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.

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Cytologic findings in effusions from patients with SARS-CoV-2 infection

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Introduction Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is associated with "flu-like" upper respiratory tract symptoms and pneumonia. Body cavity effusions develop in a subset of patients with advanced disease. Although SARS-CoV-2 is known to be present in certain body fluids (eg, blood) of COVID patients, it remains unclear if body cavity fluids are sites of infection. Our aim was to characterize the cytologic and clinical findings in COVID-19 patients with effusions.

Materials and methods A record search for all cases of body cavity effusion cytology in SARS-CoV-2 positive patients from March 1, 2020, to September 1, 2020, was performed. Clinical history, fluid chemical analysis, cytologic findings, and patient outcomes were recorded. All cytology slides were reviewed. In situ hybridization (ISH) targeting SARS-CoV-2 spike protein transcript (V-nCoV2019-S) was performed on cell block material in all cases.

Results A total of 17 effusion cytology cases were identified among 15 COVID patients, including 13 pleural, 2 pericardial, and 2 peritoneal. Most (13 of 15) patients were hospitalized for COVID complications. Eight patients died during hospitalization, 7 from COVID complications. All fluids were transudative by protein criteria. Lymphocytic or histiocytic inflammation predominated in 12 of 17 cases. Five exhibited hemophagocytosis. No viral cytopathic changes or extra-medullary megakaryocytes were seen. Viral RNA was not detected in any case by ISH.

Conclusions Body cavity effusion is an ominous finding in patients with advanced COVID-19 disease. Such effusions tend to be transudative with lymphohistiocytic inflammation, and commonly exhibit hemophagocytosis, an otherwise rare finding in effusion cytologies. No direct infection of cellular elements by SARS-CoV-2 was identified by ISH.

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Introduction

Severe acute respiratory syndrome coronavirus (SARS-CoV-2) is a novel RNA coronavirus that is the underlying cause of coronavirus disease 2019 (COVID-19), which the World Health Organization declared a pandemic in March 2020. The symptoms of COVID-19 are variable and non-specific.[1] The majority of patients infected with SARS-CoV-2 are asymptomatic or develop mild "flu-like" symptoms such as cough, fever, and fatigue. However, a portion of patients (~10%) develop more severe respiratory disease, including interstitial pneumonia and acute respiratory distress syndrome, as well as multiple organ dysfunction/failure. Severe cases of COVID have been linked to abundant release of proinflammatory cytokines, resulting in a so-called cytokine storm and hemophagocytic syndrome, a hyperactive autoinflammatory immune response that leads to tissue recruitment of T-cells, neutrophils, and macrophages with resulting end-organ damage.[2]

Chest radiographic findings in COVID-19 are typically non-specific. Common computed tomography (CT) findings include ground-glass opacities, often with consolidation, typically in a bilateral and peripheral distribution.[3,4] Body cavity effusions are relatively uncommon but are identifiable on CT imaging in a subset of COVID-19 patients, with pleural effusion present in 5.88% and pericardial effusion in 4.55% of cases in 1 meta-analysis.[4] Pleural effusions are more common in patients with severe disease. Acute perimyocarditis has been described in a small subset of COVID-19 patients, many of whom present with cardiac tamponade.

To date, literature on biopsy and/or cytology findings in living patients with COVID-19 have been scarce, and mostly limited to case studies and small case series. Pulmonary findings on biopsy have included diffuse alveolar damage, hyaline membranes, and interstitial inflammation composed predominantly of lymphocytes.[5-8] Cytology studies in COVID-19 are particularly scarce. One recent report noted plasmacytosis in a bronchoalveolar lavage specimen.[9] Rare reports of pleural effusion specimens have generally noted reactive mesothelial cells and non-specific mixed inflammation.[5] Autopsy studies of the lungs have generally shown diffuse alveolar damage, often with superimposed bacterial bronchopneumonia.[7,8] Proposed pneumocyte viral cytopathic change including hyperplasia, multinucleation, and intranuclear inclusion bodies have been reported. Systemic findings at autopsy have included hemophagocytosis, multiple thromboemboli, endotheliitis, and tissue megakaryocyte recruitment.

SARS-CoV-2 RNA has been detected in a number of bodily fluids including bronchoalveolar fluid, sputum, feces, blood, and urine.[10] In addition, recent single case studies have identified viral RNA in pleural and pericardial fluid, respectively, by reverse transcriptase polymerase chain reaction (RT-PCR).[11,12] At this time, it is not clear whether body cavities such as the pleura or pericardium may serve as reservoirs for ongoing or repeat COVID-19 disease, or whether SARS-CoV-2 infection may be present within any of the cellular elements of effusion specimens.

To the best our knowledge, no studies have examined the specific findings in patients with COVID-19 and serous cavity effusions. The goals of our study are therefore to determine the pertinent clinical and pathologic findings in patients with COVID infection and body cavity effusions, and to determine whether effusion fluids may serve as viral reservoirs. To that end, we examined the clinical findings in a subset of our patients with confirmed SARS-CoV-2 infection and sampling of serous body effusion fluid, and determined the cytologic and fluid analytic findings seen in these effusions. This study also assessed for the presence of SARS-CoV-2 RNA within sampled cytologic material.

Materials and methods

The study was performed under approval from the University of Michigan institutional review board. An ongoing search of the University of Michigan Anatomic Pathology database (SoftPathologyDx) was performed to identify cytologic cases of pleural, pericardial, or peritoneal fluids in patients who also had a positive COVID-19 nasopharyngeal PCR test from March 2020 to September 2020.

A total of 17 body cavity effusion specimens in 15 patients were identified. All cytology slides including Thinprep (Papanicolaou stained), smears (Diff-Quik stained), and sectioned cell block slides (hematoxylin and eosin stained) were retrieved from the archives along with cell block tissue cassettes. The electronic medical record was accessed to determine patient demographics (including age and sex), past medical history, history of present illness, volume of fluid collected, hospital course, and patient outcomes. In all cases, data from any concurrent fluid chemical analyses were recorded, including color, appearance, and levels of protein; pH; and glucose. Also collected were results from any associated microbiology culture findings. Finally, erythrocyte and leukocyte counts and 100 cell count differentials in these effusion samples were noted.

For comparison to pleural effusions in patients with COVID-19, we also searched our archives over a 5-year period (2016-2020) for any cases of pleural effusion with a concurrent positive test for influenza. In addition, 14 consecutive benign pleural effusion cytologies from patients with acute respiratory symptoms and pleural effusions but no established infection from November and December of 2020 were selected for microscopic review.

Cytology slides were re-reviewed by 2 cytopathologists (R.C. and L.P.) to determine the cytologic makeup of the specimens, including types of inflammatory cells present and mesothelial cell findings. The presence or absence of hemophagocytosis, megakaryocytes, and viral cytopathic changes was noted. Cell blocks were reviewed to determine adequate cellularity for in situ hybridization (ISH). ISH targeting SARS-CoV-2 spike protein transcript (V-

Table 1 Summary of patient histories and outcomes in COVID-19 patients with effusion cytology specimens.

Patient	Age, years	Sex	Clinical history	Presenting illness/symptoms	Clinical outcome	Fluid type
1	72	M	Diverticulitis	Abdominal pain, bloating. No respiratory symptoms.	Died of gastroinetstinal bleeding	Pleural fluid × 2
2	70	M	Cirrhosis, hepatocellular carcinoma	Dyspnea	Died of COVID-19	Pleural fluid × 2
3	81	F	Chronic lymphocytic leukemia	Pneumonia symptoms	Died of COVID-19	Pleural fluid
4	67	F	Follicular thyroid carcinoma metastatic to lung	Altered mental status, upper respiratory symptoms	Died of COVID-19	Pleural fluid
5	59	M	No significant past medical history	Dyspnea, bilateral pneumonia on CT	Died of COVID-19	Pleural fluid
6	75	M	Chronic kidney disease, hypertension	Acute hypoxic respiratory failure	Died of COVID-19	Pleural fluid
7	58	M	Cerebrovascular accident	Altered mental status, upper respiratory symptoms	Died of COVID-19	Pleural fluid
8	42	M	Gastroesophageal reflux disease	Dyspnea, fatigue, fever	Alive	Pleural fluid
9	49	F	Systemic lupus erythematous, asthma	Prior COVID-19 hospitalization, readmitted for dyspnea after discharge	Alive	Pleural fluid
10	76	M	End-stage renal disease secondary	Cough, fever, dyspnea, fatigue	Alive	Pleural fluid
11	70	M	Diabetes mellitus type II, hypertension, dementia	Prior COVID-19 hospitalization, readmitted for long standing effusion	Alive	Pleural fluid
12	37	F	No significant past medical history	Transferred from outside hospital with COVID-19, tamponade	Died of COVID-19	Pericardial fluid
13	32	F	No significant past medical history	Transferred from outside hospital with COVID-19, fulminant myocarditis	Alive, chest pain	Pericardial fluid
14	35	F	Adnexal mass, suspected dermoid cyst	Asymptomatic, detected on pre-surgery workup	Alive	Peritoneal fluid
15	52	M	Gastric carcinoma with peritoneal involvement	Acute hypoxic respiratory failure	Alive	Peritoneal fluid

nCoV2019-S) was performed on archived cell block material in all cases with positive and negative controls (including positive and negative RNA controls on a representative cell block and a positive SARS-CoV-2 control).

Results

We identified 15 patients who fit study inclusion parameters, among whom a total of 17 effusion cytology specimens were collected (Table 1). There were 11 (73%) patients who had unilateral pleural effusions sampled, including 2 (13%) patients with 2 samples collected each from the same site. Two patients had pericardial effusions sampled and 2 patients had peritoneal fluid sampling (1 for ascites, 1 peritoneal washing). Patients were 32-81 years old, with 9 male and 6 female patients. Four (27%) patients had a known diagnosis of malignancy (1 gastric carcinoma, 1 hepatocellular carcinoma, 1 chronic lymphocytic leukemia, and 1 follicular thyroid carcinoma). Most (13 of 15) patients had respiratory tract symptoms ranging from dyspnea and cough to acute hypoxic respiratory failure. Of the remaining 2 patients, 1 presented with abdominal pain and bloating and the other was found to have SARS-CoV-2 incidentally on pre-surgical workup.

There were 8 of 15 (53%) patients who died during hospitalization, including 7 (47%) from COVID-related illness. There were 6 of 11 (55%) patients with pleural effusion sampling who died during the course of hospitalization, including 5 of COVID-related illness and 1 from gastrointestinaI bleeding secondary to diverticular disease. One of the 2 patients with pericardial effusion died, as a result of cardiac tamponade secondary to COVID-19. Both patients with peritoneal fluid sampling are alive and were discharged.

Fluid chemical analysis was performed at the time of collection in most cases (Tables 2 and 3). Protein levels were consistently low in these effusion specimens (range, <0.8 to 5.9 g/L). The pH ranged from 6.89 to 8.15, and glucose from 19 to 150 mg/dL. Leukocyte count in these specimens ranged from 75 to 6676 cells/mL. A differential 100 cell count was performed in 14 of 17 cases. In 9 cases, lymphohistiocytic inflammation predominated, and in 5 specimens neutrophils were the predominant leukocyte present. Mesothelial cells were generally scant.

Microbiology cultures were performed in 16 of 17 specimens. Aerobic cultures showed bacterial growth in 2 (13%) cases, with 1 pleural effusion each showing growth of *Pseudomonas aeruginosa* and *Staphylococcus aureus*, respectively. Anaerobic cultures were performed in 10 cases, fungal cultures in 4 cases, and acid fast bacilli in 5 cases, with no microorganisms grown.

Cytology reports and slides were re-reviewed by 2 cytopathologists. All 17 specimens were negative for malignancy, confirmed on re-review. Lymphohistiocytic inflammation predominated in 12 of 17 cases (5

Table 2 Fluid analysis and aerobic culture results in effusion cytology specimens from COVID-19 patients.

Patient	Specimen	Fluid type	Volume collected , mL	Appearance	Color	Protein, g/L	pH	Glucose, mg/dL	Aerobic cultures
1	1A	Pleural fluid	500	Opaque	Red	2.8	6.99	80	No growth
	1B	Pleural fluid	2000	Cloudy	Red	3.7	8.15	113	No growth
2	2A	Pleural fluid	1000	Hazy	Straw	0.8	Not performed	Not performed	No growth
	2B	Pleural fluid	1000	Hazy	Straw	<0.8	7.04	150	No growth
3	3	Pleural fluid	600	Cloudy	Orange	3.5	7.23	128	No growth
4	4	Pleural fluid	400	Hazy	Straw	1.7	7.17	116	No growth
5	5	Pleural fluid	180	Opaque	Red	4.3	6.89	38	No growth
6	6	Pleural fluid	20	Cloudy	Yellow	5.1	7.27	<4	*Pseudomonas*
7	7	Pleural fluid	100	Cloudy	Red	4.2	7.63	19	*S. aureus*
8	8	Pleural fluid	1500	Not performed	Not performed	Not performed	Not performed	Not performed	No growth
9	9	Pleural fluid	400	Cloudy	Straw	5.9	7.57	97	No growth
10	10	Pleural fluid	180	Cloudy	Red	3.7	7.58	89	No growth
11	11	Pleural fluid	1000	Hazy	Straw	2.3	Not performed	Not performed	No growth
12	12	Pericardial fluid	150	Clear	Straw	2.1	Not performed	Not performed	No growth
13	13	Pericardial fluid	100	Clear	Straw	4.2	Not performed	125	No growth
14	14	Peritoneal fluid	120	Not performed	Not performed	Not performed	Not performed	Not performed	Not performed
15	15	Peritoneal fluid	1000	Hazy	Orange	4.6	Not performed	97	No growth

Table 3 Leukocyte counts and 100 cell count differential in COVID-associated effusions.

Patient	Specimen	Fluid type	Leukocyte count, cells/mL	100 cell count differential
1	1A	Pleural fluid	998	51% polymorphonuclear leukocytes, 21% histiocytes, 18% lymphocytes, 10% mesothelial cells
	1B	Pleural fluid	1326	57% polymorphonuclear leukocytes, 23% histiocytes, 20% lymphocytes
2	2A	Pleural fluid	360	86% histiocytes, 9% lymphocytes, 4% mesothelial cells, 1% polymorphonuclear leukocytes
	2B	Pleural fluid	75	70% histiocytes, 22% polymorphonuclear leukocytes, 4% mesothelial cells, 4% lymphocytes
3	3	Pleural fluid	1970	65% lymphocytes, 14% histiocytes, 13% polymorphonuclear leukocytes, 8% mesothelial cells
4	4	Pleural fluid	141	70% lymphocytes, 14% histiocytes, 12% polymorphonuclear leukocytes, 3% mesothelial cells, 1% plasma cells
5	5	Pleural fluid	2879	80% lymphocytes, 14% histiocytes, 5% polymorphonuclear leukocytes, 1% eosinophils
6	6	Pleural fluid	Not performed	98% polymorphonuclear leukocytes, 2% lymphocytes
7	7	Pleural fluid	1607	74% histiocytes, 22% lymphocytes, 4% polymorphonuclear leukocytes
8	8	Pleural fluid	Not performed	48% histiocytes, 37% lymphocytes, 13% polymorphonuclear leukocytes, 2% mesothelial cells
9	9	Pleural fluid	6676	Not performed
10	10	Pleural fluid	499	91% polymorphonuclear leukocytes, 5% mesothelial cells, 4% histiocytes
11	11	Pleural fluid	1586	Not performed
12	12	Pericardial fluid	150	91% histiocytes, 6% lymphocytes, 3% mesothelial cells
13	13	Pericardial fluid	397	53% polymorphonuclear leukocytes, 33% histiocytes, 7% lymphocytes, 5% eosinophils, 2% mesothelial cells
14	14	Peritoneal fluid	—	87% polymorphonuclear leukocytes, 11% lymphocytes, 2% histiocytes
15	15	Peritoneal fluid	1062	90% lymphocytes, 10% histiocytes

lymphohistiocytic predominant, 4 histiocytic predominant, 3 lymphocytic predominant) (Table 4; Figs. 1 and 2). The remaining 5 cases included 4 with mixed acute and chronic inflammation and 1 with predominantly acute inflammation. Notably, hemophagocytosis was present in 5 (29%) cases including erythrophagocytosis in 3 specimens as well as leukophagocytosis and erythrophagocytosis in 2 cases (Fig. 3). No megakaryocytes were identified in any case. Mesothelial cells were typically scant compared with inflammatory cells, usually being present as single cells and in small clusters. Reactive mesothelial cellular changes were noted, including prominent nucleoli, but no distinct or specific pathologic changes were seen within mesothelial cells (Fig. 3). No cellular viral changes were seen, either in mesothelial cells or inflammatory cells.

Two cases of pleural effusion in patients with recent diagnosis of influenza infection were identified. Both showed lymphocytic inflammation and mesothelial cells, without hemophagocytosis. Fourteen consecutive cases of pleural effusion in patients with acute respiratory symptoms and no known infectious cause were also reviewed; 11 showed a predominance of lymphocytic or lymphohistiocytic inflammation, 2 demonstrated mixed eosinophils and lymphocytes, and 1 showed a mixture of neutrophils and lymphocytes. In all cases, hemophagocytosis was absent.

In all cases, ISH for SARS-CoV-2 was negative in all cellular elements, including mesothelial cells and inflammatory cells (Fig. 4). All ISH slides were reviewed by 2 cytopathologists (R.C. and L.P.). Appropriate positive controls were observed.

Discussion

The signs and symptoms of COVID-19 disease are wide-ranging and may be non-specific. Though most patients present with relatively mild "flu-like" illness, approximately 10% of patients can develop more severe disease marked by lower respiratory tract involvement and/or systemic symptoms. Although only a minority of patients with SARS-CoV-2 develop body cavity effusions overall, a significant proportion of patients with severe disease will develop pleural effusions and/or pericardial effusion. One recent study found that whereas pleural effusion is rare early in the COVID-19 disease phase (2.5%), it is a relatively common occurrence in patients with more advanced-phase disease

Table 4 Cytologic findings in COVID-associated body cavity effusions.

Patient	Specimen	Fluid type	Predominant inflammation	Mesothelial cell findings	Hemophagocytosis
1	1A	Pleural fluid	Histiocytic	Moderately cellular, reactive change	Absent
	1B	Pleural fluid	Lymphohistiocytic	Hypercellular, reactive change	Absent
2	2A	Pleural fluid	Lymphohistiocytic	Moderately cellular, reactive change	Present (erythrocytes)
	2B	Pleural fluid	Histiocytic	Moderately cellular, reactive change	Present (erythrocytes)
3	3	Pleural fluid	Lymphohistiocytic	Hypercellular, reactive change	Present (erythrocytes, lymphocytes, polymorphonuclear leukocytes)
4	4	Pleural fluid	Lymphohistiocytic	Hypercellular, reactive change	Absent
5	5	Pleural fluid	Acute and chronic inflammation	Scant	Absent
6	6	Pleural fluid	Acute and chronic inflammation	Scant	Absent
7	7	Pleural fluid	Acute and chronic inflammation	Scant	Absent
8	8	Pleural fluid	Lymphocytic	Scant	Absent
9	9	Pleural fluid	Neutrophilic	Hypercellular, non-reactive	Present (erythrocytes)
10	10	Pleural fluid	Lymphocytic	Scant	Absent
11	11	Pleural fluid	Lymphocytic	Scant	Absent
12	12	Pericardial fluid	Histiocytic	Moderately cellular, non-reactive	Absent
13	13	Pericardial fluid	Histiocytic	Moderately cellular, non-reactive	Absent
14	14	Peritoneal fluid	Acute and chronic inflammation	Hypercellular, reactive change	Present (polymorphonuclear leukocytes)
15	15	Peritoneal fluid	Lymphohistiocytic	Scant	Absent

Figure 1 Lymphohistiocytic aggregate in a pleural fluid from an 81-year-old woman with COVID-19 pneumonia. Scattered acute inflammatory cells are also noted. (Papanicolaou stain, 400×).

(22.7%).[13] To date, however, the pathologic features of body cavity effusions in COVID-19 patients have not been well described.

In our study, the presence of a pleural effusion was an ominous finding, as 7 of 13 (54%) patients with a pleural effusion died of COVID-19 during the course of their hospitalization. This is in line with the high mortality associated with pleural effusions in the setting of acute Middle East Respiratory Syndrome, caused by a related coronavirus (MERS-CoV).[14] Only 2 cases were identified with pericardial effusion in our study, both of whom had severe systemic and cardiac disease. One patient died of cardiac tamponade secondary to COVID-19, and the other patient has recovered from COVID-associated myocarditis with

Figure 2 Pleural fluid from a 70-year-old male patient with a history of hepatocellular carcinoma, who presented with dyspnea and was diagnosed with COVID-19 pneumonia. Reactive mesothelial cell clusters surrounded by abundant histiocytes are shown, many exhibiting vacuolated cytoplasm, and admixed with scattered lymphocytes. No viral cytopathic effect was noted in any case. (Diff-Quik stain, 400×).

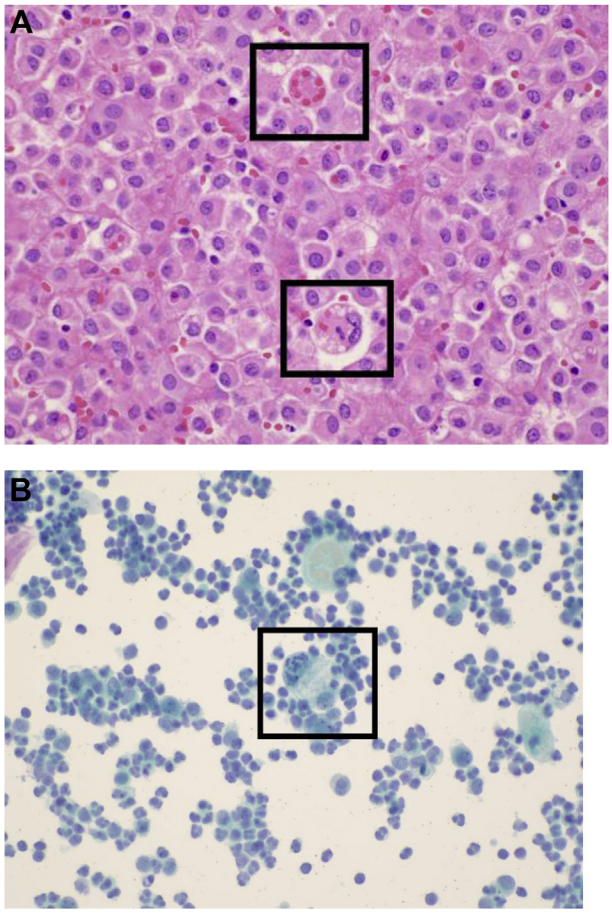

Figure 3 (A) Erythrophagocytosis and leukocytosis noted (within the squares) in a cell block from an 81-year-old female patient with COVID-19 pneumonia and a pleural effusion (hematoxylin and eosin, 400×). (B) Leukophagocytosis is shown (within the square) in the peritoneal fluid of a 35-year-old female patient with mature cystic teratoma of the ovary and who incidentally had a positive SARS-CoV-2 screening test (Papanicolaou stain, 400×).

ongoing chest pain and dyspnea. The 2 cases of peritoneal fluid were from patients with known or suspected neoplasms, 1 with a history of pancreatic carcinoma and another with an adnexal cyst which proved to be a mature cystic teratoma on resection. Both patients are alive and without COVID-19 disease.

Fluid analysis showed that, in all COVID-19 cases, the effusions were transudative in nature (<30 g/L protein), including in both cases with aerobic bacterial growth. The latter 2 cases did show reduced glucose. The quantity of inflammatory cell involvement varied widely (75-6676 cells/mL), and in most cases lymphohistiocytic inflammation predominated. The cytologic findings were overall nonspecific in nature. Mesothelial cellularity ranged from scanty and non-reactive to hypercellular and reactive. Microscopic re-examination confirmed that lymphocytic and histiocytic inflammation predominated in most cases, with only 1 case showing a predominance of neutrophils. Megakaryocytes,

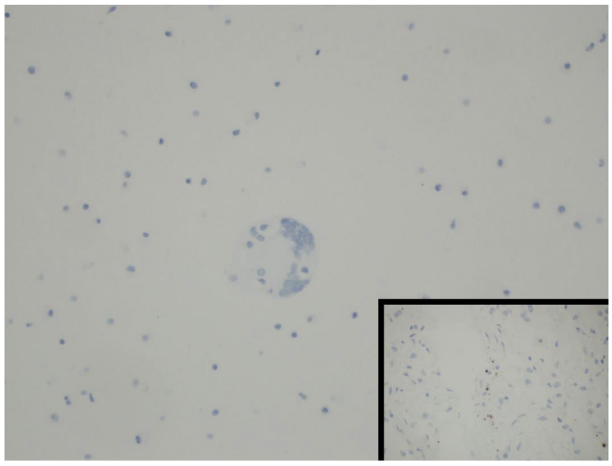

Figure 4 Mesothelial cells and inflammatory cells are negative for SARS-CoV-2 spike protein transcript (V-nCoV2019-S) by in situ hybridization (400×). Inset (bottom right) shows an adequate positive control from lung tissue from an unrelated COVID-19 autopsy patient (400×).

the presence of which has been described in biopsy and autopsy tissue from patients with COVID-19, were not detected in any case. Also absent were viral cytopathic effects.

The presence of hemophagocytosis in a subset of effusions is noteworthy. It has been hypothesized that severe cases of COVID-19 disease are linked to a cytokine storm with an associated hyperactive immune response and hemophagocytic lymphohistiocytosis.[15] Hemophagocytosis is a common histologic finding in thoracic lymph nodes, liver, spleen, and bone marrow, and it is frequently seen at autopsy in COVID-19 patients who had clinical features of hemophagocytic syndrome such as high fever, hyperferritinemia, and cytopenias.[15,16] There were 5 (29%) cases in our study that did show hemophagocytosis, being present in both pleural effusions from one patient who underwent repeat sampling. In 3 cases the only hemophagocytosis identified was of erythrocytes, and 2 cases showed hemophagocytosis of both erythrocytes and leukocytes. Interestingly, 1 of the 2 cases exhibiting phagocytosis of leukocytes was from an asymptomatic patient with an ovarian cyst who was found to be SARS-CoV-2 positive on pre-surgical workup and who did not develop symptomatic disease. Notably, 4 patients (nos. 5, 7, 8, and 12) had clinical and laboratory findings consistent with cytokine storm, including increased serum ferritin, cytopenias, and vascular accidents, but no hemophagocytosis was identified in any of their cytology samples. In total, 2 out of 4 patients with hemophagocytosis present in effusion cytology material died of COVID-related illness and 2 are alive without evidence of disease. Thus, although hemophagocytosis is a common effusion cytology finding in patients with COVID-19, in our study it was a non-specific finding that did not correlate with severity of COVID-related disease.

It has not been established whether hemophagocytosis in effusion cytologies is more common in SARS-CoV-2 infection compared to other acute and infectious causes of pleural effusion. Pleural effusions are relatively uncommon in most forms of viral pneumonia, and indeed a search of our own archives for similar effusions in patients with a concurrent diagnosis of influenza revealed only 2 such cases in the past 5 years at our institution, both of which showed chronic lymphocytic inflammation only. Notably, both were negative for hemophagocytosis on re-review of cytologic material. In addition, re-examination of 14 recent consecutive benign pleural effusions in patients with acute respiratory symptoms and new onset pleural effusion revealed no hemophagocytosis in any case.

As noted, although radiography typically does not show pleural effusion in mild and moderate cases of COVID-19, effusions are more common in severe cases, with pleural effusion present in 59% of autopsy cases in one series.[8] Although person-to-person spread of SARS-CoV-2 occurs primarily via respiratory droplet transmission, viral RNA has been detected in multiple body fluid types including bronchoalveolar lavage fluid, sputum, saliva, and feces. Recent individual case reports have detected SARS-CoV-2 by RT-PCR in pleural and pericardial fluids.[10,11] However, it has not been established whether serous cavities may be a potential viral reservoir in advanced COVID-19 cases. Angiotensin-converting enzyme 2 (ACE2), the primary receptor of SARS-CoV-2 cellular entry, is expressed on multiple human tissue types, notably epithelium of the oral, nasal, and respiratory tracts, gastrointestinal epithelium, and endothelial cells.[17] It is not typically expressed on inflammatory cells such as B and T lymphocytes and macrophages, however, and the potential expression of ACE2 in human mesothelial cells has not been well established.

ISH for SARS-CoV-2 was negative in all cases in our series, as no viral RNA was detected in either mesothelial or inflammatory elements within serous cavity samples. As noted previously, case reports have detected SARS-CoV-2 RNA by RT-PCR in effusion cytology specimens. However, it is not clear that such effusions harbor infectious SARS-CoV-2 viral particles or infected cellular elements.

One limitation of this study is that RT-PCR was unavailable to be performed in our samples. However, the effusions in our series were uniformly transudative by protein criteria (<30 g/L). Transudative effusions occur due to imbalances of hydrostatic and osmotic pressure such as congestive heart failure, cirrhosis, and pulmonary edema, whereas exudative effusions occur in settings of direct tissue damage.[18] The transudative nature of the fluids and negative findings by ISH in our study suggests that although body cavity effusions were common in these advanced COVID-19 cases, they were likely secondary in nature to acute cardiopulmonary dysfunction in COVID-19 rather than direct viral-induced tissue damage.

In summary, the presence of pleural or pericardial effusion requiring clinical intervention was an ominous finding among COVID-19 patients at our institution, with 62% (8) of patients in this small series dying, including 54% (7) from COVID-related illness. The effusions in these patients were transudative in nature in all cases. Inflammation in these effusion cytology specimens was predominantly histiocytic and/or lymphocytic in most cases. Hemophagocytosis, typically a rare finding in effusion cytology specimens, is not an uncommon finding in body cavity effusion specimens from COVID-19 patients, present in 29% (5 of 17) of cases compared with 0% (0 of 16) of pleural effusions from non-COVID-19 patients in our study.

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