Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

0003-4975/$36.00 e79
https://doi.org/10.1016/j.athoracsur.2021.11.015

Lung Cancer Surgery With Persistent COVID-19 Infection

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A 71-year-old man with a history of drug-induced interstitial pneumonia was diagnosed with COVID-19 infection and simultaneously found to have a pulmonary mass, suggesting a coexisting lung cancer. Approximately 1 month after COVID-19 pneumonia resolved, the patient electively underwent right upper lobectomy. Postoperatively, acute exacerbation of interstitial pneumonia occurred and the patient died on the fifteenth postoperative day. By quantitative reverse transcription polymerase chain reaction, high levels of COVID-19-derived RNA were detected in the specimen of lung parenchyma. Despite resolved COVID-19 infection, it may persist locally in the lungs, with the risk of acute exacerbation of interstitial pneumonia due to secondary stressors including surgery.

(Ann Thorac Surg 2022;114:e79-e81)

The pandemic of COVID-19 involves an increasing number of surgical cases of lung cancer detected in association with COVID-19 infection. Especially in cases of lung cancer associated with interstitial pneumonia, meticulous attention needs to be paid to the acute exacerbation of interstitial pneumonia in the perioperative period. However, it is not clear whether previous infection from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may persist in the local area for a long period and lead to increased morbidity and mortality for subsequent procedures even after radiologic resolution.

A 71-year-old male heavy smoker with a history of drug-induced interstitial pneumonia and its acute exacerbation (AE) was diagnosed with COVID-19 (*E484K* mutation, variant of SARS-CoV-2). Computed tomography showed a ground-glass appearance characteristic of COVID-19 and a 5-centimeter mass in the upper lobe of the right lung, suggesting the coexistence of COVID-19 and lung cancer in the same lobe (Figure 1). After treatment with remdesivir, the viral antigen test of pharyngeal swab was negative, and resolution of pneumonia was also confirmed radiologically. At 30 days after the discharge, the patient was rehospitalized and underwent surgery for lung cancer. Right upper lobectomy and lymph node dissection were performed, and the postoperative course was uneventful until, on the fifth postoperative day, the patient developed an acute exacerbation of interstitial pneumonia, which necessitated ventilator management. Steroid pulse therapy was initiated, but interstitial pneumonia was gradually aggravated and the patient died on the fifteenth postoperative day (Figure 2). Pathologic examination of resected specimens showed that the tumor was squamous cell carcinoma, staged as T2bN1M0, stage IIB (Figure 3A), and reverse transcription polymerase chain reaction (RT-PCR) revealed SARS-CoV-2 still persisted in the local lung (S2, segment 2).

From the resected specimens, several lesions were selected and snap-frozen for RNA analyses: (i) lung parenchyma with grand-glass appearance (S2), (ii) lung parenchyma without grand-glass appearance (S3), (iii) tumor tissue, (iv) central bronchus, (v) mediastinal lymph node, and (vi) mediastinal fat. These were separately dissected and kept frozen at -80°C until further analyses (Figure 3B). Total nucleic acid was isolated using the MagMAX Viral/Pathogen Nucleic Acid Isolation Kit (Thermo Fisher Scientific; Waltham, MA) as previously described.[1] Following the protocol developed by the National Institute of Infectious Diseases in Japan,[2] we performed 1-step quantitative RT-PCR to detect SARS-CoV-2 on a StepOnePlus Real-Time PCR System (Thermo Fisher Scientific). The viral load, measured as absolute copy number, was determined using a serially diluted DNA control targeting the nucleocapsid gene of SARS-CoV-2 (Integrated DNA Technologies, Coralville, IA).[1] By real-time RT-PCR, a high concentration of COVID-19-derived RNA, 6998 copies (Ct: 26.3), was detected exclusively in the S2 parenchyma, consistent with the previous pneumonic lesion of ground glass opacity. In addition, as we previously reported,[1] the Ag levels were determined quantitatively with the Lumipulse SARS-CoV-2 Ag test (Fujirebio, Inc., Tokyo, Japan), which also tested positive only in S2 lung sample. Histologically, active pneumonitis with abundant neutrophilic infiltrate was microscopically observed in S2 lung (Figure 3C).

Accepted for publication Nov 28, 2021.

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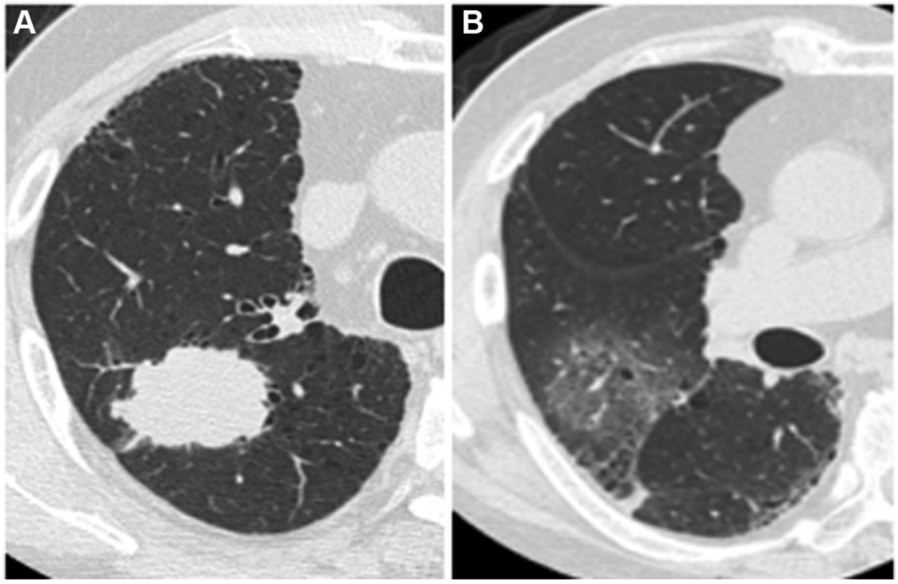

FIGURE 1 Computed tomography images of (A) lung cancer and (B) COVID-19 pneumonia in the right upper lobe.

COMMENT

The mortality risk of surgery after COVID-19 infection has been reported to be increased up to 5-6 weeks,[3] and there are few detailed reports on the cause of death and the risks. We report a case of acute exacerbation of interstitial pneumonia potentially associated with residual viral RNA and persistent inflammation in the lung after surgery. Although there have been reports of residual COVID-19 virus in autopsied organs,[4] there have been no reports of residual virus in the resected lung in vivo as far as we searched the literature. In our case, we found that COVID-19-derived RNA remained at high levels in the resected lung, approximately 1 month after confirmation of PCR-negativity and antigen-negativity of SARS-CoV-2 on pharyngeal swab samples, suggesting that latent infection may persist in the lung alveolar II cells even after its eradication in pharyngeal epithelial cells. In this study, we did not evaluate the infectivity of SARS-CoV-2 in the lungs. However, from the viewpoint of preventing infection of healthcare workers and infection in laboratories, standard precaution should be performed when examining similar lung specimens before formalin fixation.

AE of interstitial pneumonia after surgery may be caused by various enigmatic reasons, reflecting its

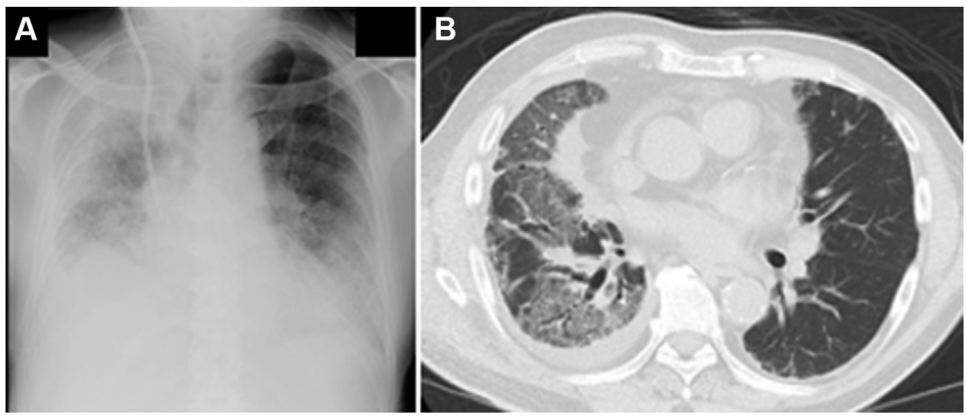

FIGURE 2 Postoperatively, (A) chest radiograph and (B) computed tomography showed acute exacerbation of interstitial pneumonia.

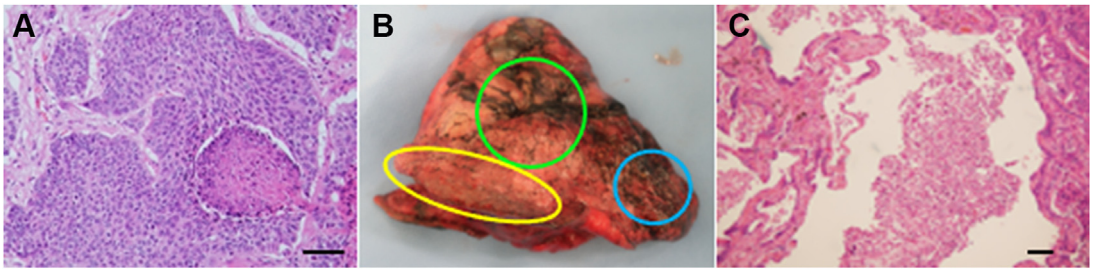

FIGURE 3 (A) Histologically, the tumor was diagnosed as squamous cell carcinoma. (B) From the resected lung specimen, 3 lesions were separately dissected and snap-frozen for RNA analyses. Green, yellow, and blue circles indicate the legions of tumor, segment 2 (previous pneumonic lesion) and segment 3 (intact lung), respectively. (C) Active pneumonitis with abundant neutrophilic infiltrate was microscopically observed in segment 2. Scale bars indicate 100 μm.

difficult-to-treat pathology.[5] A multicenter retrospective cohort study conducted by the Japanese Association for Chest Surgery with 1763 cases reported an incidence of AE in the first 30 postoperative days of 9.3% and mortality rate of 43.9%.[6] A subsequent multivariate analysis identified the following as significant respective risk factors for AE: male sex, preoperative steroid use, KL-6 $>$ 1000 U/mL, % vital capacity $<$ 80%, usual interstitial pneumonia pattern, and history of AE, segmentectomy, or a more extensive surgical procedure (reference, wedge resection). In our case, the patient, with a history of AE and on a dose of steroids, is considered to be high-risk originally, and it is possible that the residual COVID-19 infection further increased the risk of AE.

In general, viral infections are one of the risks for acute exacerbation of interstitial pneumonia. There have been reports of rheumatoid arthritis-associated interstitial lung disease exacerbation after resolution of COVID-19 infection,[7] and Kondoh and associates[8] reported high mortality in patients with COVID-19 and interstitial lung disease. Meanwhile, previous large-scale retrospective studies have included patients treated with steroids, macrolides, ulinastatin, sivelestat sodium, or other agents for the prevention of postoperative AE, although none of these agents has proven to be effective. Based on the results of our case, the most practical measures for high-risk patients with AE are considered to be postponing surgery for a longer period of time (more than 1 month) or reducing the extent of resection (reduction surgery) if possible, depending on the pathology of the lung cancer. COVID-19 patients with a history of interstitial lung disease should be aware of the risk of acute exacerbations even after COVID-19 is supposed to be resolved. Given an expected increasing number of lung cancer surgery cases after similar COVID-19 pneumonia in the future, a detailed analysis of risk factors and preventive measures for AEs in a large number of patients is expected.

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