COVID 19 Pandemic; Revealing the Concealed Infections

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As the coronavirus continues to spread, the attention of hospitals has turned to identify coronavirus infections in patients who are admitted with respiratory problems. For these patients, there is a high chance of missing another differential diagnosis. Here, we describe three cases of Pneumocystis jiroveci pneumonia (PJP) and one case of Mycobacterium tuberculosis (MTB) HIV- associated lung infections that were initially managed as COVID-19 cases, and in whom HIV was not primarily diagnosed.

Key words: COVID-19, HIV, Pneumocystis jiroveci pneumonia, Mycobacterium tuberculosis (MTB)

INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) outbreak originated in Wuhan, China in December 2019, and rapidly evolved into a global challenge[1]. The virus has been officially named "Severe Respiratory Syndrome Coronavirus 2" (SARS-COV-2). The COVID - 19 pandemic has affected nearly 7 million people in 216 countries worldwide, with a rapidly shifting epicenter[2]. Pyrexia, cough, and dyspnea are the most common presentations among COVID-19 patients. The geriatric population, particularly those with pre-existing medical conditions such as chronic cardiac failure, bronchitis, diabetes, and emphysema, is more prone to developing critical illnesses[1]. One of the most pressing global health problems, and a demanding challenge for healthcare delivery systems worldwide, is HIV. According to UNAIDS, there were approximately 1.7 million new cases of HIV reported globally, amounting to a total of 37.9 million HIV - positive people worldwide[3]. It was estimated by the Center for Disease Control and Prevention (CDC) that of the 800,000 to 900,000 HIV patients living in the US, one-third were not aware of their condition[4]. Immunodeficiency resulting from HIV affects all organ systems. It has hitherto been reported that a spectrum of respiratory illnesses affects HIV- positive people[5]. Past studies have shown that productive cough and chest pain are the most common clinical findings in HIV patients; ventilatory functions are also adversely affected[6,7]. The most common HIV-associated opportunistic infection with a high incidence is *Pneumocystis jiroveci pneumonia* (PJP)[8]. It is caused by *Pneumocystis jirovecii* and is the first serious illness often encountered by HIV-infected persons. Nearly 44% of PCP cases occur in patients who are not undergoing any medical treatment, and most of them are not aware of their HIV diagnosis[9]. Since PCP-HIV can sometimes be masked by other respiratory disorders, in low-prevalence areas such as Saudi Arabia, it can often be confused for diseases such as COVID-19. PCP- HIV and COVID-19 often present with similar clinical findings; thus, during the prevailing pandemic, HIV diagnoses can be delayed. A delayed diagnosis can result in advanced immunosuppression, in addition to a high risk of contagion. Additionally, tuberculosis (TB) is among the leading infectious diseases that cause significant morbidity and mortality in HIV-infected individuals globally. In this case series, we present three cases of PJP and one case of (MTB) HIV- associated lung infections that were initially managed as suspect coronavirus infections, and in whom HIV was not primarily considered.

CASE SERIES

Case 1: A 69-year-old male with a history of diabetes and hypertension presented to the emergency department after feeling unwell for 3 days, with the chief complaints of vomiting, diarrhea, fever, dry cough and exertional dyspnea. On initial evaluation, the patient was afebrile and required 4L of oxygen to maintain his oxygen saturation above 95%. Physical examination revealed mild respiratory distress and vital signs of 37 ° C, HR 93 bpm, RR 20/min, BP 118/80. He was noticed to have palm lesion nodule, violet colored, not tender (around 0.5 by 0.3 cm), has no punctum, firm in consistency on his right hand. In addition, two small lesions over his right and one on the left cheek (0.2 by 0.3 cm), firm in consistency. He was stabilized in the emergency department; initial laboratory investigations along with COVID-19 test were unremarkable except for his first chest X -ray, which showed bilateral infiltrates. Other blood works showed; Hb 8.8g/dl, WBC 6.5 x109/L, platelets 323 x109/L, Na 138 mEq, K 3.8 mEq, Cl 101 mEq, BUN 8.8, INR 1.22. ABGS showed PO^2 of 59.8, lactic acid 1.3, HCO_3 27. Liver function test were unremarkable. Based on the patient history, chest X -ray findings, and laboratory investigations, initial differential diagnosis of viral pneumonia including COVID-19 infection and acute gastroenteritis was made. Due to the associated hypoxia and respiratory distress and high FiO^2 requirements, the patient was intubated and was put on a ventilator, as per departmental adult respiratory distress syndrome (ARDS) protocol, and he was moved to the intensive care unit (ICU). A high-resolution computed tomography (HRCT) showed bilateral changes supporting the diagnosis of viral pneumonia, likely COVID-19 pneumonia (**Figure 1**). To rule out COVID-19 pneumonia, repeated nasopharyngeal swabs were collected for PCR, which were negative. Blood culture obtained on admission was negative. He was initially managed as a case of community acquired pneumonia and was started on antibiotics, piperacillin-tazobactam (4.5gm), and hydroxychloroquine (400mg). In addition, after consulting the infectious disease team, he was started on heparin (5,000 units) as prophylactic anticoagulation initially and later antibiotics were changed to Vancomycin (1.125g/q12), cefepime (2g/q8). As part of investigation of other causes of pneumonia, acid fast stain (AFB) and PCR for *mycobacterium tuberculosis* from sputum were ordered, and both were negative. Viral profile including Human Immune Deficiency virus (HIV) was done, and he tested positive for HIV (CD count 18). After that for highly suspicion of Pneumocystis

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jiroveci pneumonia (PJP) associated with HIV infection he was started on Atovaquone and Dexamethasone and showed mild improvement in his condition; therefore, he was gradually extubated and shifted to continuous positive airway pressure (CPAP) room and baseline workup was repeated, which was unremarkable, and a chest X -ray showed improvement. Screening for other HIV - associated infections was done and he tested negative for cryptococci, gonorrhea, tuberculosis (TB), and chlamydia. Bronchoalveolar lavage (BAL) was positive for *Pneumocystis jiroveci*. During his admission, he developed new lesions around his nose and left part of his face and both thighs which was vesicular then honey crusted, it rather spread more over his face. He was started on acyclovir and the impression was disseminated HSV. Subsequently, he was started on (intravenous) IV penicillin for presumed neurosyphilis as his syphilis serology was positive, and acyclovir for disseminated HSV.

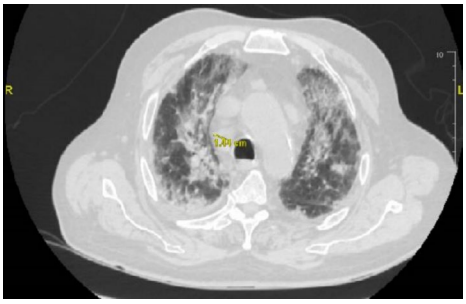

Figure 1. There are bilateral diffuse ground-glass changes with intervening areas of consolidations in peribronchovascular distribution as well as scattered nodular areas of consolidations bilaterally.

Case 2: A 51-year-old male, a new case of Diabetes Mellitus Type 2 (DMT2), recently diagnosed HIV infection, not taking any medication for either condition presented with fever, cough, shortness of breath (SOB), and tachypnea. Due to the ongoing COVID-19 pandemic, a nasopharyngeal swab was collected and was negative. On initial examination, he was ill - looking, oriented, intermittently tachypneic with 35 breaths per minute. Signs were 36. 8°C; RR:28; BP: 120/74 and maintaining saturation with 6L oxygen via mask. Chest examination revealed bilateral fine crackles. He had an inguinal hernia and genital warts. Hands, face and extremities had black lesions (**Figure 2**). Initial laboratory analysis showed results: HB 12.4mg/dl; TLC 3.8x109 /L; platelets 201 x109 /L; Na137 meq/L, K 4.1 meq/L, CL 102 meq/L, BUN 3.1, INR 0.97, troponin 5.70, ALT 26. Nasopharyngeal swabs collected on the first and second day after admission were negative for COVID-19 using real-time RT-PCR assay. Venous Blood Gas (VBG) showed; pH 7.29, p CO 56. HCO3 25. The patient showed signs of continuous respiratory distress; therefore, High-Resolution Computed Tomography (HRCT) was performed, which showed diffuse ground - glass opacity with bilateral basal consolidation, with air bronchogram and atelectatic bands more prominent in the right lung (**Figure 3**). As the clinical and CT findings suggested the diagnosis of COVID-19 pneumonia, a nasopharyngeal swab for COVID-19 testing was repeated and was negative. Investigations for other etiologies of pneumonia including HIV, bacterial, fungal and tuberculosis were conducted. Test for HIV infection was positive (CD4 count 9). AFB stain result showed no acid-fast bacilli, and PCR for mycobacterium tuberculosis was negative. Initially he was managed as community acquire pneumonia (CAP) started on IV Ceftriaxone (1gm), oral Azithromycin (500 mg BD), and treated with Bactrim for possibility of PJP. He improved clinically, with his oxygen requirement reduced from 6L to 3L to maintain saturation at >92%. He was diagnosed with pneumonia (PJP) associated with HIV infection. He completed 3 weeks of antibiotic treatment and completely recovered.

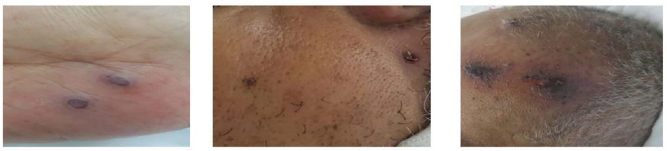

Figure 2. Demarcated black dry lesions on the palms. B. black skin lesions on the face, C. black dry scaly dry lesions over the forehead.

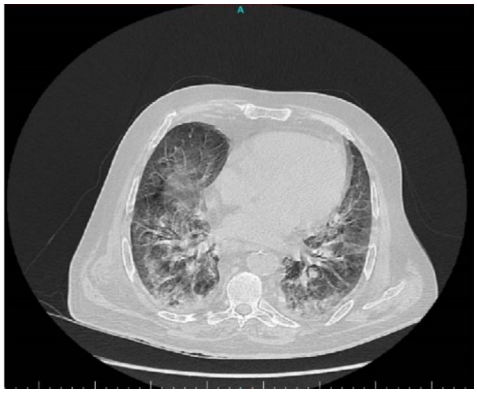

Figure 3. Diffuse ground glass opacity with bilateral basal consolidation with air bronchogram and atelectatic bands more prominent in the right lung.

Case 3: A 37-year-old male, known case of bronchial asthma, recurrent localized Herpes Zoster, and hemorrhoids presented in the emergency department with syncope, seizures, and shortness of breath. He was immediately admitted to MICU as a case of severe pneumonia and was intubated for severe acute respiratory failure. His past medical history was irrelevant except frequent travel abroad and history of high-risk behavior. On examination, he had genital ulcers and a bleeding mass in the perianal area. His chest examination revealed bilateral lung crackles and right lower limb weakness was also present. Initial laboratory investigations showed pancytopenia however the LFTs and RFTs were unremarkable and serum electrolytes were normal. COVID-19 nasopharyngeal swab was negative. He was further investigated for sexually transmitted diseases syphilis, Chlamydia, Gonorrhea, and Toxoplasma which were negative serology for hepatitis B and Hepatitis C also came out negative. HIV test was positive (CD4 count 3). As the patient presented with shortness of breath for which a high-resolution computed tomography (HRCT) was conducted which showed a scattered area of abnormalities suggestive of Adult Respiratory Distress Syndrome (ARDS), with the possibility of superadded infection **(Figure 4)**. Further investigations for bacterial, viral, and fungal etiologies of pneumonia were conducted. Bronchoalveolar lavage was positive for Pneumocystis jiroveci **(Figure 5)**, however, bone marrow biopsy and blood smear for Mycobacterium Avium Complex (MAC) were negative. AFB stains for Acid-fast bacilli also came out negative but non-tuberculous mycobacterium was isolated from the chest. Cytomegalovirus viremia was seen despite the absence of any clinical signs of CMV infection. For further investigation of his syncope, right lower limb weakness, and perianal mass, multiple imaging tests were conducted. MRI Brain showed findings which were suggestive of CMV encephalitis or possibly HIV encephalopathy **(Figure 6)**. EEG findings further confirmed the encephalopathy. For his right lower limb weakness, MRI showed mild diffuse annular disk bulge at the L4-L5 level. Nerve conduction study (NCS) showed axonal injury. According to the results of his in-depth investigations, he was treated as delirium associated with HIV encephalopathy/meningoencephalitis,

persistent, and with mixed levels of activity. As soon as the diagnosis was made the patient was started with antiretroviral therapy with a combination of Clexane (Enoxaparin) 40mg/0.4mL; PLS Efavirenz 600mg + Tenofovir 300mg + Emtricitabine 200mg (Atripla) 1 tab (s). He completed 14 days of trimethoprim/sulfamethoxazole and steroids for pneumonia (PJP). He completed 14 days of acyclovir for VZV, and 6 weeks Ganciclovir for CMV infection. IV Gabapentin 300 mg; and Levetiracetam 500 mg for epilepsy was also given. No seizure attacks were reported during his hospital stay, his consciousness level improved, and he was discharged home on oral medication.

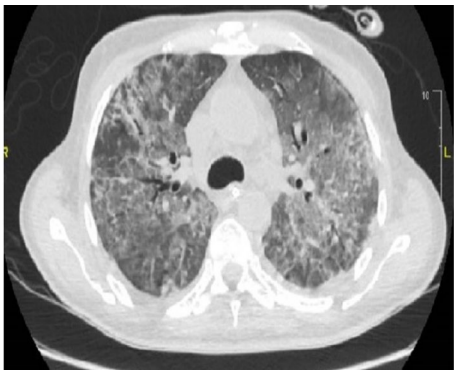

Figure 4. Scattered area of ground-glass attenuation associated with nodular and tree in bud opacities suggestive of ARDS, superadded infection might be possible.

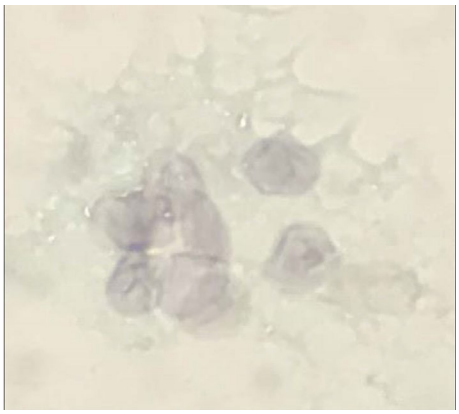

Figure 5. Scattered area of ground-glass attenuation associated with nodular and tree in bud opacities suggestive of ARDS, superadded infection might be possible.

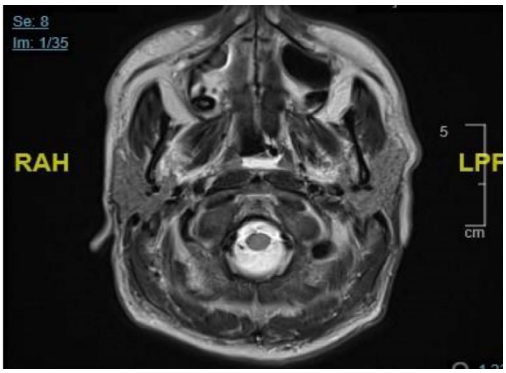

Figure 6. Bilateral relatively symmetrical patchy periventricular and deep white matter signal alteration with no corresponding enhancement or mass effect associated with smooth Dural enhancement most conspicuous at the anterior frontal convexity and middle cranial fossa.

Case 4: A 40-year-old female, working as a housemaid, with no significant past medical history, presented with shortness of breath, chronic cough, fatigability, weight loss for one month. She was recently diagnosed with COVID-19 in a public clinic and was sent home for isolation. She denied recent traveling. On physical examination, she was lethargic, dehydrated with poor oral hygiene, Temp: 37 °C (Oral) RR: 25 BP: 119 / 71 SpO2: 95% (on 1 L O2). Without oxygen, her saturation drops to 84%; chest examination shows bilateral crackles. She was stabilized in the emergency room and due to her clinical presentation and ongoing pandemic, she was shifted to COVID isolation. Chest X-ray showed diffuse micronodular opacities with left middle zone infiltrates **(Figure 7)**. Lab investigations showed: Hb 11.0 g/dl, WBC 8.59 x109, platelets 242 x109, NA:132 mEq/L, K: 3.8 mEq/L, Creatinine 78, BUN: 6.2. INR was 1.02, ALT: 89. She was treated as CAP with suspicion of COVID pneumonia. She was started on intravenous (iv) antibiotics (ceftriaxone), enoxaparin, and other supportive medication. On the second day of admission, she became hypotensive and tachycardiac and was shifted to the COVID-19 ICU. She was in respiratory distress, and febrile, and was put on Bilevel Positive Airway Pressure. Antibiotics were switched to cefepime, vancomycin, and azithromycin. She was continuously febrile, and her septic markers were high. To rule out other infections, HIV serology and tuberculosis screening were performed. HIV test turned out to be positive. On the fifth day of admission, she collapsed due to respiratory failure and was intubated and placed on a ventilator. Her Acid-Fast Bacilli (AFB) stain was positive. She was admitted with suspicion of COVID and found to have HIV complicated with tuberculosis. On the sixth day of admission, she collapsed again, and Cardiopulmonary Resuscitation (CPR) was done but she died due to cardiopulmonary arrest.

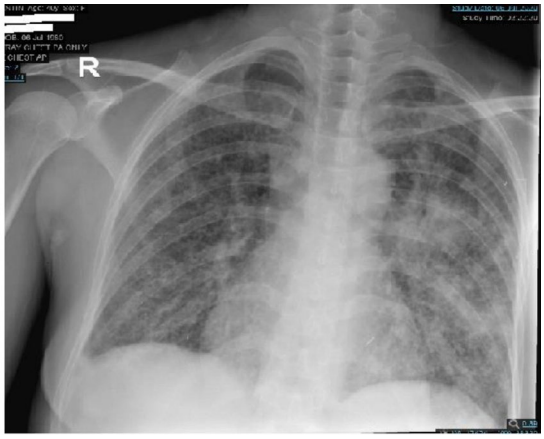

Figure 7. Chest X-ray showed bilateral diffuse alveolar and patchy opacities more prominent in left lung.

DISCUSSION

As respiratory manifestations are some of the most common features of COVID-19 infection, during the COVID-19 outbreak, hospitals have become alert to the prospect of COVID-19 being a possibility in patients presenting with respiratory manifestations. However, this method of screening poses a hazard of overlooking additional differential diagnoses. In our case series, four patients with clinical and radiologic features suggesting the diagnosis of COVID-19 were admitted with a provisional diagnosis of COVID -19 infection and were managed accordingly, following remarkably similar courses throughout the period of their stays. According to the clinical protocols, the patients were subsequently tested for SARS-COV-2 by performing real-time polymerase chain reaction (PCR) from nasopharyngeal swabs. All the RT-PCR tests were negative for COVID-19; meanwhile, the patients'

conditions deteriorated, with increasing supplemental oxygen required to stabilize them. In Saudi Arabia, between 1984 (when HIV tests were first conducted) and December 2014, the total number of reported HIV cases was found to be 21,761, of which Saudi citizens amounted to 6,334 (29.1%) cases, and 15,427 (70.9%) cases were foreigners. Moreover, the incidence of HIV per year is only 1.5 per 100,000 people; these statistics make Saudi Arabia a country with a low prevalence of HIV[10]. Due to immunodeficiency, HIV patients are susceptible to many kinds of systemic infections and respiratory symptoms deserve special attention in this regard, because of their high frequency and because opportunistic pulmonary infections remain the leading cause of hospitalization in HIV patients[11]. Productive cough, dyspnea, and wheezing are common symptoms associated with respiratory infections found in HIV patients, affecting more than 30% of these individuals[12]. Lower respiratory tract infections are usually comprised of bacterial pneumonia caused by certain typical infectious agents such as *S. pneumoniae*, *Hemophilus*, *Pseudomonas*, *Staph*, and *Klebsiella*[13]. The preeminent opportunistic infection is *Pneumocystis pneumonia* (PCP), despite the decrease in its incidence following the advent of ART[14]. Clinical findings in COVID-19 patients resemble many of the symptoms of PCP; for example, patients of both diseases typically present with fatigue, dry cough, pyrexia, dyspnea[15,16] and even similar radiological findings of bilateral symmetrical ground glass opacities in chest CTs[17]. In patients with a CD4 count below 200 cells/ L, which may manifest as lymphopenia, *Pneumocystis* pneumonia (PCP) occurs frequently. COVID-19 patients also most commonly present with leucopenia, but cases with leukocytosis and lymphopenia have also been reported[18]. One feature differentiating PCP from COVID-19 pneumonia can be dyspnea, which presents in nearly 95% of PCP patients but is only seen in 11 - 31% of COVID-19 patients[15,16,18]. A case series by Choy et al.[19] reported a delayed diagnosis of two HIV cases which were initially misdiagnosed as COVID-19 due to similar presentation. While the resemblance of symptoms is a factor that can delay the diagnosis of HIV, another factor that also contributes to delaying the diagnosis of PCP with HIV in a low-prevalence country is that due to the low likelihood of HIV, it is usually not the first differential diagnosis. While it is reasonable that a patient with respiratory symptoms may be a suspected case of COVID-19 during the pandemic, other infections that mimic the symptoms of COVID-19 should also be considered when forming differential diagnoses. With this case study, we hope to draw attention to the importance of considering PCP with HIV as a potential diagnosis in patients presenting with symptoms suggestive of COVID-19, so that HIV patients are not underdiagnosed during the COVID-19 outbreak.

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