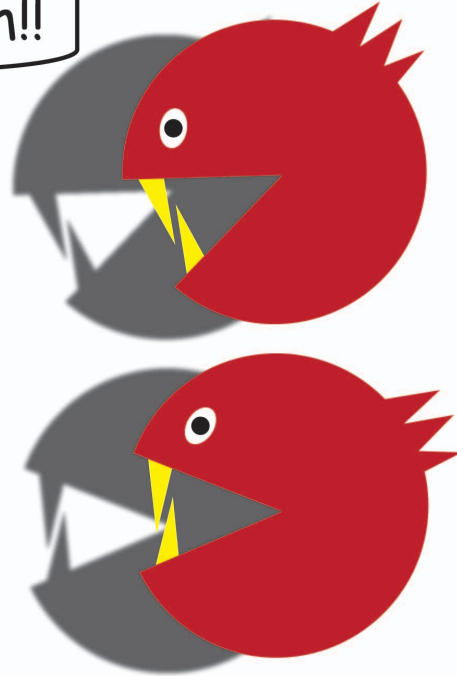
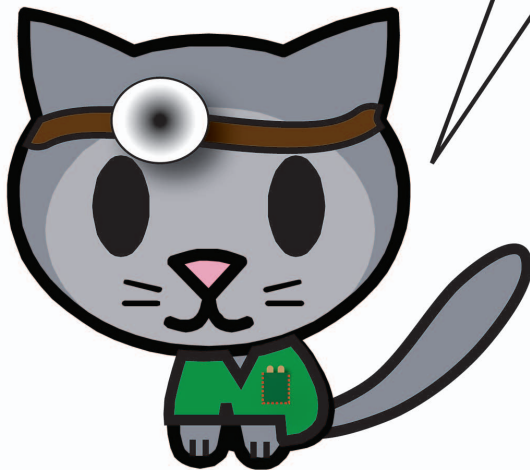


A "Doc Squirrel" and "Kid Cat" Adventure

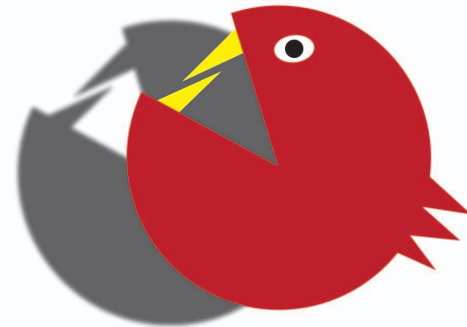
Angry Nodules Attack!

Now With Video!!!!

Save me Captain Algorithm!!



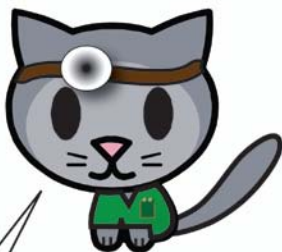
This outfit rocks!!



By Stefan Tigges MD, MSCR & Travis Henry MD



Hey Cat, looking at a CT scan, huh?



This patient has a bunch of lung nodules and I want to come up with a reasonable differential diagnosis.



Have you tried applying the high resolution CT nodule algorithm?

Yes, but it is too hard.

It gets much easier if you understand the anatomy and pathology.

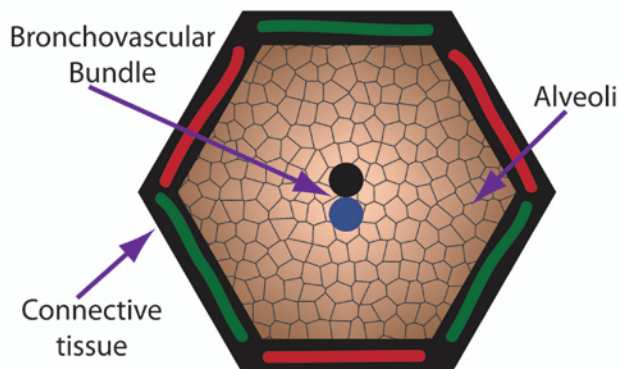
Must we start from first principles?



Of course. Ever heard of the secondary pulmonary lobule?

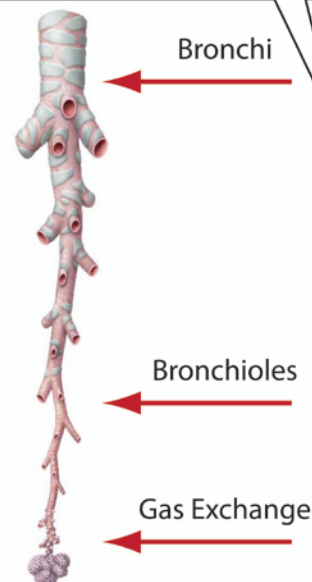
What is that?

It's the smallest unit of lung surrounded by connective tissue. In fact, it is sort of like a miniature lung, complete with airways, vessels and alveoli. Let's use some diagrams to illustrate the relevant anatomy.

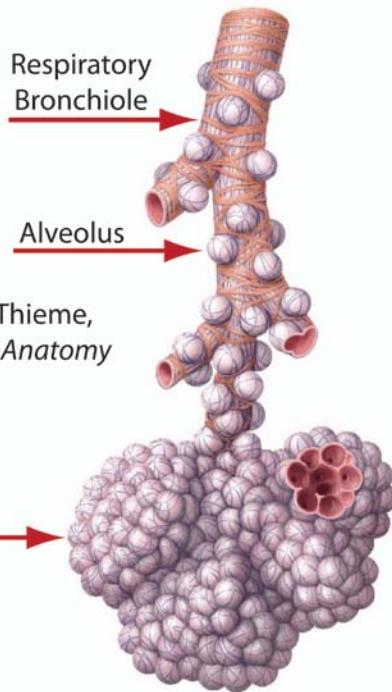


This diagram shows progressive bronchial branching. Bronchi contain cartilage, bronchioles do not. The bronchial tree is purely air conducting to the terminal bronchiole level. At the next level, respiratory bronchioles "sprout" alveoli and gas exchange begins. More distally, alveoli become increasingly numerous and form alveolar sacs.

From Thieme, *Atlas of Anatomy*



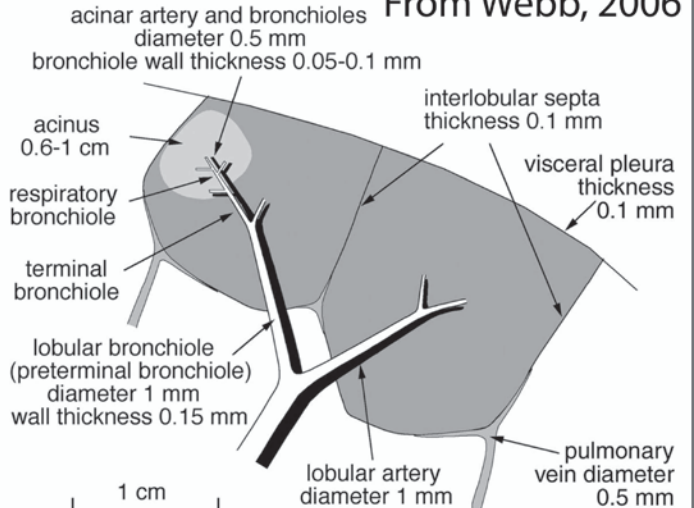
Good job. The second drawing illustrates an acinus, which are those structures distal to a terminal bronchiole that participate in gas exchange. Acini measure 6-10 mm in size.



So where is the secondary lobule?

A secondary lobule starts multiple steps proximal to an acinus. Each secondary lobule contains about a dozen acini and begins at the level of a lobular bronchiole, which is a pre-terminal bronchiole, several branchings proximal to the terminal bronchiole.

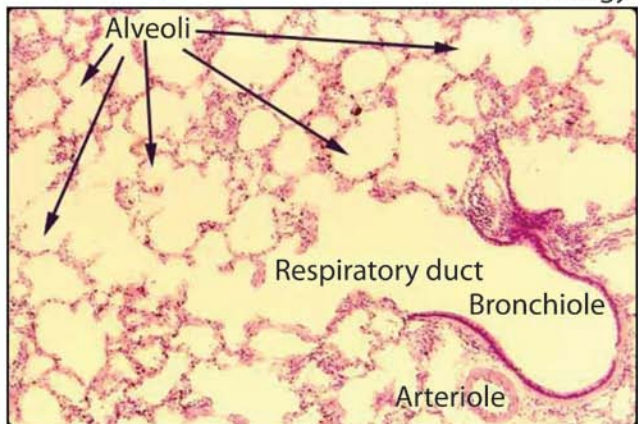
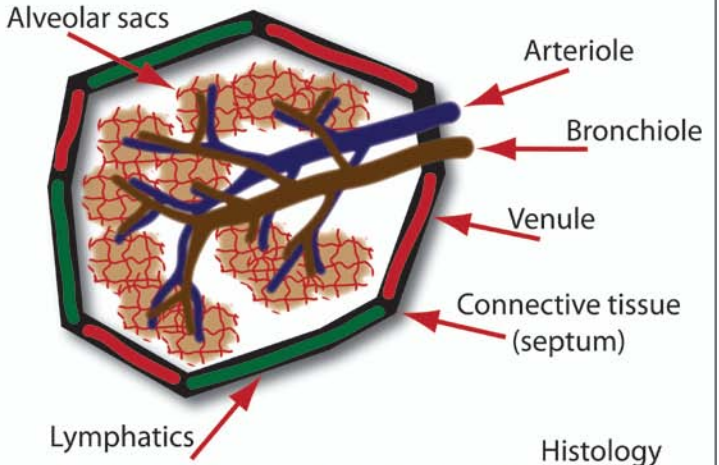
From Webb, 2006

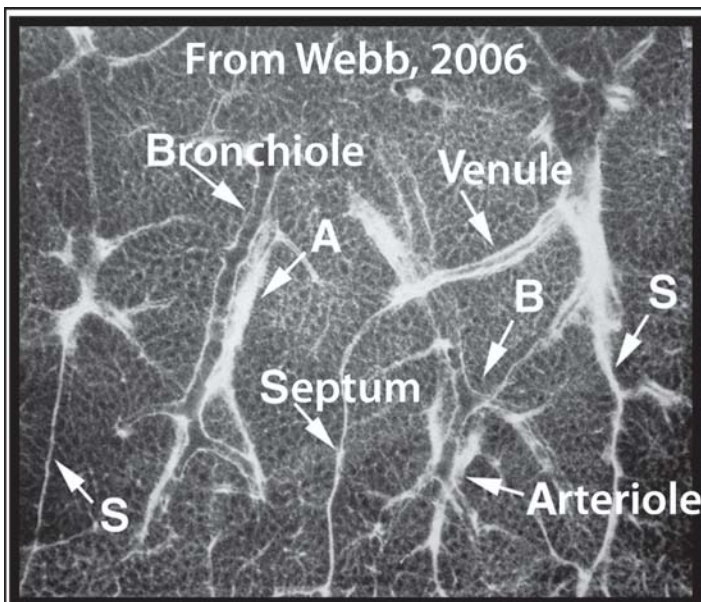


Sounds a bit vague.



You are right in the sense that I can't tell you a precise bronchiolar level where the secondary lobule begins. I can tell you that a secondary lobule is a 1-2.5 cm diameter polyhedron surrounded by connective tissue. The lobular bronchiole, arteriole & lymphatics occupy the center of the lobule and are surrounded by alveoli. The pulmonary venule and additional lymphatic tissue are contained within the peripheral connective tissue. It may be overkill, but I have included multiple illustrations to show this anatomy.

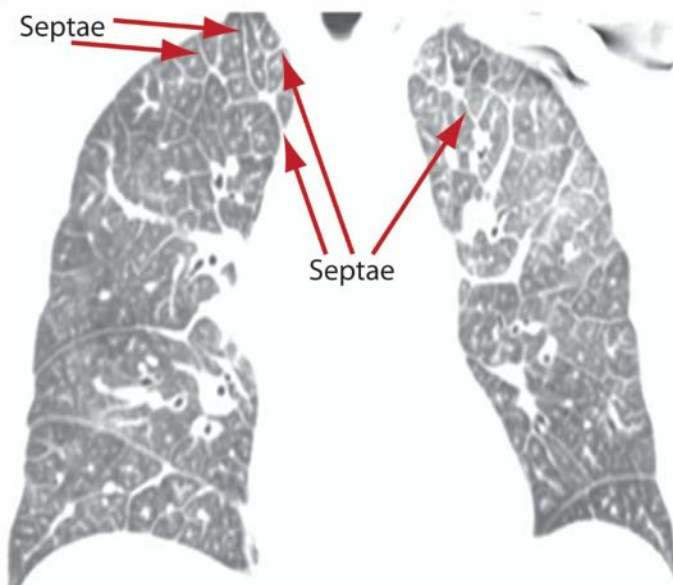




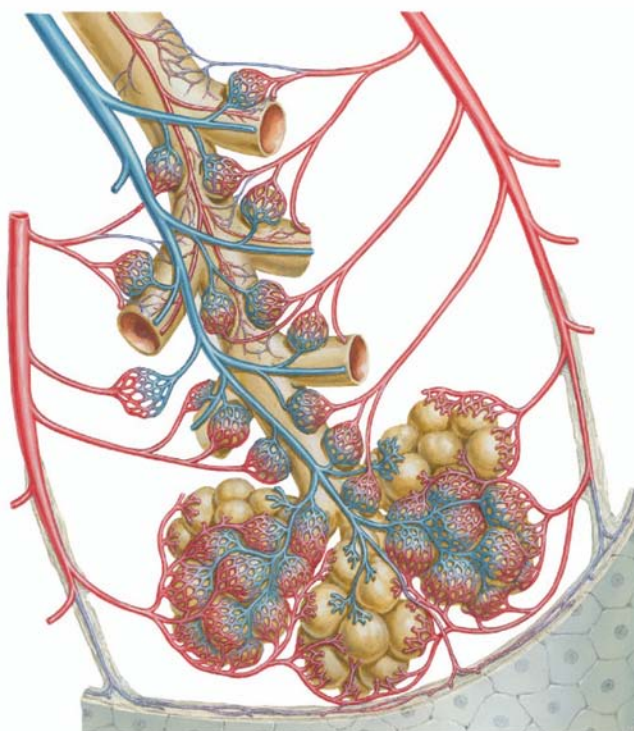
This radiograph from a 1 mm lung slice shows the secondary lobule anatomy nicely.



This patient died of heart failure. CHF fluid has distended the septal lymphatics making the septae easy to see.



This patient also has CHF. Again, the distended septal lymphatics make the septae easy to see. Note the dots in the middle of the lobules, these represent the central arteriole. Some of the lobules have more than one bronchovascular bundle.



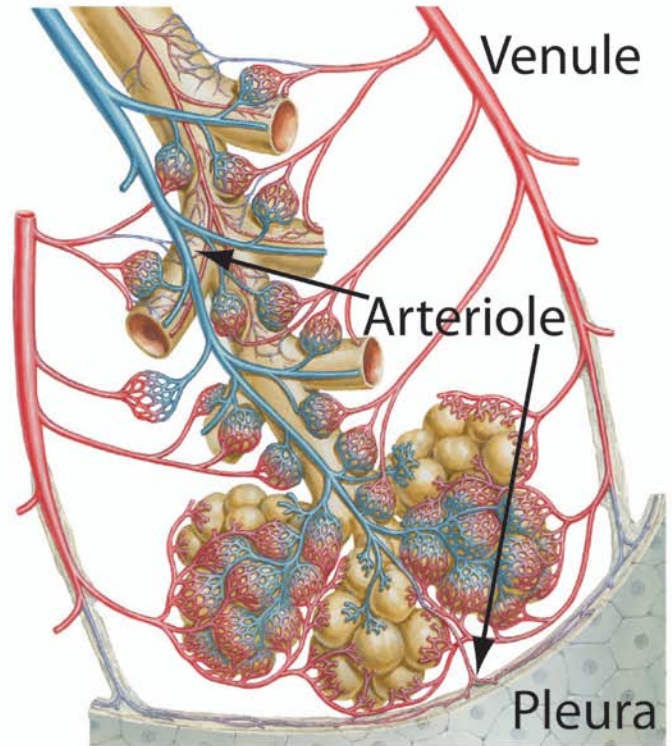
This Netter drawing is really an acinus, not a secondary lobule.



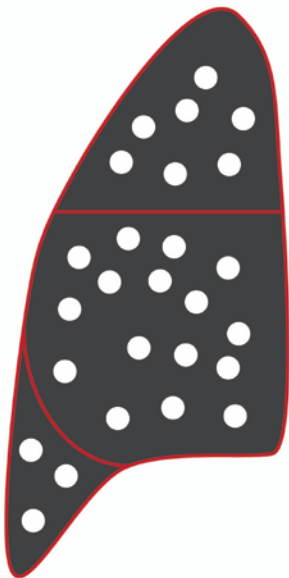
True, but it shows the lobular anatomy so beautifully that I decided to include it. I want you to notice a few more anatomic features. First, look at the pulmonary arteriole; it goes all the way to the pleural surface. Second, note that the bronchioles do not go all the way to the pleural surface; 1-2 cm proximal to the pleura you have nothing but alveoli. Finally, although not shown in the drawing, remember that there are lymphatics along the central bronchovascular bundle, within the peripheral connective tissue running along the pulmonary venule and in the pleura.



Now let's discuss the nodule algorithm.



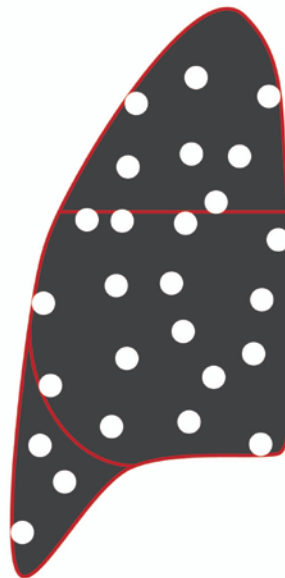
Centrilobular



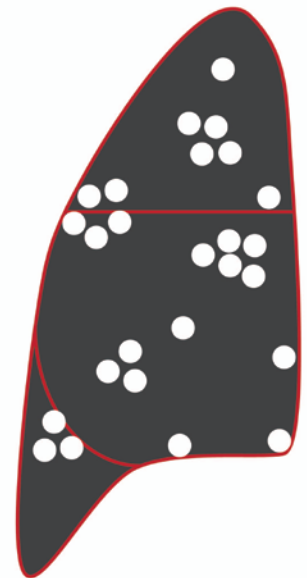
Small Airway



Random



Perilymphatic



There are four different types of nodules: 1) Centrilobular, 2) Small airway, 3) Random and 4) Perilymphatic. There is nothing distinctive about the different nodules per se; the difference lies in their distribution. Centrilobular nodules are diffuse and do not touch pleural/fissural surfaces (red). Small airway nodules are patchy or clustered and do not touch pleural/fissural surfaces. Random nodules are diffuse and may touch pleural/fissural surfaces. Perilymphatic nodules are patchy or clustered and may touch pleural/fissural surfaces.

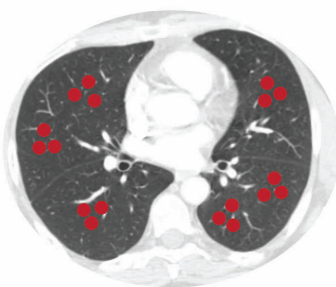
Centrilobular

Clustered: **No**
Pleura: **No**



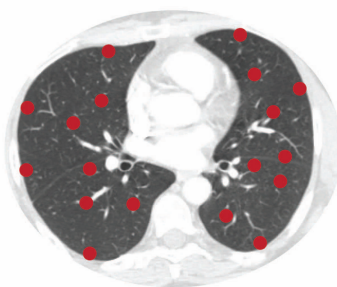
Small Airway

Clustered: **Yes**
Pleura: **No**



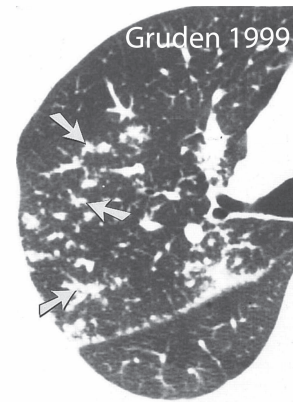
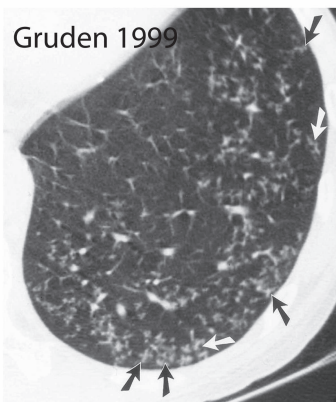
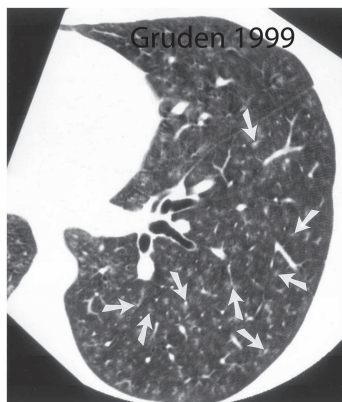
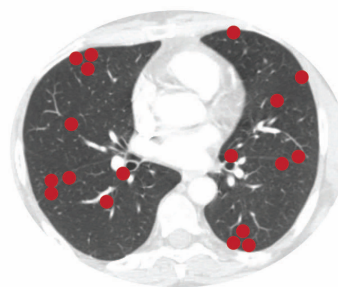
Random

Clustered: **No**
Pleura: **Yes**



Perilymphatic

Clustered: **Yes**
Pleura: **Yes**



Mock CT (top) scans and real CTs (below) illustrate the difference between the nodule types.

I assume that the difference in distribution reflects the anatomic location of the nodules.

Correct. The anatomy of the secondary pulmonary lobule determines and constrains the distribution of these different nodules. But we are getting ahead of ourselves; what is our nodule algorithm?

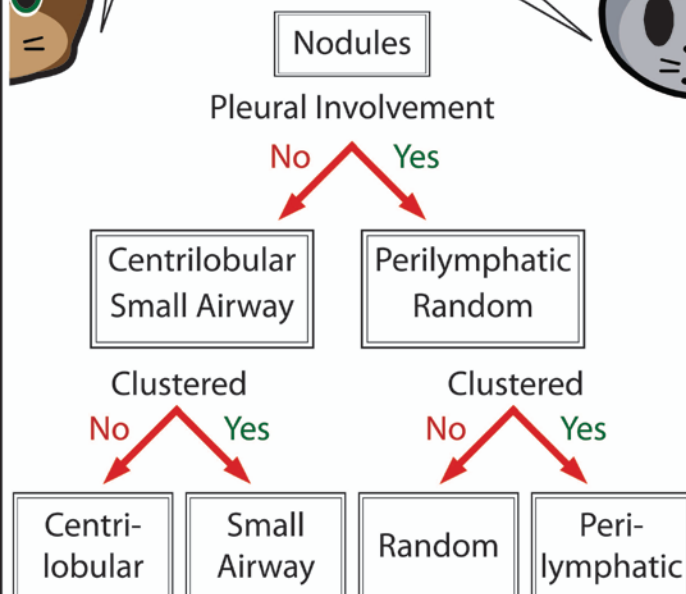
Based on what we have seen so far, we must determine whether pleural/fissural surfaces are involved and whether the nodules are patchy or diffuse.

Right. We consider pleural surfaces to be involved if 10% or more of the nodules contact the pleura. What nodules do we consider if the pleura is involved?

Random and perilymphatic nodules involve the pleura, centrilobular and airway nodules don't.

Next we determine whether the nodules are patchy/clustered or diffuse. Based on what we discussed, can you tell me what our algorithm looks like?

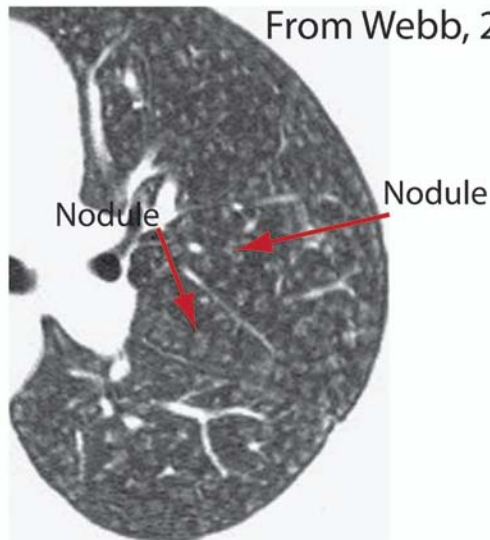
Of course.



Let's use this algorithm on multiple cases and see if we can figure out why it works based on our knowledge of pathology and the anatomy of the secondary pulmonary nodule. We'll start with this case. What see you?

These nodules do not touch pleural surfaces and are diffuse. That means that they are centrilobular nodules.

From Webb, 2006

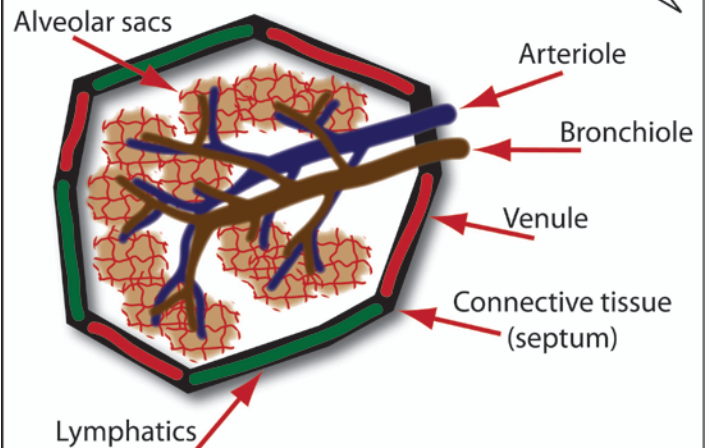


Good. Do you remember what lives in the middle of the secondary lobule?

The lobular bronchiole and arteriole.

Correct, so abnormalities related to these structures may cause centrilobular nodules. If this were a farmer exposed to moldy hay who developed a cough, what would be the diagnosis?

Hypersensitivity pneumonitis.



The inflammatory reaction involving the centrilobular bronchiole results in a centrilobular nodule. Here is a case of a marijuana smoker with centrilobular nodules. The pathology confirms pleural sparing and inflammatory nodules around multiple bronchovascular bundles.

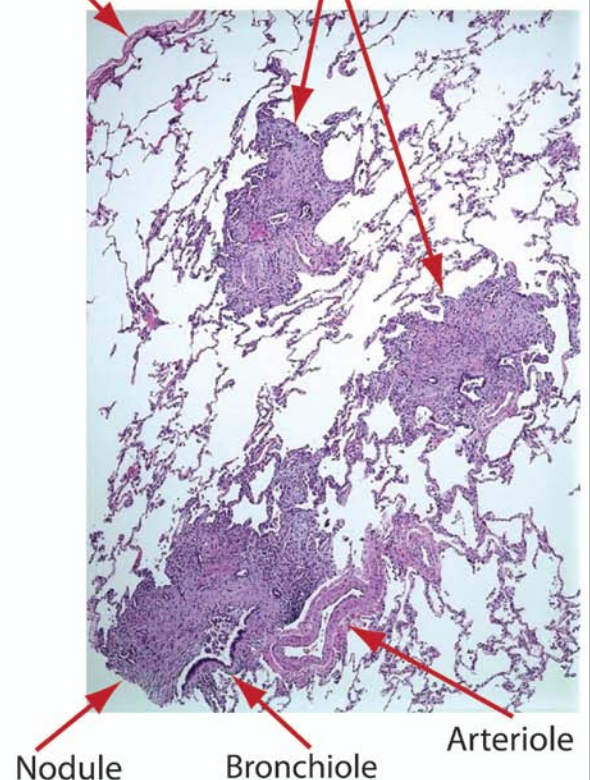


Nodule
(Tiny!)



Pleura

Nodules

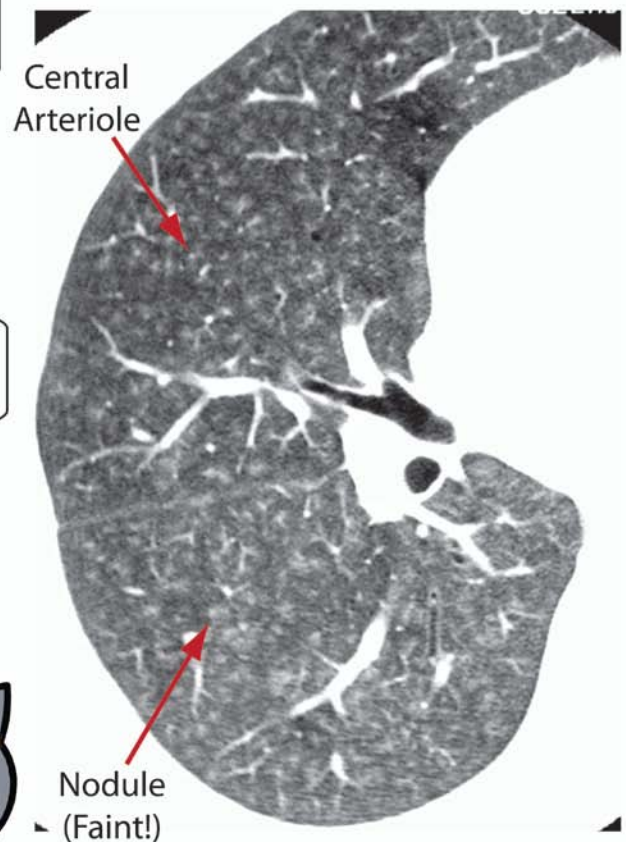


How about this case? This person also has centrilobular nodules with pleural sparing and a diffuse distribution.

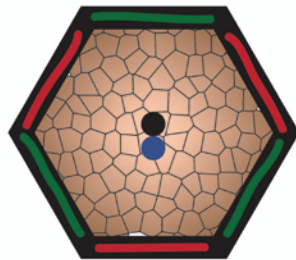
This patient presented with hemoptysis and we presume that these nodules were due to bleeding around the lobular arteriole. What do you think the small dots are in the middle of these nodules?

Those must be the central arterioles. That is another clue that the nodules are centrilobular. Most of these centrilobular nodules are very faint!

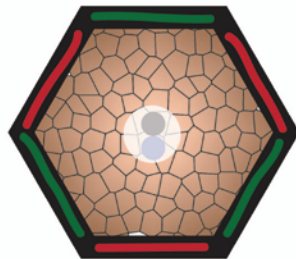
That faint increased density through which you can recognize normal structures has been called ground glass opacity or *GGO*. Centrilobular nodules are often of *GGO* and this is another helpful clue in recognizing these nodules.



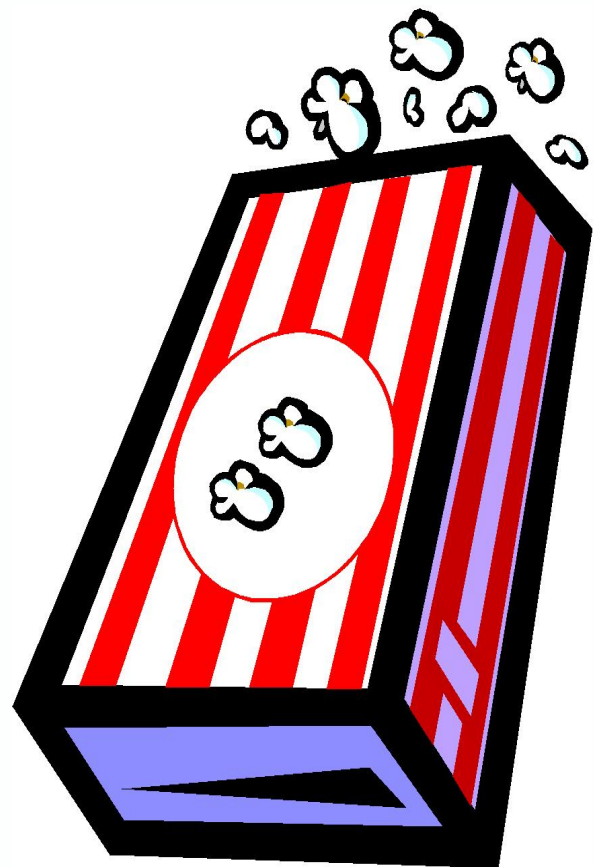
Normal secondary lobule



Abnormal secondary lobule with faint central nodule



Centrilobular nodules result from inflammation of the central bronchiole because of inhaled irritants or central arteriole bleeding. The next panel includes a brief video illustrating this pathology. Obviously, you will need to view this PDF on a computer to see the video. Just click on the popcorn box and the video should run.



Wow, that was a really lame video. I hope they get better. Let's move on to another category.



OK, what do you think about this case?



Nodules

Webb,
2006

The nodules do not involve the pleura and are patchy, so they must be small airway nodules.

Where are small airway nodules located?

In small airways?

Of course, hence the name. They are located in the lobular bronchi and its' branches.

So why aren't they called centrilobular nodules? They involve the centrilobular structures.

They actually are a special case of centrilobular nodules, but since this type of nodule is so common and has a characteristic morphology and patchy distribution, we consider them separately.

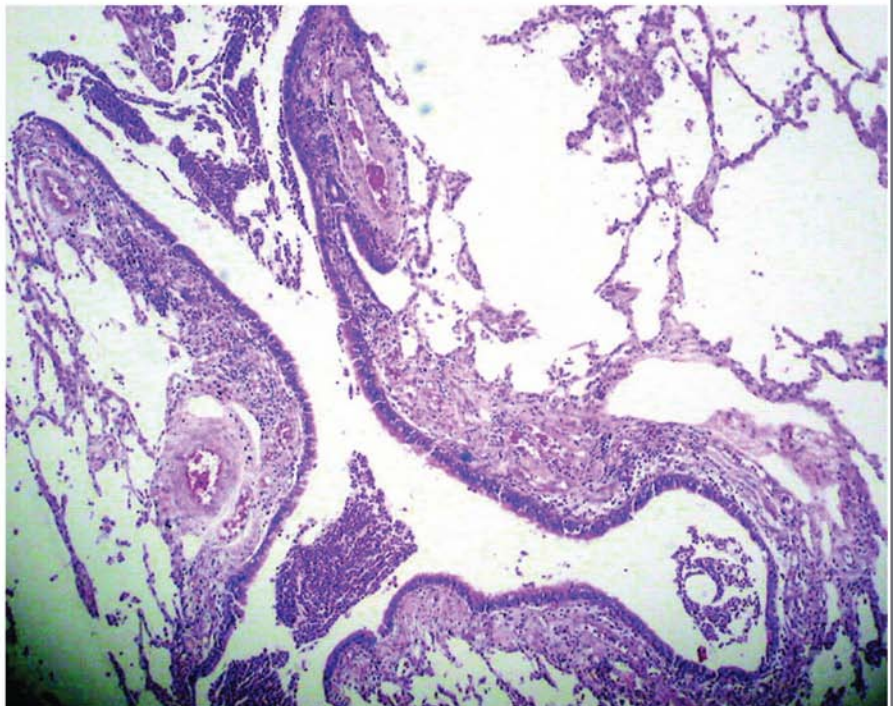


Look at this histologic section. What do you see?

A thickened branching airway containing multiple nodules.



Exactly. That is small airway disease. The nodules represent tiny foci of infection or infected bronchiolar impactions. In fact, most cases of small airway disease are caused by infection. Pus gets into the airways and either forms clustered nodules or a cast of the airway.



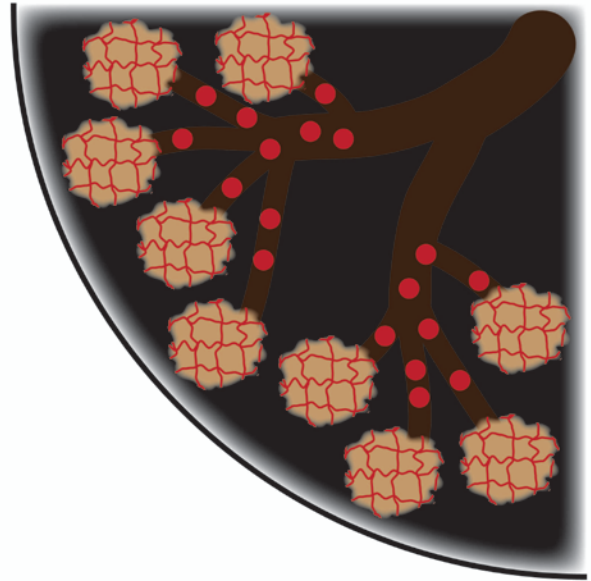
Check out the video in the next panel that shows small airway nodules!



Let's convert this histology to a drawing.

The small airway distribution results in the clustered or patchy appearance of these nodules.

Watch the movie in the next panel to see how the histology translates into a CT.



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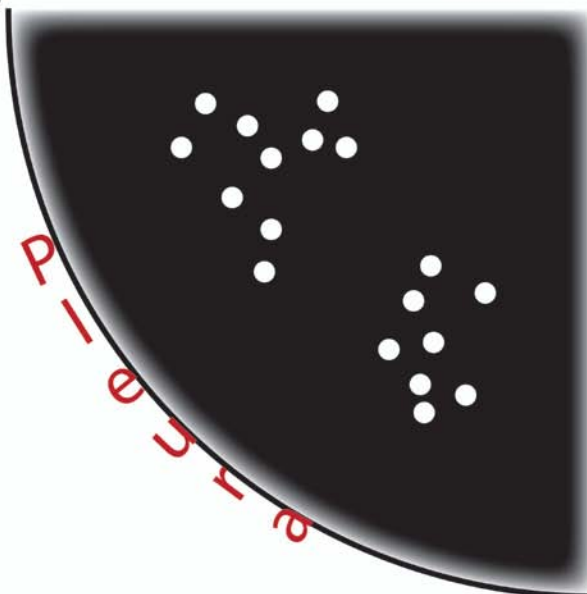
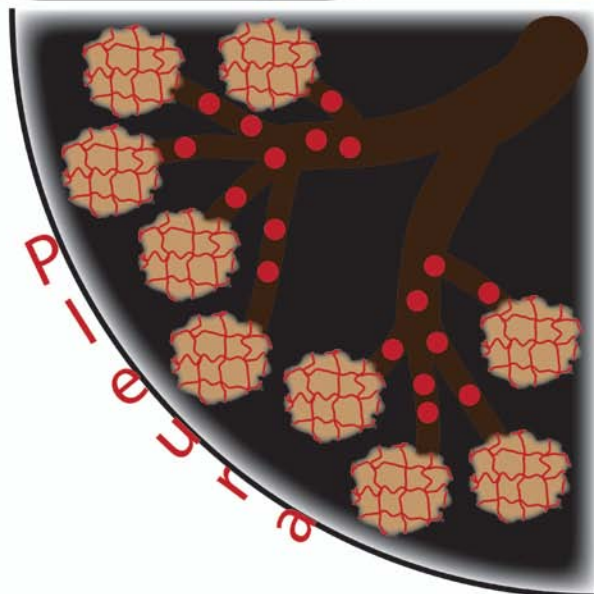
"Evidence Based Comix" are the only comics my mom lets me read.



For those without computer access, the relevant images are below. Note the clustering of the airway nodules on the illustration on the left. The nodules don't reach the pleura because the airways do not reach the pleura.



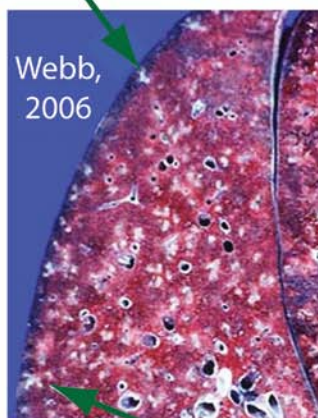
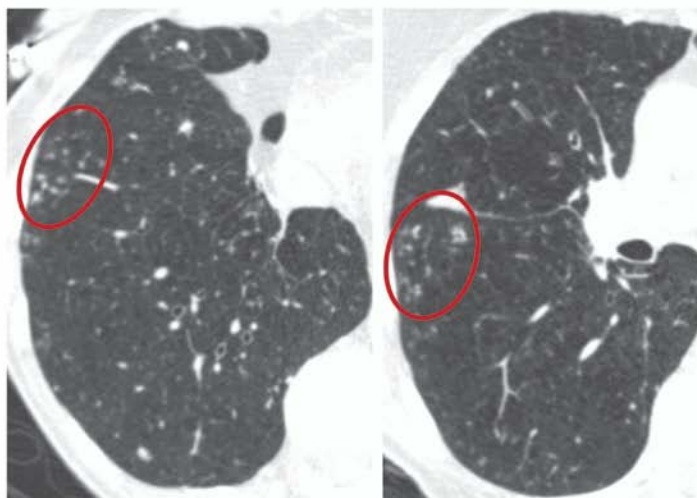
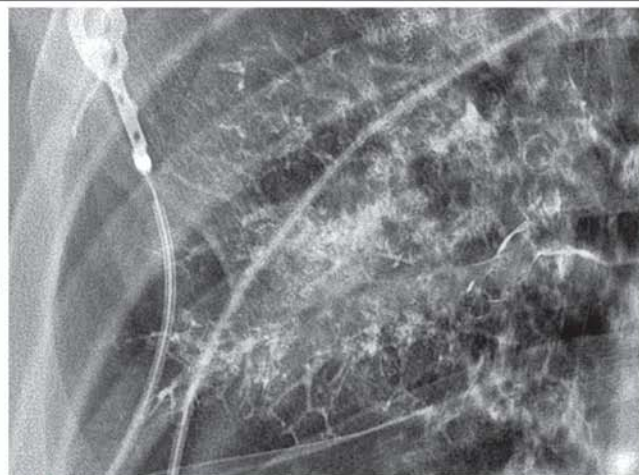
The "CT image" below nicely shows the clustering and pleural sparing.



10



When branching airways are filled with pus, a characteristic "tree in bud" morphology results. The impacted bronchi resemble a budding tree in spring or children's toy jacks in the CT below. Aspirated barium at right shows impacted branching airways well with a jacks or "tree in bud" morphology.

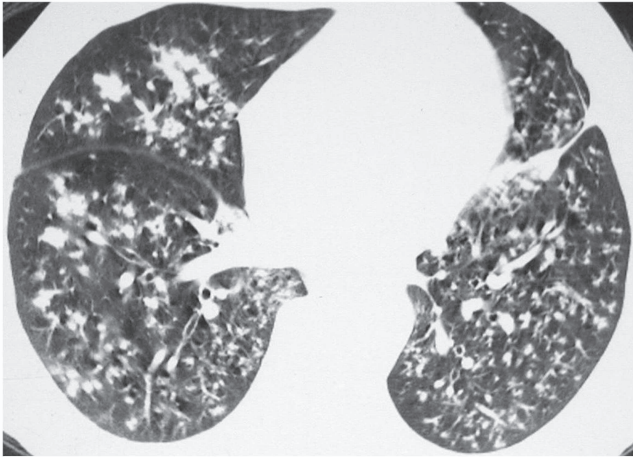


Gross pathology at left shows the same branching pattern. Nodules are near but do not touch the pleural surface.



I can see how recognizing the morphology helps. In this case the disease is so extensive that it isn't really patchy.

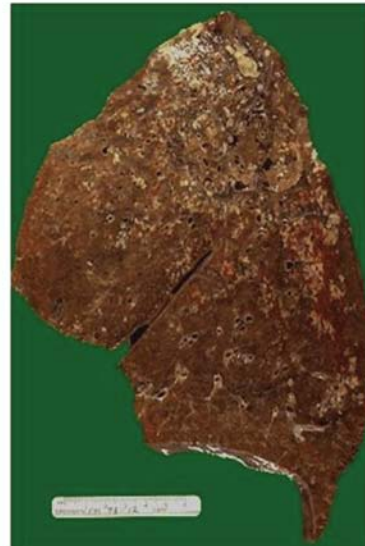
It is also important to recognize that few if any of the nodules touch pleural or fissural surfaces. Remember, the airways stop 1-2 cm proximal to the pleura.



Any particular organisms I need to keep in mind when I see this pattern?

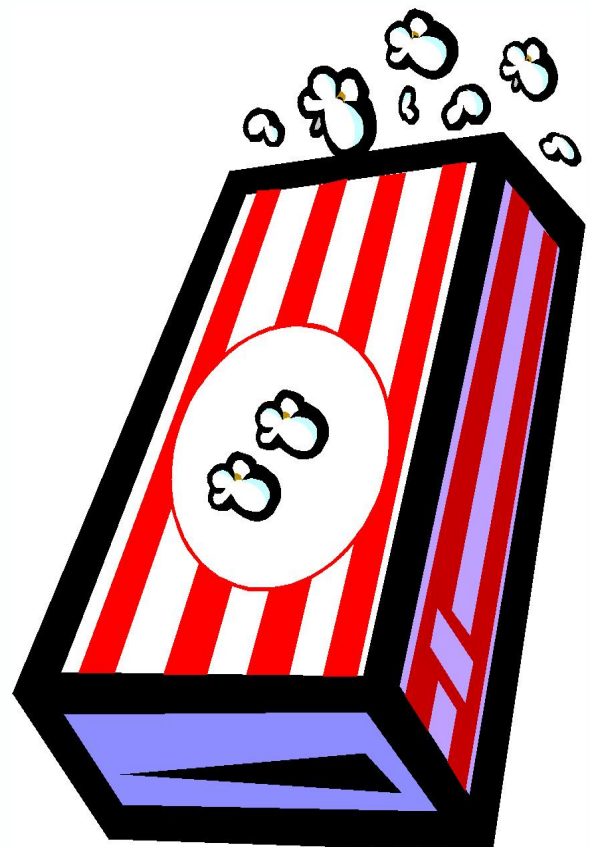
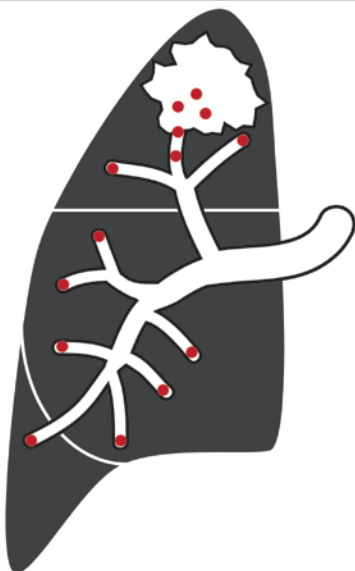
Endobronchial spread of TB. Look at this lung specimen, what do you see?

Patchy nodules that mostly spare pleural surfaces. This is a small airway pattern.

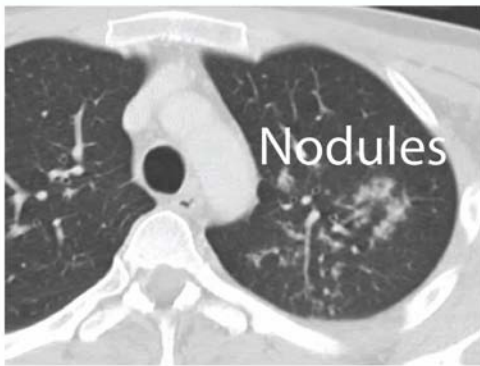


University of Utah

The previous patient died because of endobronchial TB. The infection causes lung cavitation and bronchial destruction. Once the infection has eroded into the airways, the organisms gain access to and spread through the bronchi. A small airway nodule pattern results. Check out the illustration below and the movie in the next panel.



Here is another case of cavitary TB with endobronchial spread.



How about other mycobacteria?

Mycobacterium avium-intracellulare may cause this pattern. Consider MAI if you see small airway nodules in an older woman, especially if there is predominant involvement of the right middle lobe and lingula.

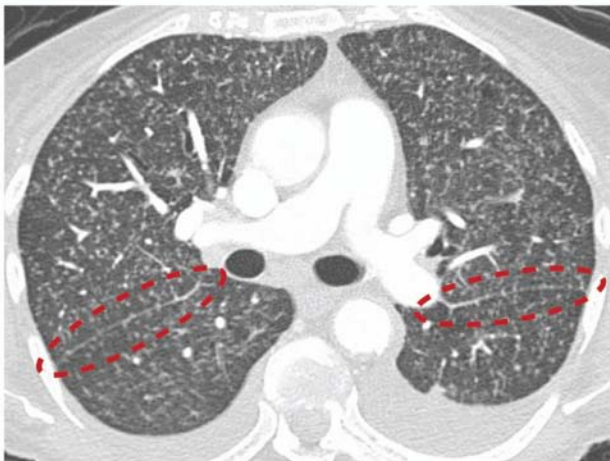
How about aspiration?

Sure. If you see a dependent small airway pattern, especially in patients with a hiatal hernia, an intrathoracic stomach or a head and neck tumor, consider aspiration.

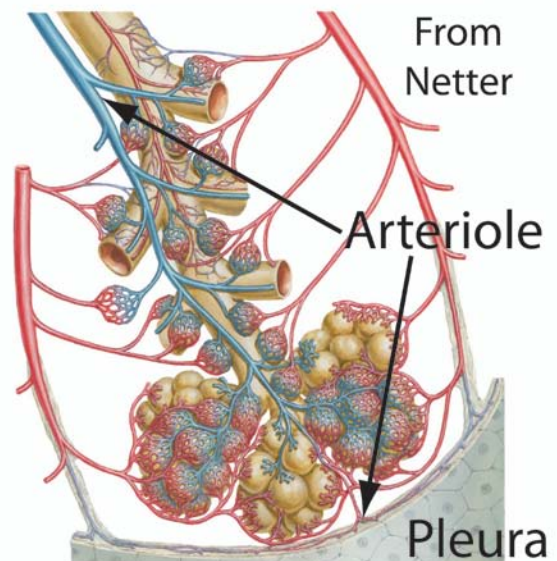


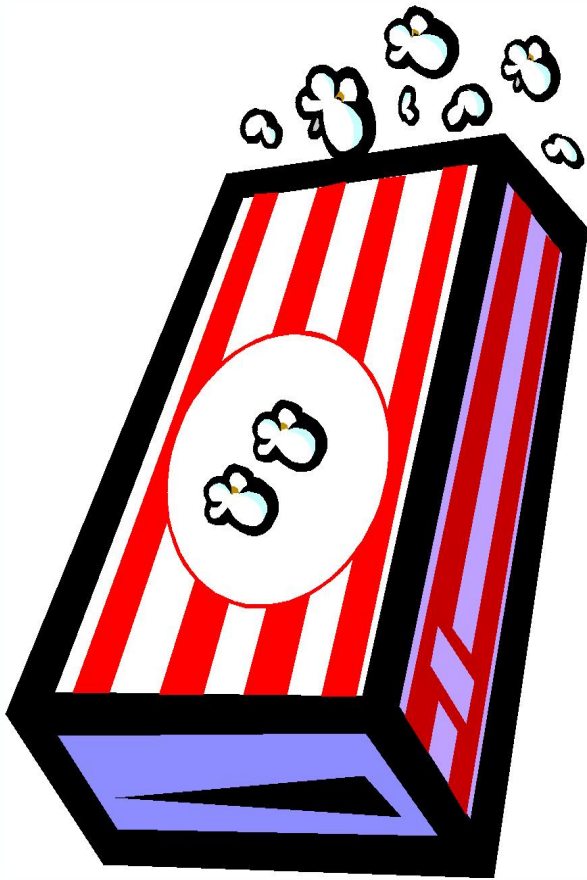
What do you think of this next case?

Since many of these nodules touch the pleura and the distribution is diffuse, the distribution is random. The pleural involvement is easiest to see when you look at the fissures (red dashed ovals).

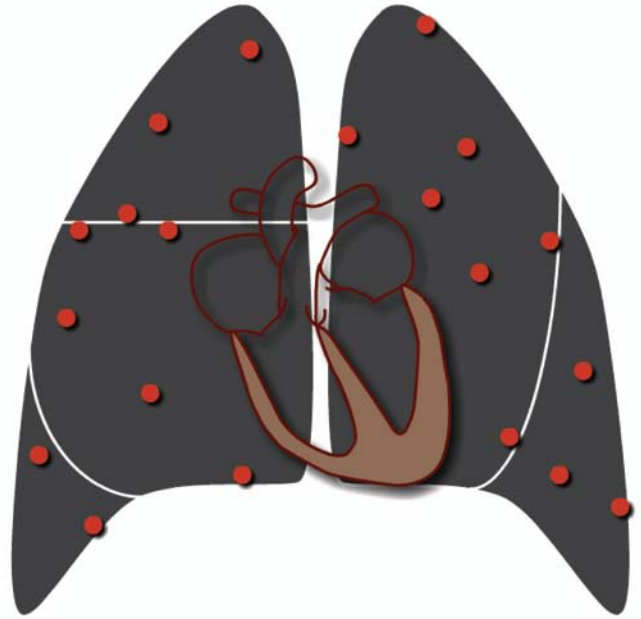


Right. Random nodules get to the lungs hematogenously and go wherever blood goes. That's why they tend to be diffusely distributed. Since some pulmonary arterioles extend all the way to the pleural surface, some nodules will contact the pleura. The next panel includes a video showing hematogenous spread of disease.





For those not at a computer, an illustration of random nodules is included below.



What 2 potential causes of random nodules come to mind?

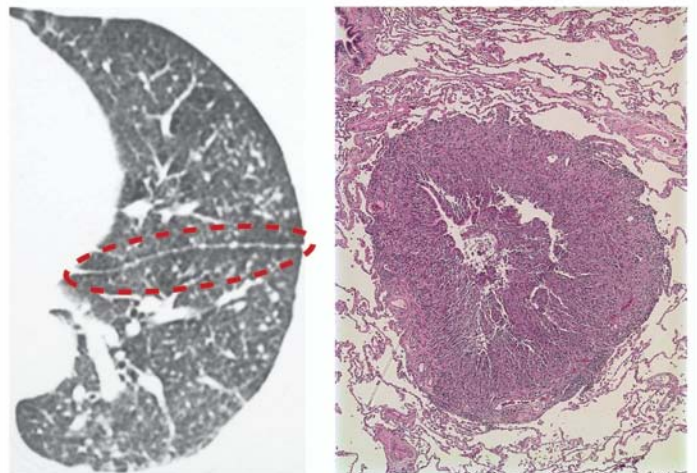
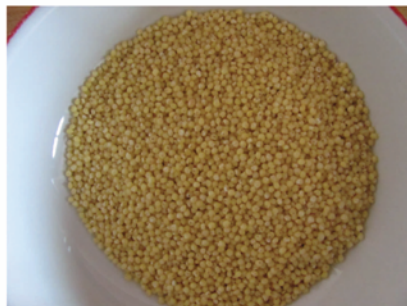
Metastases and miliary TB.

The previous case was a patient with miliary TB. Lots of cancers spread to the lung hematogenously, but thyroid cancer and renal cell carcinoma are notorious for spreading to the lung with innumerable tiny nodules in a random pattern.

These random nodules are due to renal cell carcinoma metastases. Pleural involvement is best shown along the fissures, which have a beaded appearance (**red dashed oval**). The histology shows how well defined these small nodules are.

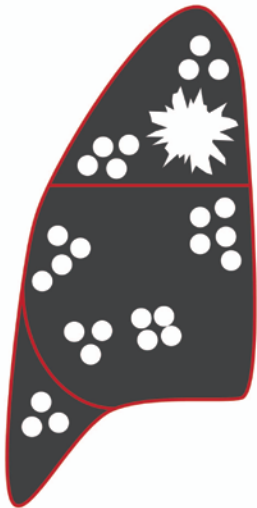
How do you tell the difference between miliary and endobronchial TB?

Millet Seeds

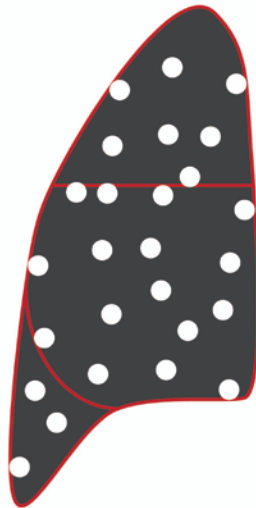


Look at nodule distribution/morphology. Endobronchial TB will have a small airway distribution and "tree in bud" morphology, while miliary TB has a random distribution with small well defined nodules. Patients with endobronchial TB will often have a visible cavity, while miliary TB may spread hematogenously to other sites.

Endobronchial



Miliary



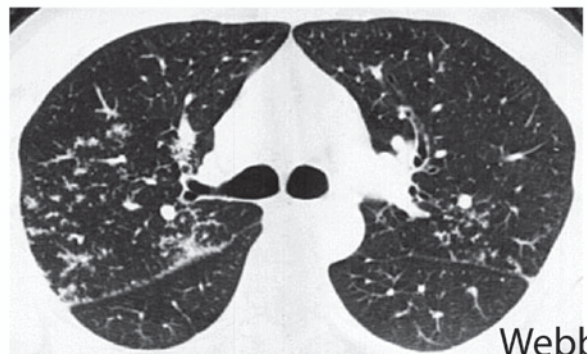
Since we only have one category left, I guess this next case is an example of perilymphatic nodules.

Right. The nodules are patchy and involve pleural surfaces. Where do you think perilymphatic nodules are located?

In lymphatic tissues.

And where is lymphatic tissue located?

Lots of places: around the bronchovascular bundles, in the connective tissue surrounding the secondary lobule and in the pleura.

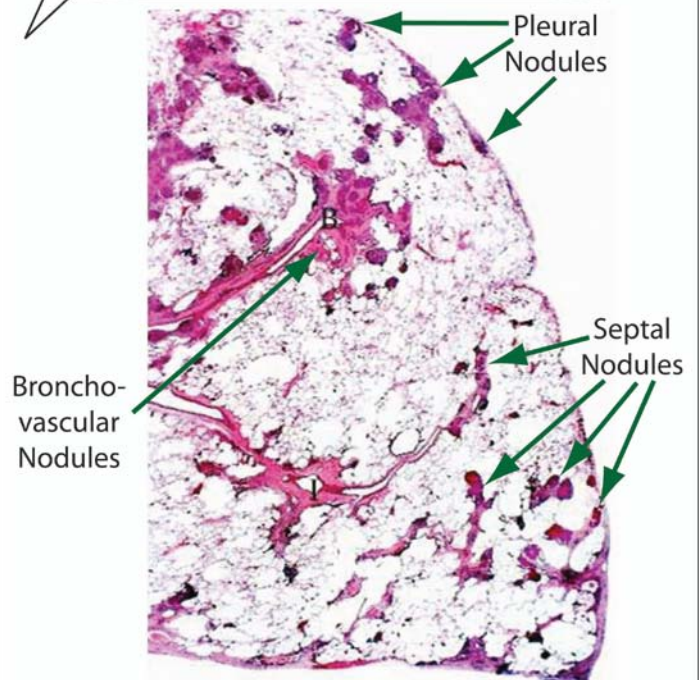


Webb

The lymphatic tissue around airways is called bronchus associated lymphoid tissue or BALT.

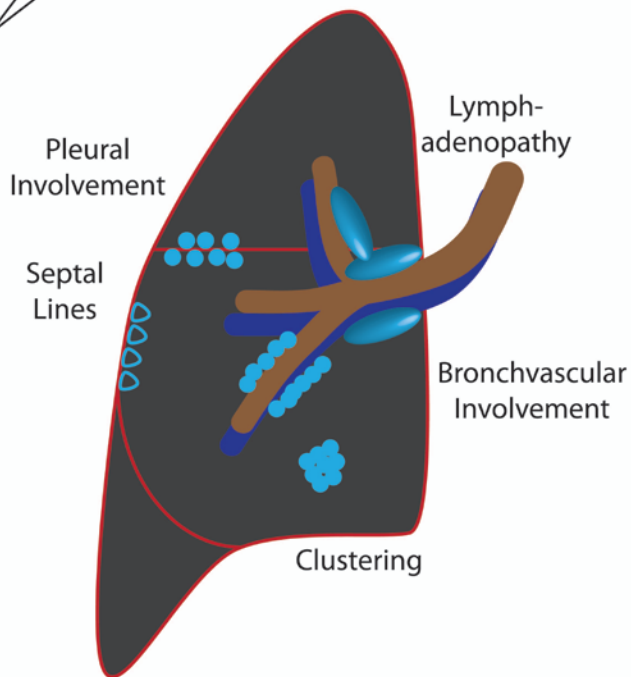


The previous case and the histologic specimen below show a perilymphatic nodule pattern due to sarcoidosis. There are septal, pleural and bronchovascular nodules.



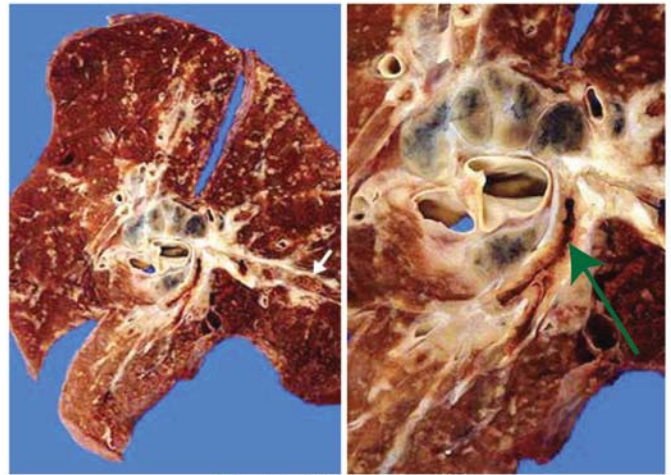
Martha Warnock MD

Don't forget lymph nodes. Although the presence of lymph node enlargement is not part of the algorithm, adenopathy is often present in patients with perilymphatic nodules.



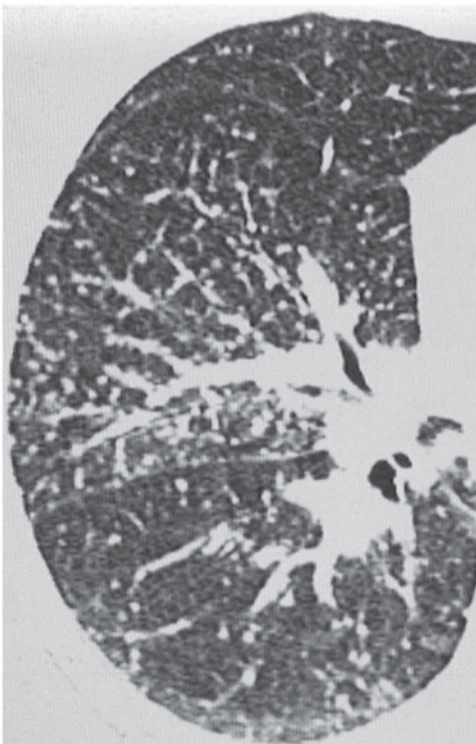
What diseases result in perilymphatic nodules?

Sarcoidosis and lymphangitic spread of cancer are the most common causes of this pattern. Look at the gross images of a case of sarcoid below that illustrates perilymphatic features like nodule distribution and bronchovascular involvement (green arrow).



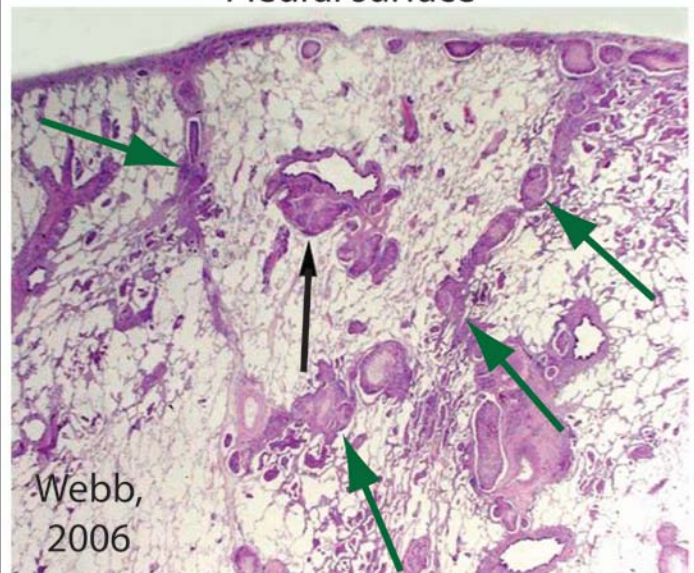
Martha Warnock MD

This case of sarcoidosis has septal, pleural and bronchovascular nodules in a patchy distribution.



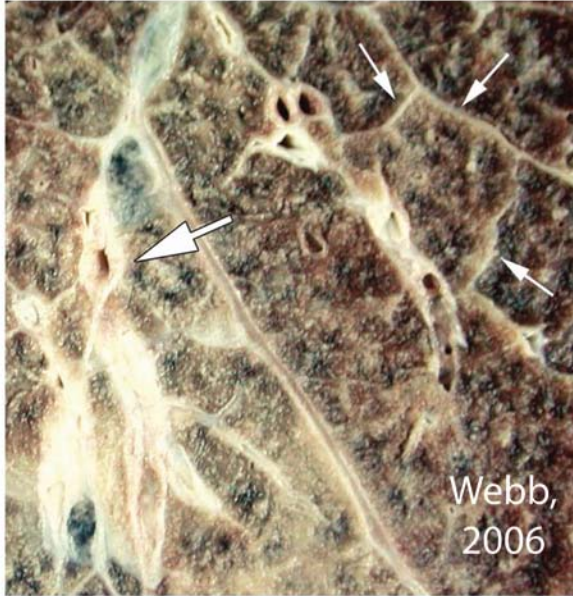
Lymphangitic spread of cancer can also result in perilymphatic nodules. This secondary lobule shows nodular lymphatic spread of tumor along the central bronchovascular bundle (black arrow), the pleura and the septae (green arrows).

Pleural surface

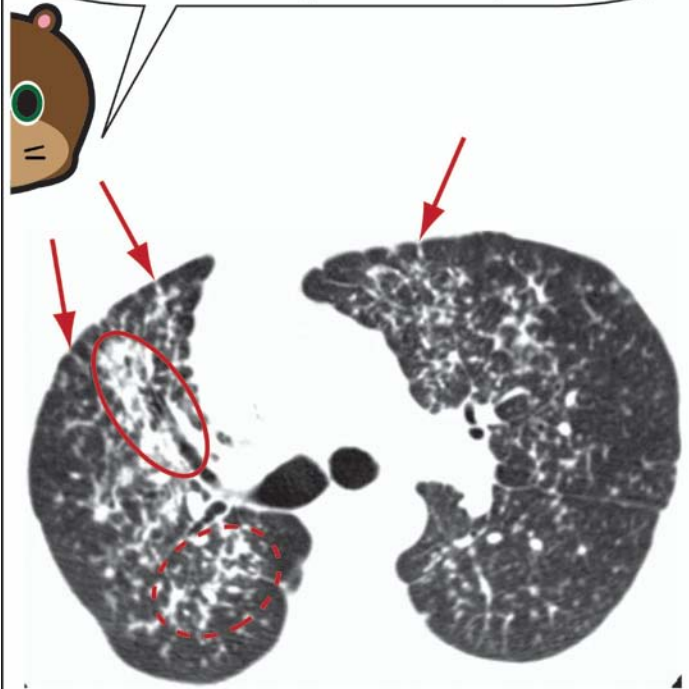


Webb, 2006

The pathology will reflect the microscopic findings. This specimen in a patient with lymphangitic cancer shows septal and broncovascular thickening (arrows) because of lymphatic tumor spread. This thickening can be either smooth or nodular depending on how prominent the metastases are.



This CT scan of a patient with lymphangitic spread of cancer shows thick septae (red arrows), patchy nodules (red dashed oval) and nodules growing along a bronchovascular bundle (red solid oval).



Hansell, Radiology 2008

I understand how lymphatic involvement can result in smooth or nodular thickening of the pleura, the septae and bronchovascular bundles, but I do not understand why perilymphatic disease is patchy.



Me neither, I cannot give you a good explanation. Sorry, it just is.

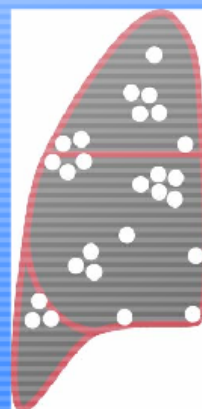
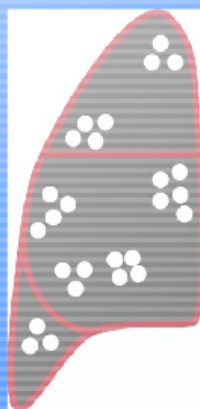
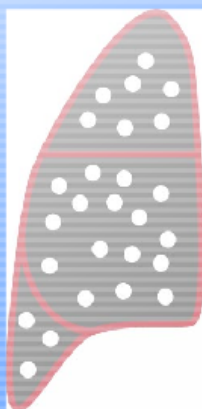
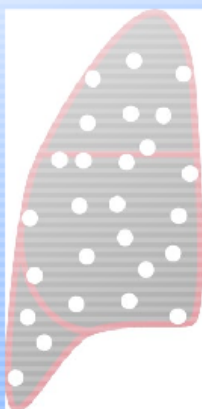
Hey kids, let's test your skill! There is a short quiz on the next panel. After the quiz, there are real cases with lung nodules that you access by clicking on the popcorn boxes. Use the algorithm to classify nodules and determine the most likely diagnosis. Be careful, these are real cases and not as clear cut as examples I have shown. Use some of the other findings we discussed to figure out the tough cases. Hints and answers are provided for each case. I am sure that you are smart enough to get the scroll function working. Mac users, open the PDF using acrobat to run the movies. Good luck from me and Algorithm Cat!



Nodule Quiz

Welcome

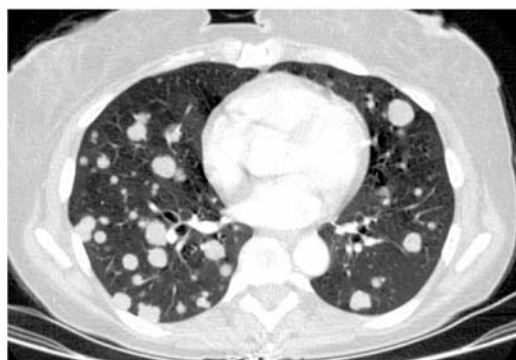
Click the next button to continue.



17



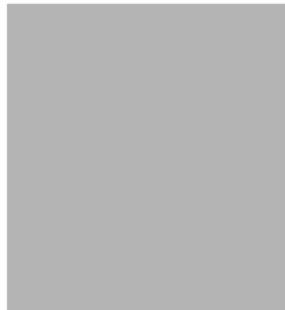
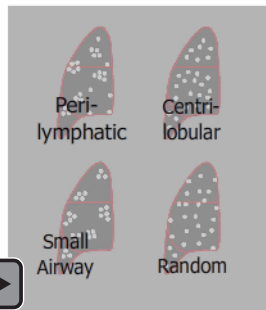
For those of you who cannot get the Flash movie to run, 2 representative images are below.



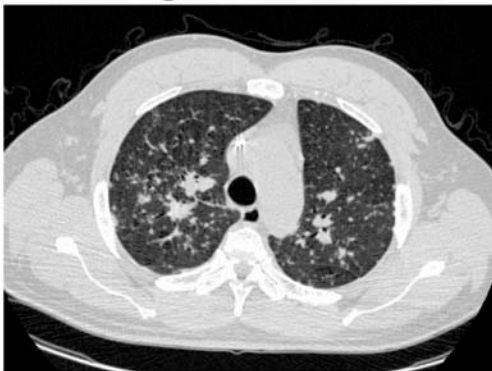
Helpful Hints/Answers



Click on the correct
nodule category



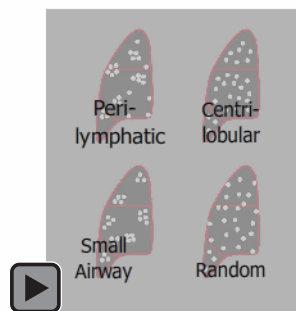
For those of you who cannot get the
Flash movie to run, 2 representative
images are below.



Helpful Hints/Answers

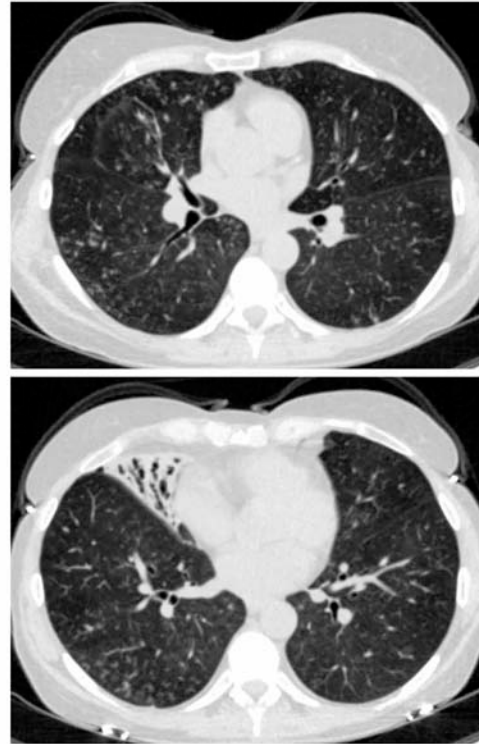


Click on the correct
nodule category





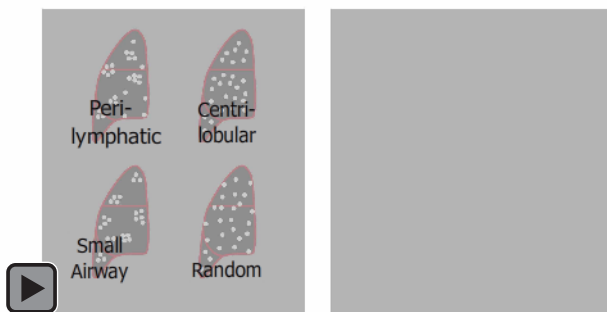
For those of you who cannot get the Flash movie to run, 2 representative images are below.



Helpful Hints/Answers



Click on the correct
nodule category



References, Acknowledgements etc.

Obviously I drew heavily on James Gruden's nodule algorithm paper published in *Radiology* in 1999 and Rick Webb's 2006 *Radiology* article on the secondary pulmonary lobule. I have simplified their approach, and I hope I haven't compromised it significantly. Both of these articles are landmarks and are required reading for all radiologists. I also used multiple pathologic images from Martha Warnock's homepage, which is well worth a visit if you want to understand the pathology behind our images. Chun-Shan Yam's 2007 *AJR* article enabled me to make the scrollable case that ends this comic. Look for more issues, coming soon!