Case Report

Pleural empyema after COVID-19: A delayed presentation

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ABSTRACT

Globally, the number of coronavirus disease-2019 (COVID-19) cases and deaths shows a declining trend since a peak in January 2022. For now, the pandemic phase looks to be ended, until a severe new variant may trigger another wave. At present, in India, small pockets of COVID-19 cases and post-COVID complications are still being reported. Therefore, physicians should remain vigilant about the atypical presentations and potential delayed or long-term complications of SARS-CoV-2 infection, even in individuals who had a mild COVID-19 infection. Here, we present the case of a 52-year-old male patient with a history of hypertension, who is a non-smoker and developed culture-negative pleural empyema 7 months after a mild COVID-19 infection. The patient was successfully treated with antibiotics and early video-assisted thoracoscopic surgery.

Key words: Complicated parapneumonic effusion, Coronavirus disease-2019 India, Post-COVID-19 lung infection, Post-COVID-19 syndrome, Video-assisted thoracoscopic surgery

Since the emergence of SARS-CoV-2 in December 2019, the coronavirus disease-2019 (COVID-19) pandemic had a significant global impact. As of April 2023, according to the World Health Organization, there have been over 764 million confirmed cases and over 6.9 million deaths worldwide [1]. These numbers underscore the severity of the pandemic and the ongoing challenges it presents. The clinical spectrum of COVID-19 varies from asymptomatic or mild illness to severe pneumonia and even death. Existing literature suggests that approximately 80% of reported COVID-19 cases were classified as mild or asymptomatic, with around 15% requiring oxygen support for severe disease and 5% necessitating mechanical ventilation for critical illness. While numerous studies have investigated the clinical characteristics and outcomes of hospitalized COVID-19 patients [2-4], our understanding of the disease course in individuals with no or mild symptoms, particularly in non-hospital settings such as home care, remains limited. Consequently, our knowledge of the long-term effects and chronic pathology in survivors, particularly those with mild disease not requiring hospitalization, is lacking. Recently, there has been emerging evidence of prolonged symptoms in recovered COVID-19 patients, commonly referred to as "post-acute COVID-19 syndrome" or "long COVID syndrome." These lingering symptoms can occur in individuals who initially had either severe or mild disease, including those who were initially asymptomatic.

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In this context, we present a unique case of a 52-year-old male, non-smoker, with a 1-year history of hypertension, who developed left-sided pleural empyema 7 months after the resolution of a mild COVID-19 infection that did not require hospitalization. While there have been reported cases of loculated empyema in hospitalized patients with severe COVID-19 disease and even instances of culture-negative pleural empyema 2 months after the resolution of severe COVID-19 infection that required hospitalization, our case stands out as the patient had only experienced a mild SARS-CoV-2 infection and developed pleural empyema after a 7-month duration [5,6].

CASE REPORT

A 52-year-old male from South India, a non-smoker, with a 1-year history of systemic hypertension and prior COVID-19 infection, presented to us with a 5-day history of intermittent dry cough and low-grade fever accompanied by chills. He also reported a 1-day history of left-sided pleuritic chest pain and breathlessness. There was no history of palpitations, myalgia, arthralgia, vomiting, abdominal pain, diarrhea, dysuria, or increased urinary frequency. There was no recent history of travel. He also denied a prior history of allergy, asthma, and pulmonary tuberculosis. Diagnosed with COVID-19, 7 months ago, he had been home isolated with constant tele-connect with the health-care facility. As he had mild disease, he was managed symptomatically with

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antipyretics, anti-histamines, and multivitamins, according to the state guidelines [7]. With these, he recovered in a week and the SARS-CoV-2 rapid antigen tested negative. There were no residual symptoms such as dyspnea or fatigue after recovery.

Upon presentation to the emergency room, the patient was conscious, oriented, febrile (100°F) with tachycardia of 112 bpm, blood pressure of 140/90 mmHg, respiratory rate of 26 breaths/min, and oxygen saturation of 92% in the room air. Respiratory system examination revealed dullness to percussion, pleural rub, and bronchial breath sounds in the area of the left lower lobe. Examination of the cardiovascular, nervous system, and abdomen were unremarkable.

Initial laboratory investigations revealed neutrophilic leukocytosis, anemia, elevated inflammatory markers (C-reactive protein [CRP]: 19.8; erythrocyte sedimentation rate [ESR]: 100), and elevated blood sugars (Table 1). Chest X-ray showed left lower lobe consolidation and effusion (Fig. 1a). Reverse transcription-polymerase chain reaction for COVID-19 was negative.

He was admitted to the medical intensive care unit and was treated with empirical IV antibiotics (piperacillin-tazobactam, metronidazole), bronchodilator nebulization, unfractionated heparin, NIV with O_2 supplementation, and other supportive measures. High-resolution computed tomography (HRCT) of thorax showed consolidation of the left lower lobe with pleural effusion, left upper lobe fibrosis, and right lower lobe interstitial thickening. There was no obvious septation or pleural thickening.

Thoracic ultrasound showed homogenously anechoic effusion and subsequently, a guided thoracocentesis was done. Pleural fluid analysis indicated borderline complicated parapneumonic effusion as per Light's classification (straw-colored; TC 7200 N90% with pH 7, lactate dehydrogenase of 453 and elevated glucose levels, negative gram stain, and sterile cultures). Tuberculosis workup including Mantoux test and pleural fluid acid–fast bacilli (AFB)/GeneXpert was negative (Table 2). Elevated blood sugar level during the hospital stay was controlled with regular insulin and oral hypoglycemic agents. HbA1c was 5. Despite being on intravenous (IV) antibiotics for 5 days, the patient had a persistent low-grade fever, left-sided

Table 1: Initial investigation results (on admission)

Investigations	Day 1	Day 2	Reference range with units
Total count	16.95	14.74	4.5–11.0×10^3 cells/mm^3
Absolute neutrophil count	14.4	11.3	2.5-6.0×10^3 cells/mm^3
Absolute lymphocyte count	1.69	2.06	1.0-4.8×10^3 cells/mm^3
Hemoglobin	11.7	10.5	14–18 g/dL
PCV	33	29.4	42–50%
Platelet	3.07	3.45	1.5–3.5 L cells/mm^3
ESR	100	90	0–10 mm/hr
CRP	19.8	25.5	0–5 mg/L
Procalcitonin	-	3.8	0.02–0.10 ng/mL
Sodium	134	136	135–145 mmol/L
Potassium	5.1	4	3.5–5.1 mmol/L
Total protein	7	-	6.6–8.7 g/dL
Albumin	3.9	-	3.5–5.5 g/dL
AST	32	-	10–40 U/L
ALT	40	-	10–40 U/L
PT/PT (control)	14/14	-	10–13 s
INR	1.1	-	0.9–1.1
Urea (mg/dL)	21	25	6-24 mg/dL
Creat (mg/dL)	0.8	0.8	0.6–1.2 mg/dL
RBS (mg/dL)	320	180	70-140 mg/dL
HbA1C	5.1	-	4%–5.6%
D-dimer	0.5	2.86	< 0.5 g/L
Ferritin	-	1856	5–200 ng/mL
LDH	174	-	100–200 U/L
Blood culture	No growth	-	-
Urine culture	No growth	-	-
SARS-Cov-2 RT-PCR	Negative	-	-
HIV card test	Non-reactive	-	-
HbSAg	Non-reactive	-	-

PCV: Packed-cell volume, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, PT: Prothrombin time, INR: international normalized ratio, RBS: Random blood sugar, HbA1c: Hemoglobin A1c, LDH: Lactate dehydrogenase, HBsAg: Hepatitis B surface antigen, HIV: Human immunodeficiency virus, RT-PCR: Reverse transcription-polymerase chain reaction

pleuritic chest pain, tachypnea, and inflammatory markers showed an uptrend. Serial chest X- rays and thoracic ultrasound showed rapidly worsening infiltrates and effusion on the left (Fig. 1b). Hence, IV antibiotics (piperacillin-tazobactam, metronidazole) were hiked to meropenem and clindamycin along with IV linezolid for methicillin-resistant *Staphylococcus aureus* coverage. Therapeutic pleural fluid aspiration (320 mL) was repeated under ultrasound guidance and pleural fluid analysis suggested a complicated effusion (straw colored; TC 3300 N95% with pH 6.5, rising lactate dehydrogenase of 965 and low glucose levels, numerous pus cells in gram stain and sterile culture) (Table 2). Repeat HRCT of thorax ruled out any loculations but showed multiple mediastinal lymph nodes. The patient felt very well after completing a 10-day course of antibiotics and was medically fit for discharge based on the bedside observations and clinical response to treatment. However, persistently raised inflammatory markers suggested that the infection had not fully resolved. A repeat chest radiograph demonstrated left lower and mid-zone consolidation with worsening effusion (Fig. 2a). This prompted further investigation with thoracic computed tomography (CT) and subsequently, video-assisted thoracoscopy.

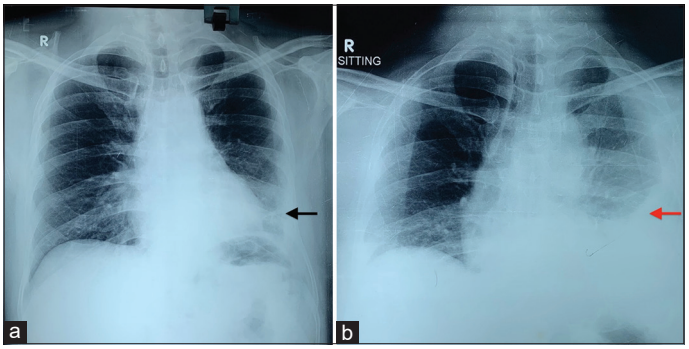

Figure 1: Chest X-ray posteroanterior view (a) day 1: Left lower zone consolidation with mild effusion (black arrow); (b) day 5: Left lower and middle zone consolidation with moderate effusion (red arrow)

The chest tube drainage approach was not successful to relieve the symptomatology and to drain the excess fluid. After a multidisciplinary discussion, a surgical approach was recommended and the patient underwent a minimally invasive thoracic surgery on the left lung. At thoracoscopy, parietal and visceral pleura were found to be thickened and the lung was entrapped and adhered to the chest wall, diaphragm, and mediastinum. Organized pus ~ 500 mL was drained, decortication was done, and pleural/lymph node biopsy specimens were sent for histopathological and microbiological examination. There were no peri and post-procedure complications. Immediate post-procedure chest X-ray showed significant improvement (Fig. 2b). Microbiological examination of the pleura showed pseudomonas species in the tissue culture on enrichment. Histopathological examination (HPE) of pleural specimens showed acute (fibrinous inflammation) on chronic pleuritis (Figs. 3 and 4). There was no evidence of granulomatous pathology, atypia, or malignancy. HPE of the lymph node showed reactive changes only. Tissue GeneXpert was negative and AFB culture was sterile. After the procedure, there was a progressive clinical and radiological improvement with a reduction in the inflammation indices (Fig. 5). Euglycemia was achieved. His hospital stay was complicated with *Klebsiella pneumoniae* infection, which was treated with IV meropenem 1 g/3 times/day for 2 weeks. Intercostal drainage tubes were removed on the 7th post-operative day when fluid was minimal. After 2 weeks, IV antibiotics were changed to oral levofloxacin. The patient was discharged and was serially followed up an on outpatient basis.

DISCUSSION

An important issue in the post-COVID era is the complication and sequelae of COVID-19. More than three-quarters of COVID-19 patients reported having at least one sequela 6 months after the disease onset [8]. Uncommon complications, such

Table 2: Pleural fluid characteristics

Parameter	Results - Day 1	Day 5
Appearance	Straw colored	Straw colored
WBC count (cells/cumm)	7200	3300
Neutrophils (%)	90	93
Lymphocytes (%)	10	5
pH	7	6.5
Total protein (g/dL)	5.2	5.2
Glucose (mg/dL)	187	12
ADA (IU/L)	17.4	22.2
Lactate dehydrogenase (IU/L)	453	965
Cytology	Numerous inflammatory cells, mainly neutrophils	Numerous inflammatory cells, mainly neutrophils, no atypical cells
Gram stain	No organism	Numerous pus cells, no organism
Culture	No growth	No growth
AFB smear	No AFB	-
TB GeneXpert	Negative	-
KOH mount	No fungal elements	-

WBC: White blood cell, ADA: Adenosine deaminase, AFB: Acid–fast bacilli. Normal reference range: pH: 7.60–7.64, Protein: 1–2 g/dL, WBC: <1000/mm^3, Glucose: Similar to that of plasma, LDH: <50% plasma concentration

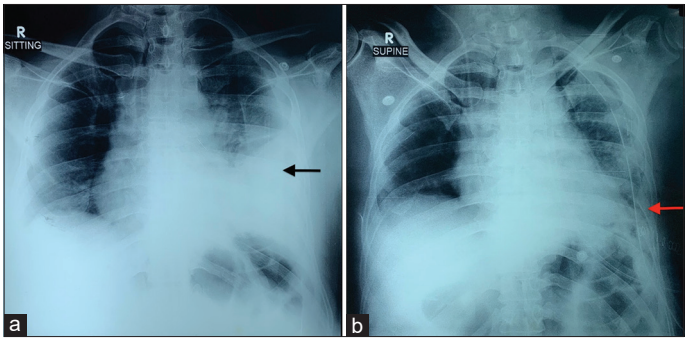

Figure 2: Chest X-ray (a) day 10: Left lower zone and mid zone consolidation with worsening effusion (black arrow); (b): Immediate post-decortication and intercostal drain placement showing left lung expansion (red arrow)

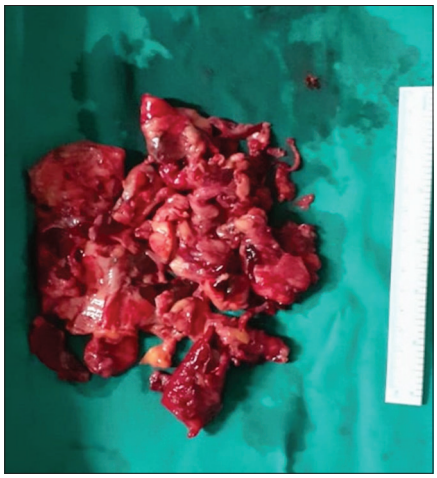

Figure 3: Histopathological examination of pleura - Gross specimen shows organized pus and thickened pleura

as parapneumonic effusions, which can be uncomplicated or complicated, have also been reported. Empyema thoracis which develops from adjacent pneumonia is a form of complicated parapneumonic effusion. It is a relatively uncommon complication but the incidence rate of empyema is increasing globally, especially in developing countries [6,9,10]. The elderly age, severe disease, and prolonged hospitalization were the main risk factors identified. Characteristic findings observed are unilateral exudative effusion with high lactate dehydrogenase (LDH) and pleural fluid-to-serum LDH ratio [10]. Chong WH *et al.* discussed three cases of pleural empyema after bilateral interstitial COVID-19 pneumonia which required combined medical and surgical treatment with open decortication [11]. Silalahi *et al.* reported a case of a 75-year-old patient who developed culture-negative pleural empyema 1 month after COVID-19 resolution without re-infection. The patient was successfully treated with IV antibiotics and chest tube drainage [6]. There was another report of a case with post-COVID-19 pneumonia complicated by Aspergillus empyema and abscess in a 38-year-old woman with a history of poorly controlled type II diabetes mellitus and uncomplicated asymptomatic COVID-19 pneumonia 2 months prior [10]. In this case, a 52-year-old male, with a 1-year history of systemic hypertension and prior COVID-19 infection, currently normotensive on a single antihypertensive drug, was admitted for community-acquired pneumonia with parapneumonic effusion.

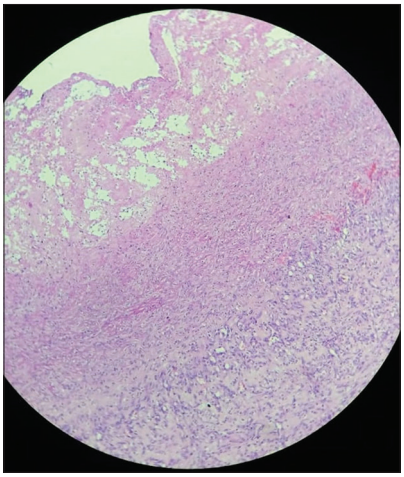

Figure 4: Histopathological examination of pleura – Microscopy H and E (×40) section shows pleura covered by fibrin rich acute inflammatory exudate on surface. Stroma shows fibrocollagenous and adipose tissue with chronic active non-specific inflammation, congestion/hemorrhage, and edema. There is no evidence of granulomatous pathology, atypia, or malignancy

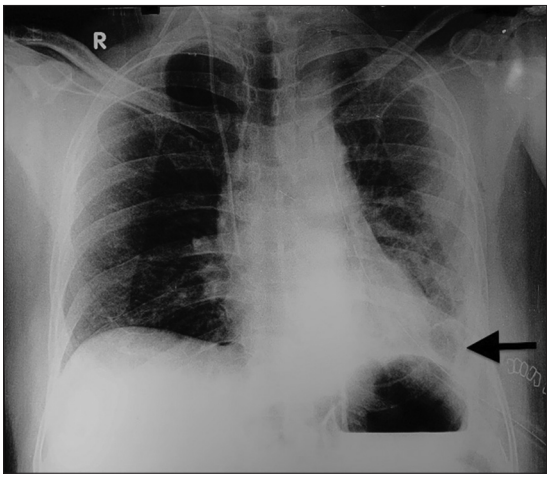

Figure 5: Chest X-ray posteroanterior view on post-operative day 5 shows significant radiological improvement (black arrow)

However, he initially failed to respond to appropriate antibiotic therapy.

As an initial step in investigating a pleural space infection, chest X-rays were combined with additional imaging, revealing a complex septated pleural effusion. Surprisingly, this was not evident on the CT scan. Bedside ultrasound played a crucial role in making the diagnosis and guiding the decision for surgical intervention after failed drainage through a chest tube. The involvement of thoracic surgeons in treating patients with COVID-related complications, as in our case, is becoming increasingly common. The delayed exacerbation of the immune response, persistent inflammation, and the susceptibility of post-COVID lungs to secondary infections are theories proposed to explain these delayed COVID-related complications.

CONCLUSION

Surgical intervention, specifically open decortication, has long been considered the primary approach for managing thoracic

empyema, as non-operative management carries a higher risk of mortality. The occurrence of culture-negative empyema is increasingly observed in post-COVID-19 patients. Despite the inherent risks associated with procedures such as decortication and pleurectomy, they must be carefully considered as viable options for treating pleural effusion/empyema in post-COVID-19 patients. In our own experience, timely surgical interventions combined with appropriate broad-spectrum antibiotics have demonstrated significant improvements in patient status and increased chances of recovery in cases of post-COVID-19-related lung complications.

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