Contarini's Syndrome in a COVID-19 Positive Patient with Viral Myocarditis and Diabetic Ketoacidosis: A Case Report

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ABSTRACT

Contarini's syndrome refers to the occurrence of bilateral pleural effusion which has different causes for each hemithorax. Based on extensive literature search, this is a rare finding and to date, only two published cases have recorded tuberculous effusion on one side. In this paper, the authors aim to present a case of Contarini's syndrome, and to give emphasis that such condition with different etiologies exists and should be considered in managing bilateral effusion.

This is a case of a 69-year-old female with a 7-week history of dyspnea, 2-pillow orthopnea, fever, and right-sided chest discomfort. Patient sought consultation and was prescribed with Diclofenac and Cefalexin with no relief. Patient was then admitted and intubated due to worsening dyspnea. Patient was managed as COVID-19 confirmed critical with viral myocarditis, CAP-HR, and diabetic ketoacidosis. Initial chest x-ray showed right-sided pleural effusion. Thoracentesis was done and revealed exudative pleural fluid (PF) with WBC of 20,000 with neutrophilic predominance and negative RT-PCR MTB. Cytology revealed acute inflammatory pattern. *Klebsiella pneumoniae* ESBL was isolated. Antibiotics were shifted to levofloxacin and meropenem. Repeat chest x-ray showed left-sided pleural effusion. Thoracentesis was done and revealed exudative PF with WBC of 1,680 with neutrophilic predominance. No organism was isolated. RT-PCR for MTB was detected. Thus, anti-TB therapy was initiated. However, ETA TB culture showed resistance to isoniazid, rifampicin, and pyrazinamide. Patient was referred to PMDT for MDR-TB treatment. Bilateral effusion has resolved with no recurrence, and with uneventful removal of bilateral chest tubes. Patient was eventually extubated and transferred to the ward. Patient however developed HAP, was re-intubated and eventually expired due to the septic shock from VAP.

This case report highlights the importance of weighing risk versus benefit in deciding to perform bilateral thoracentesis when there is a clinical suspicion of an alternate or concurrent diagnosis.

Keywords: Contarini's syndrome, pleural effusion, pleural fluid, thoracentesis, COVID-19, case report

INTRODUCTION

Bilateral pleural effusion is not an uncommon finding and usually has a single etiology. This can be secondary from a known malignancy, infection or heart failure. Contarini's syndrome refers to the occurrence of bilateral pleural effusion which has different causes for each hemithorax. Based on extensive literature search, this is a rare finding. To date, there are only two published Contarini's syndrome cases that recorded a tuberculous effusion on one side. First published case was with a contralateral empyema by Dixit R et al.[1] in 2004 and the second one was with a pancreatic effusion by Vijayan S et al.[2] in 2021. In this paper, the authors aim to present a case of Contarini's syndrome, and to give emphasis that such condition with different etiologies exists and should be considered in managing bilateral effusion.

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CASE PRESENTATION

This is a case of a 69-year-old female who presented with a 7-week history of exertional dyspnea associated with 2-pillow orthopnea. One week prior to admission, patient had onset of anorexia, generalized weakness, undocumented fever, right sided chest discomfort, and increased work of breathing. Patient denies cough, headache, nausea, vomiting, weight loss, and orthopnea. Three days prior to admission, patient sought consult with local physician and was given Diclofenac 50 mg/tab 1 tab as needed and Cefalexin 500 mg/tab 1 tab twice a day for seven days with no afforded relief. Patient was then brought to a local primary hospital due to worsening of dyspnea where chest x-ray revealed pleural effusion on right hemithorax. Patient was then referred to a tertiary hospital for admission.

Patient has no known comorbidities prior to admission. Previous surgery includes exploratory laparotomy total abdominal hysterectomy bilateral salpingo-oophorectomy with appendectomy in 2017 for alleged uterine myoma. Patient received two primary doses of COVID-19 vaccines in July 2021. Patient denies food and drug allergies. Family history includes Type II Diabetes Mellitus. Patient is non-smoker, non-alcoholic drinker, and denies illicit drug use. Patient previously worked as a dressmaker. She is a G10 P8 (8028) and currently on menopausal stage.

On admission, patient was initially hooked to oxygen support at 15 Lpm via face mask due to desaturation as low as 84%. Pertinent physical examination included decreased breath sounds at right mid to basal areas with clear breath sounds on the left. Patient however was intubated due to worsening dyspnea. COVID RT-PCR swab turned out positive and thus was admitted at the COVID ICU.

Patient was managed as COVID-19 confirmed critical with viral myocarditis, community acquired pneumonia high risk, and diabetic ketoacidosis. Piperacillin-Tazobactam 4.5gm IV every 6 hours, Azithromycin 500 mg IV every 24 hours, Remdesivir 200 mg on Day 1 then 100 mg on days 2-5, Dexamethasone 6 mg IV once a day for 10 days, Enoxaparin 0.6ml subcutaneously every 12 hours, N-Acetylcysteine 600 mg 1 tab twice a day, and Salbutamol Ipratropium 100 mcg/20 mcg MDI, 2 puffs every 6 hours were started. Patient underwent hemoperfusion due to increasing inflammatory markers.

Initial chest x-ray showed right-sided pleural effusion (Figure 1A). Ultrasound guided thoracentesis at right hemithorax was done, drained 400 ml of turbid reddish yellow output, with noted slight decrease in pleural effusion on repeat chest x-ray (Figures 1B and 1C) and studies (Table 1) revealed exudative nature with WBC of 20,000 with neutrophilic predominance 89%, Bacteria 3+/HPF, elevated glucose (PF 9.6 mmol/L HIGH and Serum 17.1), total protein 0.91 (PF 49.09 g/L: Serum TP 54), LDH 21.51 (PF 13,250 IU/L: Serum LDH 616), low triglycerides 0.42 and cholesterol <1.29, and negative RT-PCR MTB. Cytology revealed acute inflammatory pattern. *Klebsiella pneumoniae* ESBL was isolated on culture. Antibiotics were then shifted to Levofloxacin 750 mg IV every 24 hours and Meropenem 1g IV as loading dose then 500 mg IV every 8 hours. Both were given for two weeks. However, due to interval increase of pleural effusion at right, chest tube insertion at right hemithorax was eventually performed (Figure 1D). Serial chest x-ray tests along with CTT output monitoring every shift were done as follow up and monitoring of the effusion. No diagnostic challenges were experienced nor any deviation in therapeutic intervention. When the effusion resolved with noted decreased output, CTT at right was removed.

Table 1. Result of Pleural Fluid Studies

Pleural Fluid	Right	Left
Characteristics	Dark turbid reddish	Turbid yellow
Culture	*Klebsiella pneumoniae*	No growth
AFB	Negative	Negative
RT-PCR MTB	MTB not detected	MTB detected, RIF resistance not detected
Cell block cytology	Acute inflammatory pattern	Acute inflammatory pattern
Cell count ***Diff count***	RBC 9,500 x 10^6/L WBC 20,000 x 10^6/L Neutrophil 89% Lymphocyte 11% Bacteria 3+/ HPF	RBC 4,530 x 10^6/L WBC 1,680 x 10^6/L Neutrophil 71% Lymphocyte 29%
LDH	PF 13,250 IU/L Serum 616 IU/L PF: Serum 21.51	PF 309 IU/L Serum 216 IU/L PF: Serum 1.43
Total protein	PF 49.09 g/L Serum 54 g/L PF: Serum 0.91	PF 41 g/L Serum 44 g/L PF: Serum 0.93
Glucose	PF 9.6 mmol/L Serum 17.1 mmol/L	PF 9.4 mmol/L Serum 6.9 mmol/
Light's Criteria	Exudative	Exudative
Triglycerides	0.42 mmol/L (Low)	Not done
Cholesterol	<1.29	Not done

On follow up imaging (Figures 1C, 1D, and 2A), repeat chest x-ray showed increasing left-sided pleural effusion. Pertinent physical examination at this time was new finding of decreased breath sounds at left basal areas. Ultrasound-guided thoracentesis at left hemithorax was done, drained 10mL of turbid yellow fluid and studies (Table 1) revealed exudative pleural fluid with WBC of 1,680 with neutrophilic predominance 71%. There was only minimal interval decrease of pleural effusion at left (Figure 2B). No organism was isolated on Gram stain and culture. AFB smear was negative but RT-PCR for MTB was low with rifampicin and isoniazid resistance not detected. Thus, anti-TB therapy (Isoniazid 75 mg + Rifampicin 150 mg + Pyrazinamide 400 mg + Ethambutol 275 mg/tab 4 tabs once a day) was initiated. Fungal culture had no growth after 14 days. Due to progression of pleural fluid at left on serial chest x-rays

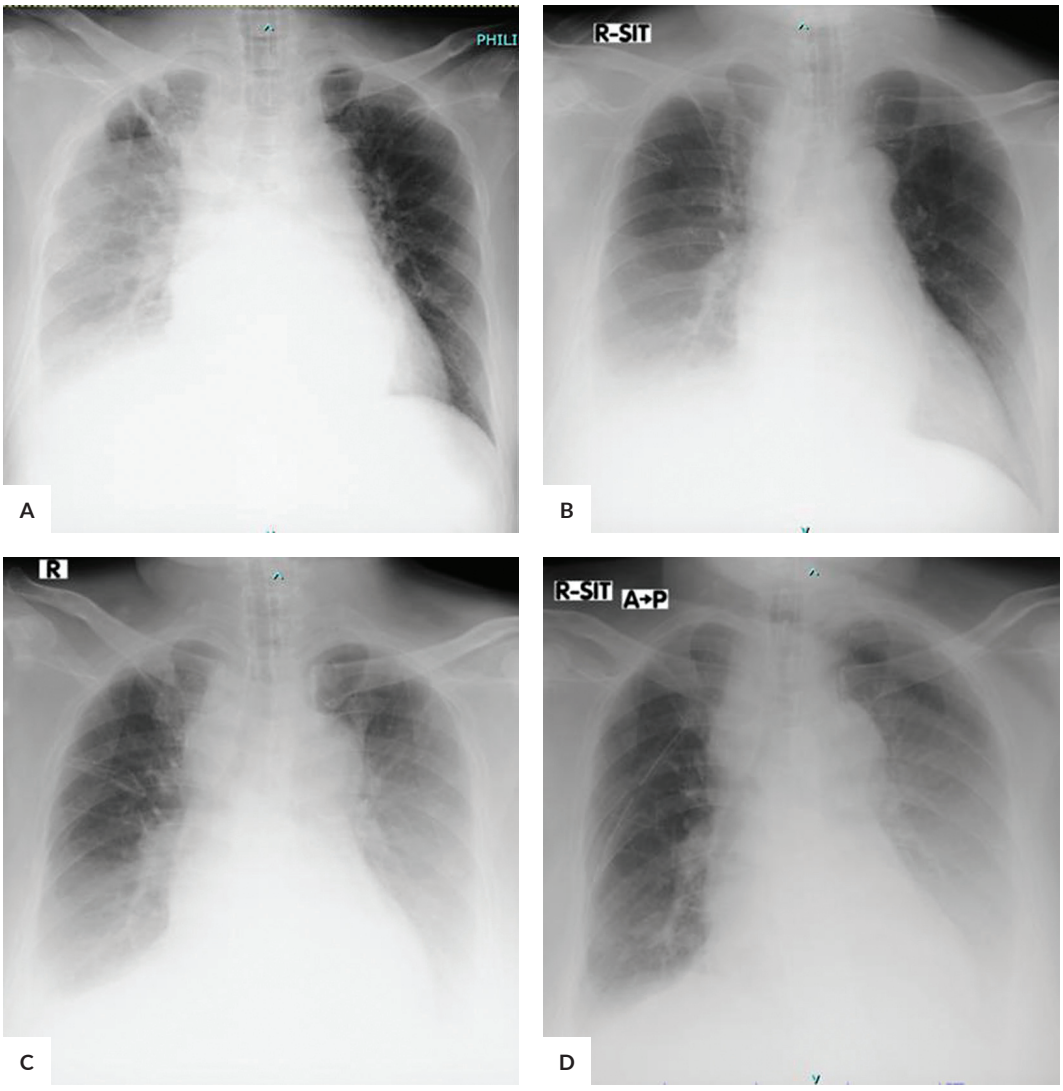

Figure 1. ***Serial chest x-ray done to show pleural effusion at right hemithorax.*** **(A)** Chest x-ray was taken during admission with noted pleural effusion at the right hemithorax. **(B)** Chest x-ray was taken after thoracentesis at right hemithorax with 400cc pleural fluid output. **(C)** On 6th day, chest x-ray showed still with effusion at the right and new onset of effusion at the left. **(D)** Chest x-ray done post-CTT insertion at the right and noted progression of effusion at the left.

(Figure 2C) and recurrent dyspnea, chest tube insertion at left hemithorax was done (Figure 2D) and drained 600cc of seropurulent fluid. Likewise, serial chest x-ray imaging and CTT output monitoring were done. After resolution of effusion at left, CTT was removed.

Cardiac cause was also worked up as contributory cause of dyspnea. Troponin I was 79 times elevated than normal, and 12-lead ECG showed sinus tachycardia with concave ST elevations at leads I, II, aVF, V5, V6. Patient was initially treated as ACS STEMI, loaded with Aspirin and Clopidogrel. Enoxaparin and Atorvastatin were also started. Echocardiography revealed mildly dilated left atrium with otherwise chamber sizes appear normal, with normal left ventricular (LV) wall thickness, no wall motion abnormality, LVEF visually estimated at 55-60%, normal RV systolic function, unremarkable valves, normal IVC, and no pericardial effusion. Coronary angiogram revealed normal coronaries. Serial ECG showed normal sinus rhythm. Although cardiac biomarkers were initially elevated, values went down to normal on serial monitoring. At this time, viral myocarditis was the cardiac working impression.

Admitting and succeeding capillary blood glucose were elevated with noted metabolic acidosis on arterial blood gas and ketones on urinalysis. Patient was then also managed as Diabetic Ketoacidosis. Insulin drip was started and titrated accordingly.

After three weeks, ETA TB culture showed resistant to isoniazid, rifampicin, and pyrazinamide. Patient was for

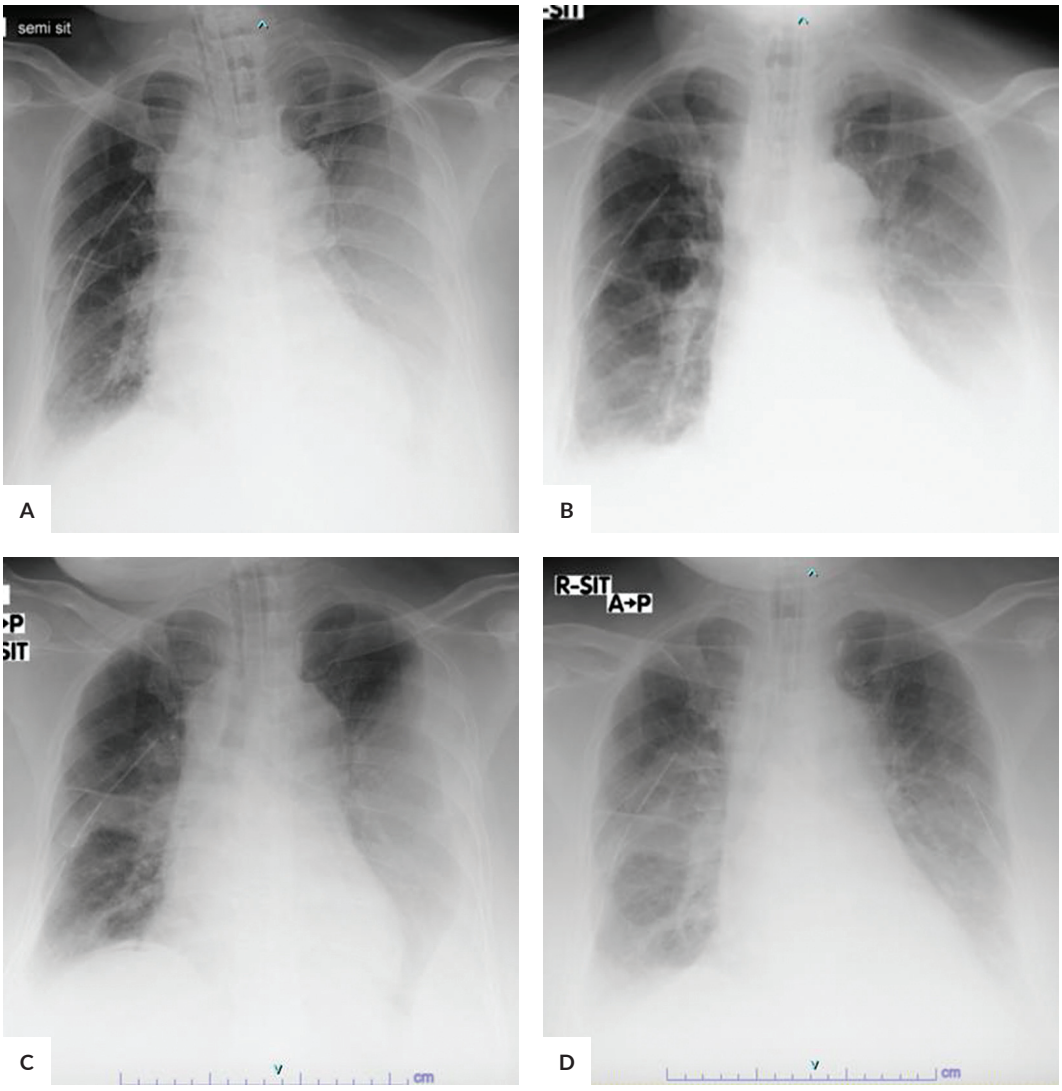

Figure 2. ***Serial chest x-ray done to show pleural effusion at left hemithorax.*** **(A)** Chest x-ray done during 10th hospital day with noted increasing left pleural effusion. **(B)** On 11th hospital day, repeat chest x-ray done after thoracentesis at left hemithorax. **(C)** On 14th Hospital day, noted progression of pleural effusion at left hemithorax. **(D)** On 15th hospital day, chest tube insertion done at left hemithorax and drained 600cc seropurulent fluid.

referral to Programmatic Management of Drug Resistant Tuberculosis (PMDT) for line probe assay for 2nd line treatment. HRZE was discontinued. Patient however was not started on MDRTB regimen. In addition to the above working impression, patient was also managed as right exudative pleural effusion with ESBL-producing *Klebsiella pneumoniae* isolate and with a left tuberculous effusion. *Acinetobacter baumannii* was isolated in blood. Antibiotics were completed for 14 days. Patient was eventually extubated and hooked to nasal cannula at 2lpm. Patient was then cleared for transfer to non-COVID ward after 28 days in the ICU. Patient however developed hospital acquired pneumonia and was re-intubated due to dyspnea and desaturation. Patient eventually expired after an addition of 26 days in the hospital due to septic shock from ventilator-associated pneumonia after being re-intubated.

DISCUSSION

Bilateral pleural effusion from different etiology is uncommon. According to a review by Porcel et al.[3], out of 2605 patients, 21% had bilateral effusion and only 0.9% had bilateral effusion with different cause. There were only 12 cases who had Contarini syndrome and four of these had chylothorax and malignant effusion.

Bilateral thoracentesis is seldom justified in routine practice. According to Jany et al.[4], patients with bilateral pleural effusions do not always need to have a diagnostic or

therapeutic thoracentesis. However, diagnostic thoracentesis is indicated if the patient has symptoms that are not compatible with the size of effusion or lack of response to treatment. In addition, according to a study of Ferreiro et al.[5], in almost 95% of bilateral pleural effusion cases, the etiology is similar in both sides. Furthermore, after analyzing cases of bilateral thoracentesis, experts recommend this approach in patients with unilateral parenchymal lung involvement, significantly disparate-sized effusions, markedly different attenuation values or appearance on CT, with atypical clinical findings such as fever or pleuritic chest pain, and no resolution of pleural effusion only on one side. However, it should be stressed that these are expert, rather than evidence-based, recommendations. This was also supported by the study of Kalomenidis that suggests diagnostic thoracentesis if there is a specific clinical indication.[6]

In our patient, due to the radiologic and clinical findings that might suggest increasing pleural effusion of new onset, it was the clinical judgement of the physician to weigh the risk and potential benefit of doing bilateral thoracentesis. This is considered the strength of this paper. Patient would benefit from the additional information and physicians will be guided on the most appropriate management. In terms of intervention adherence, our patient was able to tolerate thoracentesis as evidenced by avoidance of iatrogenic complications such as pneumothorax, bleeding, infection, and organ injury. Adverse and unanticipated events are same with unilateral thoracentesis.

Currently, there are no clinical guidelines nor firm recommendations[7] for bilateral pleural effusion. Also, there is no definite mechanism identified why pleural fluid studies resulted to markedly different characteristics. Previous case reports[3] suggested bacterial infections such as parapneumonics and empyema may precipitate an acute decompensation of heart failure, which comprise majority of cases but no data on tuberculous mechanism yet. Thus, serves as a limitation whether it is sufficient to perform a puncture on a single side or whether it is necessary to routinely perform bilateral diagnostic thoracentesis. However, dual diagnosis from performing bilateral thoracentesis and facilitating pleural fluid studies may be beneficial in coming up with more accurate diagnosis leading to an optimal management.

CONCLUSION

Contarini's syndrome is rare but may also be underreported. Physicians should always consider bilateral thoracentesis especially when there is a clinical suspicion of an alternate or concurrent diagnosis as suggested by history, physical exam or radiological studies. Therefore, the rationale to exceptionally do a bilateral diagnostic thoracentesis is to avoid missing highly likely differential diagnoses.

Ethics Approval and Consent

This case report was reviewed by the Ethics Board and was granted exemption for full board review. A written consent was obtained from the patient for reporting and presentation. Patient was fully aware and hopeful of her condition and was informed of the risks and benefits of doing bilateral thoracentesis.

No ethical issues identified in the manuscript.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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