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.

Characteristics of Pleural Effusion in Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Pneumonia

To the Editor:

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus is known to cause coronavirus disease 2019 (COVID-19). SARS-CoV-2 infection was first recognized in December 2019 in Wuhan, China, and it has spread globally, resulting in the ongoing pandemic.[1] SARS-CoV-2 frequently causes pneumonia and carries a mortality of 3.7% worldwide.[2] SARS-CoV-2 belongs to a family of coronaviruses that can cause respiratory illnesses such as severe acute respiratory syndrome (SARS-CoV-1), and Middle East respiratory syndrome (MERS-CoV).[1] The prevalence of pleural effusion, as determined by computed tomography (CT) in patients with SARS-CoV-1, was found to be similar to SARS-CoV-2-associated pleural effusions.[3–6] Three retrospective studies from China that examined the radiographic features of SARS-CoV-2 pneumonia found the prevalence of pleural effusion at 5-10%.[3,4,6] However, to date, there has been no description of the characteristics of SARS-CoV-1 or SARS-CoV-2-associated pleural effusions. We described the pleural fluid characteristics of four patients with SARS-CoV-2 pneumonia, who underwent pleural drainage. To our knowledge, this is the first description of SARS-CoV-2-associated pleural effusion.

SARS-CoV-2 infection was diagnosed with real-time reverse transcription-polymerase chain reaction (RT-PCR) from a nasopharyngeal swab. Pleural effusion was diagnosed by chest radiography or thoracic ultrasound. The decision to perform pleural drainage was made by treating clinicians. The pleural fluid obtained from these thoracenteses was sent for analysis based on the treating clinician's judgment. In almost all cases, the following pleural fluid results were obtained: visual appearance, the volume of pleural effusion drained, cell count and differential, total protein, glucose, pH, lactate dehydrogenase (LDH), and microorganism culture. Serum was routinely obtained simultaneously for inflammatory markers, LDH, and total protein levels. Pleural effusions were classified as either transudate or exudative based on Light's criteria.[7] Pleural effusions with all of the following criteria were classified as transudative: a) pleural fluid to serum protein ratio less than 0.5; b) pleural fluid to serum LDH ratio less than 0.6; and c) pleural fluid LDH less than 2/3 the upper limit of normal. If any of the above criteria for a transudative pleural effusions were not met, the effusions were classified as exudative.

We identified four patients admitted to the intensive care unit (ICU) with SARS-CoV-2 infection and required pleural drainage. A total of five pleural fluid samples were analyzed, including two samples from a patient with bilateral pleural effusions. The demographics, comorbidities, laboratory data on the day of pleural drainage, and duration from initial presentation to pleural drainage were summarized in Table 1. The study patients were predominantly male (75%), with a mean age of 57 +/- 12 years. Most of the patients (3/4, 75%) had underlying comorbidities. Chest radiography demonstrated bilateral infiltrates in all patients with negative echocardiogram findings of congestive heart failure. Markedly increased inflammatory markers on the day of pleural drainage, specifically d-dimer, fibrinogen, lactate dehydrogenase (LDH), C-reactive protein (CRP), and fibrinogen, were noted in all patients. All patients were deemed hypercoagulable and managed with systemic anticoagulation. Most patients (75%) had unilateral pleural effusion, and 75% of effusions were located on the left hemithorax. The mean duration from the time of initial presentation with SARS-CoV-2 pneumonia until pleural drainage was 18 +/- 4 days. Repeat RT-PCR test during the time of pleural drainage remained positive in all patients. The pleural fluid characteristics are summarized in Table 2. 60% (3/5) of pleural fluid drained were either serosanguineous or sanguineous in appearance. The majority of the pleural fluid drained had a high amount of red blood cells (2,000 to 1,010,000 per mm^3) compared to white blood cells (475 to 7,738 per mm^3). The white blood cell differential on pleural fluid was predominantly neutrophils and lymphocytes with minimal eosinophils present. All pleural fluid drained was exudative. Pleural fluid LDH (284 to 3,651 IU/L) and pH (7.43<) were markedly elevated in all SARS-CoV-2 patients. None of the cultures from pleural fluid returned positive for bacterial, fungal, and mycobacterial organisms. The values of glucose drained from pleural fluid were either normal or elevated at 102 to 209 mg/dL.

The majority (75%) of pleural effusions in our study were found to be unilateral, which is consistent with previously published study.[3] Pleural effusions were detected after two weeks of initial presentation. This delay in recognition could be a function of the limited use of computed tomography and pleural ultrasonography during the SARS-CoV-2 pandemic. Moreover, few observational studies have described the appearance of pleural effusion as a late manifestation of SARS-CoV-2

TABLE 1. Clinical characteristics of SARS-CoV-2 patients. Corresponding normal reference range of serum values are provided in square brackets where applicable.

	Patient 1	Patient 2	Patient 3	Patient 4
Demographics				
Age (years)	68	62	50	46
Sex	Male	Female	Male	Male
Race	Caucasian	African American	Asian	Hispanic
Body Mass Index (kg/m^2)	26	35	30	24
Presentation Characteristics				
Comorbidities	HLD	HTN, HLD, CKD, diabetes, CAD	None	HTN, HLD, CKD, diabetes, CAD, asthma
Chest Radiograph	Bilateral Opacities	Bilateral Opacities	Bilateral Opacities	Bilateral Opacities
Renal involvement	None	Present requiring hemodialysis	None	None
Echocardiography findings	No systolic or diastolic dysfunction	No systolic or diastolic dysfunction	No systolic or diastolic dysfunction	No systolic or diastolic dysfunction
Use of anticoagulation	Heparin infusion	Heparin infusion	Therapeutic enoxaparin	Therapeutic enoxaparin
Pertinent laboratory data on day of pleural drainage				
D-Dimer (mg/L) [<0.5]	35.2	6.2	6.3	6.8
Procalcitonin (ng/mL) [<0.05]	1.1	0.5	0.2	0.6
Ferritin (ng/mL) [18-270]	1,190	1,400	116	500
LDH (IU/L) [150-300]	904	434	220	160
CRP (mg/L) [<10]	3	133	18.8	60
Fibrinogen (mg/dL) [200-400]	241	554	400	500
WBC (10*3/uL) [4-11]	16	16	13	12
Platelet (10*3/uL) [150-350]	101	135	400	170
Location of pleural effusion	Left	Left	Bilateral	Right
Days from presentation to pleural drainage	23	14	20	15
SARS-CoV-2 RT-PCR on day of pleural drainage	Positive	Positive	Positive	Positive

Abbreviations: CAD, coronary artery disease; CKD, chronic kidney disease; CRP, C-reactive protein; HTN, hypertension; HLD, hyperlipidemia; LDH, lactate dehydrogenase; N/A, not available; RT-PCR, real-time reverse transcription-polymerase chain reaction; WBC, white blood cell count.

pneumonia, which is more than seven days after presentation with SARS-CoV-2 pneumonia.[4,6] An observational study on radiological findings of 62 SARS-CoV-2 patients demonstrated that the risk of developing pleural effusion was up to 23% in patients with advanced SARS-CoV-2 pneumonia.[6]

The exact pathogenesis of pleural effusion due to SARS-CoV-2 pneumonia is not known. However, our patients have significantly increased inflammatory markers, which may signify an increase in capillary and endothelial dysfunction leading to exudation of fluid into the pleural space. Only 40% of pleural effusions were lymphocytic predominant (lymphocytes >50% of nucleated cells), lower than seen in other viral infection-related pleural effusions such as avian influenza.[8,9] This finding can be explained by relative lymphopenia seen in patients with SARS-CoV-2 infection. Majority (3/5,60%) of effusions were hemorrhagic (RBC >100,000 per mm^3) [Table 2]. While it is possible that intrapleural bleeding could reflect a procedural complication in patients receiving systemic anticoagulation, anticoagulants were held prior to drainage. Furthermore, high eosinophil counts are frequently encountered in hemorrhagic pleural effusions, but the finding of low eosinophil counts (1% and less) in our study patients were similar to white cell count differentials observed in other viral-induced pleural effusions.[8,10] Moreover, most of these patients were on steroids, which can explain low eosinophils in the pleural space. A prospective study has reported no increased risk of significant bleeding associated with pleural effusion drainage in the setting of therapeutic anticoagulation.[11] We hypothesize that sanguineous pleural effusion in SARS-CoV-2 may be the result of endothelial dysfunction-related microthrombi from underlying inflammation that causes foci of hemorrhage in the lung parenchyma extending into the pleura. This has been described in autopsy findings of SARS-CoV-2 patients in New Orleans.[12]

All effusions were exudative by Light's criteria.[7]. These findings can be explained by the markedly elevated pleural fluid LDH in all pleural effusions (pleural fluid to serum LDH ratio of 0.6<) with a mean pleural fluid LDH level of 1550 (Table 2). The significantly elevated level of LDH in pleural fluid can be due to the presence of a large amount of hemolyzed red blood cells in the pleural fluid. However, this finding persisted after excluding the effusions with sanguineous appearance. A heightened immune response observed in many SARS-CoV-2

TABLE 2. Characteristics of pleural fluid samples from SARS-CoV-2 patients. Corresponding normal reference range of serum values are provided in brackets where applicable.

	Patient 1	Patient 2	Patient 3	Patient 3	Patient 4
Pleural Fluid Appearance	Sanguineous	Serous	Serous	Serosanguineous	Sanguineous
Volume Drained (mL)	3000	800	700	700	500
Type of pleural intervention	14 French pigtail catheter	14 French pigtail catheter	14 French pigtail catheter	14 French pigtail catheter	22 French chest tube
Location	Left	Left	Left	Right	Right
Pleural Fluid Cell Differentials					
Red blood cell count (per mm^3)	555,000	88,000	2000	133,000	1,010,000
White blood cell count (per mm^3)	1815	2719	476	600	7738
Neutrophil (%)	75	0	11	47	96
Lymphocyte (%)	9	75	50	30	1
Monocyte (%)	5	10	39	22	2
Eosinophil (%)	0	0	0	1	1
Pleural Fluid Chemistry					
Protein (g/dL)	4.5	3.6	2.6	2.2	3.1
LDH (IU/L)	2689	672	549	284	3651
Glucose (mg/dL)	132	116	209	191	102
pH [7.35-7.55]	7.45	7.43	7.72	7.8	7.57
Pleural Fluid Culture	No growth	No growth	No growth	No growth	No growth
Serum					
Total protein (g/dL) [6-8.5]	4.8	6.3	6.1	6.1	4.9
LDH (IU/L) [150-300]	904	434	220	220	160
Pleural Fluid/Serum Protein Ratio	0.9	0.6	0.4	0.4	0.6
Pleural Fluid/Serum LDH Ratio	3	1.5	2.5	1.3	22.8

Abbreviation: LDH, lactate dehydrogenase.

patients with extremely elevated inflammatory markers causing a high cell turnover may explain this finding.[2,4,13] A markedly elevated pleural fluid to serum LDH ratio of 1.3 and more may suggest underlying SARS-CoV-2-associated pleural effusion. Similar findings have been found in patients with either H5N1 Influenza A or Pneumocystis jirovecii-associated pleural effusions. In these observational studies, the mean pleural fluid LDH was 400 IU/L and more with pleural fluid to serum LDH ratio greater than 1.[9,14] Our study patient's pleural fluid glucose levels were within the normal range, which are similar to findings noted on other viral-induced pleural disease.[8]

Our study was limited by the small sample size. Pleural fluid was not tested for the presence of SARS-CoV-2 using RT-PCR. However, there was no alternative cause of pleural effusion identified in these patients. Repeat RT-PCR test during the time of pleural drainage on these patients remained positive. All patients were receiving systemic anticoagulation for hypercoagulability, which may explain the high prevalence of hemorrhagic effusions in these patients.

Our study demonstrated that SARS-CoV-2-associated pleural effusions are commonly unilateral and occur after a week from the presentation. The majority of pleural effusions were hemorrhagic, and pleural lymphocytosis was seen in only 40% of cases. A marked elevation in LDH was found in pleural fluid as compared to serum. These findings were consistent with features seen in other viral infection-related pleural effusions, except a higher proportion of SARS-CoV-2 patients have hemorrhagic effusion.

DECLARATION OF COMPETING INTEREST

WC: None, JH: Consultant/Advisory Boards: IBIOS [IPF]; Roche/Genentech [IPF(Nintedanib)]; Boehringer Ingelheim [IPF (Pirfenidone)], AC: None.

FUNDING

None.

Woon H. Chong,[1]
John Terrill Huggins,[2]
Amit Chopra[1,*]

[1]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Albany Medical Center, Albany, NY, United States
[2]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Ralph H. Johnson VA Medical Center, Charleston, SC, United States
E-mail: Chopraa1@amc.edu

REFERENCES

1. **Hui DS, I Azhar E, Madani TA, et al.** The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health — The latest 2019 novel coronavirus outbreak in Wuhan, China. *Int J Infect Dis*. 2020; 91:264–266. https://doi.org/10.1016/j.ijid.2020.01.009.
2. **Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ.** COVID-19: consider cytokine storm syndromes and

immunosuppression. *Lancet*. 2020;395(10229):1033–1034. https://doi.org/10.1016/S0140-6736(20)30628-0.
3. **Song F, Shi N, Shan F, et al.** Emerging 2019 novel coronavirus (2019-nCoV) pneumonia. *Radiology*. 2020;295(1):210–217. https://doi.org/10.1148/radiol.2020200274.
4. **Shi H, Han X, Jiang N, et al.** Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infect Dis*. 2020;20(4):425–434. https://doi.org/10.1016/S1473-3099(20)30086-4.
5. **Müller NL, Ooi GC, Khong PL, Nicolaou S.** Severe Acute Respiratory Syndrome: Radiographic and CT Findings. *Am J Roentgenol*. 2003;181(1):3–8. https://doi.org/10.2214/ajr.181.1.1810003.
6. **Zhou S, Wang Y, Zhu T, Xia L.** CT Features of Coronavirus Disease 2019 (COVID-19) Pneumonia in 62 Patients in Wuhan, China. *Am J Roentgenol*. 2020:1–8. https://doi.org/10.2214/AJR.20.22975. Published online March 5.
7. **Light RW, Macgregor MI, Luchsinger PC, Ball WC.** Pleural effusions: the diagnostic separation of transudates and exudates. *Ann Intern Med*. 1972;77(4):507–513. https://doi.org/10.7326/0003-4819-77-4-507.
8. **Nestor J, Huggins T, Kummerfeldt C, DiVietro M, Walters K, Sahn S.** Viral diseases affecting the pleura. *J Clin Virol*. 2013;58(2):367–373. https://doi.org/10.1016/j.jcv.2013.06.013.
9. **Soepandi PZ, Burhan E, Mangunnegoro H, et al.** Clinical course of avian influenza A(H5N1) in patients at the persahabatan hospital, Jakarta, Indonesia, 2005–2008. *Chest*. 2010;138(3):665–673. https://doi.org/10.1378/chest.09-2644.
10. **Heidecker J, Kaplan A, Sahn SA.** Pleural fluid and peripheral eosinophilia from hemothorax: hypothesis of the pathogenesis of EPE in hemothorax and pneumothorax. *Am J Med Sci*. 2006;332(3):148–152. https://doi.org/10.1097/00000441-200609000-00011.
11. **Puchalski JT, Argento AC, Murphy TE, Araujo KLB, Pisani MA.** The safety of thoracentesis in patients with uncorrected bleeding risk. *Ann Am Thorac Soc*. 2013;10(4):336–341. https://doi.org/10.1513/AnnalsATS.201210-088OC.
12. **Fox SE, Akmatbekov A, Harbert JL, Li G, Brown JQ, Vander Heide RS.** Pulmonary and cardiac pathology in Covid-19: the first autopsy series from New Orleans. *Pathology*. 2020. https://doi.org/10.1101/2020.04.06.20050575.
13. **Zhou F, Yu T, Du R, et al.** Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054–1062. https://doi.org/10.1016/S0140-6736(20)30566-3.
14. **Horowitz ML, Schiff M, Samuels J, Russo R, Schnader J.** *Pneumocystis carinii* pleural effusion: pathogenesis and pleural fluid analysis. *Am Rev Respir Dis*. 1993;148(1):232–234. https://doi.org/10.1164/ajrccm/148.1.232.