Update on 2015 WHO Classification of Lung Adenocarcinoma
Our speaker for this program is Dr. Anja Roden, an associate Professor of Laboratory Medicine and Pathology and a consultant in Anatomic Pathology at Mayo Clinic in Rochester, Minnesota.

Our speaker for this program is Dr. Anja Roden, an associate professor of Laboratory Medicine and Pathology at Mayo Clinic as well as consultant in the Anatomic Pathology Laboratory and co-director of the Immunostains Laboratory at Mayo Clinic in Rochester, MN. Dr. Roden discusses the 2015 changes in the WHO classification of lung adenocarcinoma and small biopsies of lung cancer. Dr. Roden, thank you for presenting with us today.

Thank you very much for the nice introduction.
Disclosures

• None

I have nothing to disclose.
As you view this presentation, consider the following important points regarding testing: How is the testing going to be used in your practice? When should the tests be used? How will results impact patient management?
We will start with a case presentation. I will then give you updates to the 2015 WHO classification of lung adenocarcinoma. We will discuss the handling and reporting of small biopsies, and we will finish with take-home points.
The case is that of a 73-year-old woman who was found to have ground-glass opacity in the right upper lobe lung about 10 years ago. This ground-glass opacity was slowly increasing in size and density. A wedge resection was performed.

Case

• 73-year-old woman
• Ground-glass opacity in right upper lobe lung
• Slow and subtle increase in size and density since 10 years
• Wedge resection
Here, you can appreciate the CT imaging studies, which show the ground-glass opacity in the right upper lobe lung.
On wedge resection, we appreciate 1 area that looks abnormal because of interstitial thickening and a more blue color. This area has a diameter of 2.3 cm.
On higher power, on the lower left-hand side, we appreciate unremarkable lung parenchyma and then an abrupt onset of atypical cells lining thickened interstitium.
There is a cellular crowding as evidenced by cellular overlap
and also focally pseudostratification. The interstitium is slightly thickened due to some fibrosis and chronic inflammatory cells.
What is the Diagnosis?

- Adenocarcinoma in situ

and also focally pseudostratification. The interstitium is slightly thickened due to some fibrosis and chronic inflammatory cells.
What diagnosis would you consider? This would be an adenocarcinoma in situ.
The 2015 WHO classification added adenocarcinoma in situ, minimally invasive adenocarcinoma, and invasive mucinous adenocarcinoma. Terms such as bronchoalveolar carcinoma, mixed subtype adenocarcinoma, and clear and signet ring cell carcinoma were discontinued.
Atypical Adenomatous Hyperplasia (AAH)

- Small (≤ 0.5 cm, maybe up to 1.2 cm), proliferation of mild/moderate atypical type II pneumocytes and/or Clara cells
- Line interalveolar septa
- Usually gaps between atypical cells
- Usually not seen by imaging □ not biopsied
- Cured if resected
- Morphologic continuum AAH □ AIS

Furthermore, lung adenocarcinomas were classified as preinvasive lesions, including atypical adenomatous hyperplasia and adenocarcinoma in situ, minimally invasive adenocarcinoma, and invasive adenocarcinoma.
Let’s start with atypical adenomatous hyperplasia. These are small proliferations of mildly to moderately atypical type II pneumocytes and/or Clara cells that line usually slightly thickened interalveolar septa. There are, in general, gaps between atypical cells, and these areas are not seen by imaging. Therefore they are, in general, not biopsied. If you see a biopsy that shows atypical cells lining thickened interstitium, this will not be atypical adenomatous hyperplasia, since these lesions are not biopsied. They are cured if resected, and as you can imagine, there is a morphologic continuum between the atypical adenomatous hyperplasia (AAH) and adenocarcinoma in situ.
Here is an example where you can appreciate slightly thickened interstitium
Adenocarcinoma in Situ (AIS)\(^1\)

- Usually incidental finding on CT
- CT: nonsolid – circumscribed ground-glass nodule
- Slow growing
- Grossly poorly defined nodule

that is lined by atypical cells. These atypical cells respect each other, and there are some gaps in between. This is an example of AAH.
Adenocarcinoma in situ is usually an incidental finding on CT imaging studies. It shows as a nonsolid, circumscribed, ground-glass nodule that is slowly growing. On gross examination of a specimen, adenocarcinoma in situ is usually a poorly defined nodule. Adenocarcinoma in situ and minimally invasive adenocarcinoma share some defining features, including its size. It should not be larger than 3 cm. There also should be no pleural or vascular invasion, and there should be no spread through the airspace. Also, they are usually nonmucinous; however, rarely they can be of mucinous type. Adenocarcinoma in situ should not have any stromal invasion and should have a purely lepidic growth pattern.
Here’s an example where we see the atypical lining cells of slightly interstitial thickening, and these cells have overlap and also pseudostratification.
If you diagnose an adenocarcinoma in situ on a resection specimen, the entire tumor should be sampled because the invasion can be very focal. There are prospective randomized studies going on to identify whether sublobar resection such as wedge resection or segmental resection might be sufficient for treatment. The current TNM or AJCC staging system does not address adenocarcinoma in situ. For the upcoming TNM classification, it is proposed to use Tis and in parentheses (adenocarcinoma); but currently, we have to stage these tumors by size.
Minimally invasive adenocarcinoma is also, in general, incidentally found on CT imaging where it is usually identified as a peripheral lesion. On CT scan, it presents as a part-solid nodule with a solid component, usually ≤0.5 cm in largest diameter.
Again, minimally invasive adenocarcinomas are defined by size, which is less than 3 cm, and there should be no pleural or vascular invasion and no tumor spread through airspaces. There is a predominant lepidic growth pattern; and in contrast to adenocarcinoma in situ, we do find focal stromal invasion, which should not exceed 0.5 cm.
Here is an example of such a tumor. We appreciate a 0.8-cm nodule.
On low power, there is 1 area where glands appear to be rather complex.
On high power, these small glands are in a desmoplastic stromal reaction. And this area is less than 5 mm; in fact, it is only 3 mm and, therefore, it is defined as a minimally invasive adenocarcinoma. In these tumors, the tumor cells focally infiltrate myofibroblastic stroma or desmoplastic stroma, and the invasive component is comprised of any histologic type other than lepidic growth pattern.
Also, there should not be any tumor necrosis.
Minimally invasive adenocarcinoma is also not addressed by the current TNM or AJCC staging. However, for the upcoming AJCC staging, it is proposed to be used pTmi. Currently, we have to go by tumor size.
Invasive Adenocarcinoma

- Growth patterns
  - Acinar
  - Papillary
  - Micropapillary
  - Lepidic
  - Solid
- Patterns not in WHO (yet): Cribriform
- Subtyping in 5% increments

Invasive adenocarcinomas can be comprised of different growth patterns, including acinar, papillary, micropapillary, lepidic, and solid. Cribriform pattern is also a growth pattern of invasive adenocarcinomas that has been recently described and, therefore, is not in the current WHO classification. These growth patterns should be subtyped in 5% increments.
Here is a typical invasive adenocarcinoma.
An acinar growth pattern, as you all know, is classified by these acinar glands that are lined by the neoplastic cells. Usually, there is a quite complex architecture to these neoplastic glands.
Micropapillary patterns are comprised of micropapillae that are in these neoplastic glands.
Sometimes, they can be dislodged into the lumen of the glands. However, they do not have fibrovascular growth.
Papillary patterns are comprised of papillae, which have fibrovascular cores that are lined by neoplastic cells. This pattern sometimes can be difficult to be distinguished from an adenocarcinoma in situ. Therefore, we always have to watch out for these papillae.
On high power, we recognize the fibrovascular core that is lined by the neoplastic cells.
A solid pattern of adenocarcinoma can be difficult to distinguish from a solid pattern of a squamous cell carcinoma. Therefore, if in doubt, immunostains should be performed.
In this case, the neoplastic cells were positive for TTF-1, indicating a solid pattern of lung adenocarcinoma.
Here is an example of lepidic growth pattern. We appreciate the preserved lung architecture that is lined by the neoplastic cells.
On higher power, again, the thickened interstitium lined by neoplastic cells is indicative of lepidic growth pattern.
In another area, there was clearly invasion, and this area was larger than 5 mm.
The cribriform pattern reminds us of the cribriform type of ductal carcinoma in situ in the breast.
We appreciate the tumor cells in the cookie-cutter areas of glands.
**Prognostic Parameters of Lung Adenocarcinomas**

- Stage
- Tumor grade
- Invasion
- Subtype
- Presence of micropapillary, solid, cribriform component (even if minor)
- Lymphovascular invasion
- Tumor spread through airspaces (STAS)?

Prognostic parameters of lung adenocarcinomas include stage, tumor grade, invasion, but also subtype and, specifically, the presence of micropapillary, solid and cribriform components, even if these are minor components, because they have a worse outcome. Lymphovascular invasion and likely tumor spread through airspaces are also prognostic parameters.
Here's a study that shows the prognostic value of invasion and subtype of adenocarcinoma. As you can see, adenocarcinoma in situ and minimally invasive adenocarcinoma have the best outcome, while cases of micropapillary and solid subtype have the worst outcome.
About 70% of patients with lung cancer present at an advanced stage. Therefore, small biopsies might be the only tissue we have available for further studies. Therefore, tissue preservation is key. We often have to perform immunohistochemistry for subtyping of non-small cell lung carcinoma, which is important for treatment. However, we should limit the immunohistochemical panel to only a few stains, if we can. A panel might be comprised of TTF-1 and p40 or CK5/6. If your immunostains lab is capable of doing dual stains, some appropriate combinations might be p40 and Napsin or CK5/6 and TTF-1. Also, if you have more than 1 tissue core available, you can divide these cores into multiple blocks. We do have to confirm that tumor tissue is actually present in each block by an H&E; but for ordering immunostains, we might only use 1 of the blocks. Also, if we order immunostains, we always get unstained slides in case additional stains or molecular studies need to be performed.
There are certain diagnoses that we cannot make on small biopsies, and these include adenocarcinoma in situ, minimally invasive adenocarcinoma, large cell carcinoma, and adenosquamous cell carcinoma. Because of their definitions, they require sampling of the entire tumor. If a biopsy only shows lepidic pattern, this might be signed out as a well-differentiated adenocarcinoma with lepidic growth and then “see comment,” and a comment might state that the distinction between invasive adenocarcinoma and adenocarcinoma in situ should be reserved for the resection specimen.
What is the reason? The reason is that we do not know exactly where the biopsy was taken from. If you look at the left large arrow, this biopsy is likely taken only from the ground-glass opacity, which is likely only the in situ component. However, if the biopsy was taken from the site of the small right arrow, this is the solid component, which likely will show the invasive carcinoma.
Small Biopsies

- If stains needed to differentiate adenocarcinoma from squamous cell carcinoma, "Non-small cell carcinoma, favor ___".

According to the current WHO, small biopsies, if you need stains to differentiate adenocarcinoma from squamous cell carcinoma, these biopsies should be signed out as non-small cell carcinoma, favor either adenocarcinoma or squamous cell carcinoma, dependent on what your stains showed.
Here is an example of a needle core biopsy that shows clusters of tumor cells in it but a desmoplastic stromal reaction.
On high power, these cells are large and do have some cytoplasm, indicating non-small cell carcinoma. However, there is no keratinization or gland formation that could help us to define the subtype of this tumor. Therefore, immunostains were performed,
which show that the neoplastic cells are positive for CK5/6 and negative for TTF-1. Therefore, this case was signed out as non-small cell carcinoma, favor squamous cell carcinoma.
In summary, subtyping of adenocarcinoma is important for prognostic purposes. Adenocarcinoma in situ and minimally invasive adenocarcinomas have an excellent prognosis, while micropapillary, solid, cribriform components have a worse prognosis. Tissue preservation on small biopsies is crucial.
References


- Borczuk AC: Assessment of invasion in lung adenocarcinoma classification, including adenocarcinoma in situ and minimally invasive adenocarcinoma. Mod Pathol 2012;25:S1-S10
