Conceptual Approach to
Diffuse Lung Disease

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Objectives:

- Review the differences between pathology and etiology when evaluating Pulmonary imaging/Chest Radiographs.

- Importance of morphology, distribution and duration of symptoms with regards to pulmonary diseases.

- Four major imaging findings of fibrosis

- This will be a Case Based Instructional Session

Introduction: Approaching Chest Imaging has traditionally been taught in a *disease/Etiology based format* rather than *imaging findings/pathological format*. This is backwards since many diseases can have variable imaging appearances. Terms such as 'Airspace', 'Interstitial', 'Clinical Correlation' and 'Nonspecific' are often used. These descriptions are often not helpful when you are sitting in front of the monitor with a chest imaging study trying to figure out a particular pathology.

A different conceptual approach is to focus on the *morphology, distribution and when possible, duration of symptoms*. The terms 'Airspace' and 'Interstitial' never need to be used. The frequent use of the word **'If'** can replace statements like 'Clinical correlation' and 'Nonspecific'. It's understandably difficult to break habits after years of doing things over and over the same way. It's like trying to change an *acquired reflex in the mind*. (FYI: Just because you have done the *same thing* for years doesn't mean you have 'Experience'.) This short session will be an introduction of a different Conceptual organization of

Cardiopulmonary diseases. I'll try to show that the tired old statement, *used by people who don't understand this enjoyable specialty,* that 'Chest imaging is only long differentials' **is definitely incorrect**!

Let's start:

Pathology is not the same as Etiology: As a radiologist, our primary function is for diagnosis. We examine the imaging studies based on morphology, the distribution and try to incorporate duration of symptoms as well as other ancillary findings. We combine this information to determine the ***most likely pathology present***. We can then offer *possible common* ***etiologies***.

These pathologies may overlap or evolve into another such as NSIP or UIP. Remember, ***it is the pathology that ultimately determines the prognosis and treatment options for patient***.

In medical training/radiology, we unfortunately focus our teaching based on the diagnosis (etiology), *which is a backwards approach for what we do on a daily basis*. We are presented with numerous imaging studies that have a certain *distribution and morphology of abnormalities*, but often not a diagnosis. Developing a diagnosis, or a reasonable differential for what these imaging abnormalities likely represent is what we as radiologists are supposed to do. We need to change our teaching to focus on *the imaging findings that reflect certain pathologies* since that is how most of our exams are interpreted. Teaching or writing literature based on a diagnosis/etiology is *not effective* when it's time to sit down and begin interpreting imaging studies.

For example: What does it really mean when a physician says that someone has a 'Vaping-related pneumonitis', 'lupus pneumonitis'' or 'drug toxicity'? *These are all etiologies and do not reflect the pathology*. They can manifest with various pathologies because '*People are like Snowflakes'* (Quote from Lewis Black – Comedian)

People have varied reactions to different injuries...

5 different people take Amiodarone - The lung injury could be a simple acute eosinophilic pneumonia for one person, an organizing pneumonia for a second person, no apparent injury for a third person, fibrotic NSIP for fourth person and UIP for fifth person. Each of these people has a different prognosis and treatment plan, especially regarding duration of therapy. Yet, they are all labeled under the same umbrella as 'drug toxicity' lung disease.

If you read a chapter on 'Pulmonary Infections' or a journal article on 'Drug-related lung disease', it will often be difficult to digest the information since *it is written from the point of view of the etiology*. (*It's really boring too*). The article will discuss many different pathologies leaving the reader to become a little confused and frustrated, often with the unfortunate conclusion that **'*Drug Toxicity can look like anything*'**. This is not a helpful way to organize an approach to imaging!

Note: For those residents in training, consider using the differential card as your organization for reading. Study if from the *imaging perspective first* and then *learn the about the diseases* that are associated with that imaging appearance. Skip around in the book or website to read about the pathology/diseases listed in *each category*. This allows you compare and contrast the subtleties between these diseases that tend to have a similar imaging presentation.

IMPORTANT: *Pathology is not the gold standard for any diffuse lung disease! *

Lung pathology is as confusing to general pathologists as pulmonary imaging is to non-chest radiologists. This is not a statement that reflects mediocre physicians, *but rather a reflection on how inadequately taught pulmonary medicine is in our current curriculum and how much we do not know regarding pulmonary diseases*. This is especially true when working with Diffuse lung diseases. In one study, 8/10 general pathologists could not diagnose UIP correctly. A study from the University of Michigan

demonstrated at 1/5 of *academic dedicated lung pathologists* changed their diagnosis after meeting with the radiologist. *It turns out that the pathology/prognosis of the patient with diffuse lung disease is often more closely related to imaging than the pathology report*. It is no longer acceptable for radiologists to defer their interpretation to the pathology when imaging findings suggest something else! Time to earn that paycheck, although often a smaller one for these chest imaging studies than other imaging exams.

Common Lung Pathologies:

Organizing pneumonia

Desquamative interstitial pneumonitis/RB-ILD

Lymphocytic interstitial pneumonitis/follicular bronchiolitis

Hypersensitivity pneumonitis (Extrinsic allergic alveolitis versus Internal/blood-borne allergic alveolitis)

NSIP (Cellular or Fibrotic)

Usual interstitial pneumonitis (UIP)

Sarcoidosis

Eosinophilic pneumonia (Acute and Chronic)

Hydrostatic pulmonary edema/congestive heart failure

Noncardiogenic pulmonary edema

Diffuse alveolar damage (Also could use the term *Acute Lung Injury*)

Note: '**Acute lung injury**' often refers to *diffuse alveolar damage along with various degrees of organizing pneumonia*. Some pathologists use the term AFOP: 'Acute fibrous organizing pneumonia'. Don't bother learning that one. *Acute lung injury is a much better term*.

Common Etiologies:

Drug toxicity

Collagen vascular disease/autoimmune diseases

Occupational lung diseases

Graft-versus-host disease

Infectious

Berylliosis (Sarcoidosis pathology)

Inhalational disease

Inherited diseases

Immunodeficiency-related diseases

Smoking/Vaping related diseases

Idiopathic (AIP/IPF/Sarcoidosis)

Practical Teaching point: N*SIP is not a diagnosis*, it is a pathologic reaction *along the spectrum of inflammation to fibrosis*. Most of the above pathologies, *if left untreated*, will often evolve histologically into various degrees of NSIP. Look at the distribution, morphology and duration of symptoms to try and figure out from which above pathologies may have evolved into NSIP. If disease is extensive, ***always try to look at the regions of less involvement***. Clues to the underlying pathology and possible etiology may be more easily appreciated.

There are 2 etiologies which tend to manifest very commonly with an NSIP histologic appearance, they are *collagen vascular disease/autoimmune diseases and drug toxicity*. NSIP seems to be an intermediate level of fibrosis between the inflammatory pathologies and UIP. If the underlying injury continues, then NSIP will often evolve into UIP. *UIP is the final*

pathologic endpoint from the lung.

NSIP average age of diagnosis: *45-55 yo*. Average life expectancy from diagnosis is approximately 10 years (Fibrotic NSIP). Treatment is often steroid based.

UIP average age of diagnosis: *55-65 yo*. Average life expectancy from diagnosis is approximately 3 years. Steroids have no effect on UIP, but rather simply give the patient the side effects. These patients are considered for a different therapy, which is expensive and has a number of side effects.

Honeycombing: *Honeycombing is the best morphologic finding to diagnose UIP, and one of the most difficult to figure out*. Honeycombing is rarely seen in fibrotic NSIP (likely represents a focus of evolving UIP). Honeycombing cysts have thicker walls, are spherical, share walls and *absolutely must be subpleural/directly against the pleura*. Any subpleural sparing means that these peripheral cystic abnormalities are not honeycombing, but reflect some other pathology such as peripheral bronchiectasis or cysts. Paraseptal emphysema tends to be more mid and upper lobes with thinner walls and a more elongated nonspherical shape. (Dogma still taught today: 'UIP can be caused by asbestosis'. This is likely incorrect. Pulmonary fibrosis from asbestosis is actually quite uncommon and *the histology and imaging features do not remotely resemble UIP*.)

DLCO: Another very useful clue to help distinguish between fibrotic NSIP and UIP is the patient's DLCO on pulmonary function tests. This measures the diffusion capacity of the lungs. When there is predominantly lower lobe peripheral pulmonary fibrosis without definite honeycombing, ask or mention about obtaining a DLCO. If there is a moderate amount of fibrosis and the DLCO is only minimally decreased (Number in the 70's-90's), then it is much more likely to be Fibrotic NSIP. If the degree of fibrosis is mild, yet the DLCO is less than 70, then this favors a predominantly UIP pathology. (Note: DLCO can also be most helpful for

those exams that it is questionable whether there is actual pathology versus normal variant or artifact. DLCO is often abnormal for the former, but normal with the latter.)

Pathological Explanation: The basement membrane of the alveoli is relatively spared with NSIP and therefore oxygenation/diffusion capacity remains partially intact. The basement membrane is exposed with UIP and the resulting fibroblast proliferation is much more extensive resulting in a profound impairment in the diffusing capacity and oxygenation.

Imaging signs of Pulmonary Fibrosis:

1. Irregular visceral pleura
2. Small intersecting reticular opacities (*NOT septal thickening*)
3. Traction bronchiectasis (Usually 'Varicose' in appearance)
4. Honeycombing (Most difficult to diagnose) - ***Strongly favor UIP*** - FYI: Useful UIP reporting reference: *Lynch et al. Fleischner Society White paper. Lancet Respir Med. 2017;S2213-2600(17) 30433-2*

Start with the Imaging: For many of us, we will scan through an exam and within the *first few seconds,* have a pretty good idea about what our report impression will contain. For most pulmonary imaging exams, *there are 5 main conceptual report impressions that will be generated*. This is over simplistic of course, but for those who do not have a great deal of experience, it can be helpful to have as a starting point.

- The examination is normal.
- Questionable abnormality versus artifact/normal/ or incidental variant. Consider DLCO or repeat examination
- Imaging findings are characteristic for a pathology/diagnosis.
- Imaging findings are consistent with a short differential of pathologies. Laboratory, history and/or duration of symptoms would help uncover the diagnosis.
- Imaging findings are indeterminate. Further work up will likely be

needed.(If possible, suggest which would help)

When looking at imaging studies, *focus on what you think is the most likely morphology*. Remember that more and more than one may be present.

Second, *look closely at the distribution* of whether it is diffuse, lower lobe, peripheral or central, bronchovascular or upper lobe.

Third, *how long have the patient's symptoms been present*? Hint: If there is traction bronchiectasis, the patient's symptoms have likely been subacute to chronic. The only exception to this rule is diffuse alveolar damage/Acute lung injury where you can see traction bronchiectasis/scarring develop within a few days. All other pathologies require a few weeks for traction bronchiectasis/scarring to appear.

Use the differential card to see which disease(s) are in those morphology and distribution categories. If one or two are in *two or more categories,* that is the likely diagnosis.

Conceptual approach: The morphology, distribution and duration of symptoms:

Ground Glass: Increased opacification with blurring, but still visualized pulmonary vessels. This descriptive term can be used with Chest radiographs and CT. FYI: 'Ground glass' was introduced as one of the four descriptive manifestations of diffuse lung disease *for the chest radiograph* in the Volume one Fraser & Pare Text book (1971).

Acute (Less than 7 days of symptoms): Noncardiogenic edema/diffuse alveolar damage (Small pleural effusions are common), PJP (No pleural effusion) and pulmonary hemorrhage syndrome/vasculitis (No pleural effusion).

Acute ground glass with imaging evidence of fibrosis: Diffuse alveolar damage (ARDS/AIP/idiopathic pneumonia syndrome(BMT))

Diffuse distribution: *Systemic etiologies are very likely*. Pulmonary hemorrhage syndrome/vasculitis and Noncardiogenic edema/Diffuse alveolar damage/ARDS from an etiology outside the lungs (Bacteremia, Sepsis, Transfusion related lung injury, Acute drug toxicity, Pancreatitis).

Subacute to Chronic with *no to minimal imaging evidence of fibrosis*:

Hypersensitivity pneumonitis: Both *Extrinsic/inhalational* (Mid to upper lobes/Centrilobular ground glass nodules) and *Intrinsic/blood-borne* (Patchy or diffuse) etiologies.

Cellular NSIP

Organizing pneumonia – Often Areas of consolidation

Extrinsic lipoid pneumonia/Alveolar proteinosis (Surfactant accumulation?)

DIP/RB-ILD (Smoker)

LIP/follicular bronchiolitis (Autoimmune/HIV associated)

Mucinous producing adenocarcinoma (No Fibrosis)

Chronic Ground Glass with *moderate-severe imaging evidence of fibrosis:*

Fibrotic NSIP (Subpleural sparing, bronchovascular distribution no honeycombing)

UIP (Honeycombing is the best clue along with clear involvement of the costophrenic angles)

Consolidation: Increased opacification with obscuration of the pulmonary vessels. Check for air bronchograms.

Acute: (< 1 week usually)

With air bronchograms – Organizing Pneumonia (Often Infectious),

pulmonary hemorrhage, occasional diffuse alveolar damage/AIP

No air bronchograms – Infarct (Wegener's associated vasculitis, cocaine-induced vasospasm, Aspergillus, mucormycosis, pulmonary embolus), *Consolidated pneumonia with filling of airways* – Often referred to as 'Drowned Lung' from central obstructing nodule/mass (Look for Golden S-sign). An *evolving necrotizing pneumonia* can also cause airway filling and absent air bronchograms.

Subacute to Chronic Focal Consolidation: > 1 week. Usually weeks to months

Organizing pneumonia, likely secondary to more unusual infections such as Nocardia, actinomycoses, Mycobacterium tuberculosis or fungal - Both endemic and opportunistic (Often some traction bronchiectasis)

Postobstructive consolidation and infarct - No air bronchograms

Mucinous producing indolent adenocarcinoma - No fibrosis/traction bronchiectasis with this chronic consolidation. (Ask about Bronchorrhea)

Subacute/chronic multifocal/extensive Consolidation:

Organizing pneumonia (Cryptogenic organizing pneumonia often has this appearance)

Chronic Eosinophilic pneumonia

Lipoid pneumonia

Alveolar proteinosis

Lymphoma/lymphoproliferative disease

Alveolar sarcoidosis

Mucinous producing adenocarcinoma

Note: *Enlarged lymph nodes favors Alveolar sarcoidosis, Lymphoma and Endemic Fungal infections*.

Reticular/Septal thickening:

Hydrostatic pulmonary/congestive heart failure (Small bilateral effusions)

Lymphangitic spread of tumor (Associated perilymphatic nodularity - Adenocarcinoma & lymphoma most common)

Acute eosinophilic pneumonia (Often looks like hydrostatic edema)

Sarcoidosis (Septal thickening is often prominent)

Hante virus (Early in the infection - looks like hydrostatic pulmonary edema)

Cystic pathology: (Need to differentiate from emphysema)

Langerhans' cell histiocytosis

DIP (Perihilar distribution, occasionally lower lobe and peripheral)

LIP/follicular bronchiolitis (Autoimmune associated)

LAM/Tuberous sclerosis

Birt-Hogg-Dupe Syndrome

Chronic PJP (Usually HIV/AIDS)

Focal/Multifocal Cystic (Indolent) adenocarcinoma (Subtle wall thickening/nodularity)

Honeycombing (UIP)

Cystic bronchiectasis (Fluid levels common)

Nodules:

Random: Metastases (*Vary in size*) and disseminated granulomatous disease (*Similar in size*) such as sarcoidosis, miliary tuberculosis, miliary Coccidioidomycosis/histoplasmosis and old varicella (Calcified nodules)

Perilymphatic: Sarcoidosis (Often bronchovascular/central in distribution. Septal thickening less, common) And lymphangitic spread of tumor (More peripheral/septal thickening)

Centrilobular:

- *Ill defined ground glass nodularity:* Inhalational etiologies such as extrinsic allergic alveolitis (Non-smoker) and RB-ILD (Smoker)

- *Terminal bronchial filling ('Budding-tree' appearance):* Infectious such as bronchopneumonia, (especially in HIV patients), typical viral pathogens (influenza, parainfluenza and RSV), MAC (bronchiectasis, right middle lobe and lingula most often) and aspiration.

Bronchiectasis:

Focal: Residual airway damage from prior infection or chronic stenosis/obstruction

Multifocal/Extensive: *Systemic etiologies are most likely*.

Cystic fibrosis

IgG or IgA immunodeficiency

Williams Campbell syndrome

Dysmotile cilia syndrome

Mycobacterium avium intracellular infection (*Th17 deficiency*) - Myth Alert: MAC occurs in older women from a 'decreased cough', the so-called Lady Windermere Disease. ***Please never say this***! There are studies with findings of immune dysregulation (Th2 helper cells) and decreased

localized Th17 cells in these patients. It is overwhelming likely a *subtle immune disorder*.

If there is a single or multiple large tubular branching structures, then consider a **bronchocele**, usually from ABPA (Asthma history) or cystic fibrosis.

Upper lobe distribution: (SET PARC) These diseases are usually *inhalational and/or lymphatic clearance associated*. *NOT high oxygen related*!

PJP (HIV or chronic steroid associated)

Cavitary tuberculosis/Chronic histoplasmosis

Chronic MAI (Men)

Sarcoidosis,

Silicosis

Chronic Extrinsic allergic alveolitis (Non-smoker)

Langerhans' cell histiocytosis (Smoker)

Cystic fibrosis

Centrilobular emphysema (Right upper lobe often greater than left).

Metastatic calcification – Chronic renal failure (Alkaline environment)

Bronchovascular distribution:

Sarcoidosis

Hodgkin's lymphoma

Kaposi's sarcoma (Herpes virus 8)

Aspiration (Acute Symptoms).

Gravity dependent distribution:

Hydrostatic pulmonary edema/congestive heart failure (Lungs are like wet towels on a clothesline)

Aspiration (Look for ill-defined clustered 3-4 mm nodularity)

Pleural effusions (If not dependent, *then the pleural effusion is loculated*.)

Non-postobstructive atelectasis

Final thoughts:

Please avoid the term "infiltrate" in your reports or discussions with physicians. This is not a useful term and should not be used. Strictly speaking, it is an opacification we see on imaging and the lungs. Add an adjective in front of it such as consolidative opacity, ground glass opacity or reticular opacity. Your differential should be based on that adjective. Infiltrate also *often implies* a pneumonia, especially when said to a clinician. If you think it is pneumonia, *please call it pneumonia. Consider removing 'infiltrate' from your voice recognition vocabulary.*

Reduce or avoid using the terms "airspace process" or "interstitial process" in your reports (or your thinking). This is an *artificial distinction based on historical teaching*. Why say 'Airspace consolidation'? Just say 'Consolidation' or 'Consolidative opacities'. One of the famous chest radiologists, Dr. Ben Felson from the University of Cincinnati was the one who strongly promoted and taught this method in the 60s and 70s. Late in his career, he admitted that although this Airspace and interstitial

approach was helpful for him, he found it was not as useful for most radiologists. (FYI: Dr. Felson was a wonderfully friendly and outgoing physician! His book as well as his numerous conferences were so enjoyable, and funny. He often told his residents when they began to hedge to 'Go out on a limb, that's where the fruit is.')

Pathologists have shown that almost every single disease in the lungs has both an airspace and interstitial component of varying degrees. For example - Alveolar sarcoidosis manifests as chronic multifocal consolidative opacities with enlarged mediastinal and hilar lymph nodes. I have seen many radiologists call that an 'airspace process'. Pathologically, much of the histology is actually granulomas within the pulmonary interstitium compressing the alveoli.

Plus, the terms 'airspace' and 'interstitial' lead to *vague terminology* such as "chronic interstitial markings" which is useless and should be avoided. There are peer reviewed journal articles written by academic thoracic radiologist that describe various pulmonary diseases as "a mix of airspace and interstitial opacities". How is that the vague information even remotely useful?

Note: The term 'markings', such as 'Increased vascular markings', is another strange term – A radiograph is not a drawing or painting. Say 'The vascularity' instead. *Consider removing the word 'markings' from your voice recognition vocabulary*.

'Nonspecific' and 'Clinical Correlation': Lastly, the terms 'Nonspecific' and 'Clinical correlation' *are not helpful.* These terms also help foster the propagation of the tired radiology stereotype of 'Waffling/hedging'. Try using the word **'If'** instead. '***If*** the patient has…, then consider… as a diagnosis.'

For example: Patchy bilateral ground glass involving both the upper *and* lower lobes without imaging evidence of fibrosis/effusions and no history (Super vague isn't it?). '***If*** the patient's symptoms are less than a week,

this may represent an organizing pneumonia from typical viral pathogens, especially ***if*** they have a fever. Multifocal pulmonary hemorrhage/vasculitis is conceivable and an ESR and Urine analysis may be helpful. ***If*** the patients' symptoms are more subacute to chronic, consideration for a hypersensitivity pneumonitis such as from drug toxicity should be made. Cellular NSIP or a cryptogenic organizing pneumonia are possible, although less likely. Pulmonary consultation for work up and treatment options is suggested ***if*** symptoms persist.'

These are of course all suggestions. But it is hoped that this session and handout will give you something new to consider and a different perspective/organization regarding chest imaging when you return back to work.

Summary:

Describe the morphologic pattern you see, its distribution and any ancillary findings and/or duration of symptoms in your report.

Organize your thoughts from these descriptions and report the *likely pathology* that may be present. Use the handout/card until you begin to develop a long term memory of it.

If possible, offer some some *potential etiologies/injuries* that could be causing it.

Offer some *suggestions* on how to sort out the exams that are more confusing.

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