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PII: S1556-0864(20)30132-5

DOI: https://doi.org/10.1016/j.jtho.2020.02.010

Reference: JTHO 1723

To appear in: *Journal of Thoracic Oncology*

Received Date: 18 February 2020

Revised Date: 20 February 2020

Accepted Date: 20 February 2020

Please cite this article as: Tian S, Hu W, Niu L, Liu H, Xu H, Xiao S-Y, Pulmonary pathology of early phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer, *Journal of Thoracic Oncology* (2020), doi: https://doi.org/10.1016/j.jtho.2020.02.010.

Pulmonary pathology of early phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer

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DISCLOSURES: None

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Abstract

There is currently a lack of pathologic data on the novel coronavirus (SARS-CoV-2) pneumonia, or COVID-19, from autopsy or biopsy. Two patients who recently underwent lung lobectomies for adenocarcinoma were retrospectively found to have had COVID-19 at the time of surgery. These two cases thus provide important first opportunities to study the pathology of COVID-19. Pathologic examinations revealed that, apart from the tumors, the lungs of both patients exhibited edema, proteinaceous exudate, focal reactive hyperplasia of pneumocytes with patchy inflammatory cellular infiltration, and multinucleated giant cells. Hyaline membranes were not prominent. Since both patients did not exhibit symptoms of pneumonia at the time of surgery, these changes likely represent an early phase of the lung pathology of COVID-19 pneumonia.

Key words: coronavirus; COVID-19 pneumonia, pathology; SARS-CoV-2

Report

Since December 2019, the outbreak of a novel coronavirus, SARS-CoV-2, infection (COVID-19) that started in Wuhan, Hubei Province, China[1, 2], has spread to all parts of China, other parts of Asia such as Japan and Thailand, Australia, Europe and North America. The number of confirmed cases in China has reached 42,700, including 1,017 deaths, as of February 11, 2020 [new reference, website]. Patients initially present with fever with or without respiratory symptoms, but all patients later develop various degrees of pulmonary abnormalities on chest CT imaging[1, 3]. Although the vast majority of patients only have a common, mild form of illness, about 15-20% of the patients fall into the severe group, meaning they require assisted oxygenation as part of treatment[3]. The severe group has a high mortality rate and is associated with older age, underlying diseases such as diabetes, and medical procedures (such as patients who were infected in a hospital setting while receiving surgery for other indications).

Although there have been several studies describing clinical features and characteristic radiographic findings (mainly chest CT scans) [1, 3], no pathologic studies have been conducted based on autopsies or biopsies. Some of the reasons for the lack of autopsies and biopsies include the suddenness of the outbreak, the vast patient volume in hospitals, shortage of healthcare personnel, and the high rate of transmission, which makes invasive diagnostic procedures less of a clinical priority.

Fortunately and unfortunately, we encountered two patients who underwent surgery for malignancy and were later found to have been infected with SARS-CoV-2. The surgical specimens overlapped in time with the infection, which offered us the

necessary specimens to examine the histopathology of COVID-19 pneumonia.

Case Presentation

CASE 1 was a female patient of 84 years of age who was admitted for treatment evaluation of a tumor measuring 1.5 centimeters in the right middle lobe of the lung. The tumor was discovered on chest CT scan at an outside hospital. She had a past medical history of hypertension for 30 years, as well as type 2 diabetes. On Day 6 of hospitalization, an enhanced chest CT was performed that confirmed an irregular solid nodule in the right middle lobe and bilateral ground-glass lesions (GGO). At the time, the significance of the latter findings was unknown. Her general condition was good, with no fever or respiratory symptoms, and clear to auscultation bilaterally. She underwent pre-surgical tests and preparations. On Day 12, a thoracoscopic resection of the right middle lobe was performed without event. On Day 13 (post-op Day 1), a repeat CT showed post-resection changes and bilateral GGO in the lower lobes of the lungs (**Figure 1A**). White blood cell count was 12.49×10^{12}/L, while lymphocyte count was lowered to 0.4×10^{9}/L and the differential to 5%. There was a slight wheezing sound to auscultation on the right side. On Day 16, the patient developed some difficulty in breathing, chest tightness, wheezing, and dry cough. She was diagnosed as “suspicious for viral pneumonia,” with intermittent SpO2 between 72% and 88%. On Day 24, she was transferred to the special isolation ward due to a pharyngeal swab test positive for the 2019-nCoV. The labs drawn from the day before (Day 23) showed white blood cell 33.52 ×10^9/L↑; neutrophils 89.80%↑; lymphocytes 1.90%↓; eosinophils 0%↓; neutrophil

count 30.10×10^9/L↑; lymphocyte count 0.65×10^9/L↓; monocyte count 2.50×10^9/L↑; eosinophil count 0.01×10^9/L↓; and basophil count 0.26×10^9/L↑.

Despite comprehensive treatment, including antibiotics, assisted oxygenation, and other supportive care, the patient's condition deteriorated. SpO2 lowered to 62.6% and heart rate to 40 bpm. A do-not-resuscitate (DNR) order was given. She went into coma on Day 27 and died on Day 29. She did not manifest fever during the hospital stay.

Subsequent clinical information confirmed that she was exposed to another patient in the same room who was subsequently found to be infected with the 2019-nCoV.

The right middle lobe resection specimen was delivered to the surgical pathology lab and was processed according to routine biosafety standards. Hematoxylin and eosin stained sections were reviewed. A firm area of 1.5 cm in diameter was identified grossly, which in histology was consistent with typical adenocarcinoma, with half exhibiting a lepidic and half an acinar pattern (not shown). Sections away from the tumor, as shown in **Figure 2**, revealed evident alveolar damage, including alveolar edema and proteinaceous exudates (**Figure 2A**). Prominent inspissated spherical secretions or globules were also noted (**Figure 2B**). There was vascular congestion but patchy and mild inflammatory infiltration. Focally fibrin clusters mixed with mononuclear inflammatory cells and multinucleated giant cells were noted in the airspaces (**Figure 2C**). No significant neutrophil infiltration was present in the tissue. There were patchy and severe pneumocyte hyperplasia and interstitial thickening, indicating an ongoing reparative process. Suspected viral inclusions were also noted in some of these cells (**Figure 2D**).

CASE 2 was a male patient of 73 years of age, who presented for elective surgery for lung cancer. Nine months earlier, a nodule was discovered radiologically in the right lower lobe of the lung during a health checkup. He had a past medical history of hypertension for 20 years, which had been adequately managed. A diagnosis of adenocarcinoma was made in a subsequent needle biopsy. The patient was admitted one week after the biopsy to the Thoracic Tumor ward, where he underwent a right lower lobe lung resection with lymph nodes dissection three days after admission. He recovered well and was discharged on Day 6 post-operationally. A chest CT was performed on post-op Day 2, showing postoperative changes, as well as patchy ground-glass opacity in the right upper lobe. Retrospective re-examination of the images was "suspect for atypical viral pneumonia." He developed a fever on post-op Day 9 (38.2 C), with dry cough, chest tightness, and muscle pain. A nucleic acid test for 2019-nCoV came back as positive. Other labs were significant for lowered lymphocyte count. He was re-admitted to the Infectious Disease ward. A repeat chest CT scan showed additional foci of ground-glass opacifications (GGO) in the bilateral upper lobes, consistent with viral pneumonia (**Figure 1B**). Tests for influenza virus and other infectious agents were negative. He underwent treatment for NCP. He gradually recovered and was discharged after twenty days of treatment in the Infectious Disease ward.

Upon pathologic examination of the resected lobectomy specimen, a 1.2 cm grey white nodule adjacent to the pleura was identified, which was poorly demarcated from the adjacent non-tumor lung parenchyma. Histopathologic diagnosis of the tumor was

that of adenocarcinoma, pT1bN0 (28 lymph nodes all negative). The resection margins were negative as well. Histologically, the surrounding lung parenchyma showed patchy but evident proteinaceous and fibrin exudate (**Figure 3A**). There were diffuse thickening of alveolar walls (**Figure 3B**), consisting of proliferating interstitial fibroblasts and type II pneumocyte hyperplasia. Focal fibroblast plug (arrow) and multinucleated giant cells (arrowheads) are seen in airspaces (**Figure 3C**), indicating varying degrees of proliferative phase of diffuse alveolar damage. Some areas showed abundant alveolar macrophages along with type II pneumocyte hyperplasia (**Figure 3D**).

Discussion

To our knowledge, the pathologic findings reported here represent the first for SARS-CoV-2 pneumonia, or 2019 coronavirus infection disease (COVID-19). At the time of manuscript preparation, no autopsies had been performed on patients with COVID-19. Data on lung biopsies performed for the COVID-19 is similarly lacking.

Pathologic findings from these two patients are edema and prominent proteinaceous exudates, vascular congestion, and inflammatory clusters with fibrinoid material and multinucleated giant cells. Reactive alveolar epithelial hyperplasia is seen in case 1 and fibroblastic proliferation (fibroblast plugs) in case 2 are indicative of early organization. No prominent neutrophil infiltration was seen. The significance of the large protein globules is not entirely clear, as these were described in patients with SARS, but also could represent a non-specific change with aging. More cases with sufficient controls are necessary to further clarify this change.

The two cases reported here represent “accidental” sampling of the COVID-19, in which surgeries were performed for tumors in the lungs at a time when the superimposed infections were not recognized. These provided the first opportunities for studying the pathology of COVID-19. For **CASE 1**, the surgery was performed six days after the CT findings of early GGO signs, meaning the pathologic changes of the non-tumor lung parenchyma indeed represent at least the peripheral part of COVID-19 pneumonia, as the imaging changes were more prominent towards the lower lobes. For **CASE 2**, as recognized later on, that patient was unknowingly put in the same room with patients who were positive for SARS-CoV-2 infection; the status of infection was not known to anyone at the time. He developed early lung lesions on a chest CT performed to evaluate the result of surgery. However, due to a lack of sufficient knowledge about the new infection, the lesions were recognized only retrospectively as representing the COVID-19 pneumonia.

The differential diagnoses of COVID-19 pneumonia might include, but are not limited to, acute or chronic pneumonia resulting from other infections. Comprehensive clinical analyses of the epidemiological status, CT scan, and nucleic acid test can easily exclude such possibilities. As for the original SARS, SARS-COV-19 shares high genetic homology with SARS-CoV. So the International Committee on Taxonomy of Viruses (ICTV) recently renamed the 2019-nCoV to SARS-CoV-2 and the disease as COVID-19. Compared with pathological findings in a cohort of autopsy cases of SARS, the two cases presented here also exhibited exudative and proliferative phase acute lung injury such as edema, inflammatory infiltrate, type II pneumocyte hyperplasia, and organization, but

without obvious hyaline membrane formation and other chronic process such as squamous metaplasia[5-7]. Of note, pathologic changes seen in our two cases proceeded the development of clinical symptoms, and likely represent an earlier phase of the disease. Future studies in autopsies may add to the current findings.

Although patient #1 was never febrile, her CBC profile, especially from post-op Day 1, showed high WBC counts and lymphocytopenia, which is consistent with COVID-19. This may be a good clue for early diagnosis in the future. **CASE 2** developed a fever a few days after the CT findings, suggesting a delay in symptom development in these patients. During the earlier days of the outbreak, there had been limitations in both capacity and turnaround time for the nucleic acid test, which had further caused delay in confirming the diagnosis of COVID-19[4] in many patients. It seems that the time for the early lung lesions or COVID-19 to become severe enough to cause clinical symptoms is rather long. Even among patients with fevers, the commonly used pharyngeal swab PCR test may be negative, due to the lack of viruses in the upper respiratory tract despite the presence of pneumonia. However, radiographic changes can occur early (chest CT scan is mostly employed in China during the current outbreak). Therefore, during an epidemic season, it is prudent to carefully evaluate any lung infiltration for the ground glass opacity, and an appropriate serology test be used to rule out potential infection[4].

These two incidences also typify a common scenario during the earlier phase of the SARS-CoV-2 outbreak, during which a significant number of healthcare providers became infected in hospitals in Wuhan, and patients in the same room were cross-infected, as they were exposed to unknown transmission sources. Because of this, it is important

to practice “universal precaution” in surgical pathology laboratories and regard all fresh specimens as potentially infectious. In China most surgical specimens are received already fixed in formalin. However, for larger specimens the center of a specimen may not be sufficiently fixed and still pose potential risk for infection. Therefore, proper PPE with surgical masks or N95 respirators are worn all the time in the gross room. Fortunately thus far to our knowledge, no cases of pathologists being infected by COVID-19 had occurred.

It would be beneficial if RT-PCR and/or immunohistochemical stains could be performed on these two cases to further confirm the presence of the viruses that may be associated with the pneumonia. Unfortunately, these tests are currently under development, and adaptation to tissue specimens is not yet available. Nevertheless, we believe it is imperative to report the findings of routine histopathology for better understanding of the mechanism by which the SARS-CoV-2 causes lung injury in the unfortunate tens and thousands of patients in Wuhan and worldwide.

Acknowledgement

We thank Jian Xu and Bei Qi for excellent technical and logistic assistance. This study was approved by the Ethic Consensus Committee of Zhongnan Hospital of Wuhan University in China. Data on accumulated number of cases and deaths were from the website of National Health Commission of China. Update on the epidemic of novel

coronavirus (2019-nCoV) infected pneumonia (2020-01-26) [EB/OL].

http://www.nhc.gov.cn/xcs/yqtb/202001/3882fdcdbfdc4b4fa4e3a829b62d518e.shtml

Figure legend

Figure 1. Representative images of chest CT scan. **A**. Case #1: image on post-operative Day 1 showing post-surgery changes in right lung, and increased ground glass opacities bilaterally (arrows). **B**. Case #2: foci of ground glass opacity seen bilaterally (arrows).

Figure 2. Histological changes from case #1. A. Proteinaceous exudates in alveolar spaces, with granules; B. Scattered large protein globules (arrows); C. Intraalveolar fibrin with early organization, with mononuclear inflammatory cells and multinucleated giant cells ; D. Hyperplastic pneumocytes, some with suspected viral inclusions (arrow).

Figure 3. Histologic changes of COVID-19 pneumonia in case #2. **A**. Evident proteinaceous and fibrin exudate; **B**. Diffuse expansion of alveolar walls and septa due to fibroblastic proliferations and type II pneumocytes hyperplasia, consistent with early diffuse alveolar damage (DAD) pattern; **C**. Plugs of proliferating fibroblasts or "fibroblast balls" in the interstitium (arrow); **D**. Abundant macrophages infiltrating airspaces and type II pneumocyte hyperplasia.

References

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. **Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China**. *Lancet* 2020. doi.org/10.1016/S0140-6736(20)30183-5

2. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. **A Novel Coronavirus from Patients with Pneumonia in China, 2019**. *N Engl J Med* 2020. doi.org/10.1056/NEJMoa2001017

3. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. **Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China**. *JAMA* 2020. doi.org/10.1001/jama.2020.1585

4. Xiao SY, Wu Y, Liu H. **Evolving status of the 2019 novel coronavirus Infection: proposal of conventional serologic assays for disease diagnosis and infection monitoring [Commentary]**. *J Med Virol* 2020. doi.org/10.1002/jmv.25702

5. Hwang DM, Chamberlain DW, Poutanen SM, Low DE, Asa SL, Butany J. **Pulmonary pathology of severe acute respiratory syndrome in Toronto**. *Mod Pathol* 2005; 18(1):1-10.

6. Franks TJ, Chong PY, Chui P, Galvin JR, Lourens RM, Reid AH, et al. **Lung pathology of severe acute respiratory syndrome (SARS): a study of 8 autopsy cases from Singapore**. *Hum Pathol* 2003; 34(8):743-748.

7. Nicholls JM, Poon LL, Lee KC, Ng WF, Lai ST, Leung CY, et al. **Lung pathology of fatal severe acute respiratory syndrome**. *Lancet* 2003; 361(9371):1773-1778.

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