Gefitinib-Associated *Propionibacterium acnes* Pleural Empyema

To the Editor:

Inhibition of the tyrosine kinase activity of the epithelial growth factor receptor (EGFR) by specific inhibitors (TKIs) resulted in a survival benefit in patients with metastatic non-small cell lung cancer in large placebo-controlled phase III trials. EGFR-TKIs have now full approval for treatment of patients with metastatic non-small cell lung cancer after progression with first-line platinum-based chemotherapy.[1] However, both gefitinib and erlotinib have similar dermatologic side effects that mimic acnea vulgaris and require drug withdrawal or dose reduction in up to 9% of cases. The role of *Propionibacterium acnes* colonization in these skin lesions is debated. Furthermore, skin lesions may also be an important marker of antitumor activity since they occurred more frequently in responders than in nonresponders, usually in the first weeks of treatment.[2] We report here a case of an *P. acnes* pleural empyema associated with severe gefitinib-induced skin toxicity and repeated thoracocenteses.

A 50-year-old nonsmoker woman underwent a right upper lobectomy for severe hemoptysis. Primary lung adenocarcinoma (CK7+/CK20−/TTF1+) was diagnosed and staged pT2N0M0 due to visceral pleura involvement. Four months later, adenocarcinoma-related right pleural effusion was treated by a platinum/gemcitabine doublet and pleurodesis, followed by second-line docetaxel therapy given because of progressive disease. Thoracocentesis was performed once. With further progression, gefitinib (250 mg daily) was started as TKIs response predictors were present (female gender, never-smoker, adenocarcinoma subtype, and the presence of L858R point mutation in EGFR gene exon 19). This resulted in a major clinical and radiologic response. Concurrent maculopapular erythema and follicular lesions appeared on her face and chest and were considered as a grade III skin toxicity. However, thoracocentesis was performed twice because of a symptomatic compartmentalized right pleural effusion. The pleural fluid remained repeatedly aseptic.

Three months later, the patient was hospitalized because of right rib pain, anorexia, and vomiting. Temperature was 38.5°C. Skin examination revealed persistence of EGFR-TKIs-related lesions and parietal edema at previous pleural puncture points. White blood cells were 10,200/ml with 74% neutrophils and C-reactive protein was 208 mg/l. Chest radiograph and computed tomography scan showed pulmonary infiltrates and compartmentalized right pleural effusion (Figure 1). Pleural fluid was serosanguineous, pleural-to-plasma protein and LDH ratios were 1.64 and 4.42, respectively, and pH was 7.2. Culture grew a wild *P. acnes* strain. Cytology showed infiltration with neutrophils without tumoral cells. Skin colonization by *P. acnes* was evidenced.

Amoxicillin plus moxifloxacin treatment was started. A chest tube was placed, which resulted in fever decrease and C-reactive protein level normalization. Because of the persistence of pleural effusion, a right thoracotomy was performed, which confirmed pleural space infection as brown pleural fluid was evacuated. Gram's stain evidenced gram-positive bacilli. A culture did not grow. There was no cancer identified at the thoracotomy. After surgery, the patient improved and was back home after a 43-day long hospitalization.

P. acnes is a normal commensal of skin flora and has often been considered as a contaminant of blood cultures and of other fluids secondary to skin piercing. It has more recently been recognized as a potential pathogen in acnea vulgaris and in neurosurgical and bone-joint infections.[3] In this case, the mechanism of pleural infection is not straightforward. *P. acnes* is a commensal resident of lung and lymph nodes.[4] One may therefore hypothetize that gefitinib induced an increase of *P. acnes* inoculum in lymph nodes with a subsequent pleural seeding. On the other hand, pleural inoculation might have been a consequence of repeated thoracocenteses. Bacterial superinfections have already

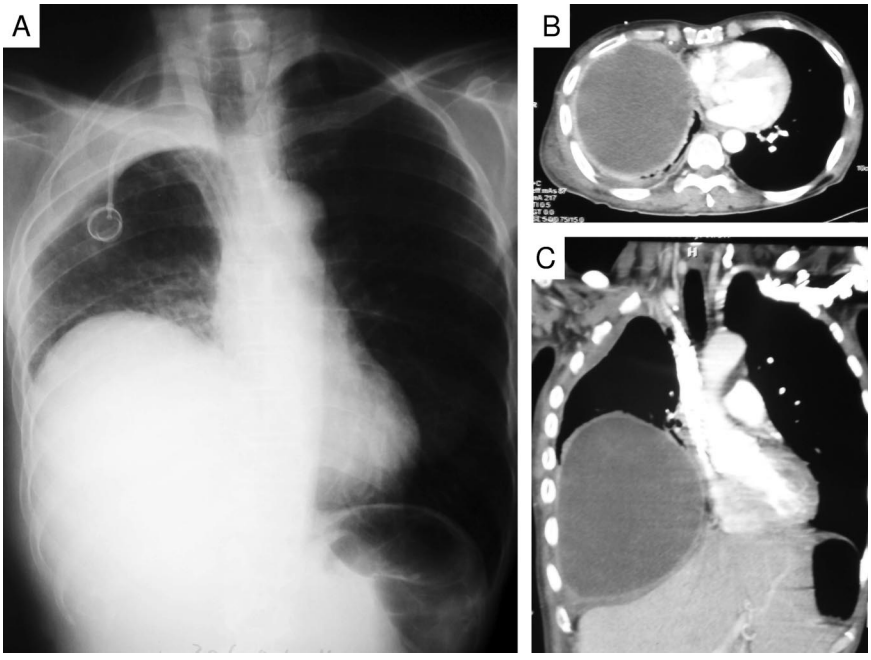

FIGURE 1. Chest radiograph showing compartmentalized right pleural effusion with pulmonary infiltrates and reduced right lung volume (*A*). Transversal (*B*) and frontal (*C*) chest computed tomography scan slices showing voluminous and compartmentalized right infrapulmonary pleural effusion with mild mediastinal contralateral deviation.

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been described in EGFR-TKIs treated patients, especially with *Staphylococcus aureus* nasal carriage or extensive midface involvement.[5] Inhibition of EGFR signaling on epidermal and adnexal epithelium may lead to skin barrier impairment with increased bacterial carriage. Then, it is still unclear if EGFR-TKIs-induced skin lesions increase *P. acnes* colonization or if *P. acnes* is directly involved in skin toxicity as it is in acnea vulgaris. Topical and systemic antibiotics have been used to treat these skin lesions.[2] Interestingly, tetracycline is used mostly for its immunomodulatory properties, but its antibiotic activity against *P. acnes* could prevent the risk of invasive infections. Moreover, prophylactic treatment should be considered before piercing an altered skin to decrease bacterial carriage and therefore, the risk of bacterial seeding.

We describe the first case of *P. acnes* pleural empyema associated with EGFR-TKIs. Increasing use of these molecules should warn clinicians of this rare but potentially lethal complication especially with thoracocenteses.

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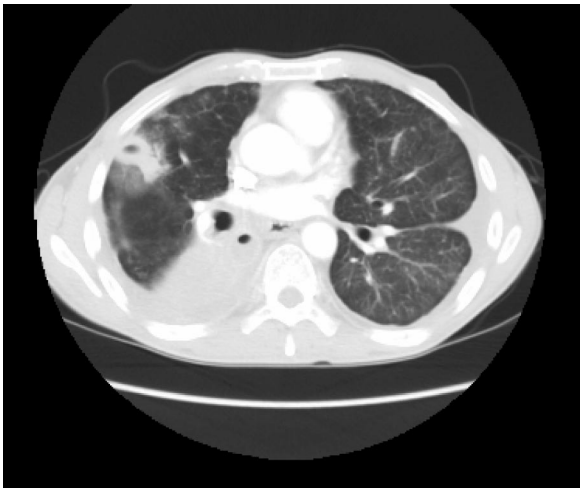

FIGURE 1. Thoracic computed tomography scan performed before bevacizumab showing bilateral pleural effusion, condensation with a small cavity in the right-lower lobe, peripheral opacity in the middle lobe with round glass opacities.

Pulmonary Epithelioid Haemangioendothelioma and Bevacizumab

To the Editor:

Pulmonary epithelioid hemangioendothelioma (PEH) is a rare tumor of the lung.[1] Surgery is proposed in case of unilateral nodules.[2] In case of bilateral nodules and/or pleural involvement, several antineoplastic agents have been used with poor beneficial effects in most cases.[3] Because PEH is a vascular tumor, the use of antiangiogenic therapy may be suggested. So, we report here the first case, to our knowledge, of a patient treated with bevacizumab and chemotherapy.

A 41-year-old man was admitted for fever, cough, and breathlessness. His weight had fallen by 4 kg. Chest radiograph and thoracic computed tomography scan showed numerous bilateral calcified nodules, condensation in the right lower lobe, alveolar infiltrate predominant in the left upper lobe, and bilateral pleural effusion (Figure 1). Positron-emission tomography exhibited an increased uptake of 18F-fluorodeoxyglucose in the condensation of the right lower lobe and pleura. Bronchoscopy with bronchoalveolar lavage and bronchial biopsies were normal. Thoracocentesis revealed bloody fluid without malignant cells. A right thoracoscopy was performed. Histologic examination of the pleural and pulmonary biopsies showed similar features with monomorphic malignant proliferation made up of cells with nuclear pleomorphism and rare atypical mitoses surrounding the vessels. Staining of the tumoral tissues was positive for antivimentin and anti-CD34 antibodies, and negative for anticytokeratin antibodies. These findings supported the diagnosis of epithelioid hemangioendothelioma. Expression of vascular epithelium growth factor receptor was highly positive.

The patient started chemotherapy with cisplatin and etoposide for one cycle. Because of progressive disease, he received interferon alpha for 1 month. However, his disease progressed and he was started with bevacizumab (450 mg). Thereafter, he remained stable and a combination of carboplatin-paclitaxel with bevacizumab (15 mg/kg) was given on day 1.

Chemotherapy was repeated every 21 days for five cycles. The patient showed a dramatic improvement in clinical status. The thoracic computed tomography scan revealed a good partial response (Figure 2).

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