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.

for industry. https://www.fda.gov/media/116860/download. Accessed XXX.
3. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Multiple endpoints in clinical trials guidance for industry draft guidance. https://www.fda.gov/media/102657/download. Accessed XXX.
4. China Food and Drug International Exchange Center. The centers for drug evaluation publicly solicits opinions on the "guidance for the statistical design of antitumor drug clinical trials.". http://www.ccfdie.org/cn/yjxx/yphzp/webinfo/2020/07/1592160852573198.htm. Accessed XXX.

Histologic Confounding Findings in Coronavirus disease 2019 (COVID-19) Pathology

To the Editor:

We read with interest the study by Cai et al.[1] on the appearance of coronavirus disease 2019 (COVID-19) in the perioperative period among seven patients undergoing lung surgical resections for oncologic purposes. The study gives some important messages concerning the findings of ground-glass opacities and lymphopenia in the early days after pulmonary surgical resection as key signs for suspecting COVID-19. However, we would like to raise concerns about the histologic features attributed to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in the peritumoral lung tissue of patient number 1.

This patient had a centrally located squamous cell carcinoma and the histologic features reported in Figure 2*A* describes a diffuse lung interstitial inflammation and a thickened alveolar septum and fibrous connective tissue proliferation with plasma cell and macrophage in Figure 2*B*. Macrophages and foam cells filling the alveolar cavities are quite different from the classic pulmonary alterations so far described in SARS-CoV-2. In fact, interstitial organizing fibrosis with inflammatory infiltrates comprising plasma cells and macrophages are rather related to obstructive pneumonia secondary to neoplastic bronchial occlusion.

Inflammatory changes are quite common in squamous cell carcinoma obstructing the airways, frequently leading to interstitial inflammatory cells, alveolar accumulation of foamy macrophages, and organizing fibrosis.[2] It is possible that these tumor-related fibroinflammatory modifications may have obscured some histologic changes caused by SARS-CoV-2, but the described features in the lung parenchyma of patient number 1 should be considered with caution as they may not be completely related to COVID-19.

Of note, these pulmonary histologic changes incorrectly assigned to SARS-CoV-2 may represent confounding data that may deter correct comprehension of the COVID-19 pathogenesis. Similarly, Goldsmith et al.[3] evidenced the possible misinterpretation of viral particles as cross-sections of the rough endoplasmic reticulum with surrounding ribosomes at the electron microscope in endothelial cells.[4]

As highlighted by Martines et al.[5] in a series of eight autoptic cases of patients with COVID-19, the tissue obtained from autopsies may reveal confounding features secondary to invasive ventilation, drugs, superimposed infections, important comorbidities (hypertension, obesity, cardiovascular diseases, diabetes mellitus), and even autolytic artifacts, partly or entirely, precluding a correct understanding of COVID-19.

The comprehensible urgency to have more details about this dramatic and poorly-known disease should not undermine a meticulous and deep exploration of pulmonary histopathologic lesions related to COVID-19 that may likely be obscured by coexisting pathologies.

Giulio Rossi, PhD
Dora Caruso, MD
Department of Pathology
Azienda Unità Sanitaria Locale della Romagna
Santa Maria delle Croci Hospital of Ravenna
Ravenna, Italy

Franco Stella, PhD
Department of Thoracic Surgery
Azienda Unità Sanitaria Locale della Romagna
Morgagni Hospital of Forlì, University of Bologna
Forlì, Italy

Fabio Davoli, PhD
Department of Thoracic Surgery
Azienda Unità Sanitaria Locale della Romagna
Santa Maria delle Croci Hospital of Ravenna
Ravenna, Italy

Address for correspondence: Fabio Davoli MD, PhD, Department of Thoracic Surgery, Azienda Unità Sanitaria Locale della Romagna, Santa Maria delle Croci Hospital of Ravenna, Viale Vincenzo Randi 5, Ravenna 48100, Italy. E-mail: fabio.davoli78@gmail.com

ISSN: 1556-0864
https://doi.org/10.1016/j.jtho.2020.06.017

References

1. Cai Y, Hao Z, Gao Y, et al. Coronavirus disease 2019 in the perioperative period of lung resection: a brief report from a single thoracic surgery department in Wuhan. *J Thorac Oncol*. 2020;15:1065–1072.
2. Colby TV, Koss MN, Travis WD. Squamous cell carcinoma. In: Colby TV, Koss MN, Travis WD, eds. *Atlas of Tumor Pathology: Tumors of the Lower Respiratory Tract*. Washington DC: Armed Forces Institute of Pathology; 1995:157–178.
3. Goldsmith CS, Miller SE, Martines SB, Bullock HA, Zaki SR. Electron microscopy of SARS-CoV-2: a challenging task. *Lancet*. 2020;395:e99.
4. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet*. 2020;395:1417–1418.
5. Martines RB, Ritter JM, Matkovic E, et al. Pathology and pathogenesis of SARS-CoV-2 associated with fatal coronavirus disease, United States. *Emerg Infect Dis*. 2020;26.

Response to Letter to the Editor

To the Editor:

We appreciate the comments and concerns raised by Rossi et al.[1] regarding our report on histologic findings in a patient with coronavirus disease 2019 (COVID-19).[2] As noted by Rossi et al.,[1] it is possible that the coexisting tumor-related obstructive pneumonitis and comorbidities might have interfered with the interpretation of the histologic findings of patient 1; we would like to address this accordingly.

Obstructive pneumonitis is always observed in the lung parenchyma distal to the bronchial obstruction by a neoplasm. Patient 1 had squamous cell carcinoma, which was located at the posterior basal segment of the right lower lobe. As described in our report, an extensive interstitial inflammation of the lung was consistently observed on multiple sections, which were multisampled far from the tumor at other segments; obviously, these findings should not be considered as the result of the obstruction by the tumor.

Moreover, interpretation of the findings, given the background of the patient's comorbidity, needs extra caution. Patient 1 had interstitial lung disease and presented the usual radiographic pattern of interstitial pneumonia. The most characteristic histologic feature of interstitial pneumonia is patchy interstitial fibrosis admixed with normal parenchyma, whereas infiltration by lymphocytes and plasma cells is generally sparse.[3] However, the pathologic examination of patient 1 revealed interstitial inflammation with numerous plasma cell infiltrations and a large number of macrophages and foam cells in the alveoli. The histologic features were distinctively different from those of interstitial pneumonia. In a recent study, a predominantly large number of activated plasma cells with scattered alveolar macrophages were found in the bronchoalveolar lavage specimen from a patient with COVID-19.[4] The findings of this study suggest that the peculiar abundance of CD138-positive plasma cells in COVID-19 may be a relevant feature.

It is definitely true that preexisting or coexisting disease might hamper the correct understanding of the morphologic changes in COVID-19, particularly in the absence of diffuse alveolar damage that has been found to be the salient feature of COVID-19 pneumonitis on microscopy.[5] Nevertheless, it should be noted that, in our report, the lung specimen was taken when the patient had no symptoms, and the pathology is always consistent with the disease severity. Although there is currently lack of solid data to make an assertion, we still have reasons to speculate that the extensive interstitial inflammation with plasma cell and macrophage infiltration, and also the numerous macrophages in the alveoli might be a pathologic change related to COVID-19.

Yixin Cai, MD
Department of Thoracic Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, People's Republic of China

Dong Kuang, MD
Institute of Pathology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, People's Republic of China

Ni Zhang, MD
Department of Thoracic Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, People's Republic of China

Address correspondence to: Ni Zhang, MD, Department of Thoracic Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 Jiefang Avenue, Hankou, Wuhan 430030, People's Republic of China. E-mail: zhangnidoc@vip.163.com

ISSN: 1556-0864
https://doi.org/10.1016/j.jtho.2020.09.025

References

1. Rossi G, Caruso D, Stella F, et al. Histologic confounding findings in coronavirus disease 2019 (COVID-19) pathology. *J Thorac Oncol*. 2020;15:e192–e193.