Course Name: Pulmonary Function Test -Interpretation and Application in clinical practice
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W2_L2_Restrictive lung disease Pathophysiology

Warm wishes to everyone. Today, we are going to discuss about restrictive lung disease and its pathophysiology. It is also called as interstitial lung disease. So, our main objectives are to define about restrictive lung disease, enumerating the types of this restrictive lung disease based on etiology, morphological presentation and sources of exposure. We are also going to discuss about the pathogenesis of restrictive lung disease and we will be showing you how macroscopically this restrictive lung disease would look in a lung disorder. As well, we would be showing some microscopic appearances.

Finally, we will be stating some complications of this restrictive lung disease. This is a picture showing how a person is doing a spirometric test. This is clinically done to differentiate between obstructive lung disease and restrictive lung disease. You could see that a person is asked to deeply inhale as well deeply exhale.

So, when he inhales, if the vital capacity of the lung is decreased, then he will be categorized as suffering from restrictive lung disease. If we forcefully expire the air and if that volume is decreased, then he will be categorized as he is suffering from obstructive lung disease. So, you can see these waves which are normal breathing of our lung and this is the peak or deep inhalation and this is the deep exhalation. So, decrease of these volumes will differentiate us between obstructive and restrictive lung disease. So, here are the types of restrictive lung disease.

How are the restrictive lung disease is actually understood. Restriction means the vital capacity that the volume has to go inside, the air volume that has to go inside is decreased. It can be decreased in two ways, either the alveolar wall and the bronchial wall would be thickened or else the space, the alveolar space and the bronchi would be obstructing or it will be filled with some kind of a substance or the cells which will block the vital capacity. So, this first two categories that is the fibrosing lung disease and granulomatous lung disease come under the thickening of the wall of the alveoli and the bronchi. So, what is fibrosing lung disease? This in simple terms if I have to tell, if you get a cut in the hand or in the skin, it will yield by formation of scar, right.

So, the scar is nothing but fibrosis. Same way here also when the lung is getting injured, it is completely replaced by fibrous structure or by the scar tissue formation that is called

as fibrosing lung disease. Granulomatous lung disease is nothing but some kind of an inflammatory response to an irritant which will, which will engage the inflammatory cells and form a nodule like thing and thicken the wall of the alveolar wall as well as the bronchial wall. So, we are going to see all these things slightly in a detailed manner. And these three things, the eosinophilia, smoking related and all are the cells which will occupy the alveolar space and the bronchial space, ok.

Coming to the fibrosing and the granulomatous lung disease, each of them are sub-typed as based on the source of the inhalant, it will be categorized as known etiology and unknown etiology. So, if you take the fibrosing lung disease, you have some of the agents which cause them. So, it could be more likely due to occupational hazardous substances, we call them as environmental agents or air pollutants we can call them. Nowadays, ionizing radiation has become very commonly causing fibrosing lung disease. Some of the drugs that that is being inhaled by some people will also end up in fibrosing lung disease.

Whereas, the other category we do not know what is the source of the thing that is triggering the fibrosing lung disease. They come under the category called as unknown etiology leading to fibrosing lung disease. We have some connective tissue diseases, some autoimmune diseases, good pressure syndrome, etc. can lead to fibrosing lung disease. Same way if you take granulomas, here also we have known etiology and unknown etiology. In known etiology, we see that most of the allergic substances will cause thickening of the alveolar wall by means of granulomatous inflammation.

And in unknown etiology, we have one famous disease called as sarcoidosis. We do not know what is the real triggering agent, but that causes granulomatous inflammation of the lung. So, we let us see in detail of all these things in the coming slides. So, this is a picture, we have two rows. The first row is showing fibrosing lung disease and the second row is showing the granulomatous inflammation of the lung.

So, here you can see the wall of the alveoli which is so thickened and you can see the dot like structures, they are the inflammatory cells and these spindled cells are all the fibrous structures or fibrous tissue. Here in this picture, you can see that alveoli are free and spacey and whereas the one in the right-hand side, you can see all fibrous structure and the space of the alveoli are all decreased. Here you can see a picture where fibrous structure is running just below the lining bronchial epithelium or the alveolar epithelium. So, in the below row, you can see this is the granulomatous inflammation. You can see these modified macrophages, we call them as epithelioid cells and which are all surrounded by the inflammatory lymphocyte cells, chronic cells and here is also another granulomatous condition and here also you could see some granuloma with some multinuclear giant cells studying the periphery of the granuloma with inflammation.

So, this is how the wall of the lung is getting thickened either by fibrosis or by granulomatous inflammation. Let us go to see about the fibrosing restrictive lung disease. So, this is unknown etiology. You can see the lung which is normally should have a very slim and thin septae of the alveolar wall and it is all lined by the pneumocytes and some macrophages are floating inside. So, this is how a normal lung should all have, but in fibrosing lung disease, you could see the septae are so thickened with fibrous cells and the inflammatory cells which is keeping the lung thickened and reducing the vital capacity.

So, this is, this kind of condition is called as idiopathic pulmonary fibrosis or also called as cryptogenic fibrosing alveolitis. Usually it happens in people in the sixth decade of their life and it is a chronic progressive disease and the median survival is just four to five years and this is the description of this microscopic picture telling us about interstitial inflammation and fibrosis of the alveolar septae. So, this is all about unknown etiology causing the fibrosing lung disease. This is overall understanding about the pathogenesis of this entire fibrosing lung disease. You could see that it will hold good for all the causes either known etiology or unknown etiology.

So, some triggering agent like smoking, occupational exposures, irritants, toxins and viral infections sometimes also will cause first and foremost thing is epithelial injury. So, when the epithelium gets injured or some antigen is exposed, you could see that inflammation is triggered. The innate and the adaptive immunity are triggered and these inflammatory cells will start to produce one very important mediator or the chemical mediator called as transforming growth factor beta. This transforming growth factor beta can activate fibroblast and myofibroblast cells and thereby can cause pulmonary fibrosis and in the same time you could see that the transforming growth factor beta can block a protein called caviolin which usually inhibits fibrosis. Since it has blocked them, they cannot inhibit the fibrosing process.

Also, the other side if you see the cells telomerase enzyme which usually maintains our genetic material and keeps our cells in. This has been affected and the telomerase cannot maintain the telomere lengths and thereby the cell undergoes aging, senescence and cell death that is called apoptosis and this becomes a vicious cycle. So, the cell is either injured and undergoes death, transforming growth factors are again produced and it keeps on circling in the vicious manner. So, when the lung gets fibroblastic and restrictive lung disease has developed, you could see there are lot of dilated spaces looking like a honeycomb. So, we call this kind of a restrictive fibrosing lung disease as honeycomb lung and this picture I have already showed where you can see the fibrosis just below the bronchial lining.

So, let us move on to the known etiology of fibrosing lung disease. It is usually caused by some inhalation of the mineral dust that is mostly exposed in an occupational field, ok. So, we call the disease that is come from the mineral dust are called as Pneumoconiosis.

Pneumo means lung, cony means mineral dust and osis means disease, ok. A person who is inhaling lot of dust will end up getting this fibrosing lung disease

So, it is not that in one day you get a fibrosing lung disease. So, what happens is it all depends on the concentration of the dust, duration of exposure and also the clearance mechanism. So, if the person is having a good clearance mechanism like ciliated, pseudo ciliated columnar epithelium cells, it will throw off the dust from our lung, but if it stays inside, it causes fibrosing lung disease. Coming to the size and shape of the dust particles, if the size is so micron sized it can go very deep into our lung. If it is bigger it will stay in the upper respiratory tract itself.

So, it all depends on the size of the dust also. Then comes the solubility. If the dust solubility is quite high that means if it is very soluble it leads to acute lung injury. It will immediately cause toxicity and it will cause acute lung injury. If it is less soluble it remains there and causes a chronic inflammation and finally ends up in fibrosing lung disease.

So, the mineral dust can club with certain other irritants like that same person might be inhaling tobacco, smoking kind of thing and that will also add up and agent the process of fibrosing lung disease. So, here in this tabular column you could see the list of dust and here you could see the diseases that is caused by these dust materials. And here in this column you can see that where the person is actually working and he is getting exposed. So, a person working in a cold dust mining area will inhale this cold dust and he will get a disease called as anthracosis. So, initially it will be asymptomatic later it becomes very severe, massive fibrosis will take place.

A person working in metal casting work, sandblasting, then silica mining etc., he will get exposed to silica and he will end up getting a disease called as silicosis. Then a person who is working in mining, milling, manufacturing, insulation areas of asbestos fibers, he will get a disease called as asbestosis. So, a person working in beryllium mining will get berylliosis, a person working in iron oxide mining will get siderosis, barium sulphate will end up getting fibrosis, tin oxide mining will end up getting stannosis. So, a person of working in a coal mine he will get a disease called anthracosis which I mentioned earlier and he will be inhaling lot of carbon dust. Anthra means it in Latin or Greek it is called charcoal.

So, inhaling charcoal will end up getting coal workers pneumoconiosis or anthracosis. Initially it will be asymptomatic, then later you will have some nodules and finally you will get a massive fibrosis. So, these are the gross pictures and the microscopic pictures. Firstly you could see a lung fully studded with the carbon particles that is black in color and you can see the macrophages which has in which has laden the pigments and you could see the fibrous structures in in between you can see those carbon laden cells. Kaplan syndrome is

generally a syndrome usually named to people having pneumoconiosis added up with another disease called as rheumatoid arthritis

So, that is nothing but a joint disease clubbed with pneumoconiosis is called Kaplan syndrome. Coming to silicosis a person can inhale silica particles it is of two types it can be either crystalline or it can be amorphous forms. So, the crystalline forms are more fibro genic and the examples are quartz, cristobalite and tridymite kind of things. So, what it does is it forms fibrosing lung disease initially with small nodules or papules, later it become ardent collagenous scars and it can be superimposed with some TB infection and became a cavitatory lesion like this. This is a gross picture of the person suffering from silicosis and if the same silica goes to the nodes nearby to the lung, we call them hilar nodes they will be showing egg shell calcification in those nodes.

So, we can diagnose by asking the patient to take a chest X-ray where you see 90 percent of them showing nodularity in the lung as well as in the nodes also. And in microscope we can see especially using a polarized microscope we can see those fibers as birefringent silica particles. So, here you could see the light will be split into two when it hits the fibers and you can see as a bi-structured light. Coming to asbestos particles this is also of two types either it can be serpentine which is flexible whereas amphiboles are straight, stiff and brittle.

So, this is more fibro genic. As well these asbestos fibers have the characteristics of free radical generation. So, it will affect the cells nearby and can also lead to cancers. So, people who are inhaling asbestos will end up in lung cancers, pleural cancers like mesotheliomas and sometimes if it goes to the colon also it will cause colorectal cancers. So, these are the list of diseases which comes to people having asbestosis. Initially with fibrous plaques, then pleural plaques, then you have some effusions in the pleural cavity and they would have some nodules with interstitial fibrosis.

They will some end up in cancers, they will end up in pleural cancers that is mesotheliomas and they will end up in colorectal cancers also. So, when you see the pleural side of the asbestosis you could see nodularity like this which are all the fibrous structures in the lung. And when you see in the microscope you see them asbestos bodies or ferruginous bodies would be present. They are nothing but rods of asbestos fibers which are beaded in the ends and they are clubbed with iron and proteinaceous complex to form these kinds of bodies. So, if it is non-asbestos fibers we call them as ferruginous bodies.

If they are asbestos fibers they are called as asbestos bodies. Now, let us go to the granulomatous disease, the thickening of the wall of the lung by means of granulomatous inflammation. Again, we are we are again going to see them as unknown etiology and known etiology. So, the prototypical example of unknown etiology is sarcoidosis. It is a

immune disorder or immune disordered immune regulation of disease which is systemic and there are lot of granulomas will be formed in these people suffering from them.

It is immune regulated disorder this to prove that we have some factual things we could see that the CD4 to CD8 ratio is increased in these people. We can also see that interleukin 2 and interferon gamma is increased which can invite T cells and macrophage activations can take place due to these mediators. Then we have seen that there are increase of cytokines which can bring in T cells in that place and form granulomas. Also, that people who have got sarcoidosis have inherited some of the genes like HLA-A1 and HLA-B8. So, they are all called as genetically predisposed individuals.

Some of the environmental agents also have triggered to form sarcoidosis like Mycobacterium avium intracellular, Propionibacterium acnes and Rickettsiae. So, these are all the ways sarcoidosis gets triggered and forms granulomas. So, here is the picture showing a normal septus and alveolar spaces in this side in the lower right hand side corner and you can see in the upper corner the granulomas, the multinucleate giant cells, the inflammatory cells which is thickening the alveolar walls. So, in the giant cells you can see these kinds of structures we call them as Schwann bodies which are laminated concretions composed of calcium and protein. This is yes, asteroid body which are star shaped or stellate shaped which are seen inside the multinucleate giant cells.

You can see some crystals also inside. Usually if you take an x-ray of these patients, we can see hilar lymphadenopathy in 90% of the cases. So, this is a diagnostic tool for us. Also, these people would have increased serum angiotensin converting enzymes and they would also have increased 24-hour calcium excretions. Now coming to the known etiology, our granulomatous inflammation is formed in the lung walls.

So, it is called as hypersensitive pneumonitis. These people get exposed to allergic substances and thereby they form granulomatous response that is the chronic inflammatory response. So, in this table you can see well that there are antigens in this side and here you can see the source from where they come from and what is the name of the disease given to those individuals. So, most of them are fungal elements which are mentioned here and some are the proteinaceous substances secreted by the animals and they all when they are exposed the kind of diseases they get. For example, a farmer working in a hay when get exposed to this antigen he gets farmer's lung. A person working in a sugarcane factory when he gets exposed to this antigen in the form of moldy fungi, he gets a disease called as bagginosis

A person working in air conditioned and humidifier areas he gets exposed to these fungal elements and he gets a humidifiers lung. A person working in malt factories when he gets exposed to aspergillus he gets a disease called malt worker's lung. Also, a person who are very closely in contact with the birds like pigeon and parrots they get bird fancier’s disease

and pigeon breeder's disease. Previously people were taking snuff powders for diabetes insipidus and they developed hypersensitive pneumonitis or alveolitis and granulomatous inflammation. So, this is how the picture will look like you could see all the wall of the alveoli are all thickened and you could see multinucleic giant cells also as evidence.

Now we have finished the thickening part of the lung was now the space of the lung is compromised due to some kind of a substance or the cells. Here the first condition is eosinophilia. So, people having acute eosinophilia or people suffering from low flow syndrome or they are having a tropical eosinophilia due to a parasite called microfilariasis also called as elephantiasis or due to secondary eosinophilia due to some fungi or bacteria or chronic eosinophilic pneumonia. They all would have eosinophils fully occupying the space of the alveoli and this will decrease the vital capacity of the lung. This way they are calling it as restrictive lung disease.

Now if you take smoking related restrictive lung disease the smoker's tobacco and the pigments will be engulfed by these macrophages. There will be sheets and sheets of macrophages occupying the space and they look like discriminated squamous cells. So, they call these diseases discriminative interstitial pneumonia. And this is the one the proteins the abnormal proteins it is also called pulmonary alveolar proteinosis and these will be abnormal proteins which will be filling the alveolar spaces. So, there are three distinct ways how this alveolus is filled with proteins.

So, 90% of them are due to a deficiency that is granulocyte monocyte deficiency where the acids are not formed since this colony stimulating factor is not there. And because of that they end up accumulating the surfactants in the alveolar space itself. Other 10% of causes are due to abnormal surfactant proteins which are misfolded and they are not being degraded well in the alveolar space. And some hemopoietic disorders, immunodeficiency disorders the macrophages are not formed properly and they cannot clear the proteins that are accumulated in the lungs in these people.

So, they end up getting a restrictive lung disease. So here is the picture you can see the alveoli filled with proteinaceous substance and thereby decreasing the volume of the lung that is the vital capacity of the lung. I hope I have finished the topic of restrictive lung disease. Thank you.