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PNEUMOTHORAX IN PATIENT WITH PNEUMONIA CAUSED BY SARS-CoV-2 - CASE REPORT

PNEUMOTORAKS KOD BOLESNICE SA PNEUMONIJOM IZAZVANOM SARS-CoV-2 - PRIKAZ SLUČAJA

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Abstract

Introduction. Coronavirus disease 2019 (COVID-19) is acute infectious multisystem disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is manifested by acute respiratory symptoms. Novel coronavirus pneumonia (NCP) is the most common serious clinical manifestation of SARS-CoV-2 infection. During severe NCP systemic manifestations of the disease were also demonstrated, and one of the rare complications, first described in Wuhan (China), is pneumothorax.

Case report. A 65-year-old female was admitted to the Pulmonary Clinic with high fever, shortness of breath, sore throat and general weakness that started five days before. Laboratory findings revealed lymphopenia, elevated values of inflammatory markers and liver lesion. A chest X-ray (CXR) demonstrated diffusely accentuated interstitial pattern and reduced parenchymal transparency left parahilar. Positive SARS-CoV-2 in a nasopharyngeal swab sample was detected in the real time-reverse transcription polymerase chain reaction (RT-PCR), confirming the diagnosis of NCP. Immediately, nasal oxygen therapy was initiated flow rate 8 lit/min, chloroquine phosphate, antibiotics, and symptomatic treatment. On day 8, she suddenly deteriorated and developed severe hypoxemia. A repeat CXR showed complete left-sided pneumothorax. Thoracic drainage was successfully performed with complete reexpansion of the lungs the very next day. She was released from the hospital in good general condition with normal arterial blood gases.

Conclusion. Pneumothorax may develop as a complication in patients with pneumonia caused SARS-CoV-2, without previous pulmonary comorbidities, due to alveolar damage. Acute deterioration with rapid oxygen desaturation in these patients should raise the suspicion of pneumothorax. Early diagnosis and prompt treatment is necessary to reduce mortality.

Key words: COVID-19, coronavirus pneumonia, pneumothorax
Apstrakt

Uvod. Koronavirusna bolest 2019 (COVID-19) je akutna, infektivna multisistemska bolest koja se najčešće manifestuje akutnim respiratornim simptomima. Izaziva je teški akutni respiratorni sindrom koronavirus 2 (SARS-CoV-2). Nova koronavirusna pneumonija (NCP) je najčešća ozbiljna klinička manifestacija SARS-CoV-2 infekcije. U teškoj NCP ispoljene su i sistemski manifestacije bolesti, a jedna od retkih komplikacija, prvi put opisana u Wuhanu (Kina) je pneumotoraks.

Prikaz slučaja. 65-godišnja žena je primljena u Kliniku za pulmologiju zbog febrilnosti, otežanog disanja, gušobolje i opšte malaksalosti koje je imala prethodnih 5 dana. Laboratorijski nalazi su otkrili limfopeniju, povišene vrednosti inflamatornih parametara i leziju jetre. Radiografija (RDG) grudnog koša je pokazala difuzno naglašen intersticijum i smanjenu transparenciju parenhima levo perihilarno. Pozitivan test na SARS-CoV-2 u uzorku nazofaringealnog brisa otkriven je lančanom reakcijom polimeraze (PCR), čime je potvrđena dijagnoza NCP. Odmah je započeta terapija kiseonikom preko nazalne kanile protoka 8 lit/min, hlorokin fosfatom, antibioticima i simptomatskom terapijom. Osmog dana, ona se naglo pogoršala i razvila tešku hipoksemiju. Ponovljena RDG grudnog koša potvrdila je kompletan pneumotoraks levo. Torakalna drenaža je uspešno izvedena uz potpunu reekspanziju pluća već sledećeg dana. Iz bolnice je otpuštena u dobrom opštem stanju sa normalnim gasovima arterijske krvi.

Zaključak. Pneumotoraks može da nastane kao komplikacija kod pacijenata sa pneumonijom izazvanom SARS-CoV-2, bez prethodnih plućnih bolesti usled oštećenja alveola. Akutno pogoršanje sa naglom desaturacijom kiseonika kod ovih pacijenata trebalo bi da pobudi sumnju na pneumotoraks. Rana dijagnoza i brzo lečenje su neophodni za smanjenje smrtnosti.

Ključne reči: COVID-19, koronavirusna pneumonija, pneumotoraks
Introduction
Coronavirus disease 2019 (COVID-19) is acute infectious multisystem disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), primarily affecting the respiratory tract. The disease was first seen in December 2019 in Wuhan, China, it spread rapidly throughout the world and was declared a pandemic by the World Health Organization (WHO) on the 11th of March 2020 [1].
Clinical presentations of SARS-CoV-2 infection has a broad spectrum that can range from asymptomatic forms to critical disease. Asymptomatic persons seem to account for approximately 40% to 45% of SARS-CoV-2 infections [2]. Even though the majority of cases result in mild symptoms of a typical viral infection, up to 5% of the cases can develop critical illness and multiorgan failure [3]. Pneumonia is the most common serious clinical manifestation of SARS-CoV-2 infection. It has been identified as a novel coronavirus pneumonia (NCP).
As the COVID-19 pandemic progresses, over the past few months, awareness and knowledge of unusual disease presentations, such as pneumothorax, has increased. Pneumothorax is a known and a well-described complication of mechanical ventilation (MV) when it supports COVID-19 treatment, and is attributed and is attributed to barotrauma [4]. Additionally, patients with COVID-19 are often treated with non-invasive ventilation (NIV) or oxygen via high-flow nasal canula (HFNC) for respiratory support. Positive pressure applied can facilitate the development of pneumothorax.
However, recent reports suggests that it pneumothorax can be present in the context of COVID-19, even in the absence of MV-related and NIV-related barotrauma [5-10].
We present a case of a patient with pneumonia caused by SARS-CoV-2 who developed spontaneous pneumothorax as a rare complication.

Case report
A 65-year-old female with a past medical history of hypertension and regulated hyperthyroidism, was admitted to the Pulmonary Clinic with high fever, shortness of breath, sore throat and general weakness that started five days before. She had never smoked and denied previous pulmonary disease. On admission, her general condition was bad, she was dyspnoic, adynamic and dehydrated. Her vital signs showed tachypnea (31 breaths/minute), with high temperature (38.5C), increased heart rate (123 breaths/minute)
and arterial blood pressure (110/70 mmHg). The initial oxygen saturation (SpO2) was 89% in room air and 95% with a binasal cannula 8 lit/min of O2. Chest examination revealed basal crackles on the left side. Other systemic examinations were orderly.

Laboratory analysis showed white blood cell (WBC) count 13.63 x 10⁹/L. The WBC differential count showed 82.84% neutrophils and lymphopenia of 8.43%. Initial laboratory tests were significant for elevated C-reactive protein (CRP) of 57.6 mg/L, aspartate aminotransferase (AST) of 62 IU/L, alanine aminotransferase (ALT) of 51 IU/L, lactate dehydrogenase (LDH) of 855 U/L, D-dimer of 1.84 μg/ml and ferritin of 609 μg/L. A chest X-ray (CXR) on admission demonstrated accentuated interstitial pattern bilaterally, linear-banded shadows perihilarly and reduced left parahilar transparency (Figure 1A). Nasopharynx swab, real time-reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2, was positive two days after admission.

The patient was labeled as moderate NCP. He was started on SARS-CoV-2 caused pneumonia treatment, guided by the local valid protocol in our country: chloroquine phosphate, parenteral antibiotics (Ceftriaxone and Aztyromycin), supplemental oxygen with nasal cannula, vitamin and symptomatic therapy, with prophylactic dose of low molecular weight heparins (LMWH) to prevent venous thromboembolism.

She was subjectively better and hemodynamically stable. For a week she had remained on 4 lit/min oxygen via nasal cannula, maintaining an oxygen saturation of 96%. No significant changes in AST and ALT values were observed in control laboratory tests (AST:55 IU/L, ALT:68 IU/L). In the electrocardiographic finding, sinus rhythm persisted, without extrasystoles and changes in the final oscillation, the value of the QTC interval was 423ms.

On day 8, she suddenly deteriorated, complained of intense shortness of breath, accompanied by irritating dry cough and developed desaturation of 78%. Gas analysis showed recorded severe hypoxemia (arterial pressure oxygen - pO2=6.0 kPa) and mild hypocapnia (pCO2=4.4kPa). The patient required 15 lit/min of oxygen via a face mask and was transferred to intensive care. A repeat CXR showed complete left-sided pneumothorax (Figure 1B). The emergency intervention by a thoracic surgeon, a chest drain was inserted, and the patient’s oxygen saturation improved. Next day, control CXR showed complete reexpansion of the lung parenchyma on the left side (Figure 1C). At no point during her stay did she require the use of NIV or oxygen via HFNC. Her oxygen requirements
decreased over the next 2 days, and she was transferred to the medical ward with a binaural cannula 3 l/min of O2. However, her condition deteriorated, she became febrile and dyspnoic with desaturation. Laboratory results showed increased value of D-dimer (3.47 μg/ml) and raised inflammatory markers (CRP:185 mg/L, procalcitonin:2.35 ng/ml and ferritin:998 μg/L), whereas CXR registered diffusely reduced left parenchymal transparency and consolidation right infraclavicular (Figure 1D).

There was clinical suspicion of bacterial superinfection but also a dilemma about the possible severe SARS-CoV-2 pneumonia. Then chest computed tomography (CT) was not available. She responded well to parenteral antibiotics (Meropenem and Vancomycin), therapeutic dose of LMWH, glucocorticoid (Lemod solu 40mg iv) with O2 supplementation for seven days. The drain was removed a week after administration. The patient was discharged from hospital in a good general condition on day 21. CXR showed marked radiological regression of the described changes (Figure 2). Arterial blood gas analysis at discharge, without oxygen therapy, showed normal values (pO2=9.6kPa, pCO2=5.6kPa, PH=7.51, HCO3=29.8, SAT=96%).

The patient felt well in the following period. She was monitored by a thoracic surgeon, who described a normal CXR. Four months later, when the epidemiological situation allowed, a chest CT scan was performed, which described bilaterally in the lower lobes ground-glass opacity with elements of interstitial fibrosis; left in the upper lobe thickening of the parietal pleura (Figure 3).

For our patient, pulmonary function testing (spirometry, diffusion capacity for CO), control chest CT and further monitoring are planned. There are currently no recommendations for the use of glucocorticoids in these patients.

Discussion
The severity of COVID-19 is variable, from mild to critical disease. The most common symptoms of SARS-CoV-2 infection, widely characterized in large studies, include fever, cough, and shortness of breath. NCP is the most common serious clinical manifestation of SARS-CoV-2 infection [11]. Patients with severe NCP usually present with dyspnea (respiratory rate > 30/min) and/or hypoxemia (SpO2 < 90% at room air) with bilateral infiltrates present on chest imaging. In very severe cases, the disease can progresses rapidly
and become complicated by acute respiratory distress syndrome (ARDS) and coagulopathies [11]. To date, it is recommended that the definitive diagnosis of SARS-CoV-2 infection be confirmed by a positive RT-PCR test or genetic sequencing [12].

Pneumothorax is uncommon and rare finding in patients with NCP, with a frequency of 1% according to the current literature [13].

Pneumothorax is a clinical entity which defined as presence of air in the pleural space [14]. It can occur spontaneously or following trauma. Spontaneous pneumothorax being the most common type and can be primary or secondary, depending on the absence or presence of an underlying lung disease [14].

The well-known risk factors for the development of spontaneous pneumothorax include male gender, tobacco use, tall stature, age-group 10–30 years, strenuous exercise. Additionally, the most frequent underlying disorders responsible for secondary spontaneous pneumothorax include chronic obstructive pulmonary disease (COPD) with emphysema, interstitial lung disease, tuberculosis, lung cancer or Pneumocystis carinii pneumonia[14].

Pneumothorax is a potential complication usually associated with cystic lung formation due to rupture of the lung tissue.

Liu et al. [15] reported that COVID-19 may independently result in pulmonary cyst formations and the development of a pneumothorax. SARS-CoV-2 infected alveolar units tend to be peripheral and subpleural, which is confirmed by radiological findings of COVID-19 in the peripheral lung parenchyma. This tropism of SARS-CoV-2 may increase the risk of peripheral cystic formation facilitating its rupture into the pleural cavity and the development of pneumothorax.

The pathophysiology mechanism of pneumothorax formation in patients with NCP is not completely understood. However, differences between the early and late stages of the disease are indicated.

It is supposed, the complication of pneumothorax occurs secondary, due to diffuse alveolar damage from the inflammation caused by a viral infection. The histology, an early phase of NCP mainly shows the migration of neutrophils, monocytes and macrophages, vascular congestion, mucus-like exudation in the alveoli, edema in the alveolar septum and microthrombosis. Due to destruction of the alveolar septa and a sudden increase of alveolar
pressure, the alveoli may be prone to rupturing and the formation of pulmonary cystic lesions [15].

At this stage, the direct cytopathogenetic effect of SARS-Cov-2 on type II cells is also suggest as a possible pathogenetic mechanism. SARS-CoV-2 propagates within type II pneumocytes, large number of viral particles are released, and the cells undergo apoptosis and die [16].

The late stages of NCP determines ischemic parenchymal damage, activation of fibroblasts, lung fibrosis, low lung compliance and inflammatory fibromyxoid exudates into alveoli and airway. Pulmonary cystic lesions may form in response to fibromyxoid exudates, which form a valve in the bronchus. Also, due to pulmonary fibrous processes, bronchioles are narrow and distorted, and the valve mechanism could cause pulmonary cystic formation [15].

Pneumothorax, associated with subcutaneous and mediastinal emphysema, is a well described complication of mechanical ventilation in patients with critical SARS-CoV-2 pneumonia [17]. However, pneumothorax may also develop as a complication of NIV. The use of NIV or the application of oxygen via HFNC, in conditions of continuous and excessive positive airways pressure delivery can lead to an increase of intra-alveolar pressure, rupture of the alveoli and formation of cyst lesions [15].

In addition, applied positive pressure may facilitate rupture of subpleural cysts and development of pneumothorax.

Our patient had no predisposing risk factors, no history of previous pulmonary diseases, was a non-smoker and of normal body weight. Initial CXR showed no abnormalities in terms of emphysema or bullae. She did not receive NIV, nor oxygenation via HFNC for respiratory support. She developed pneumothorax on the eight day of hospitalisation, in an early phase of NCP.

The literature describes patients who developed pneumothorax at different stages of the disease course. Al-Shokri et al. [18] reported three cases of SARS-CoV-2 infection complicated by pneumothorax. The first, second, and third patients developed pneumothorax on days 2, 7, and 15, respectively. Aydin et al. [5] and Chen et al. [13] reported pneumothorax as an initial manifestation in a patient with NCP.

Our case supports the opinion that pneumothorax may develop in pneumonia caused SARS-CoV-2 due to advanced alveolar damage, rupture of the alveoli and the formation of
pulmonary cystic lesions. The increase in intrapulmonary pressure, during a severe cough attack associated with viral infections, can lead to cyst rupture and secondary pneumothorax.

Our case are consistent to those recently published article Sun et al. [9]. As detailed by authors, pneumothorax could be as a consequence of a sudden increase of the alveolar pressure into the pneumonic consolidations.

A recent review of the literature Alhakeem A. et al. [19] showed 18 case reports describing COVID-19 patients with spontaneous pneumothorax. Only three were cases were female. In addition, only four cases were smokers and three had underlying lung disease. Ten of these patients were managed chest tube insertion. Three cases were on invasive mechanical ventilation. Twelve patients had a favorable clinical course. Mortality rate was 33%.

In literature, the diagnostic value of CXR is relatively low as 30–60% in NCP. Despite its potential limits, some of the complications of NCP can be diagnosed with repeated CXR, as is seen in the example of our patient.

Conclusion
Pneumothorax may develop as a complication in patients with SARS-CoV-2 pneumonia, without previous pulmonary comorbidities and without ventilator (MV and NIV) respiratory support, due to alveolar damage. Acute deterioration with rapid oxygen desaturation in these patients should raise the suspicion of pneumothorax. Early diagnosis and prompt treatment is necessary to reduce mortality.

Literatura:

1. Ghebreyesus TA. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. Geneva: World Health Organization, 2020. (https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020). (accessed on March 29th 2020).

2. Oran DP, Topol EJ. Prevalence of Asymptomatic SARS-CoV-2 Infection : A Narrative Review. Ann Intern Med 2020; 173(5): 362-367.

3. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report
of 72,314 Cases From the Chinese Center for Disease Control and Prevention. JAMA 2020; 323(13): 1239–1242.

4. Yao W, Wang T, Jiang B, Gao F, Wang L, Zheng H, et al. Emergency tracheal intubation in 202 patients with COVID-19 in Wuhan, China: lessons learnt and international expert recommendations. Br J Anaesth 2020; 125(1): e28-e37.

5. Aydin S, Öz G, Dumanli A, Balci A, Gencer A. A Case of Spontaneous Pneumothorax in Covid-19 Pneumonia. J Surg Res 2020; 3(2): 096–101.

6. Mallick T, Dinesh A, Engdahl R, Sabado M. COVID-19 Complicated by Spontaneous Pneumothorax. Cureus 2020; 12(7): e9104.

7. Ucpinar BA, Sahin C, Yanc U. Spontaneous pneumothorax and subcutaneous emphysema in COVID-19 patient: Case report. J Infect Public Health 2020;13(6):887-889.

8. González-Pacheco H, Gopar-Nieto R, Jiménez-Rodríguez GM, Manzur-Sandoval D, Sandoval J, Arias-Mendoza A. Bilateral spontaneous pneumothorax in SARS-CoV-2 infection: A very rare, life-threatening complication. Am J Emerg Med 2020; S0735-6757(20)30610-0.

9. Sun R, Liu H, Wang X. Mediastinal emphysema, giant bulla, and pneumothorax developed during the course of COVID-19 pneumonia. Korean J Radiol 2020;21(5): 541-544.

10. Rohaila S, Ahmed N, Gough K. SARS-CoV-2 infection associated with spontaneous pneumothorax. CMAJ 2020;192(19): E510.

11. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA 2020;323(11):1061- 1069.

12. Barreto HG, de PáduaMilagres FA, de Araújo GC, Daúde MM, Benedito VA. Diagnosing the novel SARS-CoV-2 by quantitative RT-PCR: variations and opportunities. J Mol Med (Berl) 2020; 17: 1–10.

13. Chen N, Zhou M, Dong X,Qu, J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395: 507-513.

14. Noppen M. Spontaneous pneumothorax: epidemiology, pathophysiology and cause. EurRespir Rev 2010; 19(117): 217- 219.
15. Liu K, Zeng Y, Xie P, Ye X, Xu G, Liu J, et al. COVID-19 with cystic features on computed tomography: A case report. Medicine (Baltimore) 2020; 99(18): e20175.

16. Zhu N, Wang W, Liu Z, Liang C, Wang W, Ye F, et al. Morphogenesis and cytopathic effect of SARS-CoV-2 infection in human airway epithelial cells. Nat Commun 2020; 11(1): 3910.

17. Xiang C, Wu G. SARS-CoV-2 pneumonia with subcutaneous emphysema, mediastinal emphysema, and pneumothorax: A case report. Medicine (Baltimore) 2020; 99(20): e20208.

18. Al-Shokri SD, Ahmed AOE, Saleh AO, AbouKamar M, Ahmed K, Mohamed MFH. Case Report: COVID-19-Related Pneumothorax-Case Series Highlighting a Significant Complication. Am J Trop Med Hyg 2020; 103(3): 1166-1169.

19. Alhakeem A, Khan MM, Al Soub H, Yousaf Z. Case Report: COVID-19-Associated Bilateral Spontaneous Pneumothorax-A Literature Review. Am J Trop Med Hyg 2020; 103(3): 1162-1165.
Figure 1. Chest X-ray. (A) Chest X-ray on admission showing diffusely accentuated interstitial pattern, linear-banded shadows perihilarly and reduced parenchymal transparency left parahilar, (B) Chest X-ray 8th day of hospitalization showing complete left-sided pneumothorax, (C) Chest X-ray showing complete reexpansion of the lung parenchyma on the left side, (D) Chest X-ray showing diffusely reduced parenchymal transparency left and consolidation right infraclavicular

Figure 2. Chest X-ray on discharge from the hospital
Figure 3. Chest computed tomography (CT) scans (A) axial, (B) coronal and (C) sagital plane showing bilaterally in the lower lobes ground-glass opacity with elements of interstitial fibrosis; left in the upper lobe thickening of the parietal pleura.