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

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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.

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

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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 (711 U/L). The patient was diagnosed with COVID-19 by RT-PCR of nasopharyngeal swabs and non-reactive 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 sub-centimeter 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), clarbid (500 mg twice per day), dexamethasone (6 mg thrice per day), ivermectin (12 mg once per day), perfinex (200 mg twice per day), mucinix (600 mg twice per day), Tazar (4.5 mg thrice per day), solu-medrol (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).
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).

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
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 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.)

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 superiority 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).
| Author                  | Published Date | Age (Years) | Gender | Chronic Diseases | Symptoms                  | Imaging Findings                                                                 | Laboratory Findings & COVID Diagnosis | Treatment                                                                 | Outcome       |
|-------------------------|----------------|-------------|--------|------------------|----------------------------|---------------------------------------------------------------------------------|--------------------------------------|---------------------------------------------------------------------------|---------------|
| Weiyi Wang              | 25 Apr 2020    | 62          | Male   | Smoker COPD      | 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           | 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               | 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 Hazarwala       | 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)
| Author Published Date | Age (Years) | Gender | Chronic Diseases | Symptoms | Imaging Findings | Laboratory Findings & COVID Diagnosis | Treatment | Outcome |
|-----------------------|-------------|--------|------------------|----------|-----------------|--------------------------------------|-----------|---------|
| Rajan Pooni26 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 Kolani27 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 Brogna28 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 IV HCQ, Lopinavir/ritonavir, low molecular weight heparin, steroids, tocilizumab, and oxygen therapy. Intercostal chest tube for pneumothorax | 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 | 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) |
| 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 | (continued on next page) |
| Author Published Date | Age (Years) | Gender | Chronic Diseases | Symptoms | Imaging Findings | Laboratory Findings & COVID Diagnosis | Treatment | Outcome |
|-----------------------|------------|--------|------------------|----------|-----------------|--------------------------------------|-----------|---------|
| Nina Goldman 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 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. |
| Author       | Published Date | Age (Years) | Gender | Chronic Diseases | Symptoms                  | Imaging Findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Laboratory Findings & COVID Diagnosis                                                                                                                                  | Treatment                                                                                         | Outcome       |
|--------------|----------------|-------------|--------|------------------|---------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------|---------------|
| Carlo Urigo  | 3 Oct 2020     | 54          | Male   | HTN DM           | Cough SOB                 | Chest x-ray: bilateral airspace 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| 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    | 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    | 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            |

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| Author                  | Published Date | Age (Years) | Gender | Chronic Diseases                  | Symptoms                         | Imaging Findings                                                                 | Laboratory Findings & COVID Diagnosis | Treatment                                                                 | Outcome       |
|------------------------|----------------|-------------|--------|-----------------------------------|----------------------------------|---------------------------------------------------------------------------------|---------------------------------------|---------------------------------------------------------------------------|---------------|
| Alvaro Quincho-Lopez   | 2 Sept 2020    | 55          | Female | HTN, Asthma, Obesity              | SOB, Chest pain, Cough           | Chest CT: GGO of peripher-eral 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         | 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            | 12 April 2020  | 64          | Male   | None                              | Fever, Fatigue                   | Chest CT on Day 17: progressive resolution of pneumonic lesions and spontaneous pneumomediastinum in the anterior mediastinum | NR                                                                                   | NR                                                        | Recovered     |
| Vinuta Mohan           | 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           | 1 April 2020   | 38          | Male   | None                              | Fever, Cough, Headache           | 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) |

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| Author Published Date       | Age (Years) | Gender | Chronic Diseases                              | Symptoms                  | Imaging Findings                                                                 | Laboratory Findings & COVID Diagnosis | Treatment                                                                 | Outcome            |
|-----------------------------|-------------|--------|-----------------------------------------------|---------------------------|--------------------------------------------------------------------------------|---------------------------------------|----------------------------------------------------------------------------|-------------------|
| Jesse Mauricio López Vega41 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 multi-lober affection. Chest CT: pneumothorax chamber and pneumomediastinum | PCR + for COVID             | Antibiotic ICU admission, and pleural drainage tube for pneumothorax       | Died (Day 18)      |
| 73                          | Male        | Basal cell epithelioma OSA 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                |
| 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 Zayet44 4 Oct 2020   | 64          | Male   | None                                          | Fever Cough hemoptysis anosmia SOB After 7 days discharged and readmitted with angina and SOB | Elevated CRP, Ferritin, Fibrinogen, D-Dimer, RT-PCR + COVID | Oxygen, antiviral, heparin, tocilizumab, Analgesics, antitussive, intercostal chest tube to treat pneumothorax | Recovered (Day 13) |
| Author Published Date | Age (Years) | Gender | Chronic Diseases | Symptoms | Imaging Findings | Laboratory Findings & COVID Diagnosis | Treatment | Outcome |
|-----------------------|-------------|--------|------------------|----------|-----------------|---------------------------------------|-----------|---------|
| Burcin Agridag Ucpinar June 2020 | 82 | Female | None | Fever, SOB, Cough | Chest CT: GGO, pneumomediastinum, left-sided massive pneumothorax, and subcutaneous emphysema. Another Chest CT after one day showed pneumothorax. | RT-PCR + COVID | HCQ, oseltamivir, antibiotic, and a chest tube for pneumothorax | Recovered (Day 11) |
| Alex Diaz, 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.
