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Letter

A Lung Cancer Patient with Dyspnea: Diagnostic Difficulties during the COVID-19 Pandemic

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In the COVID-19 pandemic of 2020, patients with cancer appear to be at higher risk for complications of COVID-19 than those without cancer (Bakouny et al., 2020; Garassino et al., 2020). High SARS-CoV-2 viral load has been associated with in-hospital mortality in patients with and without cancer (Westblade et al., 2020). While viral load is predictive of mortality risk, we urge physicians to be aware of the limitations of the current diagnostics tests, especially in patients with underlying pulmonary malignancy and in those on treatments that can result in interstitial lung disease (ILD).

False-negative tests in patients with lung cancer and COVID-19 suspicion pose a challenging and ethical dilemma with regards to therapeutic decision-making. Such decisions can only be made by multi-disciplinary judgment, as we illustrate in a recent case at our institute. A 73-year-old male presented with progressive dyspnea and fever at the emergency department in mid-April. The patient was known to have stage 4 non-small cell lung cancer (NSCLC) with a *MET* exon 14 skipping mutation treated with crizotinib (a c-Met kinase inhibitor) for 12 months. The patient was admitted to the COVID ward, supervised by a specialized COVID-19 team of pulmonologists supported by (thoracic) oncologists, intensivists, radiologists, and specialists in the field of infectious diseases and internal medicine. In the first 4 days of hospital admission, six PCR tests for SARS-CoV-2 were performed and remained negative. Previous to his presentation at the emergency department, there was no evidence of progression of NSCLC. Computed tomography (CT) imaging of the chest revealed an increase in ground glass opacities (GGO), similar to what is expected with COVID-19 but which could also be compatible with progression of his lung malignancy or with drug-induced ILD due to crizotinib treatment (Figures S1A and S1B). Each differential diagnosis required a different therapeutic approach. Therefore, multidisciplinary counsel was pivotal for the therapeutic considerations. Three days after admission, the patient developed severe respiratory failure with a need for intensive care unit admission and mechanical ventilation. As the possible diagnosis of ILD due to crizotinib emerged, high-dose corticosteroids were administered. At the fifth day of admission, a bronchial aspirate specimen tested positive for SARS-CoV-2, finally confirming COVID-19. Because of continuing deterioration, we decided, in accordance with the family, to abstain from further treatment. The patient died 9 days after admittance to the hospital.

Upon his admission to the hospital, there was a high suspicion for COVID-19 infection, based on clinical presentation. However, consecutive PCR tests for SARS-CoV-2 using nasopharyngeal swabs were negative. As the PCR test for SARS-CoV-2 RNA has high specificity but limited sensitivity, radiological features might be useful in diagnosing COVID-19, especially in clinically suspect cases with false-negative PCR results (Wang et al., 2020b; Yicheng et al., 2020). For this reason, the Dutch Association for Radiology developed a standardized assessment of non-enhanced chest CT in patients suspected to have COVID-19 with pulmonary involvement: the COVID-19 Reporting and Data System (CO-RADS) (Prokop et al., 2020). Based on CT findings, CO-RADS assigns a score to the level of suspicion of COVID-19, ranging from 1 (highly unlikely) to 5 (highly likely). Our patient had CO-RADS 4, compatible with a high level of suspicion of COVID-19. Although CT is highly sensitive for detecting pulmonary manifestation of COVID-19, the specificity of CT is low (Fujiwara et al., 2020; Prokop et al., 2020). Therefore, without PCR confirmation, alternative diagnoses should be considered. Specifically, malignancy, drug-induced ILD, and COVID-19 can all present as a combination of GGO and consolidations (Bakouny et al., 2020; Prokop et al., 2020; Nishino et al., 2017). The letter by Fujiwara et al. (2020) and our letter demonstrate the complexity of distinguishing pulmonary infiltrates in lung cancer patients that can be due to drug-induced pneumonitis, COVID-19, other infection, and cancer progression.

To stablish etiology, the clinical history of the patient is crucial. In our patient, initial diagnosis of COVID-19 was supported by the sudden onset of symptoms, i.e., acute worsening of dyspnea and fever, abnormal biochemical parameters such as elevated CRP and d-dimers, and chest X-ray (Wang et al., 2020a) (Figure S1C). Disease progression of NSCLC seemed less likely because of the previous slow disease course. Symptoms could be compatible with crizotinib-induced ILD, which can be acute, rapidly progressive, and potentially fatal (Yoneda et al., 2017). Although tyrosine kinase inhibitor (TKI)-induced ILD remains a rare complication, the emergence of targeted therapy has increased the prevalence of TKI-induced ILD (Yoneda et al., 2017). Nevertheless, the median onset of crizotinib-induced ILD is around 3 weeks after initiation of treatment, and it rarely develops after more than 1 year of treatment (Yoneda et al., 2017). Thus, timing of onset would argue against ILD in this

particular case. As our patient had a good performance status (ECOG 1) before onset of the symptoms and had subsequent treatment options, we adopted an aggressive and extensive therapeutic approach for COVID-19, including intubation. Diagnosis of COVID-19 was finally confirmed by bronchial aspirate PCR about 80 h after admittance to the hospital. Eventually, patient deteriorated quickly and was deceased within 2 weeks after onset of symptoms.

Based on our experiences, we make the following recommendations:

- The diagnosis of COVID-19 should always be considered in clinically suspicious patients, despite negative nasopharyngeal swabs and in the absence of a convincing alternative diagnosis.
- Consider a broad differential diagnosis of GGO increase, especially during and after the COVID-19 pandemic, and specifically in patients with underlying pulmonary disease and those on treatments that can result in ILD (Figure S1C).
- Always consult with an oncology specialist in patients with an active malignancy.
- The negative result of a nasopharyngeal swab might result from a sampling error, where bronchial aspirate or broncho-alveolar lavage can eventually reveal the presence of SARS-CoV-2.

SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at https://doi.org/10.1016/j.ccell.2020.10.005.

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