Panitumumab-induced pulmonary toxicity

R. Arora BMSc MD,* M. Kisiel MD PhD,† and C. MacColl BSc MD‡

ABSTRACT

Mutations in EGFR have been implicated in the pathogenesis of various types of cancer, and therefore antibody therapy directed against the epidermal growth factor receptor (EGFR) is increasingly being used in the management of various cancers. Currently, anti-EGFR antibodies are used mainly in the management of cancers of the head and neck and metastatic colorectal cancers. Because of this increasing use, we would like to inform the oncology community in North America of a rare, but life-threatening, toxicity associated with anti-EGFR antibody therapy. Although cases in white and Japanese men have been documented, we present the first known North American report of panitumumab-induced pulmonary toxicity in a white woman.

Key Words  EGFR, panitumumab, pulmonary toxicity, ARDS

BACKGROUND

Pulmonary toxicity is a rare side effect associated with targeted antineoplastic therapies. Cetuximab and panitumumab are monoclonal antibodies against the epidermal growth factor receptor (EGFR) and are used to treat colorectal and head-and-neck cancers. These antibodies use occlusion of the ligand-binding site to block activation of EGFRs, which are membrane tyrosine kinase receptors involved in cell proliferation and survival. In addition to interrupting the signalling pathway initiated by EGFRs, anti-EGFR monoclonal antibodies might be playing a role in cancer therapy by mediating immune system function, inducing cytotoxicity by antibody-dependent or complement-mediated mechanisms, or both. With anti-EGFR treatments being used with increasing frequency, an awareness of potential side effects is critical to both the clinician and the patient.

Panitumumab is a fully humanized monoclonal antibody that is well tolerated, with most adverse effects being grade 1 or 2 dermatologic toxicities that rarely result in treatment discontinuation. Infusion-related bronchospasm is the most common pulmonary toxicity. Rarely, interstitial lung disease can also occur. Interstitial lung disease has been reported in 2 patients receiving panitumumab and in 3 receiving cetuximab. Here, we present the first known case of panitumumab-induced pulmonary toxicity in a North American white woman.

CASE PRESENTATION

A 54-year-old white woman was treated with surgery for stage III colon cancer in May 2015, followed by adjuvant chemotherapy, which was completed in December 2015. In January 2018, the patient underwent surveillance computed tomography imaging, which unfortunately revealed metastases in lungs, bones, and pelvis. Thus, she was started on single-agent panitumumab. Her 1st cycle, in February 2018, caused profound hypoalbuminemia, hypomagnesemia, and hypokalemia, which necessitated hospitalization. The 2nd and 3rd cycles were tolerated at 50% dose reduction.

Approximately 7 days after the 4th cycle of panitumumab, the patient was hospitalized for small-bowel obstruction that was managed with palliative enterotomy and bypass. Seven days later, the patient developed fever, hypoxia, and cough and was started on empiric antibiotics for a presumed hospital-acquired pneumonia. During the ensuing 10 days, the patient’s respiratory status deteriorated, and she developed increased work of breathing and increased need for oxygen. At that point, the patient was started on steroids for possible acute respiratory distress syndrome (ARDS), and broad-spectrum antimicrobials were initiated for possible Pneumocystis jiroveci pneumonia and fungal infection.

Chest radiography showed marked bilateral hazy opacities of the entire lung fields (Figure 1). Intubation...
and ventilation support measures were declined, thus the patient passed away 3 days later from respiratory failure.

After the patient’s death, a chest autopsy was performed to determine whether pathology features consistent with ARDS were present in the lungs. The autopsy revealed pulmonary effusions, prominent bilateral pulmonary fibrosis, and marked edema with widespread hemorrhagic spots. Microscopic examination of the lung tissue showed interstitial expansion, with hyaline membranes lining the alveoli and sloughing of pneumocytes characteristic of the diffuse alveolar damage classically observed in ARDS (Figure 2). In addition, nodules found in the right lung were determined to be adenocarcinoma, consistent with metastatic colon cancer (Figure 3). Cultures taken from the lungs did not yield microbial growth. Cardiac examination revealed no abnormalities of the myocardium and patent coronary arteries.

**DISCUSSION**

To our knowledge, this case report is the first of ARDS potentially secondary to EGFR inhibitor use in a North American white woman. We postulate that ARDS can occur after pulmonary insult in the context of EGFR inhibitor use because EGFR is a key protein in the alveolar wall repair pathway in type II pneumocytes. In addition, EGFR inhibitors can contribute to reduced expression of surfactant A protein in lung parenchyma, which might lead to further impairment of pulmonary healing through reduced lung compliance. Recently, another monoclonal antibody to EGFR, cetuximab, has been reviewed in post-marketing surveillance and been found to be associated with a 1.2% incidence of interstitial lung disease in patients with metastatic colorectal cancer.

Diagnostic criteria for the ARDS clinical syndrome that can result in pulmonary injury are described by the Berlin definition. Histologically, the hallmarks of ARDS are diffuse alveolar damage characterized by membrane

**FIGURE 1** Chest radiograph revealing bilateral hazy opacities present over the entire lung fields.

**FIGURE 2** (A) Diffusely abnormal lung parenchyma (low power, hematoxylin and eosin stain). (B) Interstitium expanded by loose fibroblastic proliferation, and alveolar spaces lined by hyaline membranes (arrows; hematoxylin and eosin stain). (C) Martius scarlet blue stain highlights fibrin in scarlet red, corresponding to alveolar hyaline membranes (arrows).
hyalinization, interstitial edema, type 1 alveolar cell death, fibroblast or myofibroblast proliferation, and fibrosis. Although not all patients with clinical ARDS have that hallmark morphology, it is associated with higher mortality when present. Three histologic stages in ARDS are recognized:

- Exudative phase
- Proliferative phase
- Later fibrotic phase

During the exudative phase, capillary congestion and intra-alveolar edema are present. During the transition to the proliferative phase, proliferation of interstitial fibroblasts and type II alveolar cells occurs; additionally, organizing interstitial fibrosis can be present. Finally, during the last stage, collagenous fibrosis and microcystic honeycombing occur. However, ARDS is an evolving process, with considerable overlap between stages.

Results of our decedent’s lung histopathology were consistent with the proliferative phase of ARDS, with fibroblastic expansion noted in the lung interstitium. The patient in this case passed away 13 days after the onset of her pulmonary symptoms, which is consistent with the results of a recent autopsy study of 159 patients demonstrating that, after the first week, most patients show evidence of proliferative changes, and by 3 weeks, all individuals show those changes. Clinically, the radiographic severity of the decedent’s pulmonary disease (with diffuse opacities), the duration of her respiratory symptoms, and the degree of hypoxemia were all consistent with the findings of diffuse alveolar damage at autopsy, which occurs more frequently with severe ARDS. In addition to those findings, the decedent’s autopsy also demonstrated foci of colon cancer in the right lung in keeping with her known metastatic disease.

The limitations of our report include the fact that we are presenting our observations from a single case. In addition, we are unable to suggest anything more than a potential association between the use of anti-EGFR antibody therapy and the development of ARDS. The notable strength is that our findings are consistent with previous case reports in the literature.

**SUMMARY**

Ultimately, ARDS represents a rare but important potential complication for clinicians to consider on the differential diagnosis of a patient with respiratory symptoms who is receiving anti-EGFR therapy. Because the current report describes a single case, the insights that can be gleaned from it are limited. However, in highlighting this clinical entity, we hope that ARDS might be recognized and treated earlier to potentially avoid death in patients who experience this complication. As additional cases are recognized, it might be possible to determine if certain factors predispose groups of patients receiving anti-EGFR therapy to more severe pulmonary toxicities.

**CONFLICT OF INTEREST DISCLOSURES**

We have read and understood Current Oncology’s policy on disclosing conflicts of interest, and we declare that we have none.

**AUTHOR AFFILIATIONS**

*Medical Oncology, Department of Oncology, and †Department of Pathology and Molecular Medicine, McMaster University, Hamilton, ON.

**REFERENCES**