CASE REPORT

Interstitial lung disease secondary to Cetuximab in bladder cancer: an Oncologist's perspective

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SUMMARY

A wide variety of cytotoxic medications cause interstitial lung disease (ILD). For the first time, we describe ILD in an 82-year-old woman with muscle invasive bladder cancer 10 days after receiving cetuximab as part of a novel trial. She had no significant medical history or drug allergies, had good exercise tolerance and a 5 pack-year smoking history. She received neoadjuvant chemotherapy (gemcitabine, cisplatin) with a good response on MRI. She was eligible for a phase 2 trial of cetuximab with chemotherapy and radiotherapy for muscle invasive bladder cancer (TUXEDO), in which the trial arm used cetuximab plus standard chemoradiotherapy to the bladder (64 grey in 32 fractions plus mitomycin and fluorouracil). Ten days after her third infusion of cetuximab, she was presented with type 1 respiratory failure. Thoracic CT scan demonstrated new widespread ground glass change in the lungs. She received high-dose steroids (prednisolone 1 mg/kg), broad spectrum antibacterial cover and non-invasive ventilation. She survived to be discharged with residual respiratory failure.

BACKGROUND

Interstitial lung disease (ILD) is an umbrella term for inflammatory conditions of the lung, which includes acute interstitial pneumonitis (AIP). ILD is diagnosed from clinical, radiological and pathological findings using high-resolution CT (HRCT), bronchoalveolar lavage (BAL) and measurements of Krebs von der Lungen-6 (KL-6), surfactant protein (SP)-A and SP-D levels.¹

ILD can be caused by a multitude of drugs including cytotoxic agents; notable examples include bleomycin, carmustine, busulfan and cyclophosphamide.² In addition, gemcitabine and mitomycin are known to cause ILD.³ Antibodies used in the treatment of cancer also cause ILD.

The monoclonal antibody cetuximab is a radiotherapy sensitizer⁴ and therefore used within a phase 2 trial of cetuximab with chemotherapy and radiotherapy for muscle invasive bladder cancer (TUXEDO) trial (RRK 41314) in addition to gemcitabine, mitomycin and fluorouracil (5FU) in the treatment of muscle invasive bladder cancer.

Cetuximab is a chimeric monoclonal IgG1 antibody to epidermal growth factor receptor (EGFR),¹ licenced and commonly used in K-Ras wild type colorectal cancer (CRC),² non-small cell lung cancer (NSCLC) and head and neck cancer.⁵ A retrospective literature review in 2016 assessed case reports

of ILD associated with cetuximab for CRC and head and neck cancer and found nine of 10 cases resulted in death.⁶ Thus, we want to increase the awareness of the rare but often fatal toxicity of ILD due to cetuximab and emphasise the importance of early recognition and treatment.¹⁷

The number of biological agents used in oncological treatment is increasing; data published in the USA shows that 20% of the products approved by regulatory bodies in the last 5 years are biological agents.⁸ With the increasing use of biological agents, such as immunotherapy and antibody therapy in oncology, it is important that physicians in the acute hospital setting are aware of serious side effects.

This unique case describes likely AIP as a severe adverse reaction within the TUXEDO trial, likely caused by cetuximab when given with 5FU and mitomycin C chemotherapy and concurrent radiotherapy following neoadjuvant gemcitabine and cisplatin chemotherapy for muscle invasive bladder cancer.

CASE PRESENTATION

An 82-year-old Caucasian woman presented with a histologically proven solitary 3 cm left lateral wall grade 3 muscle invasive transitional cell carcinoma of the bladder (pT2cN0) on MRI pelvis. CT whole body confirmed the absence of metastasis (M0) with no reported pulmonary changes. She was well (performance status 0) with no significant medical history or drug allergies. She was not breathless, had good exercise tolerance and lived independently with good family support nearby. She had a 5 pack-year smoking history and smoked between 14 and 24 years of age. She had adequate haematological, hepatic and renal function on blood testing.

She received three cycles of standard neoadjuvant chemotherapy (Cisplatin 35 mg/m² and Gemcitabine 1000 mg/m², day 1 and day 8). She was restaged with a whole-body CT scan and pelvic MRI after completing two cycles and it was seen she had a good response, with no pulmonary changes, so was suitable for radical chemoradiotherapy to the bladder for curative intent.⁹ Gemcitabine is known to cause ILD, and it has been demonstrated (in a mixed cohort of pancreatic, urothelial, biliary tract, lung, ovarian and breast cancers) that the incidence of ILD at 3 months is 1.1%.³

Both baseline CT thorax and post neoadjuvant chemotherapy CT thorax were retrospectively reviewed by an ILD specialist radiologist and the ILD multidisciplinary meeting. Both CT scans of the thorax show evidence of age-related lung

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Figure 1 CT chest abdomen and pelvis with contrast carried out in December 2015 at the diagnosis of bladder cancer demonstrated interstitial thickening with some mild honeycombing at the left lung base.

changes consistent with 'presbyotic lung' (interstitial thickening in a subpleural distribution), alternatively this could represent mild usual interstitial pneumonia (UIP) or non-specific interstitial pneumonia (NSIP) consistent with mild idiopathic pulmonary fibrosis (IPF).¹⁰ (figure 1). This picture is often seen in the elderly and is not of prognostic significance.

Therefore, the temporal sequence of CT images suggests that gemcitabine was not implemented in the cause of her ILD.

She was eligible for the phase 2 TUXEDO, which for the first time used cetuximab plus standard chemoradiotherapy (64 Grey in 32 fractions plus mitomycin 12 mg/m² (day 1) plus 5FU 2.5 g/m² over days 1–5 and 15–20).⁹

She opted to enter the phase 2 study. She gave informed consent for all toxicities, including breathlessness. She went on to receive the loading dose of cetuximab and further weekly

Figure 2 CT pulmonary angiogram carried out 10 days after administration of cetuximab indicate widespread honeycombing.

second and third infusions and subsequently became increasingly breathless. After 10 days of the third infusion, she had type 1 respiratory failure (PO₂ 6.2 on room air, pH 7.5) with oxygen saturations of 70%.

A thoracic CT pulmonary angiogram (CTPA) demonstrated new diffuse and widespread ground glass change with air bronchograms (figure 2).

She was not clinically well enough for spirometry, gas transfer or lung biopsy.^{10 11} Biomarkers of ILD such as KL-6, pulmonary SP-A and SP-D levels were not carried out as per BTS¹¹ guidelines and NICE¹² guidelines, as there was 'no realistic possibility that the additional information will influence management'.^{11 12} However, literature suggests that levels can be helpful in the diagnosis of ILD.¹

The differential diagnosis for the cause of ILD in this case includes viral infection, pulmonary oedema, exacerbation of mild background UIP and diffuse alveolar damage (DAD), the pathological correlate of AIP.

She remained afebrile on admission and throughout her acute illness. She did not have a sustained lymphopenia or neutropenia when reviewing her serial full blood counts retrospectively. Therefore, infective causes of ILD are less likely.

It is well documented that radiotherapy to lungs can lead to ILD. Our patient received standard radical chemoradiotherapy to the pelvis. Mitomycin which is used in this context as a radiotherapy sensitizer and has long been associated with ILD.¹³

She had likely developed a severe rare toxicity from the addition of cetuximab to standard radical chemoradiotherapy, AIP with a probable DAD picture, which is the pathological correlate of AIP. The presentation with a rapidly progressive shortness of breath and acute respiratory failure was typical, as were the radiological features of ground glass change and septal thickening acutely, and subsequently distortion and traction bronchiectasis which her scans demonstrated 1 month later. This radiological picture is associated with a high mortality.⁶

INVESTIGATIONS

CT thorax abdomen and pelvis with contrast carried out at the diagnosis of bladder cancer demonstrated interstitial thickening with some mild honeycombing at the left lung base (figure 1).

CT thorax abdomen and pelvis with contrast carried out following neoadjuvant cisplatin and gemcitabine chemotherapy showed no pulmonary changes.

CTPA carried out 10 days after administration of cetuximab indicates widespread ground glass change (figure 2).

Transthoracic echocardiograms did not show significantly raised right-sided or left-sided pressures.

CT thorax carried out 2 months following acute respiratory failure demonstrates pulmonary fibrosis changes.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for extensive new ground glass opacity is wide; this case highlights the differential in an oncology patient. The likely differential diagnosis includes:

- ▶ chemotherapy (gemcitabine/mitomycin C)
- ▶ monoclonal antibodies (cetuximab)
- ▶ bacterial, viral and fungal infection
- ▶ acute hypersensitivity pneumonitis
- ▶ acute exacerbation of UIP
- ▶ AIP and DAD (secondary to drugs or idiopathic cause)
- ▶ pulmonary haemorrhage
- ▶ smoke inhalation
- ▶ alveolar proteinosis.

TREATMENT

Following clinical assessment for infective causes, with CT imaging, C-reactive protein, blood and urine cultures, our patient was treated with high-dose steroids from day 2 of admission (prednisolone 1 mg/kg orally) and required non-invasive ventilation (continuous positive pressure ventilation (CPAP)) from day 6 when her oxygen requirements escalated from 5 L/min to 15 L/min.

She was too hypoxic and haemodynamically unstable to consider diagnostic lung biopsy, bronchoscopy and lavage for exclusion of PCP (*Pneumocystis jirovecii*) and other atypical infections. However, blood PCP-PCR testing was negative. She also received empirical fluconazole, intravenous piperacillin/tazobactam and then intravenous meropenem from day 1 for 10 days followed by 7 days of oral amoxicillin/clavulanic acid. In addition, she received empirical high dose of cotrimoxazole for the first 10 days. After 14 days of high-dose steroids, the prednisolone dose was reduced to 0.75 mg/kg and to 0.5 mg/kg by day 16 and was then weaned by 5 mg/week and maintained on 20 mg daily.

Regular meetings occurred with family members to counsel them about the irreversible morbidity caused by cetuximab. After 9 days of non-invasive ventilation (NIV), she was supported with 5 L of oxygen.

OUTCOME AND FOLLOW-UP

This patient survived acute type I respiratory failure due to presumed AIP likely caused by cetuximab (non-biopsy proven).

She was rehabilitated on the ward over the period of 1 month. She could mobilise a few steps, with ambulatory oxygen and remained performance status 4 due to her degree of breathlessness. She survived the acute hospital admission and was discharged home with ambulatory long-term oxygen (5 L via nasal speculum) with 24 hours care.

DISCUSSION

We describe severe AIP, a form of ILD likely secondary to cetuximab.

Monoclonal antibodies, such as cetuximab, commonly cause enteritis, mucositis and dermatitis. More specifically side effects of cetuximab include diarrhoea, acneiform skin rash, neutropenia, and electrolyte disturbance.⁵ Cetuximab can cause severe hypersensitivity infusion reactions in up to 3% of patients.¹⁴ The SPC states the rate of acute ILD is up to 0.25% of patients and pulmonary fibrosis is 'rare'.^{5 15} A Japanese cohort demonstrates cetuximab-related acute ILD in 1.2% of patients.¹⁶

Other monoclonal antibodies causing pulmonary fibrosis include erlotinib and rituximab. Erlotinib is a human epidermal growth factor receptor-1/EGFR tyrosine kinase inhibitor used for advanced NSCLC and pancreatic adenocarcinoma. Rituximab is a chimeric anti-CD20 monoclonal antibody that targets B lymphocytes. It is currently used in a variety of B cell non-Hodgkin lymphomas, rheumatological conditions, idiopathic thrombocytopenic purpura and autoimmune haemolytic anaemia.¹⁷

ILD occurs by fibrosis of the interstitium of the lung leading to impaired gas exchange. Evidence suggests that drug-induced ILD is associated with increasing age and the presence of underlying autoimmune disease (such as rheumatoid arthritis).² For many drugs, there is an association with dose and ethnicity; however, there is no known evidence for this with cetuximab.¹²

A pubmed literature search generates many cases of severe and fatal cetuximab-induced ILD.^{6 18–21} Our patient was successfully managed with high-dose steroids and NIV but had long-term

severe breathlessness secondary to fibrosis from AIP. She entered into the TUXEDO trial; therefore, her case was documented as a serious adverse event within the trial.

Due to an early suspicion of and treatment for presumed AIP secondary to cetuximab, she survived. The alternative of immunosuppression-related opportunistic infection was considered and empirical treatment given, but this could not be confidently excluded by bronchial lavage or lung biopsy.

The radiological progression was most typical of AIP and a DAD picture. She developed breathlessness and within 10 days was admitted to hospital and then within 24 hours of admission she was diagnosed with an interstitial lung fibrosis and treatment was delivered swiftly. It has been seen previously that rapid diagnosis contributes to improved survival with AIP.¹⁸

A meta-analysis of 53 published studies assessed 7411 patients receiving either cetuximab plus standard treatment (4436) or standard treatment alone (2569) across colorectal, lung and head and neck cancers. The addition of cetuximab to standard treatment increased the incidence of adverse pulmonary reactions by 2%.^{5 18} Authors commented 'pulmonary adverse reaction' is poorly defined in many studies because breathlessness is a subjective measure. Only two of 4436 patients who received standard treatment plus cetuximab (0.04%) developed ILD. Authors conclude that cetuximab should be given with caution in those with underlying lung disease in the context of radiation.¹⁸

Learning points

- ▶ This case highlights the complexity of interstitial lung disease (ILD) in oncology patients to both the oncologists and physicians alike.
- ▶ While there are multiple chemotherapy drugs together with radiotherapy implemented in the cause of the ILD in this case, due to the temporal nature of events, we hypothesise that cetuximab is the most likely causative agent.
- ▶ Biological therapies such as cetuximab should be strongly considered as part of the differential diagnosis in oncology patients. Cetuximab is increasingly being used in a variety of settings in oncology, such as head and neck cancer, colorectal cancer, and in this case as a novel treatment in muscle invasive bladder cancer.^{8 22}

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