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Air Spaces in Patients Diagnosed with COVID-19 Pneumonitis- A Rare Complication

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Abstract

Introduction: The outbreak of coronavirus disease 2019 (COVID-19) with its overwhelming morbidity and mortality has created a significant challenge for health systems worldwide. Although peripheral ground-glass opacities are the most frequent radiologic feature of COVID-19 described in the literature, late rare complications such as cavitations, pneumatocele, lung cyst, pneumothorax, empyema or hemothorax are occasionally reported.

Methods: We performed a retrospective study and described a group of eight patients, diagnosed with COVID-19, confirmed by the RT-PCR for SARS-CoV-2 and complicated with cystic air spaces. We have searched for studies describing air spaces in subjects with COVID-19 and analyzed the probable pathophysiology of air spaces development.

Results: Among 29 patients diagnosed with COVID-19 pneumonia complicated by air spaces, 19 (65,5%) received surgical intervention. Of note, 25 (86%) were males. Of the 19 interventions, 6 (20,6%) were exclusively chest drain insertions and the rest 13 (45%) required more advanced procedures like VATS or thoracotomy. Most patients did not have any risk factor for such a complication. Among the group- 18 (62%) had no history of smoking, 16 (55%) had no history of previous diseases and only 1 (3%) had the history of COPD. More than half of the patients (18- 62%) did not require mechanical ventilation during initial viral pneumonitis.

Conclusion: According to our observation and reviewed literature, not every pneumatocele or lung cyst requires surgical intervention the decision should be taken on the individual basis. Reasons for surgical intervention included non-resolving pneumothorax, superinfection of pneumatocele, non-responding to antibiotic therapy and hemothorax.

Keywords: COVID-19; Thoracotomy; Pneumatocele; World Health Organisation (WHO)

Abbreviations: ARDS- Acute Respiratory Distress Syndrome; CM- Centimeter; COPD- Chronic Obstructive Pulmonary Disease; COVID-19- Coronavirus Disease 2019; CPAP- Continuous Positive Airway Pressure; CRP- C-Reactive Protein; CT- Computed Tomography; CTPA- Computed Tomography Pulmonary Angiography; DIC- Disseminated Intravascular Coagulation; ESBL- Extended Spectrum Beta-Lactamase; HFO_2T- High-Flow Oxygen Therapy; ICU- Intensive Care Unit; l/min- Liter Per Minute; LMWH- Low Molecular Weight Heparin; ML- Milliliter; NIC- Non-Invasive

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Ventilation; NT-proBNP- N-Terminal Prohormone of Brain Natriuretic Peptide; RT-PCR- Reverse Transcription Polymerase Chain Reaction; Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2); VATS- Video-Assisted Thoracic Surgery; VV-ECMO- Venous-Venous Extracorporeal Membrane Oxygenation; WHO- World Health Organisation

Introduction

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was initially reported to the World Health Organisation (WHO) on December 31st, 2019. As the cases of disease increased rapidly, WHO declared COVID-19 as a global pandemic [1]. Since then more than 489 million cases and more than 6 million deaths have been reported worldwide [2]. Mild to moderate cases with the clinical symptoms such as fever, dry cough, myalgia and fatigue could be community-managed. However, severe cases of viral pneumonia, which may be accompanied by Acute Respiratory Distress Syndrome (ARDS), require hospitalization and mechanical ventilation in the Intensive Care Unit (ICU) [1,3]. The most frequent radiological manifestations described in the literature are peripheral ground-glass opacities, interlobular septal and pleural thickening, crazy paving pattern and consolidations. Rare radiological presentations include: nodules, cystic changes, bronchiectasis, lymphadenopathy and pleural effusion [4]. Long-term severe thoracic complications, such as pneumatocele, lung cysts, pneumothorax, empyema or hemothorax were mostly described in the literature as case reports and case series [5-17]. We analyzed probable pathophysiology and outcome in patients with pneumatocele and lung cysts as pulmonary complication of COVID-19 supported by recent literature review.

Methods

From September 2020 to December 2021, a retrospective study was performed in patients admitted with a diagnosis of air space after SARS-CoV2 infection. Clinical and demographic variables were collected, including comorbidities, smoking history, laboratory results, infection and surgical history. We described 8 consecutive cases that exemplify uncommon complication of COVID-19 pneumonitis. Typical radiological manifestations like peripheral ground-

Table 1. Summary of our cases with the dimensions of pneumatocele.

Case	Age	Sex	Comorbidities	Smoking history	Complication	Diameter	Mechanical ventilation	Treatment	Histopathology
1	39	Male	none	<2 pack years	Cyst with hemorrhage, pneumothorax	22 × 7,5 cm	no	VATS with cyst resection	Diffuse necrosis, hemorrhage and stromal damage, parietal pleura with stromal cell reactive metaplasia, organizing fibrin and multiple organizing thromboembolism
2	70	Male	hypertension, COPD, type 2 diabetes mellitus, atrial fibrillation, depression	yes	Superinfected air space	7 × 1,4 cm	no	Conservatively with antibiotics	none
3	51	Male	Hypertension, endoprothesoplasty of the right hip joint years ago	no	Air space	2,7 cm	Yes, +ECMO	Conservatively with antibiotics	none
4	58	Male	polytrauma	25 pack years	Superinfected cyst	14,1 × 8,3 cm and 4,3 × 2,7 cm	no	VATS with cyst resection	pus collection, cellular detritus and wall of the cyst with fibrosis, congestion, granulation tissue and purulent infiltrates
5	55	Male	none	1 pack year	Pneumatocele, pneumothorax, pleural effusion	14,5 × 5,5 cm ->5,4 × 4,9 cm + pneumothorax 22-49 mm	no	VATS with pneumatocele resection secondary thoracotomy with decortication, air-leak	focal pleural congestion, oedema, granulation, fibrosis and active eosinophilic inflammation
6	62	Male	Hypertension, deep vein thrombosis	10 pack years	cyst	40 × 30 mm	no	conservatively	none
7	20	Female	none	<1 pack year	pneumatocele	3,0 × 2,6 cm and 1,3 cm	no	conservatively	none
8	64	Male	hypertension	40 pack years	Cyst, pneumatocele	7,5 × 4,4 cm and 3,5 × 1,9 cm	no	Right side thoracotomy, cyst excision	with focal organizing hemorrhages- forming cysts and surrounded by chronic inflammation and dust deposits

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glass opacities, interlobular septal and pleural thickening as well as consolidations have been described at the onset of the pandemic [3]. However, cystic abnormalities such as pneumatocele, cystic air spaces and cavitations were rarely reported. We have searched the PubMed for studies describing air spaces in subjects with COVID-19 using the free text term: "pneumatocele + lung cyst + COVID-19". The search found 13 citations (Table 2). Together with our 8 cases, we analyzed the probable pathophysiology of air spaces development. Data collection was performed on January 12th, 2022. Our cases constituted 27,5% of the group. Our patients, during recovery from COVID-19 (4-6 weeks after first onset of the symptoms) presented with worsening of the clinical condition, which required further investigation. At date there is no dependable management algorithm for such pathology.

Results

Among these 29 patients diagnosed with COVID-19 pneumonia complicated by air spaces, 19 (65,5%) received surgical intervention. Of note, 25 (86%) were males. Of the 19 interventions, 6 (20,6%) were exclusively chest drain insertions and the rest 13 (45%) required more advanced

Table 2. Recent literature review.

Authors	Case	Age	Sex	Comorbidities	Smoking history	Complication	Mechanical ventilation	Treatment	Histopathology
Abdel-Mohsen et al. [5]	1	42	Male	none	-	Pneumatocele with fluid level, compression atelectasis, right side pneumothorax	no	VATS, deroofing	Fibroblast proliferation, intra-alveolar haemorrhage, prominent hyperplasia of pneumocytes
Kunadharaju et al. [6]	1	62	Male	Hyperlipidaemia, benign prostate hypertrophy, gastro-oesophageal reflux disease, anxiety, obstructive sleep apnoea	<10 pack years	Multiple cystic changes	no	Antibiotics, fluconazole	none
	2	68	Male	none	none	Pneumatocele, pneumothorax, pneumomediastinum, subcutaneous emphysema	no	Bilateral chest drains insertion	none
	3	58	Female	hypertension	none	pneumothorax, pneumomediastinum, subcutaneous emphysema, pulmonary artery thrombosis	no	Pleural cavity decompression, anticoagulation	none
Castiglioni et al. [7]	1	55	Male	Hypertension, adipositas, impaired glucose tolerance	none	pneumatocele	yes	Left lateral muscle sparing thoracotomy with cyst resection	Pus collection, organizing pneumonia, squamous metaplasia and hemosiderin accumulation
Chang et al. [8]	1	35	Male	Pulmonary hypertension, right ventricle failure	none	Pneumatocele, recurrent right pneumothorax	yes	Left chest drainage insertion, right VATS converted to thoracotomy with right upper lobe pneumatocele resection, decortication, pericardial window	none
	2	65	Male	none	none	bleb with alveolar leak	yes	Right VATS bleb resection	Organizing pneumonia, organizing phase of diffuse alveolar damage, fibrous pleuritis
	3	60	Male	none	none	Pneumatocele, empyema,	no	Left robotic decortication, resection of pneumatocele, wedge resection of consolidated lung	Organizing pneumonia with chronic inflammation

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	4	46	Male	none	Ex-smoker	Haemothorax, bleb	Yes, ECMO	Right VATS with haemothorax evacuation and blebectomy	Pulmonary pneumatocele, thrombus, chronic pleuritis with granulation tissue
	5	43	Male	none	yes	Large pneumatocele	Yes, ECMO	Left VATS converted to thoracotomy, decortication, pneumatocele resection	Organizing diffuse alveolar damage with residual hyaline membranes, pleuritis, and pneumatocele lined by inflammation including giant cells
Sugimoto [9]	1	50	Male	none	none	pneumatocele	no	conservatively	none
Hampson et al. [10]	1	39	Male	none	-	Pneumatocele, pneumothorax, pneumomediastinum	NIV	conservatively	none
Capleton et al. [11]	1	64	Female	cANCA vasculitis, renal transplantation, hypertension, Staphylococcus aureus bacteraemia	-	Pneumatocele with air leak, pneumothorax	yes	Chest drain insertion, VATS with wedge resection	Focal pleural fibrosis, fibrotic wall of the cyst lined with cuboidal epithelium, subpleural and septal fibrosis with oedema and vascular congestion
Mallick et al. [12]	1	40	Male	none	Ex-smoker	Pneumatocele, pneumothorax	no	Chest drain insertion,	none
McCann et al. [13]	1	67	Male	Diabetes mellitus type 2, ulcerative colitis	-	Lung cyst, pneumothorax	no	Failed chest drain insertion	none
	2	71	Male	none	-	pneumatocele	yes	conservatively	none
	3	47	Male	none	none	Pneumothorax, pneumatocele	yes	Chest drain insertion,	none
Sanivarapu et al. [14]	1	40	Male	none	-	Pneumothorax, pneumatocele	yes	Right sided pig-tail catheter	none
Jamal et al. [15]	1	34	Male	hipothuroidism	none	pneumatocele	no	conservatively	none
Brahmbhatt et al. [16]	1	66	Female	Diabetes mellitus type 2, hypertension, hyperlipidemia	-	pneumatocele	no	conservatively	none
Natajaran et al. [17]	1	32	Male	none	-	Pneumothorax, pneumoediastinum, pneumatocele	no	Chest drain insertion	none

procedures like VATS or thoracotomy. Most of the above described patients did not have any risk factor for such a complication. Among the group- 18 (62%) had no history of smoking, 16 (55%) had no history of previous diseases and only 1 (3%) had the history of COPD. More than half of the patients (18-62%) did not require mechanical ventilation during initial viral pneumonitis. Reasons for surgical intervention include continued air leak, non-resolving pneumothorax in spite of drain insertion, superinfection of pneumatocele, non-responding to antibiotic therapy, with ongoing sepsis, progressive enlargement of the cyst with normal lung compression or hemothorax. The results of pathological examinations were available in 11 of the patients, who underwent a surgical procedure (Figures 1-8).

Discussion

According to the literature, including Fleishner Society Glossary [19], pneumatoceles are defined as thin-walled air-filled cysts in the lung interstitium. They often contain air-fluid level and may vary in size. Most cases of pneumatoceles are described in children or young adolescents. Pneumatocele can result from infection with *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Pneumocystis jiroveci*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *adenovirus*, *Mycobacterium tuberculosis*, *Proteus mirabilis*, *Acinetobacter*, *Hemophilus influenzae B type*, *Bacteroid species*, or noninfectious process like barotrauma from Continuous Positive Airway Pressure (CPAP) during mechanical ventilation. [20-22]. A lung cyst is described as a round parenchymal lucency with a well-defined interface with normal lung, surrounded by an epithelial or fibrous wall of variable thickness (<2mm). The both terms are used in the literature to described air spaces in COVID-19 patients. The pathophysiology of these cystic lesions in COVID-19 is not well studied, although some potential mechanisms are described. Regarding recent literature, one theory explaining the process of the development of pneumatocele, according to Manenti et al. [23] is ischemia related. Inflammatory

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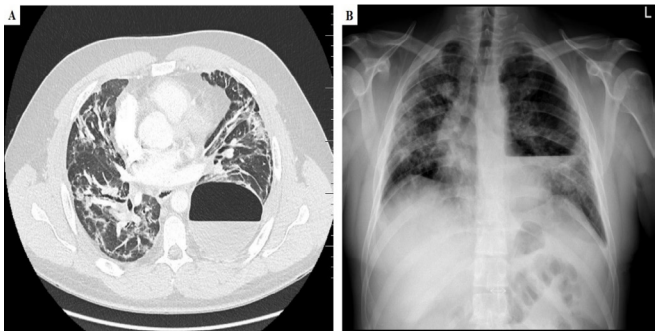

Figure 1: A− Chest CT scan, axial view delineating extend of the lung cyst with air-fluid level B− Chest X-ray showing left side air cyst with air-fluid level.

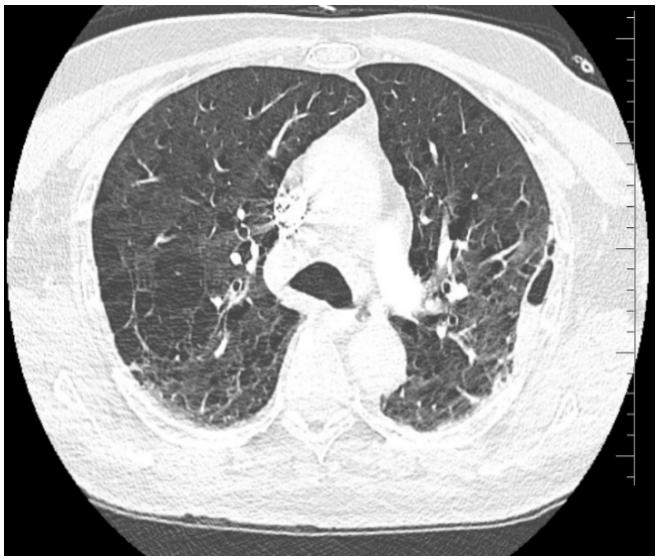

Figure 2: A chest CT scan showing an oval air space.

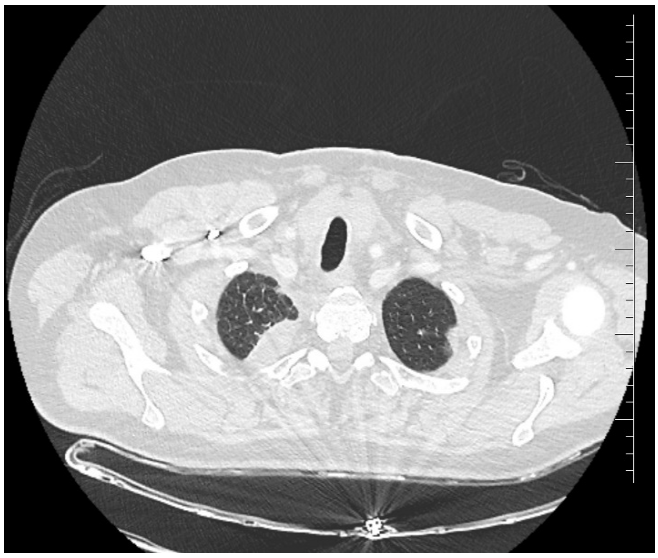

Figure 3: An axial CT scan demonstrating a superinfected lung cyst in right apical segment.

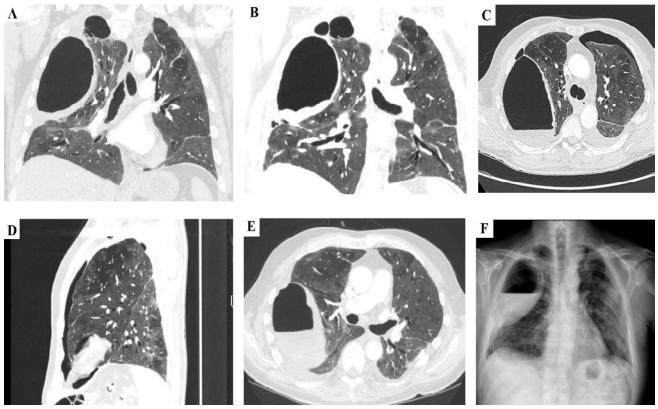

Figure 4: (A,B) − A coronal chest CT scans demonstrating a complex structure of right-sided lung cyst (C) − An axial and (D) − sagittal chest CT scan showing left-sided pneumothorax (E) − An axial chest CT scan presenting air-fluid level in the lung cyst (F) − A chest X-ray showing thickening of the cyst wall and fluid level

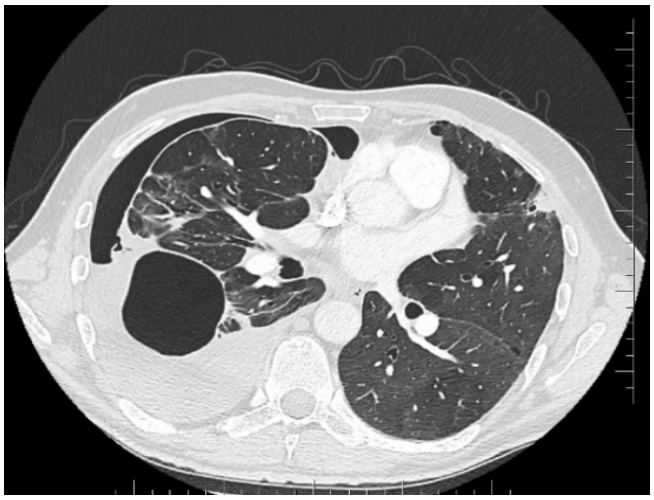

Figure 5: An axial CT scan showing right sided pneumothorax, right sided pleural effusion and a pneumatocele.

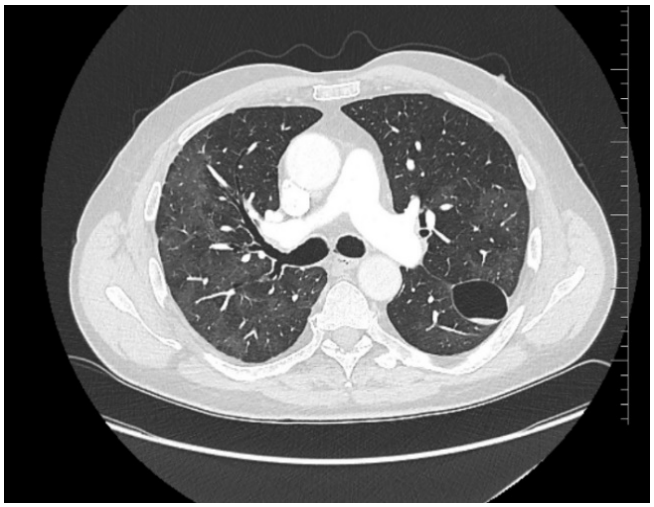

Figure 6: An axial CT scan demonstrating a lung cyst in the left lung.

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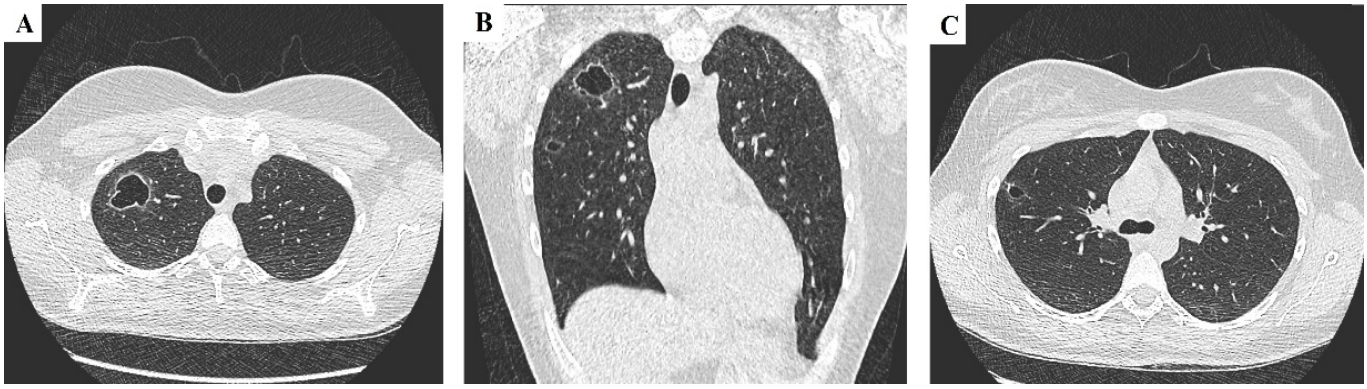

Figure 7: (A) − An axial chest CT scan presenting a pneumatocele in the right lung with a slightly thickened wall (B) − A cross-sectional chest CT scan demonstrating two pneumatocele in the right lung (C) − An axial chest CT scan presenting the second small pneumatocele in the right lung

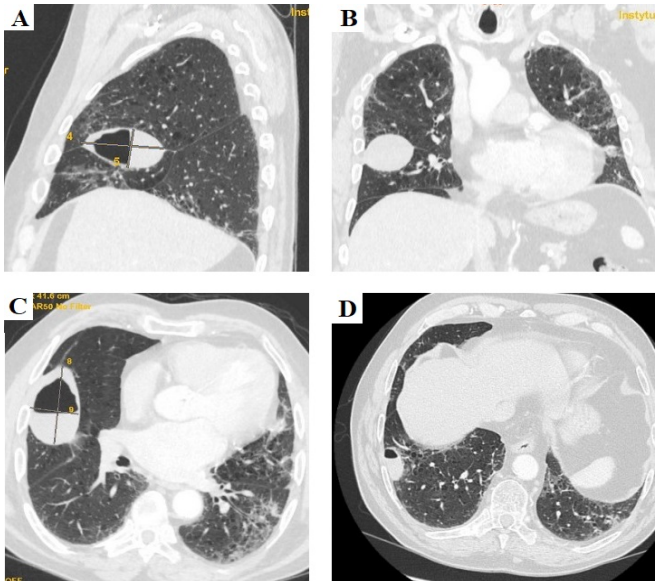

Figure 8: A− A sagittal B− coronal and C− axial CT scan presenting a large cyst in the right lung and D− small pneumatocele in the right lung.

cells infiltration and exudate lead to occlusion of alveoli and respiratory bronchioles, causing a "ball-valve mechanism"- the air is allowed to enter the cystic space but not to leave it. Presence of microthrombi in pulmonary capillaries, which are affected by endothelithis, causes ischemia, necrosis and inflammation, which lead to alveolar wall damage and accumulation of air within the lung parenchyma. Consequently, the trapped air could dissect the parenchymal tissue to the pleura or mediastinum- generating pneumothorax or pneumomediastinum or to the subpleural space, causing pneumatocele. In some of the pathological examinations of lung tissue (Table 1 and 2), diffuse necrosis, hemorrhage and thrombi are described. Nevertheless, most frequent findings are a wide range of lung interstitial inflammation with signs of organizing pneumonia, fibrosis and, in some cases, metaplasia, resulting in increased susceptibility of the lung parenchyma to damage. Supplementary factor is barotrauma, which increases intra-alveaolar pressure and leads to alveolar wall rupture [5-7,21,23]. Continuous positive airway pressure during mechanical ventilation or non-invasive ventilation may cause injury, lung tissue disruption and enlargement of air space. However, more than 50% of the patients mentioned in our review required oxygen support without the necessity of invasive ventilation. Most pneumatoceles that are not COVID-19 related resolve within a few weeks to 12 months with no additional intervention. Probably uncomplicated pneumatocele (thin-walled, with no signs of progressive enlargement) in COVID-19 patients would also resolve spontaneously. The most frequent complications of pneumatocele described in the literature are rupture resulting in pneumothorax or pneumomediastinum, superinfection or haemothorax. Among patients described in the literature, diagnosed with COVID-19 pneumonia complicated by air spaces, after unsuccessful conservative treatment, surgical intervention was necessary. Part of the patients showed clinical and radiological improvement under conservative treatment and could be discharged. Hence, CT scanning should be repeated in patients with newly discovered pneumatocele after recovering from COVID-19, which may prevent to overlook further complications. Conservative management or surgical intervention in those complications should be decided during multidisciplinary discussion (thoracic surgeon, respiratory physician, intensive care specialist) taking into consideration the patient's clinical status, radiological manifestation and expected outcome. Particular difficulties concern the proper interpretation of CT scans in patients with pneumatocele. The CT images are deceptively similar to pleural empyema. In these cases, a precise radiological diagnosis determines the appropriate surgical therapy and outcome of treatment.

Conclusions

The case series and systemic review of the literature provide a few learning points.

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−Not every infected pneumatocele or lung cyst requires surgical intervention

−Persistent air-leak, associated pneumothorax and haemothorax suggest more urgent surgical intervention

−Secondary infection of the pneumatocele not-responding to extended antibiotic therapy is a potential life threatening condition and should be considered for surgical resection. Prompt surgical approach may be lifesaving in patients in the critical clinical stage

−In patients with newly discovered pneumatocele after recovering from COVID-19, repeated imaging in 4-6 weeks may prevent further complications

−Second imaging in a prone position could help to distinguish a pneumothorax from a pneumatocele

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