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A 75-Year-Old Man With Progressive Bronchioalveolar Carcinoma

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Non-small cell lung cancer (NSCLC) is the deadliest and most frequent of cancers worldwide.^{1,2} As a subtype of non-small cell adenocarcinoma, bronchioalveolar (or bronchoalveolar) carcinoma (BAC) is a specific entity that is unique in its response to current standard chemotherapeutic options. The Principles of Pathologic Review put forth by the National Comprehensive Cancer Network (NCCN) describes the histologic features of this tumor as spread of neoplastic cells along pre-existing alveolar structures as a lepidic pattern, where invasion of stroma, pleura, or lymphatic spaces is absent.¹ In terms of classical immunohistochemical characterization, “former” non-mucinous BAC expresses thyroid transcription factor-1 (TTF-1) and CK7 but not CK20; “former” mucinous BAC lacks TTF-1 expression but does express CK7 and CK20.¹ Other subclassifications were discussed by Laskin et al in a previous issue of *Seminars in Oncology*,³ and, as will be discussed, has been further updated by the American Thoracic Society in an International Multidisciplinary Classification⁴ to include adenocarcinoma in situ, minimally invasive adenocarcinoma, invasive adenocarcinoma (includes formerly non-mucinous BAC), and variants of invasive adenocarcinoma (includes formerly mucinous BAC).³ During the preparation of this column, a report was also published highlighting further molecular profiling, which has more specifically classified BAC.^{5,6}

Indeed, molecular targeting is emerging as the prime stratification tactic for combating NSCLC; BAC, however, also has emerged as being further unique in this subclassification. While formerly non-mucinous BAC (with lepidic pattern) may more commonly exhibit *EGFR* mutations,¹ formerly mucinous BACs typically do not, but they do frequently harbor mutation for *K-RAS*, which, in some studies, may be predictive of benefit from platinum/vinorelbine chemotherapy or epidermal growth factor (EGFR) tyrosine kinase inhibitor (TKI) therapy.^{7,8} Genomic rearrangements in the *ALK* tyrosine kinase (including EML4-*ALK* mutations) have now been reported in 2%–7% of patients with NSCLC adenocarcinoma, and these are also resistant to EGFR TKIs.^{4,9} With these complex molecular determinants taken together, the choice of optimum therapy for bronchioalveolar carcinoma is a difficult one. We present a case of an elderly man observed after resection of early-stage BAC, with a crossroads in treatment decisions upon the significant progression of disease.

CASE STUDY

The patient is a 75-year-old Caucasian former light smoker who was originally seen in 2009 for evaluation of an abnormal computed tomography (CT) scan of the chest, which showed a 1.3-cm nodule in the right middle lobe. This mass was the only FDG-avid lesion on a subsequent positron emission tomography (PET) scan. There were no endobronchial lesions on bronchoscopy, and brushings plus washings were negative for malignant cells. Pulmonary function was adequate for lobectomy, and after a right middle lobe lobectomy and mediastinal lymph node sampling, pathology revealed a $3.1 \times 1.5 \times 1.2$ cm well-differentiated BAC with acinar type and focal mucinous and papillary features (Figure 1); the sampled lymph nodes were negative for any involvement of carcinoma, and the tumor was thus originally staged as T2aN0 (IB). Molecular profiling of the tumor revealed the presence of a *K-RAS*G12C mutation. EGFR expression was 1+ by immunohistochemistry, but the *EGFR* gene was wild-type at exons 18–21. When the patient met with a medical oncologist postoperatively, observation was recommended without need for adjuvant therapy, with frequent interval CT scans for surveillance. In 2010, interval imaging revealed new lesions in the right upper lobe and left lower lobe. Biopsy of the left lower lobe mass confirmed the presence of invasive mucinous adenocarcinoma (formerly mucinous BAC), repeat molecular testing revealed the presence of the same mutation, *K-RAS*G12C. Multiple treatment options were discussed, and the patient declined palliative chemotherapy. After discussion, erlotinib 150 mg daily was started but was not well tolerated by the patient, who experienced grade 2 rash unresponsive to clindamycin gel and doxycycline treatment. The patient self-discontinued erlotinib after 3 months of therapy and wished to continue with surveillance, with discussions toward possible chemotherapy treatment revisited.

In 2011, the patient began to have pain in the upper back. CT scans of the chest, abdomen, and pelvis showed progression of the known right upper lobe mass, as well as multiple new small lung nodules bilaterally. An expansile, lytic lesion was identified in the distal right clavicle, as well as two additional masses in the right paraspinal soft tissue of the right hemithorax. Biopsy of the right paraspinal soft tissue mass again confirmed the presence of invasive mucinous adenocarcinoma. The patient was started on pain control and dexamethasone to reduce inflammation. He was evaluated by a radiation oncologist for

palliative measures, including external beam radiation to the painful paraspinal and clavicular areas.

We propose the following questions: (1) What further treatment would you offer and why? (2) What other first-line options exist for BAC? For recurrent BAC?

MEDICAL ONCOLOGISTS' OPINION

The patient in this case history has biopsy-proven metastatic mucinous BAC harboring a somatic activating mutation in the *K-RAS* oncogene. Prior to discussion of treatment options, it is worth commenting both on the tumor's histology, as well as mutational status. In 2008, an international multidisciplinary panel of lung cancer experts, sponsored by the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS), and the European Respiratory Society (ERS), convened to revise the subclassifications of lung adenocarcinoma. As a result of this panel, mucinous BAC was renamed invasive mucinous adenocarcinoma.⁴ Interestingly, several retrospective studies have shown that *K-RAS* mutations are more frequently found in mucinous adenocarcinomas.^{10–13} The *K-RAS* gene encodes a small guanosine triphosphate (GTP)-ase that plays a central role in cell proliferation, survival, and differentiation and has been implicated in the pathogenesis of many types of cancer.^{14,15} *K-RAS* mutations occur with a frequency of approximately 25%^{16,17} in North American patients with lung adenocarcinoma and are much less frequent in Asian populations.^{18,19} *K-RAS* mutations are more common in tumors derived from former/current smokers than never-smokers¹⁷ and are uncommon in lung squamous cell carcinoma.²⁰ In most cases, these are missense mutations, which introduce an amino acid substitution at position 12, 13, or 61, the result of which is constitutive activation of the protein.

The detection of a *K-RAS* mutation within this patient's tumor has important implications for his treatment planning. This patient was treated with erlotinib as first-line therapy for metastatic disease. This could be considered controversial as multiple studies have shown that *K-RAS* mutations are negative predictors for radiographic response to the EGFR TKIs, gefitinib and erlotinib.^{21,22} At present, there are no direct anti-*K-RAS* therapies that have proven to be efficacious in lung cancer. Salirasib, which prevents RAS activation by blocking membrane binding, was recently evaluated in a phase II study of patients with advanced lung adenocarcinoma harboring a *K-RAS* mutation. None of the patients on study had a radiographic partial response.²³ There are several ongoing clinical trials for this cohort of lung cancer patients with targeted agents affecting other pathways. Some of the agents used in these studies include heat shock protein-90 (HSP-90) inhibitors alone and in combination with mammalian target of rapamycin (mTOR) inhibitors (NCT01427946) and K-ras-mediated activation of extracellular-regulated kinase (MEK) inhibitors (NCT01362296, NCT01395758).

At present, the standard of care for first-line therapy for invasive mucinous adenocarcinoma (mucinous BAC) is similar to that for all other non-squamous NSCLCs and consists of four to six cycles of a platinum-based doublet.^{24,25} In bevacizumab-eligible patients, carboplatin, paclitaxel, and bevacizumab²⁶ or carboplatin, pemetrexed, and bevacizumab²⁷ should be

considered. Notably, both of these regimens include maintenance therapy with either bevacizumab alone or bevacizumab in combination with pemetrexed after four cycles of chemotherapy. The maintenance regimens should be continued until disease progression or unacceptable toxicity. Of note, however, in an unplanned retrospective analysis, the combination carboplatin, paclitaxel, and bevacizumab was associated with increased toxicity and no obvious improvement in overall survival in the elderly (age >70 years) subgroup.²⁸ Certainly, this patient's age and performance status should be taken into consideration prior to initiating any therapy.

Although we would likely not consider the use of erlotinib as the firstline treatment given the numerous studies showing that *K-RAS* mutations are negative predictors for radiographic response to EGFR TKIs,^{19,20} erlotinib was approved by the US Food and Drug Administration for use in the second-/third-line setting for unselected NSCLC patients, based on a 2-month survival benefit compared to placebo.²⁹

In summary, based on his age and performance status, we would consider additional treatment for this patient with metastatic invasive mucinous adenocarcinoma (mucinous BAC) harboring a *K-RAS* mutation with a platinum-based doublet or, alternatively, a clinical trial directed specifically at this molecular cohort. This case demonstrates how histologic examination of a tumor sample can provide clues as to the underlying tumor mutational status and the importance of molecular testing in NSCLC patients. In addition, this case also reveals how understanding the molecular pathogenesis of a lung cancer can aid in planning a therapeutic strategy.

MEDICAL ONCOLOGIST'S OPINION

This case illuminates a number of important issues in the care of patients with metastatic lung adenocarcinoma. BAC is an adenocarcinoma that extends in a lepidic manner along the alveolar septae, and the World Health Organization (WHO) 2004 classification separates BAC into nonmucinous and mucinous subtypes. Recent categorization of adenocarcinoma by the ERS, IASLC, and ATS through a multidisciplinary approach has led to new definitions of BAC.⁴ In this classification, adenocarcinoma in situ refers to solitary BAC, lepidic predominant invasive adenocarcinoma corresponds to non-mucinous BAC, and invasive mucinous adenocarcinoma is associated with the previously mucinous BAC. Traditional BAC has been associated with activating mutations in the *EGFR* gene with increased responses to EGFR TKIs.^{30–32} This case exemplifies the importance of molecular testing prior to initiation of therapy since the tumor harbored a G12C mutation in the *K-RAS* gene, which is usually mutually exclusive of *EGFR* mutations, and correlates with decreased responses to EGFR TKI therapy.³³ Therefore, alternative treatments should be considered.

The majority of those diagnosed with lung cancer are over the age of 70, and are categorized as older adults. Consideration of chemotherapy for this 75-year-old patient must account for age and physiologic characteristics. Most chemotherapeutic regimens have similar efficacy in older and younger patients, and while some toxicity rates are higher in older patients, with appropriate prophylaxis and supportive care, older adults are generally able to tolerate most

chemotherapy regimens, even in combinations.³⁴ Proper selection of older adult candidates for aggressive therapy is important, and identification of issues that might limit ability to complete treatment or benefit from treatment both before and during active treatment is essential.³⁵

Therapy for metastatic lung cancer, including BAC, remains palliative rather than curative and response rates to chemotherapy are modest. This highlights the importance of implementing early palliative care into his plan of care. Temel et al demonstrated that patients with metastatic NSCLC who received early palliative care intervention in addition to standard therapy had improved quality of life and prolonged survival.³⁶

In summary, a multifaceted approach is needed to provide appropriate therapy to this patient. Initial assessment should include evaluation of the molecular subtype of adenocarcinoma to determine whether EGFR or other targeted therapy would be appropriate, and in this case *K-RAS* mutation would preclude the use of first-line EGFR therapy. Additional consideration must be made of his age and physiologic status to determine the role of combination chemotherapy. Finally, early palliative care in his treatment plan will improve outcomes for this patient.

MEDICAL ONCOLOGISTS' OPINION

BAC has been described as a subtype of adenocarcinoma with unique features, including a well-differentiated cytology, lepidic growth pattern along alveolar septae, and a tendency to present with multifocal lung lesions. It has been divided into mucinous, non-mucinous, and mixed subtypes. Currently, clinicians continue to use the term BAC to describe both the non-invasive “pure” form, as well as mixed adenocarcinoma with a BAC component. However, this classification will soon change as in 2011 the IASLC, ATS, and ERS proposed a revision to adenocarcinoma classification.⁴ This revision stipulates that the term BAC should be discontinued and that what was known as “pure” BAC will now be called adenocarcinoma “in situ” (AIS). AIS describes a localized, small lesion (<3 cm) without any invasive component and this has been associated with a 100% 5-year survival. If the specimen contains any invasive component, such as stromal, pleural, or lymphovascular invasion, this will be called invasive adenocarcinoma. Any aspect of the tumor that was previously called BAC will now be referred to as an adenocarcinoma having lepidic or acinar components and the former “mucinous BAC” will be called invasive mucinous adenocarcinoma. However, for the purposes of this discussion in keeping with the case description, the historical broader definition of BAC will be used.

The treatment paradigm for advanced or metastatic “BAC” generally mirrors that of lung adenocarcinomas in that it is individualized based on molecular and histologic features of the tumor. Ideally, the tumor should be assessed for the presence of an EGFR mutation prior to the initiation of therapy for advanced disease, and possibly for the presence of a *K-RAS* mutation or an anaplastic lymphoma kinase (ALK) fusion oncogene depending on the availability of rapid molecular testing, targeted therapies, and clinical trials.

Of note, *EGFR* mutation status more specifically in BAC was assessed in a series of 86 patients, and the mutation was present in 26%.³⁷ Interestingly, all of the *EGFR* mutations were in the non-mucinous subtype of BAC (22 of 69) compared with mucinous (0 of 17), an observation held up by other reviews.¹⁰ Three phase II studies have assessed the role of *EGFR* TKIs first-line for patients with advanced otherwise unselected BAC. Response rates ranged from 13%–22%. Higher responses were seen in female, never-smokers, who developed a rash, and had non-mucinous subtype and *K-RAS* wild-type tumors.^{31,38,39}

It is well known that the presence of an *EGFR* mutation is highly associated with sensitivity to *EGFR* TKIs, while on the contrary there is an accumulation of evidence to demonstrate that mutations in *K-RAS* are associated with primary resistance to TKIs.³³ There is some conflicting evidence regarding the sensitivity of *K-RAS*-mutated lung cancers to platinum-based chemotherapy. A recent American Society of Clinical Oncology (ASCO) presentation examined retrospective pooled *K-RAS* data from four large adjuvant chemotherapy studies and found that within the more prevalent codon 12 mutation subtype there was little variation of chemotherapy effect compared to *K-RAS* wild-type patients.⁴⁰

With this particular patient, assuming he is relatively well and willing to explore his treatment options, platinum-based doublet chemotherapy should be discussed. Historically BAC was viewed by some as chemoresistant; however, most clinical trials have shown response rates similar to patients with lung adenocarcinoma. Two prospective phase II clinical trials using paclitaxel have shown objective response rates of 54%.^{41,42} There have been no prospective clinical trials evaluating the role of contemporary chemotherapy specifically in BAC patients. It is likely that the BAC subtype of adenocarcinoma was included in NSCLC trials evaluating contemporary chemotherapy and these data may be applied to BAC.

Age alone should not be a deterrent to doublet chemotherapy, but again this assumes that the patient has a good performance status and that any comorbidities do not preclude chemotherapy. Options would include cisplatin or carboplatin plus pemetrexed, paclitaxel, gemcitabine, docetaxel or vinorelbine; personally I favor carboplatin-based therapy in patients over 70 years of age because of the more favorable toxicity profile.⁴³ Pemetrexed may be the preferred choice given the data that indicated better efficacy in nonsquamous histologies.⁴⁴ If he were less fit, single-agent chemotherapy with one of the above agents also would be reasonable.

Consideration also could be given to adding a targeted agent to his chemotherapy. His initial tumor had 1+ *EGFR* expression by immunohistochemistry, and although this is a poor predictor of a response to an *EGFR* TKI, it would fit the criteria applied to cetuximab, a monoclonal antibody to *EGFR*. The First-Line in ErbituXD in Lung Cancer (FLEX) trial demonstrated some benefit associated with cetuximab when added to cisplatin plus vinorelbine in patients who had some *EGFR* expression, though I would be less inclined to offer this patient a cisplatin combination.⁴⁵ Addition of bevacizumab to paclitaxel and carboplatin would be another option, assuming he did not have any contraindications to bevacizumab, as the E4599 trial demonstrated a survival advantage to this combination

therapy.²⁶ A note of caution should be extended to the use of this combination in patients over 70 years of age as increased toxicity in this subgroup has been noted.²⁸

In summary, this is a 75-year-old man with a history of “BAC” that has recurred after primary resection and has now metastasized presenting with symptomatic bone lesions and progression in the lungs. Given that is now symptomatic he may be more willing to accept chemotherapy, though regardless of the chemotherapy choices he should receive best supportive care including pain and symptom management and radiation to his painful bone lesions. I think this patient would benefit from standard chemotherapy as one would offer to any non-squamous metastatic NSCLC tailored to his performance status and any other health issues and preferences. The effect of different *K-RAS* mutations within tumor types and between different cancers remains an area of active exploration; at this time there is insufficient evidence to withhold platinum-based chemotherapy based on *K-RAS* status. This case highlights the changing landscape of NSCLC pathology classifications and mutation profiling as we expand our knowledge and understanding of lung cancer biology and targeted therapy.

DISCUSSION AND CONCLUSION

We present a case of a patient with mucinous BAC, who was first placed under observation after resection of early-stage disease, and upon recurrence and metastatic progression of his disease, opted for TKI treatment despite the presence of a *K-RAS* mutation. We have asked expert medical oncology opinions regarding treatment options for this particular patient’s situation. Historically, BAC has previously been described to exhibit a lower response to chemotherapy.⁴⁶ As reviewed by Laskin et al, early small phase II studies of TKIs in BAC or adenocarcinoma with BAC features showed appreciable response to erlotinib^{3,47,48} or gefitinib,⁴¹ usually with a tolerable toxicity profile. However, Miller et al recently showed that patients with *EGFR* mutations had an 83% response rate (RR; 15 of 18; 95% confidence interval [CI], 65%–94%) and 23-month median overall survival, but their response to erlotinib was negligible if *K-RAS* mutation status was positive, with an overall RR of only 22% (95% CI, 14%–31%); *EGFR* expression by immunohistochemistry was not associated with appreciable RR or progression-free survival (PFS).³¹ However, erlotinib has been used as maintenance therapy in NSCLC, in general with wildtype *EGFR* expression.⁴⁹ Thus, a relative paradigm shift has been seen in the treatment of BAC.

The role of *K-RAS* mutations as a predictor of response for patients generally with stage IV NSCLC treated with chemotherapy alone has been previously poorly understood.²² However, intriguing data were reported from a molecular analysis of tumors from patients enrolled in the phase III Tarceva Responses in Conjunction With Paclitaxel and Carboplatin/Phase III Trial of Erlotinib Hydrochloride OSI-774 Combined With Carboplatin and Paclitaxel Chemotherapy in Advanced Non-Small Cell Lung Cancer (TRIBUTE) trial, in which previously untreated patients with NSCLC were offered chemotherapy plus placebo versus chemotherapy plus erlotinib.^{7,21,22} Patients with *K-RAS* mutant tumors had a response rate for erlotinib plus carboplatin and paclitaxel actually lower (8%) than that for patients who received the chemotherapy doublet alone (23%), with an overall survival

hazard ratio of 2.1 (95% CI, 1.1–3.8); patients with *K-RAS* mutations who were treated with erlotinib along with chemotherapy had the shortest overall survival.^{21,22}

At the point of further progression for this patient, however, palliation was offered. Local radiation therapy for palliation of pain from T8–L1 via a three-field technique, with a total dose of 3,000 cGy in 10 fractions was given. Unfortunately, the patient also developed brain metastases, and these were treated with 350 cGy whole-brain irradiation in 14 fractions at 250 cGy per fraction via lateral opposing fields prior to entering hospice care. We asked how other aspects of the molecular and phenotypic makeup of BAC could affect this patient's treatment interventions.

Salvage treatments were offered. As discussed by Drs Noonan and Laskin, cetuximab—a chimeric monoclonal antibody toward *EGFR* that has modest activity and improved survival in combination with chemotherapy in advanced NSCLC—has afforded modest efficacy in the phase II setting (7% RR, 35% stable disease rate, and partial response in one of six patients with *EGFR* mutation and in one of seven patients with *K-RAS* mutation) in advanced BAC in patients with a *K-RAS* mutation⁵⁰; based on these results, this option was also discussed with the patient presented here, as was additional chemotherapy with a taxane.^{42,51,52}

However, better understanding of the subtype of the patient's lung cancer may provide more precise and individualized recommendations. As discussed by Drs Horn, Reckamp, and Laskin, new pathologic classification of BAC has stratified the disease according to evidence invasive histology,⁴ and further histologic risk stratification has recently been reported,^{5,6} with more specific pattern and pattern groups showing stage- and therapy-independent prognosticators for overall, disease-specific, and disease-free survival parameters.⁵ This should now be part of an integrated clinical, morphologic, and molecular subtyping to further improve treatment.⁶ In addition, microRNAs can currently be useful in differentiating squamous cell carcinomas from non-squamous cell carcinomas where the pathology is difficult; however, a significant research interest would now be the use of this technology in the subtypes of BAC to determine prognostics and predictors of response, as well as to identify molecular targets for therapeutic intervention.⁵³

Importantly, the type of *K-RAS* mutation may risk stratify patients according to type of amino acid substitution with Gly12Cys or Gly12Val substitution exhibiting the worse PFS as compared with other mutations or wild-type *K-RAS* status.^{54,55} In addition, ongoing clinical trials targeting other molecular pathways are discussed by Drs Lovly and Horn. Whether new pathologic classification would impact early risk stratification and prognostic information on this particular patient, and is obtainable in the community setting, is a question worth pursuing. Indeed repeat biopsy is an important tool for guiding further clinical decisions.

Medical oncologists are left with a challenge when patients decline standard chemotherapy recommendations,⁵⁶ and further personalize choices for treatment, which ultimately are a mutual decision between the patient and physician. We welcome your additional comments and discussion, and thank our coauthors for both their excellent timely review of evidence-

based recommendations as well as their expert clinical perspectives, regarding this treatment dilemma.

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At times we encounter clinical problems for which there are no directly applicable evidence-based solutions, but we are compelled by circumstances to act. When doing so we rely on related evidence, general principles of best medical practice, and our experience. Each “Current Clinical Practice” feature article in *Seminars in Oncology* describes such a challenging presentation and offers treatment approaches from selected specialists. We invite readers’ comments and questions, which, with your approval, will be published in subsequent issues of the Journal. It is hoped that sharing our views and experiences will better inform our management decisions when we next encounter similar challenging patients. Please send your comments on the articles, your challenging cases, and your treatment successes to me at dr.gjmorris@gmail.com. I look forward to a lively discussion.

Gloria J. Morris, MD, PhD

Current Clinical Practice Feature Editor

Figure 1.

(A) Biopsy of original lung mass, showing moderately to well-differentiated adenocarcinoma, and showing glands of different size and shape, and stroma between tumor glands infiltrated with chronic inflammatory cells. Hematoxylin and eosin stain, 10× magnification. (B) Biopsy of original lung mass, showing moderately to well-differentiated adenocarcinoma. Hematoxylin and eosin stain, 40× magnification. (C) Biopsy of original lung mass, showing moderately to well-differentiated adenocarcinoma with papillary features. Hematoxylin and eosin stain, 40× magnification. (D) Biopsy of original lung mass, showing moderately-to-well-differentiated adenocarcinoma, and showing mucinous areas.

Hematoxylin and eosin stain, 100× magnification. (E) Biopsy of original lung mass, showing moderately to well-differentiated adenocarcinoma, and showing bronchoalveolar features with tumor cells along alveolar septae. Hematoxylin and eosin stain, 10× magnification. (F) Biopsy of original lung mass, showing moderately to well-differentiated adenocarcinoma with bronchoalveolar features. Hematoxylin and eosin stain, 40× magnification. Slides courtesy of Dr Oh-Kee Won, Department of Pathology, Community Medical Center, Scranton, PA.