings the left heart failure but without pulmonary edema.
- Its radiography patient with autoimmune PAP reveals nonspecific, diffuse, bilateral air space disease.
- High- resolution CT (HRCT) reveals a pattern of crazy glass.

- Thickening referred to crazy paving. [30,31]

C) Bronchoscopy findings:

- It is one of the type identifications of PAP that is examination of the airway unremarkable in autoimmune PAP.
- BAC fluids have been distinctive, opaque milky white/yellow appearance in non-smoker etc.
- BAC cytology reveal scopious extracellular debris, lymphocytes, fragmented cells in various stage of delay and isolated nuclei.
- It have been neutrophils and other inflammatory cells present. [26,32,33]

D) GM-CSF Auto antibody test:

- Increase patients with autoimmune PAP but con. Do not correlate at disease severity, prognosis, PFT.
- Diagnostic testing that should be provided at specific centres located in the United States, Europe, China and Japan. [28,34-37]

E) GN-CSF Signaling test:

- It is BAP IA caused by blocking GM-CSF signalling several measures of GM-CSF neutralizing the blood.
- GM-CSF index test measures the ability of exogenously added GM-CSF to STAT5 phosphorylation in leukocytes freshly.
- GM-CSF binding affinity or decrease concentration of autoantibodies increase GM-CSF binding capacity in that test. [38-40]

F) Other laboratory test:

- It is nonspecific but is elevated in proportion of disease severity as measured by A-aDo2
- Serum concentration of SPs (SP-A-SP-D) YKL-40(chitinare-3 like protein), MCP-1, (Krebs von den Lungren protein-6) often elevated in autoimmune PAPand degree increase correlates with disease severity. [41-45]

G) Genetic test:

- It is having no genetic test are available to diagnose autoimmune PAP. [46,47]

H) Lung biopsy:

- Cardinal features of lung histopathology in autoimmune PAP that included alveoli filled with some granular eosinophilic material and well-preserved septa etc….
- Patchy involvement of the lung autoimmune PAP,lung biopsy's fail to identify the presence of PAP in a substantial number of causes 29% in one report. [48,33,49]

Diagnosis:

- It is diagnosis of autoimmune PAP is challenged is low prevalence, nonspecific, radiographic finding, minimal physical examination finding etc…
- Appropriate therapy is until pneumonia failure sever

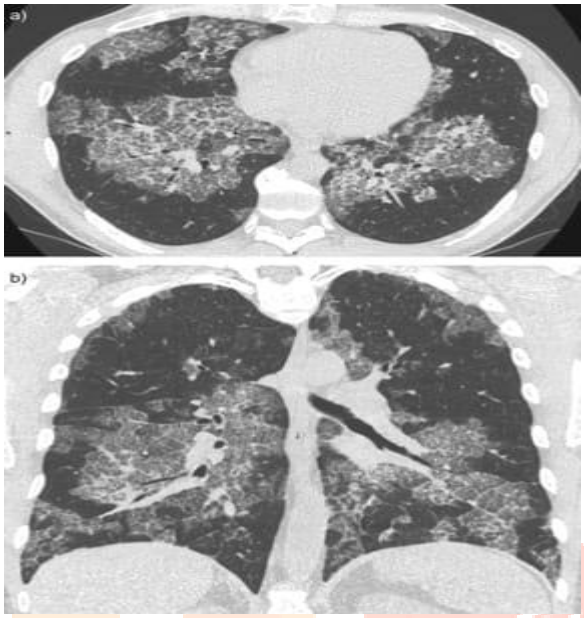

Fig.4 MRI scan of PAP

Treatment:

They are having be limited evidence comparing of various treatment Included:

A) Whole lung lavage

B) GM-CSF Supplementation

C) Rituximab

D) Plasmapheresis

E) Lung Transplantation

F) Glucocorticoids.

G) Other Agent of potential use:

H) Gene therapy

I) Supportive Care. [55-59]

A) Whole lung lavage:

- PAP use for the first line therapy**.** It is most widely used in this type but there are have no specific guidelines for patient.
- Its literature have been patient Suggested with in hypoxemiaat partial pressure of oxygen (paosless than 70 mm Hg on room (or) poorgas that exchange indicated by increase oxygen gradient greater than 40 mm Hg benefit from the WLL.

- They Including Respiratory Symptomslike that declining oxygenation, worseningdisease imaging and declining lung function. [60,61]

B) GM-CSF supplementation:

- PAP patient when they GM-CSF auto antibodies are

normal and there is no secondarycause are identified.

- It is a next diagnostic step of measurement the serum GM-CSF concentration and GM-CSFsignalling.
- GM-CSF concentration is typically >10pg/ml where is 7pg/ml in healthy.
- In this signalling test used to confirm the GM-CSF receptor dysfunction but they only used in laboratories.
- Subcutaneous Injections of GM-CSF showed a positive response48%. of small cohort of 25 patient.
- Improvement follow GM-CSF Injection was much slow than WLL. [62-64]

C) Rituximab:

- Rituximab a monoclonal antibody targeting CD20 on the B lymphocyte that explored the therapeutic option in PAP.
- It is generally considered ass the safe therapeutic agent and it used wide range of autoimmune and hematologic disorder.
- They work by depletion of B cells and can be decrease product of (GM-CSF) autoantibodies.
- The CD20 B cell and reducing antibodies the autoantibody levels that may be reduced autoimmune PAP.
- Then it not sufficient considered as first line therapy because is selected patients with refractory PAP a trial of lung be reasonable. [66-68]

D) Plasmapheresis:

- GM-CSF antibodies and plasmapheresis have a potentially reduce the circulating antibodies and restore the surfactant hemostatsis.
- They have improved the chest radiography and arterial oxygen concentration is from 50 to 70 mmHg.
- They have been no significant in clinical change. [70-72]

E) Lung transplantion:

- In this method should include by the selected candidates only used.
- Lung transplantion is possibility of patient have minimal to no response at the measurement progressive clinical deterioration.
- It is mainly having patient with progressive pulmonary fibrosis. [73,74]

F) Glucocorticoids:

- Auto immune disease they treated with the corticosteroids have been used for treatment of PAP.
- It is increasing mortality was attributed with new infection of patient.
- Corticosteroids cause at harm they under not recommended at for the PAP.[75]

G) Other agent of potential use:

- In this method mouse PAP model is lipid content at both alveolar macrophage and type 2 epithelial cells, two primary cells involved in the homestasis.
- It react publication have some reported use of pioglitazone and thiazolidinedione to ameliorate.
- They have been large-scale trials remain to be seen [76, 77].

H) Gene therpay:

- It is important role in hereditary PAP.
- Induced pluripotent stem cells (IPSC) possible at vitro generation of macrophages.
- Its functional macrophages that recapituale the pathognomonic defects of GM-CSF signalling at macrophage function. [78,79]

I) Supportive care:

- Then patient have be high risk for infectious complications give macrophage dysfunction.
- Patients counselled for immunizations, including annual influenza and appropriate the pneumococcal and COVID 19 vaccine.
- Smoking should be avoiding the patient advised.
- Like that chronic disease required management of control the systems.[80]

Conclusion:

- ✓ Therapy of PAP is the relative place of whole lung lavage, GM-CSF supplement therapy and anti-body targeted treatment.
- ✓ PAP is lung disease that accumulation of surfactant material present in the lung.
- ✓ PAP include a ‘crazy paving pattern on high resolution CT.
- ✓ In this article was the pathogenetic mechanism of three types of PAP (primary, secondarycongenital)

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