Pulmonary Journal Club; July 2018

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Reviews, Editorials, Letters, etc

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Articles for Discussion

Brcic L, Vlacic G, Quehenberger F, Kern I. ***Reproducibility of Malignant Pleural Mesothelioma Histopathologic Subtyping.*** **Arch Pathol Lab Med. 2018;142:747–752; doi: 10.5858.**

Introduction

Histologic subtype is still the most important predictor of survival in malignant mesothelioma, with epithelioid tumors having superior prognosis to sarcomatoid and biphasic examples. Thus, histologic subtyping has started to be incorporated into treatment decisions (they reference the NCNN clinical practice guidelines for meso). Epithelioid mesothelioma is also quite morphologically heterogeneous, and some proposed morphologic subtypes of epithelioid mesothelioma (pleomorphic) may be associated with worse prognosis.

Methods

200 consecutive cases of mesothelioma were chosen, including 68.5% thoracoscopic biopsies, 19.5% pleurectomy and 12% core needle biopsies. The diagnosis in all cases were confirmed by IHC (at least 2 positive meso markers, and least 2 negative ADCA markers). One representative slide was selected and digitally scanned, and then reviewed by 3 pathologists (2 pulmonary specialists with 20 and 5 years experience, 1 "young pathologist" with 1 year experience). Each case was classified as epithelioid, biphasic or sarcomatoid per 2015 WHO criteria. Epithelioid mesos were further sub classified as acinar, adenomatoid (microglandular), micropapillary, solid, tubulopapillary, trabecular, pleomorphic, clear cell, deciduoid, signet ring cell, or small cell variant. After initial review, a consensus meeting was organized, with discussion of areas of difficulty and review of cases with disagreement. Cases where then re-reviewed after 2 months.

Results

●The kappa value of initial review was 0.36; it was best for sarcomatoid mesothelioma (kappa 0.6), followed by epithelioid mesothelioma (kappa 0.5), with the worst kappa values observed for determination of biphasic mesothelioma (kappa 0.28).

● Among the subtypes of epithelioid mesothelioma, the best agreement was observed for tubulopapillary (kappa 0.54), pleomorphic (kappa 0.49), and trabecular patterns (kappa 0.42).

● In their consensus review, the most important recurrent problem seemed to be deciding if a spindle cell component was reactive versus part of the tumor using H&E alone. There were also issues regarding subclassification of epithelioid mesothelioma, with a tendency to overestimate percentages of "striking" morphologic pattern such as micropapillary or papillary growth; lack of adherence to strict criteria for deciduoid morphology; lack of agreement as to what constitutes a trabecular pattern; and lack of agreement when determining acinar and adenomatoid patterns.

●After consensus review, kappa improved to 0.63 (substantial agreement), with the most improvement in the biphasic group. Histologic subtypes of epithelioid mesothelioma showed improved kappa scores for solid, micropapillary, and deciduoid types, but not for acinar pattern.

● When considering needle biopsies, there was less improvement in the kappa values between initial review and consensus review compared larger surgical biopsies.

Conclusions

●Determination of the presence of a sarcomatoid component vs. biphasic meso seems to be the most difficult aspect of determination of mesothelioma subtype using pure morphological analysis, and they admit they may have overcalled biphasic tumors in their series because they decided in consensus to include any atypical spindle cell proliferation as sarcomatoid component. Keratin stain and BAP1 stain could help in some cases.

●Agreement seems more difficult on small biopsy compared to surgical biopsies.

●Consensus/clear criteria can lead to learning and better agreement.

●The subtyping of epithelioid mesothelioma growth patterns, as would be expected and is true in pulmonary adenocarcinoma, is subject to interobserver variability.

Butnor KJ, Pavlisko EN, Sporn TA, Roggli VL. *Malignant Mesothelioma in Individuals With Nonmesothelial Neoplasms.* Arch Pathol Lab Med. 2018;142:730–734; doi: 10.5858.

Introduction

The cancer predisposition syndrome characterized by autosomal dominant mutations in BAP-1 leads to increased frequency of malignant mesothelioma, along with other tumors including melanoma in atypical Spitz nevi, lung cancer, renal cell carcinoma, and meningioma. Carriers also seem to have an increased risk for undifferentiated sarcoma and breast cancer. The goal of this study was to perform a comprehensive assessment of secondary malignancies and patients with malignant mesothelioma unselected for BAP-1 germ line mutations.

Methods

A database of 3900 mesothelioma patients with searched for patients with preceding or synchronous non mesothelial malignancies. The frequency of these malignancies was then compared with the expected frequency in the SEER database or other published references, with some limitation for specific subtypes of tumors that are grouped together (all sarcomas, all renal cell carcinomas, etc).

Results

● 6% of the cohort (241 patients) had at least 1 non-mesothelial neoplasm, most of which were diagnosed years or decades prior to the diagnosis of mesothelioma:

-81% were men, average age was 71 years.

-61% had a history of smoking.

-84% had pleural meso, 16% had peritoneal meso

-10.8% had more than one type of non-mesothelial neoplasm

●93% of patients with non-mesothelial neoplasms had documented history of asbestos exposure. They had data regarding presence of pleural plaques, concurrent asbestosis, asbestos body count, or asbestos lung fiber count data on 121 patients, of which 75% had mesothelioma conclusively attributable to asbestos exposure.
●57 patients had tumors described to be part of the BAP1 tumor predisposition syndrome, 31% of which were conclusively attributable to asbestos exposure.
●33 patients (14%) had a history of irradiation for the non-mesothlelial neoplasm, most commonly Hodgkin lymphoma, but also for breast cancer or Wilms tumor (I don't see separate data on asbestos exposure in this group).

Conclusions

●There seems to be an increased risk of certain neoplasms in mesothelioma patients, which likely have different associations (this is based on deduction since BAP1 mutation status is not available on this cohort):

-Lung cancer=asbestos exposure, BAP1 tumor predisposition syndrome

-Hodgkin lymphoma=prior irradiation

-Clear cell renal cell carcinoma, ocular melanoma, meningioma= BAP1 tumor predisposition syndrome

-Breast carcinoma and pleomorphic sarcoma=? Probably BAP1 tumor predisposition syndrome

●It seems, as in everything, genetic and environmental factors may synergize to produce neoplasia in susceptible individuals, and it can be postulated that patients with BAP1 tumor predisposition syndrome are more susceptible to the carcinogenic effects of asbestos .

Lee W, Diao L, Wang J, Zhang J, Roarty EB, Varghese S, Chow C, Fujimoto J, Behrens C, Cascone T, Peng W, Kalhor N, Moran CA, Weissferdt A, Johnson FM, William Jr.WN, Swisher SG, Lee JJ, Hong WK, Heymach JV, Wistuba II, Futreal PA, Zhang J. ***Multiregion gene expression profiling reveals heterogeneity in molecular subtypes and immunotherapy response signatures in lung cancer.*** **Modern Pathology (2018) 31:947–955. DOI 10.1038**

Introduction

While we know quite a lot about genetic heterogeneity between individual tumors of the same type (intertumoral heterogeneity; lung cancer is a great example), we are learning more about the genetic heterogeneity within individual tumors (intratumoral heterogeneity). It is important in the emergence of resistance/treatment failure. Interestingly, it also seems that some types of cancer (renal cell, for example) show much greater amounts of intratumoral heterogeneity compared to others (prelim data indicates it is relatively low for lung cancer compared to renal cell). But we still have a lot to learn.

Methods

35 tumor samples were collected from 10 patients with NSCLC (6 adeno, 2 squam, 1 large cell, 1 pleomorphic), targeting different regions of the tumor. Gene expression profiling (Affymetrix chip) was performed, and transcription clusters were annotated. Molecular subtyping was performed: Lung adenocarcinomas can be classified into terminal respiratory unit, proximal proliferative, and proximal inflammatory subtypes, while lung squamous cell carcinomas can be classified into classical, basal, secretory, and primitive subtypes. Epithelial-mesenchymal transition scores were generated. They also looked at prognostic gene signatures and calculated scores designed to predict innate anti-PD1 resistance. They looked at tumor microenvironment scores (looking at mesenchymal and inflammatory cells), and correlated with the various factors analyzed as listed above.

Results

●There was a high degree of intertumoral heterogeneity in NSCLC, such that samples from different areas of the same tumor generally clustered together, and a lesser degree of intratumoral heterogeneity. However, some tumors did show a high degree of intratumoral heterogeneity, and they actually clustered with tumors from other patients when unsupervised hierarchical clustering was performed (occurred in 2 tumor samples).

●Different areas of the same tumor could show different molecular subtypes.

●Poorly differentiated tumors including large-cell carcinoma, pleomorphic carcinoma, and squamous cell carcinomas showed higher (i.e., more mesenchymal) scores than adenocarcinomas (p value: 0.003). Most tumors demonstrated similar epithelial–mesenchymal transition scores in different tumor areas; however, a few tumors showed considerable intratumor heterogeneity. There was also spatially heterogeneous expression of epithelial–mesenchymal transition-related genes.

●mRNA microarray-based prognostic signatures varied between different tumor regions within the same tumors. When every tumor region was classified into high- and low-risk prognostic subgroups, discordant prognostication was observed when considered different areas of the same tumor in 1 of 10

patients using the 6-gene signature and 7 of the 10 patients using the 15-gene signature. Therefore, small biopsies samples could easily miscalculate risk due to sampling. Also hard to know which area provides the "correct" risk assessment…

●In general, innate anti-PD-1 resistance score was similar within the same tumor. However, spatial heterogeneity was observed in multiple tumors (4 in 10 patients harbored at least one discordant tumor region).

●Not surprisingly, different tumor regions have different proportions of cancer cells, infiltrating stromal and immune cells. Overall gene expression variation was only weakly correlated with stromal score, immune score, or tumor purity. However, epithelial–mesenchymal transition score and innate anti-PD-1 resistance score did correlate stromal/immune score. The proximal inflammatory subtype of adenocarcinoma was positively correlated with stromal and immune scores.

Conclusions

●There was clear evidence of gene expression intra-tumor heterogeneity in all tumors studied. Interestingly, global intra-tumor heterogeneity did not always correlate with intra-tumor heterogeneity observed in the signatures with selected genes.

●They argue that PD-L1 protein expression is not a good biomarker, based on evidence of robust treatment responses in some patients with low PD-L1 protein expression. Genetic testing might be an attractive alternative. However, in this study, 40% of patients harbored substantially different innate anti-PD-1 resistance scores in different tumor regions within the same tumors that may lead to discordant prediction of response to anti-PD-1 checkpoint inhibition. It seems immune cells and other stromal cells may also contribute to impact on the anti-PD-1 response signature, making it even more complicated to predict.

●Gene expression intra-tumor heterogeneity observed in this study may be attributed to the different tumor microenvironments as well as spatial difference in gene expression profiles of lung cancer cells. Gene expression intra-tumor heterogeneity should be taken into consideration when evaluating gene expression-based biomarkers.

Enomoto Y, Matsushima S, Meguro S, Kawasaki H, Kosugi I, Fujisawa T, Enomoto N, Inui N, Nakamura Y, Suda T, Iwashita T. *Podoplanin-positive myofibroblasts: a pathological hallmark of pleuroparenchymal fibroelastosis*. Histopathology 2018, 72:1209–1215. DOI: 10.1111.

Introduction

PPFE and UIP can be difficult to distinguish from one another in some cases (UIP with more elastosis than average, or PPFE with less prominent elastosis). The elastic fiber-rich fibrosis of PPFE and pulmonary apical cap are also very similar, when one does not consider the gross and or radiographic features distinguishing the two.

Methods

Their study group was small, consisting of age and sex matched group of 4 PPFE patients, 10 UIP patients, and 3 apical cap patients; diagnoses were made using consensus multidisciplinary review. They used normal lung as control tissue. They performed IHC for podoplanin/D2-40, SMA, CK 5/6, WT1, calretinin, Cam 5.2, and desmin. They also looked at SMA and podoplanin using immunofluorescence.

Results

●Only 2 of the patients were women, and most were in their 60s/70s.

●The subpleural fibrosis was generally negative for CK-5/6, CAM5.2, WT-1 and calretinin in UIP, PPFE and apical cap.

●The subpleural fibrosis of PPFE and apical cap showed spindled cells that coexpressed podoplanin and SMA, which were not present in UIP mature fibrosis or fibroblast foci

●By IF, there were a few SMA-positive myofibroblasts in UIP which were podoplanin negative, while the SMA-positive myofibroblasts of PPFE coexpressed podoplanin

Conclusions

●The expression of podoplanin in PPFE/apical cap myofibroblasts may indicate that they are derived from “mesothelial-mesenchymal transition”. However, this cannot be confirmed with certainty, since other meso markers are not expression, and podoplanin is not a specific marker (expressed in lymphatic endothelial cells, pneumocytes, etc).

●Not sure that this will be diagnostically helpful in most cases (especially if you have access to clinical/radiographic information), but I guess could be helpful in specific cases. Might be more helpful to further apply in basic science research of pathogenesis. Limited by low case number.

Articles for Notation

Neoplastic

The IASLC Lung Cancer Staging Project: A Renewed Call to Participation
Giroux et al, JTO

The Staging and Prognostic Factors Committee of the IASLC is now issuing a call for participation in the next phase of the lung cancer staging project, which is designed to inform the ninth edition of the TNM classification. This covers data elements they are collecting and areas of focus (T and M parameters with less definitive data supporting their use, etc).

Pulmonary Non–Small Cell Carcinoma With Morphologic Features of Adenocarcinoma or "Non–Small Cell Carcinoma Favor Adenocarcinoma" in Cytologic Specimens Share Similar Clinical and Molecular Genetic Characteristics.
Hutchings et al, AJCP

When comparing FNA/cytology cases with a definitive diagnosis of adenocarcinoma (n=115), non-small cell carcinoma favor adenocarcinoma (n=43), and non-small cell carcinoma-NOS (n=18), there were no differences in the presence or absence of tested mutations, clinical stage, or survival. Stains were used to aid in classification in about 60% of cases. So I guess if you think it is probably adenocarcinoma you are likely right, and many non-small cells NOS cases are probably poorly differentiated adenocarcinoma (this group trended toward worse survival, which makes sense given the high grade/poorly differentiated nature).

Computer-aided Volumetry of Part-Solid Lung Cancers by Using CT: Solid Component Size Predicts Prognosis
Kamiya et al, Radiology

They looked at 96 sub solid nodules, and had 2 radiologists measure 2 dimensional solid component measurements, as well as three-dimensional solid component measurements using multiplanar reconstructed images, as well as the volume of the solid component. They were able to determine a cutoff for the 3D volume of the solid component using receiver operator curves, and a solid component was significantly associated with disease-free survival.

A molecular pathological study of 4 cases of ciliated muconodular papillary tumors of the lung
Kataoka et al, Pathology International

One case had *BRAF* V600E, 2 had *EGFR* mutations (exon 19 deletion in one and point mutation in one), and one had *KRAS* G12V. There particular mutations are not common in any kind of lung cancer. Similar to prior knowledge, expanded it a bit.

Extranodal extension of nodal metastases is a poor prognostic moderator in non-small cell lung cancer: a meta-analysis
Luchini et al, Virchows Archives.

Meta-analysis of 13 studies, including 1709 patients looking at patients with documented entranodal extension vs. those without in NSCLC. ENE was associated with a significantly increased risk of mortality of all causes (RR = 1.39, HR = 1.30) and of disease recurrence (RR = 1.32, HR = 1.93). They conclude that in NSCLC, requirements for assessment of ENE should be included in gross sampling and ENE status should be included in the pathology report. They propose inclusion of ENE status in oncology staging systems to allow further assessment of its role as prognostic parameter. This seems like it could be a difficult thing to assess when many of our thoracic nodes are received fragmented-can be a rather subjective thing to determine, even on the most intact nodes.

Capture of Tobacco Use Among Population-Based Registries: Findings From 10 National Program of Cancer Registries States
Siegel et al, Cancer

Their study included 1,646,505 cancer cases, and about half had known cigarette use data. 18% were current smokers, 31% were former smokers, and 51% were never smokers. The percent known for cigarette use and the prevalence of ever smoking cigarettes were highest for laryngeal cancer and tracheal, lung, and bronchus cancer.

Added prognostic value of CT characteristics and IASLC/ATS/ERS histologic subtype in surgically resected lung adenocarcinomas
Suh et al, Lung Cancer

This is a retrospectively study of 988 patients who underwent curative resection for invasive lung adenocarcinoma , looking at CT characteristics (pure GGO, predominantly GG PSN, predominantly solid PSN, solid nodule); histologic subtype (lepidic, acinar, papillary, micropapillary, solid, invasive mucinous adenocarcinoma); and presence of *EGFR* mutations. Recurrence occurred in about 25% of patients. In univariate hazard model, female sex, tumor size and stage, CT characteristics, and predominant histologic subtype were associated with tumor recurrence. When adjusted for size and stage, CT characteristics and histologic subtype were independent tumor recurrence predictors ($P < 0.05$), but they conclude CT characteristics and histologic subtype have relatively limited added prognostic values over tumor size and stage in surgically resected lung adenocarcinomas.

Hyalinizing clear cell carcinoma of the bronchial glands: Presentation of three cases and pathological comparisons with salivary gland counterparts and bronchial mucoepidermoid carcinomas
Takamatsu et al, Modern Pathology

Three cases of molecularly-proven hyalinizing clear cell carcinoma of the bronchi. Tumors occurred in patients during the fourth to sixth decades, there was no link to smoking, and there was a predilection for the right lung. All this is in line with previous literature on the topic. Tumors had clear to eosinophilic cytoplasm with hyalinizing stroma, identical to those arising in salivary gland (see photos from figure below). Tumor cells were positive for CK7, CK5/6, p40, p63, and ATF1, while they were negative for TTF1, Napsin A, HMB45, and SOX10. FISH revealed EWSR1-ATF1 fusion, and RT-PCR confirmed specificity of the chimeric gene for hyalinizing clear cell carcinoma. Rare but distinctive tumor to keep in mind when dealing with an unusual bronchial tumor, can be confirmed by molecular which can help distinguishing from entities in the differential diagnosis (especially mucoep).

Validation of the 8th TNM classification for small-cell lung cancer in a retrospective material from Sweden
Tendler et al, Lung Cancer

Study of 706 small cell lung cancer patients, with median survival of 7.7 months. The 8th TNM classification system seemed to provide more accurate prognostic information in patients with SCLC when compared to the previous versions. However, there were few cases with Stages I and II, limiting evaluation of low stage disease. Single metastatic lesions (M1b) had a better prognosis when compared to M1c disease, and they speculate that this could be due to more aggressive treatment in these patients- seems like it also could just be natural history of disease.

Mediastinal Synovial Sarcoma Clinicopathologic Analysis of 21 Cases With Molecular Confirmation
Terra et al, AJSP

We present 21 cases of molecularly confirmed mediastinal synovial sarcoma, which is a rare primary site. Patients included 15 men, and mean age was young at 38 years (range 21 to 75 years). Only 1 patient was older than 50. Tumors were large (average tumor size was 13.5 cm, range: 6.4 to 23 cm). Only one tumor was biphasic, and the rest were monophasic. Over half (11) were poorly differentiated (52%). Of 16 with follow-up, 14 recurred or progressed, and 6 had mets. Overall prognosis was poor, 70% died from disease at 5 to 45 months.

Tumor spread through air spaces is a useful predictor of recurrence and prognosis in stage I lung squamous cell carcinoma, but not in stage II and III
Yanagawa et al, Lung Cancer.

Retrospective review of 220 cases of squamous carcinoma. STAS was identified in 19% of cases. Patients with STAS had a significantly worse 5-year recurrence-free survival and 5-year overall survival in stage I, but not in stage II and III. Multivariate analysis showed STAS was an independent predictor of recurrence and an independent prognostic factor in stage I, but not in stage II and III.

The more the micropapillary pattern in stage I lung adenocarcinoma, the worse the prognosis—a retrospective study on digitalized slides
Zombori et al, Virchows Archives

243 stage I lung adenocarcinomas were reviewed, and % of each growth pattern observed was recorded by annotating growth pattern areas on digitized slides. Lepidic pattern was more common in tumors without recurrence, while solid and micropapillary were more common in tumors with recurrence. Above 25%, a growing proportion of solid or micropapillary pattern is not associated with worsening prognosis. Micropapillary pattern also seemed to confer some increased risk when it was observed as a secondary pattern. Pretty much supports what we already know about pattern-based risk.

Non-neoplastic

Diagnosis of Primary Ciliary Dyskinesia-An Official American Thoracic Society Clinical Practice Guideline
Shapiro et al, AJRCCM
Clinical algorithm for testing, I thought the flow chart below was useful for those of us that do EM for PCD evaluation.

Reviews, Editorials, Letters, etc

Malignant Mesothelioma and Its Non-Asbestos Causes

Attanoos et al, Archives.

Interesting review article. Currently thought that 70-90% of pleural mesothelioma sarcomas by asbestos exposure, with significantly lower numbers for peritoneal mesothelioma. In the U.S., is actually uncommon for asbestos exposure to be the cause of mesothelioma in women, while in Europe this is more common in certain areas. Other risk factors for mesothelioma include exposure to other minerals (erionite, fluoroedenite, and probably balangeroite), therapeutic radiation (up to 30 times relative risk), BAP-1 germline mutations (probably about 1% of cases). Discussion regarding less definitive data surrounding pleural inflammation, carbon nanotubes, and SV40 is also included. In the end they claim most non-asbestos related mesos are sporadic.

Comparison of thyroid transcription factor-1 expression by 2 monoclonal antibodies in schwannomas: the chosen clone matters
Creytens et al, Letter in Human Path

I have to say I did not know much about the high degree of TTF-1 expression in schwannomas, but this letter demonstrates that expression is much higher and stronger with SP T24 clone compared to the 8G7G3/1 clone, as might be expected.

Treatment of Gastroesophageal Reflux in Patients with Idiopathic Pulmonary Fibrosis: A Systematic Review and Meta-Analysis
Fidler et al, Chest.

This meta-analysis concludes "Low-quality evidence suggests pharmacologic treatment of GER is associated with a reduction in IPF-related mortality but not overall mortality. Randomized trials of antacid therapy in IPF are needed."

Dedifferentiated Solitary Fibrous Tumor-A Concise Review.
Olson et al, Archives.

Summary of this uncommon phenomenon in SFT, with associated worse prognosis.

The Pathogenesis of Pulmonary Sarcoidosis and Implications for Treatment
Patterson et al, Chest

Pulmonary involvement in sarcoid is associated with worse prognosis compared to thoracic lymph node involvement alone. Yet we still do not understand causes and optimal treatment. This review covers some series regarding the pathogen assess of pulmonary sarcoidosis and potential therapeutic implications.

The effect of anti-acid therapy on survival in idiopathic pulmonary fibrosis: a methodological review of observational studies
Tran et al, European Respiratory Journal

Review of 10 prior studies. They report that the apparent beneficial effects of anti-acid therapy on mortality in patients with IPF result from only observational studies affected by immortal time bias. Thus, they argue that the effectiveness of anti-acid therapy in IPF remains uncertain and needs to be reassessed with more accurate observational study methods and
randomized trials.

Case Reports

Infantile Pulmonary Teratoid Tumor

deKock et al, NEJM

I read this one with great interest, given my interest in *SMARCA4*-deficient tumors. This baby had a germ line *SMARCA4* mutation, and developed a primitive pulmonary tumor with an additional somatic *SMARCA4* mutation. Interestingly, the tumor did not look rhabdoid as most other *SMARA4* deficient tumors look, instead it had a more primitive, almost neural appearance. This certainly indicates that *SMARCA4* deficient tumors can arise in the lung outside the setting of smoking/dedifferentiated lung cancer, and thickens the plot surrounding so called "SMARCA4 deficient thoracic sarcoma". How this might be related remains to be seen.

Endobronchial epithelial-myoepithelial carcinoma of the lung.
Kim et al, Thorax.

Lymphangioleiomyomatosis-Images in Clinical Medicine.

Scalfani et al, NEJM

Malignant mesothelioma with squamous differentiation.

Tanaka, Histopathology

Yikes. Something to keep in mind on small biopsies I guess.