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Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

A rare but severe pulmonary side effect of cetuximab in two patients

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Summary

Cetuximab is a monoclonal antibody that treats malignant disease by inhibiting epidermal growth factor receptor. Many common adverse events have been reported and include skin rashes, infusion reactions, gastrointestinal complaints and headache. Up to now, cetuximab-associated pulmonary toxicity has been rarely reported in the literature. The present report describes two cases with probable interstitial pneumonitis 5–6 weeks after commencing treatment with chemotherapy combined with cetuximab. One patient recovered and the second patient died due to gastrointestinal bleeding 3 weeks after an initial response to steroids.

BACKGROUND

Cetuximab (marketed under the registered trade name Erbitux) is a chimeric (mouse/human) monoclonal antibody which inhibits the epidermal growth factor receptor (EGFR). Through binding to the extracellular domain of EGFR, it interrupts the signalling cascade resulting in inhibition of cell growth and induction of apoptosis. Furthermore, cetuximab decreases matrix metalloproteinase and vascular endothelial growth factor production.¹ It is administered by intravenous infusion for treatment of EGFR expressing metastatic colorectal cancer and squamous cell carcinoma of the head and neck.² Cetuximab-associated pulmonary toxicity has been rarely described in the literature.^{3–4} Here, we report on two patients who acquired an interstitial pneumonia most likely caused by cetuximab, since these patients did not improve despite the initiation of antimicrobial treatment.

CASE PRESENTATION

Case 1

A 61-year-old Caucasian man was admitted to our hospital with dysphagia resulting in a weight loss of 5 kg undergoing treatment for a cT4b cN2c mesopharynx carcinoma diagnosed 2 months ago. Induction chemotherapy with three cycles of docetaxel, cisplatin and 5-fluorouracil was administered. As a complication of this treatment, the patient developed febrile neutropenia without a septic focus and was empirically treated with cefepime. After partial remission, intensity-modulated radiation therapy was administered to the primary tumour including lymph nodes to a total dose of 70 Gy given in daily 2-Gy fractions combined with cetuximab (total six cycles, loading

dose 600 mg, then 400 mg). On admission, the patient had no fever and physical examination revealed an acne-like skin rash of the neck which is a common side effect of cetuximab. Laboratory tests showed an elevated C-reactive protein of 106 mg/l. White blood cell count was normal with 3560/μl. No chest x-ray was performed in the absence of pulmonary symptoms. Gastroscopy showed an erosive bulbitis which was interpreted along with the mucositis within the radiation field, as an additional cause of the dysphagia. The patient was commenced on amoxicillin/clavulanic acid on the assumption of a superinfection within the mesopharynx and on a proton pump inhibitor to treat the erosive bulbitis. In addition, a percutaneous endoscopic gastrostomy (PEG) was placed. A few days later, the patient developed pain in the upper abdomen and the PEG insertion site was slightly erythematous, suggestive of a PEG site infection. A superficial swab revealed growth of *Enterobacter cloacae* (with AmpC expression). Therefore, antimicrobial treatment was switched to ertapenem. Owing to increased infective parameter (C-reactive protein of 165 mg/l), the infectious diseases service was consulted regarding further diagnostic steps and treatment.

Patient 2

The second patient, a 65-year-old Caucasian man, was also admitted to our hospital for commencement of PEG or nasogastric feeding for management of dysphagia. He suffered from both tonsillar squamous cell carcinoma and oesophageal adenocarcinoma. For the former, radiotherapy was administered starting 4 weeks before admission in combination with cetuximab 2 weeks after starting radiotherapy. Carboplatin and taxol were added for treatment

of the oesophageal carcinoma. Four days after stopping cetuximab and carboplatin, the patient developed fever with left renal pain. Physical examination revealed no pathological findings except for dermatitis of the neck which was interpreted as cetuximab-associated skin toxicity. Empiric antibiotic treatment with ceftriaxone was started, assuming a nosocomial pyelonephritis. The infectious diseases service was consulted for advice regarding further management.

INVESTIGATIONS AND TREATMENT

Patient 1

Owing to persistent subfebrile temperatures and previous abdominal pain, nosocomial urinary tract infection or catheter-related blood stream infections were excluded by repeated blood and urine cultures. No ascites or signs of cholecystitis were observed in ultrasound and CT of the abdomen. A subsequent CT of the lung showed ground-glass consolidation in the upper lobe and a small area of consolidation in the inferior lobe of the right lung. Owing to immunosuppression, *Pneumocystis jiroveci* and *Legionella pneumophila* serovar type 1 was excluded by induced sputum (Immunofluorescence stain, Kinyoun stain) and by urinary antigen, respectively. A repeat CT due to persistent fever and development of oxygen desaturation 3 days later showed a massive pleura effusion and a large consolidation with air bronchograms in the upper and lower lobe of the right lung (figure 1A). The pleural effusion was punctured and antibiotic treatment was changed from ertapenem to meropenem. The pleural fluid showed only 610 cells with 55% neutrophils, 7.5% lymphocytes and 22% of monocytes. Microbiology testing was negative. Owing to a high risk of a need for intubation, no bronchoalveolar lavage (BAL) was performed. The clinical constellation of persisting fever in the absence of proven microbial infection, concomitant treatment with a broad spectrum antibiotic and a ground-glass pattern in the CT was not suggestive for bacterial pneumonia; therefore, treatment with oral prednisone 100 mg daily was started.

Patient 2

Pyelonephritis was excluded by ultrasound of the kidney and by repeated blood and urine cultures. Ceftriaxone was changed to piperacillin-tazobactam due to the nosocomial setting. Four days later, the patient developed a productive cough with yellow sputum and dyspnoea. Chest x-ray showed an infiltrate below the right hilum. CT excluded pulmonary emboli and revealed large ground-glass opacities in both lungs (figure 2). Owing to increased dyspnoea 5 days after the onset of fever, a BAL was performed and intravenous trimethoprim/sulfamethoxazole (320/1600 mg) four times a day and oral prednisone (40 mg) twice a day was empirically started due to possible *P jiroveci* pneumonia. BAL showed a total cell count of 100/μl (23% neutrophil granulocytes, 6.5% lymphocytes and 70.5% macrophages) without growth of bacteria, mycobacteria or fungi and immunofluorescent stainings for *P jiroveci* were negative. Molecular analyses of respiratory viruses including adenovirus, rhinovirus, cytomegalovirus, human respiratory syncytial virus, influenza and parainfluenza, were negative. No peripheral eosinophilia was documented.

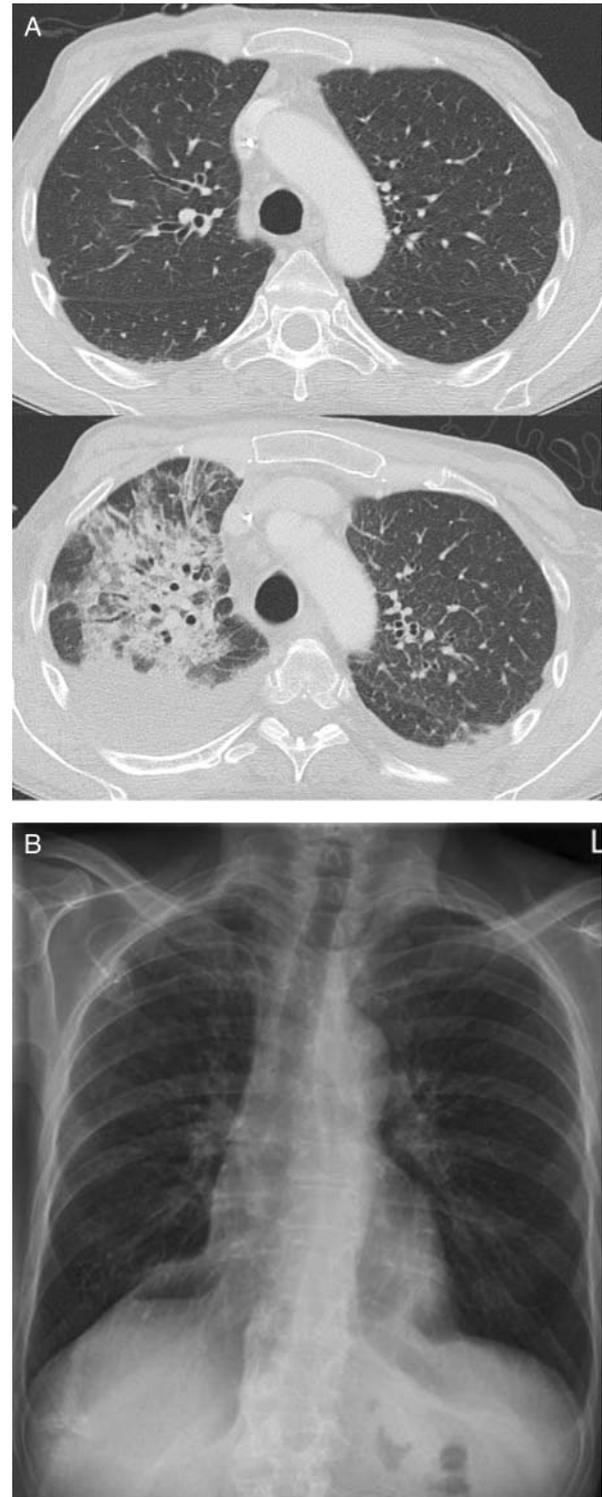


Figure 1 Radiological finding in patient number 1. (A) Two CT scans of the lung 3 days apart showing a rapid progressive infiltrate prior to steroid treatment (attached as TIFF graphic). (B) Conventional chest x-ray 7 days after steroid treatment.

DIFFERENTIAL DIAGNOSIS

Patient 1

Differential diagnosis included bacterial, viral or fungal pneumonia, or toxic pneumonitis due to cetuximab. The lung pathology as demonstrated on CT was clearly outside

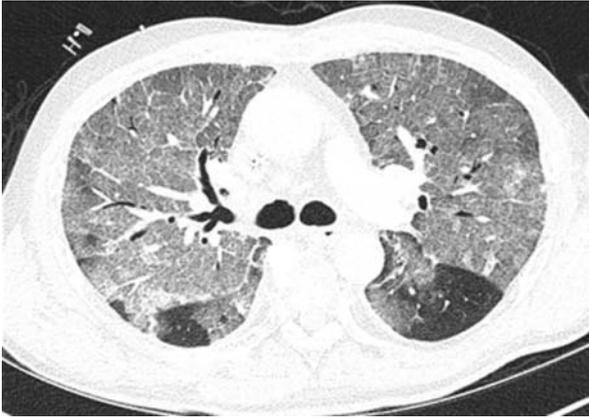


Figure 2 Radiological findings in patient number 2. CT scan of the lungs prior to steroid treatment demonstrates large bilateral ground-glass opacities.

of the radiation fields; thus, irradiation pneumonitis could be excluded.

Patient 2

Owing to administration of cetuximab and taxotere, a toxic pneumonitis was proposed. Differential diagnoses of the pulmonary damage were previous radiotherapy, lymphangitis carcinomatosa or pneumonia due to virus, atypical bacteria or fungi which was unable to be isolated in the BAL.

OUTCOME AND FOLLOW-UP

Patient 1

Fever normalised within 2 days of steroid treatment. C-reactive protein decreased from a maximum value of 126 to 8.6 mg/l in 7 days and chest x-ray was almost normal at that time (see figure 1B). The patient was discharged 10 days after starting steroids.

Patient 2

Within 5 days after starting steroids, symptoms and laboratory findings markedly improved. However, 15 days later, the patient required admission to the intensive care unit due to gastrointestinal bleeding. He developed a severe acute respiratory distress syndrome (ARDS), including a multiple organ dysfunction syndrome and died 5 days later. Autopsy showed bronchitis with diffuse alveolar dysfunction with several small lung metastases of 2 mm (squamous cell carcinoma). Additionally, a thrombotic endocarditis of the mitral valve with ischaemic infarction of the heart, brain, kidney and spleen was reported.

DISCUSSION

Five to 6 weeks after starting treatment with cetuximab both patients presented with fever, shortness of breath and pulmonary ground-glass opacities and consolidation in CT. Interstitial pneumonia was suspected. Whereas in patient 1 the CT-findings were comparable to a cryptogenic organising pneumonia caused by drugs, the ground-glass opacities in patient 2 were similar to an exogenous allergic alveolitis. Whereas no causative pathogen of the pneumonia was found (negative pleura effusion in patient 1,

negative bronchoalveolar lavage in patient 2) and no response to antimicrobial treatment was observed (table 1), toxic pneumonitis due to previous chemotherapy with cetuximab, cisplatin/carboplatin, taxol and/or docetaxel was discussed.

We favoured cetuximab because both patients suffered from active dermatitis coincidentally and developed pulmonary signs and symptoms that started 5–6 weeks after the first dose of cetuximab.

In addition to cessation of cetuximab, further strategies to treat toxic interstitial pneumonitis include symptomatic treatment and the use of corticosteroids.⁴ In both patients, fever, pulmonary signs and C-reactive protein rapidly resolved within a few days after initiation of steroid treatment. Despite an initial improvement of pneumonitis, patient 2 developed gastrointestinal bleeding with subsequent ARDS resulting in death 5 days later. Alveolar damage seen at autopsy could not distinguish between damage due to ARDS after gastrointestinal bleeding, cetuximab side effects or other reasons as the pathological findings were non-specific. Nevertheless, the alveolar damage seemed to be older than 5 days, suggesting cetuximab toxicity. Although not proven due to the non-specific signs and symptoms, we strongly believe that the interstitial pneumonia was related to cetuximab therapy.

Cetuximab is a biological treatment of malignancy which inhibits epidermal growth factor receptor (EGFR). Common adverse events are dermatologic reactions, infusion reactions, gastrointestinal complaints and headache.⁵ Up to now, cetuximab-associated pulmonary toxicity has only rarely been described in the medical literature^{3 4 6} but there are several reports of interstitial fibrosis in patients treated with other EGFR inhibitors such as gefitinib and erlotinib outside of clinical trials. In a retrospective study of Hoag *et al*,⁴ patients with colorectal, lung and head and neck cancer receiving chemotherapy combined with cetuximab had significantly more pulmonary symptoms than patients not receiving cetuximab (10.3% vs 8.3%). In the subanalysis in patients with head and neck cancer, no significant difference was observed (17.9% vs 20.1%). Interestingly, pulmonary side effects in patients with a non-small cell lung cancer were much more common in the cetuximab versus the control group (18.7% vs 12.2%, $p < 0.001$). This may suggest that an underlying lung disease could be a risk factor for pulmonary cetuximab toxicity. Although our patients lacked an underlying lung disease they both received previous radiochemotherapy. However, up to now there have been no published reports to support a potential hypothesis that radiotherapy may be an additional risk factor. Furthermore, our patients received irradiation outside of the areas where the interstitial pneumonitis was seen in CT. In a recently published study from Kang *et al*⁶ low albumin level was identified as a risk factor for developing an adverse pulmonary reaction in patient taking cetuximab, rituximab, trastuzumab or bevacizumab. The low albumin level in our two patients (28 and 24 g/l) supports this hypothesis. Both patients were of Caucasian ethnicity and therefore a genetic causality for the side effects observed cannot be ruled out. For example, it has been shown that Stevens-Johnson syndrome and its related toxic epidermal necrolysis induced by carbamazepine are strongly linked to the HLA-B 1502 allele⁷ and severe

Table 1 Characteristics of our two patients compared to the only patient reported in the literature so far

	Case 1	Case 2	Case 3 (Chua <i>et al</i>) ³
Age (year)	61	55	78
Neoplasia	Mesopharynx squamous cell carcinoma	Tonsillar squamous cell and oesophageal adeno carcinoma	Metastatic colorectal cancer
Radiotherapy	Yes	Yes	No
Chemotherapy	– Docetaxel, cisplatin, 5-FU – Cetuximab/radiotherapy	– Cetuximab/radiotherapy – Taxol/carboplatin	– Bevacizumab, 5-FU, oxaliplatin – 5-FU, irinotecan – Cetuximab, irinotecan
Smoker	Stopped 1 year ago	Stopped 5 months before death	Stopped 60 years ago
Previous lung history	No	No	Minor pulmonary fibrosis
Onset of pulmonary symptoms	– 16 days after last cetuximab dose (400 mg) – 5 weeks after starting cetuximab	– 8 days after last cetuximab dose (450 mg) – 6 weeks after starting cetuximab	– Last dose unknown – 2 months after starting cetuximab
Signs and symptoms	First fever, followed by dry cough and shortness of breath	First fever, followed by cough and shortness of breath	Cough, shortness of breath
CT scan	Ground-glass changes and consolidation predominant in upper and inferior lobe of right lung	Bilateral extensive ground-glass changes	Bilateral patchy ground-glass changes
Bronchoscopy	Not performed	– 100 cells/ μ l (23% neutrophile granulocytes) – Negative for bacteria, fungi, pneumocystis jiroveci, mycobacteria and multiple respiratory viruses	No microorganism was found (microscopy and culture)
Antibiotic treatment	– Amoxicillin-clavulanate 6 days – Ertapenem 7 days – Meropenem 14 days	– Ceftriaxone 2 days – Piperacillin-tazobactam 5 days – Cotrimoxazole 13 days	– Cefotaxime and azithromycin for 6 days
Corticosteroids	100 mg prednisone daily for 7 days→ improvement within 3 days	80 mg prednisone daily for 14 days→ improvement within 6 days	50 mg prednisone daily (unknown interval→ improvement
Control CT scan or radiography	No CT scan after clinical improvement. Recovery on chest x-ray after 10 days	No CT scan because of death	CT scan 3 weeks after hospital admission: improvement
Outcome	Alive	Death 3 weeks later after gastrointestinal bleeding (ARDS, MODS)	Death 4 months later due to pulmonary metastases
Autopsy	Not done	Diffuse alveolar damage, bronchitis	Not done

ARDS, acute respiratory distress syndrome; FU, fluorouracil; MODS, multiple organ dysfunction syndrome.

hypersensitivity reactions caused by abacavir were linked to the HLA-B 5701 allele^{7, 8}.

In summary, we recommend that clinicians should be alert to the possibility of adverse pulmonary reactions if cetuximab treatment has been given in the weeks preceding the onset of pulmonary symptoms. After exclusion of infectious pneumonia, drug-induced toxicity should be considered and treatment with corticosteroids should be promptly started.

Learning points

- ▶ Clinicians should be aware that in patients treated with cetuximab interstitial pneumonia can occur as an adverse reaction of this drug.
- ▶ After exclusion of infectious pneumonia, treatment with corticosteroids should be strongly considered for treatment of cetuximab-associated pneumonia. Rapid improvement of symptoms and signs upon steroid treatment is highly suggestive of drug-associated pulmonary toxicity.

Competing interests None.

Patient consent Obtained.

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