Kaposi's sarcoma, syphilis and neurocryptococcosis in an HIV-positive patient

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ABSTRACT

Human immunodeficiency virus (HIV) infection has become a worldwide public health problem in recent decades. The main characteristic of HIV is the suppression of the immune system by attacking CD4+ T lymphocytes, which weakens the immune system and makes the individual susceptible to opportunistic infections, secondary neoplasms, and neurological diseases. This study aims to report and discuss the case of an HIV-positive patient who presented concomitantly Kaposi's Sarcoma (KS), primary syphilis, and neurocryptococcosis, all HIV-related. This is a 31-year-old male patient who sought care at the reference hospital with violaceous skin lesions on the face, upper limbs and chest, with a three-month evolution. Dermatological examination showed infiltrative erythematous-violet plaques, with regular, elevated, scaly edges and varying diameters. He obtained positive serology for anti-HIV and VDRL antibodies, initiating antiretroviral therapy (ART) and treatment protocols for primary syphilis. The patient returned to the service 30 days after hospital discharge, complaining of severe headache, refractory to analgesia with opioids, associated with persistent vomiting. Cranial computed tomography was performed and did not demonstrate alterations; later CSF puncture showed the presence of cryptococcus. A therapeutic scheme for neurocryptococcosis was started, and two other CSF punctures were performed to relieve the pain. This report agrees with the medical literature, reaffirming that HIV-positive patients present a greater predisposition to conditions such as KS, syphilis, and neurocryptococcosis. Thus, the study illustrates with uniqueness the simultaneous occurrence of complex clinical manifestations in the same immunosuppressed patient.

Keywords: Opportunistic infections, Sarcoma Kaposi, Cryptococcosis, Acquired Immunodeficiency Syndrome, HIV.

INTRODUCTION

Human immunodeficiency virus (HIV) infection has become a global public health problem in recent decades. It is estimated that by the end of 2019, 38 million people worldwide were living with HIV, and among them, approximately 7.1 million were unaware of their infection[1]. The main characteristic of HIV is the suppression of the immune system due to the attack on CD4+ T lymphocytes, which weakens immunity and makes the individual susceptible to opportunistic infections, secondary neoplasms, and neurological diseases[2].

Acquired syphilis (AS), a sexually transmitted infection (STI) prevalent in HIV-positive patients, caused by the spirochete *Treponema pallidum*, leads to clinical manifestations such as genital ulcers, skin lesions, fever, meningitis, neurological syndromes, and others, in the three clinical stages if not adequately treated. Although syphilis does not have defining characteristics that determine the advanced stage of HIV infection, such as opportunistic diseases and secondary neoplasms, the presence of ulcerative lesions caused by syphilis increases the risk of HIV co-infection by approximately 18 times[3,4]. This correlation is reinforced by risky sexual behaviors that expose the sexually active population to STIs, as well as the increase in syphilis cases in Brazil over the past five years[4,5].

In addition to the aforementioned co-infection issue, this study highlights Kaposi's Sarcoma (KS) among the opportunistic diseases secondary to HIV. KS, first described in 1872 by Moritz Kaposi as an angioproliferative tumor in elderly men, is the most common neoplasm associated with Acquired Immunodeficiency Syndrome (AIDS). Therefore, it is one of the main indicators for suspecting the disease. KS has been stigmatized among HIV-positive patients due to its characteristic visible cutaneous manifestation. While most cases have a benign

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course with a good response to various treatments, severe cases can lead to complications[6].

Among the opportunistic diseases, HIV also predisposes the individual to cryptococcosis, a systemic mycosis caused by two etiological agents: *Cryptococcus gattii* and *Cryptococcus neoformans*. The latter is responsible for the majority of cases with meningoencephalic presentation, affecting nearly all immunosuppressed patients[7]. It is estimated that neurocryptococcosis has an annual incidence of 223,000 cases and 180,000 deaths among individuals infected with the human immunodeficiency virus, with most of these cases occurring in the African continent[8].

The most severe clinical presentation, also discussed in this study, affects the central nervous system. Transmission usually occurs through inhalation of infected propagules or spores found in the feces of pigeons of the *Columba livia* species. Subsequently, they reach the lungs and then spread to the central nervous system (CNS). This form is considered the most dangerous due to its neurological repercussions, often accompanied by intracranial hypertension. If left untreated, it can lead to complications such as amaurosis[9].

Therefore, this review aims to highlight, through a case report, the unprecedented occurrence of these aforementioned pathologies infecting the same individual, causing synergistic and conflicting repercussions. The project was approved by the Ethics and Research Committee of Univás (Opinion number 4,845,542) and the participant signed the Free and Informed Consent Form authorizing their participation and the future use of the data generated.

CASE REPORT

WCG, male, 31 years old, physical educator, without previous comorbidities, born in a city in the south of Minas Gerais (MG), currently resident in the state of Rio de Janeiro (RJ), phototype III according to the Fitzpatrick Classification.

He presented violaceous skin lesions on his face, upper limbs, and posterior thorax, with three months of evolution. He sought medical care in the city of origin, where serology tests revealed positive antibodies for HIV and a positive rapid test for syphilis. He then returned to MG to initiate antiretroviral therapy (ART) and was hospitalized for further investigation and evaluation by the Oncology team.

The patient had the necessary medications, as he had been in consultation at an Infectology outpatient clinic before returning to MG, but had not started it. During hospitalization, a VDRL test was performed, resulting in a positive titer of 1:32. As he had not yet been treated for syphilis, he received two doses of Benzathine Penicillin, 2,400,000 units each. For further investigation, the following tests were requested: bronchoscopy, upper digestive endoscopy (UGE), biopsy of skin lesions, and computed tomography (CT). The head CT showed subcutaneous nodules, the chest CT revealed mediastinal lymphadenopathy and focal consolidations in the right and left regions, as well as subpleural micronodules. The abdominal CT indicated lymph node enlargement in the pelvic, mesenteric, and retroperitoneal regions. Serological tests were also performed to screen for other potential opportunistic infections, including cytomegalovirus, toxoplasmosis, hepatitis B and C, and sputum bacteriology to detect Koch's bacillus. All these serologies yielded negative results, and no Koch's bacillus was found. Lymphocyte count and viral load were monitored to assess immune function, with the following results: CD3: 1176 cells/mm³ (718-2494), CD4: 43 cells/mm³ (456-1492), CD8: 1064 cells/mm³ (272-1144), and viral load: 1320 copies/mm³.

Dermatological examination revealed erythematous violaceous infiltrative plaques with regular, raised, scaly, non-pruritic edges and variable diameters. The most prominent lesion was located on the nasal region of the face (Figure 1), and another smaller lesion was observed on the upper part of the posterior chest (Figure 2). The anatomopathological and immunohistochemical exams showed moderate capillary proliferation of the superficial and reticular dermis, branching, and cytological atypia in endothelial cells associated with chronic inflammatory infiltrate and hemosiderin deposits. Macroscopically, the findings are characteristic of dermal KS, plaque stage. Following evaluation by the Oncology team and investigation of the KS progression, the patient was discharged.

However, he returned to the hospital 30 days later, complaining of a severe unresponsive headache to opioid analgesics. He also had persistent vomiting but no fever. Cranial CT was performed at the time, and it showed no abnormalities compared to the previous scan performed on the first hospitalization. It was opted to perform a cerebrospinal fluid puncture (CSF). A China ink test on the CSF sample revealed the presence of cryptococcus. The patient was started on Amphotericin B at a daily dose of 40 mg, with a target dose of 800 mg. Due to ongoing severe headache despite analgesic treatment, two additional CSF punctures were performed to alleviate the pain. Symptoms started improving. After reaching the target dose, a search for cryptococcus using China ink in the CSF sample yielded negative results. Consequently, the patient was discharged. He is currently undergoing outpatient follow-up at the Oncology service and the STD-AIDS clinic in the municipality.

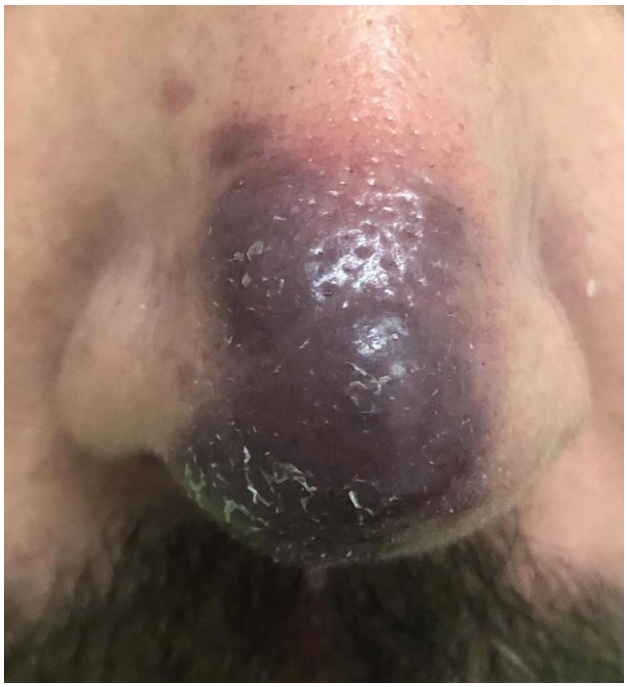

Figure 1: Nose- infiltrative erythemo-violaceous plaque.

DISCUSSION

Briefly, due to the natural history of the disease, in the first weeks, the virus infects the CD4+ T lymphocytes in the lymphoid tissues, spreads throughout the body, and there is the development of the host's immune response specific to HIV. Even in a state of stable viremia, the period is silent until around the first to third weeks, when some non-specific clinical manifestations, such as fever, headache, and pharyngitis, illustrate the acute retroviral syndrome (RAS). It is self-limited and very similar to other viral infections, comprising the acute phase of the disease. In untreated patients, it is estimated that ten years is the average time between infection and the onset of the disease[10,11]. Chronic infection encompasses the clinical latency phase and the symptomatic phase, which have repercussions due to the actions of HIV. During this time, HIV kills a significant number of mucosal CD4+ T lymphocytes, leading to manifestations such as mild leukopenia, frequent bacterial infections, low fever, fatigue, oral lesions, and enteropathies. These manifestations result in diarrhea, increased gastrointestinal permeability, inflammation, and malabsorption. Without proper treatment, this

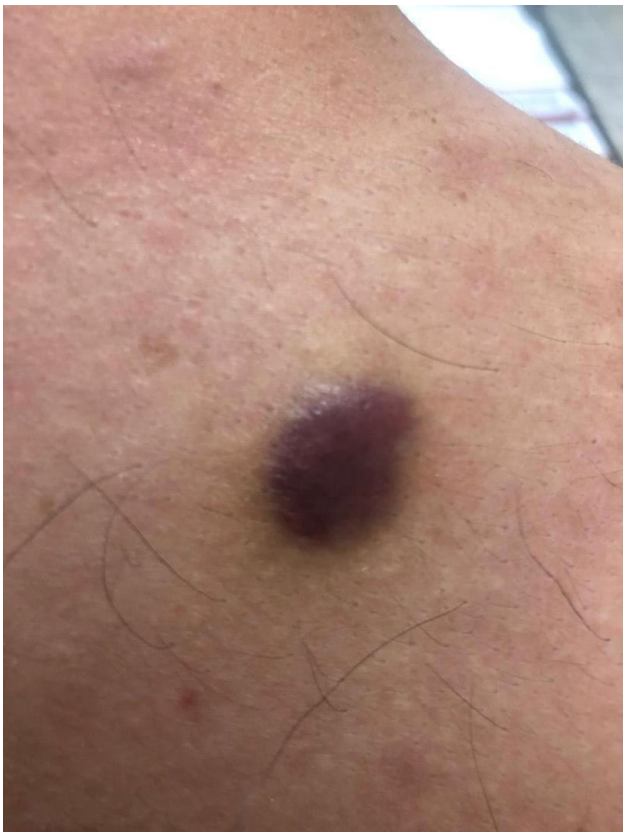

Figure 2: Posterior upper chest - infiltrative erythemo-violaceous plaque.

syndrome weakens the patient and may lead to a progressive condition characterized by weight loss, anemia, dehydration, malnutrition, and other manifestations. This scenario increases the risk of several opportunistic infections, especially cryptococcosis, and secondary neoplasms like KS and neurological diseases. The manifestation of opportunistic infections and neoplasms is decisive and defines the last phase of the disease: acquired immunodeficiency syndrome (AIDS)[11].

It is worth noting that, although there is no cure for HIV infection, drug treatment with antiretrovirals prevents the multiplication of the virus in the body, avoiding damage to the immune system and, consequently, increasing the lifespan and quality of life of infected individuals. This drug treatment has been free of charge by the Unified Health System (SUS) since 1996 and is part of the therapeutic itinerary along with other behavioral and structural interventions, such as access to information, counseling, adherence support, and follow-up with a multidisciplinary team[12].

KS originates from endothelial and immune cells infected with human herpesvirus type 8 (HHV-8), also known as Kaposi's sarcoma-associated herpesvirus (KSHV). The condition is divided into four types: epidemic (associated with AIDS), iatrogenic, classic, and endemic, with HHV-8 being the common causative agent, present in more than 95% of all cases. The clinical course of each form is different; therefore, it is believed that there is an influence of other factors, such as the extent of immunosuppression. HIV-associated KS has worse evolution compared to other types because the infection leads to increased HHV-8 replication. Presentation is less aggressive in patients already receiving highly active antiretroviral therapy (HAART). It usually has a variable clinical course, ranging from indolent mucocutaneous lesions to extensive visceral involvement[13].

The multicentric nature of the tumor contributes to the fact that KS cutaneous lesions can occur simultaneously in any region of the body, although they are generally concentrated in the lower extremities and the head and neck region. They are pigmented, painless, palpable, and non-itchy. They may appear pink and red initially, and with the progression of the disease, they can turn violet and brown, evolving from a macular appearance to plaques that can further develop into larger nodules (tumor lesions) and vary in size from millimeters to centimeters in diameter. Tumors can also involve lymph nodes and visceral organs, such as the gastrointestinal and respiratory tracts. Differential diagnoses for KS include cutaneous lymphoma, bacillary angiomatosis, pyogenic granuloma, aneurysmal fibrous histiocytoma, and acroangiodermatitis, among others[14,15].

The report also studied the presence of neurocryptococcosis, a common opportunistic fungal infection in patients with AIDS. Neurocryptococcosis is caused by the fungi *Cryptococcus neoformans* or *Cryptococcus gattii*, with meningitis and meningoencephalitis being the most common manifestations[7]. The patient experienced an atypical headache that was unresponsive to medications due to the neurotropism of the fungus in the body. Additionally, fever may present from the early stages of the infection and worsen when lying down. Other typical manifestations include intracranial hypertension, nausea, vomiting, blurred vision, and drowsiness. While there have been reports of coexistence between KS and infections such as cryptococcosis in HIV-infected patients, the incidence of such cases has decreased in developed countries since the introduction of ART. Cryptococcal disease usually develops when the CD4+ lymphocyte count drops below 100 cells/μL[16].

Co-infection between syphilis and HIV has great clinical relevance, given its increasing incidence and the synergy between these two sexually transmitted infections[17]. This phenomenon can be attributed to the fact that HIV accelerates the natural progression of syphilis by altering components of the infected individual's immune system. In addition, syphilis facilitates the transmission and acquisition of HIV, as demonstrated in several studies where infection with *Treponema pallidum* nearly tripled the risk of acquiring HIV. This correlation can be explained by the syphilitic ulcers in the genitalia, which significantly increases the transmission and acquisition rates of HIV due to the compromised protective epithelial barrier. Moreover, the ulcer site is rich in macrophages and activated lymphocytes, creating an immune microenvironment with highly expressed receptors for HIV[18].

Since the literature is quite clear about the relationship between HIV and syphilis, we know

that both STIs can often occur associated with co-infection situations. According to studies, there is a predominance of 9.5% of cases of syphilis in patients with HIV. In contrast, patients infected with *Treponema pallidum* are between 2 and 9 times more likely to be contaminated with HIV, mainly due to the lesions in the mucous membranes and epithelial damage caused by syphilis, illustrating the opportunistic characteristic of this disease. This can be explained because HIV accelerates the natural history of syphilis by modifying elements of the infected individual's immune system. Furthermore, the injury site is rich in activated macrophages and lymphocytes, which serves as an immuno-microenvironment for highly expressed HIV receptors[18,19].

As indicated in the literature, the patient under discussion presents the proven co-infection simultaneously in his pathological history. Despite the early diagnosis and rapid intervention of the case, the correlation between the STIs may lead to a temporary condition of increased HIV viral load and a decrease in the CD4 T cell count - mainly in secondary syphilis -, opening up room for a greater probability of developing neurosyphilis[19].

Additionally, the diagnosis and, consequently, the therapeutic management of these STIs is impaired due to HIV infection falsifying serology for syphilis and modifying its classic manifestations, making it difficult to differentiate its stages, creating challenges in decision-making. There are also obstacles in controlling the "cure" of syphilis in people co-infected with HIV, as it alters parameters to guide successful treatment[20,21].

No similar reports were found regarding the occurrence of the three pathologies in the context of immunosuppression in the main databases of the medical literature, evidencing the originality of the presented case. Thus, it reinforces the importance of thoroughly investigating all possible pathologies and clinical manifestations in immunosuppressed patients. It also recommends adopting a therapeutic approach based on scientific evidence to enable early detection of patients and implement measures that enhance their quality of life.

Finally, discussing this case emphasizes and illustrates the variety of each clinical manifestations and their correlations, as presumed by the medical literature. It reaffirms that patients who test positive for HIV have a more significant predisposition for manifestations such as Kapos's sarcoma and/or neurocryptococcosis.

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1. Collection of clinical history;
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3. Analysis and interpretation of data, laboratory and imaging tests;
4. Organization of collected data;
5. Research on topics in the medical literature;
6. Writing of the preliminary version;
7. Preparation of the introduction, case report and discussion;
8. Resume writing;
9. Final revision;
10. Standardization in the norms according to the magazines;
11. Compliance with being responsible for the integrity of any part of the study.

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