First Case of COVID-19 N501Y Variant of Concern Infection in a Patient with Chronic HIV Infection

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Abstract
COVID-19 pneumonia continues to have high global prevalence, mortality, and morbidity with the emergence of new variants of concerns due to vaccination inequality. There continues to be limited data on the outcomes of HIV-infected patients with COVID-19. In this report, we present the case of a 62-year old male with chronic HIV who presented with unexplained fever and initial negative COVID-19 PCR, and no radiographic evidence of COVID-19 on chest x-ray or CT Chest. Due to the increased prevalence of COVID-19 and the emergence of variants of concern, diagnostic testing for COVID-19 should be repeated in patients who are persistently febrile despite previous negative swabs and lack of exposure. Patients with immunocompromised states, such as HIV infection, may have atypical clinical presentations, time to PCR positivity, or imaging findings of COVID-19. A thorough investigation for other causes of unexplained fever should also be conducted despite the community prevalence of COVID-19.

Case presentation
A 62-year-old male was admitted to a tertiary care center with abdominal pain and one-month history of constitutional symptoms (fatigue, weight loss, subjective fevers, and chills). His medical history included decompensated alcoholic cirrhosis (model for end-stage liver disease score 15 [1]), and...
HIV treated with dolutegravir, abacavir, and lamivudine for the past 3 years. His absolute CD4 count was $0.17 \times 10^9$/L (normal $0.43 – 1.69 \times 10^9$/L), with an absolute CD8 count of $0.24 \times 10^9$/L (normal $0.15 – 1.11 \times 10^9$/L), and a CD4/CD8 ratio of 0.6 (normal >0.9). The viral load 1 year prior was <40 copies per mL. The patient did not receive a COVID-19 vaccine.

Upon presentation, the patient was febrile at 38.0°C. He had symptoms of abdominal pain, with no other focal signs of infection, including shortness of breath, cough, headache, neck stiffness, dysuria, painful joints, or erythematous rashes. He did not have any travel history or known COVID-19 exposures. Vital signs other than temperature were normal while breathing ambient air. Physical examination showed evidence of ascites but was otherwise unremarkable.

His complete blood count showed chronic anemia and thrombocytopenia at baseline and new neutropenia with an absolute neutrophil count (ANC) of $0.9 \times 10^9$/L (normal $2 – 7 \times 10^9$/L). COVID-19 PCR on a nasopharyngeal swab on the date of admission was negative. His C-reactive protein (CRP) was 17.8 mg/L (normal <10 mg/L). A chest x-ray (CXR) showed low lung volumes, with no acute intrathoracic abnormality (Figure 1A). Diagnostic paracentesis showed a fluid leukocyte count of $98 \times 10^6$/L and a negative gram stain and culture, with no evidence of spontaneous bacterial peritonitis (SBP). A computed tomogram (CT) of the chest showed bibasilar pulmonary atelectasis secondary to mass effect on the bilateral hemidiaphragm and centrilobular emphysematous changes, with no features of atypical pneumonia or COVID-19 infection (Figure 2).

Given these results, we considered COVID-19 to be “ruled out” and proceeded to complete the workup necessary for unexplained fever. Blood cultures, urine cultures, and peritoneal fluid cultures were all negative. The infectious diseases team was consulted for unexplained fever, and the hematology team was consulted for new neutropenia. Abdominal ultrasound showed no evidence of cholecystitis. Head CT showed no mass or evidence of lymphoma, as did CT of the chest and abdomen performed a month prior to admission. The patient had positive serology for cytomegalovirus (CMV), Epstein-Barr virus (EBV), and parvovirus B19. CMV PCR was negative. We did not perform EBV or parvovirus B19 PCR due to a lack of clinical findings of active infection such as lymphadenopathy, rash, and arthralgia. Hepatitis B core antibody and Hepatitis A antibody were reactive; however, liver enzymes were stable compared to the patient’s baseline. Hepatitis C antibodies were non-reactive. Peripheral blood film examination revealed no immature forms or leukoerythroblastosis. The patient’s pancytopenia and new neutropenia were thought to reflect multiple etiologies, including alcohol consumption, use of antiretroviral medications, and splenic sequestration from known portal hypertension and hypersplenism.

Figure 1. CXR on day 1 (A), day 4 (B), and day 7 (C) of admission demonstrating worsening bilateral infiltrates in keeping with COVID-19 infection.

Figure 2. CT Chest showing evidence of bibasilar pulmonary atelectasis secondary to mass effect on the bilateral hemidiaphragm and centrilobular emphysematous changes.
On day 4, the patient became hypoxic, requiring 2 – 3 L/min of supplemental oxygen via nasal prongs. Repeat CXR at this time showed increased atelectasis, with no consolidation (Figure 1B). Given persistent fever and new hypoxia, a repeat nasopharyngeal swab was performed on day 5 and was positive for the N501Y COVID-19 variants of concern (VOC). Treatment was initiated with dexamethasone, together with ceftriaxone and doxycycline for possible concurrent pneumonia. On day 7, the patient developed worsening hypoxemia requiring admission to the intensive care unit. A CXR showed worsening bilateral airspace disease in keeping with COVID-19 infection (Figure 1C). Unfortunately, the patient deteriorated despite optimal medical treatment and died of COVID-19 pneumonia on day 12 of admission. This is the first reported case of a COVID-19 N501Y variant in a patient with HIV infection.

Discussion

COVID-19 pneumonia continues to have high global prevalence, mortality, and morbidity. Typical presentation of COVID-19 includes fever, cough, shortness of breath, and other minor symptoms such as fatigue, diarrhea, anosmia, ageusia, and myalgia.1-3 Risk factors for severe COVID-19 include increasing age, co-morbidities such as cardiovascular disease, diabetes mellitus, chronic respiratory illness, cancer, chronic kidney disease, smoking, and solid organ or hematologic stem cell transplant.3 COVID-19 should remain high on the differential diagnosis for patients with typical symptoms and compatible imaging findings despite negative COVID-19 PCR. However, there have been reported cases of delayed diagnosis of other causes of fever and shortness of breath due to premature diagnostic closure secondary for COVID-19.4 In this manuscript, and we report a case of delayed COVID-19 diagnosis in a patient with chronic HIV infection who presented with fever characterized as being of unknown origin. This is also the first report of a COVID-19 N501Y VOC in an HIV-infected patient.

COVID-19 and HIV

There is limited data on the outcomes of HIV-infected patients with COVID-19. Patients with HIV may be more affected by the virus due to their immunosuppressed state. A case series of 27 patients with well-controlled HIV infection suggests that HIV-infected patients are not protected from severe COVID-19 infection and present in similar ways compared to the general population with fever, cough, and dyspnea.5 In this case series, antiviral therapy was held in all patients. Antiviral therapy was continued in our patients, but it is unclear how it contributed to their COVID-19 presentation or course of infection. A subsequent prospective cohort study confirmed that HIV-infected patients were not protected from severe COVID-19 infection and presented clinically like the general public (6). In addition, a prospective study showed age, male sex, metabolic disorder, and sub-Saharan African ethnic origin as risk factors for severe COVID-19 infection in HIV-positive patients in Italy, similar to the general population.7

The N501Y mutation has been found in the B.1.1.7 (alpha) VOC identified in the United Kingdom and the B.1.351 (beta) VOC identified in South Africa.8,10 VOC with the N501Y mutation has been detected in higher numbers among young people and may cause more severe disease than other variants.2 Our patient had no previous known exposures or travel history. Therefore, the clinical significance of this variant in our patient is unclear.

Atypical presentations with COVID-19 infection have also been reported in immunosuppressed populations such as those with solid organs or hematological transplantations.11 Transplant recipients are less likely to present with fever and have more significant lymphopenia.11 There are also reports of increased COVID-19 severity in immunocompromised patients; however, this may be due to increased co-morbidities such as cardiovascular disease or diabetes.12 Interestingly, the presentation of COVID-19 in patients with autoimmune disease does not appear significantly different from the general population.13 The management of immunosuppression medications in patients with COVID-19 infection remains unclear.13

Role of COVID-19 Vaccine

Although Health Canada has approved four COVID-19 vaccines, only two COVID-19 vaccines (Pfizer Biotech and Moderna) are currently available in Canada for the prevention of severe COVID-19. Both vaccines have been shown to have greater than 95% efficacy in preventing COVID-19 infection and have been shown to be greater than 90% effective in preventing infection from the beta and alpha VOC, which express the N501Y mutation (14, 15). It has been shown that immunosuppressed populations such as those with organ transplantation or on immune-modulating medications have a reduced response to the vaccine, with some studies showing more than 75% of patients do not mount a humoral response to COVID-19 vaccination.16 The immune response to COVID-19 vaccination in patients with chronic HIV remains unclear.

Treatment of Sepsis in Patients with Neutropenia

Patients with neutropenia are at increased risk of infection and may not present with typical symptoms such as fever, chest x-ray infiltrate, abdominal pain.17 Treatment of patients with...
fever should be initiated rapidly in clinically unstable patients. Empiric treatment for concurrent CAP was initiated in our patient due to neutropenia despite lack of clear consolidation on chest x-ray and COVID-19 alternative explanation for instability. This clinical scenario could have considered broader antimicrobial coverage for pseudomonas and MRSA; however, it is unclear if it would ultimately change the outcome given the patient's severe COVID-19 infection. There are no clear indications for the use of granulocyte colony-stimulating factor (G-CSF) in patients with fever and neutropenia, particularly in the setting of presumed splenic sequestration, but can be considered in patients with poor clinical outcome including prolonged or profound neutropenia, age <65, pneumonia, or sepsis syndrome.\(^{18}\) The patient in our case report did not receive G-CSF.

**Diagnostic Delay & COVID-19 PCR**

Diagnostic delay refers to an increased time interval between the presentation of symptoms and confirmation of an accurate diagnosis and can be attributed to various factors, including cognitive failure and premature diagnostic closure.\(^{19}\) In our patient, no-fault errors caused by the lack of information on COVID-19 symptoms, imaging findings, and timing to PCR positivity specifically in HIV populations led to a diagnostic delay.

As per the Infectious Disease Society of America (IDSA) COVID-19 Diagnostic guidelines, repeat testing has been recommended within 24 – 48 hours for patients with a high pre-test probability of COVID-19 and an initial negative test. Repeat testing in symptomatic patients with low clinical suspicion of COVID-19 is not recommended.\(^{10}\) Repeat COVID-19 testing in 24 – 48 hours in individuals with a pre-test probability of less than 10% had a false negative rate of less than 2% (20). These guidelines have not specifically looked at immunocompromised patients with atypical symptoms. Overall, repeat COVID-19 testing in 24 – 48 hours should be pursued in patients who are immunocompromised with atypical symptoms and those who have classic symptoms of COVID-19 (Figure 3).

The sensitivity for COVID-19 PCR has been reported to be approximately 71–98% and may vary significantly based on the stage of disease and the site sampled.\(^{21}\) Individuals should be tested within 2–7 days of exposure due to the viral shedding period during which the virus can be transmitted to other individuals.\(^{22}\) Due to this period of viral shedding, patients with one negative swab may test positive later based on disease stage, disease site (upper versus lower respiratory tract), and viral multiplication or clearance. Additional challenges for COVID-19 testing include the lack of a diagnostic gold standard to compare PCR testing results. A multitude of factors is considered when deciding the pre-test probability of COVID-19, including symptoms, exposure history, and imaging findings. The sensitivity and specificity of COVID-19 PCR for VOC are not clear. Serology for COVID-19 antibodies have a reported 95% sensitivity and 99.5% specificity.\(^{23}\) Unfortunately, serologic testing is not readily available in many hospital settings, and its implications about COVID-19 exposure or immunity are unclear.

In our patient, there was no other clinical evidence of COVID-19, such as cough or positive findings on initial imaging. The only initial symptom was fever, which could have multiple other etiologies in a patient with HIV. It was thought to be essential to consider other causes of unexplained fever in our patient, particularly given his pancytopenia. The differential diagnosis for unexplained is broad and summarized

![Figure 3. Diagnostic progress for repeat COVID-19 PCR after initial negative test.](image)
in Table 1. Our patient had multiple potential causes, including SBP, chronic CMV infection, atypical respiratory infection, other viral upper respiratory tract infections such as influenza A and cholecystitis. We did not explore inflammatory causes of fever due to the lack of historical and physical findings that would suggest an autoimmune phenomenon. All these etiologies were thoroughly investigated between the date of admission and the date of COVID-19 PCR positivity. Given the lack of known exposure, previous negative COVID-19 PCR, low CRP, and CT chest with no findings in keeping with COVID-19, we felt there was sufficient evidence that the patient’s fever was not due COVID-19. This case serves as an important reminder that immunocompromised patients such as those with HIV infection may have delayed COVID-19 positivity on PCR or atypical findings on imaging.

**Conclusion**

COVID-19 remains prevalent in our community and can cause high mortality and morbidity. Diagnostic testing for COVID-19 should be repeated in persistently febrile patients despite previous negative swabs and lack of known exposure. It is essential to recognize that there may be atypical or delayed presentations in immunocompromised patients and repeat COVID-19 PCR etiologies were thoroughly investigated between the date of admission and the date of COVID-19 PCR positivity. Given the lack of known exposure, previous negative COVID-19 PCR, low CRP, and CT chest with no findings in keeping with COVID-19, we felt there was sufficient evidence that the patient’s fever was not due COVID-19. This case serves as an important reminder that immunocompromised patients such as those with HIV infection may have delayed COVID-19 positivity on PCR or atypical findings on imaging.

Table 1. Differential Diagnosis for Unexplained Fever in Immunosuppressed Patients

<table>
<thead>
<tr>
<th>Etiologies</th>
<th>Infectious</th>
<th>Malignancy</th>
<th>Autoimmune/Inflammatory</th>
<th>Others</th>
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<tbody>
<tr>
<td></td>
<td>Brucellosis</td>
<td>Acute leukemia and lymphoma</td>
<td>Giant cell arteritis</td>
<td>Drug fever</td>
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<td>Chikungunya</td>
<td>Multiple myeloma</td>
<td>Inflammatory bowel disease</td>
<td>Pulmonary emboli</td>
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<td>Antiphospholipid syndrome</td>
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<td>Granulomatosis with polyangitis</td>
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<td>Sarcoïdosis</td>
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should be considered for persistent fevers and hypoxia with no other origin. In addition, a thorough investigation for other causes of unexplained fever should be conducted despite the community prevalence of COVID-19 and VOC.

**References**