

## *Pneumocystis jirovecii* Pneumonia Mimicking COVID-19 Pneumonia in a Patient with Newly Diagnosed Advanced HIV Disease

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### Abstract

During the pandemic, diagnosis of COVID-19 infection must be excluded in patients presenting with respiratory features, especially in the area where the incidence was high. This case report highlights a man who came with respiratory infection symptoms and the chest radiograph suspicious of COVID-19 pneumonia; however, his swab test for RT-PCR was negative for COVID-19. Later he was found to have a positive anti-HIV antibody and developed advanced HIV infection by multiple opportunistic infections. A 45-year-old man presented with chronic cough and dyspnea for three months which worsened five days before the presentation. It was associated with diarrhoea, dysphagia, weight loss, left lower limb weakness, with bowel and urinary incontinence. Chest auscultation revealed generalized crepitations. The first chest radiograph showed bilateral reticular opacities extending to the lung peripheries when the suspected diagnosis of COVID-19 pneumonia was made. The nasopharynx swab for RT-PCR for COVID-19 was negative, and the sputum was

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positive for *Pneumocystis jirovecii*. The contrast-enhanced CT (CECT) brain revealed changes consistent with brain abscess. The cerebrospinal fluid (CSF) examination was consistent with cryptococcal infection. He was initially treated in the Severe Acute Respiratory Infection (SARI) ward because of the initial impression of COVID-19. He was tested positive for Human Immunodeficiency Virus (HIV) rapid test and PCR, RPR and TPHA for syphilis. He was diagnosed with *Pneumocystis jirovecii* pneumonia, cryptococcal meningitis, brain abscess, oral and oesophageal candidiasis and syphilis. He was treated with co-trimoxazole, Amphotericin B, flucytosine, fluconazole, penicillin G and Nystatin. He initially improved upon treatment but later succumbed to his illnesses. Given the current situation of COVID-19, any patient with acute respiratory symptoms must be tested to rule out COVID-19 pneumonia. However, in a newly diagnosed advanced HIV patient presented with respiratory infection symptoms and extrapulmonary symptoms, opportunistic infections should be excluded along with COVID-19.

**Keywords:** COVID-19, *Pneumocystis jirovecii*, pneumonia, HIV, cryptococcal meningitis

## 1. Introduction

COVID-19 has proven to be not only a massive public health challenge but also a clinical puzzle. The nature of the disease, which has pulmonary and extrapulmonary manifestations, makes it a mimicker of various diseases (Lai et al., 2020). In turn, the wide range of COVID-19 manifestations also makes it a possible differential for various other diseases.

The virus invades host cells via angiotensin-converting enzyme 2 (ACE2), mostly found on type II alveolar cells. Thus, respiratory manifestations, such as cough and dyspnoea, remain the most common symptoms following fever (Letko et al., 2020). Upper airway symptoms such as nasal congestion and sore throat are observed in mild cases. All of these are typical symptoms of respiratory infections caused by various bacteria, viruses and fungi. This makes it difficult to distinguish them clinically. To further compound the problem, there are numerous extrapulmonary manifestations of COVID-19, including cardiac, gastrointestinal, neurological, hepatic, renal, olfactory, gustatory, ocular, haematological and cutaneous manifestations (Lai et al., 2020). These extrapulmonary manifestations may be the initial or the only symptom of COVID-19 infection. At the same time, any patient presenting with multisystemic symptoms may have COVID-19, with or without another concurrent disease. COVID-19 mimics are also increasingly being reported (Hanfi et al., 2020). There should be a high index of suspicion, and any patient presenting with respiratory symptoms amid the pandemic should be tested for COVID-19. A chest radiograph is the first-line imaging study, but COVID-19 pneumonia features are non-specific and can be similar to other infections (Kelly et al., 2020). Initial chest radiography only had a sensitivity of 69% compared with the initial reverse transcriptase-polymerase chain reaction (RT-PCR) testing (Wong et al., 2020). Typical chest radiographic findings mirror those described for chest computed tomography(CT) scan, bilateral, peripheral, consolidation, or ground-glass opacities, and a normal chest radiograph does not exclude COVID-19 (Wong et al., 2020). A chest CT-scan is the most practical choice of imaging but compared to RT-PCR, it only has a sensitivity of 87% and a specificity of 46% (Khatami et al., 2020). Reverse transcriptase-polymerase chain reaction (RT-PCR) remains the operational gold standard with a reported sensitivity and specificity of greater than 95% (Böger et al., 2021). Even so, it must be pointed out that a single RT-PCR is unable to rule out COVID-19 entirely. It

requires a repeated RT-PCR three times to give 99% accuracy (Böger et al., 2021). Besides, it can take up to 48 hours to get the result. This period may be problematic if a patient with possible COVID-19 presented with life-threatening severe respiratory distress or shock.

In an immunocompromised patient with advanced HIV and multiple opportunistic infections, a careful clinical, biochemical and radiological assessment may help the clinician catch the various diagnoses. We bring a case of a patient with newly diagnosed advanced HIV infection and *Pneumocystis jirovecii* pneumonia (PJP) mimicking COVID-19 infection.

## 2. Case report

A 45-year-old man with no known medical illness presented to the hospital with a 3-months history of intermittent chronic cough and dyspnea. The symptoms worsened for the past five days before the current presentation. It was associated with diarrhoea, dysphagia, weight loss and anorexia with a BMI of 19.83 kg/m<sup>2</sup>. He also had left lower limb weakness with bowel and urinary incontinence. On physical examination, he was cachexic with extensive oral candidiasis, generalized crepitations upon chest auscultation, and had upper motor neuron lesion signs on the left lower limb.

Vital signs showed a temperature of 37.0 °C, pulse rate of 88 beats/min, respiratory rate of 20 breaths/min and oxygen saturation of 95% under room air. Blood pressure was 100/71 mmHg with inotropic support of intravenous noradrenaline 3mcg at 2.3ml/hour. Full blood count revealed a low-normal total white cell count of  $4.3 \times 10^9/L$  but with the neutrophil predominance of 94.3% ( $4.05 \times 10^9/L$ ) and severe lymphopenia with lymphocyte of 2.7% ( $0.12 \times 10^9/L$ ). The neutrophils-lymphocyte ratio (NLR) was 34. He had microcytic hypochromic anaemia with a haemoglobin of 9 g/dL and hematocrit of 27.9%. Arterial blood gas showed a pH of 7.45, pO<sub>2</sub> of 81.3 mmHg, hypocapnia with pCO<sub>2</sub> of 28.2 mmHg, bicarbonate of 21.8 mmol/L, base excess of -4.2 mmol/L, and oxygen saturation of 96.2% on the nasal cannula.

Chest radiograph showed bilateral symmetrical ill-defined air space opacities with air bronchogram and reticular infiltrates mainly in the upper and middle zones, with the central and peripheral distribution. There was no hilar lymphadenopathy and no pleural effusion. The findings were concluded as indeterminate of COVID-19. Based on his current presentation, he was triaged as possible COVID-19 stage 4 and was initially treated in the Severe Acute Respiratory Infection (SARI) ward until COVID-19 was excluded. A subsequent test of the nasopharynx swab for SARS-CoV-2 RT-PCR was negative. A sputum sample was positive for *Pneumocystis jirovecii* on PCR and negative for tuberculosis. He had no prior history of *Pneumocystis jirovecii* pneumonia (PJP) and had neither recent travel histories nor contact with confirmed COVID-19 cases. Human immunodeficiency virus (HIV) rapid test and PCR was positive with a viral load of 5.43 log<sub>10</sub>, a CD4 count of 9 cells/mm<sup>3</sup> and a CD8 count of 62 cells/mm<sup>3</sup>. He developed a generalized tonic-clonic seizure on day 2 of admission. A plain CT brain and contrast-enhanced CT (CECT) brain revealed ill-defined hypodensities in the right centrum semiovale and occipital lobe, suggestive of a cerebral abscess. Lumbar puncture was performed, and the cerebrospinal fluid (CSF) examination showed positive for India ink, establishing the diagnosis of cryptococcal meningitis. A rapid plasma reagin (RPR) and Treponema pallidum haemagglutination (TPHA) for syphilis were also positive. He was diagnosed with AIDS, syphilis and brain abscess with multiple opportunistic infections, including *Pneumocystis jirovecii* pneumonia, cryptococcal meningitis and oral candidiasis. He was

treated with oral co-trimoxazole, intravenous Amphotericin B, oral flucytosine, fluconazole, intramuscular penicillin G and syrup Nystatin. He initially responded well to the treatment and improved clinically, but unfortunately succumbed to his illness a few days later. He developed septic shock secondary to brain abscess with multiple opportunistic infections due to advanced retroviral disease.

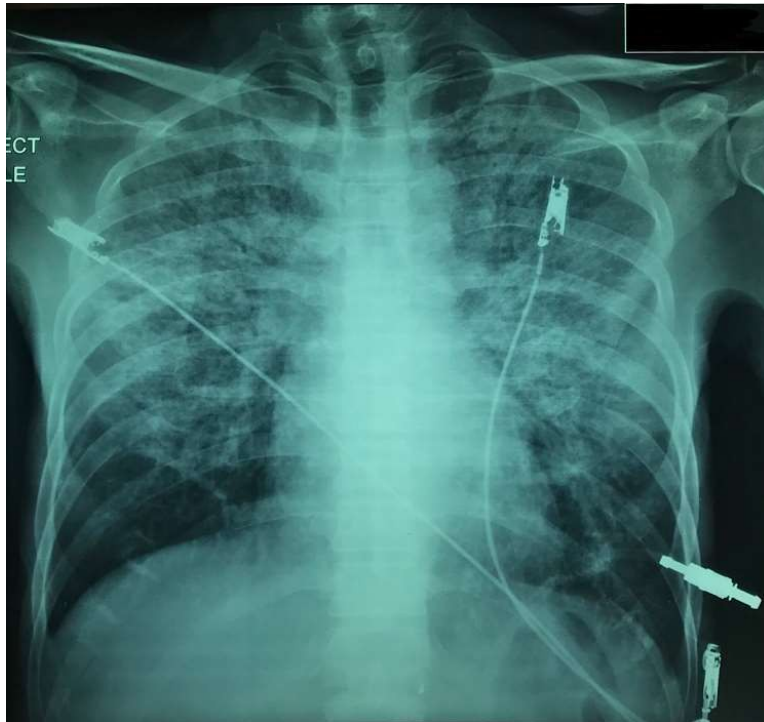


Figure 1: An erect chest radiograph of the patient in AP view taken upon presentation, showing ill-defined air space opacities with air bronchogram and reticular infiltrates mainly in both upper and mid zones with the central and peripheral distribution. No pleural effusion or hilar lymphadenopathy.

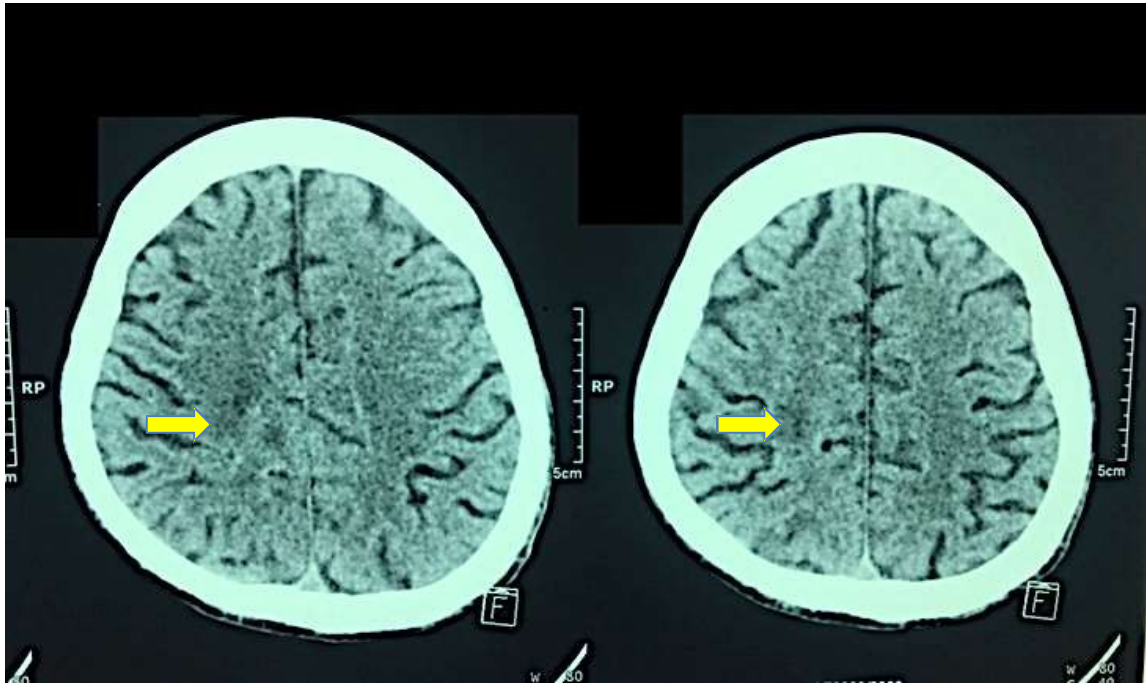


Figure 2: A plain CT-brain of the patient showing the right cerebral hypodensities in the right centrum semiovale, consistent with cerebral abscess (arrow).

### 3. Discussion

Reports of missed or delayed treatment for conditions that mimic COVID-19, such as *Pneumocystis jirovecii* pneumonia (PJP), are emerging during the pandemic (Coleman et al., 2020). Without a high index of suspicion, alternative diagnoses may be overlooked while pursuing a diagnosis of COVID-19. The most common symptoms of COVID-19 are fever (77.0%), cough (55.6%), myalgia or fatigue (31.0%), dyspnea (21.4%) (Rodriguez-Morales et al., 2020). This patient presented with cough, dyspnea and diarrhoea. The dyspnea and cough were longstanding but had worsened acutely five days before the admission. The recent deterioration in symptoms reinforces the suspicion of COVID-19. Diarrhoea has been reported as one of the gastrointestinal manifestations and even an initial symptom of COVID-19, with 6.3% of COVID-19 patients experiencing diarrhoea (Suresh et al., 2020). This patient was afebrile upon presentation and throughout his admission. A nationwide national study done in Malaysia has found that less than 30% of cases had a fever on admission (Sim et al., 2020). This finding was consistent with extensive cohort studies done in China (Guan et al., 2020) and New York (Richardson et al., 2020).

Despite not being fully understood, patients with severe COVID-19 are at a similar risk of invasive fungal infections as seen in severe influenza (Alanio et al., 2020). Colonization with *Pneumocystis jirovecii* is common in COVID-19 patients, a finding that may further bring challenging diagnostic

scenarios. A recent study of 108 critically ill patients with COVID-19 found that 9% had a positive PCR test for *Pneumocystis jirovecii* on bronchial alveolar lavage (A Alanio et al., 2020). Clinically, COVID-19 respiratory symptoms have been noted to be very similar to those caused by *Pneumocystis jirovecii* pneumonia, including oxygen desaturation with exertion, which is highly suggestive of SARS-CoV-2 infection. However, in *Pneumocystis pneumonia*, dyspnoea typically develops insidiously over weeks, not days (Cohen et al., 2020). Except for fever, anosmia and hypogeusia, which were absent in this patient, history and physical examination findings are usually unhelpful to distinguish COVID-19 from other respiratory infectious conditions that mimic SARS-CoV-2, which presents itself to the emergency department (ED) (Carpenter et al., 2020). He also had upper motor neuron lesion signs of the left lower limb, which, upon initial presentation and along with the respiratory symptoms, might be suspicious for a neurological manifestation of COVID-19, which includes demyelination, neuropathy, and stroke (Montalvan et al., 2020). This patient was also hypotensive upon presentation and required inotropic support, which was suspicious for severe or critical COVID-19 infection, defined as severe hypoxemia with or without the presence of other organ failures, including shock (Wu & McGoogan, 2020).

The typical appearance seen in chest radiographs of COVID-19 pneumonia consists of middle and lower lobe opacities reaching the lung peripheries adjacent to the chest wall and peripheral predominant, multiple, bilateral areas of consolidation. However, this patient’s chest radiograph was reported as indeterminate as it does not fit the typical descriptors, despite showing bilateral infiltrates involving the lung peripheries (Rodriguez-Morales et al., 2020). Concurrent infection of COVID-19 with *Pneumocystis jirovecii* pneumonia has been reported in a severely immunocompromised patient with advanced HIV. Some overlap in radiographic features makes it potentially difficult to distinguish them (Bhat et al., 2020). With chest CT, bilateral symmetrical ground-glass opacities are frequently seen on chest CT scans in PJP and COVID-19. However, a peripheral and lower zone distribution is more commonly seen in the latter (Zhao et al. 2020). In contrast, features favouring diagnosis of PJP include relatively central lung involvement and upper lobe predilection, which are the opposite of the peripheral and lower lobe predilection seen in COVID-19 pneumonia (Duzgun et al., 2020). Cystic lesions may occur in one-third of patients with advanced PJP, but its absence makes the diagnosis of co-infection even more challenging based on radiographic changes (Kanne et al., 2012).

A chest radiograph should be used in conjunction with clinical findings to form an overall clinical assessment as no single feature on chest radiography is diagnostic of COVID-19 pneumonia. The chest radiograph may appear normal in the early course of the disease or throughout mild or moderate disease forms (Wong et al., 2020). Thus, sole reliance on chest radiograph should be avoided in making a diagnosis of COVID-19 pneumonia. Currently, RT-PCR is the gold standard diagnostic test, and numerous radiology professional organizations and societies recommend against using an only chest CT scan to diagnose COVID-19 (Jha et al., 2020). In COVID-19, the total white cell count (TWCC) is expected to be normal to low. The haemoglobin and haematocrit are expected to be normal to low (Frater et al., 2020). This patient had mild leukopenia with low haemoglobin and haematocrit. He also had features that might be interpreted as warning signs that predict deterioration for COVID-19, which are absolute lymphocyte count (ALC) of less than 1, NLR of  $\geq 3.13$ , and multilobular involvement on chest radiograph (Ministry of Health, Malaysia, 2020). Immunocompromised patients, including those with HIV/AIDS and malnutrition such as this patient, maybe at a high risk of severe COVID-19 infection (Centers for Disease Control and Prevention, 2021). Several HIV/SARS-CoV-2 co-infection cases have been reported (Ruan et al., 2020). It is crucial to identify it not only because of the possible variations in the clinical presentation

but also HIV co-infection may delay the detection of plasma SARS-CoV-2 antibodies and affect the fidelity of SARS-CoV-2 serological tests (Zhao et al., 2020). This case brings up the possible effect of HIV-induced immune dysfunction on the immune responses and clearance of SARS-CoV-2.

In the current setting, where the confirmatory test will take time to be ready, physicians who treat severely ill patients with pneumonia may face a dilemma in making appropriate diagnosis and pre-emptive management. Thus, empirical treatment for COVID-19 should be initiated early without a confirmatory test; however, a higher index of suspicion towards other possible diagnoses should always be kept in mind. Even though there is currently no specific treatment for severe COVID-19, consultation with infectious diseases specialists and national guidelines will help the treating physicians towards better decision making in the management of the patient. While the connection on how HIV affects the management of COVID-19 is unclear, it is clear that COVID-19 has affected access to the HIV care continuum, which could negatively affect the disease course of HIV (Jiang et al., 2020). With the significant disruption in the way routine care is delivered during the COVID-19 pandemic, it is imperative for governments, community organizations, and international groups to collaborate to ensure that the HIV care continuum is maintained through telemedicine innovations and optimal communication to ensure minimal disruption of routine HIV services.

#### **4. Conclusions**

In the current pandemic, all patients with severe acute respiratory symptoms should be assessed for the possibility of COVID-19. Newly diagnosed HIV patients who present with prolonged respiratory and extrapulmonary symptoms should be investigated for opportunistic infections together in addition to investigations for the possibility of COVID-19. This paper highlights the importance of an individual approach to each patient admitted to a COVID hospital and in performing a differential diagnosis, whether COVID-19 is confirmed or not, to not miss other possible diagnoses, in this case, *Pneumocystis jirovecii* pneumonia in an immunocompromised patient.

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