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Epidermal growth factor receptor tyrosine kinase inhibitor: both the culprit and the solution

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Case history

A 63-year-old gentleman, who was an ex-chronic smoker of 40 pack-year, presented with dry cough for 3 months in November 2012. His past medical history was unremarkable. He had chest X-ray done in general out-patient clinic which showed left hilar opacity, left lower lobe collapse and left pleural effusion. He was then referred to the respiratory clinic in Queen Mary Hospital for management. He had contrast computer tomography of the thorax done which showed a 3.7x3.5x5cm mass with necrosis at left infra-hilar region and multiple lytic lesions in T8, T11 vertebral bodies and left 8th rib. Diagnostic pleural tapping was performed and it revealed exudative pleural effusion with negative microbiological investigations. Pleural fluid cytology revealed metastatic carcinoma but it was inadequate for tests on epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangement. Bronchoscopic assessment showed that the left lower lobe apical segment was completely blocked by tumorous growth. Endobronchial biopsy and bronchoalveolar lavage confirmed that diagnosis of adenocarcinoma of pulmonary origin by morphology and immunohistochemistry. Molecular studies found activating EGFR mutation at L858R in exon 21 of the EGFR gene. Therefore, he was managed as stage IV (M1b) adenocarcinoma of lung with left malignant pleural effusion and bone metastases.

He received palliative radiotherapy to lower thoracic spine 20 Gray for 7 days while the left lung tumor and rib metastasis were not included or otherwise radiation field would be too extensive. He was then started on Gefitinib

(Iressa®) on 6th December 2012. He had symptomatic and radiological improvement, upon reassessment 7 weeks after starting Gefitinib.

He was admitted to medical ward on 8th February 2013, which was around 2 months after starting on Gefitinib. He presented with acute onset of dyspnoea for 2 days. There was fever, cough and mucoid sputum. Travel and contact history was unremarkable. On admission, he showed signs of respiratory distress and required 50% mask to maintain oxygen saturation at 91%. His blood pressure was stable and his body temperature was 37.4°C. Investigations on admission showed leucocytosis with neutrophilia. Arterial blood gas showed type I respiratory failure with pO_2 7.3 kPa while he was on 50% mask. Liver and renal function tests were normal. Chest X-ray revealed new ground glass infiltrate bilaterally especially over right lung and increase in left pleural effusion (Figure 1). Microbiological investigations including sputum bacterial culture, acid fast bacilli smear; nasopharyngeal aspirate for respiratory viruses; blood culture and urine legionella antigen were all negative. Urgent computer tomography showed bilateral ground glass opacities and left pleural effusion (Figure 2). The differential diagnoses include infection, radiation pneumonitis, TKI-related pneumonitis and progression of lung cancer.

He had ultrasound-guided drainage of left pleural effusion for symptomatic relief. Gefitinib was stopped on admission. Empirical broad-spectrum antibiotics with Timentin and Azithromycin were started. We discussed the case with oncologist and confirmed that lung tissue was not covered during radiotherapy to lower thoracic spine. But he still had high oxygen requirement despite the above treatment. Systemic steroid with pulse methylprednisolone 500 mg was started 3 days after admission and was given for total 5 days. He showed clinical and radiological improvement with steroid treatment and the steroid was tapered down to oral prednisolone 50 mg daily for 3 days. He was discharged one week after the steroid treatment. A 3-month tapering course of steroid was given.

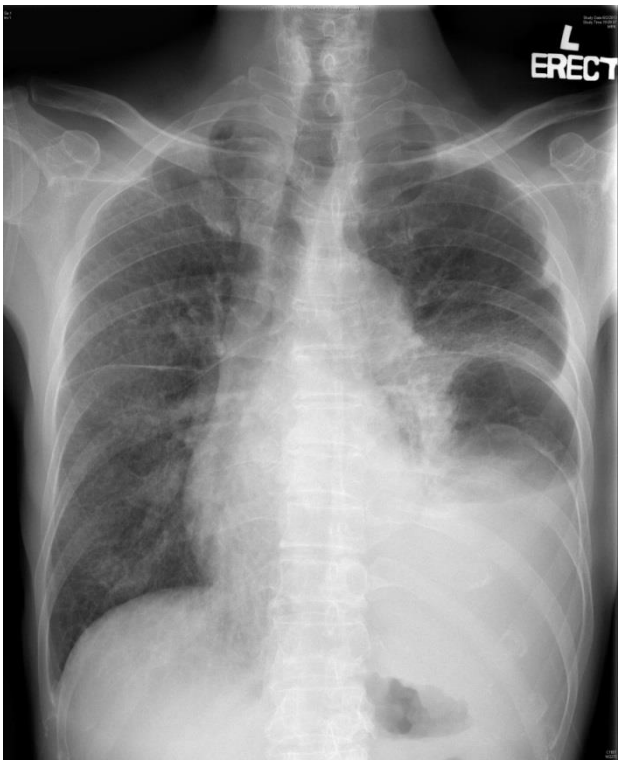

Figure 1. CXR on admission, showing new ground glass infiltrate bilaterally especially over right lung and increase in left pleural effusion

He then received pemetrexed and cisplatin for 4 cycles as second line treatment. But his disease progressed despite chemotherapy. He declined further chemotherapy as he could not afford financially. He developed multiple brain metastases presented with progressively worsening slurring of speech and received whole brain irradiation at 20Gy/5fr. After discussing with patient and family, they agreed to start afatinib 30 mg daily with steroid cover as third line treatment knowing that there is increased risk of TKI-related pneumonitis. But his condition continued to deteriorate and he developed aspiration pneumonia while he was staying in the palliative medical unit and subsequently died of pneumonia.

Discussion

Lung cancer is the commonest cancer in men and the third commonest in women, after breast cancer and colorectal cancer(1). It accounted for 16.0% of new cancer cases in 2013. In2013, there were 4631 new cases of lung cancer, with 2994 cases of males and 1637 cases of females. The age-standardized incidence rates were 51.0 for male and 24.3 for female per 100000 standard population.(1) For non-small cell lung cancer, EGFR is the most common molecular target and identification of this target significantly changes the paradigm in lung cancer treatment. In the PIONEER study, which included 7 Asian countries and regions, EGFR mutation was positive in around 50% of the patients, with exon 19 deletion and L858R mutations being the most common ones.(2)

There are 3 commercially available EGFR tyrosine kinase inhibitors (EGFR TKI) in Hong Kong, with the “first generation” erlotinib and gefitinib and “second generation” afatinib. Though EGFR-TKI are shown to be effective in treating lung cancer expressing sensitizing EGFR mutations, adverse effects do occur while drug related pneumonitis is the most serious one. In the IPASS study, 2.6% (n=16) of the patients in the Gefitinib arm had interstitial lung disease events while 3 out of 16 of these patients died of this adverse reaction.(3) Ethnicity is one of the factor affecting the occurrence of this adverse reaction, with it being more common in Japanese.(4) Other risk factors of EGFR-TKI related pneumonitis include male sex, being a smoker, type of EGFR-TKI (More common for gefitinib), older age, pre-existing idiopathic pulmonary fibrosis, poor performance status, concurrent cardiac disease and previous radiotherapy to lung. The presentation of EGFR-TKI related pneumonitis is non-specific and the common symptoms include cough, fever, dyspnea and hypoxemia. 75% of the cases occur within 3 months of drug use and the majority occur within 4 weeks. (6) EGFR-TKI related pneumonitis is one of the most common cause of discontinuation of EGFR-TKI and it is a potentially fatal complication. (4) The occurrence of EGFR-TKI related pneumonitis may be partly related to the role of EGFR. EGFR signaling pathways help coordinate the process of recovery from lung injury by stimulating epithelial repopulation and restoration of barrier integrity. In a rodent model of bleomycin-induced pulmonary fibrosis, treatment with gefitinib was shown to augment fibrosis.(10) Therefore, inhibition of EGFR signalling by gefitinib could impair the repair of and, thereby, exacerbate pulmonary injury, especially in patients with pulmonary comorbidities(5-6).

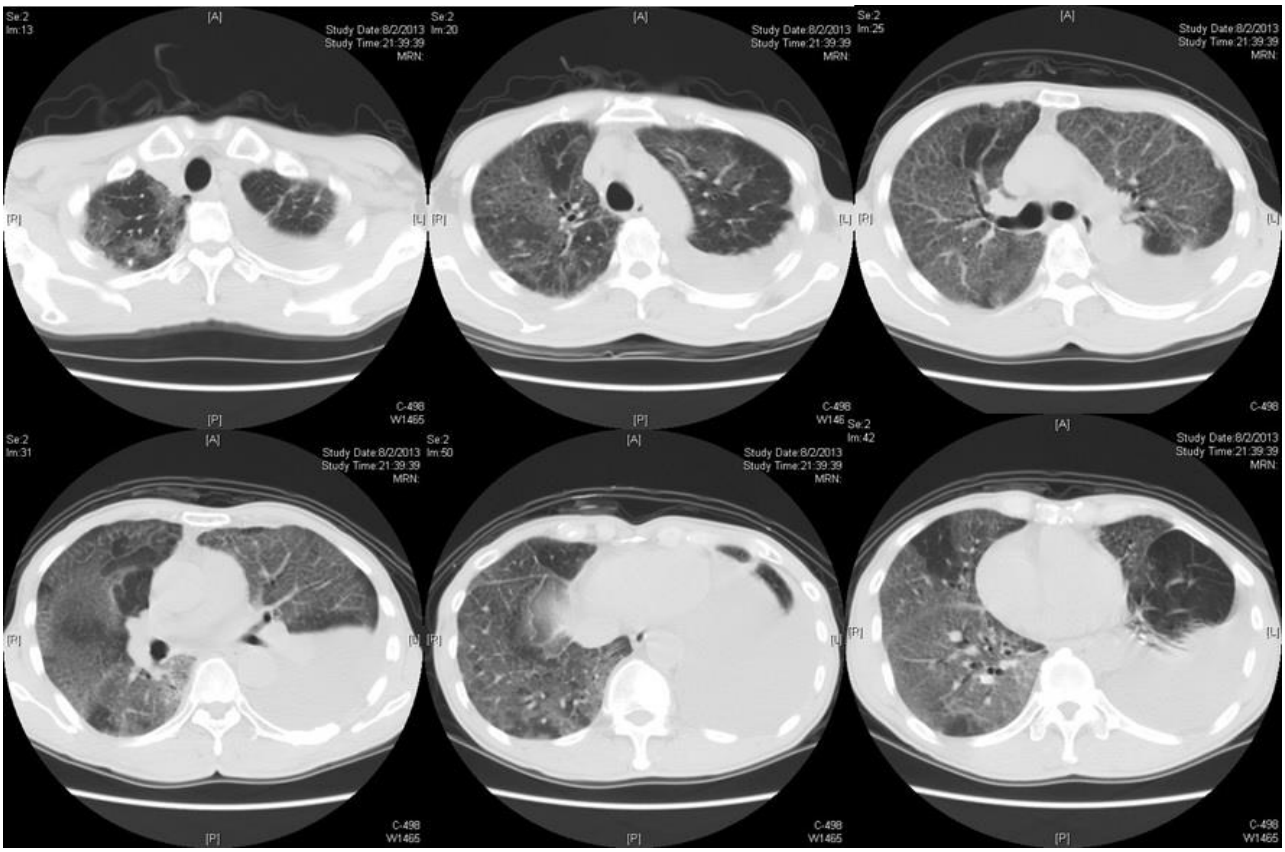

Figure 2. Computer tomography on admission showed bilateral ground glass opacities and left pleural effusion.

There are different histological and radiological variants for EGFR-TKI related pneumonitis and they are summarized in table 1.(6) However, it is not easy to diagnose this condition as the symptoms and signs are non-specific. Also, the radiological pattern is suggestive but non-specific for drug-related pneumonitis. It is possible to have inter-current infection and patients may have radiotherapy before start of EGFR-TKI. Furthermore, patients often run a rapidly deteriorating clinical course and are usually in respiratory failure within days, and with the background of palliation as the primary goal of management for such patients with disseminated cancer, the undertaking of bronchoscopy with attempts of lung tissue sampling or alveolar lavage is sometimes considered too risky or inappropriate, with risk of incurring further harm or need of mechanical ventilation. . Based on our experience, it is often

impossible to perform proper lung function test for these patients to document the severity of gaseous exchange impairment and most of them are diagnosed based on typical clinical (temporal relationship with drug exposure and development of symptoms, exclusion of alternative diagnoses) and compatible radiological features. Clinicians taking care of patients on EGFR TKI for lung cancer should stay highly vigilant on any new symptoms or subtle radiological changes in order to make an earlier diagnosis for timely management. The management of EGFR-TKI related pneumonitis includes supportive treatment and discontinues the EGFR-TKI. Corticosteroid has been used to treat EGFR-TKI related pneumonitis but the evidences are mainly from retrospective series. The reported regime: is intravenous methylprednisolone 1 gram per day for 3 days, then of oral prednisolone 60 mg per day and decrease by 10 mg per week.(7) According to literatures, successful use of erlotinib in a patient who developed gefitinib-related pneumonitis is reported with concurrent use of prednisolone 10 to 30mg per day with the EGFR TKI, with or without gradual tapering the steroid to lowest dose.(8-9)

Conclusion

EGFR-TKI related pneumonitis is a infrequent but severe adverse effects of EGFR-TKI. The diagnosis relies on typical temporal relationship between commencement of the drug and the presentation, compatible radiological features, proper workup for alternative causes and response towards drug withdrawal with or without steroid therapy. Steroid treatment has been used to treat this condition with success, though evidences are from retrospective series only. For patients who developed pneumonitis on one EGFR-TKI may tolerate another EGFR-TKI, at least with steroid cover.

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Patterns	**Radiological features**
Diffuse alveolar damage	Patchy/Confluent ground-glass opacity Bilateral consolidation involving the dependent area
Bronchiolitis obliterans	Patchwork of regions of differing attenutaion
Organizing pneumonia	Multiple patchy alveolar opacities with peribronchial and peripheral distribution
Hypersensitivity pnuemonitis	Poorl defined centrilobular nodules a Bilateral ground-glass opacity Lobular areas of decreased attenuation and vascularity
Interstitial pneumonia	Subpleural ground-glass opacity Reticulation Traction bronchiectasis
Progression of idiopathic pulmonary fibrosis	Progression of reticular shadow with interlobar septal thickening, architectural distortion with traction bronchiectasis, honeycombing and ground-glass opacity

Table 1. Subtypes of EGFR-TKI related pneumonitis and their radiological features