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Spontaneous Pneumomediastinum without Pneumothorax in Non-ventilated COVID-19 Pneumonia: A Case Report

İnvazif-Non-İnvazif Ventilasyon Uygulanmayan COVID-19 Pnömonisinde Pnömotoraks Olmadan Spontan Pnömomediastinum: Olgu Sunumu

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Abstract

Spontaneous pneumomediastinum (SPM) is among the rare complications of Coronavirus Disease-19 (COVID-19) and usually involves patients with a severe form of disease who are undergoing treatment with invasive/non-invasive ventilation or high-flow oxygen therapy. A very low percentage of SPM cases are detected in non-ventilated COVID-patients, the underlying causes of which are still to be understood. We report here on the case of a 65-year-old patient with no clinical history of cardiovascular or pulmonary disease who developed SPM within a few days following hospital admission. SPM was detected on chest CT-angiography, and was unrelated to high-flow oxygen treatment.

Key words: *COVID-19, Spontaneous pneumomediastinum, SARS-CoV-2.*

Özet

Spontan pnömomediastinum (SPM) korona virüs (COVID-19) hastalığının nadir komplikasyonları arasında bulunmaktadır. Genellikle invazif / non-invazif ventilasyon veya yüksek akışlı oksijen tedavisi alan ve hastalığı ağır şekilde geçirmekte olan hastalarda görülür. Ventilasyon kullanılmayan COVID-19 hastalarında çok düşük oranda SPM tespit edilmektedir. Ancak SPM gelişmesinin altında yatan nedenler hala tam olarak anlaşılmamıştır. Bu makalede 65 yaşında, klinik olarak kardiyovasküler veya pulmoner hastalık geçmişi olmayan, hastaneye yatışından sonraki birkaç gün içinde SPM gelişen bir olguyu sunmaktayız. Toraks BT-anjiyografisinde SPM tespit edilmiş olup yüksek akımlı oksijen tedavisi kullanmamıştır.

Anahtar Sözcükler: *COVID-19, spontan pnömomediastinum, SARS-CoV-2.*

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As of May 2021, more than 133 million confirmed coronavirus cases have been reported in 220 countries around the world, along with more than 3 million deaths. Coronavirus Disease-19 (COVID-19), the clinical manifestation of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection(1), is known to present with a wide range of symptoms and signs, such as fever, cough, dyspnoea, myalgias and asthenia, as well as digestive symptoms, although in most cases the course of infection is asymptomatic.

ARDS (Acute Respiratory Distress Syndrome) is the main cause of death, usually following a hyperinflammatory state, and develops rapidly in 5% of patients with coronavirus infection (2,3). The RT-PCR (reverse transcription-polymerase chain reaction) detection of SARS-CoV-2 mRNA is the standard approach for in-hospital and out-hospital diagnosis, although in recent months CT scans have been used as a fundamental tool not only for diagnosis, but also for measuring the extent of the compromised parenchyma in COVID patients (4,5). Chest CT scans, together with laboratory inflammatory markers, can help clinicians decide upon an appropriate therapy, and CT examinations, in particular, may be useful for revealing some atypical signs that would not otherwise be detectable from a physical examination. Up to 1% of COVID patients have been stated to develop spontaneous pneumothorax (6), while spontaneous pneumomediastinum (SPM) is a rarer complication, remaining anecdotic, and has been described in only a few reports (7,8). SPM, defined as an air-flap in the mediastinum that is not associated with trauma, is a well-known complication in many infections of the lung (9-11), and is often associated with pneumothorax and/or subcutaneous emphysema, resulting from alveolar rupture, and often occurs secondary to acute increases in intrathoracic pressure.

Common causes include exercise, drugs, asthma, vomiting or Valsalva maneuvers. It is rarely benign and self-limited, and is more prevalent in young males. Typical symptoms include the triad of pneumomediastinum, being thoracic pain, dyspnea and subcutaneous emphysema. Hamman's sign, being crepitus heard on auscultation of the heart, is a common finding, and may be the only abnormal physical finding (12). A physical examination is often insufficient for a diagnosis of SPM, with a need for CT scans for confirmation. Released alveolar air dissects centripetally through the pulmonary interstitium along the bronchovascular sheaths, toward the pulmonary hila and into the mediastinum, which is a pathophysiological mechanism that was described by Macklin et al. in 1944, and is known as the Macklin effect (13).

High-flow oxygen therapy, when supplied, increases the risk of complications, such as those cited above; while CPAP, NIV and HFNC increase intra-alveolar pressure, and considering that acute lung deterioration with rapid desaturation is per se a reason favouring alveolar rupturing, it is easy to understand how severe forms of pneumonia treated with high-flow oxygen therapy can result in poor outcomes.

We report here on the case of a 65-year-old male who developed SPM after being hospitalized for COVID-19, even without receiving high-flow or high-pressure oxygen therapy.

CASE

In April 2021, a 65-year-old male presented to the emergency ward of M. Bufalini Hospital in Cesena, Italy, with a 10-day history of fever, dry cough and diarrhoea, and was subsequently diagnosed with SARS-CoV-2 infection after a RT-PCR detection of viral mRNA on a nasopharyngeal swab.

He was a non-smoker with a history only of celiac disease, and had been on no drug-therapy prior to hospital admission. Upon arrival, he was awake, alert and oriented, with a body temperature of 36°C, respiratory rate of 30 breaths per minute, blood pressure 125/70 mmHg, pulse 92 beats per minute and arterial oxygen saturation (SpO2) 90% at rest. The Modified Early Warning Score (MEWS), calculated at the time of admission, was 3, while the National Early Warning Score (NEWS) score was 6. Both scores were calculated to assess the patient's clinical stability (14).

The patient was placed on low-flow oxygen therapy through a non-rebreather mask, despite no signs of respiratory fatigue being reported. An arterial blood sample examination and routine blood tests were performed, the former of which revealed respiratory insufficiency with a PaO_2/fiO_2 ratio of 296, while the latter showed increased serum LDH (384 U/L) and CPK (479 U/L), neutrophilic leukocytosis (WBC 12500/mmc, N 11500/mmc) with lymphopenia (L 600/mmc) and high serum CRP (15.7 mg/dl). Urinary antigen testing for L. pneumophila and S. pneumoniae was negative, as were the blood cultures. Table 1 presents a summary of the blood test results during the patient's hospital stay.

Table 1: Laboratory exams of patient during hospitalization

	Day 1	Day 2	Day 7	Day 11	Day 13	Range
WBC (n/mmc)	12510		11620	13340	9370	4000-10000
RBC (n*106/mmc)	4.62		5.12	5.19	4.83	4.50-5.70
Hb (g/dl)	15.1		16.5	17.1	15.8	13.50-17.00
Hct (%)	44		50	48	45	40-52
MCV (fl)	94		97	92	92	80-95
MCHC (%)	34.6		33.3	36	35	32-36
Neutrophiles (n/mmc)	11510		8200	10770	6490	2000-8000
Lymphocytes (n/mmc)	600		2540	1470	1960	1000-4000
Monocytes (n/mmc)	370		810	790	860	200-1000
Eosinophils (n/mmc)	0		10	290	50	0-500
Basophils (n/mmc)	200		60	20	10	0-20
Platelets (n/mmc)	207000		464000	354000	214000	150000-450000
Creatinine (mg/dl)	0.88	0.83		0.68	0.75	0.70-1.20
eGFR (ml/min)	90	92		100	96	>90
Azote (mg/dl)	24					<71
Tot bilirubin (mg/dl)	0.36			0.6		<1.20
Direct bilirubin (mg/dl)	0.2			0.2		<0.30
Sodium (mmol/l)	132	138	138	135	134	136-145
Potassium (mmol/l)	3.8	4.8	4.5	4.3	4.4	3.5-5.1
Chlorine (mmol/l)	95					98-107
Calcium (mg/dl)					9.5	8.6-10.2
AST (U/L)	43					<40
ALT (U/L)	25			88		<41
GGT (U/L)				33		8-61
CPK (U/L)		479				30-240
LDH (U/L)	384					135-225
Troponin T (ng/ml)	9					<15
C-Reactive Protein (mg/dl)	15.7	20.5	1.6			<0.5
PT (INR) (ratio)	1.1					0.80-1.20
aPTT (ratio)	0.93					0.80-1.20
D-dimer (ng/ml)	440					<500
Quantiferon		Negative				Negative
IL-6 (pg/ml)		116				<5.9
Ferritin (mg/dl)		1390				30-400
Procalcitonin (ng/ml)		0.24				<0.5

WBC= White Blood Cells; RBC= Red Blood Cells; Hb= Haemoglobin; Hct= Hematocrit; MCV= Medium Corpuscular Volume; MCHC= Mean Corpuscular Haemoglobin Concentration; eGFR= estimated Glomerular Filtration Rate; AST= Aspartate Transferase; ALT= Alanine Transferase; GGT= Gamma Glutamyl Transpeptidase; CPK= Creatine Phosphokinase; LDH= Lactic Dehydrogenase; PT= Prothrombin Time; aPTT= activated Partial Thromboplastin Time; IL-6= Interleukin-6

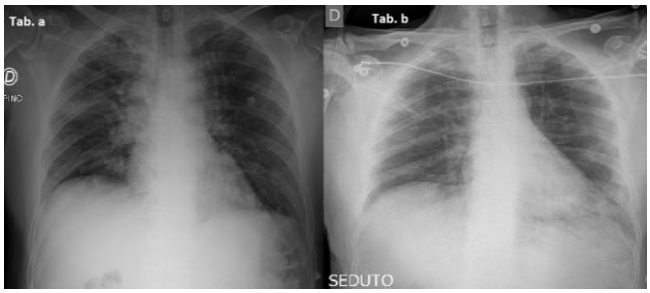

Figure 1: *Chest X-ray executed on day 1 of admission in the supine position* ***(a)****, second chest X-ray executed on day 8 in the sitting position* ***(b)***

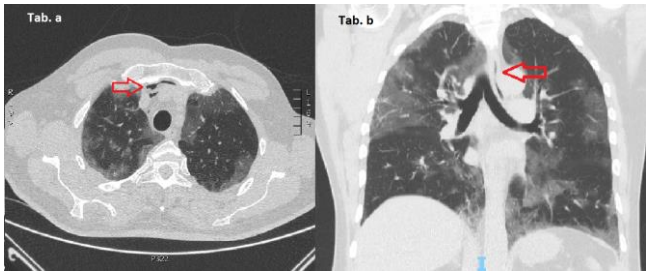

Figure 2: *Chest CT-angiography executed on day 8 of admission; axial scanning plane* ***(a)*** *and coronal scanning plane* ***(b)****. The red arrow indicates an upper pneumomediastinal leak in the anterior mediastinum*

A chest X-ray revealed parenchymal thickening in the right middle lung field and accentuated broncho-vascular markings (signs compatible with interstitial pneumonia) (Figure 1a), and the patient was subsequently admitted to our Internal Medicine department dedicated to COVID inpatients.

Steroid therapy with dexamethasone was administered starting on the first day at a dose of 6 mg/day together with low molecular weight heparin (LMWH) at a prophylactic dosage; empiric oral treatment for the persistent dry cough with dihydrocodeine was also administered, together with acetylcysteine and PPI. In line with regional and local guidelines criteria, we decided to treat the patient with Tocilizumab, an immunosuppressive drug that is used mainly for the treatment of rheumatoid arthritis to reduce the hyperinflammatory response to SARS-CoV-2(15).

The patient was placed on low-flow oxygen therapy with simple face mask until day 7. SpO_2 was within the 94-96% range for the duration of observation. The patient remained apyretic, and was advised to sleep in the prone position at night. Other vital parameters (blood pressure, respiratory rate and heart rate) also remained within the normal ranges. An arterial blood examination was repeated on the 3rd and 7th days with similar PaO_2/fiO_2 ratios (196 with fiO_2 33%, and 173 with fiO_2 37%, respectively).

On day 8 following admission, we decided to increase the oxygen supply and to perform an arterial blood examination with 10 LPM and non-rebreather mask due to an increase in respiratory fatigue and lower SpO_2 levels (92% with an oxygen flow of 6 litres per minute, LPM, fiO_2 40%), leading to a mild worsening of pulmonary gas exchange (PaO_2/fiO_2 133 with fiO_2 45%).

A chest CT-angiography was performed to allow a better assessment of parenchyma involvement in the lung and to exclude signs of pulmonary embolism, revealing bilateral extended areas of parenchymal "ground glass" involvement in both the upper and lower lobes of the lungs, in addition to some areoles with a greater density that were suggestive of interstitial and alveolar pneumonia.

In contrast, a thorax study highlighted the presence of air within the adipose tissue of the anterior mediastinum with a 2 cm thick and 6 cm long air leak. Figure 2 shows the pneumomediastinal leak in the axial and coronal scanning planes (a and b, respectively).

We consulted hospital intensivists to decide upon the best course of treatment for our patient, who recommended only a conservative approach. For the better definition of the patient's healthcare pathway, we transferred him to our dedicated rooms with parameter monitoring systems where he again underwent a chest X-ray, revealing a slight extension of the interstitial involvement already described in the lower-left pulmonary field (Figure 1b). As a result of a progressive improvement in the patient's clinical condition, we were able to reduce oxygen support until complete weaning, and the patient was discharged from hospital on day 20.

DISCUSSION

SPM has already been associated with severe acute respiratory syndrome (SARS) with a prevalence of 11.6% in a Chinese study in 2004 (16).

A group of researchers from Mexico recently published a report on the frequency of SPM and the related risk factors in a healthcare facility dedicated to COVID inpatients (17). Within a cohort of 271 patients, nine developed SPM (3.3%), while four developed spontaneous pneumothorax (1.47%). None of the patients received mechanical ventilation at the time of admission, although the authors did not clarify whether or not continuous positive airway pressure (CPAP) or high flow nasal cannulas (HFNC) were administered during hospitalization. The authors confirmed that SPM is not related exclusively to the mechanical ventilation of COVID-19 patients, and can involve subjects with risk factors such as young age, tobacco

smoking, asthma and/or pulmonary emphysema, and the male gender. Similarly, Jones et al., in their study of 83 critically ill COVID inpatients, found that seven patients developed pneumomediastinum, with a prevalence of 8.4%, and all were reported to develop pneumomediastinum after CPAP or non-invasive ventilation (NIV) therapy were administered.

Pneumomediastinum can also occur independently of assisted ventilation, and although it is rarely reported among non-ventilated COVID inpatients, previous studies have described it as a possible complication in patients with Severe Acute Respiratory Syndrome (SARS), leading to poor outcomes.

In general, SPM has a reported incidence in non-COVID patients of 1 in 25,000, and is more common in males and children (7). The exact prevalence of SPM in COVID patients is not known, and literature contains only a few some case reports. Consequently, it is necessary to identify the precise cause of cases occurring independently of mechanical invasive ventilation or non-invasive ventilation. In our case, the patient was treated only with low-flow oxygen, aside from in the few hours preceding the chest CT-angiography, when he was treated with 10 LPM via a reservoir mask. The patient was not placed on high-flow oxygen therapy, nor did he need non-invasive ventilation until complete oxygen weaning.

CONCLUSION

Spontaneous pneumomediastinum is still a rare complication in COVID-19 patients, and occurs with more frequency in patients on high-flow oxygen therapy or those being ventilated, even non-invasively. In other conditions, as happening for patients receiving low-flow oxygen therapy without being ventilated, only a few cases were described and often with poor outcomes, even if the underlying causes of the development of SPM are still unknown. As is the case for other complications related to COVID-19, further studies of the topic are needed.

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CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - S.G., E.G., G.L.C., N.G., P.S., M.T.M., G.M., A.L., E.M., R.D., E.P., L.M.; Planning and Design - S.G., E.G., G.L.C., N.G., P.S., M.T.M., G.M., A.L., E.M., R.D., E.P., L.M.; Supervision - S.G., E.G., G.L.C., N.G., P.S., M.T.M., G.M., A.L., E.M., R.D., E.P., L.M.; Funding - E.P., L.M.; Materials - S.G., M.T.M., G.M., E.P., L.M.; Data Collection and/or Processing - S.G., E.G., G.L.C., N.G., G.M., R.D.; Analysis and/or Interpretation - S.G., P.S., G.M., E.P., L.M.; Literature Review - S.G., P.S., E.P., L.M.; Writing - S.G., E.P., L.M.; Critical Review - P.S., E.P., L.M.

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