# PULMONARY PATHOLOGY JOURNAL CLUB

(June 2015 articles)

July 27, 2015

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## Articles for Notation

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I. Articles for Discussion


Purpose: To determine the prognostic impact of tumor spread through air spaces (STAS) in pulmonary adenocarcinoma.

Methods: A series of 569 surgically resected pulmonary adenocarcinomas was retrospectively evaluated for the presence of STAS, which the authors defined as “detachment of small solid cell nests (at least 5 tumor cells) < 3 alveolae away from the main tumor mass as limited STAS and tumor cell nests > 3 alveolae away from the main tumor mass as extensive STAS.” They further required that nests be arranged in loose small groups with no direct connection to the main tumor mass. The findings were correlated with other clinicopathologic parameters.

Results: Just over one-half (50.6%) of cases of pulmonary adenocarcinoma exhibited STAS, which was limited in 21.6% and extensive in 29% of cases. There was a significant correlation between the presence and type of STAS and specific growth patterns. Only 4.6% of lepidic-predominant tumors exhibited STAS, but 91.3% of micropapillary tumors had STAS that was extensive in the majority of cases. STAS was significantly more prevalent in high-stage, node-positive tumors with distant metastasis and tumors with BRAF mutations. STAS was associated with reduced overall and disease-free survival independent of growth pattern, but not independent of stage. EGFR mutations were significantly less prevalent in tumor with STAS than those without STAS.

The authors noted that the distinction between micropapillae and STAS is not necessarily clear-cut and that the size of tumor nests, number of nests, and distance from the main tumor that qualify as STAS must be further refined.
FIGURE 1. Histomorphologic examples of STAS. Hematoxylin and eosin–stained slides of representative ADC invasion fronts without (A and B), with limited (C and D; arrows), and with extensive STAS (E and F; arrows).
Discussion: With some similarities to the Kadota et al. study on STAS presented in the June journal club, the present study found STAS is highly associated with a micropapillary growth pattern.

Take Home Message: While the authors suggest STAS should be routinely evaluated and reported in lung cancer resection specimens, a compelling argument can be made for not doing so, as this morphologic parameter has not been shown to impact prognosis independently of stage.

Yeh et al. Using frozen section to identify histological patterns in stage I lung adenocarcinoma of ≤3 cm: accuracy and interobserver agreement. Histopathology 2015;66:922–938

Purpose: Histologic subtyping is becoming recognized as an important predictor of clinical behavior. Having this information available intraoperatively on wedge resections could be helpful in determining whether to proceed to completion lobectomy. This study evaluated the accuracy, limitations, and interobserver agreement of frozen sections for predicting histologic subtype of pulmonary adenocarcinoma.
Methods: The predominant histologic subtype and presence or absence of lepidic, acinar, papillary, micropapillary, and solid patterns were assessed in 1 frozen section slide and permanent slides from 361 stage I resected pulmonary adenocarcinomas ≤ 3 cm in size. Interobserver agreement was determined by having 3 pathologists review 50 of the cases. Additionally, 5 pathologists retrospectively assessed frozen section slides from 35 of the cases with a lepidic-predominant pattern for degree of invasion.

Results: There was only moderate agreement (κ = 0.565) between the predominant histologic subtype on frozen section and final diagnosis. The predominant subtype diagnosed on frozen section did not correlate with outcome. Although there was high specificity for micropapillary (94%) and solid (96%) patterns on frozen section, the sensitivity was low (37% and 69%, respectively), but their identification on frozen section correlated well with recurrence. Sampling error rather than interpretative error was the major cause of discrepancy between frozen section and final diagnosis. Good interobserver agreement was seen, except for acinar-predominant tumors (κ > 0.6). Frozen section overestimated the degree of invasion, with 52% of cases diagnosed on frozen section as lepidic-predominant invasive adenocarcinoma reclassified as MIA at final diagnosis. Over 75% of the frozen section slides in this study were rated as “average or poor” quality by the authors.

| Table 4. Reason for discrepancy between frozen section diagnoses and permanent section diagnoses |
|---------------------------------|-----------------|-----------------|-----------------------------|-----------------|
| Parameters                      | No. (%) of each type of error |                |                            | Total           |
| Predominant histological subtype| Sampling error   | Interpretation error | Sampling + interpretation error |                |
| Overall                         | 58 (69.0)        | 17 (20.2)        | 9 (10.7)                    | 84 (100)        |
| Lepidic                         | 8 (57.1)         | 5 (35.7)         | 1 (7.1)                     | 14 (100)        |
| Acinar                          | 19 (79.2)        | 4 (16.7)         | 1 (4.2)                     | 24 (100)        |
| Papillary                       | 18 (78.3)        | 4 (17.4)         | 1 (4.3)                     | 23 (100)        |
| Micropapillary                  | 5 (41.7)         | 3 (25.0)         | 4 (33.3)                    | 12 (100)        |
| Solid                           | 8 (72.7)         | 1 (9.1)          | 2 (18.2)                    | 11 (100)        |
| Presence/absence of histological pattern |                |                |                            | Total           |
| Lepidic                         | 32 (64.0)        | 18 (36.0)        | 0 (0)                       | 50 (100)        |
| Acinar                          | 20 (74.1)        | 7 (25.9)         | 0 (0)                       | 27 (100)        |
| Papillary                       | 44 (67.7)        | 21 (32.3)        | 0 (0)                       | 65 (100)        |
| Micropapillary                  | 47 (62.7)        | 28 (37.3)        | 0 (0)                       | 75 (100)        |
| Solid                           | 26 (72.2)        | 10 (27.8)        | 0 (0)                       | 36 (100)        |

| Table 5. Frozen section diagnoses by five pathologists in 35 cases of AIS/MIA/LPA |
|---------------------------------|-----------------|-----------------|-----------------------------|-----------------|
| Permanent section diagnosis     | Frozen section interpretation by five pathologists (%) |                |                            | Total           |
| AIS (n = 2)                     | AIS  100 | MIA  0 | LPA  0 | Total  100               |
| MIA (n = 15)                    | AIS  6.7 | MIA  41.3 | LPA  52.0 | Total  100               |
| LPA (n = 18)                    | AIS  3.3 | MIA  17.7 | LPA  79.0 | Total  100               |

AIS, adenocarcinoma *in situ*; LPA, lepidic-predominant adenocarcinoma; MIA, minimally invasive adenocarcinoma.
Discussion: Due to sampling issues, frozen section does not reliably predict the predominant histologic subtype of pulmonary adenocarcinomas, although there is a high specificity for
aggressive patterns, such as micropapillary and solid patterns. The authors suggest that the inflation method of handling tissue intraoperative may improve diagnostic accuracy.

Take Home Message: While accurate for detecting invasion, frozen section is not appropriate for determining degree of invasion (i.e. MIA versus lepidic-predominant adenocarcinoma), nor can it adequately predict predominant histologic subtype.


Purpose: To detail the clinicopathologic features of ciliated muconodular papillary tumor (CMPT), a rare tumor of the lung that has histologic features that are similar, if not identical to lesions that have been previously reported as “solitary peripheral ciliated glandular papillomas,” “mucinous adenomatous hyperplasia,” and “peripheral pulmonary papillary/glandular neoplasm with ciliated cells.”

Methods: Ten resected cases were retrospectively identified from 2006-2014.

Results: The cases occurred in 7 males and 3 females, 5 of whom had smoking history. The median age was 62 years. Nine were discovered incidentally and cough was the presenting feature in one case. The mean diameter was 1.0 cm and all lesions were peripheral and non-endobronchial solid or semi-solid with irregular contours on imaging. A central cavity was present in 3 cases. Two cases initially followed radiographically showed slow growth over 2-3 years. One case was treated by lobectomy and the remaining cases were managed by sublobar resection. No recurrences were detected in a mean of 43 months of follow-up (range 2-88 months). The tumors were characterized by a glandular and/or papillary architecture with vaguely organized tripartite elements including bland ciliated columnar cells admixed with mucous cells and basal cells, typically enveloped by copious alveolar mucin. In none of the tumors were there mucous or ciliated cell proliferations devoid of basal cells. Mitoses and necrosis were absent. Discontinuous alveolar septal growth and micropapillary tufts were occasionally seen. TTF-1 and p40 positivity was present in the ciliated and basal cells, respectively.
FIGURE 2. At low power, CMPTs show overall growth patterns ranging from predominantly glandular (A, case 3) to papillary (B, case 1).
Discussion: CMPT is distinguished from peribronchiolar metaplasia by its greater degree of architectural distortion and appearing as a solitary distinct nodule on CT. The rarity of mucous cells in peribronchiolar metaplasia is also a helpful distinction. Histologically, CMPT resembles mixed papilloma, but by definition, the latter is endobronchial.
Take Home Message: These rare tumors behave in a benign fashion and should be distinguished from adenocarcinoma. Treatment with conservative resection appears adequate.


Purpose: To compare the clincoradiopathologic features of non-infectious alveolar-filled patterns that resemble pneumonia, namely, COP, AFOP, and granulomatous organizing pneumonia (GOP).

Methods: Surgical lung biopsies and the clinicoradiographic data from 61 consecutive patients referred with OP to a major cancer center were reviewed. GOP cases had pathologic features of both granulomas and OP. Cases were excluded if a specific cause was known (e.g. evidence of collagen vascular disease) or could not be ruled out clinically (e.g. sarcoid).

Results: Study patients included 35 males and 26 females with a mean age of 61.5 years (range 8-85 years). About one-half of patients had respiratory symptoms such as cough, dyspnea, and/or wheezing. Seventy percent had 1 or more prior cancers, 44% had received chemotherapy, and 30% had received radiation. There were 36 cases of COP, 10 of AFOP, and 15 of GOP. Focal fibrin in less than 10% of the lesional area was present in 22% of patients classified as having COP. All AFOP cases showed prominent fibrin in > 50% of the lesional area. In cases of GOP, the granulomas were non-necrotizing, in the interstitium in of areas of OP, small, non-confluent, and lacked a peribronchiolar distribution. Focal fibrin did not comprise more than 10% of the lesional area in the cases of GOP. Mortality and symptoms did not differ between the patterns, but fever was more common among patients with AFOP, while patients with GOP were less likely to have received chemotherapy and more likely to present with masses/nodules.

Discussion: The authors argue that AFOP and GOP are not only histologically, but also clinicoradiologically distinct from OP. In contrast to the AFOP study by Beasley et al., mortality was similar among patients with AFOP, COP, and GOP in the present study, potentially because many patients were asymptomatic at diagnosis.

Take Home Message: AFOP may not be associated with as poor of an outcome as initially reported, but the conclusions drawn from this study are based on a very different patient population than in the initial study. Determining the etiology and extent to which GOP differs
clinically from other forms of organizing pneumonia will require evaluation of a larger number of patients.

**Ventana Medical Systems Media Release - Ventana receives FDA approval for the first fully automated IHC companion diagnostic to identify lung cancer patients eligible for XALKORI® (crizotinib)**

**Discussion:** There is big news on the molecular testing of lung cancer front! VENTANA ALK (D5F3) IHC has been approved by the FDA as a companion diagnostic to aid in the identification of patients for Pfizer’s FDA approved targeted therapy, XALKORI® (crizotinib). Compared to the wait associated with traditional fluorescent in situ hybridization (FISH) ALK testing methods, Ventana touts that “with an approved ALK IHC test, physicians and their ALK positive patients now have the option to learn their ALK status and start an ALK-targeted therapy within days.” The media release implies that a positive result by IHC does not need confirmation by another methodology before initiation of crizotinib therapy. Looking at Ventana’s multi-page interpretive guide (see PDF in Dropbox), assessing staining does not appear to be as simple as just “positive” or “negative.” It will be interesting to see how rapidly laboratories adopt this test.

**II. Articles for Notation**

**Original Articles**


**Purpose:** To elucidate the role of programmed cell death-ligand (PD-L1) and driver mutations in lymphoepithelioma-like carcinoma (LELC) of the lung.

**Methods:** Immunoexpression of PD-L1 was analyzed in 66 pulmonary LELCs and driver gene analysis was performed.

**Results:** PD-L1 overexpression (≥ 5% of tumor cells) was observed in 75.8% of cases, while EGFR mutations were seen in 12.1%. Genetic alterations in KRAS, BRAF, ALK, or ROS1 were not detected. PD-L1 staining was not associated with driver mutations, nor did it correlate patient outcome, although it does not appear that any patients in this study were treated with monoclonal antibodies targeting the PD-1/PD-L1 axis.

**Take Home Message:** The high frequency of PD-L1 expression in LELC suggested a potential role for targeted anti-PD-1/PD-L1 therapies in these tumors.


**Purpose:** To compare androgen receptor (AR) and GATA3 to traditional markers for differentiating metastatic breast carcinoma from primary lung carcinoma and mesothelioma.
Methods: Immunoexpression of AR, GATA3 (HG3-31 clone), ER, PR, mammaglobin, and GCDFP-15 was analyzed in 33 breast carcinomas metastatic to the lung, 566 primary lung tumors (including adenocarcinomas, squamous cell carcinomas, and a spectrum of neuroendocrine tumors), and 42 malignant mesotheliomas.

Results: Immunostaining for AR, GATA3, ER, PR, mammaglobin, and GCDFP-15 was observed in 81.8%, 72.7%, 78.8%, 39.4%, 36.4%, and 27.3% of metastatic breast carcinomas, respectively. Among primary lung tumors and malignant mesothelioma, 3% stained for AR, none stained for mammaglobin, and less than 1% stained for GATA3, ER, PR, and GCDFP-15. No primary lung adenocarcinomas stained positively for either AR or GATA3. One mesothelioma was GATA3-positive and no mesotheliomas were positive for AR. For AR-positive primary lung tumors, high expression was restricted to neuroendocrine neoplasms. Specificity of AR and GATA3 for metastatic breast carcinoma was 97% and 99.5%, respectively, as compared to 99.3% for ER, 99.7% for PR, 100% for mammaglobin, and 99.7% for GCDFP-15.

Discussion: The authors recommend AR or GATA3 over ER to distinguish metastatic breast carcinoma from primary lung carcinoma, as 1.8% of lung adenocarcinomas are positive for ER. However, the authors do not provide histologic subtyping information for the breast carcinomas evaluated in their study and therefore it is not possible to discern whether substantive differences in immunoexpression exist between ductal and lobular carcinomas. Additionally, the pooling of data from a spectrum of lung tumors and mesothelioma impacts the clarity of the results and the relatively low sensitivity of mammaglobin in this study is not addressed.

Take Home Message: AR and GATA3 are sensitive markers for metastatic breast carcinoma, but it should be noted that specificity for GATA3 is clone dependent. In prior studies using a different clone (L50-823), as many as 58% of malignant mesothelioma, 8.5% of lung adenocarcinomas, and 12% of lung squamous cell carcinomas stained for GATA3. In addition, it is important to be mindful that AR also stains salivary gland tumors and GATA3 expression is seen in urothelial carcinoma.


Purpose: To explore the prognostic impact of angiolymphatic invasion (ALI) and tumor necrosis (TN) in resectable locally advanced non-small cell lung carcinoma (LA-NSCLC) treated with prior induction therapies.

Methods: The impact of ALI and TN on survival was analyzed retrospectively on 47 resected LA-NSCLC treated with prior platin-based chemotherapy or chemoradiotherapy.

Results: The incidence of ALI and TN was 23.4% and 29.8% of cases, respectively. ALI and TN were associated with decreased disease-free and overall survival.
**Discussion**: While the authors argue that ALI and TN should be included in the pathology report, they did not quantify the extent of the either parameter in their cases.

**Take Home Message**: ALI and TN appear to be adverse prognostic factors in neoadjuvantly-treated locally resectable NSCLC, but the amount of either necessary to effect a poorer prognosis needs to be more clearly defined.


**Purpose**: To describe the clinical, radiographic, and pathologic characteristics of primary pulmonary NUT midline carcinoma (NMC), a poorly differentiated t(15;19) rearrangement-driven tumor.

**Methods**: The consult files from the past 8 years at 3 major teaching institutions were retrospectively examined for cases diagnosed as primary pulmonary NMC. Additionally, in-house biopsies for lung cancer between 2002 and 2010 were retrospectively screened for NUT IHC to better understand the frequency of this tumor in a more routine setting.

**Results**: Eight consult cases and 1 additional case was identified by retrospective IHC screening of 166 (0.6%) consecutive in-house lung carcinoma biopsies. Median age at presentation was 30 years (range 21-68). Six of 8 patients had negligible smoking history and all presented with cough. Imaging on all cases showed a large central primary mass with a predilection for the lower lobes, mediastinal nodal and pleural involvement, and sparing of the contralateral lung. Brain metastases were not observed, but lytic bone metastases were common. Median overall survival was 2.2 months. Histologically, all cases showed nests and sheets of primitive-appearing round to epithelioid cells that were at least focally keratin, p63 or p40, and NUT protein-positive by immunohistochemistry. TTF-1 expression was weak to absent. Focal expression of neuroendocrine markers was observed in 2 cases. Eight of the cases had confirmatory FISH-proven NUT rearrangements.

**Take Home Message**: While rare, reported cases of primary pulmonary NMC had have strikingly similar clinicopathologic and radiographic features, which include cough at presentation, young (although not always) age, a light or absent smoking history, short survival, a large unilateral central lower lobe mass with confluent nodal involvement, lytic bone metastases, and primitive-appearing tumor cells. Extensive p63 or p40 staining with focal TTF-1 immunoreactivity in the same tumor cells should prompt consideration of NMC.


**Purpose**: To identify potential therapeutic markers for adenosquamous carcinoma.

**Methods**: Resected adenosquamous carcinomas from 65 patients were evaluated by tissue microarrays composed of representative squamous and adenocarcinoma components of each tumor for a variety of biomarkers.
Results: Mutations in EGFR and KRAS were detected in both tumor components in 21.5% and 10.9% of cases, respectively. One ALK-rearranged case and 1 ROS1-rearranged case (1.5%) were identified, which likewise exhibited the respective genetic aberration in both tumor components.

Take Home Message: The presence of targetable gene alterations in both components of adenosquamous carcinoma supports these tumors being subjected to driver gene analysis.


Purpose: To assess the overall accuracy of EGFR mutation detection in plasma or serum.

Methods: A meta-analysis of 26 studies was performed.

Results: The pooled specificity (0.97) for EGFR detection in plasma or serum was exceptionally high with a relatively moderate sensitivity (0.65).

Take Home Message: Plasma or serum are reliable surrogate samples for EGFR mutation detection when tissue samples are unavailable.


Purpose: To investigate the clinicopathologic characteristic and molecular features of colloid lung carcinoma.

Methods: The files of a major cancer center were retrospectively reviewed for cases of colloid lung carcinoma that had adequate accompanying clinicoradiographic information.

Results: Thirteen cases were identified, including 9 females and 4 males with an age range of 48-86 years, 9 of which had a positive smoking history. Pathologic stage was as follows: T1N0M0 (7 cases), T2N0M0 (3 cases), T2N1M0 (2 cases), T2N0M1 (1 case). In 9 cases, 100% of the tumor was mucinous. The remainder had a non-colloid adenocarcinoma component admixed with mucin pools comprising 50-90% of the tumor. Ten patients were alive at 35-128 months of follow-up with 3 developing recurrent disease. One patient died of disease and 2 died of unrelated causes. None of the patients with pure colloid carcinomas died during follow-up. Two of the 3 patients who recurred had a significant non-colloid component. All tumors expressed CK7, CK20, and CDX2, while TTF-1, surfactant A, and napsin A expression was absent to focal. KRAS was mutated in 2 cases. No ALK rearrangements or EGFR mutations were detected.

Take Home Message: Adenocarcinomas with abundant extracellular mucin have a relatively favorable prognosis. The presence of even a minor a non-colloid component is associated with a poorer prognosis, irrespective of stage.

**Purpose:** To evaluate the expression and prognostic significance of HoxB9, a transcription factor shown to be involved in cancer progression, in lung adenocarcinoma.

**Methods:** The relationship between immunoexpression of HoxB9 and survival was analyzed.

**Results:** HoxB9 was expressed in 21.3% of lung adenocarcinomas. Staining intensity correlated with high tumor stage and shorter survival.

**Take Home Message:** HoxB9 is a potential prognostic marker in lung adenocarcinoma in that high expression is associated with adverse prognosis.


**Purpose:** To evaluate the value of ALK testing of malignant pleural effusion samples.

**Methods:** ALK status was determined by IHC with the D5F3 clone, RT-PCR, and FISH on 52 tumor tissue samples and 41 matched malignant pleural effusion cell block samples.

**Results:** Eight (15.4%) tumor tissue samples were ALK-positive by FISH. Five of the matched effusion samples were positive for ALK by FISH, 7 by RT-PCR, and 8 by IHC, for a concordance rate of 78.9% by FISH, 98.1% by RT-PCR, and 100% by IHC. IHC sensitivity in the effusion samples was superior to FISH and RT-PCR.

**Take Home Message:** The diagnostic performance of ALK testing of malignant pleural effusions is comparable to tumor tissue samples, with IHC being the most suitable methodology. Effusion cell blocks appear to be a valid alternative for ALK testing in cases where tissue is not available.

**Review Articles**


A very comprehensive review of predictive and prognostic biologic parameters in malignant pleural mesothelioma, including a discussion of angiogenic molecules, cell cycle inhibitors, and DNA repair proteins.


In this article and the accompanying editorial (Mathai et al. Taking the “I” out of IPF. Eur Respir J 2015;45:1539–1541), the authors provide evidence that IPF is a misnomer. Although the pathogenesis is still not known, a number of inherited factors have been identified that are linked
to the development of pulmonary fibrosis. Rare variants in surfactant protein genes (SFTPA2 and SFTPC) are associated with familial pulmonary fibrosis, while variants of telomerase-related genes (hTERT and TERC) and MUC5B have been linked to both familial and sporadic IPF. Individuals with the MUC5B variant have reduced disease progression and improved survival, which is an important consideration when designing clinical therapeutic trials.


This review discusses the functions of a variety of transcription factors as they relate to the histogenesis of pulmonary neuroendocrine tumors and includes a nice schematic thereof.

**Figure 3** A schematic representation depicting the possible histogenesis of lung neuroendocrine tumors based on data obtained from recent studies. TC, typical carcinoid; AC, atypical carcinoid; SmCC, small cell carcinoma; LCNEC, large cell neuroendocrine carcinoma; TRU, terminal respiratory unit; DNTF, developmental neural transcription factor; MEN1, multiple endocrine neoplasia type 1; TKI, tyrosine kinase inhibitor; M01, well differentiated columnar cell; N01, neuroendocrine cell; N02, non-ciliated cuboidal cell; B01, bronchial basal cell; R01, respiratory cell; P01, type I pulmonary cell; P02, type II pulmonary cell.

**Case Reports**


**Case Summary:** A 67-year-old male with a pleural effusion and multiple small intrapulmonary nodules on imaging had no macroscopic pleural lesions at thoracoscopy, but lung biopsies disclosed microscopic nodules of epithelioid tumor cells along bronchovascular bundles and adjacent alveolar spaces and septa with marked lymphovascular invasion. Immunohistochemically, the tumor cells were positive for calretinin, D2-40, CK5/6, focally positive for Ber-EP4, and negative for WT-1, TTF-1, CK7, CK20, CEA, MOC31, and CD68. FISH analysis demonstrated homozygous deletion for p16. Based on the findings, a diagnosis of diffuse intrapulmonary malignant mesothelioma was made. In some other studies, this entity has been referred to as miliary mesothelioma.
**Take Home Message:** The findings are not “perfect” for mesothelioma, given the negative staining for WT-1, the focal Ber-EP4 positivity, and the fact that homozygous deletion of p16 is not specific for malignant mesothelioma and can be seen in up to 40% of lung adenocarcinomas. Several esteemed members of this journal club have published on this topic (Larsen et al. Am J Surg Pathol 2013) and the question would be do you buy the diagnosis in this case?


**Case Summary:** A 64-year-old male with longstanding RA treated with steroids and MTX developed 2 cavitary lung lesions for which he underwent VATS resection, showing an *Aspergillus* fungus ball filling a cryptococcasis cavity.

**Take Home Message:** Coexistence of these fungi is rare, but even in the presence of a fungal ball, cryptococcasis should be considered as a possible etiology of a necrotizing cavity.


**Case Summary:** A 45-year-old Chinese female with an 8 pack-year smoking history presented with pericardial and bilateral pleural effusions, enlarged mediastinal nodes and a hilar mass. Nodal biopsy showed metastatic adenocarcinoma that had isolated 5’ ALK signals on FISH (which is considered a negative result according to FISH interpretation criteria), but strong IHC ALK expression. Next-generation sequencing disclosed a novel ALK partner gene, *BIRC6*. The patient has responded well to crizotinib.

**Take Home Message:** This case bolsters the argument for using IHC, rather than FISH to identify tumors with an ALK fusion. The FISH assay likely did not detect the inversion in this case due to the short distance between 2 breakpoints in *ALK* and *BIRC6*. 