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MINI REVIEW

Drug-induced interstitial lung disease in tyrosine kinase inhibitor therapy for non-small cell lung cancer: a review on current insight

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Abstract
Purpose With recent advances in targeted therapy such as tyrosine kinase inhibitor (TKI) therapy for non-small cell lung cancer (NSCLC), pulmonary toxicity has emerged as a problem. The recognition of common CT findings and patterns of TKI-induced interstitial lung disease (ILD) is mandatory for achieving a timely diagnosis and for the appropriate management of this condition. Therefore, familiarity with this complicating ILD is crucial.
Methods We reviewed all published literature in the English language regarding the ILD among NSCLC patients receiving TKIs.
Results The previous reports focused on the incidence, mortality rate, and risk factors of TKI-induced ILDs. This review elaborates on the diverse CT findings and predominant patterns of ILDs associated with TKI therapy. Emphases will be given on the role of CT, in particular, for the diagnosis of the subacute or chronic appearance of ILDs. This review also offers information about the pathogenesis and risk factor for the development of TKI-induced ILD. Representative cases will be presented as a pictorial review.
Conclusions It is important to recognize the various patterns of TKI-induced ILDs, which increase in incidence with the introduction of diverse types of molecularly targeted agents. Poor prognoses are expected when there is a short interval from the initiation of target therapy to the onset of ILD, acute interstitial pneumonia pattern of ILD, and preexisting pulmonary fibrosis.

Keywords Tyrosine kinase inhibitors · Drug-associated interstitial lung disease · Pulmonary toxicity · Gefitinib · Erlotinib · Sorafenib

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Introduction

Recent advances in our understanding of cancer biology have ushered in a new era of molecular-targeted therapy, and the current advent of tyrosine kinase inhibitors (TKIs) for the treatment of advanced non-small cell lung cancer (NSCLC) has shown significant improvements on response rate (RR) and progression-free survival (PFS) with acceptable toxicity over cytotoxic agents with their unique mechanism of action on epidermal growth factor receptor (EGFR) [1, 2].

Since the first report of gefitinib-associated interstitial lung disease (ILD) from Japan [3], ILD associated with the use of molecularly targeted agents has become the focus of considerable attention. As is true with most cases of drug-induced ILD, the diagnosis of chemotherapy-induced ILD may prove difficult to confirm. The mode of onset (acute or insidious) of clinical features is variable, and ILD may develop during the initial cycle of treatment, or even some years later. Although chest radiography is frequently the

first diagnostic imaging study conducted, computed tomography (CT) is more sensitive in terms of detecting subtle parenchymal diseases. In particular, CT is the most commonly employed imaging tool for the evaluation of tumor response, by applying the response evaluation criteria in solid tumors (RECIST). Thus, patients usually receive scheduled follow-up CT scans. In this way, the presence of pulmonary toxicity can also be readily evaluated on these CT images, not to mention tumor response evaluation. Therefore, thorough knowledge regarding the various CT manifestations of TKIs-induced ILD is essential for the early recognition and management of the drug-induced pulmonary toxicity.

Previous reports [4–13] regarding the occurrence of ILD among NSCLC patients receiving TKIs have dealt narrowly with fatal cases being encountered in the acute phase of drug-induced ILD. Sequential imaging changes over time or the interrelationship of the drug-induced ILD with preexisting ILD have yet to be well documented. Moreover, given the fact that the continuous administration of cytostatic TKIs over a prolonged time period is required for their treatment effect [14, 15], the early recognition of the TKI-induced ILDs and their appropriate management are important. This article elaborates on the diverse CT findings and predominant patterns of ILDs associated with TKI therapy. Emphases will be given on the role of CT, in particular, for the diagnosis of the subacute or chronic appearance of ILDs.

Clinical features and incidence rates

The clinical manifestations of TKI-induced ILD are nonspecific and include cough, fever, dyspnea, and hypoxemia [16]. The patterns and severity of clinical manifestations may differ, depending on the patient's underlying illness and the relevant drug factors [17]. Additionally, the time to onset of pulmonary complications is somewhat unpredictable. Although it was reported that in >75% of cases, the complications occur within 3 months of drug use, the majority of these complications do arise within 4 weeks of the therapy [18]. In another detailed analysis on 408 cases of ILD among the 50,005 patients receiving gefitinib, the median time to onset of ILD was 24 days in the Japan group and 42 days in the US group [19]. Its clinical manifestations appear to be severe, occasionally culminating in acute or life-threatening conditions [3, 4, 20–23].

Gefitinib (Iressa®, AstraZeneca, UK) is an epidermal growth factor receptor (EGFR) TKI. Gefitinib is recognized as a relatively safe oral agent, and most commonly reported toxicities associated with its usage are mild and self-limiting diseases, including eczema and diarrhea. With regard to pulmonary toxicity, a significant number of reports have illustrated various patterns of pulmonary toxicity (Table 1). The frequency of ILD in the Japanese series was reported to range between 2.4 and 8.3% in previous clinical trials [6–9, 24], which is higher than that (<1%) observed in the rest of the world [17, 25]. Specific increased genetic susceptibility to ILD development among

Table 1 Reported incidence, mortality rate, and risk factors of gefitinib-induced interstitial lung disease from clinical trials conducted in Japan

Year	Study group	Period	*n*	No. cases ILD (%)	Mortality (%)	Onset	Risk factors
2004	WJTOG [10][a]	2002/8–2002/12	1,976	64 (3.2%)	25 (1.3%)	NA	Preexisting pulmonary fibrosis, male, smoker
2004	NCCH [9][b]	2002/7–2002/12	112	6 (5.4%)	4 (3.6%)	Acute	Preexisting pulmonary fibrosis
2005	JMTO [24][c]	2002/7–2003/2	399	33 (8.3%)	17 (4.3%)	NA	Preexisting pulmonary fibrosis, decrease of serum albumins, concomitant radiotherapy, absence of history of chemotherapy
2005	OLCSG [7][d]	2000/11–2003/10	330	15 (4.5%)	8 (2.4%)	NA	Preexisting pulmonary fibrosis, poor PS, prior thoracic irradiation
2006	WJTOG [6][a]	2002/8–2002/12	1,976	70 (3.5%)	31 (1.6%)	31 d (18–50)	Preexisting pulmonary fibrosis, male, smoker
2010	OLCSG [8][d]	2000/11–2003/10	330	8 (2.4%)	5 (1.5%)	13 d (4–23)	Preexisting pulmonary fibrosis, poor PS

PS performance status, *NA* not applicable, *d* day

[a] The West Japan Thoracic Oncology Group

[b] National Cancer Center Hospital

[c] The Japan-Multinational Trial Organization

[d] The Okayama Lung Cancer Study Group

Table 2 Reported individual cases of erlotinib-associated interstitial lung disease

Case	Year	Sex	Age	Smoke	Underlying comorbidity	Previous treatment	Onset	Respiratory symptom	Treatment	Outcome	Pathology
1 [12]	2007	M	66	Ex-smoker	No PF	Chemo	5 d	Mild fever, dry cough	Steroid	Improved	NA
2 [12]	2007	F	46	Nonsmoker	No PF	No	6 d	Mild fever, dry cough, short of breath	Steroid	Improved[a]	NA
3 [5]	2007	M	60	Ex-smoker	PF	op	4 w	Dyspnea, hypoxemia	Steroid	Death	DAD
4 [4]	2007	M	55	Smoker	COPD	chemo	2 m	Nonproductive cough, severe dyspnea after 2 ws	Steroid (2 ws later)	Death	DAD (after 3 ws)
5 [51]	2009	M	60	Smoker	No PF	chemo	9 d	Exertional dyspnea	Steroid	Improved	NA
							24 d	Dyspnea, dry cough	Steroid	Improved	Interstitial pneumonia
6 [13]	2010	M	63	Nonsmoker	No PF	chemo	7 w	Dyspnea, progressive respiratory failure	Steroid	Improved	NA
7 [11]	2010	M	53	Smoker	No PF	chemo	3 w	Cough, fever	Steroid	Improved	NA

PF pulmonary fibrosis, *NA* not applicable, *DAD* diffuse alveolar damage, *chemo* chemotherapy, *op* surgery, *d* day, *w* week

[a] Patient died of *Klebsiella* sepsis

the Japanese population may be one reason for the disparity of ILD occurrence rates [17].

Erlotinib (Tarceva®, Roche, Switzerland) is another orally available EGFR-TKI. The reported incidence of ILD was less than 1% in erlotinib pivotal trials [26]. A phase III trial TRIBUTE [27] reported five severe ILD-like events in the erlotinib arm of 526 patients (1.0%), versus one event in the placebo arm of 533 patients (0.2%). All ILD-like events proved fatal. In another report with 3,320 patients, drug-induced lung diseases were noted in 125 patients (3.8%), and the mortality rate was reported to be 0.8% [28]. A recent study from Japan [8], which compared the incidence and pattern of ILDs during erlotinib and gefitinib treatment, demonstrated that the incidence of severe erlotinib-induced lung disease has not been high as compared with that of gefitinib, despite the lack of any detectable statistically significant difference. In patients for whom concrete case-based clinical information is available (Table 2), in contrast to gefitinib-related ILD, all patients except one improved gradually after the discontinuation of erlotinib treatment and steroid therapy.

Sorafenib (Nexavar®, Bayer, Germany) is an oral multikinase inhibitor which targets the inhibition of both tumor growth and angiogenesis [29]. Nowadays, as an optional treatment in NSCLC, it is being evaluated in several phase III studies [30]. It was reported that four patients among approximately 2000 Japanese patients treated with sorafenib had interstitial pneumonia [31].

Table 3 CT Features of molecularly targeted agent-induced interstitial lung disease

Patterns	Radiographic manifestations on CT
Diffuse alveolar damage (DAD)	Patchy or confluent GGO
	Bilateral areas of consolidation involving mainly the dependent lung regions
Bronchiolitis obliterans (BO)	Patchwork of regions of differing attenuation representing obliterative small-airways disease
Cryptogenic organizing pneumonia (COP)	Multiple patchy alveolar opacities with peribronchial and peripheral distribution
Hypersensitivity pneumonitis (HP)	Poorly defined small centrilobular nodules
	Bilateral GGO
	Lobular areas of decreased attenuation and vascularity
Interstitial pneumonia (NSIP or UIP form)	Widespread subpleural GGO with associated reticulation and volume loss, traction bronchiectasis and bronchiolectasis
	May be diffuse or involve mainly the lower lung zones
Progression of underlying PF	Obvious progression of reticular attenuation with interlobular septal thickening, architectural distortion with associated traction bronchiectasis, a honeycomb pattern, and GGO

GGO ground-glass opacity, *NSIP* nonspecific interstitial pneumonia, *UIP* usual interstitial pneumonia, *PF* pulmonary fibrosis

Risk factors

As in cases associated with conventional anti-neoplastic drugs [17], preexisting pulmonary fibrosis has been regarded as a risk factor for the development of ILD in targeted therapy [6–9, 24]. Other risk factors include male sex, a history of smoking, poor functional status, concomitant radiation therapy, absence of chemotherapy history, and a reduction in serum albumins. According to a study conducted by the West Japan Thoracic Oncology Group (multivariate analysis, a retrospective survey from 1976 patients) [6, 10], the predictive risk factors for the development of ILD were as follows: male, smoking, and the existence of idiopathic pulmonary fibrosis. Hotta et al. [7] demonstrated that a short interval from the initiation of gefitinib treatment to the onset of ILD, an acute interstitial pneumonia pattern, and the presence of preexisting pulmonary fibrosis are all associated with poor prognosis. In general, favorable outcomes (marked improvement in symptoms and radiologic signs) are observed upon the immediate cessation of target agent and when corticosteroids were administered as a management regimen.

Pathogenesis

The pathogenesis of TKI-induced pulmonary toxicity may be explained by dividing the mechanism into acute and chronic processes. A histopathologic finding commonly found in the acute process is diffuse alveolar damage (DAD) with hyaline membrane formation [5]. DAD initially manifests as an acute exudative phase caused by alveolar and bronchial epithelial injuries, occasionally followed by a chronic reparative process. According to the original hypothesis regarding the pathogenesis of pulmonary fibrosis [5], acute injury appears to progress to chronic inflammation, aided by T-lymphocytes and macrophages. Continued exposure to an antigen or the failure

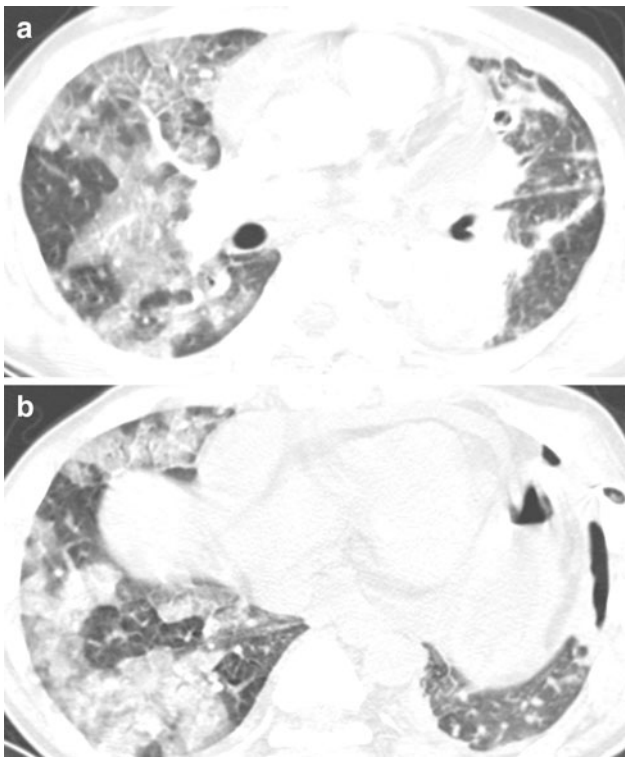

Fig. 1 Diffuse alveolar damage pattern of drug-induced lung disease; a 40-year-old nonsmoking man with stage IV adenocarcinoma of the lung. Thirteen days after gefitinib treatment, the patient complained of dyspnea. Gefitinib treatment was withheld. After 2 days, the patient developed a fever and chills, and antibiotic therapy was initiated. CT scans (5.0 mm section thickness) obtained at levels of bronchus intermedius (**a**) and liver dome (**b**), respectively, show extensive and patchy bilateral areas of consolidation and ground-glass opacity. The patient expired on the following day

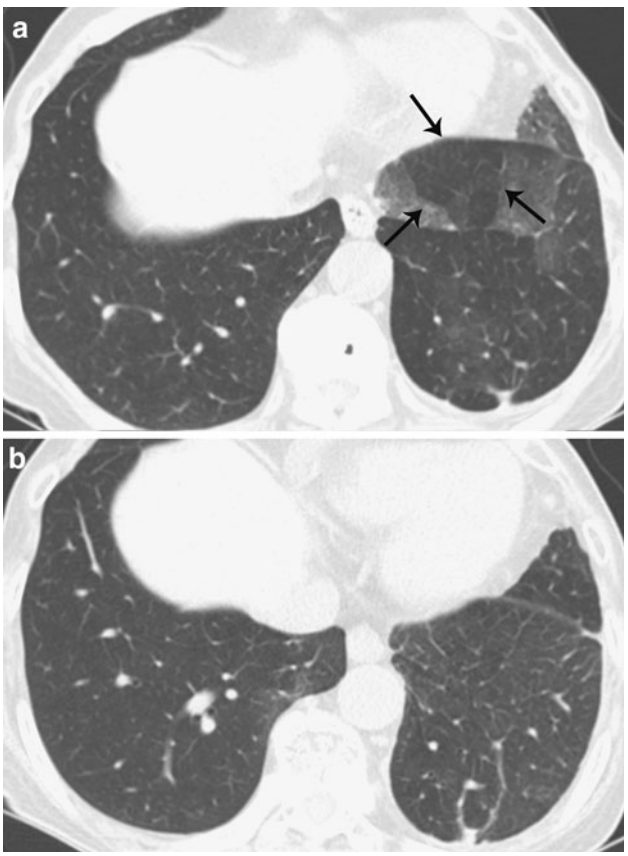

Fig. 2 Bronchiolitis obliterans pattern of drug-induced lung disease; a 59-year-old nonsmoking woman with stage IV adenocarcinoma in the left lower lobe. **a** After 23 days of erlotinib treatment, follow-up CT scan (2.5 mm section thickness) shows patchy areas of differing attenuation with mosaic perfusion (*arrows*). At that time, she denied any respiratory symptoms. Because pleural seeding and lung-to-lung metastasis (not shown here) were documented, erlotinib therapy was discontinued. **b** Fifty days after cessation, radiologic findings of ILD were definitely improved without any treatment

of lungs' intrinsic anti-inflammatory mechanisms has been suggested as a cause of persistent inflammation. Chronic inflammation stimulates the ability of fibroblasts to migrate, proliferate, and produce the extracellular matrix, thus leading to parenchymal fibrosis [32].

However, this original idea has been challenged by a new concept suggesting that the inappropriate regeneration of the sequentially injured epithelium is sufficient to stimulate fibroblasts, without the need for ongoing inflammation [33]. This concept implies that alterations in the epithelial cells function as a trigger for fibrogenesis. One article [34] supports this theory by demonstrating that the blockage of EGFR-dependent epithelial proliferation by EGFR-TKIs augments pulmonary fibrosis. One of key initiating factors for the development of ILD is likely to be the apoptosis of non-neoplastic type I and II pneumocytes [35]. Mitochondrial-mediated apoptotic pathways, which are activated in the lung tissues of patients suffering from idiopathic interstitial pneumonia, may be involved in the pathophysiology of the disease [36]. While EGFR signaling probably represents yet another potential mechanism that helps to coordinate the process of recovery from lung injury by stimulating epithelial repopulation and restoration of barrier integrity [37], it is possible that EGFR inhibition, such as is seen with gefitinib therapy, will at least partially impair the ability of pneumocytes to respond to lung injury.

CT features

The CT features of ILDs associated with the use of drugs should be assessed with regard to the distribution and pattern of each parenchymal lesion, including ground-glass opacities (GGO), airspace consolidation, reticular lesions, small centrilobular nodules, interlobular septal thickening, honeycombing, and traction bronchiectasis. These features are observed in a patchy distribution, usually a bilateral one.

A single chemotherapy agent can be associated with multiple injury patterns [16]. In most situations, the clinician relies on the temporal relationship between the administration of chemotherapeutic agents and the onset of lung injury, along with the exclusion of other potential causes, particularly infections and metastatic disease [38].

Taking into consideration the predominant pattern and distribution of lung abnormalities, the CT features of target agent-related ILDs can be classified into six categories of disease (Table 3): (a) diffuse alveolar damage (DAD) or

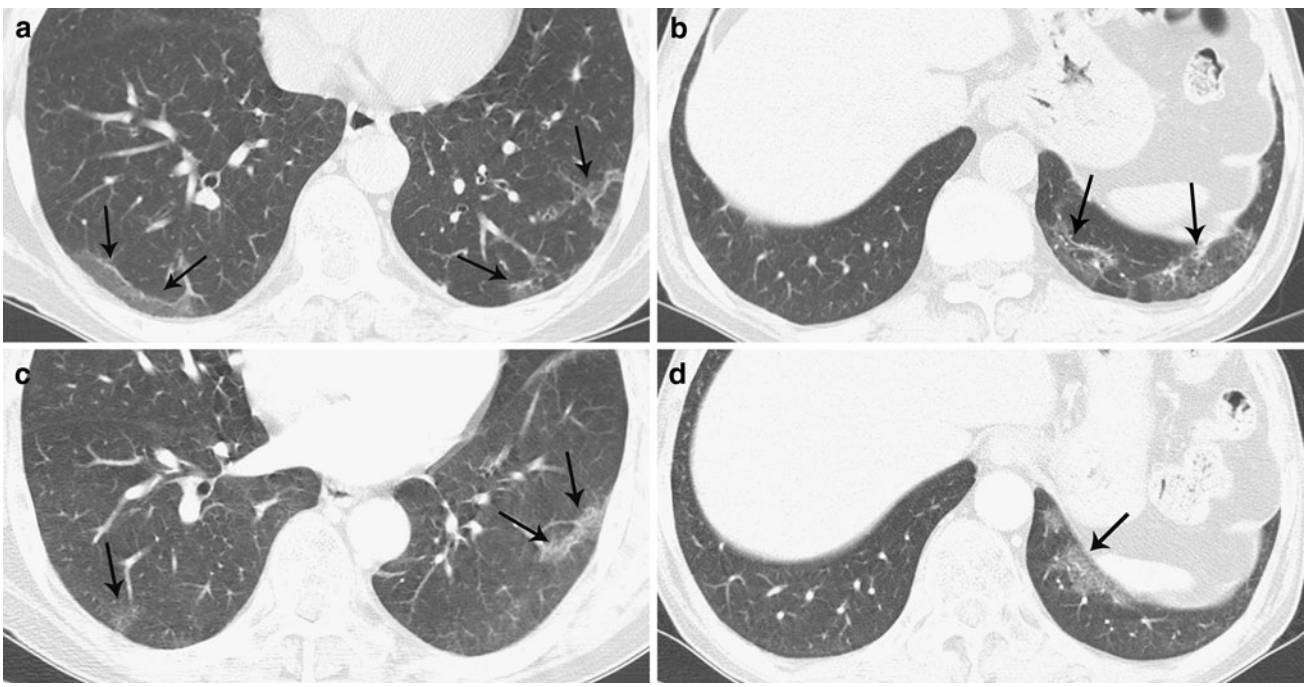

Fig. 3 Cryptogenic organizing pneumonia pattern of drug-induced lung disease; a 69-year-old smoker male with stage IV squamous cell carcinoma receiving erlotinib therapy. Patient complained of cough and dyspnea, while he was on erlotinib therapy for 55 days. CT images (2.5 mm section thickness) obtained at levels of ventricle (**a**) and liver dome (**b**), respectively, show new, patchy area of ground-glass opacity (*arrows*) with subpleural predominance in the bilateral lower lobes. Erlotinib therapy was continued, because the patient was well tolerated. Two-month follow-up CT scans (not shown here) without any treatment demonstrated obvious improvement of lung lesions. **c, d** Four-month follow-up CT scans obtained at similar levels to **a** and **b**, respectively, show subpleural ground-glass opacity (*arrows*). Due to the progression of primary disease (not shown here), erlotinib therapy was discontinued

acute interstitial pneumonia, (b) bronchiolitis obliterans (BO), (c) cryptogenic organizing pneumonia (COP) or COP-like pattern, (d) hypersensitivity pneumonitis (HP), (e) interstitial pneumonia of either nonspecific interstitial pneumonia (NSIP) or usual interstitial pneumonia (UIP) pattern, and (f) progressive disease of underlying ILD.

Diffuse alveolar damage (DAD), which corresponds clinically to adult respiratory distress syndrome, is one of the most common histologic manifestations of pulmonary drug toxicity [39]. DAD manifests as diffuse bilateral GGO and regions of consolidation mainly involving the dependent lung regions on CT scans (Fig. 1) [40]. This disease pattern is reported in gefitinib-treated patients. In the early exudative phase, patchy areas of bilateral GGO are noticed often with some sparing areas of individual lobules, producing a geographic appearance [41]. The areas of GGO rapidly become confluent and may be associated with smooth linear opacities, resulting in a crazy-paving pattern. With further progression, areas of consolidation may predominate. In the organizing phase, architectural distortion, traction bronchiectasis, cysts, and reticular opacities can be identified [42].

Bronchiolitis obliterans (BO), also referred to as constrictive bronchiolitis, is a condition characterized histologically by submucosal and peribronchiolar fibrosis with consequent bronchiolar narrowing or obliteration of the corresponding bronchiolar lumen [43, 44]. Under this condition, high-resolution CT (HRCT) scans obtained at

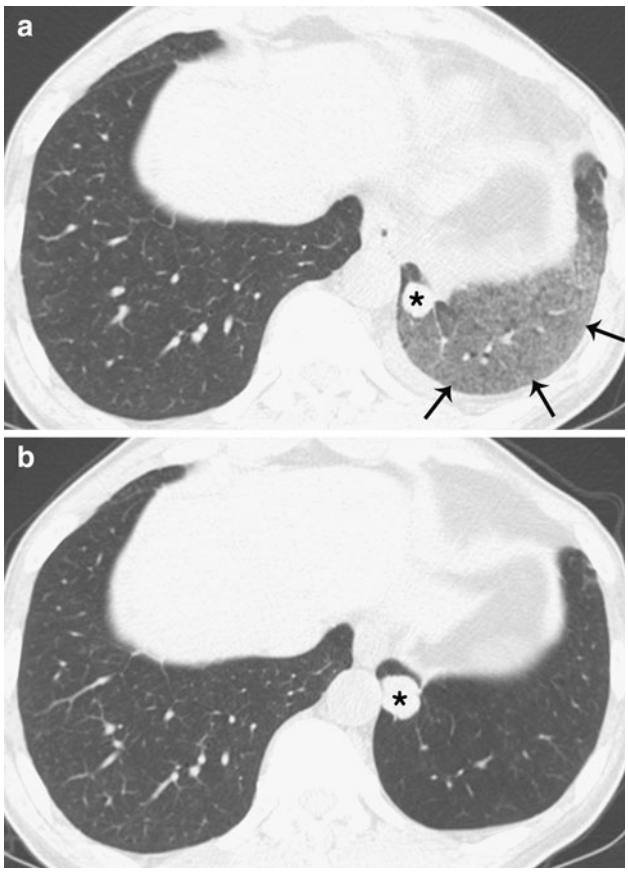

Fig. 4 Hypersensitivity pneumonitis pattern of drug-induced lung disease; a 61-year-old male smoker with stage IV squamous cell carcinoma in the left upper lobe. Chest radiograph (not shown here) revealed newly appeared localized ground-glass opacity lesions in the left lower lung zone 18 days after the initiation of erlotinib treatment. The patient had no respiratory symptoms. **a** Regular follow-up CT scan (2.5 mm section thickness) obtained 1 week after chest radiograph acquisition shows an extensive area of ground-glass opacity containing centrilobular small nodules in the left lower lobe. Additionally, note the lung-to-lung metastatic nodule (*asterisk*) in the same left lower lobe. **b** After the cessation of erlotinib therapy owing to progressive disease, follow-up CT scan demonstrates the complete disappearance of ground-glass opacity lesions

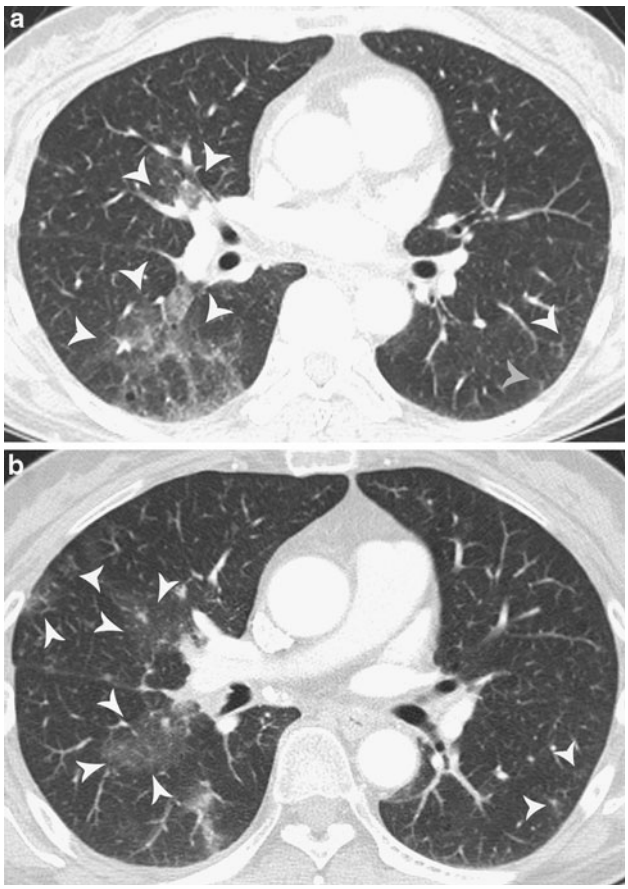

Fig. 5 Hypersensitivity pneumonitis pattern of drug-induced lung disease; a 47-year-old smoking man with stage IV adenocarcinoma in the left lower lobe. When erlotinib treatment was started, no evidence of interstitial lung disease was detected on imaging studies. CT scans (2.5 mm section thickness) obtained at the levels of aortic arch (**a**) and liver dome (**b**), respectively, and 33 days after erlotinib therapy, small poorly defined nodules (*arrows* in **a**) are noted in both upper lobes (*arrows*) and patchy peribronchial distribution of ground-glass opacity (*arrows* in **b**) in the lower lobes. Erlotinib therapy was discontinued due to lung cancer progression. Follow-up CT scans demonstrated interval improvement of drug-induced interstitial lung disease itself (not shown here)

end inspiration show a patchwork of regions of differing attenuation (the so-called mosaic attenuation areas) (Fig. 2). This abnormality may occur after erlotinib or sorafenib treatment.

Cryptogenic organizing pneumonia (COP) is histologically characterized by the presence of buds of organizing granulation tissue in respiratory bronchioles, alveolar ducts, and the adjacent alveoli [43]. The COP-like pattern is observed as multifocal areas of parenchymal opacification or nodules with subpleural or peribronchial distribution [45]. The parenchymal abnormality of opacification or nodules ranges in their extent from a few centimeters to whole lobe involvement, and in their attenuation from GGO to airspace consolidation with internal CT air bronchograms. The consolidation usually appears in an asymmetric bilateral distribution with no zonal predilection. A COP-like pattern may be observed in patients treated with erlotinib or sorafenib (Fig. 3).

Hypersensitivity pneumonitis (HP) is a relatively uncommon manifestation of drug-induced lung toxicity [46]. HP is histologically characterized by the presence of cellular bronchiolitis, peribronchiolar non-caseating granulomas, and lymphocytic interstitial pneumonia [46]. On HRCT scans, HP is shown as small, poorly defined centrilobular nodules or widespread areas of GGO. HRCT images obtained at the end of maximal expiration may exhibit lobular areas of decreased attenuation and vascularity, representing air trapping [46]. Conditions of HP may occur after gefitinib or erlotinib treatment (Figs. 4, 5).

The interstitial pneumonia of either an NSIP or UIP pattern, which is histologically characterized by the presence of varying proportions of interstitial inflammation and fibrosis [47], can occur in cases of gefitinib or sorafenib treatment. The interstitial pneumonia presents on HRCT scans as widespread subpleural GGO lesions frequently associated with reticular lesions (interlobular septal lines and intralobular linear lesions), and traction bronchiectasis or bronchiolectasis (Fig. 6). One of the most common forms of drug-induced interstitial pneumonia is NSIP, and the corresponding HRCT findings usually consist of patchy or diffuse GGO. With disease progression, there may be some evidence of fibrosis, including reticulation, traction bronchiectasis, and honeycombing; these are typically predominant in the lung bases. In some patients, the fibrosis demonstrates a patchy distribution and is predominantly peribronchovascular. The predominant findings on the HRCT of UIP are those of fibrosis. The fibrosis is characterized by the presence of irregular reticular opacities, honeycombing, architectural distortion, and traction bronchiectasis. On HRCT, the abnormalities are generally bilateral and symmetric, with predominant lower lung zone involvement. Peripheral and subpleural distribution of abnormalities is common [48].

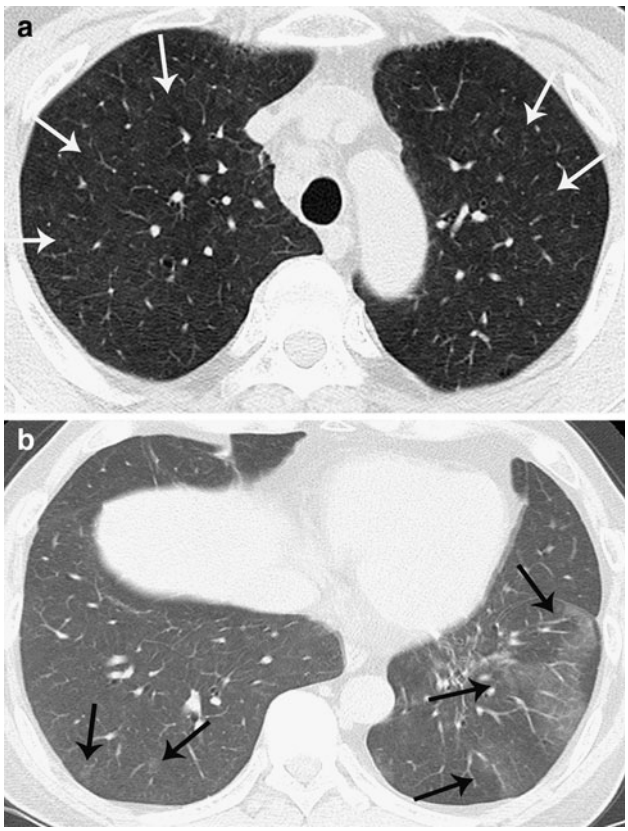

Fig. 6 Interstitial pneumonia pattern of drug-induced lung disease; a 54-year-old nonsmoking woman with stage IV adenocarcinoma in the right upper lobe. Gefitinib treatment was well tolerated without any respiratory symptoms. **a** CT scan (2.5 mm section thickness) obtained 80 days after gefitinib therapy shows patchy areas of ground-glass opacity (*arrowheads*) in both lungs. **b** Follow-up CT obtained 5 months after (**a**) demonstrates increased extent of ground-glass opacity lesions. Some reticular areas also appeared within ground-glass opacity lesions. The lesions waxed and waned in extent and pattern for 7 months without specific treatment

The ILD can exhibit progression with obvious increases in the extent of reticulation, interlobular septal thickening, architectural distortion with associated traction bronchiectasis and bronchiolectasis, honeycombing, and GGO lesions. This progressive disease of prior pulmonary fibrosis can occur with gefitinib (Fig. 7) or erlotinib treatment. Preexisting pulmonary fibrosis can be defined as bilateral symmetrical opacities with a predominantly basilar distribution, with areas of apparently normal lung tissue and associated areas with a honeycomb pattern on the baseline CT scan prior to treatment.

Management

Recently, Yoh et al. [49] suggested avoiding the use of amrubicin, a novel anticancer drug, in patients with small cell lung cancer who have preexisting pulmonary fibrosis

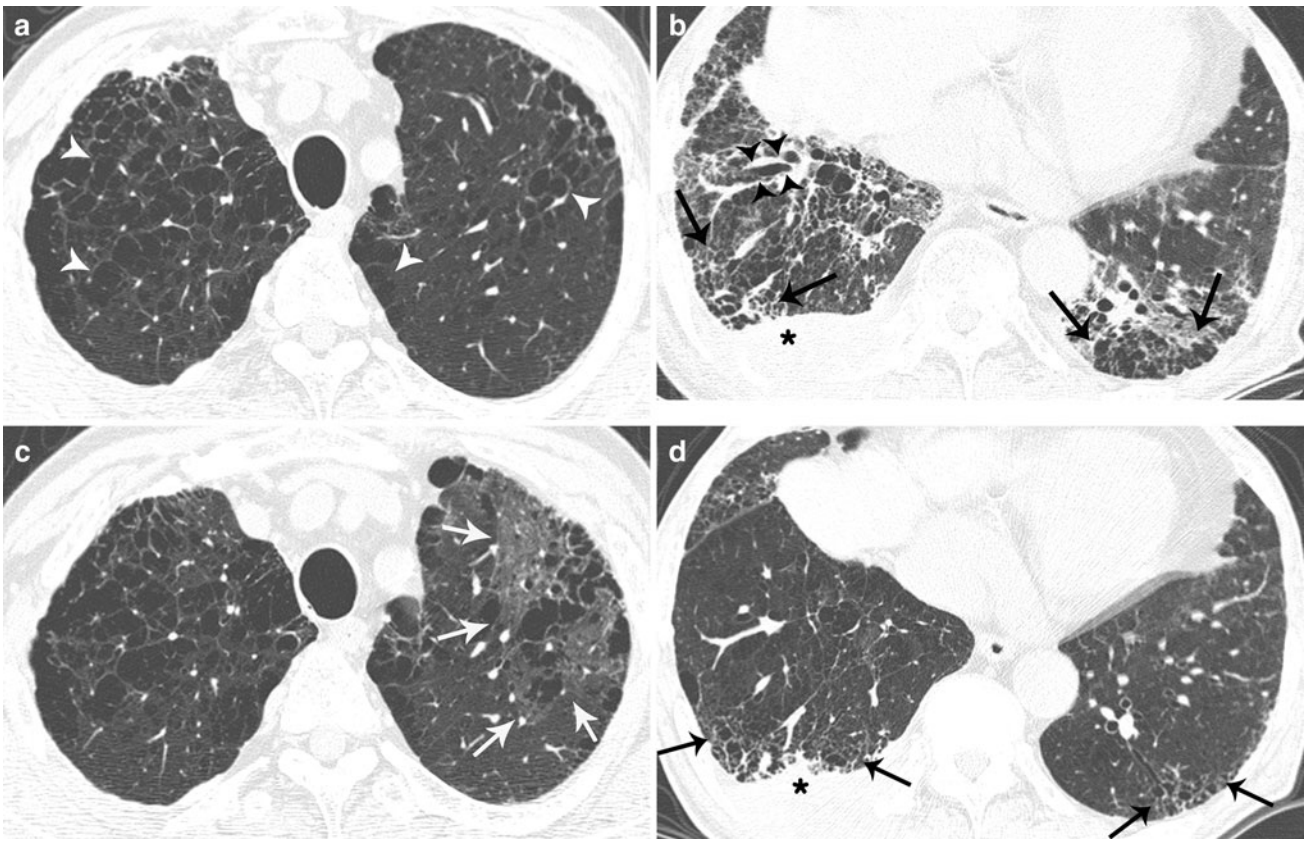

Fig. 7 Progression of preexisting interstitial lung disease; a 69-year-old smoking (40-pack years) man with stage IV squamous cell carcinoma of the lung. Since his disease progressed despite cytotoxic chemotherapy, gefitinib therapy (250 mg per day) was given. CT scans (2.5-mm-section thickness) obtained at the levels of great vessels (**a**) and liver dome (**b**), respectively, and before gefitinib treatment demonstrate reticular lesions and probable honeycombing (*arrows* in **b**) in the lower lung zones; findings consistent with usual interstitial pneumonia. These findings are predominantly basal and peripheral in distribution. Also note primary lung cancer lesion (*asterisk*) in the posterior basal segment of right lower lobe. Emphysema (*arrowheads* in **a**) predominantly affecting the upper lobes is also observed. **c, d** Follow-up CT scans obtained at the similar level to **a** and **b** and 26 days after gefitinib therapy demonstrate increased extent of reticulation and honeycombing (*black arrows* in **d**) and extensive traction bronchiectasis (*arrowheads* in **d**). Additionally, new areas of ground-glass opacity (*white arrows* in **c**) are present, suggestive of acute exacerbation (progression of underlying interstitial pneumonia) of underlying interstitial pneumonia

Table 4 Patterns and their relative frequency of drug-induced interstitial lung disease associated with the use of various tyrosine kinase inhibitors

	DAD	BO	COP	HP	IP
Gefitinib	++			+	+
Erlotinib		+	+	+	
Sorofenib		+	+		+

DAD diffuse alveolar damage, *BO* broncholitis obliterans, *COP* cryptogenic organizing pneumonitis, *HP* hypersensitivity pneumonia, *IP* interstitial pneumonia

Plus signs indicate the relative frequency of the findings from occasional (++) to rare (+)

because the risk of pulmonary toxicity is substantial in this subset of patients. Although there have not yet been any similar studies elucidating the guidelines for TKI therapy in patients with underlying PF, physicians should be aware of ILD development when using TKIs to treat NSCLC patients with preexisting PF. This is because preexisting PF has also been reported as the most significant risk factor for the development of TKI-associated ILD. Moreover, patients with idiopathic pulmonary fibrosis (IPF) have an increased risk of developing lung cancer as compared with patients without IPF. According to one study [48], patients with IPF develop lung cancers 5- to 14-fold more

frequently than do subjects without IPF. When considering this condition, the standard management guidelines become even more necessary.

However, this raises questions regarding where the cutoff point should be in diagnosing preexisting "pulmonary fibrosis" based on chest imaging studies, since CT findings associated with ILD can be encountered in asymptomatic individuals [38]. More than half of patients with HRCT evidence of interstitial lung disease may be asymptomatic and may exhibit normal pulmonary function [49]. The application of an appropriate CT acquisition technique (high-resolution CT) is also a prerequisite for the optimal evaluation of preexisting PF or ILD occurring with TKI treatment, particularly to clarify the progression of subtle interstitial lung abnormalities. This includes, most importantly, the use of thin (1- to 2-mm) collimation CT scanning and high-frequency algorithm (bone window) image reconstruction. However, depending on the condition of patients with ILD, the diagnosis of ILD should often be rendered on the sole basis of chest radiographic findings. Ordinary, not high resolution, CT may also provide diagnostically important information, even when breath-holding is poor, and may prove useful in indicating the extent of lung damage or in predicting patient prognosis by noticing the pattern of drug-associated interstitial lung diseases. Therefore, the accurate diagnosis of ILD in the early stage, based on the clinical course as well as on the chest radiographic or CT findings, may prove important for early treatment [8].

For the assignation of TKI-induced ILD, four specific findings were required: (1) progressive dyspnea with or without cough or fever, (2) lack of evidence of infection, (3) radiographic findings consistent with drug-induced ILD, and (4) consistent pathologic findings if available. Infection is a very common cause of pulmonary infiltrates and respiratory failure in cancer patients [50]. Appropriate cultures and serology can be helpful to differentiate pneumonitis from infectious pneumonia. Bronchoscopy with bronchoalveolar lavage (BAL) is very useful to exclude an infectious process. Bronchoscopy with BAL is also important to exclude alveolar hemorrhage. The diagnosis of TKI-induced ILD can be made when pneumonitis develops shortly after the initiation of treatment (i.e., hours to weeks), lack of an alternative explanation for respiratory failure, and the resolution of pneumonitis after corticosteroid treatment and withdrawal of the presumed agent.

Treatment of EGFR-TKI-induced ILD is largely supportive, including supplemental oxygen, empirical antibiotics, and mechanical ventilation. Immediate discontinuation of the drug is recommended and systemic corticosteroids are usually prescribed, although no controlled trials have been conducted to evaluate their benefits.

Conclusion

Oncologists and radiologists should be aware of TKI-induced ILDs, which increase in incidence with the introduction of diverse types of molecularly targeted agents. Additionally, it is important to recognize the diverse radiologic manifestations of these kinds of pulmonary complications for the early diagnosis and treatment of these unwanted diseases (Table 4). Although the DAD pattern is most commonly observed, various patterns of ILD can occur with EGFR-TKI therapy. Physicians planning to use TKIs for the treatment of NSCL should be thoroughly familiar with the CT findings of the complications. Poor prognoses are expected when there is a short interval from the initiation of target therapy to the onset of ILD, acute interstitial pneumonia pattern of ILD, and preexisting pulmonary fibrosis.

Conflict of interest The authors have no conflicts of interest to disclose.

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