Pleural diseases and COVID-19: *ubi fumus, ibi ignis*

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There is both direct and circumstantial evidence that SARS-CoV-2 is responsible for the generation of pleural effusions and secondary spontaneous pneumothorax/pneumomediastinum https://bit.ly/3gZqA7Z

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More than 45 000 articles in the PubMed database and around 3200 studies registered in ClinicalTrials.gov, of which greater than half are clinical trials, are the result of ongoing and relentless research into the global pandemic nature of an acute respiratory disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which made its initial appearance in December 2019 in China. As of 28 August 2020, the total confirmed cases of coronavirus disease 2019 (COVID-19) surpasses 24.5 million, with more than 830 000 global deaths [1]. An estimated 40% to 45% of persons infected with SARS-CoV-2 will remain asymptomatic, but they can transmit the virus to others for an extended period, perhaps longer than 14 days [2]. The primary presentation of symptomatic infection is that of an influenza-like illness or viral pneumonia, with about 20% of these patients developing severe or critical manifestations [3].

Pleural disease encompasses pleural effusion and pneumothorax. In the context of COVID-19, both are considered to be so atypical or unusual that they should compel clinicians to seek alternative diagnoses [4]. This might be challenged by new observations, including those of Martinelli *et al.* [5] in this issue of the *European Respiratory Journal*. According to several systematic reviews [6–10], pooled prevalences of pleural thickening and pleural effusions on computed tomography (CT) scans are approximately 38% and 5%, respectively (table 1). However, the frequency of pleural effusions varies with age and disease severity. For example, in an Iranian study of 552 COVID-19 symptomatic patients, CT detected pleural effusions in 7.6% of cases overall; a percentage which was significantly higher in those over 50 years of age *versus* under (10% *versus* 5.2%; p=0.037) [11]. Additionally, in a multicentre study of 476 patients with COVID-19, more patients in the critical than in the severe or moderate disease groups had pleural effusions on CT images at admission (18%, 7.4% and 3.1%, respectively; p<0.001) [12]. It may be argued that most, if not all, of these pleural effusions may be secondary to comorbid conditions rather than being directly related to the viral infection. About half of COVID-19 patients have comorbidities [12, 13], including pre-existing cardiovascular diseases (12.6%) or heart failure (6.5%) [14]. Moreover, more than 25% of infected patients exhibit myocardial injury of potential inflammatory pathogenesis (a cause of impaired cardiac function) as demonstrated by elevation of troponin T levels [14] and, at least 20% develop heart failure during disease course [15]. On the other hand, the incidence of pulmonary embolism was 8.3% among 1240 infected patients who were subjected to a CT pulmonary angiography [16]. And

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TABLE 1 Prevalence of pleural effusions and thickening on chest computed tomography imaging of adult coronavirus disease 2019 patients: relevant systematic reviews

Systematic review	Studies n	Patients n	Pleural thickening[#]	Pleural effusion
Adams *et al.* [6]	28	3466	34.7%	5.2%
Bao *et al.* [7]	13	2738	52.5%	5.8%
Ojha *et al.* [8]	45	4410	41.7%	5.0%
Zheng *et al.* [9]	15	2150	ND	3.0%
Zhu *et al.* [10]	34	4121	27.1%	5.3%

[#]: pleural thickening adjacent to underlying lung involvement. ND: not done.

both, heart failure and pulmonary embolism [17], in addition to respiratory co-infections [18], are well-recognised aetiologies of pleural effusions. Despite the fact that a certain number of patients may have pleural effusions derived from the preceding causes, SARS-CoV-2 undoubtedly gives rise to fluid formation since it has been detected by RT-PCR in pleural fluid specimens [19, 20].

Non-COVID-19 viral pneumonias share many CT features with COVID-19, except for a higher prevalence of pleural effusions. In a systematic review of 33 studies, comprising 1911 patients equally distributed between COVID-19 and non-COVID-19 viral pneumonias (mainly influenza A and adenovirus), pleural effusions were observed in 3% and 25% of the cases, respectively [21]. Regarding other beta-coronaviruses, very few small series on CT appearances have been reported and, therefore, firm conclusions cannot be drawn. The true prevalence of pleural effusions in SARS-CoV-1 infections is conflicting, ranging from two (6.8%) of 29 patients [22] to seven (26%) of 27 [23] in two different reports. In one study of 55 patients infected with Middle East respiratory syndrome coronavirus (MERS-CoV), pleural effusions were visible in the chest radiographs of 17 (31%) and represented a poor prognostic indicator [24]. A previous retrospective study by the same authors found that nine (60%) of 15 patients with MERS-CoV had pleural effusions on CT [25].

Martinelli *et al.* [5] describe the occurrence of pneumothorax and pneumomediastinum as important, though infrequent, clinical features of COVID-19 [5]. In their retrospective study, clinical details were reported for 60 cases of pneumothoraces that occurred among an estimated 6574 COVID-19 admissions across multiple centres in the UK. This represents an incidence of 0.91%, which is consistent with previous observations. For instance, in a series of 92 deceased patients with COVID-19, one death was attributed to pneumothorax (1.1%) [26]. Similarly, this complication was described in one (1%) of 99 patients by others [27], while seven spontaneous air leaks (five pneumomediastinum and two pneumothoraces) were found as part of 976 COVID-19 cases (0.7%) in an American institution [28]. Notably, of the 60 pneumothorax patients reported in this issue, 75% were older than 50 years, and more than half had never smoked, which is difficult to reconcile with the primary spontaneous variety [5]. Also, one-third of the patients were not submitted to invasive or non-invasive mechanical ventilatory support at the time of diagnosis, thus ruling out iatrogenic causes [5]. Consequently, the existence of a true secondary spontaneous pneumothorax due to SARS-CoV-2 should be admitted, as in other respiratory infections. For example, about 1% of patients with active tuberculosis [29], up to 9% of those with *Pneumocystis jirovecci* pneumonia [30], and 1.7% of SARS-CoV-1 infected subjects [31] may develop pneumothorax. As far as MERS-CoV is concerned, the clinical course of nine (16%) of 55 patients complicated with pneumothorax, but all of them were intubated and so, the contribution of barotrauma and/or volutrauma was probably meaningful [24]. The pathological basis for pneumothorax in non-ventilated COVID-19 patients is uncertain. While not usually seen in autopsy reports, lung cavitation and/or cystic lesions unrelated to the use of mechanical ventilation can occur in COVID-19 [32]. The severe cough that may be associated with COVID-19 and the corresponding increase in intrapulmonary pressure may precipitate the rupture of viral-induced damaged alveoli of peripheral location and pneumothorax formation. Pneumothorax should be managed following standard guidelines, wearing personal protective equipment for chest tube placement and considering strategies to minimise droplet exposure *via* the chest drain circuit (*e.g.* connecting anti-viral filters on suction ports or adding bleach to the water seal chamber) [33].

Many of the preceding statements for pneumothorax in the setting of SARS-CoV-2 infection hold true for pneumomediastinum. It is a rare entity, frequently related to mechanical ventilation, which may also appear spontaneously in the context of respiratory infections, like influenza [34]. In the series reported by Martinelli *et al.* [5], only 1 (9%) of 11 pneumomediastinum cases was labelled as spontaneous [5]. It appears, however, to be a more frequent characteristic feature of SARS-CoV-1 infection, with two separate

series of 75 and 112 patients reporting a 12% incidence of this complication [35, 36]. Pneumothorax and pneumomediastinum, in addition to pulmonary embolism or progression of the primary disease, should be considered in any COVID-19 patient with acute respiratory deterioration.

In brief, there is direct evidence that SARS-CoV-2 infection produces pleural effusion, and circumstantial evidence that it may cause secondary spontaneous pneumothorax and pneumomediastinum. Although alternative explanations primarily related to comorbidities and iatrogenic effects should always be sought, the Latin aphorism "*ubi fumus, ibi ignis*" (where there's smoke, there's fire) is perfectly applicable to pleural involvement in the setting of COVID-19.

Conflict of interest: None declared.

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