A typical presentation of a patient with constitutional syndrome and HIV

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Case presentation

We present the clinical case of a 28-year-old patient who was seen as an outpatient by infectious disease, having been diagnosed with stage III HIV infection three months prior to the visit. The patient reported having started highly active antiretroviral therapy with tenofovir/emtricitabine two weeks before, and, since then, had experienced objective fevers (38.3-39°C), chills, nocturnal diaphoresis, anorexia and unquantified weight loss.

On the systems review, the patient mentioned episodes of holocranial headaches which improved with nonsteroidal anti-inflammatory drugs (NSAIDs). The patient›s relevant history included a previous hospitalization during which he was diagnosed with meningeal tuberculosis through a positive cerebrospinal fluid polymerase chain reaction for tuberculosis (PCR-TB). Severe cytomegalovirus (CMV) retinitis was also found, along with oropharyngeal candidiasis, and he was therefore taking rifampicin/isoniazid, trimethoprim/sulfamethoxazole, fluconazole and pyridoxin. On admission, he had a fever (38.4°C), a violaceous pigmented lesion on the right nasal ala and decreased breath sounds throughout. Infectious disease decided to immediately refer the patient to the emergency room for testing.

Specialist

This was a 28-year-old patient with an inpatient diagnosis of HIV infection with a $CD4^+$ count of 6 cells/mm^3, who required complementary tests during his hospital stay (Table 1).

On consult, he presented with a prolonged febrile syndrome associated with unintentional weight loss and headache related to the beginning of antiretroviral therapy, which could initially indicate a paradoxical immune reconstitution inflammatory syndrome (IRIS) (1). Likewise, the physical exam was directed toward looking for a common infectious site and, given the generalized breath sound reduction, it was considered to likely be pulmonary (2). An additional point of interest was a violaceous lesion on the right nasal ala.

The possible syndromes included fever of unknown origin (FUO) with special considerations for HIV patients (3). Acute retroviral syndrome was proposed among the possible options, which occurs two weeks after the primary infection, coinciding with the peak HIV viremia, and manifests as a mononucleosis-like syndrome, usually with a nonconfluent skin rash (4). However, this skin manifestation was not present in this case and, due to the timing of the symptoms, was considered unlikely. In this case, IRIS was a valid option, supported by the timing (1-2 weeks after beginning antiretroviral therapy), low CD4+ count and history of opportunistic infections (Table 2) (5).

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Table 1. *Paraclinical tests from previous hospitalizations.*

Paraclinical tests prior to admission		
Date	Paraclinical test	Result
06/16/21	Nasal ala skin biopsy	Interstitial infiltrate with a multifocal lymphoid appearance with flattened nuclei extending to the deep areas.
	Anti HIV	Reactive 46.9
07/07/21	VDRL	Nonreactive
	FTA-ABS	Nonreactive
	HCV antibodies	Negative
	Toxoplasma IgG IgM	Negative
07/09/21	HIV viral load	177,337 cop/mL
	CD4 count	6 cel/mm^3
	CSF	Glucose: 43 mg/dL, protein: 56 mg/dL, VDRL nonreactive, Gram with no germs. KOH negative, India ink negative, lactate: 0.8 mmol/L
07/11/21	Urinary *Histoplasma capsulatum Ag*.	Negative
07/14/21	Bronchoalveolar lavage	MTB PCR negative, KOH negative
08/03/21	CMV viral load	613 copies/mL
	MTB PCR in CSF	Detectable, rifampicin-sensitive
10/28/21	Cryptococcal Ag.	Negative

Ag: Antigen; CMV: Cytomegalovirus; PCR: Polymerase chain reaction; MTB: Mycobacterium tuberculosis

However, this should be a diagnosis of exclusion, and HIV-related diseases should be ruled out. These are basically categorized into two large groups, the first being opportunistic infections like tuberculous and non-tuberculous bacteria, which were ruled out in this patient since he was receiving second phase treatment for meningeal tuberculosis with good treatment adherence. Other causes could be endemic mycoses, particularly histoplasmosis and cryptococcosis, as well as toxoplasmosis, which is important to rule out in an immunosuppressed patient with febrile syndrome, adenomegaly (especially cervical) and a holocranial headache (6).

The second large group that must be studied consists of HIV-related malignancies, especially B-cell lymphomas, with the most common being diffuse large B-cell lymphoma, followed by multicentric Castleman disease and Kaposi sarcoma, the latter two related to profound cellular immunodeficiency and human herpesvirus-8 (HHV-8) infection (7).

Moderator: the initial tests performed on the patient on admission to the emergency room are detailed in Table 3.

In addition, a chest computed tomography scan showed significant changes compared to previous images (Figure 1), which led to a pulmonology consult.

Diagnostic imaging of patients with HIV and pulmonary involvement usually begins with a chest x-ray, the findings of which may be similar to those of immunocompetent patients (8). However, the characteristics of the lesions are determinant in specifying complementary tests (Figure 2) and contribute to the diagnosis based on whether they are solid lesions or have a diffuse alveolar occupation pattern, and whether they are accompanied by effusions, atelectasis or decreased lung volume. Their location gives guidance regarding the various types of causal germs and thus determines if they are likely to indicate an infectious or malignant process in patients with HIV (Figure 3).

Table 2. *CD4 count.*

CD4 Count	Opportunistic infection
<500	Tuberculosis, Bacterial pneumonia, Herpes zoster, Oropharyngeal candidiasis, Non-typhoidal salmonellosis, Kaposi sarcoma, Non-Hodgkin lymphoma,
<200	*Pneumocystis jirovecii pneumonia*, Chronic herpes simplex ulcers, esophageal candidiasis, Isospora belli diarrhea, HIV wasting syndrome, HIV-associated dementia
<100	Cerebral toxoplasmosis, Cryptococcal meningitis, Cryptosporidiosis, Microsporidiosis, Disseminated cytomegalovirus and *Mycobacterium avium* complex infections
<50	Cytomegalovirus, *Mycobacterium avium* complex (MAC), *Toxoplasma gondii* infections

Source: Compiled by the authors.

Table 3. *Admission laboratory tests.*

Admission laboratory tests (10/12/2021)	
Laboratory parameter	**Result**
Leukocytes	13,400 mm^3
Neutrophils	12,500 mm^3
Lymphocytes	340 mm^3
Eosinophils	0 mm^3
Hemoglobin	7.7 g/dL
Hematocrit	24 g/dL
MCV	95 fL
MCH	30 pg/c
Platelets	140,000 mm^3
Creatinine	1.6 mg/dL
BUN	41 mg/dL
Potassium	3.8 mEq/L
Sodium	135 mEq/L
Chloride	108 mEq/L
Ferritin	1,690 ng/mL
Transferrin saturation	13 %
Reticulocytes	0.24 %

MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; BUN: Blood urea nitrogen

Specialist

Pulmonary tomography revealed the presence of seven nodular lesions on the right and five on the left, approximately 2-3.5 cm in size. These lesions, especially the apical ones, had increased in number and size compared with previous studies. Given their peribronchovascular distribution, the differential diagnosis should focus on infectious diseases like aspergillosis, cryptococcosis and cytomegalovirus (8).

The possibility of HIV-related malignancies should also be considered, including dissemination, such as Kaposi sarcoma which typically shows peribronchovascular interstitial thickening, described as flame-shaped, irregular or poorly defined nodules, and thickening of the interlobular septa secondary to tumor cells or perilesional edema. Lymphadenopathy and pleural effusion may also be found. Macular reddish-purple lesions at the bronchial bifurcations should also be looked for on fibrobronchoscopy (9).

Moderator: the pulmonology consult suggested a broad differential, highlighting the need to rule out Kaposi sarcoma, since the previous molecular and microbiological tests were negative, ruling out any type of opportunistic infection. Therefore, a wedge biopsy of the lung parenchyma was proposed.

Thoracoscopy report

A violaceous subpleural nodule with approximately 1 cm of pleural puckering in the right lower lobe, and a second approximately 2 cm violaceous nodule close to the hilum in the middle lobe, which could not be resected due to its proximity to the vessels.

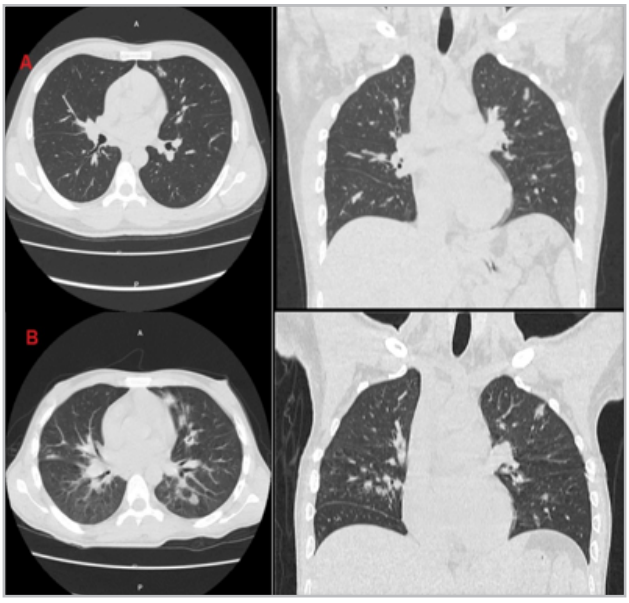

Figure 1. *Pulmonary tomograpphy.* **A.** *Tomography taken during the first hospitalization, three months before.* **B.** *Tomography taken on admission..*

Microscopic description of the biopsy

The lung tissue sections showed neoplastic infiltration consisting of short, spindle-shaped elements with moderate pleomorphism and anisokaryosis, forming small rays around multiple vascular canals with a prominent endothelium. Several mitoses were found, without necrosis. The neoplastic cells were HHV-8 and CD34^{+} positive and AML, desmin, CK and S100 negative. The adjacent pulmonary tissue showed no significant abnormalities.

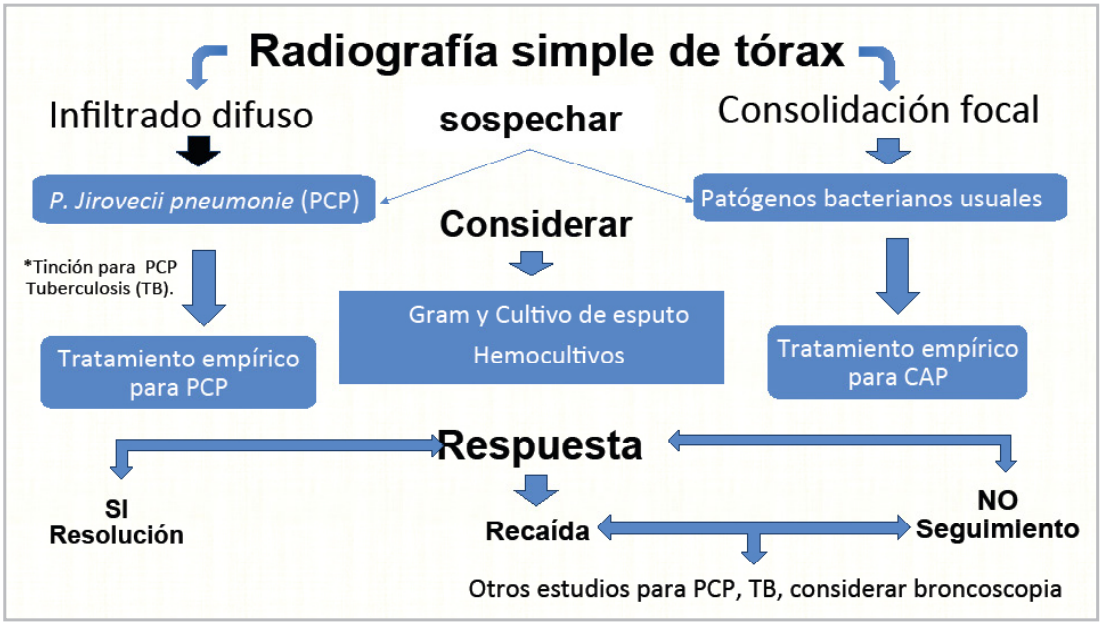

Figure 2. *Complementary tests.*

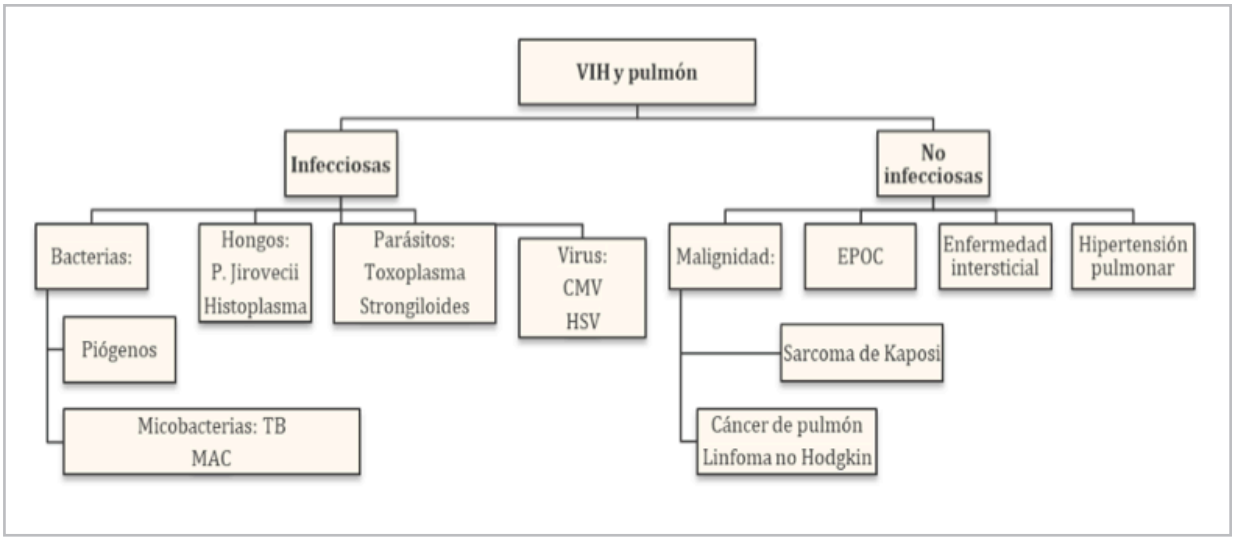

Figure 3. *Differential diagnosis of patients with HIV and pulmonary involvement.* (**Source:** *Compiled by the authors.*)

Specialist

These histopathological findings confirmed the diagnosis of Kaposi sarcoma. The classic findings, such as fusiform cells on hematoxylin-eosin staining, vascular proliferation and erythrocyte extravasation, support this diagnosis, which is the most common AIDS defining malignancy (males: 49%) (10). The markers, $CD34^{+}$ and HHV-8 staining, rule out other pathologies. Since pulmonary involvement suggests widespread involvement, treatment is aimed at controlling immunodeficiency, along with high intensity antiviral treatment. Systemic treatment, ideally with liposomal doxorubicin, is considered appropriate (11). Although the evidence has shown a favorable survival of patients with HIV and Kaposi sarcoma, the overall survival will depend on each patient's antiretroviral therapy complications, cancer relapses, infectious complications and intrinsic immunological response. In this case, the patient was discharged to continue antiretroviral treatment under the infectious disease department and follow up with pulmonology, oncology and dermatology.

Moderator: This case allowed us to conduct an extensive literature search to evaluate the diagnostic algorithm for patients with advanced HIV coupled with a constitutional syndrome.

Specialist

Once again, we recognize history taking as an invaluable tool for arriving at the correct diagnosis. The various clinical presentations must be kept in mind to personalize and adjust the context, as in this case with a patient who had severe multifactorial immunosuppression.

One of the main considerations to keep in mind in approaching the case of an immunocompromised patient is the local epidemiology. The most common germs affecting immunocompetent patients will also be the main agents infecting immunocompromised patients, without disregarding the importance of opportunistic pathogens in this clinical scenario.

Human immunodeficiency virus infection has been closely related to a higher risk of developing various types of cancer, mainly due to sustained immunosuppression which reduces the ability of the immune system to control abnormal cell growth. Of these cancers, Kaposi sarcoma, non-Hodgkin lymphoma and certain types of skin cancer are among the most prevalent. Understanding the specific interactions between HIV and hemolymphatic and solid organ malignancies continues to be crucial for guiding prevention, early detection and treatment strategies in this vulnerable population.

References

1. **Gopal R, Rapaka RR, Kolls JK.** Immune reconstitution inflammatory syndrome associated with pulmonary pathogens. *Eur Respir Rev* 2017;**26**. https://doi.org/10.1183/16000617.0042-2016.
2. **Knight CL.** Physical Examination in Human Immunodeficiency Virus Disease. *Med Clin North Am* 2022;**106**:527–36. https://doi.org/10.1016/J.MCNA.2022.01.001.
3. **Hot A, Schmulewitz L, Viard JP, Lortholary O.** Fever of unknown origin in HIV/AIDS patients. *Infect Dis Clin North Am* 2007;**21**:1013–32. https://doi.org/10.1016/J.IDC.2007.08.003.
4. **Haidar G, Singh N.** Fever of Unknown Origin. Https://DoiOrg/101056/NEJMra2111003 2022;386:463–77. https://doi.org/10.1056/NEJMRA2111003.
5. **Kazer SW, Walker BD, Shalek AK.** Evolution and Diversity of Immune Responses during Acute HIV Infection. *Immunity* 2020;**53**:908–24. https://doi.org/10.1016/J.IMMUNI.2020.10.015.
6. **Stephens RJ, Liang SY.** Central Nervous System Infections in the Immunocompromised Adult Presenting to the Emergency Department. *Emerg Med Clin North*

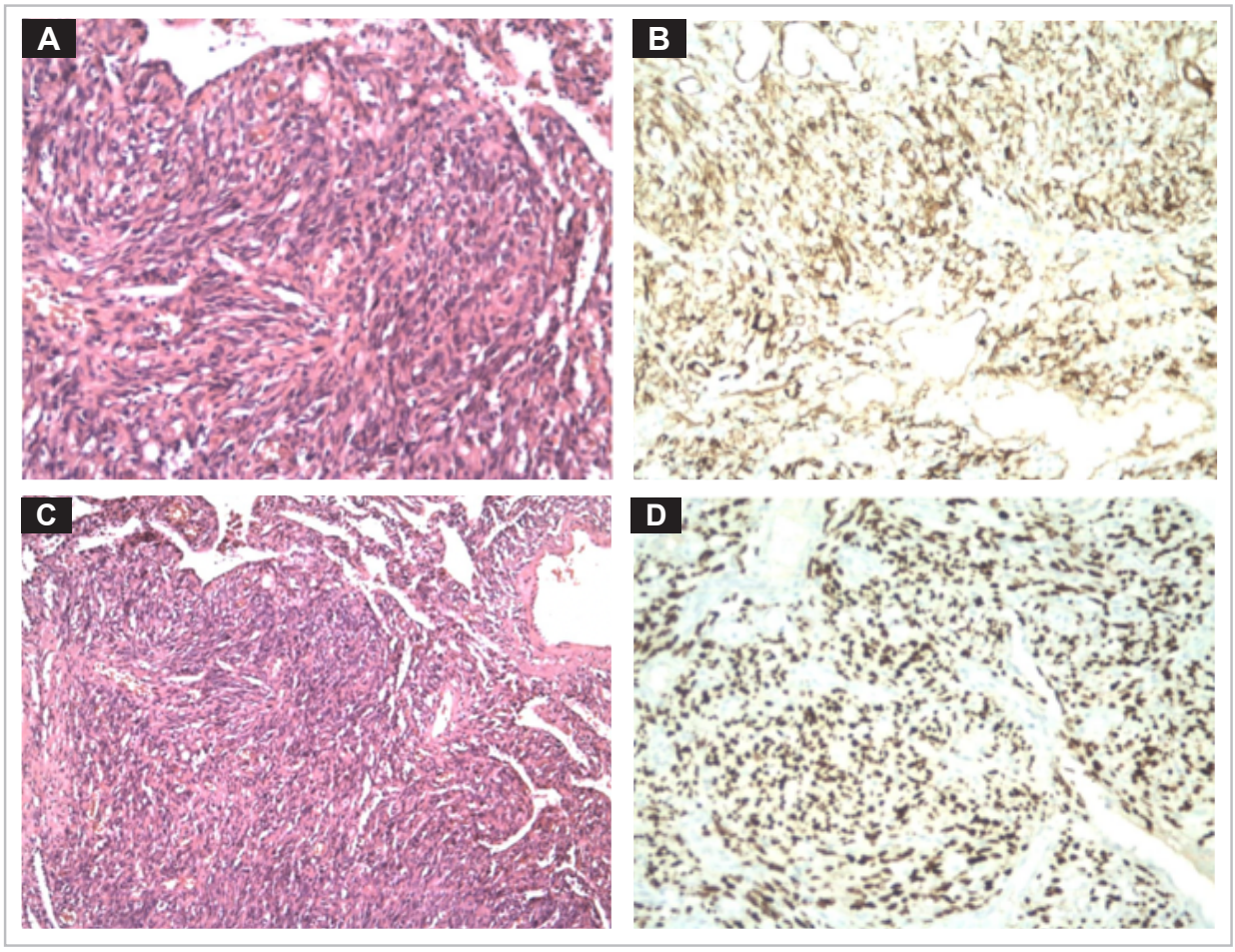

Figure 4. *Histopathological tests* **A.** *Hematoxylin-Eosin, 10x. Neoplasm constituted of fusiform cell nodules forming rays; there are vascular spaces interspersed in the center. Towards the periphery of the lesion there are irregular ectatic vessels.* **B.** *Hematoxylin-Eosin, 40x, showing vascular spaces and fusiform cell rays without atypia.* **C.** *Positive immunohistochemical staining for the CD34 marker showing positivity for malignant cells and confirming the vascular source.* **D.** *Positive immunohistochemical staining for the human herpesvirus-8 (HHV-8) marker that confirms the Kaposi sarcoma diagnosis.*

Am 2021;**39**:101–21. https://doi.org/10.1016/J.EMC.2020.09.006.

7. **Carbone A, Vaccher E, Gloghini A.** Hematologic cancers in individuals infected by HIV. *Blood* 2022;**139**:995–1012. https://doi.org/10.1182/BLOOD.2020005469.
8. **Lamm C, Ahlfors F.** HRCT: pattern recognition and differential diagnosis of lung disease 2013.
9. **Everett CK, Fei MW, Huang L.** Respiratory emergencies in HIV-infected persons. *Emerg Med Clin North Am* 2010;**28**:283–98. https://doi.org/10.1016/J.EMC.2010.01.014.
10. **Requena C, Alsina M, Morgado-Carrasco D, Cruz J, Sanmartín O, Serra-Guillén C, et al.** Kaposi Sarcoma and Cutaneous Angiosarcoma: Guidelines for Diagnosis and Treatment. *Actas Dermosifiliogr* 2018;**109**:878–87. https://doi.org/10.1016/J.ADENGL.2018.10.003.
11. **Hoffmann C, Sabranski M, Esser S.** HIV-Associated Kaposi's Sarcoma. *Oncol Res Treat* 2017;**40**:94–8. https://doi.org/10.1159/000455971.