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Fatal Infusion Reaction to Cetuximab: The Need for Predictive Risk Factors and Safer Patient Selection

Case Report

A 63-year-old man with a history of metastatic colon cancer and a wild-type *KRAS* genotype visited our institution as an outpatient. The patient had previously received oxaliplatin- and irinotecan-based chemotherapy and pulmonary resection. At our institution, he received the first course of a combined irinotecan and cetuximab treatment. He was in excellent health with no significant complaints or tumor-related symptoms. His medical history was uninformative, and he reported no comorbidity and no known allergies.

A few minutes before the infusion, the patient had normal vital signs (including blood pressure and heart rate) and a normal blood count. The protocol at our institution required premedication with chlorpheniramine (10 mg intravenously [IV]), dexamethasone (8 mg IV), and atropine (0.25 mg subcutaneously) before the administration of cetuximab (400 mg/m^2 IV infusion delivered over 120 minutes) and irinotecan (180 mg/m^2 IV infusion delivered over 90 minutes). A few minutes after this treatment finished, the patient began to exhibit sialorrhea, sweating, and diarrhea, which was indicative of irinotecan-induced cholinergic syndrome. However, despite the administration of atropine (0.5 mg subcutaneously), the symptoms rapidly deteriorated. He experienced dyspnea, expectoration of a white, frothy mucus, and initial decrease in the level of consciousness. The patient's oxygen saturation fell to 70% in ambient air, and bilateral rales and ronchi were detected on chest auscultation. The patient was admitted to the intensive care unit. He underwent intubation and mechanical ventilation with supplemental oxygen, but he rapidly developed marked respiratory distress with severe acidosis.

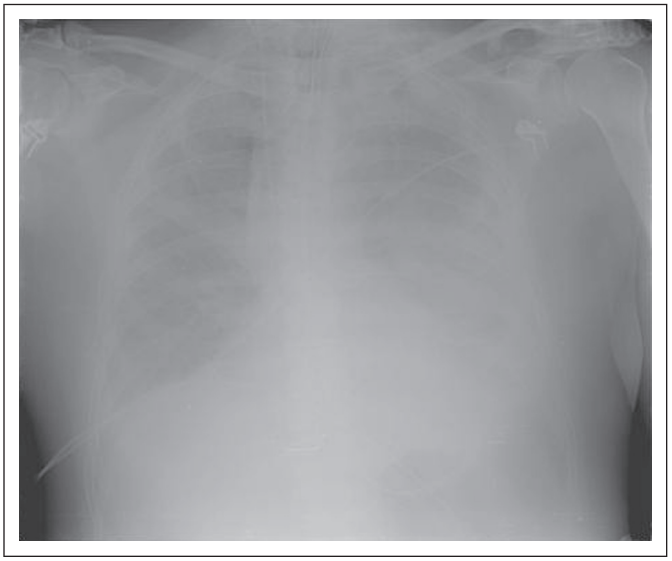

Fig 2.

A first chest x-ray performed two hours after the drug infusion showed bilateral pulmonary infiltrates and initial lower pulmonary lobes hypoventilation. These findings were particularly noted in the lower pulmonary lobes (Fig 1). A subsequent chest x-ray performed three hours later showed a significant worsening of pulmonary hypoventilation and the likely appearance of right pleural effusion (Fig 2). No left ventricular dysfunction was demonstrated on transthoracic echocardiography. Ten hours after the onset of symptoms

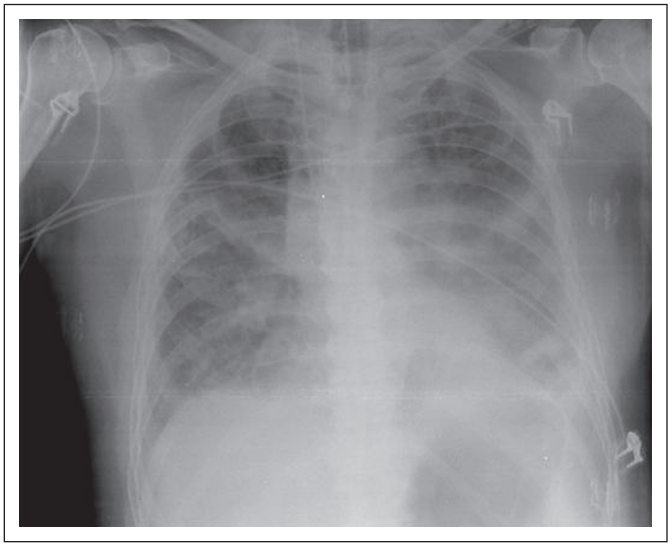

Fig 1.

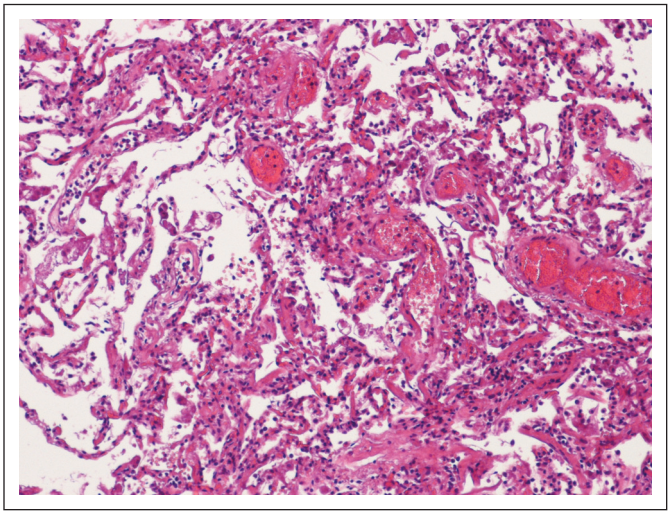

Fig 3.

and after two successive cardiac arrests, the patient died. The autopsy revealed diffuse, acute, alveolar hematic congestion without any accompanying acute cardiac events or other causative conditions (Fig 3).

Discussion

Cetuximab is a chimeric anti–epidermal growth factor receptor monoclonal antibody created by combining the antigen-binding regions of the mouse antibody with the constant region of the human immunoglobulin.[1] Severe infusion reactions have been estimated to occur in 1% to 8% of patients.[2-4] The most common signs and symptoms are chills, fever, urticaria, hypotension, bronchospasm, and other respiratory conditions. For most patients, the reaction is reversible with the use of IV fluids, steroids, antihistamines, bronchodilators, and epinephrine. Most patients who experience a reaction, particularly when the symptoms are mild to moderate, can safely continue the treatment with proper medication and close monitoring.[5,6] However, infusion reactions can occasionally cause death[1] ($< 0.1\%$ of cases).

The pathogenic mechanisms underlying the development of this phenomenon remain to be elucidated. Its early occurrence (during the first infusion in $> 90\%$ of cases) supports the role of an immunoglobulin E–independent mechanism.[5] Atopic history and previous hypersensitivity have been suggested to increase the risk of developing an infusion reaction. However, no definitive data exist about the exact role of these factors.[4] Despite the generally favorable outcome of cetuximab-associated reactions, the potential occurrence of fatal events, as described in this report, warrants the search for reliable risk factors that can facilitate the safe selection of patients as candidates for cetuximab-based treatment.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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