Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Special Review

Spontaneous Pneumomediastinum in Patients Diagnosed with COVID-19: A Case Series with Review of Literature

Anisa Chowdhary, MD, Lalit Nirwan, MD, Alain S. Abi-Ghanem, MD, Uroosa Arif, MBBS, Simmy Lahori, MBBS, Mohamad B. Kassab, MD, Samar Karout, PharmD, Rania Mazen Itani, PharmD, Rasha Abdalla, MD, Lena Naffaa, MD[#], Lina Karout, MD[#]

Background: Spontaneous pneumomediastinum (SPM) is a rare condition defined by the presence of air in the mediastinum in the absence of traumatic or iatrogenic injury. Although the imaging findings and complications of SARS-CoV-2 infection have been reported many times, there are few reports of the prevalence and outcomes of patients with SPM.

Purpose: In this paper, we aimed to illustrate the different manifestations, management, and outcome of three cases of SPM in COVID-19 patients and provide an extensive review available literature.

Materials and Methods: Detailed report of patients' demographics, clinical presentation, management, and outcome of three cases of COVID-19 induced SPM seen in our institution was provided. Additionally, literature search was employed through March 2021 using Pubmed and Google scholar databases where a total of 22 articles consisting of 35 patients were included.

Results: Statistical analysis of the reviewed articles showed that SPM in COVID-19 occurs in patients with a mean age of 55.6 ± 16.7 years. Furthermore, 80% of the 35 patients are males and almost 60% have comorbidities. Intriguingly, SPM in COVID-19 is associated with a 28.5% mortality rate. These findings are consistent with our case series and are different from previous reports of SPM in non-COVID-19 cases where it most commonly occurs in younger individuals and has a self-limiting course with a good outcome.

Conclusion: Therefore, SPM in COVID-19 patients occurs in older patients and is potentially associated with a higher mortality rate. Further studies are necessary to assess its role as a prognostic marker of poor outcome.

Key Words: Spontaneous pneumomediastinum; Prognostic factor; SARS-CoV-2; COVID-19.

Abbreviations: **SARS-CoV-2** Severe Acute Respiratory Syndrome CoronaVirus-2, **WHO** World Health Organization, **GGO** Ground-glass opacities, **SPM** Spontaneous Pneumomediastinum, **DM** Diabetes, **HTN** Hypertension, **ER** Emergency Room, **SOB** Shortness of Breath, **CT** Computed Tomography, **RT-PCR** Reverse Transcriptase Polymerase Chain Reaction, **ICU** Intensive Care Unit, **HCQ** Hydroxychloroquine, **CRP** C-Reactive Protein, **LDH** Lactate dehydrogenase, **CTA** Computed Tomography Angiography, **OSA** Obstructive Sleep Apnea, **CPAP** Continuous positive airway pressure, **NIV** Noninvasive ventilation, **HFpEF** Heart failure with preserved ejection fraction, **RF** Renal failure, **WBC** White blood cells, **SpO2** Oxygen saturation, **IgM** Immunoglobulin M, **IgG** Immunoglobulin G, **COPD** Chronic Obstructive Pulmonary Disease

INTRODUCTION

On March 11, 2020, the World Health Organization (WHO) declared a pandemic caused by the novel Severe Acute Respiratory Syndrome CoronaVirus-2 (SARS-CoV-2) (1-3). This virus is responsible for the novel coronavirus disease-19 (COVID-19) which as of July 13, 2021, has infected almost 190 million people and led to the death of more than 4 million (4). Although the definitive diagnosis of SARS-CoV-2 infection is made by a positive reverse transcriptase-polymerase chain reaction assay (RT-PCR), high false-negative results are observed due to suboptimal specimen collection, inadequate detection, and extraction techniques during nasopharyngeal swabs, variability in viral shedding or testing in the early stage of disease (5). This has resulted in the need for alternative diagnostic tools such as

Acad Radiol 2021; 28:1586–1598

From the Institute of nuclear medicine and allied sciences, New Delhi, India (A.C.); Meditrina Institute of Medical Sciences, Nagpur, Maharashtra (L.N.); Khyber Medical College, Peshawar, Pakistan (U.A.); Pramukhswami Medical College, Karamsad, India (S.L.); Department of Medicine, Division of Cardiology, Massachusetts General Hospital, Boston (M.B.K.); Beirut Arab University. Beirut, Lebanon, Riad El Solh, Lebanon (S.K., R.M.I., R.A.); Department of Radiology, Division of pediatric imaging, Nemours Children's Hospital, Orlando Florida (L.N.); Department of Radiology, American University of Beirut Medical Center, Beirut, Lebanon, Lebanon. P.O.Box: 11-0236 Riad El-Solh, Beirut, Lebanon (A.S.A.-G., L.K.). Received April 1, 2021; revised July 13, 2021; accepted July 20, 2021. **Address correspondence to:** L.K. e-mail: linakarout25@gmail.com

[#] Equally contributed

https://doi.org/10.1016/j.acra.2021.07.013

chest computed tomography which currently plays a major role in the diagnosis, assessment, and surveillance of COVID-19 (5-7). Several publications have described the radiological manifestations of COVID-19 in the chest, with one of the most common findings being the detection of bilateral multilobar peripheral ground-glass opacities (GGO) (8). Chest CT allows the clear detection of ground-glass opacities and other COVID-19 complications such as pneumomediastinum.

Pneumomediastinum, also known as "mediastinal emphysema", is the presence of air in the mediastinum (9). Spontaneous pneumomediastinum (SPM) is a rare condition characterized by the presence of free air in the mediastinum without any causative factor such as trauma, mechanical ventilation, or iatrogenic injury (10). The pathophysiology of SPM was first described by Macklin et al and known as the Mackling effect where SPM was suggested to result from alveolar rupture due to high intra-alveolar pressure or low perivascular pressure or due to both (11). Common risk factors include underlying asthma, COPD, bronchiectasis, interstitial lung disease, vomiting, pneumonia, and malignancy (12,13). The use of recreational drugs such as cocaine, methamphetamine, and marijuana are also identified as risk factors (14,15). In this study, we illustrate the clinical manifestation, management, and outcome of three cases of SPM in COVID-19 patients. We additionally provide a literature review of 22 related case reports and series consisting of 35 COVID-19 patients who developed SPM.

CASE ONE

A 71-year-old man with a past medical history of DM and HTN of 10 years duration presented to the ER on August 22, 2020, with 8-day history of fever, productive cough, and SOB. The patient was conscious and hypoxemic on arrival at the hospital (SpO2=80%). He was immediately started on BIPAP with moderate improvement (SpO2=89%). Pulmonary examination showed bilateral crepitations. On admission, laboratory findings were remarkable for hyponatremia (117 mEq/L), normocytic anemia, and elevated BUN (29 mg/dL), LDH (711 U/L), D-dimer (1013 ng/mL), ferritin (868 ng/mL), ESR (32 mm/hr) and CRP (40 mg/L). The patient was diagnosed with COVID-19 by RT-PCR of nasopharyngeal swabs and had reactive IgM and non-reactive IgG antibodies with ELISA. Chest radiograph showed bilateral consolidations and air space haziness in the mid to lower lung zones (Fig 3). Chest CT demonstrated extensive peripheral ground-glass opacities with consolidations in both lungs affecting multiple segments, predominantly in the lower lobes, and bronchiectasis. The CT CO-RADS was 6 and the CT severity score was 16/25. In addition, pneumomediastinum, bilateral pleural effusions, cardiomegaly, and subcentimeter mediastinal reactive lymph nodes were noted (Fig 4).

The patient was admitted to the ICU and treated with Remdesivir (100 mg once per day), clexane (0.6 mg twice per day), claribid (500 mg twice per day), dexamethasone (6 mg thrice per day), ivermectin (12 mg once per day), zinc (once per day), perfinex (200 mg twice per day), mucomix (600 mg twice per day), Tazar (4.5 mg thrice per day), solumedrol (80 mg once per day) and nebulization of duoline and budecort (once and twice per day respectively). The patient was put on NIV and on day 3 of hospital admission, the patient improved and was taken off NIV and was transferred to the hospital ward on oxygen. On day 6, patient was discharged after follow-up chest CT showing resolving changes.

CASE TWO

A 61-year-old man with a past medical history of diabetes mellitus (DM) and hypertension (HTN) of 5 years duration presented to the emergency department (ER) on September 4, 2020, with a 9-day history of fever, non-productive cough, shortness of breath (SOB) and weakness. On admission, his vital signs were remarkable for tachycardia (heart rate=109 beats/minute) and hypoxemia (SpO2=80%). Laboratory tests showed normocytic anemia, hypernatremia (158 mEq/L) and hyperglycemia (random blood glucose= 308 mg/dL) and elevated urea (BUN=77 mg/dL), creatinine (1.43mg/dL), LDH (708 U/L), D-dimer (2900 ng/mL), IL-6 (111.8 pg/mL), ferritin (1650 ng/mL), ESR (30 mm/hr.) and CRP (68.5 mg/L). On physical examination, the patient was conscious and oriented. Pulmonary auscultation showed decreased bilateral air entry and crepitations. COVID-19 was suspected and diagnosed by a reverse-transcriptase polymerase chain reaction (RT-PCR) of nasopharyngeal swabs and non-reactive antibodies with ELISA. Chest radiograph showed bilateral homogeneous peripheral air space haziness, mainly in the mid to lower lung zones (Fig 1).

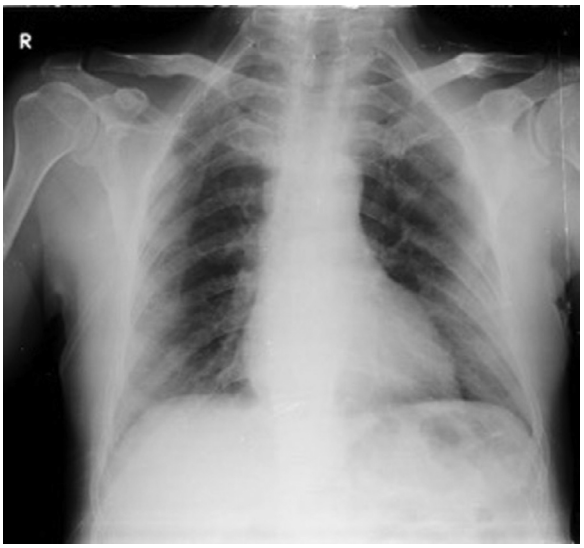

Figure 1. Chest radiograph of Patient One showing mild peripheral haziness, mainly in the mid to lower lung zones.

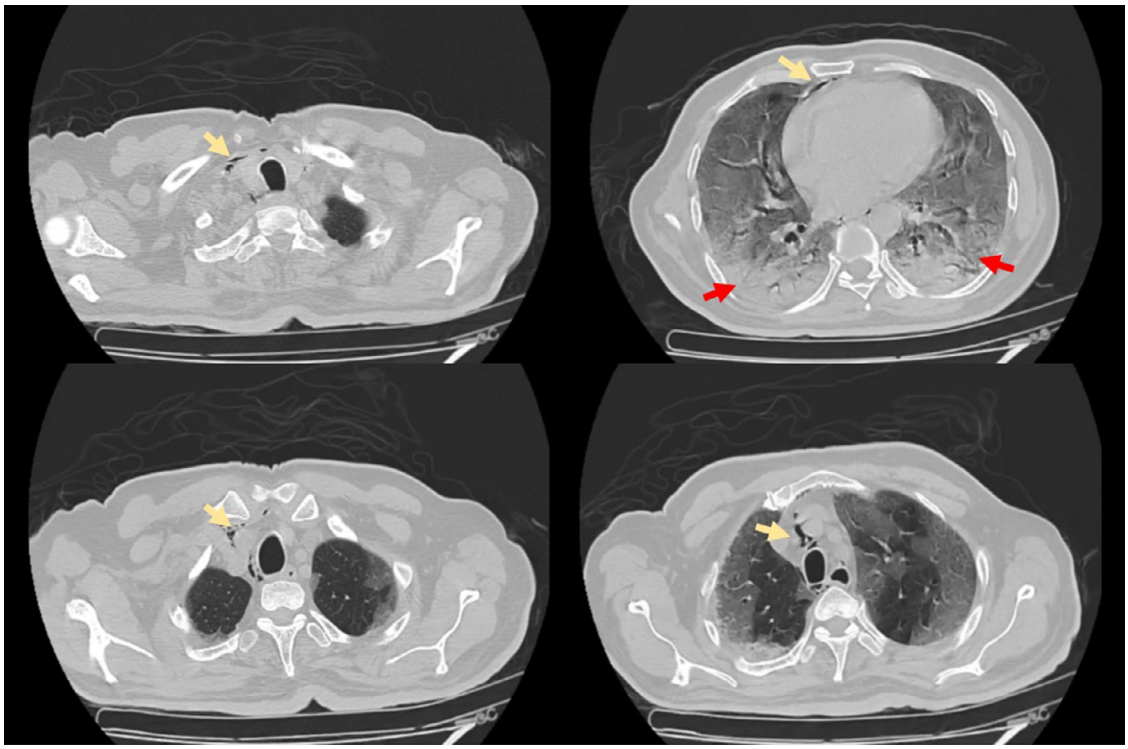

Figure 2. Chest CT of Patient One showing diffuse ground-glass attenuation, consolidations in the posterior basal segments of the lower lobes (red arrows), and SPM (yellow arrows). (Color version of figure is available online.)

The patient underwent successive computed tomography (CT) of the chest which showed extensive bilateral diffuse ground-glass attenuation with a crazy-paving pattern and consolidations with air bronchogram in the posterior segments of the upper lobes and posterior-basal segments of the lower lobes. Computed Tomography (CT) COVID-19 Reporting and Data System (CORADS) was 6 and the CT severity score was 23/25. Furthermore, minimal pneumomediastinum and pneumopericardium were noted (Fig 2).

Figure 3. Chest radiograph of Patient Two showing bilateral consolidations and air space haziness in the mid to lower lung zones.

After COVID-19 diagnosis, the patient was admitted to the intensive care unit (ICU) and was given, Remdesivir (100 mg once per day), Meropenem (1 mg thrice per day), clexane (0.6 mg twice per day), doxycycline (100 mg twice per day), dexamethasone (6 mg thrice per day), ivermectin (12 mg once per day), zinc (once per day), perfinex (200 mg twice per day) and nebulization of duoline and budecort (once and twice per day respectively). Despite being placed on non-invasive ventilator (NIV), his clinical condition deteriorated on day 3 of hospitalization due to labored breathing. The patient was then intubated and placed on mechanical ventilation, however, he developed bradycardia followed by cardiac arrest and expired after unsuccessful CPR attempts.

CASE THREE

A 30-year-old man, previously healthy, presented to the ER on October 9, 2020, with a 5-day history of fever, productive cough, and SOB. On admission, the patient was conscious and oriented. Respiratory examination showed bilateral crepitations with decreased air entry. SpO2 was 88% which improved to 92% after BIPAP. No other remarkable physical finding was noted. Laboratory tests showed normocytic anemia with elevated BUN (34 mg/dL), LDH (402 U/L), d-dimer (300 ng/mL), ferritin (1650 ng/mL), vitamin B12 (2000 pg/mL), ESR (39 mm/hr) and CRP (69 mg/L). The patient was suspected then confirmed to have COVID-19 by RT-PCR of nasopharyngeal swabs. On admission, chest

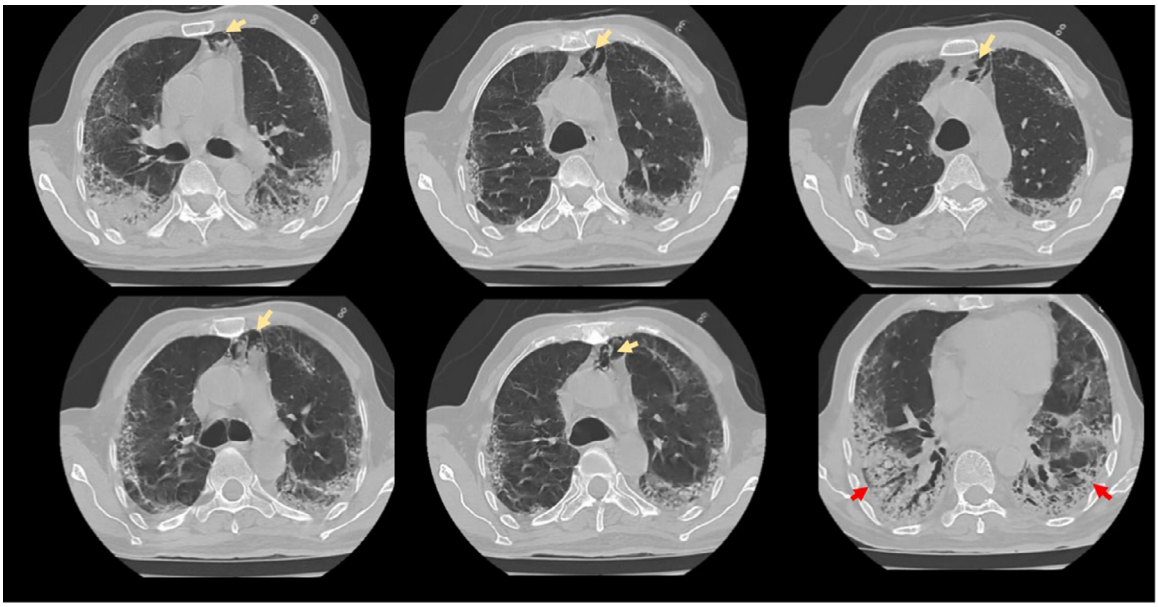

Figure 4. Chest CT scan of Patient Two showing SPM (yellow arrows), bilateral peripheral ground-glass opacities, and consolidations (red arrows). (Color version of figure is available online.)

imaging was not performed since the patient had a chest CT prior to admission showing typical features of COVID-19 (imaging not available). He was admitted to the hospital COVID isolation ward for management. The patient received Remdesivir (100 mg once per day), Meropenem (1 mg thrice per day), Clexane (0.6 mg twice per day), doxycycline (100 mg twice per day), dexamethasone (6 mg thrice per day), Ivermectin (12 mg once per day), Zincovit (once per day), nebulization of duoline (once per day) and budecort (twice per day). The patient was placed on NIV support. On day 5 of hospitalization, his shortness of breath increased, and a chest CT was performed showing multilobar

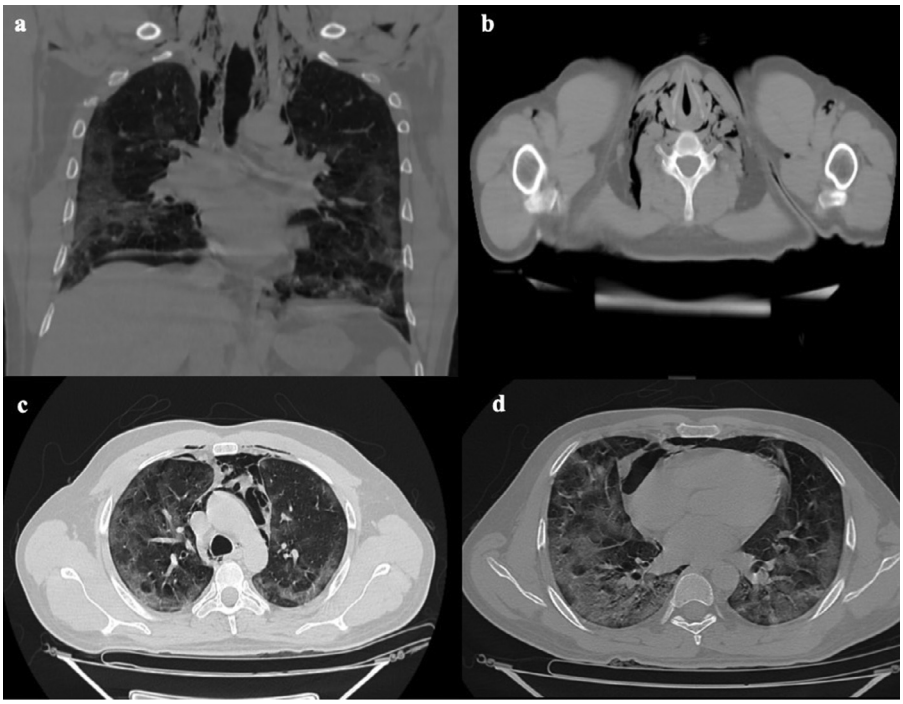

Figure 5. Patient Three coronal CT scan of the chest (a) and axial CT of the neck at the level of thyroid cartilage (b) revealing soft tissue emphysema tracking superiorly within the upper chest wall and neck spaces. Axial images through the chest showing multilobar peripheral ground-glass attenuation and consolidation in both lungs associated with SPM (c and d).

TABLE 1. Literature review Of 22 Published Case Reports and Series Of 35 Patients With COVID-19-Associated Spontaneous Pneumomediastinum.

Author Published Date	Age (Years)	Gender	Chronic Diseases	Symptoms	Imaging Findings	Laboratory Findings & COVID Diagnosis	Treatment	Outcome
Weiyi Wang[23] 25 Apr 2020	62	Male	SmokerCOPD	Fever cough	Chest CT: multiple GGO with parenchymal consolidation, pneumothorax, pneumomediastinum, and subcutaneous emphysema	RT-PCR + for COVID, Elevated procalcitonin, and CRP	Oxygen, lopinavir/ritonavir antibiotics, and steroids	Recovered
Nicola Romano[24] 05 Jun 2020	30	Male	NR	Fever SOB	Chest CT: small GGO bilaterally, and pneumomediastinum	Elevated leukocytes, CRP	NR	Recovered (2 weeks)
	65	Male	NR	Fever SOB	Chest CT: bilateral GGO and consolidations and abundant pneumomediastinum with emphysema	Elevated leukocytes, CRP, LDH, and PCR + for COVID	NR	Recovery (2 weeks)
Jing Wang [22] 06 Apr 2020	36	Female	Mastitis	Fever Cough SOB Chest tightness	Chest CT: diffuse patchy consolidation, GGO in both lungs and pleural effusion, bronchiectasis and pneumomediastinum	Leukopenia Elevated CRP, ESR, D-Dimer, AST, ASLT	Oxygen followed by ventilator, antiviral, anti-inflammatory drugs, and supportive care	Died (Day 2)
Vikisha Hazariwala[25] 07 Oct 2020	57	Female	Asthma HTN Obesity	Cough SOB	Chest X-ray: bibasilar interstitial airspace disease. After 10 days, chest X-ray showed pneumomediastinum, small bilateral pneumothorax, and subcutaneous emphysema	Elevated CRP, Fibrinogen, D-Dimer, LDH, Ferritin	HCQ, Zinc, Antibiotics, Steroids, enoxaparin, Oxygen, intubation then ECMO	Died
	55	Male	Asthma, DM HTN Dyslipidemia Smoker Obesity	Cough Fever SOB Chest pain	Initial Chest X-ray: patchy left basilar and right suprahilar airspace opacities After 9 days Chest x-rays: pneumomediastinum and Chest CT: revealed extensive subcutaneous emphysema, large pneumomediastinum, and small pneumoperitoneum	Elevated CRP, Fibrinogen, D-Dimer, LDH, and Ferritin	HCQ, zinc, Oxygen, Antibiotics, Steroids, Intubation	Died (Day 50)

(*continued on next page*)

TABLE 1. (Continued)

Author Published Date	Age (Years)	Gender	Chronic Diseases	Symptoms	Imaging Findings	Laboratory Findings & COVID Diagnosis	Treatment	Outcome
Rajan Pooni[26] 24 July 2020	56	Male	DM2 HTN Asthma	Cough SOB Fever	Chest X-ray: Bibasal opacities suspicious for COVID-19 on admission. On day 5, Chest CTA: pneumomediastinum	Elevated Ferritin LDH D-Dimer CRP RT-PCR + For COVID	CPAP and Antibiotics. On day 5 after pneumomediastinum diagnosis: Admitted to ICU and put on CPAP	Recovered (Day 18)
Sylvie Kolani[27] 7 May 2020	23	Female	None	None	Chest CT: Inconspicuous GGO in lower lobe and small pneumomediastinum.	RT-PCR + for COVID	Antibiotic and Chloroquine	Recovered (Day 10)
Barbara Brogna[28] 13 June 2020	78	Female	DM HTN	Cough Fever SOB Chest pain	Chest CT: Classic appearance of COVID-19 pneumonia and pneumomediastinum	Leukopenia, elevated LDH, CRP SpO2=86%, RT-PCR + for COVID	Lopinavir/ritonavir, antibiotics, steroids, low molecular weight heparin, and NIV	NR
	41	Male	NR	Fever Myalgia SOB Chest pain	Chest CT: GGO in the left superior lobe, consolidation in the left inferior lobe, loculated pneumothorax and pneumomediastinum, and subcutaneous emphysema	Leukopenia, low platelet, elevated LDH D-Dimer SpO2=82% and RT-PCR + COVID	HCQ, Lopinavir/ritonavir, low molecular weight heparin, steroids, tocilizumab, and oxygen therapy. Intercostal chest tube for pneumothorax	NR
Mohammed Al-Azzawi [29] 24 July 2020	36	Male	DM1	SOB Fever Cough	Chest X-ray: bilateral GGO, diffuse, subcutaneous emphysema. On day 5 Chest CT: bilateral GGO, pneumomediastinum, and moderate-sized subcutaneous emphysema	Elevated CRP D-Dimer Procalcitonin RT-PCR + for COVID Anion gap metabolic acidosis due to ketoacidosis	Antibiotic, Vitamin C, HCQ, oxygen then intubated and admitted to ICU. Tocilizumab, high dose solumedrol. Prone position for 18 hrs./day and on day 9 venovenous extracorporeal membrane oxygenation	Died (Day 15)

(*continued on next page*)

TABLE 1. (Continued)

Author Published Date	Age (Years)	Gender	Chronic Diseases	Symptoms	Imaging Findings	Laboratory Findings & COVID Diagnosis	Treatment	Outcome
	47	Male	Drug and alcohol abuse	SOB Fever	On day 3 chest X-ray: right subcutaneous emphysema and pneumomediastinum On day 8, the patient had a right spontaneous apical pneumothorax	SpO2=75%, elevated ferritin CRP D-Dimer LDH	Oxygen, followed by intubation due to desaturation, HCQ, Antibiotic, Zinc, prone position for 18 hrs/day, and tocilizumab. Chest tube was placed to treat pneumothorax	Improved and moved to the floor
	78	Male	Dyslipidemia HTN	SOB Confusion	Chest X-ray on day 5: subcutaneous emphysema and pneumomediastinum, which were not seen on the chest X-rays were taken on day 1 and 3	Hemodynamically unstable, SpO2=88%	HCQ, Antibiotic, Zinc, Vitamin C, vasopressors due to hypotension	Died
Nina Goldman[30] 22 May 2020	64	Male	DM2 OSA previous COVID (3 weeks ago)	Chest pain Tachycardia	Chest X-ray: GGO both lungs CTA: pneumomediastinum, consolidation consistent with COVID-19	None	No therapy needed	Recovered (24 hrs)
Megan Gillespie [31] 23 Sept 2020	70	Male	Hyperlipidemia, HTN	Chills, Cough SOB Chest pain, loss of taste Dizziness	Chest X-ray: normal Chest X-ray on day 7: spontaneous pneumomediastinum, subcutaneous emphysema, and bilateral patchy airspace disease Chest CT: extensive pneumomediastinum, bilateral GGO Chest CTA: extensive GGO, pneumomediastinum, subcutaneous emphysema in the neck, and a new finding of a small right pneumothorax	SpO2=89%, RT-PCR COVID + hyponatremia, elevated AST, LDH, CRP, ferritin D-Dimer	Oxygen, HCQ, Steroids, heparin, and later after CTA patient was intubated	The family decided to extubate the patient.

(*continued on next page*)

TABLE 1. (Continued)

Author Published Date	Age (Years)	Gender	Chronic Diseases	Symptoms	Imaging Findings	Laboratory Findings & COVID Diagnosis	Treatment	Outcome
Carlo Urigo [32] 3 Oct 2020	54	Male	HTN DM	Cough SOB	Chest x-ray: bilateral air-space opacification in a subpleural and basal distribution, subcutaneous emphysema Chest CT: subcutaneous emphysema and gas locules were noted adjacent to the anterior aspect of the right heart border. Extensive GGO typical of severe Covid-19	SpO2=83%, RT-PCR + for COVID Elevated CRP, WBC Neutrophils, lymphopenia.	Oxygen, Patient had a cardiac arrest and was revived and admitted to ICU. Family decided not to intubate and resuscitate.	Died
Joris Janssen[33] 30 July 2020	52	Male	None	Fever SOB Cough	Chest CT: bilateral GGO and parenchymal consolidation, a small amount of mediastinal air with the left-sided parabronchial distribution.	SpO2=85%, Elevated CRP Neutrophils, lymphopenia, elevated ferritin D-dimer RT-PCR + for COVID	Antibiotic, Chloroquine then 3 days later decompensated and was admitted to ICU and put on mechanical ventilator	Recovered (5 weeks)
Ning Kong [34] 26 Aug 2020	62	Male	Bronchitis	Fever, Cough SOB Myalgia, Nausea Vomiting Day 12 of admission chest pain	Chest CT: multiple GGO with an interlobular septal thickening at the time of his admission. On day 12, (chest pain): chest CT showed parenchymal consolidation and scattered pneumomediastinum	RT-PCR + COVID	Oxygen, gamma globulin, antibiotics, antiviral, steroid bronchodilators.	Recovered
Salvatore Marsico [35] 27 Aug 2020	71	Male	None	Fever	CTPA: pulmonary thromboembolism and multiple peripheral bilateral GGO and bronchiectasis. On day 19 CTA: pulmonary interstitial emphysema and pneumomediastinum.	Elevated D-Dimer	Anticoagulants	NR

(*continued on next page*)

TABLE 1. (Continued)

Author Published Date	Age (Years)	Gender	Chronic Diseases	Symptoms	Imaging Findings	Laboratory Findings & COVID Diagnosis	Treatment	Outcome
Alvaro Quincho-Lopez[36] 2 Sept 2020	55	Female	HTN Asthma Obesity	SOB Chest pain, Cough	Chest CT: GGO of peripheral subpleural location, with pneumothorax and pneumomediastinum	Elevated CRP Leukocytosis, Reactive IGM, IGG for COVID	Antibiotics, Steroids, Oxygen.	Died (Day 2)
	31	Male	Chronic gastritis, High cholesterol	SOB Malaise Cough Fever	On day 15 Chest CT: foci of consolidation in posterior segments of both lower lobes, with pneumomediastinum	Elevated CRP WBC, Reactive IGG, and IGM for COVID	Antibiotics, Steroids, oxygen	Recovered (Day 7)
Maxime Lacroix [37] 19 May 2020	57	Male	None	SOB Fever Cough, Diarrhea Anosmia	Chest X-ray: diffuse subcutaneous emphysema and bilateral consolidations. CT: pneumomediastinum, subcutaneous emphysema, consolidations, GGOs, and crazy paving	NR	Intubated	NR
Pinggui Lei[38] 12 April 2020	64	Male	NR	Fever Fatigue	Chest CT on Day 17: progressive resolution of pneumonic lesions and spontaneous pneumomediastinum in the anterior mediastinum	NR	NR	Recovered
Vinuta Mohan[39] 14 May 2020	49	Male	HTN DM2	Cough SOB Anosmia	Chest X-ray: bilateral infiltrates. Chest CT: severe pneumomediastinum with extensive subcutaneous emphysema	SpO2=85%, Elevated WBC neutrophils, D-dimer, LDH, RT-PCR + for COVID	Antibiotics, steroids, enoxaparin, HCQ, Oxygen. NIV	Recovered (Day 15)
Changyu Zhou[40] 1 April 2020	38	Male	NR	Fever Cough headache On Day 11 developed angina	Chest CT: GGO with bilateral parenchymal consolidation and interlobular septal thickening, subcutaneous emphysema, and pneumomediastinum	Elevated leukocytes, neutrophils, monocytes, RT-PCR + for COVID	Antibiotics, Ribavirin, steroids, supplemental oxygen, bronchodilators, and human recombinant interferon alfa-1b	Recovered (Day 30)

(*continued on next page*)

TABLE 1. (Continued)

Author Published Date	Age (Years)	Gender	Chronic Diseases	Symptoms	Imaging Findings	Laboratory Findings & COVID Diagnosis	Treatment	Outcome
Jesse Mauricio López Vega[41] 11 June 2020	84	Female	Prosthetic valve, RF HFpEF, HTN High Cholesterol	Fever, Cough SOB	CT: right hydropneumothorax, left hydropneumothorax, and pneumomediastinum and COVID-19 findings	RT-PCR + for COVID	HCQ, antibiotics, steroids, and oxygen.	Died (Day 18)
	67	Male	NR	Fever SOB	Chest X-ray: bilateral opacities with multilobar affectation. Chest CT: pneumothorax chamber and pneumomediastinum	NR	Antibiotic ICU admission, and pleural drainage tube for pneumothorax	Died (Day 18)
	73	Male	Basal cell epitheliomaOSA Obesity Depression	Fever SOB	Chest X-ray: alveolar opacity with a bibasal air bronchogram. CT: extensive bilateral involvement by coronavirus, and a minimal chamber of pneumomediastinum	PCR + for COVID	HCQ, Antibiotic, tocilizumab, steroids, oxygen, anticoagulant, and NIV with CPAP	Died (Day 15)
Marta Nobre Pereira [42] 15 Sept 2020	88	Male	None	Fever Fatigue	Chest CTA: pneumomediastinum	NR	HCQ, Lopinavir/ritonavir antibiotics, steroids, and Oxygen	NR
Hamid Reza Samimgham[43] 18 Sept 2020	34	Male	None	Cough, Hemoptysis, Respiratory distress 8 days of admission: neck pain	Chest CT: Severe bilateral subcutaneous emphysema of the neck with intense diffusion into the mediastinum and pneumomediastinum and severe compression on the heart, without pneumothorax	Increased LDH, CRP	Favipiravir, interferon-beta, steroids, bronchodilators, aspirin, atorvastatin, heparin, Oxygen, Remdesivir, hemoperfusion, plasmapheresis, Pirfenidone	Recovered (Day 21)
Souheil Zayet[44] 4 Oct 2020	64	Male	None	Fever Cough hemoptysis anosmia SOB After 7 days discharged and readmitted with angina and SOB	Chest CT: GGO with bilateral parenchymal consolidation, associated with pulmonary embolism. Discharged and readmitted and chest CT: GGO bilaterally with pneumomediastinum	Elevated CRP, Ferritin, Fibrinogen, D-Dimer, RT-PCR + COVID	Oxygen, antiviral, heparin, tocilizumab, Analgesics, antitussive, intercostal chest tube to treat pneumothorax	Recovered (Day 13)

(*continued on next page*)

TABLE 1. (Continued)

Author Published Date	Age (Years)	Gender	Chronic Diseases	Symptoms	Imaging Findings	Laboratory Findings & COVID Diagnosis	Treatment	Outcome
					and subcutaneous emphysema Another Chest CT after one day showed pneumothorax.			
Burcin Agridag Ucpinar[45] June 2020	82	Female	None	Fever SOB Cough	Chest CT: GGO, pneumomediastinum, left-sided massive pneumothorax, and subcutaneous emphysema.	RT-PCR + COVID	HCQ, oseltamivir, antibiotic, and a chest tube for pneumothorax	Recovered (Day 11)
Alex Diaz,[46] December, 2020	51	Male	Obesity	Chills Fever Cough Dyspnea On day 15 of hospitalization: chest pain and hypoxemia	Initial chest x-ray showed bilateral diffuse infiltrates. On day 15 of hospitalization chest x-ray showed right sided pneumothorax and pneumomediastinum.	Elevated CRP, LDH, D-dimer, and Ferritin	HCQ, azithromycin, methylprednisone. At day 15: chest tube placed.	Recovered
	31	Male	Obesity	Cough Fever Dyspnea On day 14 of hospitalization: persistent hypoxemia	Chest x-ray: bilateral diffuse infiltrates. On day 14, chest CT: complete GGO of bilateral lungs, diffuse pneumomediastinum and small pneumopericardium.	Elevated creatinine, CRP, LDH, D-dimer, and Ferritin	HCQ, azithromycin, methylprednisone, tocilizumab, convalescent plasma, oxygen.	Recovered (Day 27)
	34	Male	None	Cough, Diarrhea Vomiting On day 26 of hospitalization respiratory distress worsened.	Chest x-ray: bilateral diffuse infiltrates. Chest CT: patchy bilateral pulmonary consolidation. On day 26: chest x-ray showed pneumomediastinum.	Lymphocytopenia Elevated CRP, LDH and D-dimer, ferritin.	HCQ, azithromycin, methylprednisone, tocilizumab and convalescent plasma. On day 18: Hypoxemia worsened so oxygen was administered	Recovered (Day 42)

SOB, Shortness of breath; CT, computed tomography; GGO, Ground Glass opacities; RT-PCR, Reverse transcriptase-polymerase chain reaction;
+, positive; HCQ, Hydroxychloroquine; CRP, C-Reactive Protein; LDH, Lactate dehydrogenase; CTA, Computed Tomography Angiography;
OSA, Obstructive Sleep Apnea: CPAP, Continuous positive airway pressure: NIV, Noninvasive ventilation: NR, Non reported: ICU, Intensive Care Unit; HTN, Hypertension; DM, Diabetes; DM1, Diabetes mellitus type 1; DM2, Diabetes mellitus type 2; HFpEF, Heart failure with preserved ejection fraction; RF, Renal failure; WBC, White blood cells; SpO2, Oxygen saturation; IgM, Immunoglobulin M; IgG, Immunoglobulin G; COPD, Chronic Obstructive Pulmonary Disease.

peripheral ground-glass attenuation with consolidations in both lungs, predominantly in the lower lobes. Additionally, moderate pneumomediastinum with soft tissue emphysema in the neck spaces was noted. The CO-RADS was 6 and CT Severity Score was 16/25 (Fig 5). The patient was transferred to the ICU for further management. On day 11 of admission, the patient showed significant improvement in shortness of breath and was tapered off from NIV. The patient was discharged on day 16th"

METHODS

The literature search was employed through March 2021 using Pubmed and Google scholar databases. The search strategy consisted of the following keywords and MeSH terms ["spontaneous pneumomediastinum" or "SPM" or "spontaneous mediastinal emphysema"] and ["COVID-19″ or "COVID 19″ or "SARS-CoV-2″ or "SARS Cov 2″ or "novel coronavirus" or "SARS-CoV"]. Case reports and series published in English were included in our review.

All articles were initially screened by title and abstract by two independent authors. In case of different opinions in a specific article, a third author screened it for inclusion or exclusion. Therefore, the most recent 22 screened articles were included in our review.

Analyses were conducted using SPSS 24 for Windows (SPSS Inc, IBM). Patients' demographics, chronic disease, clinical presentation, radiological and laboratory findings, and outcomes were calculated. Categorical variables were presented as frequencies with percentages, and continuous variables were presented as means +/- standard deviations.

DISCUSSION

SPM is a rare condition associated with an incidence rate of 1/25,000 patients. It commonly affects patients aged 5-34 years with 76% of the cases being males (16). It usually resolves by itself with conservative treatment such as oxygen, bed rest, and analgesics, however, protracted cases up to 2 months, although rare, have also been reported (12,17). In the context of viral infection, SPM has been reported in patients with influenza virus and severe acute respiratory syndrome coronavirus (SARS-CoV-1)(18). The mechanism of SPM in viral infection is suggested to be attributed to inflammation and diffuse alveolar injury which is combined with an increased intra-alveolar pressure due to coughing resulting in alveolar rupture and alveolar air to pass to the lung interstitium which flows to the hilum and mediastinum (19,20). This pathophysiology is suggested to be responsible for the increased incidence of SPM in SARS-COV2 infected patients (21).

In our manuscript, we illustrated the demographic characteristics, clinical presentation, hospital management, radiological and laboratory findings and outcomes of three patients diagnosed with COVID-19 who developed SPM. Additionally, we reviewed similar data from 22 published case reports and case series of 35 COVID-19 patients who developed SPM (Table 1). Of 35 reported patients: 28 patients (80%) were male, the mean age was 55.6 ± 16.7 years, 17.1% (6 out of the 35 patients) had no information related to the presence of chronic diseases, 57.1 % (18 out of the 35) had chronic diseases that varied from hypertension, diabetes, heart failure, renal failure, obesity and asthma, and 25.7% (9 out of the 35) were previously healthy. Furthermore, 28.5% (10 patients) of the reported patients died, 51.4% (18 patients) recovered and were discharged, 2.8% (1 patient) had a significant clinical improvement and was extubated and transferred to the floor and 2.8% (1 patient) was palliatively extubated. These findings are in line with our three cases where the mean age was 54 ± 17.4 years, 66% (2 patients) had chronic diseases and 33.3% (1 patient) died. The only major difference in our series compared with the literature is the 100% prevalence of pneumomediastinum in males vs. 78% in the literature.

When comparing the literature between SPM in non-COVID-19 and COVID-19 patients we noticed that SPM in COVID-19 patients occurred in the older population (38.9-72.3 years vs. 5-34 years for non-COVID-19). However, this age discrepancy can be a true difference or result from selection bias of elderly patients who tend to have a more severe course of COVID-19 prompting more imaging and SPM detection than in the younger population. Additionally, studies have reported SPM usually as a benign self-limiting condition with minimal mortality (11). However, reports of SPM in SARS-CoV-1 infected patients have been associated with a more severe course of the disease and portends a poor outcome (18). Similarly, our literature review of SPM in COVID-19 patients showed a high mortality rate which reached 28.5% (10 of 35 patients) of the published cases and 33.3% (1 of 3) of our cases and suggested that SPM may potentially be a prognostic marker of an adverse event in COVID-19 patients. The high mortality rate could also be attributed to COVID-19 where SPM is associated with poor outcome when it occurs on a background of extensive pulmonary parenchymal damage (22). It is worth noting, that a definitive conclusion should not be drawn from our review and small case series.

CONCLUSION

SPM occurs in older COVID-19 patients and could potentially be associated with a severe course of disease and a high mortality rate. Further studies are needed to assess whether SPM is an indicator of disease severity and poor outcome.

CONFLICT OF INTEREST

All authors had nothing to declare.

REFERENCES

1. Karout L, Serwat A, El Mais H, et al. COVID-19 prevalence, risk perceptions, and preventive behavior in asymptomatic latino population: a cross-sectional study. Cureus 2020; 12(9):e10707.

2. Mercedes BR, Serwat A, Naffaa L, et al. New-onset myocardial injury in pregnant patients with coronavirus disease 2019: a case series of 15 patients. Am J Obstet Gynecol 2021; 224(4):387.e1−387.e9.
3. Rawashdeh MA, Saade C. Radiation dose reduction considerations and imaging patterns of ground glass opacities in coronavirus: risk of over exposure in computed tomography. Radiol Med (Torino) 2020; 126 (3):380–387.
4. WHO Coronavirus Disease (COVID-19) Dashboard. https://covid19.who.int. Published 2020. Accessed 10/12/ 2020.
5. Aljondi R, Alghamdi S. Diagnostic value of imaging modalities for COVID-19: scoping review. J med Int res 2020; 22(8):e19673.
6. Gandhi D, Ahuja K, Grover H, et al. Review of X-ray and computed tomography scan findings with a promising role of point of care ultrasound in COVID-19 pandemic. World J radiol 2020; 12(9):195.
7. Li M, Lei P, Zeng B, et al. Coronavirus disease (COVID-19): spectrum of CT findings and temporal progression of the disease. Acad Radiol 2020; 27(5):603–608.
8. Simpson S, Kay FU, Abbara S, et al. Radiological society of north america expert consensus statement on reporting chest CT findings related to COVID-19. endorsed by the society of thoracic radiology, the American college of radiology, and RSNA. Radiol: Cardiothorac Imag 2020; 2 (2):e200152.
9. BODEY GP. Medical mediastinal emphysema. Ann Intern Med 1961; 54 (1):46–56.
10. Potz BA, Chao LH, Ng TT, et al. Clinical significance of spontaneous pneumomediastinum. Ann Thorac Surg 2017; 104(2):431–435.
11. Alemu BN, Yeheyis ET, Tiruneh AG. Spontaneous primary pneumomediastinum: is it always benign? J Med Case Rep 2021; 15(1):1–8.
12. Caceres M, Ali SZ, Braud R, et al. Spontaneous pneumomediastinum: a comparative study and review of the literature. Ann Thorac Surg 2008; 86(3):962–966.
13. Chu CM, Leung YY, Hui JY, et al. Spontaneous pneumomediastinum in patients with severe acute respiratory syndrome. Eur Respir J 2004; 23 (6):802–804.
14. Perna V, Vilà E, Guelbenzu JJ, et al. Pneumomediastinum: is this really a benign entity? When it can be considered as spontaneous? Our experience in 47 adult patients. Eur J Cardiothorac Surg 2010; 37(3):573–575.
15. Iyer VN, Joshi AY, Ryu JH. Spontaneous pneumomediastinum: analysis of 62 consecutive adult patients. In: Paper presented at: Mayo Clinic Proceedings; 2009.
16. Jougon JB, Ballester M, Delcambre F, et al. Assessment of spontaneous pneumomediastinum: experience with 12 patients. Ann Thorac Surg 2003; 75(6):1711–1714.
17. Gerazounis M, Athanassiadi K, Kalantzi N, et al. Spontaneous pneumomediastinum: a rare benign entity. J Thorac Cardiovasc Surg 2003; 126 (3):774–776.
18. Chu C, Leung Y, Hui J, et al. Spontaneous pneumomediastinum in patients with severe acute respiratory syndrome. Eur Respir J 2004; 23 (6):802–804.
19. MACKLIN MT, Macklin CC. Malignant interstitial emphysema of the lungs and mediastinum as an important occult complication in many respiratory diseases and other conditions: an interpretation of the clinical literature in the light of laboratory experiment. Medicine (Baltimore) 1944; 23(4):281–358.
20. Macia I, Moya J, Ramos R, et al. Spontaneous pneumomediastinum: 41 cases. Eur J Cardiothorac Surg 2007; 31(6):1110–1114.
21. Kalpaxi A, Kalokairinou M, Katseli P, et al. Spontaneous pneumomediastinum and COVID-19 pneumonia: report of three cases with emphasis on CT imaging. Radiol Case Rep 2021; 16(9):2586–2592.
22. Wang J, Su X, Zhang T, et al. Spontaneous pneumomediastinum: a probable unusual complication of coronavirus disease 2019 (COVID-19) pneumonia. Korean J Radiol 2020; 21(5):627.
23. Wang W, Gao R, Zheng Y, et al. COVID-19 with spontaneous pneumothorax, pneumomediastinum and subcutaneous emphysema. J Travel Med 2020; 27(5):taaa062.
24. Romano N, Fischetti A, Melani EF. Pneumomediastinum related to COVID-19 pneumonia. Am J Med Sci 2020; 360(6):e19–e20.
25. Hazariwala V, Hadid H, Kirsch D, et al. Spontaneous pneumomediastinum, pneumopericardium, pneumothorax and subcutaneous emphysema in patients with COVID-19 pneumonia, a case report. J cardiothorac surg 2020; 15(1):1–5.
26. Pooni R, Pandey G, Akbar S. Broadening the differential: pneumomediastinum and COVID-19 infection. BMJ Case Rep CP 2020; 13(8):e237938.
27. Kolani S, Nawfal H, Haloua M, et al. Spontaneous pneumomediastinum occurring in the SARS-COV-2 infection. IDCases 2020: e00806.
28. Brogna B, Bignardi E, Salvatore P, et al. Unusual presentations of COVID-19 pneumonia on CT scans with spontaneous pneumomediastinum and loculated pneumothorax: a report of two cases and a review of the literature. Heart Lung 2020; 49(6):864–868.
29. Al-Azzawi M, Douedi S, Alshami A, et al. Spontaneous Subcutaneous Emphysema and Pneumomediastinum in COVID-19 Patients: An Indicator of Poor Prognosis? Am J Case Rep 2020; 21:e925557–925551.
30. Goldman N, Ketheeswaran B, Wilson H. COVID-19-associated pneumomediastinum. Clin Med. 2020; 20(4):e91–92.
31. Gillespie M, Dincher N, Fazio P, et al. Coronavirus disease 2019 (COVID-19) complicated by Spontaneous Pneumomediastinum and Pneumothorax. Respirat Med Case Rep 2020; 31:101232.
32. Urigo C, Soin S, Sahu A. Spontaneous pneumomediastinum as a complication of a COVID-19 related pneumonia: case report and review of literature. Radiology Case Reports, 2020.
33. Janssen J, Kamps MJ, Joosten TM, et al. Spontaneous Pneumomediastinum in a male adult with COVID-19 pneumonia. Am J Emerg Med 2020; 40:e3–228.
34. Kong N, Gao C, Xu M-S, et al. Spontaneous pneumomediastinum in an elderly COVID-19 patient: A case report. World J Clin Cases 2020; 8 (16):3573.
35. Marsico S, Bellido LADC, Zuccarino F. Spontaneous pneumomediastinum and macklin effect in COVID-19 Patients. Arch Bronconeumol 2020; 57:67.
36. Hurtado-Medina FD, Quincho-Lopez A, Quincho-Lopez DL. Case report: pneumothorax and pneumomediastinum as uncommon complications of COVID-19 pneumonia—literature review. Am J Trop Med Hyg 2020; 103(3):1170–1176.
37. Lacroix M, Graiess F, Monnier-Cholley L, et al. SARS-CoV-2 pulmonary infection revealed by subcutaneous emphysema and pneumomediastinum. Intensive Care Med 2020; 46:1620–1621.
38. Lei P, Mao J, Wang P. Spontaneous pneumomediastinum in a patient with coronavirus disease 2019 pneumonia and the possible underlying mechanism. Korean J Radiol 2020; 21(7):929.
39. Mohan V, Tauseen RA. Spontaneous pneumomediastinum in COVID-19. BMJ Case Rep CP 2020; 13(5):e236519.
40. Zhou C, Gao C, Xie Y, et al. COVID-19 with spontaneous pneumomediastinum. Lancet Infect Dis 2020; 20(4):510.
41. Vega JML, Gordo MLP, Tascón AD, et al. Pneumomediastinum and spontaneous pneumothorax as an extrapulmonary complication of COVID-19 disease. Emerg Radiol 2020: 1–4.
42. Pereira MN, Blanco R, Areias V. Pneumomediastinum: An uncommon complication of COVID-19 pneumonia. Archivos De Bronconeumologia. 2020; 57:68.
43. Samimagham HR, Kazemi Jahromi M, Kazemi Jahromi L. COVID-19 with Pneumomediastinum and Emphysema, A Case Report. Shiraz E-Medical Journal. 2021. doi:10.5812/semj.109424.
44. Zayet S, Klopfenstein T, Mezher C, et al. COVID-19 with spontaneous pneumothorax, pneumomediastinum and subcutaneous emphysema. New Microbes New Infect 2020; 38:100785.
45. Ucpinar BA, Sahin C, Yanc U. Spontaneous Pneumothorax and subcutaneous emphysema in COVID-19 patient: case report. J Infect Public Health 2020; 13:887–889.
46. Diaz A, Patel D, Sayedy N, et al. COVID-19 and spontaneous pneumomediastinum: a case series. Heart Lung 2021; 50(2):202–205.