Course Name: Pulmonary Function Test -Interpretation and Application in clinical practice
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W2_L1_Obstructive Lung Diseases: Pathophysiology

This session, we will be seeing about obstructive lung diseases, the pathophysiology of obstructive lung diseases. So, I will be dealing with this topic in these objectives, introduction, risk factors, pathogenesis, pathology and finally summary. So, the introduction, obstructive lung diseases are mostly chronic, there are only acute exacerbations. So, chronic obstructive lung diseases are characterized by an increase in resistance to air flow due to diffuse airway disease, which may affect any level of the respiratory tract. And what is chronic obstructive pulmonary diseases? So, these are different and they comprise of chronic bronchitis and emphysema. So, COPD that is chronic obstructive pulmonary disease, chronic bronchitis and emphysema with bronchial asthma and bronchitis, constitute the entire spectrum of chronic obstructive lung diseases which are called cold.

So, with regard to pulmonary function test, this code shows decreased maximal airflow rates during forced expiration, usually expressed as forced expiratory volume at 1 second, which is called FVV1 over forced ventilatory capacity that is called FVC. So, an FVV1 FVC ratio of less than 0.7 generally indicates obstructive diseases. The expiratory airflow obstruction may be caused by a variety of conditions, each with characteristic pathologic changes and different mechanisms of airflow obstruction.

However, these divisions between the entities are not clean and many patients have diseases with overlapping features like how we see here. So, chronic bronchitis and emphysema are generally small airway diseases due to chronic injury. In chronic bronchitis, it is chronic cough with airway obstruction. In emphysema, it is alveolar wall of destruction with overinflation. A subset of these patients can also have bronchial asthma, which is reversible obstruction due to bronchial hyper-responsiveness triggered by allergen infections and pollutants.

So, you see that there is a central watershed area, which comprises of patients with all three overlapping features and those are the patients who are called as chronic obstructive pulmonary diseases. Moving on to the etiology of the chronic obstructive pulmonary diseases, 85 percent of these obstructive pulmonary disease patients are smokers, 15 percent of them are non-smoker, where in developing countries especially non-smoking

COPDs 30 to 50 percent due to what is called biomass fuel, where wood, cow dung and crop residues are burnt and these lead to release of air pollutants like sulphur dioxide, carbon monoxide, nitric oxide and formaldehyde and particulate matter smaller than 10 micron in size, which is PM 10 in the ambient indoor and outdoor air. There are also occupational smoke and dust, which are important causes for COPDs. Tuberculosis in India especially has 2 to 6 times increased lifetime risk for COPD. Recurrent respiratory infections in childhood are thought to be an increased risk factor.

Poorly treated bronchial asthma also leads to chronic obstructive pulmonary diseases. Aging is one of the important factor and amongst the genetics, it is very important because there is what is called deficiency of alpha 1 antitrypsin, which is in the gene serpine up coding and that deficiency generally leads to emphysema. Coming to risk factors, it can be classified as modifiable risk factors and non-modifiable risk factors. Coming to modifiable risk factors, we see that cigarette smoking is one major risk factor followed by occupational environmental exposures, socioeconomic status, dietary factors, tuberculosis, intravenous drug abuse and immunodeficiency status. Coming to non-modifiable, of course genetics is the major and gender developmental factors like presence of small lungs at birth and vascular connective tissue disorders, which are also genetic in nature.

Coming to various hypothesis with regards to pathophysiology of chronic obstructive lung diseases, Reed in 1960 highlighted the increased mucus gland size in his pathologic studies and developed the Reed index and highlighted the anatomic basis for chronic bronchitis. And there was Dutch hypothesis where bronchial asthma and airway hyperreactivity was thought to lead to the fixed airflow limitation. And British hypothesis where mucus hyperis secretion is thought to be the major factor, which leads to airway remodelling and airflow limitation. And then comes the protease and antiprotease hypothesis, which is very important, which is from the Swedish hypothesis, where association of homozygous alpha 1 protease inhibitor deficiency is associated with M5-sema. And American hypothesis is the latest which says that American pathologist Avril Lebo emphasized that altered repair mechanisms contribute to the development of chronic obstructive pulmonary diseases and that deficient maintenance of lung structure could lead to M5-sema.

Coming to the pathogenic factors, there are four important pathogenic factors, which play an important role in development of chronic obstructive pulmonary diseases or lung diseases. The first and foremost is inflammation, persistent inflammation. Second is of course, the balance between the proteinase and antiprotease or what are called protease and antiprotease imbalance. And we have oxidative stress and apoptosis that is programmed cell death. All these four factors play an important role in the pathogenesis or development of chronic obstructive lung diseases.

Coming to inflammation and COPD. So, the inflammatory cells which participate in chronic obstructive pulmonary diseases or COLD are macrophages mainly, neutrophils

more important, natural killer cells and T-lymphocytes linked through dendritic cells. This release of oxidants and proteases perpetuating the imbalance in favor of lung destruction. This is what these inflammatory cells do and specially the neutrophil elastase increases the macrophage and epithelial cell activation as well and represent a major stimulus for mucus production and secretion by goblet cells, which are the lining cells of the bronchial epithelium and the mucus glands which are present underneath and this is supposed to be the hallmark of chronic obstructive pulmonary disease that is secretion of mucus and increased production of mucus. So, the chemical mediators from all these cells also play a very important role in chronic obstructive pulmonary diseases.

So, what are these chemical mediators specially interleukin 8, which is a chemotactic factor for neutrophil and then we have these chemokine ligands. These are the CHC chemokine ligand 1 and 8 and also the presence of increased CC chemokine ligand CCL2, 4, 17 and 22 along with CXC chemokine receptor CXCR2. These play a major role in the inflammation of the COPD. Also, there are certain oxidants which are released from these inflammatory cells, which are also responsible for the destruction and airway. One is hydrogen peroxide and second is superoxide anion and as I already said the balance between proteases and anti-proteases.

So, if there is an increased proteases because of these inflammatory cells that is the matrix metalloproteinases and the tissue metalloproteinases, which is MMP 9 and some of the growth factors as well are responsible. And lastly in bronchial asthma, it is leukotriene B4 and tumor necrosis factor alpha which are also responsible for airway obstruction. Coming to the protease anti protease theory in alpha 1 and anti-tubercin deficiency, these two are related together the balance between matrix degrading proteases and their endogenous inhibitors that is anti-proteases determines whether the lung is protected or susceptible to proteolytic injury. So, these proteases come from neutrophil, which is the neutrophil elastases and the matrix metalloproteinases. These are released from inflammatory cells specially neutrophil and also the epithelial cells that break down connective tissue components.

And alpha 1 antitrypsin, this is normally present in serum tissue fluid and macrophages is considered to be the major inhibitor of the proteases which are coming from the inflammatory cells and the epithelial cells, specially neutrophil elastase and this alpha 1 antitrypsin is encoded by proteinase inhibitor locus PI on the chromosome 14. So, there is a genotype associated with very low serum levels of alpha 1 antitrypsin in the Z allele and 80 percent of these ZZ homozygous individuals develop what are called symptomatic pan-acinar M5 sigma occurring at an earlier age and is of greater severity if the individual also smokes, which increases the protease level and which cannot be dealt with alpha 1 antitrypsin due to their deficiency. So, it is postulated that any injury example that induced by smoking, which increases the activation and influx of neutrophils into the lung will lead to local release of proteases, which in the absence of alpha 1 antitrypsin, which is an anti-

protease activity result in excessive digestion of the elastic tissue of the lung and with time leads to M5 sigma. So, it forms one of the major pathogenic mechanisms. Oxidative stress and apoptosis, substances in tobacco smoke and along with alveolar damage and the presence of inflammatory cells, all these produce oxidants, which may be get tissue damage, endothelial dysfunction and inflammation.

The NRF2 is a transcription factor that serves as a sensor for oxidants in many cell types, including alveolar epithelial cells. Also, intracellular oxidants activate this NRF2, which upregulates the expression of genes that protect cells from oxidant damage. There are genetic variants in NRF2, NRF2 regulators and NRF2 target genes, which are all associated with smoking related oxidative damage leading to lung disease in humans, especially obstructive lung diseases. So, cell death by injury or apoptosis can be an initiating trigger for M5 sigma. And this was proved by experimental models showing that non-inflammatory cell death can initiate airspace enlargement, inhibition of vascular endothelial growth factor receptor being the major responsible factor or sometimes installation of active caspase 3, which is considered to be an apoptotic factor in lung epithelial cell tissue leading to apoptosis and damage to the alveolar wall leading to what is called M5 sigma.

So, actually coming to what happens. So, at one end of the spectrum is genetic susceptibility where there is long term deficiency of alpha 1 antitrypsin. And the other side is the environmental insults to lung, which are sometimes inevitable, but also associated with smoking, pollution in the air and certain infections. So, all these together, the genetic susceptibility leads to decrease lung's ability to prevent damage to lung parent schema, whereas environmental insults to lung will lead to increase production of free radicals in the lung and also inactivation of the lung anti proteases because of infection and smoking which leads to accumulation of neutrophil, which releases the proteases as well. And these two, three together, that is, decreased lungs ability and free radical inactivation of lung anti proteases will lead to lung inflammation, where there is increased oxidative stress, inflammatory cytokines and protease function.

So, these three factors together will either lead to continued repeated injury to bronchial tree or may lead to increased proteolytic destruction of the lung parent schema. Depending on which side is the balance, if it is continued repeated injury to bronchial tree, the patient may have these things that is infiltration by neutrophils, goblet cell proliferation leading to mucus secretion, death of airway-sealated epithelial cells. These three factors will lead to bronchial fibrosis and lumen narrowing and the trapped mucus in the airway will serve as a source for further infection leading to more neutrophils and together bronchial fibrosis, lumen narrowing and trapped mucus is what is called chronic, leads to chronic bronchitis. So, these are called the blue bloaters. Whereas, if the balance is that there is increased proteolytic destruction of lung parent schema leading to decreased airway elasticity that is

less recoiling of the lung and decreased structural support of airway patency and permanent damage to airway epithelium.

So, if these three happens, then there is trapping of air within the lung because of decreased elasticity and there is airway narrowing and collapse because of decreased structural support of the airways and due to permanent damage of the airway epithelium, lung goes in for hyperinflation and there is boule formation because of the ruptured air sacs. So, when there is hyperinflation and boule formation and there is trapping of air within the lung, there is what is called emphysema where the lung is over inflated with more air within it and appears very darker in color and this is called emphysema. So, depending on which is more, if the bronchial tree injury is more, the patient will become chronic bronchitis patient. If there is increased proteolytic destruction of lung parent schema leads to emphysema.

These are pink puffers. Now, cigarette smoking and inflammation, a very, very important pathogenic mechanism because smoking is one of the major causes for chronic bronchitis or emphysema. So, smoking leads to persistent stimulus for inflammation. How? One is by activating epithelial cells. Second is senescence of fibroblasts where the fibroblasts undergo degradation. So, this activation of epithelial cells leads to increased growth factors that is mainly the platelet derived growth factor and the TGF beta.

So, this transformation growth factor beta is responsible for fibrosis as well and the senescence of fibroblasts leads to increased matrix metalloproteinases. So, there is also activation of macrophages and lymphocytes when there is smoking increase persistent of the stimuli and that leads to increased cytokines and chemokines which we already saw, the ones being interleukins, mainly interleukin 13, tumor necrosis factor alpha and the monocyte chemotactic factor 1, protein 1. All these three leads to one side matrix synthesis, the other side matrix degradation because of matrix metalloproteinases. So, this matrix synthesis with matrix degradation leads to what is called a scar or lung fibrosis. So, when the lung undergo fibrosis, obviously, the patient airway is obstructed and there is what is called collapse as well.

So, coming to the morphology of chronic bronchitis that is pathology. In chronic bronchitis, there is thickening of the bronchial wall by mucous gland, enlargement and edema resulting in encroachment on bronchial lumen. This is very important. There is increased mucous gland, enlargement and edema resulting in encroachment on bronchial lumen. So, there is narrowing of the lumen.

Excess mucus because of the increased mucous gland in the central and the peripheral airways is another important pathology. An increase in the number of goblet cell, what is called goblet cell hyperplasia in the bronchial epithelium is seen in all these cases and increased smooth muscle which may indicate bronchial hyper reactivity is also present. And because of all these changes, there can be metaplastic changes of the bronchial

epithelium leading to squamous metaplasia of the bronchial epithelium reflecting the epithelial damage from tobacco smoke, which is probably independent of other changes in chronic bronchitis. So, these are the major pathologic changes we see in chronic bronchitis. Here it is seen that what is Reed index.

This Reed index determines whether patient has got a severe or mild bronchitis. So, Reed index is actually what is called A that is thickness of the mucous layer in the mucosa and the ratio of the thickness of the entire wall thickness of the epithelial lining that is from the epithelial lining to the cartilage. So, this length of the mucous gland or depth of the mucous gland along with the entire length of the mucosa, so the ratio between them determines the Reed index. And in case of chronic bronchitis, this is what actually happens. This is a normal lumen where it is patent, airway patency is maintained.

But when there is chronic bronchitis because of smoking and epithelial damage and inflammation and mucous secretion, the lumen is narrowed and there is what is called a very small pinhole and this leads to chronic bronchitis. Coming to morphology of emphysema, there is irreversible enlargement of air spaces distilled to the terminal bronchial accompanied by destruction of their walls. That is what is the major change in emphysema that is irreversible enlargement of the air spaces which is in the terminal bronchial or beyond the terminal bronchial accompanied by destruction. Here you can see that these are the normal acinas where these are the respiratory bronchial and these are the alveolar duct and the alveolus. In case of centriacinar emphysema, what is called a central enlargement? There is enlargement of these respiratory bronchioles or what is called irreversible enlargement without much inflammation and the terminal part is normal.

Whereas in case of pan emphysema, that is emphysema affecting the entire acini, then you have the what is called the respiratory bronchial along with the alveolar duct is also enlarged and that is what is called pan emphysema emphysema. So, major morphological types are the centri-acinar, the centri-lobular what we saw here, which is commonly seen in smokers. Whereas the second major type is the pan acinar or the pan lobular emphysema, which is associated with alpha 1 antitrypsin deficiency. And we also have distal acinar which is called the paracentral emphysema and we have the air space enlargement with fibrosis which leads to irregular emphysema. So, this is how a lung will appear when it is emphysema where there is overinflation with increased air trap and also at grossly you will see that the lung becomes almost like a tubule and you can see this increased dark pigment, these are the anthropotic pigments.

And here you see in the microscopy, these are the alveoli which this is the normal alveoli you see with the normal site and here you see that this is M5C matters where you see dilated air spaces with minimal inflammation in the interstitium. So, diagrammatically panacinar is where the entire alveoli, alveolar duct and acini are all enlarged whereas centriacinar is where only the respiratory bronchial is enlarged whereas the peripheral part that is the

alveolar duct and alveolar acini are maintained. Now, coming to the other aspects of chronic obstructive lung diseases that is bronchial asthma most important the itchy pathogenesis and types asthma as we all know is a heterogeneous disease where there is chronic airway inflammation and variable expiratory air flow obstruction leading to wheezing, shortness of breath, chest tightness and cough. There are four major types, one is called the atopic IgE mediated allergen induced bronchial asthma. Second is non-atopic where infections, environmental fumes and pollution are the causative agents in non-atopic and there is also drug induced bronchial asthma where most of the patients have history of taking aspirin, aspirin sensitive asthma inhibiting the cyclooxygenase pathway of the arachnid acid metabolism leading to a rapid decrease in prostaglandin E2.

And occupational asthma is where the fumes, the organic and the chemical dust, gases and chemicals like formaldehyde will lead to due to the occupational exposure. Once they are taken out of the occupational exposure these patients do not have any kind of symptoms. So, coming to the pathogenesis as we know bronchial asthma is characterized by reversible bronchial obstruction or what is called bronchoconstriction caused by airway hyper responsiveness to a variety of stimuli. So, in atopic asthma it is mainly caused by what is called a Th2 response and an IgE mediated immunological reaction to the environmental allergens and is characterized by acute phase that is immediate and late phase reaction. The Th2 cytokines are mainly the interleukin 4, interleukin 5 and interleukin 13.

These are the three major important mediators for Th2 cytokine leading to atopic asthma. And out of these, isophels are the key inflammatory cells in atopic asthma. Other inflammatory cells implicated in its pathogenesis include the mast cell which is the equivalent of basophil, the neutrophils and the T lymphocytes. Now, triggers for non-atopic asthma are less clear, but majorly include the viral infections and inhaled air pollutants which can also trigger atopic asthma sometimes leading to IgE production and isophels.

Genetics and asthma, this is very important. This is a very recently upcoming field where we have seen that more than 100 genes are implicated and the most important being a gene in chromosome 5q and ADAM33 and these mutations can lead to development of bronchial asthma. And airway remodeling is considered to be the latest theory where there is a sub-basement membrane fibrosis, hypertrophy of the bronchial gland and smooth muscle hyperplasia will add on to the irreversible component to the obstructive diseases. So, these form the major pathogenesis of bronchial asthma. Coming to Th2 cells, this is very important because most of the bronchial asthma cases are atopic cases and this Th2 cell releases cytokines which are interleukin 4, 5 and 13, which these interleukins promote allergic inflammation and stimulate the B cells to produce what type of antibody, mainly IgE antibodies. So, interleukin 4 is responsible for production of IgE from the stimulated B cells, whereas interleukin 5 activates the recruited isomorphism which has come because

of IgE and interleukin 13 is responsible for mucus secretion from the bronchial submucosal glands.

So, all three together are responsible for the changes seen in bronchial asthma. So, what do we see in early phase that is immediate hypersensitivity reaction, here the patients will have bronchoconstriction, increased mucus production, vasodilatation and increased vascular permeability. Whereas in the late phase reaction, the inflammation is more severe with recruitment of mainly eosinophils, neutrophils, T lymphocytes and also more and more T cells leading to more and more obstruction and airway hyper responsiveness. There are three major types of mediators which are implicated and why have they divided into three major classes because of the drugs acting on it. So, putative mediators are the ones which produce bronchospasm.

This is the major important clinical factor in bronchial asthma patient coming seeking treatment. So, bronchospasm could be acute or chronic if it is acute patient generally comes with what are called acute exacerbation of status asthmaticus. So, the putative mediators for bronchospasm are leukotriene C4, D4 and E4. So, there are drugs targeting these chemical mediators or what are called leukotriene. These are extremely potent mediators that cause prolonged bronchoconstriction as well as increased vascular permeability and increased mucus secretion.

Then the other important putative mediator is acetylcholine which is released from the intra-pulmonary motor nerves which can cause airways smooth muscle constriction by directly stimulating the muscarinic receptor. So, these are non-mediator or what are called neurogenic construction. Then we have the second group of mediators which are called the potent asthma like effect. So, these mediators produce something like potent asthma like effect and acute allergic asthmatic reaction.

The major of this is the histamine. Histamine is a potent bronchoconstrictor which is secreted by mast cell and basophil. Prostaglandin D2 which comes from the arachnoidic acid pathway elicits bronchoconstriction and vasodilatation. And the third major factor is platelet activating factor which causes aggregation of platelets and release of histamine and serotonin from their granules as well. So, again there is increased histamine production which is a potent bronchoconstrictor. So, these are the second type of mediators which produce potent asthma like or acute allergic asthmatic reaction.

Then we have a third group of mediators which form the larger group of mediators comprising some of the cytokines that is interleukin 1, tumor necrosis factor alpha and interleukin 6. And also comes the chemokines of which eotaxone is very important and we have the neuropeptides, the nitric oxide, the bradykinin and the endothelins. All these are major group of mediators which can also be targeted by drugs. Now coming to the pathophysiology to in a simple way to make it clearer, we have a trigger factor which could

be an atopy, which could be an allergen, which could be drug induced or which could be genetically induced.

And this trigger factor leads to airway inflammation. This airway inflammation on one side leads to increased mucus hyper secretion because of increased bronchial hyper responsiveness. And also, same time, there is increased bronchial membrane swelling and at the same time, the smooth muscle also undergoes constriction. So, all these three things together produce airway obstruction, which leads to wheezing for the patient, persistent cough, shortness of breath and tightness in chest. So, to re-trait that chemical mediators are very, very important and inflammatory cells are important in the production of this airway obstruction that is wheezing, cough, shortness of breath and tightness in chest. We have enumerated these cells and mediators along with their effects.

So, these are the important cells, mainly the eosinophil, mast cell, TH2 lymphocyte, basophil, platelet and along with the epithelial cells, endothelial cells, smooth muscle and fibroblast. And amongst the mediators, as I already told you histamine, platelet activating factor, prostaglandins, leukotrienes, kinins, nitric oxide, growth factor, cytokine, chemokine and these are the major effects that is the bronchospasm, mucus secretion, plasma exudation and structural changes. So, these form the important cells and mediators of inflammation in bronchial asthma. So, pathology of bronchial asthma, the first point to remember is occlusion of bronchi and bronchioles by thick tenacious mucus plugs. These are the mucus plugs, which contain worlds of shed epithelium and what is called the well-known spiral shaped mucus plug in the sputum when we see when we do a sputum examination called Kirschmann spirals.

So, collections of these crystalloid made up of an eosinophil, lyso-phospholipase binding protein called galactin 10 produces what are called the Shaker-Claden crystals which are also seen in the sputum. So, two important things to be seen in sputum examination Kirschmann spiral, the Shaker-Claden crystal. Coming to airway remodeling, there you may see that there is an overall thickening of the air airway wall where there is subbasement fibrosis increase in both type 1 and type 3 collagen. There is also increased vascularity and increase in the sub-mucosal glands of the airway epithelial cells and there is hypertrophy and the hyperplasia of the bronchial wall muscle. Here you can see there are a lot of inflammatory cells, hypertrophy of the muscle inflammation, increase in goblet cell and there is hypertrophy of the muscle all these lead to what are called airway remodeling.

Now, coming to the last of the chronic obstructive lung diseases bronchitis. Bronchitis as the name suggests it is a disease characterized by dilatation, permanent dilatation or ectasia of the bronchi and the bronchioles caused by destruction of the muscle that is the bronchial muscle and the elastic tissue resulting from or associated with chronic necrotizing infection. So, two important parameters need to be addressed in bronchitis. One is there should be a presence of infection and there should be a presence of obstruction.

Only when these two are present, you will get bronchitis. Coming to the types there are congenital or hereditary type which is cystic fibrosis, intra lobular sequestration of the lung, immunodeficiency stage and primary ciliary dyskinesia and Kartegner syndrome. So, these are the most important congenital hereditary conditions out of which cystic fibrosis, Kartegner syndrome, primary ciliary dyskinesia are all important and should be diagnosed at a very early age. Coming to second important type of the bronchiectasis is post infectious or necrotizing pneumonia. So, this is very important because when a patient has pneumonia, the consequence of the pneumonia could be bronchiectasis. So, especially when it is due to mycobacterium tuberculosis, staphylococcus aureus, haemophilus influenzae and pseudomonas and some of the viruses namely the adenovirus, the influenza virus, the human immunodeficiency virus and the fungi that is the aspergillus species.

All these are supposed to produce what are called post infectious necrotizing pneumonia leading to bronchiectasis. Sometimes there can be bronchial obstruction because of tumor, foreign body and mucus impaction leading to infection and bronchiectasis. There are also other conditions which are responsible for leading I mean which can lead to bronchiectasis in patients, patients with rheumatoid arthritis, systemic lupus erythematosus, these are what are called autoimmune diseases where patient can end up with bronchiectasis because of infection and because of obstruction. Also, inflammatory bowel diseases post transplantation that is chronic lung rejection and chronic GVHT that is graft versus host disease after bone marrow transplantation. So, one must remember that bronchiectasis can occur in these settings as well.

So, what is the pathophysiology of bronchiectasis? There is epithelial injury and there is mucus hypersecretion because of mucus secretogox, ciliotoxin, reactive auxin species, proteinase enzyme, these are all the consequences of infection leading to epithelial injury, mucus hypersecretion. This epithelial injury and mucus hypersecretion will lead to reduce mucociliary clearance and there is plugging of airway due to mucus plug and that leads to chronic bronchial infection. Also, this epithelial injury and mucus hypersecretion can itself lead to chronic bronchial infection and it can again lead to same. So, vice versa it can be. And this mucus secretogox, ciliotoxin, reactive auxin species and the proteinases can we know that they all lead to inflammation and this inflammation because of the chemical mediator interleukin A, tumor necrosis factor alpha and the leukotriene B4 again are important in producing chronic bronchial infection and chronic bronchial infection itself can produce inflammation.

So, however B and whatever B the relationship, the reduced mucus, mucociliary clearance and plugging of airway along with inflammation and chronic bronchial infection together will lead to airway damage and producing what is called a permanent dilatation of the bronchi and this inflammation again leads to reactive oxygen species and increase elastase from the neutrophils due to inflammatory cell influx and also matrix metalloproteinases from the epithelial cell. All these things further aggravate the airway damage and resulting

in bronchiectasis. Coming to the morphology or pathology of bronchiectasis, grossly there are three types. One is called the cylindrical bronchiectasis. Here we have this is the normal bronchi and this is cylindrical where there is uniform permanent dilatation or of the bronchi leading to cylindrical type and there is what is called a varicose type which is kind of spiraling and which is kind of undulating and there is saccular or cystic which is seen in very typically seen in cystic fibrosis that is why the name cystic fibrosis has come.

Coming from microscopy, what do we see under the microscope? We see that the airways are dilated. So, these dilated airways you can see there is a dilatation of the bronchus with ulceration, acute and chronic inflammatory cell infiltrate in the bronchial wall and the lining epithelium undergoes ulceration of what is called discontinuity and desquamation. There can also be squamous metaplasia because of the chronic irritant and pseudo stratification and finally necrosis of lung tissue with abscess formation and fibrosis. And when you look at the lung grossly you have what is called this typical honeycomb appearance where you see multiple dilated bronchi leading to something like a honeycomb appearance. So, in summary coming to the pathogenesis of chronic obstructive pulmonary diseases that is COPD, chronic obstructive pulmonary disease is a preventable common condition with a high morbidity and mortality characterized by progressive permanent airflow limitation that is not fully reversible.

So, this is what is very important. There is a progressive permanent airflow limitation which is not fully reversible and substantial overlap and coexistence of the types that is emphysema, chronic bronchitis and bronchial asthma may occur in many patients. So, we will have to be careful which stage and what disease is prominent and what disease is predominant and likewise treat the patient accordingly. Then injury from smoking most important factor in development of chronic obstructive pulmonary diseases excites inflammation which leads to cellular and extracellular matrix injury which heals with incomplete and disorganized repair mechanisms finally leading to permanent progressive airflow obstruction leading to either bronchitis or emphysema and also may be a trigger in bronchial asthma. The airflow limitation is associated with an abnormal inflammatory response on exposure to noxious particles or gases particularly cigarette smoking again the emphasis on smoking. And other important emphasis on deficiency of anti-protease activity makes individuals particularly susceptible to the pathologic process with earlier and more severe disease presentation that is emphysema.

Patients with COPD present late with chronic respiratory symptoms and majority of the early stage is asymptomatic and that is why it becomes very important to diagnose at an earlier stage and hence needs a high index of suspicion for diagnosis. And pulmonary function tests reveal airflow obstruction that is a forced expiratory volume in 1 second FEV1 bar the forced vital capacity FVC. If the ratio is less than 0.7 it is considered to be a diagnostic or a suspicious markup for what is called chronic obstructive pulmonary disease

which is incompletely reversible. So, with this I finish the entire pathogenesis of chronic obstructive lung diseases including chronic obstructive pulmonary diseases. Thank you.