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A CASE REPORT: SERIAL CASE OF SPONTANEOUS PNEUMOMEDIASTINUM AND SUBCUTANEOUS EMPHYSEMA IN COVID-19 PATIENTS

Faradilla Novita Anggreini[1,2], Putu Utami Dewi[1,2], Firman Parulian Sitanggang[1,2], Dewa Gde Mahiswara Suadiatmika[1,2]
[1]Radiology Specialist Doctor Education Program, Faculty of Medicine, Universitas Udayana Jl. P.B. Sudirman, Dangin Puri Klod, Denpasar Barat, Denpasar, Bali 80232 Indonesia
[2]RSUP Prof. Dr. I.G.N.G. Ngoerah, Jl. Diponegoro, Dauh Puri Klod, Denpasar Barat, Denpasar, Bali 80113 Indonesia
*dilla.anggreini@unud.ac.id

ABSTRACT
Coronaviruses are pathogens that affect both humans and animals and play a significant role in one of the most persistent disease outbreaks to date, known as Coronavirus Infectious Disease 2019 (COVID-19). The COVID-19 pandemic, declared by the World Health Organization (WHO) in March 2020, was classified as a global public health emergency due to its continued transmission, widespread impact, and the emergence of various viral variants. Before the development of vaccines, at the early stage of the pandemic, there were 5,596,550 confirmed COVID-19 cases worldwide, with a mortality rate of 353,373 cases. This study present Serial Case of Spontaneous Pneumomediastinum and Subcutaneous Emphysema in COVID-19 Patients. This study was a case report that describing detailed account of a patient's diagnosis, treatment, and follow-up a rare case. A critical review of the case report was conducted to assess the validity and reliability of the findings and to identify any limitations of the study. We present a serail case of Spontaneous Pneumomediastinum and Subcutaneous Emphysema in COVID-19. Various case reports and studies have shown that subcutaneous emphysema and pneumomediastinum can occur in COVID-19 patients both with and without mechanical ventilation (spontaneously). Extensive subcutaneous emphysema causing airway compression is an extremely rare manifestation of COVID-19 infection. Subcutaneous emphysema and pneumomediastinum are uncommon conditions associated with COVID-19 and can indicate a poor prognosis, leading to increased morbidity and prolonged hospitalization. Pneumomediastinum, pneumothorax, and subcutaneous emphysema may arise as complications of COVID-19 itself or as consequences of its management, such as mechanical ventilation or other iatrogenic interventions.

Keywords: COVID-19; spontaneous pneumomediastinum; subcutaneous emphysema; X-rays

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INTRODUCTION

Coronaviruses are pathogens that affect both humans and animals and play a significant role in one of the most persistent disease outbreaks to date, known as Coronavirus Infectious Disease 2019 (COVID-19). At the end of 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan, a city in Hubei Province, China. The virus spread rapidly, leading to an epidemic across China and eventually a global pandemic. The virus responsible for COVID-19 was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), initially referred to as 2019-nCoV (Clark, 2021).

SARS-CoV-2 belongs to the same RNA virus family as Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) (Lomoro P, Verde F, Zerboni F,

Simonetti I, Borghi C, Fachinetti C, et al. 2020). The COVID-19 pandemic, declared by the World Health Organization (WHO) in March 2020, was classified as a global public health emergency due to its continued transmission, widespread impact, and the emergence of various viral variants. Before the development of vaccines, at the early stage of the pandemic, there were 5,596,550 confirmed COVID-19 cases worldwide, with a mortality rate of 353,373 cases (Han & Yang, 2019).

As of December 19, 2021, more than 273 million cases and over 5.3 million deaths had been reported globally (WHO, 2021). The African region reported the highest weekly increase in new cases (53%), followed by the Western Pacific region with a 12% increase. In contrast, the Southeast Asia and Eastern Mediterranean regions both reported a 12% decline, while the Americas saw a 10% decrease. The number of weekly cases in the European region remained similar to the previous week. Africa was the only region to report an increase in weekly deaths (15%), while the Americas saw the largest decrease (15%), followed by the Eastern Mediterranean (12%), Europe (7%), and both the Western Pacific and Southeast Asia regions (6%) (WHO, 2021).

The pathogenesis of SARS-CoV-2 is still not fully understood, but it is believed to be similar to that of SARS-CoV, which has been more extensively studied (Li X, et al, 2020). In humans, SARS-CoV-2 primarily infects respiratory tract cells lining the alveoli. The virus binds to specific receptors, allowing it to enter the cells. The spike glycoprotein on the viral envelope attaches to the cellular receptor angiotensin-converting enzyme 2 (ACE2). Once inside the cell, SARS-CoV-2 replicates its genetic material and synthesizes the necessary proteins to form new virions, which then emerge on the cell surface (Li X, et al, 2020; Liu Y, et al., 2020).

In the case of SARS-CoV, the spike (S) protein has been identified as a crucial determinant in viral entry into host cells (De, et al., 2016). The entry process begins with the fusion of the viral membrane and the host cell plasma membrane(Guan, et al., 2020). This process is mediated by the S2' protein, which plays a key role in proteolytic cleavage, facilitating membrane fusion. In addition to membrane fusion, clathrin-dependent and clathrin-independent endocytosis also contribute to the entry of SARS-CoV into host cells. Both viral and host factors influence SARS-CoV infection (Qin, et al., 2020).

The cytopathic effects of the virus and its ability to evade the immune response determine the severity of the infection. Immune system dysregulation plays a significant role in tissue damage caused by SARS-CoV-2 infection. An inadequate immune response can lead to uncontrolled viral replication and tissue destruction, while an excessive immune response may also result in severe tissue damage (Guan, et al., 2020). The clinical manifestations of COVID-19 vary widely, ranging from asymptomatic cases to mild symptoms, pneumonia, severe pneumonia, acute respiratory distress syndrome (ARDS), sepsis, and septic shock (Guan, et al., 2020). Approximately 80% of cases are classified as mild or moderate, 13.8% develop severe illness, and 6.1% progress to critical conditions (Guan, et al., 2020). Mild symptoms include upper respiratory tract infections without complications, which may present with fever, fatigue, cough (with or without sputum), anorexia, malaise, sore throat, nasal congestion, or headache. These patients do not require oxygen supplementation. Severe COVID-19 pneumonia is characterized by fever accompanied by at least one of the following: (1) respiratory rate > 30 breaths per minute, (2) severe respiratory distress, and/or (3) oxygen saturation ≤ 93% without oxygen support (Guan, et al., 2020).

The disease progression begins with an incubation period lasting approximately 3–14 days (median of 5 days), during which leukocyte and lymphocyte counts remain normal or slightly

decreased, and patients remain asymptomatic. In the next phase (early symptoms), the virus spreads through the bloodstream, primarily affecting tissues that express ACE2, such as the lungs, gastrointestinal tract, and heart. Symptoms at this stage are generally mild. A second attack occurs four to seven days after symptom onset, during which patients continue to experience fever and begin to develop dyspnea. Lung lesions worsen, lymphocyte levels decline, inflammatory markers increase, and hypercoagulation begins. If left uncontrolled, this inflammatory response escalates, leading to a cytokine storm, ARDS, sepsis, and other complications (Hunag, et al., 2020).

Laboratory tests such as complete blood count, differential count, renal function, electrolyte analysis, arterial blood gas analysis, hemostasis, lactate levels, and procalcitonin may be performed based on clinical indications. Thrombocytopenia is commonly observed and may resemble dengue infection. A study in Singapore by Yan et al. reported cases of false-positive dengue serology results that were later confirmed as COVID-19 (Yan et al., 2020) . IgM and IgA antibodies are detected from day 3–6 after symptom onset, while IgG appears between days 10–18 (Guo, et al., 2020) The recommended and gold-standard diagnostic method for detecting the virus is nucleic acid amplification using real-time reverse transcription polymerase chain reaction (rRT-PCR) and sequencing. A case is confirmed as SARS-CoV-2 positive if rRT-PCR detects at least two specific SARS-CoV-2 genome targets (N, E, S, or RdRP) or if a positive betacoronavirus rRT-PCR result is supported by partial or complete viral genome sequencing consistent with SARS-CoV-2 (WHO, 2020)

The primary imaging modalities for diagnosing COVID-19 are chest X-ray and computed tomography (CT) scan. Chest X-rays may reveal ground-glass opacities, infiltrates, peribronchial thickening, focal consolidations, pleural effusion, and atelectasis. However, chest X-rays have lower sensitivity than CT scans, as approximately 40% of cases show no abnormalities on X-ray (Nasir, et al., 2020). A thoracic ultrasound study has also identified a diffuse B-line pattern as a key finding, with posterior subpleural consolidations observed in rare cases(Lomoro P, Verde F, Zerboni F, Simonetti I, Borghi C, Fachinetti C, et al. 2020). The objective of this study present Serial Case of Spontaneous Pneumomediastinum and Subcutaneous Emphysema in COVID-19 Patients.

METHOD

This study was a case report that describing detailed account of a patient's diagnosis, treatment, and follow-up. Case reports were often written as stories and can be a cornerstone of medical progress. Sample was a unique case with total 3 cases on Covid-19. The following criteria were used to define a rare case in this study: low prevalence, low incidence, high complexity, uniqueness of the case, and significant clinical implications. Case report describe and interpret an individual case, provide new ideas in medicine. Data was collected from document unusual or novel occurrences and document unexpected events that may yield new information. A critical review of the case report was conducted to assess the validity and reliability of the findings and to identify any limitations of the study.

RESULT

Case description, diagnosis and management

First case

Patient IMP, a 38-year-old male of Balinese ethnicity, working in the private sector, Hindu, and married, presented with shortness of breath since one day before hospital admission. The shortness of breath did not improve with changes in position. The patient also complained of a dry cough for nine days prior to hospital admission, which worsened over the last three days. The presence of phlegm or blood in the cough was denied. Fever was experienced for eight days before hospital admission, which subsided with antipyretics and was sometimes

accompanied by headaches. The patient also reported loss of smell and taste and swelling in the neck. He had a history of contact with a confirmed COVID-19 patient, as he worked as a radiographer. The patient had a history of smoking one pack per day but had quit approximately two years prior. He denied any history of hypertension, asthma, diabetes mellitus, kidney disease, or heart disease. The patient's COVID-19 vaccination history included the first Sinovac dose on 21/01/2021, the second Sinovac dose on 04/02/2021, and the third Moderna dose on 06/08/2021. The first RT-PCR swab on 14/08/2021 was positive at Mangusada Regional Hospital, with a thoracic examination revealing pneumonia and subcutaneous emphysema.

Upon initial admission to Sanglah General Hospital, the patient's vital signs were as follows: blood pressure 110/70 mmHg, pulse 84 beats per minute, respiratory rate 22 breaths per minute, axillary temperature 36.7°C, Glasgow Coma Scale (GCS) E4V5M6, and SpO2 96-97% (with nasal cannula at 4 L/min) and 90-92% (in the general ward). Physical examination findings were within normal limits. The patient was diagnosed with severe COVID-19 pneumonia, grade III subcutaneous emphysema, suspected transaminitis, and dyspepsia. Treatment included IV infusion of 0.9% NaCl at 20 drops per minute, oxygen therapy via nasal cannula at 2-4 L/min, oral Favipiravir 1600 mg every 12 hours (Day 1), followed by 600 mg every 12 hours (Days 2-5), oral Azithromycin 500 mg once daily for five days, intravenous Dexamethasone 6 mg once daily for ten days, intravenous Acetylcysteine 5 g once daily for three days, oral Paracetamol 500 mg every 8 hours, oral Zegavit once daily, oral Curcuma every 8 hours, intravenous Ranitidine 50 mg every 12 hours, subcutaneous Lovenox 0.4 mL once daily, a 2300 kcal diet with 110 g protein, and two daily servings of Peptisol 110/050.

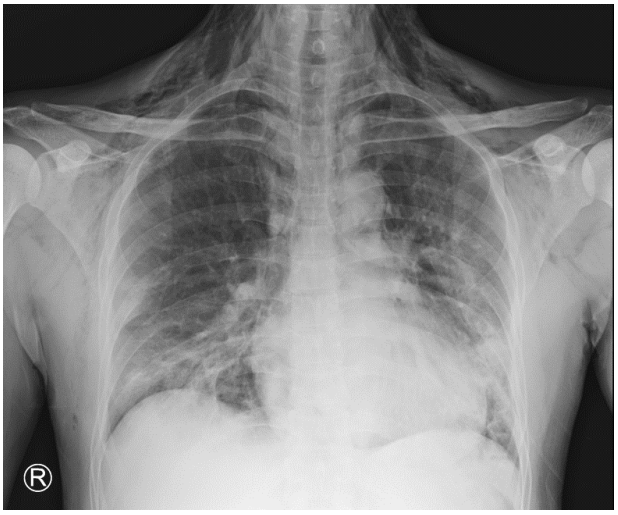

Figure 1. A chest X-ray taken on 15/08/2021 showed subcutaneous emphysema, pneumomediastinum, and pneumonia after the positive RT-PCR result from the previous day.

The patient was treated in the Flamboyan Ward at Sanglah General Hospital from 14/08/2021 to 24/08/2021 (10 days). On 15/08/2021, the patient’s vital signs were: blood pressure 110/70 mmHg, pulse 80 beats per minute, respiratory rate 22 breaths per minute, axillary temperature 36.7°C, and SpO2 96% with nasal cannula at 4 L/min. Additional therapy included Combivent inhalation (one ampoule every 8 hours), and a consultation with the surgical team was conducted. Crepitus was palpable in the right and left neck regions extending to the supraclavicular area. Chest examination revealed symmetrical movement, equal vocal fremitus, resonant percussion sounds, and vesicular breath sounds without rhonchi or wheezing. The surgical team decided not to perform surgery for the subcutaneous

emphysema. A follow-up chest X-ray showed radiolucent streaks in the soft tissues of the neck, supraclavicular region, and bilateral hemithorax, as well as a radiolucent area in the perimediastinal region bilaterally. There was also consolidation in the mid-lower zones of both lungs with increased bronchovascular markings, suggesting pneumonia, suspected pneumomediastinum, and subcutaneous emphysema extending from the neck to the supraclavicular area bilaterally.

On 16/08/2021, the patient's condition improved, with SpO2 at 96% in the general ward, minimal shortness of breath, and persistent cough. Chest physiotherapy was recommended. By 17/08/2021, the patient's SpO2 improved to 98% on room air, and Codeine 10 mg every 8 hours was added to the treatment regimen. On 18/08/2021, the patient still reported neck swelling and hoarseness, with stable vital signs and SpO2 at 96% using a nasal cannula at 3 L/min. On 19/08/2021, neck swelling decreased, and SpO2 improved to 98% with a nasal cannula at 1 L/min. By discharge, the patient showed significant improvement, with gradually increasing oxygen saturation and decreasing neck swelling.

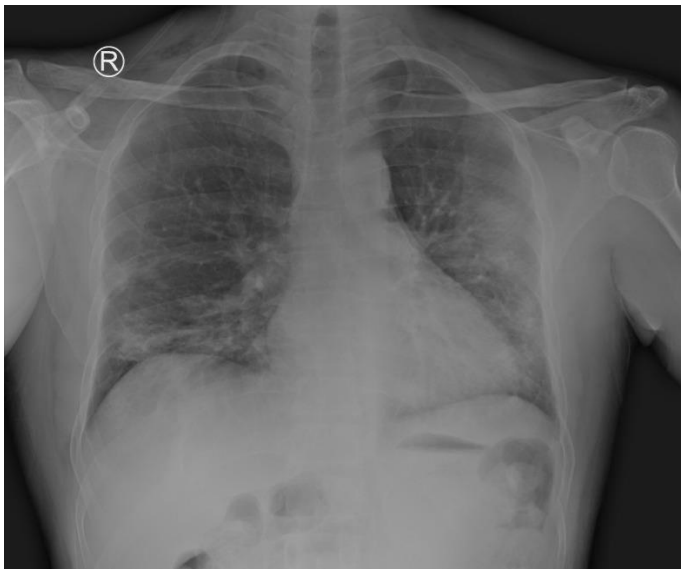

Figure 2. A chest X-ray taken on 23/08/2021 showed significant improvement, with reduced subcutaneous emphysema and pneumomediastinum.

While pneumonia remained. RT-PCR results on 20/08/2021 were negative but became positive again on 21/08/2021. The patient was discharged on 24/08/2021 with SpO2 at 98% on room air and improved subcutaneous emphysema. A follow-up chest X-ray before discharge showed residual avascular radiolucent lesions in the bilateral supraclavicular soft tissue and persistent consolidation in the mid-lower zones of both lungs, suggesting ongoing pneumonia and decreased subcutaneous emphysema: Male

Second Cases

The patient, IMM, a 46-year-old Balinese male, self-employed, Hindu, and married, was referred from Kasih Ibu Hospital with a diagnosis of suspected COVID-19 (PDP COVID-19). The patient complained of shortness of breath for several hours before hospital admission. The shortness of breath did not improve with positional changes and was accompanied by stabbing chest pain. He also reported coughing with white phlegm. Fever had been present for seven days before hospital admission, described as fluctuating. Additionally, the patient experienced diarrhea for six days before hospitalization, which was intermittent and not accompanied by mucus or blood. He had no history of contact with confirmed COVID-19 patients. The patient denied any history of hypertension, asthma, diabetes mellitus, kidney disease, or heart disease. He had not received a COVID-19 vaccination. At Kasih Ibu Hospital, the patient was treated with intravenous Levofloxacin 750 mg/24 hours, oral

Azithromycin 500 mg/24 hours, oral N-acetylcysteine 200 mg/8 hours, and oral Vitamin C 500 mg/8 hours.

Previous laboratory results showed reactive IgM SARS-CoV-2 and non-reactive IgG SARS-CoV-2 while at Kasih Ibu Hospital. The first and second RT-PCR swab tests, conducted on June 23 and 24, 2020, at Udayana University Hospital, returned positive results. A chest X-ray (AP view) revealed an enlarged superior left mediastinum with a sail sign appearance, indistinct bilateral hila, heterogeneous consolidation in the mid-to-lower lung fields bilaterally, and radiolucent areas in the soft tissue of the right neck region extending to the paramediastinum and paracardial area, particularly on the right side. These findings were suggestive of pneumonia, a suspected superior mediastinal mass, suspected pneumomediastinum, and subcutaneous emphysema in the right neck region.

Upon admission to Udayana University Hospital, the patient's vital signs were as follows: blood pressure 100/70 mmHg, pulse rate 112 bpm, respiratory rate 30 breaths per minute, axillary temperature 36.7°C, Glasgow Coma Scale (GCS) E4V5M6, and oxygen saturation (SpO2) 96% on a non-rebreather mask (NRM) at 15 L/min. Physical examination findings were within normal limits. The patient was diagnosed with Pneumonia (CAD) PSI Class IV with Type I Respiratory Failure, suspected COVID-19 (PDP COVID-19), acute gastroenteritis (GEA) of suspected viral or bacterial etiology, and suspected transaminitis of reactive or viral origin. The patient received treatment consisting of intravenous RL 1500 cc/24 hours, oxygen therapy via NRM at 15 L/min, intravenous Levofloxacin 750 mg/24 hours, oral Azithromycin 500 mg/24 hours, oral N-acetylcysteine 200 mg/8 hours, oral Vitamin C 500 mg/8 hours, oral Lacto B 2 sachets/8 hours, and subcutaneous Lovenox 0.4 cc/24 hours.

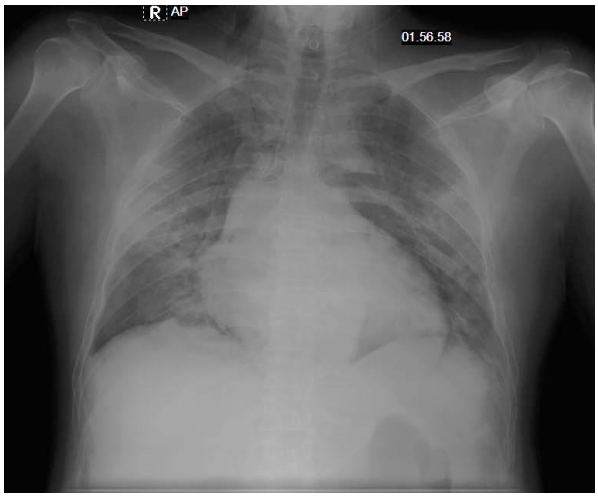

Figure 3. The patient's chest X-ray (AP view) on June 23, 2020, showed pneumonia, a suspected superior mediastinal mass, suspected pneumomediastinum, and subcutaneous emphysema in the right neck region.

The patient was treated in Isolation Ward B at Udayana University Hospital from June 22 to June 25, 2020 (three days). His condition deteriorated starting June 23, 2020, with SpO2 dropping to 70%, prompting intubation by the anesthesia team. Additional therapies included oral Vitamin D3 133 IU/24 hours, intravenous Omeprazole 40 mg/24 hours, titrated Midazolam infusion targeting RASS with three doses (5 mg/hour), Fentanyl drip (300 mg in 50 cc NaCl 0.9%) at a dose of 12.5 mg/hour, Oxynorm infusion at 1.5 mg/hour with an initial bolus of 5 mg, and titrated Norepinephrine infusion targeting a MAP of 65-100 mmHg. The patient was pronounced deceased at 18:00 WITA on June 25, 2020. The primary cause of death was respiratory failure due to COVID-19 pneumonia.

Third Cases

"Patient IKS, a 59-year-old male, Balinese, employed as a state-owned enterprise employee, Hindu, married, was referred from Kasih Ibu Saba Hospital for HFNC treatment due to confirmed COVID-19, pneumonia, and thrombocytopenia.The patient had previously been treated at Kasih Ibu Saba Hospital on August 18, 2021, with complaints of fever for 4 days prior to admission. The patient also complained of cough and runny nose. Appetite was decreased. The patient received treatment in the isolation room at Kasih Ibu Saba Hospital for 8 days, but there was no improvement, and the complaints worsened.

Upon arrival at Udayana University Hospital, the patient complained of shortness of breath, which worsened, accompanied by cough. The patient was known to have a history of contact with a friend who was confirmed COVID-19 positive. The patient had not received COVID-19 vaccination. The patient had a history of hypertension. There was no history of other diseases such as asthma, diabetes mellitus, kidney and heart disorders. The first RT-PCR swab test on August 19, 2021, was positive at the Universitas Warmadewa Laboratory, and the second test on August 26, 2021, was also positive at Udayana University Hospital. The first chest X-ray on August 26, 2021, showed bilateral pneumonia. On August 28, 2021, a repeat chest X-ray showed improvement with decreased pneumonia, but there was subcutaneous emphysema and pneumomediastinum.

Upon initial treatment at Udayana University Hospital, the patient's vital signs were: blood pressure 152/90 mmHg, pulse 78 beats/min, respiratory rate 22 breaths/min, axillary temperature 36.4°C, GCS E4V5M6 with SpO2 92% (on NRM 15 lpm). Physical examination of the patient was still within normal limits. The patient was diagnosed with suspected COVID-19 with moderate severity, pneumonia, thrombocytopenia, and hypertension. The patient received therapy in the form of IVFD NaCl 0.9% 20 tpm, O2 NRM 15 lpm/NC 4 lpm, Favipiravir 1600 mg/12 hours (H1) followed by 600 mg/12 hours (H2-5) orally, Sucralfate 1 tablespoon/8 hours orally, Fluimucil 200mg/8 hours orally, Ondansetron 4 mg/8 hours intravenously, Vitamin D 1000 IU/12 hours orally, Dexamethasone 6 mg/24 hours (for 10 days) intravenously, Zegavit 1 tablet/24 hours orally, Curcuma 1 tablet/12 hours orally, Methylprednisolone 125 mg/12 hours intravenously, Ceftriaxone 2 gr/24 hours intravenously for 7 days, Nebulization Ventolin+Pulmicort+Fluimucil every 6 hours, Nebulization Lidocaine 2 cc in 3 cc NaCl 0.9% every 6 hours, Forixtra 5 mg/24 hours orally, Codiprant 1 tablet/12 hours orally, and Amlodipine 10 mg/24 hours orally. The patient was consulted with the Anesthesiology team and transferred to isolation room J with HFNC 60/100 administration.

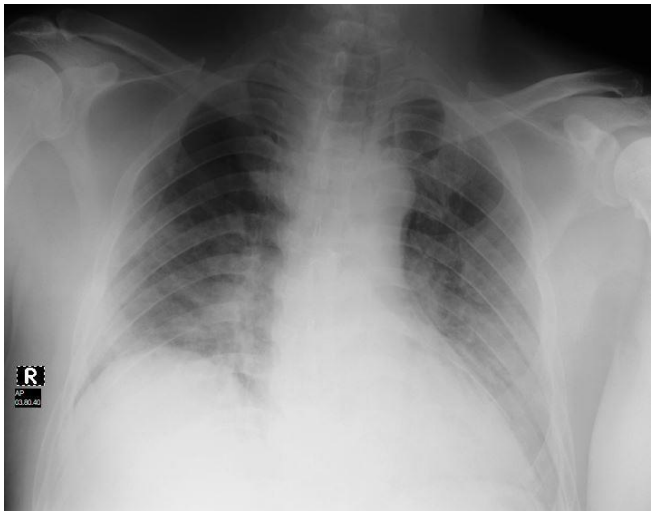

Figure 4. Chest X-ray of patient IKS on August 26, 2021, showing bilateral pneumonia.

During treatment in isolation room J at Udayana University Hospital, the patient's condition was stable with SpO2 81-99% using HFNC 60/100. During treatment, the patient received additional therapy in the form of OH Chlorhexidine every 12 hours, Phentophyline 400 mg/8 hours, Melatonin 1 tablet/24 hours, Aspilet 80 mg/24 hours, Atorvastatin 80 mg/24 hours, drip Heparin bolus 5600 IU/hour followed by 1200 IU/hour at a rate of 2.4 cc/hour, drip Nicardipine 2 cc/hour. However, on August 28, 2021, the patient experienced bradycardia with a heart rate of 44 beats/min at 21.00 WITA and was declared to have cardiac arrest. The patient was then declared dead at 22.15 WITA with the underlying cause of death being severe ARDS with suspected pulmonary thromboembolism.

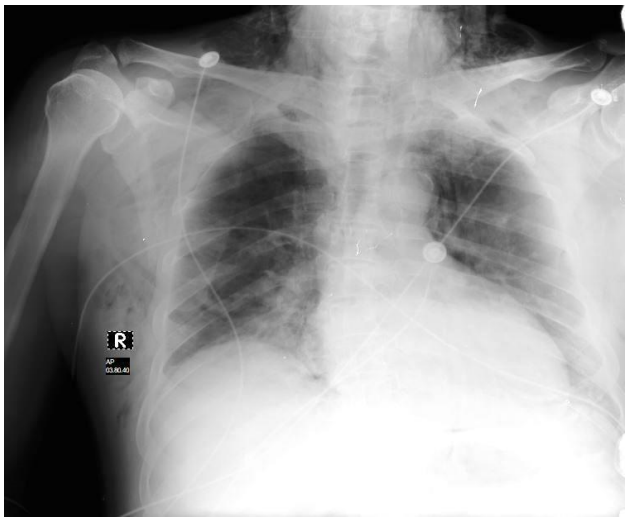

Figure 5. The chest X-ray AP of patient IKS taken on August 28, 2021, demonstrated significant radiographic improvement, characterized by decreased pneumonic infiltrates, accompanied by the presence of subcutaneous emphysema and pneumomediastinum

DISCUSSION

This case series focuses on the development of subcutaneous emphysema and spontaneous pneumomediastinum in three COVID-19 cases without a prior history of intubation. Subcutaneous emphysema and pneumomediastinum are most commonly caused by increased airway pressure and typically occur secondary to mechanical ventilation or airway obstruction. Other causes include increased intrathoracic pressure (such as during the Valsalva maneuver), strenuous activity, severe vomiting, chest trauma, esophageal rupture, thoracic surgery (particularly with resultant tracheobronchial injury), and alveolar damage due to underlying conditions such as infections (Agrawal, et al., 2021).

Subcutaneous emphysema is defined as the presence of air in the subcutaneous tissue, while pneumomediastinum refers to the presence of air along the mediastinum. Subcutaneous emphysema appears as radiolucent areas on chest radiographs in the subcutaneous region (seen as radiopaque shadows with soft tissue density) and, in severe cases, may present as the "Ginkgo leaf sign." Meanwhile, pneumomediastinum appears as radiolucent areas surrounding the mediastinum on chest X-rays. In the three cases presented in this series, radiolucent areas were predominantly found in the cervical (neck), supraclavicular, and hemithorax regions. The patient, IMP, showed improvement in subcutaneous emphysema and pneumomediastinum with conservative treatment. However, for the other two patients (IMM and IKS), no follow-up evaluation of subcutaneous emphysema and pneumomediastinum was available on chest radiographs before their demise (Bahera, et al., 2021; Bello, et al., 2021).

Contrary to previous reports stating that these conditions are more commonly associated with mechanical ventilation, this case series identified subcutaneous emphysema and pneumomediastinum in patients who had not undergone prior mechanical ventilation. Some

case reports have described patients without invasive ventilation developing subcutaneous emphysema, pneumomediastinum, and pneumothorax, suggesting a possible link between these conditions and SARS-CoV-2 infection (Xiang & Wu, 2020). Thus, the spontaneous occurrence of subcutaneous emphysema and pneumomediastinum in these three patients is suspected to be a symptom or complication of COVID-19 itself. Dyspnea is a nonspecific symptom that appears in moderate to severe COVID-19 cases and may be accompanied by subcutaneous emphysema, pneumomediastinum, and pneumothorax. All three patients in this case series experienced dyspnea, cough, and fever during the course of their illness.

Oxygen therapy is the mainstay of treatment and can be administered via oxygen masks, noninvasive ventilation, including high-flow nasal cannula (HFNC), bilevel positive airway pressure (BIPAP), or invasive ventilation in severe cases (Wadhawa et al, 2021). The first patient (IMP) received oxygen therapy at 4 L/min via nasal cannula, which was tapered off during treatment, while patient IMM received oxygen therapy at 15 L/min via a non-rebreather mask (NRM), both of whom had been diagnosed with spontaneous subcutaneous emphysema and pneumomediastinum. Meanwhile, patient IKS was referred for HFNC therapy at a pressure of 60/100 during treatment. HFNC itself is considered a potential factor in triggering spontaneous subcutaneous emphysema and pneumomediastinum. According to WHO guidelines, HFNC is positioned before intubation and invasive ventilation in the overall management plan for COVID-19 to improve oxygenation and alleviate respiratory distress in patients. HFNC provides increased positive airway pressure, which has the potential to cause air leaks (Wadhawa et al, 2021). In a study by Wadhawa et al., radiological evidence of spontaneous air leaks was found in six patients, with an onset of 10.33 ± 1.86 days (mean ± SD) from the onset of COVID-19 symptoms. Two of the six patients required intubation; however, all cases of pneumomediastinum/pneumothorax occurred before intubation (Wadhawa et al, 2021). Pneumomediastinum unrelated to mechanical ventilation has also been reported in COVID-19 and SARS, with a mean onset of 19.6 days after symptom onset, potentially leading to sudden clinical deterioration and oxygen desaturation (Wadhawa et al, 2021).

One possible mechanism of injury involved in this case series is diffuse alveolar damage in severe COVID-19, which makes alveoli susceptible to rupture. All three patients in this series experienced coughing, which could be an additional factor contributing to alveolar rupture. This process may lead to subcutaneous emphysema and spontaneous pneumomediastinum through the Macklin phenomenon. Interstitial air may then dissect into the mediastinum, pleural cavity, and subcutaneous tissue. Similar pathological developments have been observed in other viral pneumonias. Macklin described how air released from ruptured alveoli travels along the peri-bronchial vascular sheaths toward the mediastinum (Agrawal, et al., 2021).

This case series focuses on the development of subcutaneous emphysema and spontaneous pneumomediastinum in three COVID-19 cases without a prior history of intubation. Subcutaneous emphysema and pneumomediastinum are most commonly caused by increased airway pressure and typically occur secondary to mechanical ventilation or airway obstruction. Other causes include increased intrathoracic pressure (such as during the Valsalva maneuver), strenuous activity, severe vomiting, chest trauma, esophageal rupture, thoracic surgery (particularly with resultant tracheobronchial injury), and alveolar damage due to underlying conditions such as infections (Agrawal, et al., 2021).

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(seen as radiopaque shadows with soft tissue density) and, in severe cases, may present as the "Ginkgo leaf sign." Meanwhile, pneumomediastinum appears as radiolucent areas surrounding the mediastinum on chest X-rays. In the three cases presented in this series, radiolucent areas were predominantly found in the cervical (neck), supraclavicular, and hemithorax regions. The patient, IMP, showed improvement in subcutaneous emphysema and pneumomediastinum with conservative treatment. However, for the other two patients (IMM and IKS), no follow-up evaluation of subcutaneous emphysema and pneumomediastinum was available on chest radiographs before their demise (Bahera, et al., 2021; Bello, et al., 2021).

Contrary to previous reports stating that these conditions are more commonly associated with mechanical ventilation, this case series identified subcutaneous emphysema and pneumomediastinum in patients who had not undergone prior mechanical ventilation. Some case reports have described patients without invasive ventilation developing subcutaneous emphysema, pneumomediastinum, and pneumothorax, suggesting a possible link between these conditions and SARS-CoV-2 infection (Xiang & Wu, 2020). Thus, the spontaneous occurrence of subcutaneous emphysema and pneumomediastinum in these three patients is suspected to be a symptom or complication of COVID-19 itself. Dyspnea is a nonspecific symptom that appears in moderate to severe COVID-19 cases and may be accompanied by subcutaneous emphysema, pneumomediastinum, and pneumothorax. All three patients in this case series experienced dyspnea, cough, and fever during the course of their illness.

Oxygen therapy is the mainstay of treatment and can be administered via oxygen masks, noninvasive ventilation, including high-flow nasal cannula (HFNC), bilevel positive airway pressure (BIPAP), or invasive ventilation in severe cases (Wadhawa et al, 2021). The first patient (IMP) received oxygen therapy at 4 L/min via nasal cannula, which was tapered off during treatment, while patient IMM received oxygen therapy at 15 L/min via a non-rebreather mask (NRM), both of whom had been diagnosed with spontaneous subcutaneous emphysema and pneumomediastinum. Meanwhile, patient IKS was referred for HFNC therapy at a pressure of 60/100 during treatment. HFNC itself is considered a potential factor in triggering spontaneous subcutaneous emphysema and pneumomediastinum. According to WHO guidelines, HFNC is positioned before intubation and invasive ventilation in the overall management plan for COVID-19 to improve oxygenation and alleviate respiratory distress in patients. HFNC provides increased positive airway pressure, which has the potential to cause air leaks (Wadhawa et al, 2021). In a study by Wadhawa et al., radiological evidence of spontaneous air leaks was found in six patients, with an onset of 10.33 ± 1.86 days (mean ± SD) from the onset of COVID-19 symptoms. Two of the six patients required intubation; however, all cases of pneumomediastinum/pneumothorax occurred before intubation (Wadhawa et al, 2021). Pneumomediastinum unrelated to mechanical ventilation has also been reported in COVID-19 and SARS, with a mean onset of 19.6 days after symptom onset, potentially leading to sudden clinical deterioration and oxygen desaturation (Wadhawa et al, 2021).

One possible mechanism of injury involved in this case series is diffuse alveolar damage in severe COVID-19, which makes alveoli susceptible to rupture. All three patients in this series experienced coughing, which could be an additional factor contributing to alveolar rupture. This process may lead to subcutaneous emphysema and spontaneous pneumomediastinum through the Macklin phenomenon. Interstitial air may then dissect into the mediastinum, pleural cavity, and subcutaneous tissue. Similar pathological developments have been observed in other viral pneumonias. Macklin described how air released from ruptured alveoli travels along the peri-bronchial vascular sheaths toward the mediastinum (Agrawal, et al., 2021).

CONCLUSION

Subcutaneous emphysema and pneumomediastinum are uncommon conditions associated with COVID-19 and can indicate a poor prognosis, leading to increased morbidity and prolonged hospitalization. Pneumomediastinum, pneumothorax, and subcutaneous emphysema may arise as complications of COVID-19 itself or as consequences of its management, such as mechanical ventilation or other iatrogenic interventions. Various case reports and studies have shown that subcutaneous emphysema and pneumomediastinum can occur in COVID-19 patients both with and without mechanical ventilation (spontaneously). Extensive subcutaneous emphysema causing airway compression is an extremely rare manifestation of COVID-19 infection. The high incidence of pneumomediastinum and subcutaneous emphysema observed during the COVID-19 crisis is concerning and warrants further evaluation. Clinicians should be aware that subcutaneous emphysema may be an initial clinical finding that could indicate life-threatening conditions such as tension pneumothorax or esophageal rupture. Although mortality rates do not differ significantly between patients with and without pneumomediastinum or subcutaneous emphysema, further studies are needed to determine the long-term effects, particularly on lung function or the potential development of chronic pulmonary diseases such as chronic obstructive pulmonary disease (COPD) or pulmonary fibrosis following COVID-19 infection..

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