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Spontaneous pneumomediastinum in Covid-19 : a case of complete resolution despite invasive positive pressure ventilation

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Abstract : We present the case of a 65-year-old patient who was admitted to the intensive care unit (ICU) due to Covid-19 respiratory failure. During his hospital stay, he developed a spontaneous pneumomediastinum (SP). To date, there have been few reports of SP associated with Covid-19 and even less is known about the impact of positive pressure ventilation on these patients.
Our patient was first treated with high-flow nasal cannula oxygen therapy (HFNC). Because of further respiratory deterioration, he was supported with non-invasive ventilation (NIV). Later, he required intubation and ventilation with invasive positive pressure ventilation. Despite this, a complete spontaneous resolution of the pneumomediastinum was observed 13 days after the initial diagnosis.

Keywords : Spontaneous pneumomediastinum ; covid-19 ; lung protective ventilation ; patient self-inflicted lung injury ; case report.

Introduction

Spontaneous pneumomediastinum (SP) refers to the presence of free air in the mediastinum, leaking from ruptured alveoli and dissecting through bronchovascular sheaths towards it (1, 2). It is a rare condition most frequently affecting younger males and patients with underlying airway disease. It is typically associated with a benign course and usually resolves spontaneously without the need for invasive management. However, in some cases, significant amounts of air may be present in the mediastinum and airway compression and tamponade can occur. In those cases, invasive interventions such as needle drainage, chest drain insertion, video-assisted thoracoscopic surgery or even thoracotomy may be required (3).

Little is known about invasive and non-invasive positive pressure ventilation after the occurrence of SP given the usually benign course of the condition. Positive pressure ventilation may worsen the air leakage and subsequently, the pneumomediastinum (3).

Currently, we are facing a major health crisis due to the Covid-19 pandemic. In December of 2019, a novel coronavirus was identified in a cluster of pneumonia cases in Wuhan, China. This enveloped RNA coronavirus was named severe acute respiratory syndrome coronavirus 2 (Sars-Cov-2) (4). The viral disorder caused by this virus is called Covid-19.

Some clinical characteristics of Covid-19 mimic those of severe acute respiratory syndrome (SARS), for example fever and cough being the dominant symptoms (4). Spontaneous SP is a recognized complication of severe acute respiratory syndrome (SARS) frequently seen during the SARS-outbreak in 2002-2004 (1, 5, 6). A study by Chu et al. showed an incidence of 11.6% in not mechanically ventilated SARS-victims. SP was associated with a significantly higher intubation rate and mortality. In survivors, the resolution of SP took a median of 28 days (1). Beside SARS, other pneumonia-related cases of SP have been described (3).

Several publications regarding computed tomographic (CT) findings in cases of Covid-19 state that SP is a finding more typically associated with SARS infection than with the novel Sars-Cov-2 virus disease (5-11). To date, there have been only a few reports of SP in patients suffering from Covid-19 (6, 12-17).

Case description

The patient

A 65-year-old man was admitted to the general hospital in Roeselare, Belgium on March 31, 2020, after being referred by his general practitioner (GP)

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with a few days history of a worsening productive cough and general malaise. The GP had started amoxicillin 2 days earlier. However, the symptoms progressed, and the man was referred to the hospital after he was found to have an oxygen saturation at 92%, measured by pulse oximetry. The patient had a medical history of hypertension, diabetes (treated with oral antidiabetics), obstructive sleep apnea syndrome (OSAS) for which he used nightly nasal CPAP at home, a mechanical aortic valve prosthesis because of aortic valve insufficiency and an ischemic cerebrovascular accident in the past 3 months.

Clinical course

At presentation to the emergency department, the patient was stable. He had no fever (35.6°C) and he had a normal oxygen saturation of 99%. He showed no signs of tachypnoea or increased work of breathing. Lung auscultation revealed bilateral symmetrical crepitations in de lower lung fields.

Arterial blood gas (ABG) analysis showed a normal pH of 7.42, a normal pCO2 of 38mmHg and hypoxemia, with an arterial partial pressure in oxygen (PaO_2) of 65mmHg at room air. Lactate levels were low (16 mg dL^{-1}, normal values between 4 and 20). Blood analysis showed a normal leukocyte count (5.07 10^3 μm^{-3}, normal values between 4.20 and 9.80) with a normal formula but mildly decreased absolute lymphocyte count (0.98 10^3 μL^{-1}, normal values between 1.00 and 3.20). The C-reactive protein (CRP) was 33 mg L^{-1} (normal value <5), the D-dimers were at 438 ng mL^{-1} (normal value <500), and LDH was at 446 U L^{-1} (normal value between 135 and 225).

A CT-scan of the thorax was performed, which showed a typical pattern of Covid-19 disease : ground glass opacities and crazy paving. It was scored 17/25 on the CT severity score. The CT severity score is part of a standardized reporting system used for CT-scans of the thorax in the diagnosis of Covid-19. It is based on the amount of lung parenchyma involved and was established by the Dutch Radiological Society (18).

The diagnosis of Covid-19 pneumonia was made, and the patient was admitted to the Covid-19 unit. According to local protocols at that time, hydroxychloroquine and azithromycin were started. The amoxicillin prescribed by the GP was stopped because of low CRP. Oxygen was administered through a nasal canula, and titrated to a peripheral oxygen saturation of >94%.

Because of dyspnoea and an increasing oxygen demand, an PaO_2 of 52 mmHg on 13 L min^{-1} oxygen administration through a non-rebreathing mask, the patient had to be transferred to the intensive care unit on April 3, 2020. An arterial line was inserted for regular arterial blood gas analysis and blood pressure monitoring. High-flow nasal cannula (HFNC) oxygen therapy was started with Airvo 2 (Fisher & Paykel Healthcare, Auckland, New Zealand).

Because of further hypoxic respiratory failure (PaO_2 of 47mmHg, despite HFNC at 90%), non-invasive ventilation (NIV) was started one day later using the Respironics V60 (Philips, Eindhoven, Netherlands). NIV/BiPAP was only used during the first 3.5 hours, after which a more lung protective strategy with NIV/CPAP was applied. After the initiation of NIV/CPAP 70%, the PaO_2 increased to 66 mmHg.

The patient was treated alternately with HFNC and NIV/CPAP. It was the intention to use HFNC during the day and NIV/CPAP during the night, since the patient used nasal CPAP at home for his OSAS. However, even during daytime, the patient was put on NIV/CPAP intermittently for his comfort. During NIV, there was a median respiratory rate of 30 min^{-1} (IQR 26-34), a median inspiratory fraction in oxygen (FiO2) of 90% (IQR 70-90), a median positive end-expiratory or continuous positive airway pressure (PEEP/CPAP) of 10 cmH_2O (IQR 8-12), and a median tidal volume of 586 mL (IQR 537-656). This equates to 8.6 mL Kg^{-1} (IQR 7.9-9.6) based on ideal body weight (68 Kg) and 5.9 ml Kg^{-1} (IQR 5.5-6.7) based on real body weight (98kg). The patient's median oxygen saturation measured by pulse oximetry was 93% (IQR 90-94).

Because of further increasing oxygen demand and a clinical diagnosis of supraclavicular sub-cutaneous emphysema, a new CT-scan of the chest was performed on April 13, 2020. It showed, in addition to Covid-19 disease progression, an extensive pneumomediastinum, expanding to the cervical region (Figure 1). There were no arguments for external trauma or rupture of air-containing organs such as the esophagus. A "spontaneous", Covid-19-related, pneumomediastinum was the most plausible explanation.

The SP did not cause hemodynamic instability, neither were there clinical signs or symptoms of cardiac tamponade. Thoracic surgical advice was sought and there was no indication for surgical intervention.

Because of the SP, our strategy was to postpone intubation and invasive positive pressure ventilation as long as possible, since we feared that this could lead to an expansion of the SP. However, because of

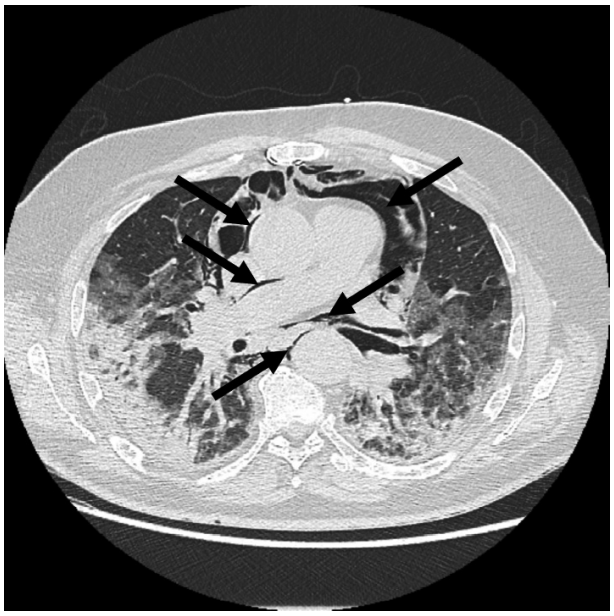

Fig. 1. — CT-scan of the thorax on April 13, 2020 (day 11 after ICU admission) showing typical Covid-19 characteristics such as ground glass opacities and crazy paving, but also pneumomediastinum (indicated by black arrows).

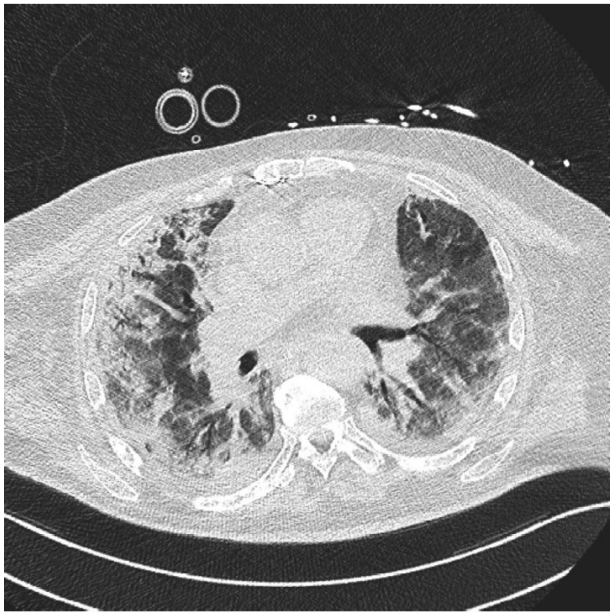

Fig. 2. — CT-scan of the thorax on April 29, 2020 (day 27 after ICU admission) showing Covid-19 disease progression, but complete resolution of the pneumomediastinum.

progressing respiratory failure with overt respiratory distress, increased work of breathing and imminent exhaustion, intubation and invasive ventilation were necessary on April 17, 2020. The used ventilator was a Dräger Evita XL (Dräger, Lübeck, Germany). Bi-level positive airway pressure (BiPAP) was the mode used most of the time.

The ABG before intubation showed a PaO_2 of 41 mmHg (P/F ratio = 43), a $PaCO_2$ of 38 mmHg, and a lactate level of 13 mg dL^{-1}. The first ABG after intubation and initiation of mechanical ventilation showed a PaO_2 of 60 (P/F ratio = 62) and a $PaCO_2$ of 53. Several hours later, the ABG showed a PaO_2 of 72 mmHg (P/F ratio = 88) and a $PaCO_2$ of 38 mmHg. The ventilatory settings and measurements at that moment were as follows : plateau pressure of 31 cmH_2O, PEEP of 8 cmH_2O with a tidal volume of 420 mL reached at a dynamic compliance of 23 mL cmH_2O^{-1}, a respiratory rate of 25 min^{-1} and a minute ventilation of 10.5 L min^{-1}. During invasive ventilation, there was a median respiratory rate of 27 min^{-1} (IQR 26-30), a median FiO2 of 75% (IQR 70-80), a median PEEP of 8cmH2O (IQR 8-10) and a median tidal volume of 404 mL (IQR 348-463), which equates to 5.9 mL Kg^{-1} (IQR 5.1-6.8) based on ideal body weight, and 4.1 mL Kg^{-1} (IQR 3.6-4.7) based on real body weight. The patient had a median dynamic compliance of 22 mL $cmH2O^{-1}$ (IQR 19-26) and a median plateau pressure of 31 cmH2O (IQR 29-32). The median oxygen saturation was 93% (IQR 91-94%).

The subcutaneous emphysema was monitored clinically and the SP through daily chest x-ray. No increase was observed.

On 21/4/2020, prone ventilation was initiated due to progressive hypoxemia. The PaO_2 was 59 mmHg with an FiO_2 of 90% (P/F-ratio = 66). In total, the patient underwent 4 prone sessions of a duration of between 16 to 24 hours per session. The third and fourth session needed to be aborted earlier, after 7 and 8 hours respectively, because of a significant increase in $PaCO_2$ and respiratory acidosis. Prone positioning was carried out by a team of at least 3 nurses and one physician who managed the head and the airway. The position was checked for possible pressure points and the abdomen was kept free. The position of arms and head was alternated approximately every 2 hours to prevent pressure ulcers or possible nerve injuries.

Guided by microbiological cultures and infectious parameters in blood analysis, the patient received a course of ceftriaxone and later a course of piperacillin-tazobactam. Furthermore, two trials of therapy with corticoids were done. The patient received methylprednisolone 125 mg intravenously during two consecutive days, followed by a tapering schedule for 10 days.

Despite maximal efforts, respiratory deterioration continued and hypercapnic respiratory failure ensued. Ventilation became very challenging with a maximal $PaCO_2$ of 147 mmHg and very low

compliance despite cautious titration to optimize PEEP and very careful recruitment maneuvers.

A third CT-scan of the chest was performed on April 29, 2020. It showed a fulminant disease progression of the Covid-19 with a CT severity score of 25/25 (Figure 1). Against all expectations, a complete resorption of the SP was seen despite non-invasive and invasive positive pressure ventilation.

Shortly after, the situation escalated further to a terminal respiratory failure. After repeated multidisciplinary conversations including with the patient's family, all supportive therapy was withdrawn, and comfort therapy was initiated. The patient passed away thereafter.

Discussion

Literature stated that SP is a complication of SARS rather than of Covid-19 (5-11). Few case reports are available regarding SP in Covid-19. All but one patient suffered acute respiratory deterioration which was the reason for additional radiological imaging (6, 12-16). This was the same in our case. This illustrates the importance of the avoidance of diagnostic tunnel vision. Respiratory deterioration could have been due to Covid-19 itself, but in these 6 cases, it was due to a rare complication, namely SP.

Many cases of SP may be missed if no follow-up imaging is taken, as in some patients the occurrence SP can remain completely asymptomatic during the entire course of the infection (6, 12-16). The real prevalence of SP in Covid-19 is still unknown. Most cases of SP occur later in the course of the disease. There is also the possibility that patient self-inflicted lung injury (P-SILI) might play a role in SP. Several cases confirm the occurrence of SP in Covid-19 without any preceding form of non-invasive or invasive positive pressure ventilation. An abrupt increase in intrathoracic pressures during coughing or multifactorial "lung frailty" could also play a role (17).

As of today, we could only find one case report of invasive ventilation in a Covid-19 positive patient after the diagnosis of SP. Unfortunately, this case report by Lacroix et al. focusses more on the diagnosis of SP and not on the outcome after the initiation of mechanical ventilation (15).

In our patient, ventilatory support was initiated using NIV. Two other cases used NIV: one patient survived and had complete resorption of the pneumomediastinum, the other patient died two days later because of respiratory failure and acute respiratory distress syndrome (6, 14). Two further case reports describe the complete resolution of SP in patients who did not require any ventilation support : one patient was treated with regular supplemental oxygen, the other patient needed HFNC (12, 13). Kolani et al. describe a case of a young asymptomatic woman with a limited pneumomediastinum who was tested positive for Sars-Cov-2. She remained asymptomatic during the entire course of hospitalization and a control CT-scan of the thorax 7 days later showed complete resolution (16).

Existing literature shows a time to resolution of the SP of 8, 11, 12, 14 and 20 days (6, 12-15). In our case, it was 13 days, although this could of course be an overestimation because of the timing of the follow-up CT-scan. However, it is much shorter than de median of 28 days found by Chu et al. during the SARS epidemic (1).

In addition to our clinical follow-up strategy, we performed daily chest x-rays and the three CT-scans as mentioned above. We performed these CT-scans on clinical indication, not routinely for follow-up of the SP.

Management of SP is mainly conservative. It is unclear whether a specific treatment adjustment is needed if, for example, if a bulla is diagnosed prior to formation of a pneumothorax or SP. Wink et al. state in their recent work on non-invasive ventilation management of Covid-19 that a "protective-NIV" with lower tidal volumes between 6-8 mL Kg^{-1} should be pursued. However, oftentimes in the Covid-19 patient population this target is impossible to achieve and patients breathe higher tidal volumes. A higher tidal volume was associated with NIV failure (19). These increased tidal volumes probably reflect the increased respiratory drive in Covid-19. Increased minute ventilation, primarily by increasing tidal volumes (up to 15-20 mL Kg^{-1}) is a normal response to hypoxemia. Undetermined factors other than hypoxemia also stimulate the respiratory drive in these patients with Covid-19 (20). This makes NIV a debatable option for Covid-19. We saw relatively high tidal volumes during NIV (both in BiPAP and CPAP mode) with a median tidal volume of 586 (IQR 537-656). For this patient with an ideal body weight of 68 Kg, this equated to a median tidal volume of 8.6 mL Kg^{-1} (IQR 7.9-9.6). Whether or not biotrauma, caused by relatively high tidal volumes during HFNC or NIV/CPAP, played a role in the fatal deterioration of the patient's condition rather than solely disease progression due to Covid-19, is unclear. Since we feared expansion of the SP after initiation of invasive positive pressure ventilation, we were more

reluctant for early intubation and so we tolerated those tidal volumes of 8.6 mL Kg^{-1} of ideal body weight in our strategy to postpone intubation and invasive ventilation as long as possible.

During invasive positive pressure ventilation, we had high plateau airway pressures with a median plateau airway pressure of 31 cmH2O (IQR 29-32) and median tidal volumes of 404 mL (IQR 348-463). That equaled a median tidal volume per kg of ideal body weight of 5.9 mL (IQR 5.1-6.8). In the other case reports, only one other patient received invasive positive pressure ventilation after intubation. Unfortunately, no outcome concerning the pneumomediastinum or the survival of the patient is described (15). In our patient a complete resorption of the SP was seen without specific treatment and in spite of non-invasive and invasive ventilation.

During the pandemic we gained new insights, which helped us to improve our strategy. In concordance to the advice from Marini and Gattinoni and the Surviving Sepsis Campaign Guidelines on Covid-19 (21, 22)., we preferred to start HFNC in the hypoxic patient. If this was insufficient, we only used a short trial of NIV/CPAP - provided the patient does not exert excessive respiratory efforts. If the respiratory drive (e.g. the tidal volume) was not reduced after a couple of hours, or the patient shows clinical signs of increased work of breathing or persistent respiratory distress despite high oxygen supplementation, intubation was performed and invasive ventilation initiated. Hence, we tried to avoid the so-called P-SILI, which is thought to be a consequence of the decreased negative intrathoracic pressures which are associated with increased tidal volumes, in combination with the diseased lung with increased lung permeability due to inflammation, resulting in (more) interstitial lung edema (20, 22).

The etiology of SP remains rather unclear, but, besides known risk factors such as emphysema, bullae or abrupt pressure increases during coughing, we think that lung frailty – possibly aggravated by P-SILI – might play an important role (17). Some other authors, such as Tobin et al., are rather reluctant to support the theory of P-SILI and suggest that it is instead, a recent invention lacking in evidence or clinical relevance (23). They state that even if high tidal volumes and so-called P-SILI would play a role in disease progression of Covid-19 (for which there is no convincing evidence according to them), this would not justify the early intubation strategy, since there are known and well-documented fatal complications associated with it (23).

It is still too early to come to an evidence-based solid conclusion concerning the optimal approach to Covid-19. Optimal timing of intubation, risks of intubation and risks of delayed or even avoided intubation remain an important topic for debate, particularly in special circumstances such as the presence of a SP. In one case report concerning a patient without Covid-19 but with severe interstitial lung disease and both a pneumomediastinum and a pneumothorax, veno-venous ECMO was applied after ongoing respiratory failure on maximal lung protective ventilation. The clinical condition of the patient improved rapidly after several hours on ECMO. Chest x-ray showed complete resorption of the pneumothorax and subcutaneous emphysema after 3 days. Unfortunately, the evolution of the pneumomediastinum is not explicitly discussed (24). ECMO is a resource-intensive, highly specialized, and expensive technique with the need for experienced healthcare workers and adequate infrastructure. It does however have a place in some carefully selected critically ill patients, whose disease is refractory to conventional management strategies (22). It is unclear whether or not a SP itself, apart from the other classical indications, is an indication for early initiation of ECMO to avoid risks of invasive positive pressure ventilation. Insofar as we saw a complete spontaneous resolution of the SP despite non-invasive and invasive positive pressure ventilation, careful weighing up of the risks and benefits of early ECMO should be done. In this patient, we did not use ECMO. However, we did use it in selected other Covid-19 patients who were refractory to conventional management strategies (proning, neuromuscular blockade, appropriate PEEP-titration, careful recruitment maneuvers). Those patients need to meet the criteria for ECMO as proposed by the European Life Support Organization (ELSO) Covid-19 Interim Guidelines (25). A very recent correspondence of Lorusso et al. reports a survival rate of up to 55% for patients on ECMO with severe refractory respiratory or cardiac failure secondary to Covid-19 (26). So, ECMO can be considered in carefully selected patients with refractory respiratory failure despite conventional optimal care (25, 27, 28).

Conclusion

There might be a higher incidence of spontaneous pneumomediastinum in Covid-19 acute respiratory distress syndrome as compared to non-Covid-19 acute respiratory distress syndrome, but further research is needed to confirm this

assertion. A patient with Covid-19 pneumonia and acute respiratory deterioration should get early additional CT-scan imaging, notably to detect such complication.

We delayed intubation and invasive ventilation out of fear that it could cause a deterioration of the pneumomediastinum and hence we tolerated borderline tidal volumes on NIV/CPAP and the associated increased risk of potential P-SILI. However, we did see a complete resolution of the pneumomediastinum despite non-invasive and invasive ventilation. Early intubation, if needed to guarantee a proper lung protective strategy, should therefore not be avoided because of SP.

ECMO seems to be a feasible option for carefully selected Covid-19 patients whose disease is refractory to conventional optimal care and could be an option for the subgroup of Covid-19 patients with a SP. Further research is needed again to confirm the utility of ECMO in that case.

Ethics Committee

Commissie medische ethiek, Deltalaan 1, 8800 Roeselare, Belgium. Chairperson ethics committee : Dr. Luc Harlet. Internal reference : IRB study reference 20084. Clinical Trial Number : B1172020000025. Date of approval : 29/7/2020

Informed consent

This case report was reviewed by the local Ethics Committee of AZ Delta (study reference 20084) and was determined to be exempt from the requirement of informed consent. Because of the retrospective nature of the case and in line with Belgian law, an informed consent did not have to be obtained.

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