Death due to multiple organ failure in a patient with severe COVID-19, AIDS, cardiovascular impairment, and previous lung infections

Morte por falência múltipla de órgãos em paciente com COVID-19 grave, AIDS, comprometimento cardiovascular e infecções pulmonares prévias

Muerte por insuficiencia multiorgánica en un paciente con COVID-19 grave, SIDA, deterioro cardiovascular y infecciones pulmonares previas

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RESUMO
Objetivo: Relatar um caso de coinfeção pelo SARS-CoV-2/HIV em um paciente com histórico recente de infecções pulmonares, que teve parada cardiopulmonar no dia de sua internação para tratar da COVID-19, falecendo alguns dias depois de falência múltipla de órgãos. Detalhamento de caso: Um homem de 33 anos, imunossuprimido (em abandono de tratamento para o HIV) deu entrada no serviço de pronto-atendimento com sintomas respiratórios e testou positivo para SARS-CoV-2. Durante a internação, o paciente teve parada cardiopulmonar e apresentou intenso perfil inflamatório, infecção fúngica, sepse, acidose metabólica, hipertensão arterial, trombose, hemorragia, além de lesão hepática, muscular e renal. Por fim, o paciente evoluiu para falência de múltiplos órgãos, indo à óbito. Considerações finais: A grave imunodeficiência causada pelo HIV, associada a doenças cardiopulmonares de base, contribuiu para desfechos letais da COVID-19.


ABSTRACT
Objective: To report a case of SARS-CoV-2/HIV coinfection in a patient with a history of recent lung infections who had a cardiopulmonary arrest on the day of hospitalization for COVID-19 treatment, dying some days after multiple organ failure. Case detail: A 33-year-old immunosuppressed male patient (abandoning treatment for HIV) was admitted to the emergency department with respiratory symptoms and tested positive for SARS-CoV-2. During hospitalization, the patient had a cardiorespiratory arrest and presented a robust inflammatory profile, fungal infection, sepsis, metabolic acidosis, arterial hypertension, thrombosis, hemorrhage, and hepatic, muscular, and renal injury. Finally, he evolved with multiple organ failures, leading to death. Conclusion: Severe immunosuppression caused by HIV, associated with underlying cardiopulmonary diseases, contributes to lethal outcomes of COVID-19.

Keywords: COVID-19, HIV, coinfection, multiple organ failure.

RESUMEN
Objetivo: Comunicar un caso de coinfección por SARS-CoV-2/HIV coinfección en un paciente con antecedentes recientes de infecciones pulmonares, que sufrió una parada cardiopulmonar el día de su hospitalización para tratar el COVID-19, falleciendo pocos días después por fallo multiorgánico. Detalle del caso: Un hombre inmunodeprimido de 33 años (que había abandonado el tratamiento contra el VIH) ingresó al servicio de emergencia con síntomas respiratorios y dio positivo en la prueba del SARS-CoV-2. Durante la hospitalización, evolucionó a fallo múltiple de órganos, y falleció.

Palabras-clave: COVID-19, HIV, Coinfección, Fallo multiorgánico.

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el paciente sufrió una parada cardiopulmonar y presentó un perfil inflamatorio intenso, infección fúngica, sepsis, acidosis metabólica, hipertensión, trombosis, hemorragia, así como lesiones hepáticas, musculares y renales. Finalmente, el paciente evolucionó a un fallo multiorgánico y falleció. **Conclusión:** La inmunodeficiencia grave causada por el VIH, asociada a enfermedades cardiopulmonares subyacentes, contribuye a los resultados letales del COVID-19.

**Palabras clave:** COVID-19, HIV, coinfeción, fallo multiorgánico.

**INTRODUCCIÓN**

COVID-19 es una enfermedad multisistémica causada por el SARS-CoV-2 que se volvió una pandemia en 2019 (MIR T, et al., 2021) y llevó a una muerte aproximadamente de 7 millones de personas alrededor del mundo por marzo de 2023 (WHO, 2023). Los síntomas del COVID-19 varían de ligeros a severos, principalmente caracterizados por fiebre, tos seca, disnea, dolor de cabeza, faríngea y nasal, y cada vez más hemoptisis con a menudo síntomas no específicos (KADIRVELU B, et al., 2022).

Sin embargo, otros patrones ya han sido descritos, como la síndrome respiratoria aguda severa, coagulopatías, tromboembolismo, malabsorción intestinal, colitis hemorrágica, fallo renal, arritmias, isquemia y hemorragias en el sistema nervioso central, entre otros (MIR T, et al., 2021).

Entre los grupos de riesgo frecuentemente reportados, resaltamos a aquellos que ya tienen comorbilidades como obesidad, hipertensión, y diabetes, cuyos daños sistémicos pueden ser agraviados por la infección (NAVEED M, et al., 2021).

Las personas con inmunodeficiencias son también más a riesgo de adquirir SARS-CoV-2 infección y desarrollar severas complicaciones de COVID-19 ya que la respuesta antiviral se vuelve ineficaz (BANSAL N, et al., 2021), con el Virus Human Immunodeficiency (HIV) siendo uno de los más inmunosupresores patógenos, una vez el VIH lleva a la disminución de CD4 T- linfocitos, resultando en un debilitamiento de la respuesta inmune adaptativa (MAARTENS G, et al., 2007).

Hay importantes discrepancias en la literatura respecto a la diferencia en el patrón de morbimortalidad causada por SARS-CoV-2 entre las personas con HIV y aquellas que no. Algunos estudios ya han señalado que los casos de COVID-19 en pacientes con HIV no difieren significativamente de la población no-HIV (KANWUGU ON, ADADI P, 2021; DÍEZ C, et al., 2021). Por otro lado, dos metanálisis mostraron un mayor riesgo de mortalidad de COVID-19 entre las personas viviendo con HIV (MELLOR MM, et al., 2021; HARIYANTO TI e ROSALIND J, 2021).

En esta población, cuando la CD4+ cuenta < 200 células/µL, un mayor uso de la unidad de cuidados intensivos, una mayor utilización de ventilación mecánica, y una menor tasa de supervivencia fueron observadas, debido a la debilitación de la respuesta inmune (DANDACHI D, et al., 2021; KARMEN-TUOHY S, et al., 2020).

Además, la disminución de la inmunidad inducida por el VIH favorece la emergencia de infecciones oportunísticas, algunas de las cuales pueden afectar el hígado e intensificar el daño causado por SARS-CoV-2, como se ha observado para la histoplasmosis (PIPISTÒ L, et al., 2023; BASSO RP, et al., 2021, BERTOLINI M, et al., 2020), Pneumocystis jirovecii (ALSHARIF N, et al., 2023) y tuberculosis (WHO, 2021). COVID-19 también agrava las clínicas manifiestaciones de candidiasis oral (HAPID MH e DEWI TS, 2023) y herpes zoster (DAODU J, et al., 2022) en pacientes con AIDS.

En este contexto, el presente artículo reportará el clínico y laboratorio evolución de un caso de muerte debido a fallo multiorgánico resultante de SARS-CoV-2/HIV coinfección en un inmunocomprometida paciente con una historia de infecciones pulmonares recientes (tuberculosis y neumocistosis) y cardiopulmonar arresto que ocurrió en el día de hospitalización. Nuestro grupo pidió que el Comité de Ética de Investigación del Hospital Gaffrée y Guinle University Hospital use el datos disponibles en el sistema de registros médicos del hospital y el sistema digital para investigación. El proyecto fue evaluado y aprobado (CAAE: 52743721.4.0000.5258/Parecer 5.220.441).
CASE REPORT

An HIV-positive 33-year-old man (poor adherence to treatment), with a history of pulmonary tuberculosis in 2017 and reactivation in 2020, was admitted to the University Hospital's emergency room in November 2021 due to dyspnea and desaturation. On this occasion, computed tomography of the lung revealed a bilateral ground-glass pattern with a distribution suggestive of pneumocystosis (Figure 1A). The patient was then hospitalized and treated with Sulfamethoxazole and Trimethoprim, in addition to corticosteroid therapy with Prednisone. This protocol allowed him to evolve with an improvement of the symptomatology and subsequent discharge from the hospital.

Four months later, the patient returned to the University Hospital’s emergency department complaining of cough, fever, and diarrhea for seven days. During this visit to the hospital, he was agitated and tachypneic, with a heart rate of 150 beats per minute and an electrocardiogram profile compatible with sinus tachycardia. After acute pulmonary respiratory failure, oxygen catheter therapy was performed, but without response. Next, an oxygen mask with a reservoir at 15L/min was used, but the patient maintained tachypnea and agitation. To be hospitalized, the patient underwent a qRT-PCR test, and an active SARS-CoV-2 infection was verified. The patient was not yet vaccinated for COVID-19. The X-ray also found a ground-glass opacity pattern and a deep groove on the left side, indicating pneumothorax (Figure 1B).

On the same day, the patient evolved with cardiorespiratory arrest in pulseless electrical activity. The reversal of the picture occurred six minutes later with the use of 2 ampoules of adrenaline. Upon this scenario, the patient was transferred to a COVID-19 dedicated treatment center located in the same hospital with the diagnosis of severe COVID-19.

Figure 1. Thorax imaging exams of patient. Computed tomography with axial sectional plane showing ground-glass opacities (arrow) (A). Chest X-ray on the day of admission showing ground-glass opacities at the arrow and deep groove (circle on the left side) (B). Chest X-ray showing the pneumothorax on the left side (C).

The patient, at the time of hospital admission, was severely ill, sedated (Richmond Agitation-Sedation Scale -4), normotensive in use of amine (129/66 mmHg), tachycardic (134 beats per minute), tachypneic (25 respiratory incursions per minute), with myotic pupils and hemodynamically unstable. In the clinical evaluation, fungal lesions were found throughout the chest length and cyanotic right hand. During his stay in a few hours, it evolved to RASS -5 and became febrile (39°C), which motivated the opening of a sepsis protocol with 1L of crystalloid, in addition to treatment with Rocefin and Carithromycin, thinking about a probable pulmonary focus.

At this moment, arterial blood gas analysis showed metabolic acidosis, with a pH of 6.97, pCO₂ of 37mmHg, HCO₃ of 7mmHg, and lactate of 5mmol/L. Additional laboratory investigations were performed. The results also showed changes in urea and creatinine that were maintained throughout the hospitalization period (Figure 2A). The patient was also oliguric and had amber urine staining. Due to the picture suggestive of renal damage, the nephrology team started renal replacement therapy. On the third day after admission, an X-ray confirmed
pneumothorax (Figure 1C), and an ultrasound showed the absence of pleural slippage. As a conduct, surgery for closed pleural drainage was adopted. On the same day, a routine laboratory examination detected creatine phosphokinase (CK) of 5,185 IU/mL (reference value: 0 to 170 IU/mL) and creatine phosphokinase-MB (CK-MB) of 155 IU/L (reference value: 0 to 25 IU/L). On his fourth day, the CK value rose to 6,876IU/mL. Simultaneously, liver damage was observed through aspartate aminotransferase (AST) and alanine aminotransferase (ALT) parameters, as well as the pro-inflammatory state through ultrasensitive C-reactive protein (CRP) (reference values of 10 to 40mg/dL, 0.7 to 1.3mg/dL, and 0 to 5 mg/L, respectively) (Figure 2B).

On the following days of his admission, in addition to mechanical ventilation and hemodialysis, the patient began to need sodium nitroprusside to control the evolution of hypertension; his D-dimer dosage reached 10,000ng/mL (reference value: 500ng/mL) and returned to febrile peaks. On the eleventh day, a bronchoscopy was performed, in which an abundant amount of diffuse purulent secretion, reddish lesions with small whiteish blisters at the entrance of the lower lobes, and some areas of white lesion adhered diffusely to the mucosa were observed. When the examination was performed with entry through the right nostril, similar lesions were identified at the base of the tongue, epiglottis, and hypopharynx. Bronchoalveolar lavage culture identified the growth of *Escherichia coli* sensitive to Meropenem, so treatment with this antibiotic was initiated. The condition remained severe with evolutionary worsening, need for amines, fever, maintenance of elevated inflammatory parameters, metabolic acidosis, and anuresis. The bilirubin dosage (which until then was within the normal range) reached a value of 4.04mg/dL, increasing daily until reaching 8.80mg/dL seven days later (reference value: less than 1.30mg/dL). The blood count showed a high global count and percentage of neutrophils and lymphopenia (Figure 2C).

**Figure 2.** Biochemical and hematological parameters of the patient. Classic renal biomarkers (A), liver injury biomarkers and nonspecific markers of systemic inflammation (B), leukocyte variation (C), and red blood cell parameters. The dotted line represents exam reference values. CRP = C-reactive protein; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

Source: Junior F, et al., 2024.
On his 16th day of hospitalization, the patient had spontaneous bleeding from the nostril. Simultaneously, a drop in platelet count, global red blood cell count, and hemoglobin levels were observed (Figure 2D), constituting anemia of hemorrhagic origin. In addition, the patient progressed from hyper to hypotension, requiring suspension of sodium nitroprusside and administration of noradrenaline. Cyanosis, which was already occurring in the hands, also began in the feet. On the same day, the result of the CD4+ cell count was also released, which was only four cells/mm³ (severe immunodepression; AIDS).

On the following day, the 17th after the admission, the vascular surgery team evaluated cyanosis of the upper and lower limbs, defining the need to wait for the delimitation of the lesion for amputation.

After twenty-six days of hospitalization, the patient was already diagnosed with multiple organ failure and, upon realizing that he was severely hypotensive (60 x 20mmHg), the doses of amine were quickly increased, and the Propofol used for sedation was stopped. However, when performing this procedure, the patient evolved with a disorganized rhythm on the monitor and absence of pulse on palpation, configuring cardiac arrest in electrical activity without a pulse. Cardiac resuscitation measures were initiated, but without success, thus verifying the death of the patient.

**DISCUSSION**

This case report was intended to discuss the coinfections of HIV/AIDS and COVID-19 of a single patient with a recent history of pulmonary tuberculosis and pneumocystosis. In this case study, the patient was admitted and was observed during 26 days of hospital stay. Although COVID-19 affects all types of individuals, patients with HIV and multiple comorbidities, including advanced chronic obstructive lung disease, are reported to be at risk of the worst outcome (YANG et al., 2020).

COVID-19 is a contagious disease with recurrent and severe pulmonary involvement, which can lead to viral pneumonia, hospitalizations, and deaths. According to the literature, SARS-CoV-2 recognizes ACE-2 receptors for entry into target cells, and depletion of these molecules, especially in the lung, stimulates increased production of angiotensin II, which in turn stimulates angiotensin II receptor type 1a. This cascade causes increased vascular permeability in the lung and causes acute lesions (HOFFMANN M, et al., 2020) that, on imaging tests, can be visualized as ground-glass opacities (Figure 1). This finding represented 90.95% of the elemental lesions observed in a study of tomographic aspects of pneumopathies associated with COVID-19 (TIEMTORE-KAMBOU BM et al., 2022). In general, the patient's symptomatology at the time of admission is characteristic of severe cases of COVID-19 (KADIRVELU B, et al., 2022), and recent previous damage caused by tuberculosis and pneumocystosis may have aggravated pulmonary manifestations. A non-fatal case of spontaneous pneumothorax in a patient with pulmonary infections, AIDS, and COVID-19 had already been reported (PHILIP et al., 2023). Additionally, angiotensin II is vasoconstrictive (BUDHIRAJA R, et al., 2004), which partly explains the blood pressure changes observed in the patient.

It is important to note that it is already well-described that COVID-19 is a highly inflammatory disease that can affect several organs (MIR T, et al., 2021). In the case described, C-reactive protein changes show this intense and constant inflammation, which is also a consequence of uncontrolled HIV infection (PENG X, et al., 2020). It is also possible to observe liver damage (by increasing AST and ALT) to skeletal and cardiac striated muscles (by increasing total CK and CK-MB) and severe renal impairment (by alteration of urea, creatinine, and need for hemodialysis). At the end of the interaction period, multiple organ failure had already been observed.

These conditions are rare and mainly affect individuals with comorbidities. In this reported case, the low CD4+ cell count allowed a favorable environment for the proliferation and action of the virus without an adequate immune response. This reduction is characteristic of both untreated HIV infection and severe cases of COVID-19 (BO XU, et al., 2020). In addition to tuberculosis that was not fully resolved, the patient had already developed pneumocystosis four months earlier, a classic opportunistic disease among people with HIV in the framework of AIDS (DE FIGUEIREDO IR, et al., 2019). During his stay, the patient also presented fungal lesions on the chest and presented sepsis at different times along the days of hospitalization.
The high values of D-Dimer reflect a context of coagulation imbalance that, associated with reduced platelet count, suggests intense thrombus formation. It has already been reported that severe cases of COVID-19 have a pro-thrombotic profile. In a study conducted with 150 COVID-19 patients admitted to intensive care units, 64 (42.6%) had significant thrombotic complications associated with virus infection (HELMS J, et al., 2020). These thrombi may have been the cause of cyanosis with subsequent necrosis of the extremities reported in this study, as well as the drop in platelet count. On the other hand, thrombocytopenia caused hemorrhagic episodes, which culminated in anemic conditions and increased absolute and relative neutrophil counts. The increase in these cells is evidence of the progression to sepsis, which could contribute to establishing biomarkers for clinical usage (LEITE RO, et al., 2023). Decreased lymphocyte counts are joint in severe cases of COVID-19 and are usually associated with a worse prognosis (PENG X, et al., 2020).

Finally, it is worth highlighting that the overlapping damage caused by infections and low immunological levels are added to the impact of cardiopulmonary impairment occurring after successive cardiorespiratory arrests, which, it themselves, already have a solid potential to damage the cardiovascular, neurological, pulmonary, renal, and metabolic systems (RAVETTI CG, et al., 2009). The severe manifestations of COVID-19 can be prevented through vaccination. Studies already show that people living with HIV can present similar protection results from the vaccine when compared to individuals without HIV (PLUMMER MM e PAVIA CS, 2021). Vaccination is still highly recommended, especially when the individual already has AIDS (CDC, 2023). However, a systematic review with meta-analysis showed that vaccine acceptance among people living with HIV is still less than 70%. Among the main factors associated with this resistance would be higher monthly income, history of chronic disease, being non-homosexual, COVID-19-related medical mistrust, not knowing anyone who died of COVID-19, general vaccine refusal, believing oneself to be immune to COVID-19, negative attitude to the vaccine, safety, and side effects, concerns about efficacy, distrust in familiar sources of vaccine-related information and using social media as a source of information on COVID-19 (EJAMO JY, et al., 2023).

At the time of the patient's death, vaccines against COVID-19 had already been available in the Unified Health System for a few months. Still, the patient was not immunized. Considering that he had also abandoned treatment for HIV, the success of protection against COVID-19 among people living with HIV must begin by combating the natural resistance that a large part of this population has against the vaccine and raising awareness about the importance of immunization, especially among those who already evolved to AIDS.

This reported case highlights the understanding of the relationship between HIV and SARS-CoV-2 and its importance in public health implications. This fatal case due to multiple organ failure showed the importance of treatment of HIV infection and vaccination against SARS-CoV-2 to reduce the chances of evolution to severe and fatal COVID-19. It also underlines the main severe manifestations in a single patient, who simultaneously presented an inflammatory solid, thrombotic, hemorrhagic profile with cardiovascular dysregulation and pulmonary, hepatic, muscular, and renal lesions.

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