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Tazawa et al. Inhaled granulocyte/macrophage-colony stimulating factor as therapy for pulmonary alveolar proteinosis. AJRCCM 2010; 181: 1345-1354
I. Articles for Discussion


Clinicopathologic features:
- Rare although not known real incidence because underdiagnosed
- Currently 22 proven cases in literature
  - Mean age 25 yo range 3-78, so not limited to the young only
  - M:F 0.69 so predominance of women
  - Occur along the midline including nasopharynx and sinus, orbit, epiglottis, larynx, mediastinum, bladder, iliac bone
  - Great mimicker and wrongly diagnosed as SNUC, ES/PNET, PD or undiff carcinoma/squamous cell ca, germ cell tumor
  - Mean survival 9.5 mos
  - No good treatment, does not respond to usual chemo-radiation
- Histologically, looks like a poorly diff carcinoma. One characteristic although not always present is focal abrupt squamous differentiation. Otherwise no specific characteristic. IHC usually all negative for everything. Need to think about the dx if in the midline.
- Probably derived from primitive neural crest cells

Molecularly defined:
- Rearrangement of the NUT gene (15q14), 2/3 with BRD4 (19p13.1) thus known as the t15,19 carcinoma, 1/3 with BRD3 or other uncharacterized genes.
- NUT is only active in the adult testis and ciliary ganglion. Restricted to mammals and function not known
- BRD4 is thought to provide a cellular memory to ensure re-initiation of transcription after mitosis of G1 genes. BRD3 function less known but highly homologous to BRD4
- The fusion of NUT and BRD results in blockage of differentiation thus the morphology of the tumor
- Potentially a therapeutic target?

How and when to diagnose
- Since morphology not specific, the dx is made based on demonstrating the NUT rearrangement.
  - IHC exist for NUT but 60% sensitive although 95% specific
  - RT-PCR captures only the BRD4 and BRD3 partners
  - FISH the best test
- Who to test:
  - Any poorly diff malignancy occurring along the midline neg for any lineage specific marker
  - The main reason to make this dx is basically because of such a poor prognosis and no good treatment


Background:
- Mycobacterial infections are a major global health system
Occasionally, the only material available for diagnosis is FFPE tissue and ZN staining and very time consuming to screen (no mention of data stating how good we are at finding organisms using this method)

**Purpose:**
- To use computer assisted screening and develop an algorithm to detect AAFB

**Methods:**
- 2 cases with sparse AAFB, one section from each, scanned at 60x dry, at a single focus plane with also small series of images at different degree of defocus was used to assess for blur in the algorithm
- Algorithm (very complex too much for me to understand very well):
  - Color theory described and details of developing an algorithm based on color and contrast
  - Algorithm also includes shape to distinguish the mycobacteria from larger blobs or any staining artifact, give it a probability score of having a AAFB
  - Each image is given a probability number so images are ranked

**Results:**
- For each data set, top 5 images were reviewed and confirmed to indeed have the bacilli present.
  - The bacilli were often in the periphery of the images and initially missed by the human eye
  - The algorithm was flexible enough to allow for color variation and size variation (like bacilli cut on end)
  - And detects only if on focus
- Since it is not a dichotomous algorithm ie AAFB present or not and thus not a dx test per se, can not actually calculate sensitivity and specificity
- Continuous algorithm meant to assist in detecting, identifying potential AAFB that then requires human confirmation

**Take Home Message:**
- As the author mentions in his discussion, needs to validate this and compare human eye to the computer eye.
- Sounds promising. We use a similar concept but instead of computer we have our cases screened by cytotechs.

3- Yousem et al. The pulmonary histopathologic manifestations of the anti-Jo-1 tRNA synthetase syndrome. Mod Pathol 2010; 23:874-880

**Background:**
- Subgroup of idiopathic inflammatory myopathies characterized by anti-Jo-1 antibodies associated with higher incidence of ILD and poorer prognosis.
- Goal of the study was to review the histologic findings in this specific subgroup

**Methods:**
- 1982-2009, U of Pitt myositis database
  - Confirmed anti-Jo-1 antibodies
  - ILD before bx with PFTs showing restriction and abnormal x-ray or CT showing interstitial infiltrates
  - Surgical bx (13), explanted lung (3) or autopsy (4) if died due to ILD
  - ATS classification
Results:
- 20 patients
  - 4:1 W:M, mean age 47, 35% smoker
  - 70% arthritis and 40% Raynaud
- Pulm symptoms
  - Group A = 6, rapidly progressive hypoxemia and bilateral alveolar infiltrates
  - Group B = 9, slowly progressive SOB over 6 months
  - Group C = 5, SOB for months to years with abrupt worsening
- HRCT in 15
  - 8 with UIP
  - 2 with NSIP
  - 4 with ARDS
  - 1 with OP
- Histopathology and prognosis
  - 7 with UIP – 1 DOD 1 mo, 5 AWED 38-146 mos, 1 Lost to FU- All in group B
  - 5 with DAD – 2 DOD at 1 month and 3 AWED 12-59 mos- All in group A
  - 2 with NSIP – AWED 14-19 mos – All in group B
  - 5 with acute on chronic, the chronic being UIP in 3 (all DOD 1-29 mos) and fibrosing NSIP in 2 ( 1 DOD 1 mo, 1 AWED 84 mos) and the acute DAD – All in group C
  - 1 with OP – AWED at 31 mos – In Group A
  - No cases of infection, vasculitis/DAH, granulomatous disease or malignancy

Take Home Message:
- Compared to literature of DM/Myositis, anti-Jo-1 syndrome has more UIP than NSIP, commonly presents with acute decompensation with or without underlying chronic disease
- Don’t mention how many myositis cases they started with, how many of the Jo-1 had clinical evidence of ILD and although give survival we don’t have data regarding the overall group


Background: Vascular Ehlers-Danlos syndrome formerly known as ED type IV, autosomal dominant, due to mutation in COL 3A1 gene, which encodes type III procollagen and mutation results in structural, synthesis and secretion abnormalities and tissue fragility.

Previous article by Corrin et al describing fibrous pseudotumors and cysts

Goal: Document the pleuropulmonary features of these patients

Methods:
- 9 patients with dx confirmed by skin fibroblast culture or molecular analysis, only 1 dx prior to histopathology examination:
  - 6 had SLB for abnormal “shadows” or pneumothorax
  - 2 had lobectomy for hemothorax or hemoptyisis
  - 1 had autopsy
- H&E, VVG and iron stain, mean 5 slides.
Assessed for lesions related to fragility of pleuropulmonary tissues:
- Pleural fibrosis or adhesions
- Pulm hematomas
- Acute pulm hemorrhage or hemosiderosis
- Fibrous nodule with or without ossification
- Vascular disruption
- OP
- Emphysematous changes including bullea, paracicatricial emphysema
- Cysts and blebs

Assessed for secondary iatrogenic injury such as lacerations confirmed by the surgeon

Results:
- 6M, 3F, mean 23 yo, total 11 specimens assessed
  - Lesions related to fragility of pleuropulmonary tissues:
    - Acute pulm hemorrhage in 9
    - Hemosiderosis intraluminal in 9 and interstitial in 7
    - Emphysematous changes including bullea, paracicatricial emphysema in 8
    - Fibrous nodule in 8 with ossification in 6
    - Pleural fibrosis or adhesions in 7
    - Pulm hematomas in 7
    - Vascular disruption in 5, usually one vessel, focal per slide
    - OP in 4
    - Cysts and blebs in 2
    - Hemothorax with healed lacerations in 2
  - Secondary iatrogenic injury such as lacerations confirmed by the surgeon involving pleura in 7 and lung in 8

Take Home Message:
- Lesions described are consistent with the injuries expected in vED and mutation in procollagen 3 seen in wall of vessels and alveolar walls (nice Figure 4 to illustrate this).

5- Shimada et al. Extratumoral vascular invasion is a significant prognostic indicator and a predicting factor of distant metastasis in non-small cell lung cancer. JTO 2010; 5: 970-975

Background:
- Vascular invasion reported as a predictor of poor outcome. Not clear if intratumoral vs extratumoral vascular invasion differs

Purpose: Assess if location (intra vs extra tumoral) of vascular invasion predicts outcome and patterns of recurrence in NSCLC

Methods:
- 1000 consecutive NSCLC resections median FU of 4.1yrs
- v0= no vasc invasion, v1= intratumoral vasc invasion, v2= extratumoral vasc invasion as assessed in elastic stain
Statistics using age, gender, pathologic staging, tumor diameter, nodal involvement, vascular invasion, v2 vs v0-1, pleural invasion, histologic subtype, grade, extent of resection

Results:
- 5-yr OS 69.7% and RFS 59.6%
- v1= 428 and v2 = 32
  - 5yr RFS v0= 76.1%, v1=41.9%, v2= 21.8% (p= or<0.001)
  - 5yr OS v0= 82.5%, v1= 55.9%, v2= 44.0% p<0.001 and =0.01
- In univariate, age, gender, p-staging, tumor diameter, LN mets, pleural invasion, vasc invasion, histologic subtype and grade all predictors of survival
- v2 seen more in higher stage, LN mets, subtypes other than adeno, and poorly diff tumors
- In a multivariate, just saying vasc invasion or not was not prognostic, but v2 vs v0-1 was
  - Other predictors in multivariate were age, tumor size, LN mets, pleural invasion
- v2 also correlated better with risk of developing distant mets vs local recurrence than v1 (p=0.026), v2 correlated with met in contralateral lung and v1 with brain met

Take home message:
- When we state vascular invasion in our reports, should focus on only extratumoral or mention both? What do folks do?

6- Sholl et al. EGFR mutation is a better predictor of response to tyrosine kinase inhibitors in non-small cell lung carcinoma than FISH, CISH and immunohistochemistry. Am J Clin Pathol 2010; 133: 922-934

Background:
- 20% of adenocarcinomas harbors an EGFR mutation and respond to EGFR inhibitor therapy
- 10% of unselected patients respond to EGFR inhibitor therapy, 75% of which will have the activating mutation and 25% not, so undetermined mechanism
  - So FISH, CISH assessing amplification predictor?
  - IHC for EGFR predictor?

Purpose: To determine which approach best predicts response to TKI in advanced NSCLC

Methods:
- Tumors with mutation and matched wild-type was selected retrospectively for a balanced study population (but don’t say what matched for and what balanced is) part of clinical trial
- 40 cases, 21 open lung, 2 needle bx, 17 metastatic sites
- Used RECIST criteria for tumor response
- PCR, FISH, CISH, IHC for EGFR

Results:
- Clinical info in Table 1, no stats for this data but more older, men and smoker in the wild type group. All adenocarcinomas
- Response: 13 partial, 11 stable, 15 progressive, 1 stopped because of side effects
- No FISH or CISH in 3 and no IHC in 8. Results summarized in Table 2 but I don’t understand how to read it?
  - No correlation between mutation and amplification or IHC
Good correlation between amplification and IHC

Based on statistics (Table 3), only mutation predicted for response

However, 8 cases 1 responder and 7 stable did not have mutation, 2 were amplified and 6 IHC +

Mutation most sensitive and specific in predicting response (Table 4). IHC as good specificity as mutation

Looking at mutated cases vs non-mutated, cases that also had amplification were on responders vs the cases not amplified. Numbers too small for statistics.

Mutation the only statistically significant predictor of time to progression 13.2mos vs 3.7mos, not stat significant for OS

Take Home Message:

Nothing much new, enforces mutation as best test

Mechanism underlying responder without mutation still not clear and still not clear how to identify these patients

Possibly cases with mutation that don’t respond initially are the ones without amplification?

II. Articles for Notation

Original Articles

1- Bong Yoo et al. Epidermal growth factor receptor mutation and p53 overexpression during the multistage progression of small adenocarcinoma of the lung. JTO 2010; 5: 964-969

In this study, the authors looked at EGFR mutation and p53 overexpression in AAH, BAC and small adenocarcinomas as a progression model. They assessed 110 lesions, 20 AAH, 43 BAC all non-mucinous and 47 adenocarcinomas, largest 20mm.

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<td>AAH</td>
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<td>BAC</td>
<td>15 (34.9%)</td>
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<tr>
<td>Adeno</td>
<td>23 (48.9%)</td>
<td>15 (37.5%)</td>
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</table>

Nothing much new. Not applicable to us as we don’t have that high % of mutated adeno. We always knew there were genetic abnormalities in common between the 3, in different proportions.

2- Tanvetyanon et al. Relationship between tumor size and survival among patients with resection of multiple synchronous lung cancers. JTO 2010; 5: 1018-1024

Using only the Martini criteria to assess for multiple synchronous primaries, the authors looked at tumor size as outcome measure in 116 patients (4.5% of all resected tumors between 1997-2008). But following pathology assessment, 12 would not meet the Martini criteria and not clear if part of the 116 analyzed or not?

Tumor size either measured as the largest or the sum of tumor sizes did affect survival OS and PFS by Kaplan Meier curves and univariate. Interestingly, their univariate analysis did not show many of the usual factors that affect survival (in fact only had FEV1, tumor size and positive margins were significant, staging was not significant which is odd?) and thus potentially affected
their multivariate. They did 2 models (largest tumor and sum of sizes) for multivariate and only FEV1 and tumor size remained significant. Not sure what this means when even staging to start with had no significance prognostically? Problem is how the tumors were staged? If same histology tumors were staged like tumor mets and if different histology staged separately and higher stage use for the stats so this could potentially explain this. Basically don’t think this is scientifically very sound.

3- Luina et al. Mediastinal germ cell tumors with an angiosarcomatous component: a report of 12 cases. Hum Pathol 2010; 41: 832-837
Mediastinal GCT more commonly than GCT from other sites have a somatic component, usually sarcoma, more commonly rhabdomyosarcoma and rarely angiosarcoma. The study focuses on 12 GCT with angiosarcoma:
   9 of which had angiosarcoma in primary and 3 in the met not the 1ary
   Needle bx usually did not show the angiosarcoma, in one case it showed the angiosarcoma only
   The component of angiosarcoma varied between 5 to 95% and they state even a little angiosarcoma predicts for poor outcome, but the case with 5% was still AWNED
   Using Suster and Moran’s staging system, they were mostly Stage III (of III) and a few stage II. They state that stage predicts outcome not angiosarcoma component with (of 3) stage
   Overall, nothing unexpected and new and not very well written and some of their conclusions not supported by their data
   *** One information interesting to me was one paper showed i12 in the somatic component not only the CGT component which I would not have expected
4- Moreira et al. Progenitor stem cell marker expression by pulmonary carcinomas. Mod Pathol 2010; 23: 889-895
Goal was to look at progenitor cell markers and how they are expressed in the different subtypes of lung cancer by IHC. The table summarizes the data.
Try to claim that the more poorly diff, more likely you are to have markers of stem cell. Not sure if one can say that uniformly as SQCC, even poorly diff except for Musashi-2 didn’t really show so many stem cell markers except focally and all had a marker of committed lineage ie p63.
PS: another example of how p63 not so specific for SQCC.

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PS: another example of how p63 not so specific for SQCC.
5- Scheble et al. ERG rearrangement in small cell prostatic and lung cancer.
Histopathology 2010; 56: 937-943

ERG rearrangements have been shown in a subset of prostatic adenocarcinoma, usually aggressive ones. Small cell carcinoma do occur in the prostate and there are no good markers to distinguish these from SCLC (which is not entirely true as occasional PSA and PaCP still + in prostatic small cell ca). The goal was to look at ERG in prostatic and lung small cell and compare to IHC markers.

Table 1 in their study summarizes their data. ERG was the most sensitive and specific.

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<td>Small cell lung cancer</td>
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<td>&gt;50%</td>
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Due to the small amount of material available in some cases we could not perform each study on each sample. P-values indicate the significance level of each marker to differentiate between the two tumour types.

TTF1, thyroid transcription factor 1; GOLPH2, Golgi phosphoprotein 2; PSA, prostate-specific antigen; AR, androgen receptor; PSMA, prostate-specific membrane antigen; CANT1, calcium activated nucleotidase 1; EMA, epithelial membrane
Radiology only paper but was interesting as the results were different to those doing a similar comparison with histology being the enrollment criteria.
In this study looked at Definite UIP on HRCT in RA patients vs IPF. Of 82 patients with RA that had ILD, 20 (42%) had UIP pattern on HRCT, compared to IPF, these patients were more women slightly younger (by 3 yrs) at time of dx. RA-UIP, vs RA-nonUIP vs IPF all had similar function abnormalities.
Median survival of RA-nonUIP was 6.6 yrs, RA-UIP 3.2 yrs and IPF 2.6 yrs.
So in this study if HRCT is used, UIP pattern in RA as bad as IPF.

More data to support first line therapy of EGFR inhibitors in metastatic adenocarcinoma with EGFR mutation compared to standard chemotherapy. In a clinical trial, first 200 patients interim analysis : Longer median PFS – 10.8 mos vs 5.4mos, higher response rate – 73.7% vs 30.7%, no difference in median OS, lesser toxicity.
Of note, they had some supposedly SQCC and adenosquamous with EGFR mutation.

8- Tazawa et al. Inhaled granulocyte/macrophage-colony stimulating factor as therapy for pulmonary alveolar proteinosis. AJRCCM 2010; 181: 1345-1354
Phase II trial looking at inhaled GM-CSF in the treatment of alveolar proteinosis. Dx made on basis of lung bx or cytology and elevated serum GM-CSF. First a 12 week observation for any spontaneous improvement of PFT. Then entered on sequential treatment high-dose, followed by low-dose, followed by observation. 35 patients completed treatment, 24 improved. There was no serious adverse event. Remained stable on FU.
Seems like safe and potentially effective treatment.