ISSN 2218-6255 (online)

World Journal of *Respirology*

World J Respirol 2021 August 8; 11(1): 1-17

Published by Baishideng Publishing Group Inc

WJR

World Journal of Respirology

Contents

Continuous Publication Volume 11 Number 1 August 8, 2021

CASE REPORT

World Journal of Respirology

Continuous Publication Volume 11 Number 1 August 8, 2021

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Respirology*, Fizza Ghulam Nabi, PhD, Assistant Professor, Institute of Quality and Technology Management, Punjab University, Lahore, Lahore 54000, Punjab, Pakistan.
engr.fizza@yahoo.com

AIMS AND SCOPE

The primary aim of *World Journal of Respirology* (*WJR*, *World J Respirol*) is to provide scholars and readers from various fields of respirology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. *WJR* mainly publishes articles reporting research results and findings obtained in the field of respirology and covering a wide range of topics including bronchial diseases, ciliary motility disorders, respiratory tract granuloma, laryngeal diseases, lung diseases, nose diseases, pleural diseases, respiration disorders, respiratory center abnormalities, neuromuscular disorders, respiratory hypersensitivity, respiratory system abnormalities, pulmonary vascular diseases, respiratory tract fistula, respiratory tract infections, respiratory tract neoplasms, thoracic diseases, and tracheal diseases.

INDEXING/ABSTRACTING

World Journal of Respirology is now abstracted and indexed in China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Jia-Hui Li*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Ya-Juan Ma.*

NAME OF JOURNAL
World Journal of Respirology

ISSN
ISSN 2218-6255 (online)

LAUNCH DATE
December 30, 2011

FREQUENCY
Continuous Publication

EDITORS-IN-CHIEF
Kazuhiro Yamaguchi

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2218-6255/editorialboard.htm

PUBLICATION DATE
August 8, 2021

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Respirology

Submit a Manuscript: https://www.f6publishing.com

World J Respirol 2021 August 8; 11(1): 1-11

DOI: 10.5320/wjr.v11.i1.1

ISSN 2218-6255 (online)

CASE REPORT

SARS-CoV-2 with concurrent coccidioidomycosis complicated by refractory pneumothorax in a Hispanic male: A case report and literature review

Joscilin Mathew, Sundar V Cherukuri, Fatma Dihowm

ORCID number: Joscilin Mathew 0000-0002-5908-2034; Sundar V Cherukuri 0000-0001-9076-049X; Fatma Dihowm 0000-0001-8420-2758.

Author contributions: Cherukuri S and Dihowm F participated in the direct medical care described in this manuscript; Mathew J and Cherukuri SV contributed to the manuscript's concept, design and drafting, the acquisition of data, and the analysis and interpretation of the data; Mathew J, Cherukuri SV, and Dihowm F were responsible for the revision of the manuscript for important intellectual content.

Informed consent statement: Informed consent for surgical procedures performed were obtained.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

CARE Checklist (2016) statement: The manuscript was revised according to the CARE Checklist.

Joscilin Mathew, Sundar V Cherukuri, Fatma Dihowm, Department of Internal Medicine, Texas Tech University Health Sciences Center El Paso, El Paso, TX 79905, United States

Corresponding author: Joscilin Mathew, MBBS, MD, Doctor, Department of Internal Medicine, Texas Tech University Health Sciences Center El Paso, 4800 Alberta Ave. MSC 41007, El Paso, TX 79905, United States. joscilin.mathew@gmail.com

Abstract

BACKGROUND

The incidence of secondary coinfections particularly fungal infections among severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is not well described. Little is known of the complications that could be encountered in such conditions.

CASE SUMMARY

A 50-year-old Hispanic male who was a prior smoker presented with shortness of breath. He was diagnosed with SARS-CoV-2. He improved and was discharged with home oxygen. A month later, he presented with sudden onset cough and shortness of breath. Chest X-ray showed development of right-sided tension pneumothorax, right pleural effusion and an air-filled cystic structure. Computed tomography thorax showed findings suggestive of pulmonary coccidioidomycosis. Coccidioides antigen was positive, and fluconazole was initiated. For pneumothorax, a pigtail catheter was placed. The pigtail chest tube was later switched to water seal, unfortunately, the pneumothorax re-expanded. Another attempt to transition chest tube to water seal was unsuccessful. Pigtail chest tube was then swapped to 32-Fr chest tube and chemical pleurodesis was performed. This was later transitioned successfully to water seal and finally removed. He was discharged on a four-week oral course of fluconazole 400 mg and was to follow up closely as an outpatient for continued monitoring.

CONCLUSION

Pneumothorax is associated with a worse prognosis, especially with comorbidities such as diabetes, immunosuppression and malignancy. Suspicion for concomitant fungal infection in such patients should be high and would necessitate further investigation.

Manuscript source: Unsolicited manuscript

Specialty type: Medicine, general and internal

Country/Territory of origin: United States

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: March 17, 2021
Peer-review started: March 17, 2021
First decision: March 31, 2021
Revised: April 14, 2021
Accepted: July 9, 2021
Article in press: July 9, 2021
Published online: August 8, 2021

P-Reviewer: Coelho AC, Gedik IE
S-Editor: Wang JL
L-Editor: A
P-Editor: Li JH

Key Words: SARS-CoV-2; COVID-19; Coccidioidomycosis; Co-infection; Fungal infection; Tension pneumothorax; Refractory pneumothorax; Case report; Literature review

Core Tip: This case highlights the presence of a concomitant infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coccidioidomycosis. This was further complicated by the formation of a refractory pneumothorax. Fungal infections in SARS-CoV-2 patients appear underdiagnosed and may have an increased prevalence in patients with comorbidities, such as malignancies, diabetes, and chronic lung disorders. Total 39 case reports were included in our literature review. The risk of pneumothorax and pneumomediastinum formation does not necessarily increase from a history of smoking or underlying lung pathology; however, the incidence of a prolonged cough prior to pneumothorax formation seems to be consistent across several reported cases.

Citation: Mathew J, Cherukuri SV, Dihowm F. SARS-CoV-2 with concurrent coccidioidomycosis complicated by refractory pneumothorax in a Hispanic male: A case report and literature review. *World J Respirol* 2021; 11(1): 1-11
URL: https://www.wjgnet.com/2218-6255/full/v11/i1/1.htm
DOI: https://dx.doi.org/10.5320/wjr.v11.i1.1

INTRODUCTION

Novel coronavirus disease 2019 (COVID-19) first emerged in Wuhan, China and is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1]. Radiological findings include multi-lobar bilateral ground glass opacities and consolidative opacities[2]. An uncommon complication of the infectious process is the development of pneumothorax[1,3,4]. Although often correlated with risk factors, such as smoking, subpleural bleb formation, and as a sequalae of other pulmonary diseases, such as cystic fibrosis, malignancies, and chronic obstructive pulmonary disease, there are few reported cases worldwide that link pneumothorax formation with SARS-CoV-2, making it one of lesser encountered adverse effects. Though little is known about the association between pneumothorax and SARS-CoV-2, its presence tends to quantify a worsening prognosis.

As the disease continues to be more rampant worldwide several cases of co-infection of SARS-CoV-2 with other infections were reported. These cases included co-infection with other viral infections, such as influenza and molluscum contagiosum virus, less commonly bacterial infections, and rarely fungal infections[1-4].

Coccidioidomycosis is a fungal infection caused by Coccidioides immitis and is predominantly seen in Southwestern America, Mexico, and parts of South America[5]. Coccidioidomycosis has been found to affect various organ systems, though pulmonary manifestations appear to be the most common. It is spread through inhalation of airborne fungal spores (arthroconidium) and dust exposure increases the risk of acquiring infection. Clinical presentations can range from asymptomatic, to influenza-like pneumonia, to severe respiratory distress syndrome (ARDS) and sepsis [6]. Radiographic findings range from diffuse pneumonia-like consolidations, nodular parenchymal lesions, and hilar thickening to cavitation and effusions[6,7].

Symptomatology can be very non-specific and can mirror the symptoms of SARS-CoV-2 closely, making it difficult to differentiate without appropriate testing. Though little is known about clinical presentations involving both coccidioidomycosis and SARS-CoV-2, it is very likely that co- infection worsens prognosis, increases the risk of complications, and impacts treatment options pursued. In this case report, we discuss the coinfection of SARS-CoV-2 with concomitant coccidioidomycosis infection, that was further complicated by refractory pneumothorax.

CASE PRESENTATION

Chief complaints

A 50-year-old Hispanic male presented to our facility after experiencing sudden onset cough and shortness of breath of one day duration.

History of present illness

One day prior to admission, he started noticing sudden onset cough and shortness of breath. He was admitted to our facility one month prior and was diagnosed with SARS-CoV-2 at the time. Of note, he had an approximately 7.5 pack year history of cigarette smoking and had quit approximately four months prior to hospitalization. A chest x-ray obtained at admission showed multifocal airspace opacities in mainly bilateral middle and lower lobes, as well as a 6.1 cm pneumatocele or bulla in the medial right lower lung adjacent to the cardiac border. He was started on azithromycin, as well as a regimen including vitamin C, vitamin D, and zinc (institutional practice at that time). Additionally, he was requiring supplemental oxygen at 3 L *via* nasal cannula. He was discharged under stable conditions with home oxygen. He had discontinued supplemental oxygen usage at home approximately 2 wk prior to current hospitalization. Apart from new onset of non-productive cough and worsening shortness of breath, he denied any other accompany symptoms.

History of past illness

Past medical history consisted of type 2 diabetes mellitus.

Personal and family history

Social history was significant for approximately 7.5 years smoking history, occasional alcohol use and no illicit drug use. He worked as an electrician. Family history was significant for type 2 diabetes mellitus in his father and sister.

Physical examination

In the Emergency department, he was tachycardic with a heart rate of 120 and hypoxic, with an O_2 saturation of 88% on room air, and diminished breath sounds, hyperresonance with percussion, and asymmetric chest wall excursion on right side were noted on examination. On our examination, post placement of a pigtail chest tube, he was noted to have non-labored respirations, normal respiratory rate, and an O_2 saturation of 94% on room air; physical exam findings included significantly diminished breath sounds to auscultation in the right lower lung fields, midline trachea, and yellow pleural fluid output from the pigtail catheter. SARS-CoV-2 nucleic acid testing on admission remained positive and he was saturating at 94% oxygen on room air.

Laboratory examinations

The following laboratory values were noted: Serum protein of 9, pleural protein of 7.2, serum lactate dehydrogenase (LDH) of 242, and pleural LDH of 2401, and met Light's criteria for an exudative effusion. Serologic studies were obtained to investigate the etiology of his cavitary lesions and were positive for coccidioides antigen.

Imaging examinations

An initial chest X-ray, obtained at time of emergency department evaluation, showed early development of a right-sided tension pneumothorax, with an associated collapse of the right lung and depression of the right diaphragm, and a right pleural effusion. Additionally, it also showed a 3.7 cm × 2.9 cm air filled cystic structure with a round solid dependent component in the right lung lower zone, adjacent to the right cardiac border (Figure 1). A 14 Fr Wayne pigtail catheter thoracostomy was performed by an Emergency Medicine physician and drainage was noted. After stabilization of the patient, a computed tomography (CT) scan of the chest was also obtained to better visualize the cavitary lesion. It showed the thin walled cavitary lesion with a fungal ball in the superior segment of the right lower lobe, as well as multiple cavitary nodules in bilateral upper lobes and in the superior segment of the lower lobes, suggestive of pulmonary coccidioidomycosis (Figure 2).

Further diagnostic work-up

The patient was started on an antibiotic regimen that initially consisted of amphotericin B liposomal due to suspicion for central nervous system involvement.

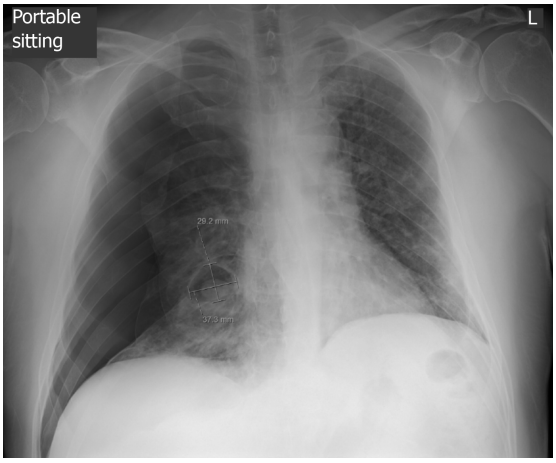

Figure 1 Chest radiograph of the patient. The image shows development of large right-sided pneumothorax with associated collapse of the right lung, as well as a 3.7 cm × 2.9 cm air-filled cystic structure with a round solid dependent component in the right lower lung.

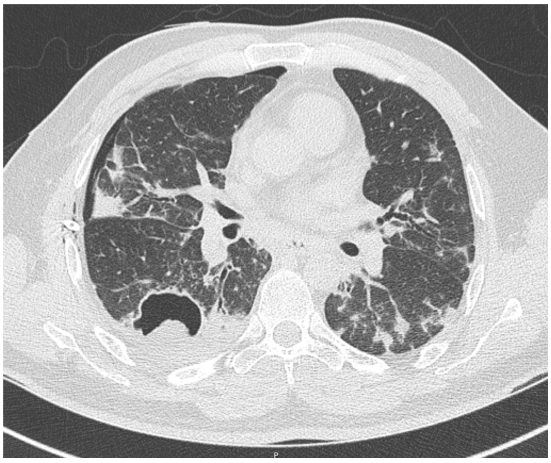

Figure 2 Computed tomography thorax image. The thorax image depicting thin wall cavitary lesion with a fungal ball in the superior segment of the right lower lobe, right pneumothorax, and diffuse ground glass opacities and densities in bilateral lungs.

The chest tube was placed to suction at 20 mm to address his pneumothorax. The patient's antibiotic regimen was later switched to fluconazole 600 mg PO daily after the patient developed an acute kidney injury after initiating amphotericin.

Once there was observed interval improvement of the pneumothorax on follow up chest X-rays, the pigtail chest tube was switched to water seal, but unfortunately, the pneumothorax re-expanded. Another attempt was made with the chest tube set to suction and transitioned to water seal; however, re-expansion occurred again. The pigtail chest tube was then swapped to a 32-Fr sized chest tube and chemical pleurodesis was performed by the cardiothoracic surgical team. With the new chest tube set to suction, follow up chest X-rays showed improvement. After 48 h of suction, it was transitioned to water seal and no re-expansion of the pneumothorax was noted. The chest tube was then removed and follow up chest X-rays confirmed no residual pneumothorax.

FINAL DIAGNOSIS

The final diagnosis of the presented case is SARS-CoV-2 with concurrent coccidioidomycosis infection complicated by refractory pneumothorax development.

TREATMENT

Throughout the hospital course, the patient continued to saturate well above 92% on room air and required minimal to no supplemental oxygen. He had no further episodes of respiratory distress, though a repeat nucleic acid test continued to show positivity for SARS-CoV-2. He was discharged with a four-week oral course of fluconazole 400 mg and was to follow up closely as an outpatient for continued monitoring.

OUTCOME AND FOLLOW-UP

The patient has had an uneventful post-hospital clinical course. He has continued his anti-fungal medication outpatient with his primary care physician. The latest chest radiograph has shown resolution of the right lower lung cavitary lesion.

DISCUSSION

Literature review methods

MEDLINE and SCOPUS were the database accessed to seek relevant articles listed from March to October 2020. Articles were searched using the keywords- "COVID-19", "coronavirus" and "pneumothorax". Reports that were not indexed on MEDLINE and SCOPUS were excluded from our review. Only articles originally written in English were selected in this review (Figure 3).

Literature review results

Table 1 and Table 2 summarizes the findings of several case reports of pneumothorax and pneumomediastinum in SARS-CoV-2 infection. Total 39 case reports were included in our literature review. Pneumothorax and pneumomediastinum have been reported in people aged 20-80 with median age being 56. More cases have been reported in men (74%) as compared to women (26%). The presence of cough was reported in 67% of patients. Only 3 out 19 (15.8%) patients with known smoking history were smokers, while 16 out of 19 (84.2%) were non-smokers. Of the patients with recorded past medical history, only 5 in 34 patients had underlying lung pathology (asthma). The presence of blebs was described in 5 patients (12.8%). Tension pneumothorax was noted in two cases only. Invasive mechanical ventilation prior to development of pneumothorax or pneumomediastinum was recorded in 12 (30.7%) patients. While 24 out of 35 (68.5%) patients required intervention for pneumothorax or pneumomediastinum. Review of the outcomes in these patients revealed 21 of 36 (58%) patients showed favorable response while 15 in 36 (41.6%) patients did not survive. Among the patients who required invasive mechanical ventilation, only 5 in 12 (45.5%) patients survived.

Discussion of the case

Our patient presented with pneumothorax, a rare finding in SARS-CoV-2 infections. A 52-patient retrospective study by Yang *et al*[4] noted 1 patient (extrapolated to 2% of all cases) who had pneumothorax development. Similarly, another study by Chen *et al*[1] noted only 1 out of 99 patients in their analysis developed a pneumothorax in the setting of SARS-CoV-2. Given the scarcity of cases, it is difficult to anticipate what factors could have contributed to the development of pneumothoraces.

While our patient was a prior smoker, several case reports show history of smoking or underlying lung pathology does not necessarily increase risk of developing pneumothorax[8-10]. While prolonged smoking history does make the lung more vulnerable, ARDS has been shown to be a greater risk factor for developing pneumothorax. ARDS is associated with decreased lung compliance and higher propensity for barotrauma, increasing the opportunity for developing pneumothorax[11,12]. ARDS continues to be one of the most common indications for invasive mechanical ventilation. Invasive ventilation escalates the danger of alveolar injury and formation of cystic lesions, bullae and pneumothorax[1-3,11-13]. Incidence of pneumothorax secondary to invasive mechanical ventilation is high and is even greater in the setting of ARDS. According to Zantah *et al*[14], the duration and severity of ARDS along with barotrauma sustained with the use of high tidal volume and minute ventilations, high peak inspiratory pressures (PIP) and high positive end expiratory pressures

Table 1 Literature review on reported pneumothorax cases in severe acute respiratory syndrome coronavirus 2 among non-ventilated patients

Ref.	Gender/Age	Presence of cough	Smoking history	Underlying lung disease	Presence of blebs/bullae on CT	Other CT findings	Intervention provided for PT	Management provided	Outcome
Sun *et al*[13]	38/M	+	None	None	Yes (bullae)	GGO, consolidation, giant bulla	Unknown	Symptomatic careHFNC	Unknown
López Vega *et al*[16], Case 1	84/F	+	None	None	CXR- none	Hydropneumothorax, pneumomediastinum	Unknown	HCQ, ceftriaxone, methylpredisone	Died
López Vega *et al*[16], Case 2	67/M	No	None	None	None	PT, GGO, thickening of septa	Pleural drainage tube	Zosyn, AZM	Died
López Vega *et al*[16], Case 3	73/M	No	None	OSA	None	Pneumomediastinum + PTE	AG +CPAP	HCQ, AZM, tocilizumab, methyl prednisone	Died
Spiro *et al*[11]	47/M	+	None	None	None	GGO + consolidations +tension PT	Chest drain (Buelau) + open thoracotomy	AZM	Survived
Wang *et al*[3]	36/F	+	None	None	None	GGO + interlobular septal thickening with pl effusion and bronchiectasis	Supportive care	Combined anti-viral and anti-inflammatory	Died
Flower *et al* [9]	36/M	+	+ 10 Pack yr	Asthma	Yes(bullae)	Initial CXR- tension pneumothorax; CT- Patchy consolidation + bullae	Emergency needle decompression with chest tube placement	Unknown	Survived
Wang *et al* [23]	62/M	+	None	None	None	GGO + consolidations + PT + pneumomediastinum + SC emphysema	Spontaneous resolution	Lopinavir/ritonavir, antibiotics, methylprednsiolone	Survived
Ucpinar *et al* [24]	82/F	+	None	None	No	GGO + pneumomediastinum + PT+ SC emphysema	Chest tube	HCQ, oseltamivir, ceftriaxone	Survived
Rohailla *et al* [25]	26/M	None	None	None	None	CXR-PT	Chest drain	Supportive care	Survived
Zantah *et al* [14], Patient 1	49/M	+	None	None	None	GGO + consolidations	Chest tube	Abs, CS, CP + Tocilizumab	Died
Zantah *et al* [14], Patient 3	81/F	No	Unknown	None	None	GGO + consolidative changes + consolidation in RUL	Chest tube	Abs, CS + Remdesivir	Died
Hazariwala *et al*[8]	67/M	+	Unknown	None	None	GGO + SC emphysema + PT	Conservative measures	Ab, antiviral, methylprednisolone	Survived
Kolani *et al* [26]	23/F	No	Unknown	None	None	GGO + pneumomediastinum	Spontaneous resolution	AZM, HCQ	Survived
Zhou *et al* [27]	38/M	+	Unknown	None	None	GGO + consolidations + pneumomediastinum + SC emphysema	Spontaneous resolution	Abs, antiviral, CS	Survived
Mohan *et al* [28]	49/M	+	None	None	None	Pneumomediastinum + SC emphysema	Spontaneous resolution	Abs, HCQ, CS, AG	Survived
Corrêa Neto *et al*[29]	80/F	+	No	No	No	CT- GGO + PT. pneumomediastinum	Chest drain	Abs, antiviral	Died
Hollingshead *et al*[30]	50/M	No	Unknown	Unknown	None	CTA- GGO + loculated PT	Chest tube	Unknown	Survived
Lei *et al*[31]	64/M	No	Unknown	Unknown	None	CT- resolution of pneumonic lesions + spontaneous	Unknown	Unknown	Unknown

						pneumomediastinum			
Ahluwali *et al*[32]	31/M	+	No	None	None	CXR- tension PTCT- pneumomediastinum + pneumopericardium + PT + consolidations + multilobar PNA	Chest tube	HCQ + tocilizumab	Survived
Sahu *et al*[17]	61/M	No	No	None	None	CXR- pneumomediastinum + pneumopericardium	Supportive care	Remdesivir + CP + tocilizumab	Died
Hazariwala *et al*[8], Patient 1	57/F	+	Unknown	Asthma	None	CT pneumomediastinum+ PT + SC emphysema	Chest tube	HCQ +zinc+ AZM+ CS	Died
Hazariwala *et al*[8], Patient 2	55/M	+	+ 50 pack year	Asthma	None	CT- pneumomediastinum+ + SC emphysema + pneumoperitoneum	Supportive care	HCQ +zinc+ AZM+ CS	Died
Al-Shokri *et al*[33], Patient 1	55/M	+	No	None	None	CT- pneumomediastinum + PT	Chest tube	HCQ + AZM	Survived
Al-Shokri *et al*[33], Patient 3	50/M	+	Unknown	Unknown	No	CT- PT + mediastinal shift	Thoracostomy + Chest tube	HCQ + AZM	Survived
Chen *et al*[34]	66/M	+	Unknown	None	No	CT- GGO + PT	Thoracic closed drain	Anti-viral + Abs + Immunoglobulins + methylprednisolone	Survived

IMV: Invasive mechanical ventilation; PT: Pneumothorax; GGO: Ground glass opacities; HFNC: High flow nasal cannula; AG: Anticoagulation; HCQ: Hydroxychloroquine; AZM: Azithromycin; CP: Convalescent plasma.

correspond to the increase rates of pneumothorax seen in mechanically ventilated patients. The frequency of pneumothorax was noted to be higher in ARDS patients on longer duration of mechanical ventilation according to Gattinoni *et al*[15].

Another finding that seems to be consistent across several reported cases, is the incidence of prolonged cough prior to the development of pneumothorax (Table 1). Persistent cough can increase alveolar pressure and induce alveolar rupture causing air leaks resulting in pneumothoraces, pneumomediastinum, and subcutaneous emphysema[8,13,16]. Another risk factor is the presence or development of a pneumatocele or bulla during the early stages of SARS-CoV-2 pneumonia[9,12,13]. Our patient was noted to have developed a bulla or pneumatocele during his first admission, and approximately 30 days later, presented with acute symptoms, secondary to a new pneumothorax. Literature review shows most instances of pneumothoraces occurred spontaneously with only two reports of tension pneumothorax noted[9,11].

There have been several reports of coccidioidomycosis cases with pneumothorax development. Rashid *et al*[10] noted three different cases of exposure, with initial presentations of either an absence of systemic symptoms or presence of low-grade fevers, fatigue, in combination with sudden onset dyspnea and chest pain. These patients were subsequently found to have large pneumothoraces alongside the coccidioidomycosis cavitary lesion. Treatments varied for these cases, ranging from brief antifungal courses of ketoconazole and amphotericin B therapies to requiring additional lung wedge resections. Coccidioidomycosis can lay dormant for many years, though reactivation of disease state is noted with immunosuppression. Interestingly, in our patient it flared up after initial treatment of COVID-19. It remains unclear whether a SARS-CoV-2 associated cytokine storm could have possibly triggered the fungus. While our patient did show several features that elevates the possibility of developing pneumothorax, it is unclear at this time whether the presence of concomitant coccidioidomycosis could have potentially been a confounding factor. Though we would need more studies to confirm this.

In our case, it is unclear whether pneumothorax was caused by SARS-CoV-2, Coccidioides or a combination of both. However, the pattern of pneumothorax formation seems to be similar between the two with bleb formation. Review of literature shows the development of pneumothorax tends to increase as the SARS-CoV-2 disease progresses and appears to be associated with a bad prognosis[2]. In patients with prolonged history of dry cough or intubated patients who are noted to have increasing oxygenation requirement, low threshold is advised to conduct

Table 2 Literature review on reported pneumothorax cases in severe acute respiratory syndrome coronavirus 2 among ventilated patients

Ref.	Gender/Age	Presence of cough	Smoking history	Underlying lung disease	Presence of blebs/bullae on CT	Other CT findings	Intervention provided for PT	Management provided	Outcome
Xiang *et al* [35]	67/M	No	Unknown	Chronic bronchitis, emphysema and obsolete pulmonary TB	Unknown (no CT)	No CT- CXR showing SC emphysema	Chest close drainage	Anti-viral, anti-bacterial therapy, vasoconstrictors	Died
Zantah *et al*[14], Patient 2	59/M	+	Unknown	None	None	GGO + consolidations + crazy paving pattern	Chest tube	Abs, CS, CP + Tocilizumab	Survived
Zantah *et al*[14], Patient 4	45/F	+	Unknown	None	None	GGO + consolidative changes	Chest tube	Abs, CS, CP + Tocilizumab	Survived
Zantah *et al*[14], Patient 5	47/F	+	Unknown	None	None	GGO + consolidations	Chest tube	Abs, CS, AG, Tocilizumab	Died
Zantah *et al*[14], Patient 6	76/F	No	Unknown	Pulmonary sarcoidosis	None	Consolidations	Chest tube	Unknown	Died
Al-Azzawi *et al*[36], Patient 1	36/M	+	Unknown	None	None	GGO + pneumomediastinum + SC emphysema	Improved without intervention	AZM, Vit C, zinc, HCQ, Tocilizumab, CS, ECMO	Died
Al-Azzawi *et al*[36], Patient 2	47/M	No	Unknown	None	None	CXR- SC emphysema + pneumomediastinum	Chest tube	HCQ, zinc, AZM, tocilizumab,	Survived
Al-Azzawi *et al*[36], Patient 3	78/M	No	Unknown	None	None	CXR- SC emphysema + pneumomediastinum	None	AZM, Vit C, zinc, HCQ	Died
Aiolfi *et al* [37], Patient 1	56/M	+	Active smoker	Unknown	Superficial bleb +	CXR – pneumothorax; CT – GGO	Pleural darin, 3 port thoracoscopy, bleb resection, mechanical pleurodesis	Unknown	Survived
Aiolfi *et al* [37], Patient 2	70/M	No	No	No	Superficial bleb +	CT- GGO	Chest tube, 3 port thoracoscopy, bleb resection	Unknown	Survived
Al-Shokri *et al*[33], Patient 2	33/M	+	Unknown	Unknown	Yes (bulla)	CT- tension PT + bulla and mild pneumomediastinum	Chest tube	HCQ + AZM	Survived
Abushahin *et al*[38]	47/M	+	Unknown	None	No	CT- spontaneous PT	Pigtail chest tube	Abs + HCQ +	Survived

IMV: Invasive mechanical ventilation; PT: Pneumothorax; GGO: Ground glass opacities; HFNC: High flow nasal cannula; AG: Anticoagulation; HCQ: Hydroxychloroquine; AZM: Azithromycin; CP: Convalescent plasma.

imaging to rule out pneumothorax. Along with other radiological studies to rule out other common etiologies like pulmonary thromboembolism, flash pulmonary edema, cardiac tamponade or worsening pneumonia[17]. Apart from roentgenograms, lung ultrasound is a convenient study that can be done at bedside[18]. Though CT continues to be the preferred modality. If pneumothorax is noted and its requires the use of a chest tube drain, Akhtar *et al*[19] noted use of an anti-viral filter attached to pleural drain bottle reduced the risk of aerosolization.

Although, our patient did not require active management of SARS-CoV-2, we anticipate dual treatment for SARS-CoV-2 and coccidioidomycosis would require tailoring of medications. When utilizing Remdesivir, a nucleoside analog targeting RNA-dependent RNA polymerase activity approved by the United States Food and Drug Administration for use against SARS-CoV-2, elevations in liver enzymes are

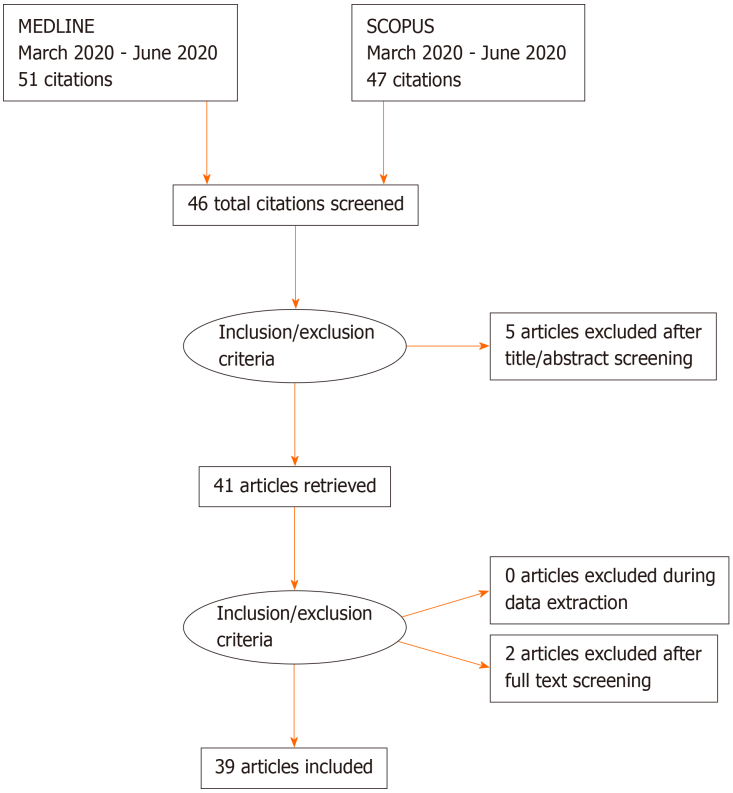

Figure 3 PRISMA 2009 checklist.

common. AST and ALT levels above five times the normal formed an exclusion criteria in the study conducted by Goldman *et al*[20]. In the initial treatment of a coccidioidomycosis infection, azole agents are used, and hepatotoxicity is often noted as a common adverse effect[21]. A potential combination of these two pharmacological agents could cause an additive effect on worsening liver function, thereby requiring therapy modification. Additionally, glucocorticoids, that have shown promising results in the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial, might require reconsideration in SARS-CoV-2 infection with concomitant fungal infection [22].

CONCLUSION

This case highlights the presence of concomitant infection of SARS-CoV-2 and coccidioidomycosis, complicated by refractory pneumothorax. To the best of our knowledge, this is the second reported case of SARS-CoV-2 and coccidioidomycosis and the first co-infection case to report a complication of refractory pneumothorax. Fungal infections in COVID-19 patients appear underdiagnosed and tends to be more prevalent in patients noted to have ARDS, underlying malignancy, diabetes, chronic lung disorders or prolonged course of corticosteroids. A high index of suspicion should be maintained for co-infection or superinfection of COVID-19 with fungal infection in such patients.

REFERENCES

1 **Chen N**, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; **395**: 507-513 [PMID: 32007143 DOI: 10.1016/S0140-6736(20)30211-7]

2 **Salehi S**, Abedi A, Balakrishnan S, Gholamrezanezhad A. Coronavirus Disease 2019 (COVID-19): A Systematic Review of Imaging Findings in 919 Patients. *AJR Am J Roentgenol* 2020; **215**: 87-93 [PMID: 32174129 DOI: 10.2214/AJR.20.23034]

3 **Wang J**, Su X, Zhang T, Zheng C. Spontaneous Pneumomediastinum: A Probable Unusual

Complication of Coronavirus Disease 2019 (COVID-19) Pneumonia. *Korean J Radiol* 2020; **21**: 627-628 [PMID: 32323507 DOI: 10.3348/kjr.2020.0281]

4 **Yang X**, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020; **8**: 475-481 [PMID: 32105632 DOI: 10.1016/S2213-2600(20)30079-5]

5 **Centers for Disease Control and Prevention (CDC)**. Increase in reported coccidioidomycosis--United States, 1998-2011. *MMWR Morb Mortal Wkly Rep* 2013; **62**: 217-221 [PMID: 23535687]

6 **Taylor AB**, Briney AK. Observations on primary coccidioidomycosis. *Ann Intern Med* 1949; **30**: 1224-1236 [PMID: 18150185 DOI: 10.7326/0003-4819-30-6-1224]

7 **Shah AS**, Heidari A, Civelli VF, Sharma R, Clark CS, Munoz AD, Ragland AS, Johnson RH. The Coincidence of 2 Epidemics, Coccidioidomycosis and SARS-CoV-2: A Case Report. *J Investig Med High Impact Case Rep* 2020; **8**: 2324709620930540 [PMID: 32493147 DOI: 10.1177/2324709620930540]

8 **Hazariwala V**, Hadid H, Kirsch D, Big C. Spontaneous pneumomediastinum, pneumopericardium, pneumothorax and subcutaneous emphysema in patients with COVID-19 pneumonia, a case report. *J Cardiothorac Surg* 2020; **15**: 301 [PMID: 33028398 DOI: 10.1186/s13019-020-01308-7]

9 **Flower L**, Carter JL, Rosales Lopez J, Henry AM. Tension pneumothorax in a patient with COVID-19. *BMJ Case Rep* 2020; **13** [PMID: 32423911 DOI: 10.1136/bcr-2020-235861]

10 **Rashid HR**, Hunter LK. Pleural coccidioidomycosis presenting as spontaneous pneumothorax. *BMJ Case Rep* 2018; **2018** [PMID: 30061139 DOI: 10.1136/bcr-2018-225854]

11 **Spiro JE**, Sisovic S, Ockert B, Böcker W, Siebenbürger G. Secondary tension pneumothorax in a COVID-19 pneumonia patient: a case report. *Infection* 2020; **48**: 941-944 [PMID: 32557347 DOI: 10.1007/s15010-020-01457-w]

12 **Liu K**, Zeng Y, Xie P, Ye X, Xu G, Liu J, Wang H, Qian J. COVID-19 with cystic features on computed tomography: A case report. *Medicine (Baltimore)* 2020; **99**: e20175 [PMID: 32358406 DOI: 10.1097/MD.0000000000020175]

13 **Sun R**, Liu H, Wang X. Mediastinal Emphysema, Giant Bulla, and Pneumothorax Developed during the Course of COVID-19 Pneumonia. *Korean J Radiol* 2020; **21**: 541-544 [PMID: 32207255 DOI: 10.3348/kjr.2020.0180]

14 **Zantah M**, Dominguez Castillo E, Townsend R, Dikengil F, Criner GJ. Pneumothorax in COVID-19 disease- incidence and clinical characteristics. *Respir Res* 2020; **21**: 236 [PMID: 32938445 DOI: 10.1186/s12931-020-01504-y]

15 **Gattinoni L**, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, Camporota L. COVID-19 pneumonia: different respiratory treatments for different phenotypes? *Intensive Care Med* 2020; **46**: 1099-1102 [PMID: 32291463 DOI: 10.1007/s00134-020-06033-2]

16 **López Vega JM**, Parra Gordo ML, Diez Tascón A, Ossaba Vélez S. Pneumomediastinum and spontaneous pneumothorax as an extrapulmonary complication of COVID-19 disease. *Emerg Radiol* 2020; **27**: 727-730 [PMID: 32524296 DOI: 10.1007/s10140-020-01806-0]

17 **Sahu KK**, Mishra AK, Goldman Y. A rare case of Pneumopericardium secondary to COVID-19. *Heart Lung* 2020; **49**: 679-680 [PMID: 32861883 DOI: 10.1016/j.hrtlng.2020.08.017]

18 **Mongodi S**, Orlando A, Arisi E, Tavazzi G, Santangelo E, Caneva L, Pozzi M, Pariani E, Bettini G, Maggio G, Perlini S, Preda L, Iotti GA, Mojoli F. Lung Ultrasound in Patients with Acute Respiratory Failure Reduces Conventional Imaging and Health Care Provider Exposure to COVID-19. *Ultrasound Med Biol* 2020; **46**: 2090-2093 [PMID: 32451194 DOI: 10.1016/j.ultrasmedbio.2020.04.033]

19 **Akhtar MR**, Ricketts W, Fotheringham T. Use of an antiviral filter attached to a pleural drain bottle to prevent aerosol contamination with SARS-CoV-2. *Clin Med (Lond)* 2020; **20**: e60-e61 [PMID: 32457134 DOI: 10.7861/clinmed.2020-0246]

20 **Goldman JD**, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, Spinner CD, Galli M, Ahn MY, Nahass RG, Chen YS, SenGupta D, Hyland RH, Osinusi AO, Cao H, Blair C, Wei X, Gaggar A, Brainard DM, Towner WJ, Muñoz J, Mullane KM, Marty FM, Tashima KT, Diaz G, Subramanian A; GS-US-540-5773 Investigators. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. *N Engl J Med* 2020; **383**: 1827-1837 [PMID: 32459919 DOI: 10.1056/NEJMoa2015301]

21 **Galgiani JN**, Ampel NM, Blair JE, Catanzaro A, Geertsma F, Hoover SE, Johnson RH, Kusne S, Lisse J, MacDonald JD, Meyerson SL, Raksin PB, Siever J, Stevens DA, Sunenshine R, Theodore N. 2016 Infectious Diseases Society of America (IDSA) Clinical Practice Guideline for the Treatment of Coccidioidomycosis. *Clin Infect Dis* 2016; **63**: e112-e146 [PMID: 27470238 DOI: 10.1093/cid/ciw360]

22 for COVID-19: preliminary findings. *Drug Ther Bull* 2020; **58**: 133 [PMID: 32690491 DOI: 10.1136/dtb.2020.000045]

23 **Wang W**, Gao R, Zheng Y, Jiang L. COVID-19 with spontaneous pneumothorax, pneumomediastinum and subcutaneous emphysema. *J Travel Med* 2020; **27** [PMID: 32330274 DOI: 10.1093/jtm/taaa062]

24 **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 [PMID: 32475804 DOI: 10.1016/j.jiph.2020.05.012]

25 **Rohailla S**, Ahmed N, Gough K. SARS-CoV-2 infection associated with spontaneous pneumothorax. *CMAJ* 2020; **192**: E510 [PMID: 32317275 DOI: 10.1503/cmaj.200609]

26 **Kolani S**, Houari N, Haloua M, Alaoui Lamrani Y, Boubbou M, Serraj M, Aamara B, Maaroufi M,

Alami B. Spontaneous pneumomediastinum occurring in the SARS-COV-2 infection. *IDCases* 2020; **21**: e00806 [PMID: 32395425 DOI: 10.1016/j.idcr.2020.e00806]

27 **Zhou C**, Gao C, Xie Y, Xu M. COVID-19 with spontaneous pneumomediastinum. *Lancet Infect Dis* 2020; **20**: 510 [PMID: 32164830 DOI: 10.1016/S1473-3099(20)30156-0]

28 **Mohan V**, Tauseen RA. Spontaneous pneumomediastinum in COVID-19. *BMJ Case Rep* 2020; **13** [PMID: 32457032 DOI: 10.1136/bcr-2020-236519]

29 **Corrêa Neto IJF**, Viana KF, da Silva MBS, da Silva LM, Oliveira, de Gustavo C, da Silva Cecchini AR, Rolim AS, Robles L. Perforated acute abdomen in a patient with COVID-19: an atypical manifestation of the disease. *J Coloproctol* **40**: 269-272 [DOI: 10.1016/j.jcol.2020.05.011]

30 **Hollingshead C**, Hanrahan J. Spontaneous Pneumothorax Following COVID-19 Pneumonia. *IDCases* 2020; **21**: e00868 [PMID: 32596131 DOI: 10.1016/j.idcr.2020.e00868]

31 **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**: 929-930 [PMID: 32524794 DOI: 10.3348/kjr.2020.0426]

32 **Ahluwalia AS**, Qarni T, Narula N, Sadiq W, Chalhoub MN. Bilateral pneumothorax as possible atypical presentation of coronavirus disease 2019 (COVID-19). *Respir Med Case Rep* 2020; **31**: 101217 [PMID: 32934903 DOI: 10.1016/j.rmcr.2020.101217]

33 **Al-Shokri SD**, Ahmed AOE, Saleh AO, AbouKamar M, Ahmed K, Mohamed MFH. Case Report: COVID-19-Related Pneumothorax-Case Series Highlighting a Significant Complication. *Am J Trop Med Hyg* 2020; **103**: 1166-1169 [PMID: 32662394 DOI: 10.4269/ajtmh.20-0713]

34 **Chen X**, Zhang G, Tang Y, Peng Z, Pan H. The coronavirus diseases 2019 (COVID-19) pneumonia with spontaneous pneumothorax: a case report. *BMC Infect Dis* 2020; **20**: 662 [PMID: 32907540 DOI: 10.1186/s12879-020-05384-x]

35 **Xiang C**, Wu G. SARS-CoV-2 pneumonia with subcutaneous emphysema, mediastinal emphysema, and pneumothorax: A case report. *Medicine (Baltimore)* 2020; **99**: e20208 [PMID: 32443345 DOI: 10.1097/MD.0000000000020208]

36 **Al-Azzawi M**, Douedi S, Alshami A, Al-Saoudi G, Mikhail J. Spontaneous Subcutaneous Emphysema and Pneumomediastinum in COVID-19 Patients: An Indicator of Poor Prognosis? *Am J Case Rep* 2020; **21**: e925557 [PMID: 32703927 DOI: 10.12659/AJCR.925557]

37 **Aiolfi A**, Biraghi T, Montisci A, Bonitta G, Micheletto G, Donatelli F, Cirri S, Bona D. Management of Persistent Pneumothorax With Thoracoscopy and Bleb Resection in COVID-19 Patients. *Ann Thorac Surg* 2020; **110**: e413-e415 [PMID: 32353441 DOI: 10.1016/j.athoracsur.2020.04.011]

38 **Abushahin A**, Degliuomini J, Aronow WS, Newman T. A Case of Spontaneous Pneumothorax 21 Days After Diagnosis of Coronavirus Disease 2019 (COVID-19) Pneumonia. *Am J Case Rep* 2020; **21**: e925787 [PMID: 32798215 DOI: 10.12659/AJCR.925787]

World Journal of Respirology

Submit a Manuscript: https://www.f6publishing.com

World J Respirol 2021 August 8; 11(1): 12-17

DOI: 10.5320/wjr.v11.i1.12

ISSN 2218-6255 (online)

CASE REPORT

Like father, like son: Pulmonary thromboembolism due to inflammatory or hereditary condition? Two case reports

Pedro Hannun, Walter Hannun, Hugo Hyung Yoo, Lucilene Resende

ORCID number: Pedro Hannun 0000-0003-1508-5361; Walter Hannun 0000-0002-7044-4905; Hugo Hyung Yoo 0000-0003-3226-2788; Lucilene Resende 0000-0002-7635-2016.

Author contributions: All authors were responsible for the study conception and design; Hannun P wrote the manuscript; all authors contributed to the manuscript revision and final version approval.

Informed consent statement: Informed written consent for publication of this report and use of any accompanying images was obtained from both patients.

Conflict-of-interest statement: The authors report no conflict of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Pedro Hannun, Hugo Hyung Yoo, Lucilene Resende, Department of Internal Medicine, Botucatu Medical School, São Paulo State University - UNESP, São Paulo 18618-687, Brazil

Walter Hannun, Department of Institutional Relations, Santa Catarina Hospital, São Paulo 01310-000, Brazil

Corresponding author: Pedro Hannun, MHSc, Department of Internal Medicine, Botucatu Medical School, São Paulo State University - UNESP, Prof. Mário Rubens Guimarães Montenegro Avenue, s/n, São Paulo 18618-687, Brazil. pgch2003@gmail.com

Abstract

BACKGROUND

Venous thromboembolism, which includes deep venous thrombosis and pulmonary embolism, is a well-known causal disorder with high morbidity and mortality rates. Inherited or acquired conditions affecting components of coagulation and fibrinolysis systems have been linked to venous thromboembolism pathogenesis as they may lead to a pro-inflammatory state in human bodies. Toxoplasmosis is a zoonosis that potentially leads to acute systemic cachectic-inflammatory effects in experimental animal models but is not yet proven in humans. It is known that venous thrombosis can occur during acute inflammatory/infectious diseases, although it is not well established with regard to toxoplasmosis alone.

CASE SUMMARY

A 70-year-old Caucasian man and his 32-year-old son developed general malaise, chills, fever, and myalgia, having established a diagnosis of toxoplasmosis. Twenty days later, they presented dry cough leading to further investigations that revealed an incidental deep venous thrombosis plus pulmonary embolism in them both. Thrombophilia screening showed both patients had a factor V Leiden mutation heterozygosis. Father and son completely recovered without any sequalae after anticoagulant treatment. They have not presented symptom recurrence of either medical disorder during 1 year of follow-up.

CONCLUSION

Toxoplasmosis may enhance the risk of venous thromboembolism in patients showing factor V Leiden mutation heterozygosis.

Key Words: Factor V Leiden mutation; Thrombophilia; Venous thromboembolism; Deep

Manuscript source: Unsolicited manuscript

Specialty type: Respiratory system

Country/Territory of origin: Brazil

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: March 7, 2021
Peer-review started: March 7, 2021
First decision: May 6, 2021
Revised: May 17, 2021
Accepted: July 14, 2021
Article in press: July 14, 2021
Published online: August 8, 2021

P-Reviewer: Protopapas AA
S-Editor: Zhang H
L-Editor: Filipodia
P-Editor: Li JH

venous thrombosis; Toxoplasmosis; Inflammation; Case report

Core Tip: This paper describes two closely related patients simultaneously infected by *Toxoplasma gondii* who concurrently presented their first venous thromboembolism episode. Further investigation revealed a factor V Leiden mutation in them both. The association between these two morbid conditions suggests that systemic infection/inflammation may enhance the risk of venous thromboembolism in people carrying this kind of pro-thrombophilia mutation. As far as we know, this is the first report of that association. We believe that this paper provides an insight into this important issue bringing potential help for clinical decision-making processes by doctors around the world.

Citation: Hannun P, Hannun W, Yoo HH, Resende L. Like father, like son: Pulmonary thromboembolism due to inflammatory or hereditary condition? Two case reports. *World J Respirol* 2021; 11(1): 12-17
URL: https://www.wjgnet.com/2218-6255/full/v11/i1/12.htm
DOI: https://dx.doi.org/10.5320/wjr.v11.i1.12

INTRODUCTION

Inflammation and coagulation are intrinsically related processes that communicate at various levels; either can be the cause or consequence of the other[1,2]. The mechanism that links inflammation (originally infectious or not) and thrombosis is complex and not fully understood. The most commonly accepted hypothesis states that aseptic inflammations or infection-related inflammations promote the secretion of several cellular mediators, mostly related to the innate immune response. Inflammation activates endothelial cells, leukocytes, and platelets, resulting in cell dysfunction and/or injury and platelet aggregation[2]. Concomitantly, an infection can result in antiphospholipid antibodies that trigger the overproduction of tissue factor and thromboxane A_2[3]. All together this could initiate the blood clotting cascade[1,2].

Toxoplasmosis, a common zoonosis caused by the *Toxoplasma gondii* protozoan, is a systemic infection that may cause cachectic-inflammatory effects in experimental animal models[4] and even the development of antiphospholipid syndrome in humans [3,5]. Hence, toxoplasmosis by itself might eventually provoke a venous thromboembolism (VTE) event in a given patient.

In addition to having toxoplasmosis, our studied patients carried factor V Leiden (FVL) mutation heterozygosis, a well-known cause of thrombophilia. The combination of these two morbid conditions might have increased the risk of VTE in both patients.

CASE PRESENTATION

Chief complaints

A 70-year-old Caucasian man and his 32-year-old son had developed general malaise, chills, fever, and myalgia. Dry cough appeared approximately 20 d after initial symptoms in both patients.

History of present illness

At the beginning of 2019, a 70-year-old Caucasian man and his 32-year-old son had lunch together at a steakhouse in São Paulo City, Brazil. After 5 d, the older man developed general malaise, chills, fever, and myalgia; he also noticed enlarged cervical and occipital lymph nodes. One week later, he took a 10 h flight to the United States remaining abroad for 10 d without any clinical improvement. During this time, his son who had stayed in Brazil, started having similar symptoms. About 20 d later they both developed a persistent dry cough. One month after initial symptoms, they were hospitalized after being radiologically diagnosed with pulmonary thromboembolism.

History of past illness

The older man had a prostatic carcinoma *in situ* operated 5 years earlier; he was also a former smoker.

The younger had only a right shoulder capsuloplasty 9 years earlier; he was a non-smoker.

Personal and family history

The older man had current controlled hypertension and type II diabetes. There was no history of family disorders.

Physical examination

The relevant findings were enlarged cervical and occipital lymph nodes in both patients and muscular stiffness in the right calf of the younger man.

There were no respiratory signs or low oxygen saturation levels on room air.

Laboratory examinations

The following laboratory tests were normal in both patients: Blood cell count, prothrombin time, activated partial thromboplastin time, four hereditary alterations for thrombophilia (protein C, protein S, and antithrombin serum levels; G20210A prothrombin gene mutation search), and three acquired alterations for thrombophilia (anticardiolipin antibodies, anti-beta- 2-glycoprotein I antibodies, and lupus anticoagulant).

Tests with abnormal results in both patients were (Table 1): Presence of high serum C-reactive protein, presence of positive IgM antibodies for *Toxoplasma gondii*, and presence of FVL mutation heterozygous status (gene F5, c.691G>A, p.R506Q).

D-dimers were only analyzed in the older patient with a high result.

Imaging examinations

Imaging studies are shown in Table 1.

In the father, pulmonary computed tomography angiography showed bilateral pulmonary embolism (Figure 1A), and a further Doppler ultrasound (US) found deep venous thrombosis (DVT) in the left lower limb (anterior tibial, posterior tibial, and fibular veins). In the son, pulmonary computed tomography angiography and Doppler US respectively showed a bilateral pulmonary embolism (Figure 1B) and DVT in the right lower limb (anterior tibial, posterior tibial, fibular, and popliteal veins).

FINAL DIAGNOSIS

The final diagnosis of both patients was identical, corresponding to pulmonary VTE associated with acute toxoplasmosis plus FVL heterozygous mutation status.

TREATMENT

Although clinically stable, both patients were admitted to the hospital to start anticoagulant therapy with enoxaparin (60 mg, subcutaneously, twice a day for 4 d) followed by rivaroxaban (15 mg, orally, twice a day) according to local standards. They were discharged completely free of symptoms, under oral anticoagulation for 1 year.

Regarding toxoplasmosis, treatment of immunocompetent adults with lymphadenopathic toxoplasmosis is rarely indicated due to its usually self-limited evolution[6]. The only prescription being bed rest.

OUTCOME AND FOLLOW-UP

Father and son have totally recovered without sequelae. After 1 year of follow-up, patients have not presented a recurrence of either morbid condition.

Table 1 Laboratory tests and imaging studies for both patients showing altered findings

Laboratory tests and imaging studies	Father (older patient)	Son (younger patient)	Normal values and conditions
C-reactive protein (mg/L)	4.6	44.8	< 1.2
Toxoplasma gondii IgM antibodies (UI/mL)	19.8	30.8	< 0.5
FVL mutation status (gene F5, c.691G>A, p.R506Q)	Heterozygosis	Heterozygosis	Unmutated
D-dimer (ng/mL)	5.724	Not performed	< 500
Lower limbs Doppler ultrasound	Absent blood flow in anterior tibial, posterior tibial, and fibular veins in the left leg	Absent blood flow in anterior tibial, posterior tibial, fibular, and popliteal veins in the right leg	Presence of blood flow in the veins
Chest CT scan	Filling defects in segmental and subsegmental arterial branches in upper and lower lobes of both lungs (Figure 1A)	Filling defects in segmental and subsegmental arterial branches in lower lobes of both lungs and in apical subsegmental artery of right lung(Figure 1B)	Absence of filling defects in the arteries

FVL: Factor V Leiden; CT: Computed tomography.

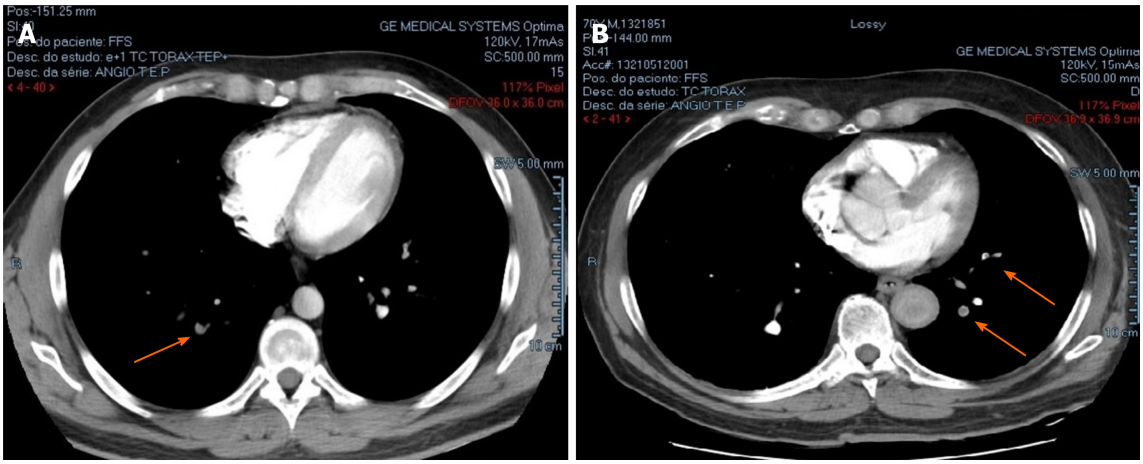

Figure 1 Pulmonary computed tomography angiography. A: Father's pulmonary computed tomography angiography transversal slice of lungs showed filling defects in subsegmental arterial branches characterizing left pulmonary embolism (arrows); B: Son's pulmonary computed tomography angiography transversal slice of lungs showed right pulmonary embolism (arrow).

DISCUSSION

Toxoplasmosis is a usually asymptomatic zoonosis with wide geographical distribution. According to the São Paulo Sanitary Surveillance Agency, at the beginning of 2019 there was an increased number of acute toxoplasmosis cases in São Paulo City, including asymptomatic cases only detected by positive serological tests due to a foodborne disease outbreak. Of the 165 notified cases, only 9% had severe complications, none being DVT or pulmonary embolism[7].

The relationship between toxoplasmosis and venous thrombosis is uncertain. There is evidence of direct[8,9] and indirect[3,5] toxoplasmosis effects that may lead to thrombotic events. Toxoplasmosis was described as resulting in cerebral vein thrombosis in severe cases of its congenital form in humans[8]. Placental thrombosis was also seen in abortions during experimental *Toxoplasma gondii* infection in sheep [9]. However, indirect toxoplasmosis effects have been more consistently reported in literature, especially human Toxoplasma-induced antiphospholipid syndrome[3,5]. However, our studied cases did not show positivity for any antibodies related to antiphospholipid syndrome.

Being a systemic infectious disease, the potential for toxoplasmosis to trigger a venous thrombosis *via* an inflammatory pathway cannot be neglected[1,2], especially in patients with FVL mutation heterozygous status, the most common type of inherent thrombophilia[10]. In association with a pre-existing prothrombotic state, the inflam-

matory and pro-hemostatic environment caused by the infection may have caused endothelial dysfunction and changes in coagulation homeostasis resulting in VTE[2]. Considering a scenario without direct endothelial damage, it is also possible that the inflammation itself had increased the genetic expression of tissue factor (factor III), thus initiating the extrinsic coagulation pathway[2]. These two hypothetical situations would favor activation of mutated factor V, therefore amplifying thrombus formation given the mutated factor V resistance to activated protein C[2].

Some experimental and clinical studies corroborate the interaction between congenital thrombophilia and systemic infections/sepsis leading to exacerbation of thrombotic activity[11-13]. Although they differ regarding the impact of the thrombophilia gene mutation heterozygosis on survival of infected individuals, most agree that there is a significant increase in thrombin generation markers and in the conversion of fibrinogen to fibrin, both of which represent more frequent and severe episodes of thrombosis[11-13].

Regarding other predisposing factors for DVT, only the older of the two patients had a long period of immobility during a flight concurrently with toxoplasmosis. It is also important to highlight that both patients had undergone previous surgeries with no venous thrombosis.

Considering father and son had been living with the FVL heterozygous mutation throughout their lives without any thrombotic events, it does not seem a simple coincidence that they both simultaneously had VTE with concurrent toxoplasmosis.

CONCLUSION

This paper reports the unusual clinical cases of two closely related patients carrying the hereditary thrombophilia FVL heterozygous mutation who have concomitantly experienced the so far only VTE episode during concurrent *Toxoplasma gondii* acute infection. Their sharing of these three events does not seem to be mere coincidence and suggests a potential synergistic effect between toxoplasmosis and heterozygous mutation state for FVL as triggers of the thromboembolic events.

REFERENCES

1 **Perez-Pujol S**, Aras O, Escolar G. Factor v leiden and inflammation. *Thrombosis* 2012; **2012**: 594986 [PMID: 22666576 DOI: 10.1155/2012/594986]

2 **Aksu K**, Donmez A, Keser G. Inflammation-induced thrombosis: mechanisms, disease associations and management. *Curr Pharm Des* 2012; **18**: 1478-1493 [PMID: 22364132 DOI: 10.2174/138161212799504731]

3 **Sène D**, Piette JC, Cacoub P. Antiphospholipid antibodies, antiphospholipid syndrome and infections. *Autoimmun Rev* 2008; **7**: 272-277 [PMID: 18295729 DOI: 10.1016/j.autrev.2007.10.001]

4 **Hatter JA**, Kouche YM, Melchor SJ, Ng K, Bouley DM, Boothroyd JC, Ewald SE. Toxoplasma gondii infection triggers chronic cachexia and sustained commensal dysbiosis in mice. *PLoS One* 2018; **13**: e0204895 [PMID: 30379866 DOI: 10.1371/journal.pone.0204895]

5 **Shapira Y**, Agmon-Levin N, Selmi C, Petríková J, Barzilai O, Ram M, Bizzaro N, Valentini G, Matucci-Cerinic M, Anaya JM, Katz BS, Shoenfeld Y. Prevalence of anti-Toxoplasma antibodies in patients with autoimmune diseases. *J Autoimmun* 2012; **39**: 112-116 [PMID: 22297145 DOI: 10.1016/j.jaut.2012.01.001]

6 **Montoya J**, Boothroyd J, Kovacs J. Toxoplasma gondii. In: Mandell G, Bennett J, Dolin R, Eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 8th ed. Philadelphia: Churchill Livingstone Elsevier, 2017: 3122-3153

7 **Coordenadoria de Vigilância em Saúde de São Paulo**. Toxoplasmose: Boletim epidemiológico, São Paulo, n 1, 2019. [cited 2021 Mar 7]. Available from: https://www.prefeitura.sp.gov.br/cidade/secretarias/upload/saude/boletim_toxoplasmose_2019.pdf

8 **Wiebe B**, Fremerey C, Ehlen M. 539 Severe form of Congenital Toxoplasmosis with Extensive Cerebral findings. *Arch Dis Childhood* 2012; **97**: A156-A7 [DOI: 10.1136/archdischild-2012-302724.0539]

9 **Castaño P**, Fuertes M, Ferre I, Fernández M, Ferreras Mdel C, Moreno-Gonzalo J, González-Lanza C, Katzer F, Regidor-Cerrillo J, Ortega-Mora LM, Pérez V, Benavides J. Placental thrombosis in acute phase abortions during experimental Toxoplasma gondii infection in sheep. *Vet Res* 2014; **45**: 9 [PMID: 24475786 DOI: 10.1186/1297-9716-45-9]

10 **Campello E**, Spiezia L, Simioni P. Diagnosis and management of factor V Leiden. *Expert Rev Hematol* 2016; **9**: 1139-1149 [PMID: 27797270 DOI: 10.1080/17474086.2016.1249364]

11 **Kondaveeti S**, Hibberd ML, Booy R, Nadel S, Levin M. Effect of the Factor V Leiden mutation on the severity of meningococcal disease. *Pediatr Infect Dis J* 1999; **18**: 893-896 [PMID: 10530586

DOI: 10.1097/00006454-199910000-00011]

12 **Kerlin BA**, Yan SB, Isermann BH, Brandt JT, Sood R, Basson BR, Joyce DE, Weiler H, Dhainaut JF. Survival advantage associated with heterozygous factor V Leiden mutation in patients with severe sepsis and in mouse endotoxemia. *Blood* 2003; **102**: 3085-3092 [PMID: 12869495 DOI: 10.1182/blood-2003-06-1789]

13 **Elmas E**, Suvajac N, Jilma B, Weiler H, Borggrefe M, Dempfle CE. Factor V Leiden mutation enhances fibrin formation and dissolution in vivo in a human endotoxemia model. *Blood* 2010; **116**: 801-805 [PMID: 20410502 DOI: 10.1182/blood-2009-03-213215]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com