EGFR Tyrosine Kinase Inhibitor–Associated Interstitial Lung Disease During the Coronavirus Disease 2019 Pandemic

To the Editor:

EGFR tyrosine kinase inhibitor (TKI)–associated interstitial lung disease (ILD) and coronavirus disease 2019 (COVID-19) infection share similar clinical and imaging findings. How to distinguish between the two diseases is a crucial issue during the current COVID-19 pandemic.

Lung cancer is the leading cause of death worldwide. TKIs targeting *EGFR* have been reported to improve progression-free survival in patients with NSCLC harboring sensitive *EGFR* mutations. The most serious adverse drug reaction in patients receiving *EGFR* TKIs is ILD, with an incidence in Japan of 1.6% to 4.3% and 0.3% to 1% worldwide.[1] The median interval to onset is 1 to 2 months from the first dose, and the mortality rate can reach 13% to 50%.[1] Chest computed tomography (CT) findings of *EGFR* TKI–associated ILD can be divided into the following four patterns[2]: nonspecific areas with ground-glass opacity (GGO), multifocal areas of airspace consolidations, patchy distribution of GGO accompanied by interlobar septal thickening, and extensive bilateral GGO or airspace consolidations with traction bronchiectasis. The latter has the worst prognosis. Symptoms of *EGFR* TKI–associated ILD are nonspecific, with the most common being dyspnea (94.3%), fever (51.4%), and cough (20%); 5.7% of patients are asymptomatic.[1]

EGFR TKI–associated ILD is diagnosed essentially by the exclusion of other diseases. Early diagnosis, discontinuing *EGFR* TKIs, and starting high-dose steroid treatment as soon as possible are recommended.

At the time of writing, 2,927,523 people have been confirmed to be affected with COVID-19 infection and 202,107 people have died worldwide, with a mortality rate of 6.9%. The median incubation period of severe acute respiratory syndrome coronavirus 2 is 5.1 days, with 97.5% of patients becoming symptomatic within 11.5 days. Chest radiograph (CXR) is most often used to detect lesions in patients with COVID-19 infection in most countries; however, only 33.3% to 69% of patients with COVID-19 infection have abnormalities on CXR.[3] In addition, the severity on CXR peaks at 10 to 12 days from symptom onset. Chest CT for patients with COVID-19 infection is highly sensitive, and the cardinal hallmarks of COVID-19 on chest CT are bilateral distribution of GGO with or without consolidation in posterior and peripheral lungs, and the most common picture on chest CT includes GGO at 14% to 98%, consolidation at 2% to 64%, GGO with consolidation at 19% to 59%, and interlobular septum thickening at 1% to 75%.[4] The most common symptoms of patients with COVID-19 include fever (85%–90%), cough (65%–70%), fatigue (35%–40%), sputum production (30%–35%), shortness of breath (15%–20%), myalgia or arthralgia (10%–15%), headaches (10%–36%), sore throat (10%–15%), and chills (10%–12%).

Taken together, it is very difficult to distinguish between COVID-19 infection and *EGFR* TKI–associated ILD with clinical and imaging presentations. For an early diagnosis, rapid tests for severe acute respiratory syndrome coronavirus 2 are necessary, such as reverse transcriptase-polymerase chain reaction, isothermal amplification assays, or serology tests to differentiate COVID-19 infection from *EGFR* TKI–associated ILD, especially in the first 1 to 2 months after starting *EGFR* TKI therapy. In addition, the standard treatment for *EGFR* TKI–associated ILD is to discontinue TKIs and start high-dose steroids immediately; however, high-dose steroid treatment has been reported to be harmful for patients with COVID-19 infection.[5]

In Table 1, we summarize the differences between *EGFR* TKI–associated ILD and COVID-19 infection.

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Table 1. The Differences Between EGFR TKI-Associated ILD and COVID-19 Infection

	Gefitinib	Erlotinib	Afatinib	Osimertinib	COVID-19 Infection
Incidence, (%)	Overall 1.3[1] Japan 1.6-4.3; non-Japanese 0.3-1	1.1%-4.3	1.6	3.9	—
Interval to onset	Median time 24-42 d; majority within 4-8 wk.	Median time 39 d; majority within 4 wk.	Median time 26.5 d (in Japan)	Median time 54 d (14-240 d)	Median incubation period of 5.1 d, with 97.5% becoming symptomatic within 11.5 d
Mortality	13%-50%[1]				6.95% (to April 25, 2020)
CXR	NA				33.3%-69% patients positive with COVID-19 had abnormalities on CXR[3] 47%-80% consolidation, 20%-38% GGO The severity of CXR peaked at 10-12 d from symptom onset.[3]
Chest CT	Includes four patterns as below[2] A nonspecific area with GGO. A multifocal area of airspace consolidations. Patchy distribution of GGO accompanied by interlobar septal thickening. Extensive bilateral GGO or airspace consolidations with traction bronchiectasis.				Bilateral distribution of GGO with or without consolidation in posterior and peripheral lungs was the cardinal hallmark of COVID-19. Included the following patterns[4]: GGOs 14%-98%; consolidation 2%-64%; GGO + consolidation 19%-59%; interlobular septum thickening 1%-75%; reticular pattern 1%-22%; crazy paving 5%-36%; air bronchogram 21%-80%; bronchial wall thickening 11%-23%; pleural thickening 32%; subpleural line 20%; nodules 3%-13%; reversed halo sign 2%-3%; pleural effusion or pericardial effusion 1%-8%; lymphadenopathy 4%-8%
Diagnosis	Diagnosis of EGFR TKI-associated interstitial pneumonitis is made essentially by exclusion of others				RT-PCR, isothermal amplification assays, serology tests
Symptoms	Nonspecific, dyspnea 94.3%, fever 51.4%, cough 20%, asymptomatic 5.7%				Fever 85%-90%, cough 65%-70%, fatigue 35%-40%, sputum production 30%-35%, shortness of breath 15%-20%, myalgia or arthralgia 10%-15%, headaches 10%-36%, sore throat 10%-15%, chills 10%-12%.
Treatment	Early detection, discontinue EGFR TKI, and start high-dose steroids as soon as possible.				No FDA-approved drugs as yet. Steroids may be harmful[5]

COVID-19, coronavirus disease 2019; CXR, chest radiograph; FDA, Food and Drug Administration; GGO, ground-glass opacity; ILD, interstitial lung disease; NA, not applicable; RT-PCR, reverse transcriptase-polymerase chain reaction; TKI, tyrosine kinase inhibitor.

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The Use of Positron Emission Tomography in Coronavirus Disease 2019 Cases

An excellent visual demonstration was provided by Polverari et al.[1] of a novel coronavirus disease 2019 case on positron emission tomography (PET) combined with computed tomography (CT) using the radiotracer fluorodeoxyglucose. Along the same lines, the largest series published, primarily in English, on this topic is that of Qin et al.[2] They also reported unmistakable changes on the PET and CT components. PET clearly complemented the CT findings in all cases (as described in both articles).

The most common CT findings in those affected with coronavirus disease 2019 have been well described.[3] It seems that in all of the PET–CT cases, these typical appearances were clearly apparent on the CT component (primarily ground-glass opacities, consolidation, or a combination of both) of the study and the PET findings were, realistically, a little superfluous. Although in these instances PET–CT played a role in supporting the diagnosis, it seems that the diagnosis would have been established with CT alone. Using CT alone would also have resulted in a lower radiation exposure.[4] How much did the PET findings really contribute to the diagnosis? Was PET truly necessary? Would a CT scan have established the same outcome at a lower cost, lower radiation exposure, and greater efficiency?

Having said that, how can PET be better used in this setting? Is it more useful potentially for follow-up purposes? In the same way as has been postulated with cardiac lymphoma, PET may be more useful for functionally assessing disease activity after treatment even in the presence of unresolved morphologic changes.[5] Would this be a better use of PET for such patients? After all, as is common knowledge, pulmonary parenchymal changes may persist for quite a long time after resolution of respiratory infective symptoms.

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