ORIGINAL ARTICLE

Pneumomediastinum associated with severe pneumonia related to COVID-19: diagnosis and management

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ABSTRACT

BACKGROUND: Pneumomediastinum (PNM) can develop as a severe complication of severe COVID-19 and may be correlated with greater morbidity and mortality. PNM is a rarely reported complication in COVID-19 patients and usually associated with endotracheal intubation.
METHODS: Our aim was to describe the characteristics of patients with PNM in twenty-one patients with COVID-19 related pneumonia and acute respiratory failure in a retrospective case series.
RESULTS: Twenty-one patients were diagnosed, four were treated with high-flow nasal cannula, thirteen with non invasive ventilation and four with invasive mechanical ventilation. In five cases PNM was massive and associated to subcutaneous emphysema; more rarely PNM was associated with pneumothorax. Conservative management was the most used therapeutic strategy.
CONCLUSIONS: PNM is a serious and not extremely rare complication of severe forms of pulmonary involvement of COVID-19. The clinician should consider this rare complication; moreover, we suggest being careful when clinicians start mechanical ventilation.

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KEY WORDS: COVID-19; Pneumonia; Pneumomediastinum, diagnostic.

Pneumomediastinum (PM) is defined by confirmation of free air in the mediastinum on chest X-ray or chest computed tomography (CT) and spontaneous PM occurs in absence of surgical or medical procedures and chest trauma or mechanical ventilation.[1] Because underlying lung disease such as lung cancer or interstitial lung disease can affect the course of spontaneous PM, one may define spontaneous PM occurring with such problems as secondary PM.[1, 2]

The recently diagnosed virus that was initially recognized in Wuhan City, Hubei Province, China, in late 2019, resulted in a global pandemic. The WHO declared COVID-19 a global health emergency on January 31, 2020, few months after the first case discovered in China; and subsequently, a pandemic on March 11, 2020. Globally, the disease has been reported in more than 210 countries with 111,762,965 confirmed cases and 2,479,678 deaths as of February 2020.

The number of reported cases is 49,700,102 in USA, 37,974,729 in Europe, and 13,415,064 in Asia. The USA has reported the highest deaths due to COVID-19.[3] The International Committee on Taxonomy of Viruses (ICTV) determined that virus belongs to the Coronavirus family and named the new virus as severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2). Later, the disease caused by SARS-CoV-2 was labelled as COVID-19. SARS-CoV-2 is considered one of the seven members of the CoV family that infect humans; however, it is genetically distinct from others. The novel virus is suspected to be originated from an animal host (zoonotic origin), *e.g.* bats, with human-to-human transmission. Modes of transmission of the virus are by direct contact *via* contaminated surfaces, foodborne, and respiratory droplets. The virus could remain viable for hours in aerosols and up to days on surfaces. The mean incubation period ranges from 2 to 11 days with a mean of 6.4 days.[4, 5] Disease manifestation varies from mild flu like symptoms to severe respiratory failure with multiple organ involvement. The risk of death among individuals infected with COVID-19 is 0.3% to 0.6%, which is comparable to that of a previous Asian influenza pandemic (1957 to 1958).[1] The respiratory system is the most commonly organ affected by the COVID-19. The clinical manifestations include cough, sore throat, fever, and dyspnea. In severe cases, the clinical course can progress to pneumonia with hypoxic respiratory failure and acute respiratory distress syndrome (ARDS). Guan *et al.* reported incidence of cough, sputum production, and dyspnea in 67.8%, 33% and 18.7%, respectively.[2] Johnson *et al.* published the summary of studies reporting pulmonary manifestations in COVID-19.[3] They observed that the incidence of fever (82-91%), cough (57-72%), dyspnea (21-45%) and sputum production (26-28%).[4-6] There are studies which have described the patterns of lung involvement on computer tomography (CT) scan of the thorax by COVID-19.[5, 7] CT findings can be diagnostic of COVID-19 among patients with RT-PCR negative patients. Common radiological abnormalities on CT scans included ground glass opacity (14-98%), consolidation (2-64%), consolidation plus GGO (19-59%), and interlobular septal thickening (1-75%), reticular pattern (1-22%), crazy paving (5-36%), air bronchogram (21-80%) and bronchial wall thickening (11-23%).[7] COVID-19 is usually a mild disease in majority (85%) of the patients; nevertheless, the remainder develop severe disease manifesting as respiratory failure.[4] A Chinese study reported that 5.0% of patients required admission in the ICU and 2.3% underwent invasive mechanical ventilation (MV).[4] Another epidemiological study reported 25% of patients with severe or critical disease required MV.[8] In USA, 2.3% of hospitalized patients were admitted to ICU.[3] ARDS is the most severe form of hypoxemia associated with high mortality.[4, 5] By the end of 2019, several cases of pneumonia with unknown etiology were reported in Wuhan, China. Most cases progressed to acute respiratory distress syndrome (ARDS).[4] The most important mechanisms of the severe pathogenesis of SARS-CoV-2 are not fully understood. Extensive lung injury in SARS-CoV-2 has been related to increased virus titers; monocyte, macrophage, and neutrophil infiltrations into the lungs; and elevated levels of pro-inflammatory cytokines and chemokines. Thus, the clinical progression of SARS-CoV-2 infection may be in consequence of a combination of direct virus-induced cytopathic and immunopathological effects due to excessive cytokinesis.[4, 8] The estimates of disease severity may be classified in this way: mild (no or mild pneumonia) in 81%, severe (with bilateral pneumonia, hypoxia, or >50% lung involvement on imaging within 24 to 48 hours) in 14%, and critical (with severe respiratory failure, shock, or multiorgan dysfunction) in 5%. Severe and critical forms are treated with MV (invasive [IMV] or noninvasive [NIV]).[5] Both pneumomediastinum (PNM) and pneumothorax (PNX) are documented complications of IMV due to endotracheal intubation or NIV.[9, 10] Pneumomediastinum (PM) is an uncommon occurrence and commonly referred to a thoracic surgeon.[11] It most often affects young males and is generally self-limiting.[1, 12] However, both have also been described in COVID-19 in absence of intubation and/or MV -related barotrauma or volutrauma.[10, 13] Only a few cases have been reported in literature[10, 14-17] with the exception of a large study which has reported 23 patients' cases in a cohort of 169 patients with SARS-CoV-2

ARDS admitted to Intensive Care Unit (ICU).[18] Eleven patients with PNM cases were noted in a multicenter case series of 71 non-intubated patients with pneumothorax.[19] In total, six patients presented a favorable evolution, whereas five died. Subcutaneous emphysema was a radiological finding present in 35% of the patients.[10] The treatment was conservative in more 50%; 40% required chest drainage only in presence of PNX.[10] In one patient a tension PNM required surgical intervention.[20] The present study describes the presentation, management and outcome of 21 cases observed in a twenty-week period during COVID-19 second wave in a COVID-Intensive and Intermediate Care Unit (ICU).

Materials and methods

Study design and participants

The retrospective observation study was carried out at COVID-19 Center of General Hospital of Sestri Levante, Genoa, Italy. The Local Institutional Review Board approved these studies as minimal-risk research using data for routine clinical practice. We collected patients' medical data according to the Helsinki Declaration and our Institution's Ethics policy. The boards waived the need of consent from individual patients due to retrospective nature of the study. We evaluated patients with severe respiratory failure (RF) related to COVID-19 related pneumonia (PaO_2/FiO_2 [P/F] ratio <250) observed from October 2020 to January 2021 during the second wave of the pandemic. The inclusion criteria were: 1) older than 18 years; 2) confirmed diagnosis of severe respiratory failure due to microbiologically confirmed pneumonia related SARS-CoV-2; and 3) the need for ventilatory support (invasive or non-invasive). Exclusion criteria were patients with COVID like or non-confirmed SARS-CoV-2 related pneumonia, rapid endotracheal intubation for cardiopulmonary resuscitation, respiratory arrest. The center health care team consisted in physician expert in critical care, intensive care and mechanical ventilation.[5] The available assisting techniques were: 1) high flow nasal cannula (HFNC); 2) continuous positive expiratory pressure (CPAP); and 3) NIV delivered both with helmet and oronasal mask and IMV.

Outcome measures and explanatory variables

The objective of this report is to evaluate the prevalence of PNM in severe and critical COVID-19 patients as well as to describe the characteristics of these patients, the relationship with endotracheal intubation, and PNM along with their comorbidities, respiratory parameters and ventilation modes. Furthermore, we compared the characteristics, respiratory parameters, ventilatory modes hospital stay and outcomes and prevalence of PNM of patients treated in the first wave of COVID-19 (from March to September 2020); and in the second wave (from October 2020 to March 2021).

Statistical analysis

Variables have presented as percentage for categorical variables and as mean±standard deviation for normal distributed variables. The differences in explanatory variables were assessed using χ^2 test or Fisher's Exact test for dichotomous variables, and t-test for normally distributed continuous variables. A P value lower than 0.05 was considered significant. Statistical analysis was performed with R Project (R Core Team 2020; R Foundation for Statistical Computing, Vienna, Austria).

Results

Among 111 patients admitted because of severe RF due to pneumonia and who underwent ventilatory support we found twenty-one patients who developed PNM. Their P/F at admission ranged from 49 to 248. Four patients initially received invasive mechanical ventilation (IMV) because of the severity of RF. All were intubated using direct laryngoscopy; in two patients a size 9 tracheal tube was used and in the other a size 8 tracheal tube was employed initially. Patients were treated with noninvasive ventilatory support (NIVS) (HFNC, CPAP, NIV). At admission NIV was delivered by helmet in ten patients, three with oronasal mask and four patients by HFNC. The positive expiratory pressure (PEEP) ranged from 8 to 12 cm H_2O and pressure support (PS) from 8 to 16 cmH_2O. HFNC was delivered from 50 to 60 liters gas flow and oxygen inspiratory fraction (FiO_2%) from 60 to 70%. The four patients that were initially intubated were treated

using controlled pressure ventilation (PCV) with PEEP ranged from 7 to 9 cm H_2O, and PS from 8 to 14 cmH_2O.The time to development of PNM after beginning ventilatory support ranged from four to twelve days. Twenty of 21 patients presented with subcutaneous emphysema and eleven PNX (eight monolateral and three bilateral). At the time of diagnosis seven patients were treated with NIVS (four HFNC, four CPAP and nine NIV). PNM was diagnosed in patients with thoracic computed tomography (CT) after a chest X ray demonstrating signs of PNM. In three patients the PNM was discovered following a control CT. In five patients PNM was considered massive, and in four also a tension PNM. Moreover, three were associated with bilateral PNX. No visible tracheal injury was found at high resolution CT scan in any of these cases, nor was seen in eleven bronchoscopies. The clinical characteristics at baseline are reported in Table I and those at time of diagnosis and patients' outcome in Table II. Fifteen patients had one or more comorbidities at admission. The most frequent comorbidities were obesity, hypertension, cardiac disease and chronic obstructive pulmonary disease. Eight of the 21 were smokers and six had a diagnosed COPD. Thirteen patients were intubated during their hospital stay, while four continued NIVS for their hospital stay. Nine patients died (42.8%) and twelve were discharged. The average hospital stay was 23.9±5.7 days. Among the patients who survived three had been treated with HFNC, three with NIV and six with IMV. In all but four of cases of PNM conservative treatment was employed. In the other four cases chest drain and tracheostomy were used to resolve PNM and PNX. Subcutaneous emphysema was present in 19 of the 21 cases and in four cases was the first and only clinical manifestation of PNM. We finally performed a comparison between patients admitted in the first wave and those from the second wave. The patients were treated by the same team, the same ventilators and equipment. We observed an increased number of PNM during the second wave (21 cases *vs.* 2 cases P<0.0001) as well as PNX (11 cases *vs.* 2 P<0.0007) and subcutaneous emphysema (19 *vs.* 2 P<0.0001), despite an unvaried severity of illness, hospital stay and in-hospital mortality (Table III).

TABLE I.—*Characteristics of patients at admission.*

Parameters	Values
Age	
20-60	6 (28.6%)
Over 60	15 (71.4%)
Gender	
Female	3 (14.3%)
Male	18 (85.7%)
Smoking status	
Never	9 (42.8%)
Current smoker	8 (38.0%)
Ex-smokers	4 (19.2%)
Pulmonary comorbidities	
COPD	7 (33.3%)
None	14 (66.7%)
Other comorbidities	
Systemic hypertension	7 (33.3%)
Obesity	7 (33.3%)
Diabetes	2 (9.6%)
Cardiac disease	4 (19.2%)
Pulmonary lobes involved	
<4	1 (4.8%)
4 or >4	20 (95.2%)
Severity of respiratory failure	
P/F>200 mmHg	6 (28.6%)
P/F<200 mmHg	15 (71.4%)
BMI	
<30	14 (66.7%)
>30	7 (33.3%)
Mode of ventilatory support at admission	
HFNC	6 (28.6%)
NIV	11 (52.2%)
IMV	4 (19.2%)
Laboratory findings at admission	
Lymphocytes	714.7±589.5
CRP	12.9±10.44
IL-6	60.4±36.7
Ferritin	929.6±666.3
LDH	388.3±239.7
D-Dimer	8.15±5.09

Data are expressed as percentage (%) or mean±standard deviation [SD].
P/F: PaO_2/FiO_2 ratio; BMI: Body mass index; HFNC: high flow nasal cannula; NIV: noninvasive ventilation; IMV: invasive mechanical ventilation; CRP: C-reactive protein; IL-6: interleukin 6; LDH: lactate dehydrogenase.

Discussion

Pneumomediastinum results from a sudden rise in intra-alveolar pressure resulting in the rupture of alveoli and subsequent dissection of air along the bronchovascular sheath into the mediastinum (Macklin effect).[21, 22] Air may then enter the pleural, pericardial, and peritoneal spaces or the soft tissues of the chest wall, neck or face causing subcutaneous cervicothoracic emphysema. The mechanism involved in spontaneous interstitial,

TABLE II.—*Baseline characteristics, initial ventilatory mode, and patient outcomes words.*

Parameters	Values
Mode of diagnosis	
On admission	0 (0%)
Clinical change	17 (81.0%)
Incidental	4 (19.0%)
Dimension of pneumomediastinum	
Massive	5 (23.8%)
Not massive	12 (57.2%)
Tension	4 (19.0%)
Subcutaneous emphysema	
Present	19 (90.4%)
Not present	2 (9.6%)
Pneumothorax	
Monolateral	6 (28.5%)
Bilateral	2 (9.6%)
Mode of ventilatory support at diagnosis	
HFNC	4 (19.0%)
NIV	13 (62.0%)
IMV	4 (19.0%)
PS cmH_2O	14.1±6.2
PEEP cmH_2O	9.5±3.9
FiO_2%	65.4±15.8
TV	6.61±1.24
Intubation rate	
Not intubated	6 (28.5%)
Intubated	15 (71.5%)
Management of pneumomediastinum	
Conservative	17 (81.0%)
Drainage/surgery	4 (19.0%)
Hospital stay (days)	23.9±5.77
In-hospital mortality	
Dead	9 (42.8%)
Survived	12 (57.2%)

Data are expressed as percentage (%) or mean±standard deviation [SD].
HFNC: high flow nasal cannula; NIV: noninvasive ventilation; IMV: invasive mechanical ventilation; PS: pressure support; PEEP: positive end expiratory pressure; FiO_2%: fraction of inspired oxygen; TV: tidal volume.

TABLE III.—*Comparison of COVID patients admitted with severe respiratory distress in the first and second waves.*

Variable	COVID 1 (110 pts)	COVID 2 (111 pts)	P value
Sex (male)	64.5%	67.3%	0.12
Age	66.71±14.16	63.52±18.1	0.21
BMI	27.11±4.82	28.44±3.89	0.19
PNM	21 (19.0%)	2 (1.8%)	0.0001
Pulmonary lobes involved	3.77±1.04	3.82±1.12	0.09
PaO_2/FiO_2 at admission	185.44±34.96	177.56±58.77	0.08
Respiratory rate	32.8±2.0	29.9±4.7	0.08
Heart rate	100.66±6.27	98.6±9.43	0.11
NIVS	74 (6.7%)	72 (6.48%)	0.23
IMV	36 (32.7%)	39 (35.1%)	0.19
PS	14.6±7.4	12.7±8.8	0.09
PEEP	9.5±3.1	8.8±4.6	0.12
FiO2	62.1±14.6	66.7±22.5	0.18
TV	6.72±1.74	6.37±2.01	0.10
Tension PNM	0	4 (3.6%)	0.001
Subcutaneous emphysema	2 (1.8%)	19 (17.1)	0.0001
Pneumothorax	2 (1.8%)	11 (9.9%)	0.0007
Conservative treatment	2 (1.8%)	19 (17.1%)	0.0001
Hospital stay	19.2±4.5	18.7±6.2	0.39
In-hospital mortality	26.8%	27.1%	0.18
C-RP	11.99±9.36	12.28±8.44	0.08
Lymphocytes	695.7±528.2	714.7±589.5	0.13
IL-6	32.7±57.77	60.4±36.7	0.11
Ferritin	816.6±904.3	929.6±704.3	0.09
LDH	378.2±222.5	388.3±254.4	0.08
D-Dimer	4.46±7.99	8.15±5.09	0.14

Data are expressed as percentage [%] or mean±standard deviation [SD].
COVID 1: patients admitted during first wave; COVID 2: patients admitted during second wave; BMI: Body Mass Index; PNM: pneumomediastinum; P/F: PaO_2/FiO_2; NIVS: noninvasive ventilatory support; IMV: invasive mechanical ventilation; PS: pressure support; PE ratio EP: positive end expiratory pressure; FiO_2: fraction of inspired oxygen; TV: tidal volume; C-RP: C reactive protein; IL-6: interleukin 6; LDH: lactate dehydrogenase.

mediastinal and subcutaneous emphysema; however, was delineated by Macklin *et al.*[23] Their experimental work with various animal models led to the hypothesis that over distended alveoli rupture into the pulmonary vascular sheaths. The rupture creates pulmonary interstitial emphysema (air within the pulmonary vascular sheaths), an entity well described in newborns but rarely visible in adults.[21, 24] The basic requirement for rupture is the existence of a pressure gradient between the alveolus and its surrounding structures. The pressure within adjacent alveoli is generally assumed to be equal, so that interalveolar walls should remain intact. However, when certain situations increase intra-alveolar pressure or de-

crease perivascular interstitial pressure (or both), a gradient is created.[24, 25] Air from torn alveolus first enters perivascular interstitium, dissecting proximally within bronchovascular sheath toward mediastinum. As mediastinal pressure rises, decompression occurs in cervical, subcutaneous and retroperitoneal soft tissue spaces and may even cause pleural rupture producing pneumothorax. Overinflation and increased alveolar pressure commonly occur with obstructed expiratory airflow. Spontaneous alveolar rupture caused by a reduction in lung interstitial pressure may result either from extreme respiratory effort as hap-

pens in ARDS.[18, 22] The pathophysiological basis of air-leak disease in COVID-19 patients is not well-known, though postulations can be made by applying current understandings of the disease to existing concepts. COVID-19 pneumonia, like SARS, has been shown to cause severe diffuse alveolar damage (DAD).[18, 24, 26, 27] The rupturing of alveoli secondary to DAD may cause pulmonary interstitial emphysema. Similar pathological progression has been previously observed in a variety of viral pneumonias[14, 19]. Recent studies have demonstrated COVID-19 viral entry *via* angiotensin converting enzyme-2 (ACE-2) receptor into target cells including surfactant-producing type II pneumocytes. Such cellular injury could theoretically lead to dysregulation of surfactant production contributing to PNM development from impaired lung compliance, analogous to the pathophysiology of subcutaneous emphysema development and barotrauma-related air leak in premature neonates.[14-16, 18] Also, the virus binding to the ACE-2 receptors could facilitate endothelial dysfunction. Moreover, patients with life-threatening Sars-CoV-2 disease had associated cytokine release syndrome (CRS). The associated CRS could exacerbate both lung parenchymal and microvascular inflammation, promoting thus refractory forms of ARDS with associated hypercoagulable states and micro thrombosis ("dual hit" injury).[18] A second mechanism is caused by a reduction in the caliber of the pulmonary vessels, without a corresponding diminution of the alveolar pressure. This will increase the pressure gradient causing air leak to the sheath. Examples include forced expiration against obstruction which will dam the blood back to the venous side decreasing the vascular caliber, but the alveolar end-expiratory pressure is higher than normal. This can increase the pressure gradient, resulting in air leak and PM. Both mechanisms can occur simultaneously in which the alveoli are overdistended while the blood supply is decreased. This will increase the pressure gradient significantly, inducing air leak more easily.[14-18, 24] In our study we have presented patients with severe RF due to bilateral pneumonia, one of the largest series of PNM in COVID-19 patients, including intubated and non-intubated patients. PNM is a well-known complication of severe forms of COV-

ID-19 and always associated to MV.[4, 6-8] In our case series only 4 patients (27.2%) were initially intubated; the other seventeen were treated with NIVS. Four of fifteen intubated patients (36.4%) showed PNM only after intubation; the other seventeen developed PNM during NIVS. It is important to highlight that moderate to mild ventilation pressures were used by the physicians. Despite this we observed a high rate of PNM in patients not intubated (63.7%) and high mortality rate (54.5%). Comparing to the largest series described by Lemmers *et al.*[18] who described 26 cases of PMN, we observed a similar mortality rate (54.5% *vs.* 56.5%) but a higher length of stay (25 [21-27] *vs.* 15 [9-24] days). We agree with the authors who concluded that PNM was linked to lung friability (lung lobes involved and severity of RF) more than barotrauma or volutrauma due to intubation and IMV. They observed that the occurrence of PNM is rare in no COVID-ARDS, but more frequent in patients with COVID-19, despite the same ventilatory approach applied. In our case report, most patients were treated at starting with NIV or oxygen *via* HFNC with lower risk of barotrauma. PNM was a rare complication of intubation even after NIVS failure. In the first wave of COVID-19 we observed only two cases of PNM in patients with ARDS and intubated at starting, despite twenty-one in the second wave. We can postulate in accordance with some authors[17, 18] that PNM can be caused both by barotrauma and lung frailty linked to COVID-19 related lung involvement, the latter is the cause principally in cases in which low tidal volume and low positive airway pressure are used.

Limitations of the study

We are aware that the retrospective design and the small sample do not allow definitive Conclusions about the principal cause of PNM. Moreover, the most cases are diagnosed by a chest X ray: some cases of radiological occult PNM only evident on CT could be missed.

Conclusions

We can conclude that PNM should be considered as serious but not extremely rare complication of severe forms of pulmonary involvement of CO-

VID-19. The clinician should consider this rare complication; moreover, we advise careful attention when clinicians start mechanical ventilation.

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