GENERAL APPROACH OF THE PATIENT WITH DIFFUSE PARENCHYMAL LUNG DISEASE

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Definition: multiple disorders characterized by inflammation and fibrotic changes affecting no only the interstitium, but pleura, airways, vessels, and epithelial cells of the alveoli and bronchioles. For this reason, the term Diffuse Parenchymal Lung Disease (DPLD) is considered correct. Generally, both lungs are affected. The clinical presentation can be Acute, Subacute or Chronic. There are identified causes in some cases, being the more common, Connective Tissue disease (CTD), Granulomatous disorderes and Drugs or environmental exposures. There are specific forms of DPLD as well, like Lymphoangiogliomyomatosis (LAM) or Pulmonary Langerhans Cell Hystiosytosis (PLCH), and finally the most important group corresponds to The Idiopathic Interstitial Pneumonias (IIP).

Initial evaluation of the patient with suspected DPLD:

Is fundamental creates a clinical, radiological and pathological correlation in each case. Like other medical entities, is necessary start with a good clinical history and complete physical exam characterizing gender, age and smoking history. Then, do a careful documentation of past medical history and occupational and environmental exposures. Follow with evaluation of CXR/HRCT, some specific blood tests and Bronchoscopy (BC), Bronchialveolar lavage (BAL) and Pulmonary Biopsy (Transbronchial or open) when indicated. Among exposures, evaluate for smoking habit, asbestos, silica, beryllium, hard metals, environmental (hobbies), drugs.

Signs and Symptoms:

Dyspnea: patients with Sarcoidosis, Silicosis, PLCH can have extensive parenchymal lung disease without significant symptoms. Cough: when there is airway involvement. Main causes: Sarcoidosis, Organizing Pneumonia (OP), Respiratory Bronchiolitis (RB), PLCH, Hypersensitivity Pneumonitis (HP), Hemoptysis: seen in cases of Diffuse Alveolar Hemorrhage (DAH), LAM, Pulmonary Veno-occlusive disease (PVOD), vasculitis. Wheezing and Chest Pain: are rare symptoms in DLD. Findings consistent with CTD: musculoskeletal pain, arthritis, rash, fever, fatigue, raynaud's phenomenon, dry eyes-mouth, gastro-esophageal reflux (GERD). Physical Exam: there are not specific findings, but is necessary look for: Clubbing, which is seen mostly in Idiopathic Pulmonary Fibrosis (IPF) and Non-Specific Interstitial Pneumonia (NSIP).

Bibasilar crackles ("Velcro"), which are documented in 85% of IPF patients. Cutaneous findings: in cases of Polymyositis or Dermatomyositis (PM/DM). Extrapulmonary findings: specially in cases of Sarcoidosis and CTD. Laboratory Tests: often not helpful in the differential diagnosis, but at the time of the initial evaluation, the more important tests are:

For possible associated CTD: Antinuclear Antibodies (ANA), Rheumatoid Factor (RF), Anti-DNA/Anti-Sm, Anti-Jo antibody, CPK, anti-Ro, anti-SSA. For possible. HP: Hypersensitivity Precipitin panel, If possible Vasculitis, ANCA. Others: ESR/CRP/ACE levels.

Chest Image: the CXR can be normal up to 10% of cases, specially in HP. The more important tool in DPLD, is the High Resolution Chest CT (HRCT), when detailed evaluation of the pattern and distribution is done.

-This topic will have a special review forward.-

Pulmonary Function Tests (PFT):

Spirometry – Lung Volumes – DLCO – Resting ABG. Most of cases of DPLD have a Restrictive Pattern with reduction in TLC, FRC and RV. Flow rates are decreased (FEV1 – FVC) with normal or increased FEV1/FVC ratio. A pattern of airflow obstruction is suggestive of Sarcoidosis, LAM, RB-ILD, PLCH or COPD with associated DPLD. Severe decreased DLCO: in cases of Scleroderma, PVOD, PLCH, LAM, PAP, associated Emphysema. 6 Minute Walking Test (6MWT): indicated to evaluate severity, the need for supplemental O2 and follow up evolution.
Laboratory test | Indications | Interpretation
--- | --- | ---
CBC count, LFT, creatinine, BUN | All patients suspected to have ILD | Cosinophilia (CEP, drugs), normocytic anemia (CTD), Fe-deficiency anemia (DAH), leukopenia/thrombocytopenia (CTD, sarcoidosis, lymphoma), liver disease (sarcoidosis, amyloidosis), renal disease (CTD, amyloidosis, WG, Goodpasture’s syndrome)
Aldolase, creatine kinase, Jo-1 antibody immunoglobulins | Muscle pain, weakness clinically suspected or histopathologic diagnosis of LIP | Elevated values are supportive of PM low levels of immunoglobulins may indicate a diagnosis of CVID
Urinary sediment | Suspected vasculitis (CTD, WG, MPA, Goodpasture syndrome) | RBC casts or dysmorphic RBCs suggest systemic vasculitis
ANA, RF | Suspected ILP, IP; CTD or ILD for which CTD cannot be ruled out | Low titters of ANA (<1:160) a nd RF occur in 10-20% of patients who have IPF Positive C-ANCA or antiproteinase 3 is most suggestive of WG; P-ANCA may be seen in WG, but suggest MPA
C-, P-ANCA | Suspected Goodpasture syndrome (i.e. DAH) | Positive result in patient who has DAH is diagnostic of Goodpasture’s syndrome Interpret within clinical context; a negative result does not rule out HP; a positive result is not diagnostic of HP Suggests possibility of sarcoidosis, but is insensitive and nonspecific for sarcoidosis
Anti-GBM antibody | Exposure history appropriate for HP sarcoidosis | Specific serum precipitins
Scrum ACE | Subacute symptoms (weeks to months):
- Organizing Pneumonia (OP).
- Acute Hypersensitivity Pneumonitis (HP).
- Drugs or CTD related.
Chronic: months to years:
- Idiopathic Pulmonary Fibrosis (IPF)
- No-specific Interstitial Pneumonia (NSIP).
- Chronic HP.
- Chronic occupational related .
- CTD related.
Symptoms:
Cough: indicates compromise of the airways, so, in this case, the diagnosis of RB-ILD, Sarcoïdosis, HP or GERD need to be considered. In case of chronic irritable cough, the differential is Lymphangitic carcinomatosis and in case of purulent sputum, associated bronchiectasis is a possibility.
Hemoptysis: in DAH, in cases of pulmonary capillaritis or vasculitis such as Wegener Granulomatosis or Goodpasture syndrome. Pleuritic Chest pain: rule out Pneumothorax, which could be related with LAM or PLCH.
Wheezing: is rare is cases of DPLD. If present, consider diagnosis like Allergic Broncho Pulmonary Aspergillosis (ABPA), Churg Strauss Syndrome or Chronic Eosinophilic Pneumonia.

Bronchoscopy and BAL

BAL is a helpful tool when is necessary rule out infectious processes like Tuberculosis (TB), Histoplasmosis, Coccidioidomycosis or other fungal infections. The cell profile will help if Lymphocytosis, which will favor Sarcoïdosis diagnosis, or when over 50%, indicating HP, or in case of eosinophilia (eos over 25%) in chronic or acute Eosinophilic Pneumonia (EP).

Regards Transbronchial Biopsy (TBB): is helpful in cases of suspected Sarcoïdosis and LAM, but due to small size and sampling variability can not establish the diagnosis of entities like IPF or ILD. For this reason the open lung Biopsy is really important. Its need to be considered in patients younger than 50 y/o, with atypical features like fever, weight loss, progressive course, signs of vasculitis, or when unexplained extra-pulmonary manifestations or pulmonary vascular disease of unexplained origin are found. Other indications are: evaluate disease activity, exclude neoplastic or infectious processes and make a definitive diagnosis and predict prognosis before proceeding with therapies with a lot of side effects.

Clinical evolution:

History of onset of Pulmonary symptoms:

Acute symptoms: days to a few weeks:
- Rule out infection.
- If not, then, consider: Organizing Pneumonia (OP), Acute interstitial Pneumonitis (AIP), Acute Eosinophilic Pneumonia (AEP), Drug induced toxicity or Hypersensitivity Pneumonitis (HP).
- When rapid progress to Respiratory Failure, more possible diagnosis are Acute Interstitial Pneumonia or Acute Eosinophilic Pneumonia.

Other: birds contact, sauna, hot tub: HP

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Since 1892, Osler used the term «cirrhosis» of the lung, referring to Interstitial Lung Disease. Later in 1940, Hamman and Rich, described 4 cases of Acute Diffuse Interstitial Fibrosis, and then, the term Hamman-Rich syndrome was coined in cases of any diffuse idiopathic fibrotic lung disease, chronic or acute. In 1964, Scadding, used the term «Diffuse Fibrosing Alveolitis» and later this entity was divided based on etiology and histopathology.

In the same decade (1969), Liebow and Carrington, proposed the pathologic classification for Interstitial Pneumonia. The term «idiopathic» became attached to this group of interstitial pneumonias in subsequently as it was recognized that these entities occurred in the absence of detectable cause. This first classification of Interstitial Idiopathic Pneumonias was based on 5 groups: Usual Interstitial PNA (UIP), which was called Hamman-Rich Syndrome in case of acute clinical presentation, Bronchiolitis Obliterans Interstitial Pneumonia (BOOP), Lymphocytic Interstitial PNA (LIP), Desquamative Interstitial PNA (DIP) and Giant Cell interstitial Pneumonia (GIP).

In 1998, Katzenstein and Myers redefined (including 2 Liebow’s entities) and included 4 categories: Usual Interstitial PNA, Desquamative Interstitial PNA/ Respiratory Bronchiolitis Interstitial Lung Disease, Acute Interstitial PNA, Nonspecific Interstitial PNA. This classification did not include BOOP. Later, Muller & Colby included its. At this time, GIP was known be related with hard-metal exposure and LIP was considered lymphoproliferative disorder and associated with HIV infection and CTD, so, both entities were excluded from the IIP group.

CURRENT CLASSIFICATION:

The ATS/ARS concensus in 2002, defined the IIP:

Usual Interstitial PNA
Desquamative Interstitial PNA
Bronchiolitis Obliterans Interstitial Pneumonia
Respiratory Interstitial Pneumonia
Acute Interstitial PNA
Nonspecific Interstitial PNA

Usual Interstitial PNA
Desquamative Interstitial PNA
Bronchiolitis Obliterans Organizing PNA
Acute Interstitial PNA
Nonspecific Interstitial PNA

Respiratory Bronchiolitis Interstitial Lung Disease
Desquamative Interstitial Lung Disease
Nonspecific Interstitial Lung Disease

And this classification was reviewed later:

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IDIOPATHIC INTERSTITIAL PNEUMONIAS

USUAL INTERSTITIAL PNEUMONIA (UIP): is an histologic pattern seen in the setting of diffuse, bilateral interstitial lung disease, characterized by patchy, temporally heterogeneous fibrosis, distributed mostly along the subpleural and paraseptal regions. In idiopathic clinicopathologic syndrome, UIP is synonymous with idiopathic Pulmonary Fibrosis, but, if the etiology is identified is wrong call UIP as an equivalent to IPF: for instance, UIP associated with Reumathoid Arthritis (or talk about «UIP pattern»).

Histologic features of the UIP pattern: hallmark of the UIP is the patchy interstitial fibrosis, often in subpleural and/or paraseptal distribution, alternating with areas of normal lung. Clinical features: most common in men, Age 50 – 70 y/o. Cigarette smoking results in a 1.6 – 2.3 fold excess risk of developing pulmonary fibrosis. Long term exposure to metal dust or wood has also been shown to be an independent risk for IPF. Clinical presentation is characterized by an onset of shortness of breath plus no productive cough, over 12 to 18 months. Constitutional symptoms are uncommon. At PE tachypnea, clubbing and «Velcro» crakles are found.

The PFT can show Restriction and decreased DLCO. Increased neutrophils and eosinophils may be a characteristic in th BAL. Now, is recognized that a clinical diagnosis of IPF can be made with a high degree of certainty. Careful exclusion of alternative etiologies through multidisciplinary discussion between pulmonologist, radiologists and pathologists experienced in the diagnosis of ILD is the utmost importance to an accurate diagnosis. Given the high quality evidence regarding HRCT specificity for the recognition of histopathologic UIP pattern, surgical lung biopsy is not essential, and in the appropriate clinical setting, the presence of a UIP pattern in the HRCT is sufficient for the diagnosis of IPF. Thus, the major and minor criteria for the clinical (no-pathological) diagnosis of IPF have been eliminated. Then, the diagnostic criteria for IPF are:

- Exclusion of other known causes of ILD (exposures, CTD, drug toxicity).
- Presence of UIP pattern on HRCT in patient no subjected to lung biopsy.

NONSPECIFIC INTERSTITIAL PNEUMONIA (NSIP): An idiopathic interstitial pneumonia with a histologic appearance that does not conform to the characteristics features of UIP/DIP/RIB-ILD/DAD or COP. Recently been recognized as a distinctive IP that can occur either as an idiopathic disease or associated with a variety of conditions: CTD, resolving DAD, Drug reactions. Most common cases are idiopathic, but, main relation is with CTD and Drug reaction.

Main histologic feature of NSIP is the temporally, uniform, homogeneous appearance of either inflammation or fibrosis. The relative amounts of cellular infiltrates, assign to the «cellular» and «fibrotic» variants of NSIP, and this grading is prognostically relevant.

Average duration of symptoms, prior to diagnosis is 8 to 18 months. More common in women. Age 45 to 57 years. Most patients are current or former smokers. Patients present with dry cough, progressive dyspnea, fever. Laboratory are non-specific. The BAL may show increased lymphocytes. Restrictive pattern in the IPF and decreased DLCO are also characteristic.

CRYPTOGENIC ORGANIZING PNEUMONIA: is a distinct clinicopathologic entity, characterized by the presence of widespread organization (proliferation of granulation tissue) within the alveolar ducts and alveoli, with or without bronchiolar intraluminal involvement. The alveolar filling process is produced by the accumulation of contractile fibroblasts (myofibroblasts), which form branching or isolated polymoid formations (known before as Masson’s bodies). The main difference of this Masson’s bodies here v/s UIP is the location: mural in UIP and intra-alveolar in COP. On of the problems with understanding the concept of COP is that the histologic pattern is a common nonspecific reaction to a wide variety of types of lung injury. Infections, CTD, inhalation injuries, HP, lung radiation are the most frequently associated conditions. Given this, is considered a diagnosis of exclusion.

Age of presentation is between fifth to sixth decade of life. Patients present with symptoms of less than 2 months duration, with persistent no productive cough and shortness...
of breath. Fever, malaise, fatigue and weight loss could be present as well. ESR and CRP may be elevated. PFT shows Restrictive pattern and DLCO is decreased. Increased lymphocytes, eosinophils or neutrophils may be a characteristic in the BAL. The CD4/DC8 ratio is decreased.

**DIFFUSE ALVEOLAR DAMAGE (DAD) / ACUTE INTERSTITIAL PNEUMONIA**: is a form of acute lung injury that progresses through an exudative phase with pneumocytes and endothelial cell necrosis, edema and formation of hyaline membranes, to an organized phase with interstitial fibrosis and type 2 pneumocyte proliferation. Endo-alveolar organization similar to that observed in Organizing Pneumonia and areas of NSIP can be observed. In 50% of the cases there is total recovery to the original state, and in the other 50% of cases there is progression to the fibrotic phase. If not etiology is identified, is considered Acute Interstitial Pneumonia. The clinical syndrome associated with DAD is the Acute Respiratory Distress Syndrome (ARDS).

**Diagnostic criteria:**
- acute onset of illness
- bilateral opacities on CXR
- PaO2/FIO2 ratio less than 200
- PAC wedge pressure less than 18

**Histologic findings are characterized by three phases:**
- The exudative phase: present during the first week. Congestion of alveolar edema, intra-alveolar hemorrhage and hyaline membranes, which are the histologic hallmark of this phase.
- The proliferative (organizing) phase: at the end of the first week, the exudate within the interstitium and alveolar spaces begins to organize and there is proliferation of pneumocytes type II and fibroblasts.
- The fibrotic (chronic) phase: seen in after three or four weeks on ventilator. There is remodeling with dense fibrous tissue, in both lungs.

**ACUTE FIBRONOUS AND ORGANIZING PNEUMONIA (AFOP):** histologic pattern consisting of prominent intra-alveolar fibrin and organizing pneumonia, but lacks of hyaline membranes or eosinophilia. Appears to be the answer to acute lung injury but differs from DAD/COP or EP. Can be idiopathic or an etiology could be identified. Clinical course is similar to DAD.

The dominant histologic finding is the presence of intra-alveolar fibrin (different from COP), in the form of fibrin "balls" within the alveolar spaces.
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No hyaline membranes (different from DAD). There is association with organizing pneumonia consistent in intraluminal loose connective tissue within the alveolar ducts and bronchioles.

RESPIRATORY BRONCHIOLITIS-ILD (RB-ILD): is a mild form of ILD characterized by chronic bronchiolitis in which pigmented macrophages accumulate within respiratory bronchioles and adjacent alveolar spaces.

Has a strong relationship with smoking (cigarette smokers): current or between 6 months of diagnosis. Average age of diagnosis 36 years. No gender difference. Clinical presentation is characterized by cough and dyspnea. Fine, bibasilar, end inspiratory crepitations are found. Laboratory findings are non specific. In the PFT, mixed pattern: Restrictive/Obsrictive is characteristic, with associated decreased DLCO.

DESQUAMATIVE INTERSTITIAL PNEUMONIA (DIP): pathologic entity found almost exclusively in current or former smokers. Characterized by diffuse accumulation of macrophages in the airspaces without prominent fibrosis or honeycombing.

Present at fourth or fifth decade of life. Clinical presentation is subacute (weeks, months), with dyspnea and cough as main symptoms. Restrictive pattern if found in the PFT and the BAL shows hypercellularity with increased number of macrophages.

LYMPHOCYTIC INTERSTITIAL PNEUMONIA (LIP): clinicopathologic disorder characterized by diffuse lymphocytic infiltrate with important follicular reaction along lymphatic routes. The majority of cases are associated with immunologic disorders, dysproteinemias or viral infections (particularly HIV), but, in some cases is idiopathic, and for this reason was classified initially as a ILP, but, a reviewed ATS/ARS concers left this entity as a no ILP.

LIP is seen mostly in HIV-infected children (specially HIV perinatally acquired), with 6% incidence. Between HIV-infected adults, the incidence is only 1%. Clinical presentation of cough, dyspnea and fever in a patient with known HIV-Complex. In cases no associated with HIV: the adults can have different disorders, the more common being Sjogren's Syndrome: up to 0.9% of patients with Sjogren's develop LIP and up to 25% of patients with LIP have Sjogren's. Most common in women, between 50 – 70 y/o.

The clinical presentation is characterized by the baseline process (CTD) plus dyspnea and cough. Dysproteinemia with hypergammaglobulinemia are found. Increased lymphocytes in BAL with restriction pattern in the PFT and decreased DLCO, are characteristic.

OTHER FORS OF ILD

HYPERSENSITIVITY PNEUMONITIS (HP): also known as an Extrinsic Allergic Alveolitis. Is a diffuse interstitial lung disease that represent granulomatous reaction to inhaled organic antigens or simply chemicals. HP or allergic processes involving the lung include HP, ABPA, Drug reactions. Is a syndrome of varying intensity, clinical presentation and natural history, rather than a single, uniform disease.

No smoker related. Only a minority of individuals expose to the Antigen develops the disease. Could be Acute, Subacute or Chronic. Acute HP: follows heavy exposure to an Antigen in a previously sensitized person, with abrupt onset, 4-6 hours after the exposure, with fever, chills, malaise, cough, chest tightness and dyspnea without wheezing. These symptoms subside over hours or days.

Subacute HP: breathlessness and cough over days or weeks, which presents insidiously. Chronic HP: insidious or chronic form which result from continued, usually low level of antigen exposure. Irreversible lung changes like fibrosis, are characteristic. Airway obstruction may become troublesome in this kind of HP.

BAL may have an important lymphocytosis, until 50%, which is rare in other disorders. CD4/CD8 ratio is decreased (sometimes even less than 1). Histology: acute form is characterized by neutrophilic infiltrate in the alveoli and respiratory bronchioles. Subacute form shows lymphocytic interstitial pneumonitis, granulomas, organizing pneumonia and fibrosis. Chronic type has bronchiolocentric cellular interstitial pneumonia, noncaseating granulomas and intraluminal fibrosis or organizing pneumonia.

SARCOIDOSIS: is a multiorgan disease of unknown etiology, which frequently affect the lung (most frequent target of the disease).

The diagnosis is done based in clinical and radiologic presentation and the demonstration of noncaseating granulomas. At the lung, multiple noncaseating granulomas are distributed in the interstitium, pleura, interlobular septa and bronchovascular bundles (bronchiolar submucosa: for this reason the TBB us accurate in 90% of cases).

Worldwide occurrence. Individuals of all ages are affected. Both genders, all races. More common in young adults (20-40 y/o) and more common in women. More prevalent between African-american in USA, Irish and Scandinavians. The clinical presentation is wide variety.
90 – 95% of the time, the lungs are involved, so, no productive cough, dyspnea, chest pain are present. The constellation of Erythema nodosum, bilateral hilar lymphadenopathy or CRX and pilarthralgia, is called Lofgren’s Syndrome, which occurs in 20-50% of these patients. Pulmonary function test will show Restriction. Sometimes, mild airway obstruction may be present. Airway hyperactivity occurs in 20% of the patients. BAL shows increased CD4/CD8 ratio (sometimes over 3.5) and lymphocytosis.

PULMONARY LANGERHAN’S CELL HISTIOCYTOSIS (PLCH): chronic progressive disorder characterized by proliferation of Langerhan’s cells infiltrates which form multiple, bilateral, interstitial peribronchial nodules that frequently cavitate. Strongly associated with smoking. The lesions of PLCH are similar to those seen in LCH (without lung involvement) but the later is considered to be clonally neoplastic, while PCLCH is considered to be caused by a reactive proliferative response of Langerhans cells to cigarette smoke.

Different phases of the disease occur: an early cellular phase can be with centriflobular accumulation of LC. In chronic phase, the LC can be missed. Cystic lesions can be produced by central splitting of large nodules and by dense fibrosis surrounding dilated alveolar spaces. Is a rare entity. More common in young adults: 20 – 40 y/o. More in men. Smokers. Could be asymptomatic (25%), with extrapulmonary involvement (10-15% of cases). Clinical presentation with cough, chest pain, fatigue, fever, pneumothorax (25% of cases), hemoptysis, diabetes insipidus. There is a marked DLCO reduction.

LYMPHANGIOLEIOMYOMATOSIS (LAM): rare disorder that affects mainly women of reproductive age. It is characterized by abnormal proliferation of smooth muscle cells (LAM cells) in the lungs, as well in lymphatics and lymphs nodes of the thorax and retroperitoneum. Clinically radiologically and physiologically, LAM has more in common with pulmonary emphysema, with a significant airway obstruction.

Age of presentation, 20-40 y/o. Associated with spontaneous pneumothorax, hemoptysis, chylothorax, chylorperitonum, chyluria, chylopericardium. Marked decrease of DLCO. PFT may show mixed or obstructive pattern.

EOSINOPHILIC PNEUMONIA (EP): group of diseases of known or unknown etiology, characterized by the accumulation of eosinophils in the alveolar spaces and/or interstitium and commonly with associat peripheral eosinophilia. In the BAL, eosinophilia (over 5%) help with the diagnosis. But, many other ILD cause eosinophilia in BAL (IPF, Sarcoidosis, HP, SLE). Also, HIV and drug reactions. Extremaly high number of eosinophil in BAL can be seen in parasitic infections, ABPA, hypersinophilic syndrome and Chung-Strauss, drug reactions and acute and chronic eosinophilic pneumonias.

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