Micropapillary Histology

A Frequent Morphology of Mutation-Associated Lung Adenocarcinoma?

Alain C. Borczuk, MD

DOI: 10.1309/AJCP9NA3YQSWDYUN

Non–small cell lung carcinoma is a histologically diverse group of tumors that until recently has been treated homogeneously. As a result, pathologists recognized major classes of squamous, adenocarcinoma, and large cell carcinoma, with subclasses and variants to ensure accurate diagnosis, to identify rare subtypes, to assist pathologist communication, and to create uniformity in research despite the fact that these classes did not generally influence clinical decision-making.

This has changed radically in the last few years. Chemotherapeutic regimens may be tailored based on histologic subtype, and targeted therapies are contraindicated in certain histologic subtypes. Molecular classification has led to insights into tumor pathogenesis, prognostication, and therapeutics.

While the molecular age in lung cancer diagnostics and targeted therapeutics is driving the movement towards personalized medicine, it needs to be emphasized that pathologists have been providing personalized information all along. In fact, if we divide the patient-specific information into 4 categories—histologic classification, pathologic staging, prognostic markers of survival, and predictive markers of therapeutic response—pathologists can better understand the interplay of existing practice and novel findings in their current and future practice.

In this issue of the American Journal of Clinical Pathology, Achcar and colleagues1 provide an example of how morphologic classification and molecular classification provide complementary data that serve different components of personalized patient-specific information. In fact, this work demonstrates the issues that exist once these distinct data sets are merged, and shows us the challenges that face the surgical pathologists, thoracic pathologists, and molecular pathologists of the future.

Micropapillary adenocarcinoma of the lung is a histologic subgroup that is considered to be an aggressive adenocarcinoma with greater likelihood of presentation at an advanced stage. It was not defined in the 1999 and 2004 World Health Organization (WHO)/International Association for the Study of Lung Cancer (IASLC) classification,2 and as a result the specific criteria for inclusion in this group remain elusive. In their work, Achcar et al1 use an established definition of Silver and Askin3 for papillary carcinoma, but this may not have been the case in other studies of micropapillary adenocarcinoma. The importance of a precise definition in the lung is underscored by the fact that this may not be the same pattern that bears that name in primary tumors of other organs. Therefore histologic classification requires a pulmonary definition for this entity in the next IASLC classification that is reproducible and generalizes for all pathologists who apply it.

Identification of an aggressive subgroup of tumors may also impact staging and the consequences of staging. Should the higher probability of lymph node metastasis suggest to the surgeon a more extensive lymph node sampling if micropapillary histology is identified preoperatively?4 Does the aggressive behavior of micropapillary adenocarcinoma have a stage- and size-independent impact on survival?5,6 If so, should the oncologist consider adjuvant chemotherapy in stage I micropapillary adenocarcinoma? These considerations merge with prognostic factors that may be determined by histopathology.

The prediction of therapeutic response in lung adenocarcinoma requires a short review of epidermal growth factor receptor (EGFR) targeting tyrosine kinase inhibitor (TKI) therapy. Studies performed earlier in this decade identified a
group of patients with high-stage lung adenocarcinoma who had significant response to EGFR targeting TKI therapy. These studies indicated that female gender, younger age, non-smoking history, Asian ethnicity, and adenocarcinoma with bronchioloalveolar histology were predictive of response.\textsuperscript{7,8} In a separate series of studies, it was found that mutations and in-frame deletions in the EGFR gene cause constitutive activation of the EGFR tyrosine kinase domain, and that EGFR-targeting agents are effective in tumors harboring such mutations.\textsuperscript{9,10} This high response rate may have associated with it a survival benefit.\textsuperscript{11,12}

In conjunction with such studies, activating mutations in codon 12 of the oncogene K-ras, which were previously known to be relatively common in adenocarcinoma of the lung (20%-30% of cases), were not seen in tumors harboring kinase domain EGFR mutations.\textsuperscript{11} In addition, adenocarcinomas with K-ras mutation are nonresponders to EGFR targeting TKI therapy.\textsuperscript{14}

As noted by Achcar and colleagues,\textsuperscript{1} the characteristic demographic of patients with EGFR mutation (female gender, nonsmoker) may hold more in East Asian populations with a higher EGFR mutation rate and lower K-ras mutation rate than in Western populations with a lower EGFR mutation rate and higher K-ras mutation rate. In recent studies, stratification of demographic parameters indicate that EGFR mutation is the better predictor of response and survival when compared to smoking status or gender.\textsuperscript{12}

This data provides the rationale for testing for EGFR mutation in lung adenocarcinoma patients in which EGFR targeting TKI therapy is considered. While initial studies emphasized bronchioloalveolar histology as a predictor of mutation status, this is neither sufficiently sensitive nor specific to provide guidance in a particular patient.\textsuperscript{6} This further underscores the need for EGFR mutation testing in therapeutic prediction.

In the United States population, this leaves about 85% to 90% of patients as EGFR mutation negative.\textsuperscript{15} (Achcar et al\textsuperscript{1} report an EGFR mutation of 10%, K-ras mutation of 23%, and BRAF mutation of 5.5%.) In a series of EGFR targeting TKI response, some responders (up 25%) do not harbor EGFR mutation.\textsuperscript{16,17} While this is not the majority of responders, it is a consistent finding. The presence of K-ras mutation may be used to define the subgroup of EGFR mutation–negative patients that will not respond to EGFR targeting TKI therapy.

There then remains a “double-negative” group that harbors neither EGFR kinase domain mutations nor K-ras–activating mutations. Emerging data on this group found rare instances of mutations in other genes along the same pathway. Recent work by Yousem and colleagues\textsuperscript{18} exploits the fact that K-ras, EGFR, and BRAF mutations do not coexist in the same tumor, resulting in a 5% rate of BRAF mutation in EGFR and K-ras “double-negative” tumors. It is possible that the detection of such a mutation would have the same impact on the clinical decision tree for therapeutics as a K-ras mutation, ie, a decision not to use EGFR targeting TKI therapy. However, little to no data exist as to whether BRAF mutations in lung adenocarcinomas lead to primary EGFR targeting TKI resistance among nonresponders.

The identification of a micropapillary pattern as defined by Achcar et al\textsuperscript{1} was associated with a higher rate of mutation in K-ras, EGFR, and BRAF and specifically a notably higher rate of EGFR and BRAF mutations, albeit with a relatively low total number of cases ($n = 15$). Using the same logic as described above, while it could be argued that a 5% rate of BRAF mutation is too low to justify testing in all “double-negative” tumors, a micropapillary pattern could potentially increase that rate substantially among “double-negative” tumors. The exclusion of cases with K-ras and EGFR mutations in their series would leave 3 of 7 or 43% of micropapillary carcinomas with BRAF mutation.

Examining these issues from the point of view of personalizing care, histopathologic classification, staging, prognostication, and prediction of therapeutic effect are all potentially impacted. Does mutation profiling, however, sufficiently unify these different points of view to justify a mutation-based molecular classification of lung adenocarcinoma? If mutation is of more importance than histology in classification, then biological/clinical behavior needs to be captured by the mutational classification. In the case of micropapillary adenocarcinoma, once optimally defined and histologically classified in the WHO/IASLC lung tumor classification, the histology captures a tumor type more likely to be at higher stage at presentation and which may be independently associated with survival when corrected for size and stage. Unfortunately, a primarily mutational classification would have micropapillary cases in K-ras, EGFR, and BRAF groups.

Is there significance to the high rate of mutation (K-ras, EGFR, or BRAF) independent of the therapeutic prediction in micropapillary adenocarcinoma? Recent studies have indicated that K-ras and EGFR mutation may represent early events in lung adenocarcinogenesis.\textsuperscript{19,20} Given the mutually exclusive nature of these mutations and BRAF mutation as well as the importance of this pathway to persistent growth, one could hypothesize that BRAF mutation is also an early event. Is the micropapillary histology, therefore, 1 common manifestation of the uncontrolled growth exhibited by persistent downstream activation of the EGFR/K-ras/BRAF pathway?

In the pre-TKI era, harboring a K-ras mutation was adversely associated with survival,\textsuperscript{21} and in a more recent study retrospectively analyzing patients from the pre-TKI era, patients with EGFR-mutated adenocarcinomas had better survival.\textsuperscript{22} Survival data on patients with BRAF-mutated adenocarcinoma are not available. However, it is not clear...
that harboring a mutation alone would explain a more aggressive clinical behavior. The molecular reason for aggressive behavior in micropapillary histology remains a missing link in lung adenocarcinomagenesis from growth to invasion to metastasis.

The article by Achcar and colleagues\(^1\) reflects the growing interest in the molecular characterization of lung adenocarcinoma. It helps us understand the different reasons that we characterize tumors, and that these reasons must remain intact not only for us to treat the current patient as an individual for classification, staging, prognostication, and therapeutics but to continue to put a diagnostic entity in the larger context of the historical medical literature and future discovery.

From the Department of Pathology, Columbia University Medical Center, New York, NY.

References


