Case Report

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Kaposi sarcoma-induced immune reconstitution syndrome: a case report

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Introduction and importance: Kaposi sarcoma (KS) is an angioproliferative disease, that mostly affects HIV-infected patients with a high viral load and a low CD4 count. In rare cases, the paradoxical worsening of a pre-existing or previously unrecognized opportunistic infection occurs in a phenomenon known as immune reconstitution inflammatory response (IRIS).

Case presentation: The authors presented a male patient in his 30s with HIV, who developed a series of complications caused by KS following the initiation of antiretroviral therapy. Despite ongoing antiretroviral therapy (ART), chemotherapy, and supportive measures, the patient developed KS-related IRIS, characterized by rapid clinical deterioration, multiorgan failure, and ultimately succumbed to the disease.

Clinical discussion: To the best of our knowledge, very rare cases have been reported with KS-IRIS after the initiation of ART. Many predictors of KS-IRIS development have been identified. Patients must meet the known diagnostic criteria to be diagnosed with IRIS. The treatment of KS-IRIS depends on the stage of KS. ART alone is usually adequate in mild cutaneous KS. Chemotherapy and ART are recommended for patients with severe cutaneous and visceral KS.

Conclusion: HIV patients with KS undergoing ART initiation or modification should be closely monitored, particularly during the early stages and in those with extensive disease. Treating opportunistic infections before ART initiation may reduce the risk of KS-IRIS. The increasing prevalence of KS in ART-treated patients with HIV warrants further attention and highlights the need for better management strategies in this population.

Keywords: antiretroviral therapy, case report, HIV, immune reconstitution syndrome, Kaposi sarcoma

Background

Kaposi sarcoma (KS) is a vascular tumour aetiologically associated with human herpesvirus-8 (HHV-8), also known as Kaposi sarcoma-associated herpesvirus (KSHV). It mostly affects HIV-infected patients with a high viral load and a low CD4 count. KSHV-related malignancies include KS, primary effusion lymphoma (PEL), and multicentric Castleman disease (MCD).

KS remains the most common cancer in patients with HIV, associated with high morbidity and mortality[1], although its incidence has declined after the use of effective ART[2,3]. In rare cases, a new onset (unmasking) or worsening picture (paradoxical) of KS was found to occur after ART initiation, a rare phenomenon known as immune reconstitution inflammatory response (IRIS). KS-IRIS is explained by the restoration of immune responses after ART initiation, which suppresses HHV-8 replication while causing immune dysregulation with a cytokine storm, including high levels of tumour necrosis factor inhibitors, interferon-gamma, and interleukin-1-beta, which ultimately results in latent HVV8 activation and upregulation of vascular endothelial growth factor receptors in the endothelial cells, resulting in angiogenesis, inflammation, and cellular and vascular proliferation, leading to KS tumorigenesis and progression[4,5]. The SCARE 2020 criteria were followed while reporting this case study[6].

Recently, a new syndrome, KSHV inflammatory cytokine syndrome (KICS), was discovered in HIV patients infected with HHV-8. It is clinically identical to MCD, as both manifest with lymphadenopathy, pancytopenia, HIV and HHV-8 viremia, and signs of systemic inflammatory syndrome (SIRS). To differentiate between these two entities, lymph node, bone marrow, or spleen biopsy is required. Herein, we report a case of a 30-year-old

HIGHLIGHTS

- Kaposi sarcoma (KS) is a vascular tumour aetiologically associated with human herpesvirus-8 (HHV-8).
- In rare cases, a new onset or worsening picture of KS was found to occur after antiretroviral therapy (ART) initiation, a rare phenomenon known as immune reconstitution inflammatory response (IRIS).
- Diagnosis of IRIS should rely on the known diagnostic criteria.
- The treatment of KS-IRIS depends on the stage of KS.

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African-American male patient with HIV, who presented with progressive worsening of disseminated KS in the form of KICS.

Case presentation

A 30-year-old African American male patient, with a medical history significant for HIV controlled with emtricitabine and tenofovir/dolutegravir, presented to our hospital with signs suggestive of acute hypoxic respiratory failure: shortness of breath, cough, and expectoration of brownish sputum, in addition to a tonic-clonic seizure, headache, and profound weakness in his left arm.

A chest radiograph revealed several cavitary nodules. A computed tomography (CT) scan showed bilateral cavitary lesions and subcentimeter pulmonary nodules (Fig. 1).

Consequently, and considering possible pyogenic abscesses, the patient was administered a 6-week course of ceftriaxone and metronidazole but with no signs of clinical improvement. Subsequently, he underwent bronchoscopy and bronchoalveolar lavage (BAL) with rapid cytology demonstrating fungal elements. Transbronchial biopsy (TBB) indicated the presence of necrotizing granulomas and thin septate hyphae with regular branching at acute angles consistent with aspergillus fumigatus resulting in invasive pulmonary aspergillosis. Thus, voriconazole was started.

His brain MRI showed a ring-enhancing, frontal brain lesion that measures 2.1 cm on the right side (Fig. 2). He was initially treated for suspected toxoplasmosis, but given the lack of clinical improvement and negative serum Toxoplasma gondii antibodies, a brain biopsy was performed, which showed signs of chronic inflammation. Acid-fast bacillus (AFB), grocott's methenamine silver (GMS), and gram stains were all negative. The pathological report was negative for malignancy and lymphoma. Levetiracetam and dexamethasone, along with voriconazole, were started with a presumed diagnosis of invasive pulmonary and central nervous system aspergillosis. The patient's clinical status improved, and a repeat chest CT scan revealed resolution of the pulmonary nodules. Serial brain MRIs showed a continued decrease in the size of the brain lesion.

Six months later, the patient was readmitted with signs and symptoms of acute hypoxic respiratory failure similar to his last presentation, with the addition of a new onset hemoptysis. On physical examination, multiple violaceous, dark purple, raised skin lesions were noted on the face, scalp, back, abdomen, and thighs. An oral examination revealed several dark purple papulonodular masses on the tongue and palate, with no ulcers or thrush. Lymphatic examination was notable for non-tender right inguinal lymphadenopathy. He was found to have a low CD4 count (87 cells/mm^3) and a high viral load, as he was non-compliant with his medications, including ART.

A full-body CT scan revealed resolution of the previous pulmonary cavitary lesions but was positive for new peribronchovascular lesions and bilateral mediastinal and hilar lymphadenopathy. New nodules in the chest, liver, and spleen with lymphadenopathy were also observed (Fig. 3).

His CT scan was followed by bronchoscopy showing bright red mucosal lesions at the level of the trachea, carina, and below suggesting pulmonary KS (Fig. 4). BAL results were negative for bacterial and fungal growth, Pneumocystis jiroveci virus (PJV), cytomegalovirus (CMV), Legionella, Mycoplasma, and galactomannan testing, but returned positive for HHV-8, which is aetiologically associated with all forms of KS. TBB in addition to an excisional inguinal lymph node biopsy confirmed the diagnosis of disseminated KS and significantly decreased the likelihood of MCD being the cause. The patient resumed ART medications and was started on four cycles of liposomal doxorubicin and paclitaxel.

A few weeks later, the patient was admitted for the third time after presenting with worsening hypoxia and constitutional symptoms, including fever, night sweats, weight loss, and loss of appetite, in addition to a new episode of seizure, while maintaining a therapeutic level of levetiracetam. The patient was compliant with his medications consisting of voriconazole, trimethoprim-sulfamethoxazole, emtricitabine, and tenofovir/dolutegravir. His CD4 count was greater than 200 cells/mm^3 with an undetectable viral load.

A repeat body CT scan revealed worsening pulmonary findings with diffuse ground-glass opacities, mass-like consolidation, and nodular consolidation in the lungs (Fig. 5). It also revealed severe progression of KS, with new lesions in the spine, spleen, adrenals, and bone marrow. The bone marrow biopsy results were negative for lymphoma and Castleman disease. Brain MRI showed a slight worsening and an increase in the size of the right frontal lesion with surrounding oedema.

A new bronchoscopy showed no evidence of infection on the BAL panel, and a repeated lung biopsy was consistent with KS. The TBB was complicated by bleeding, which is not surprising given a highly vascular tumour with angiogenesis. He was also noted to have right-loculated pleural effusion. Thoracentesis was performed, and no lymphoproliferative disorders were observed. His blood tests were consistent with acute renal failure and acute liver cell failure.

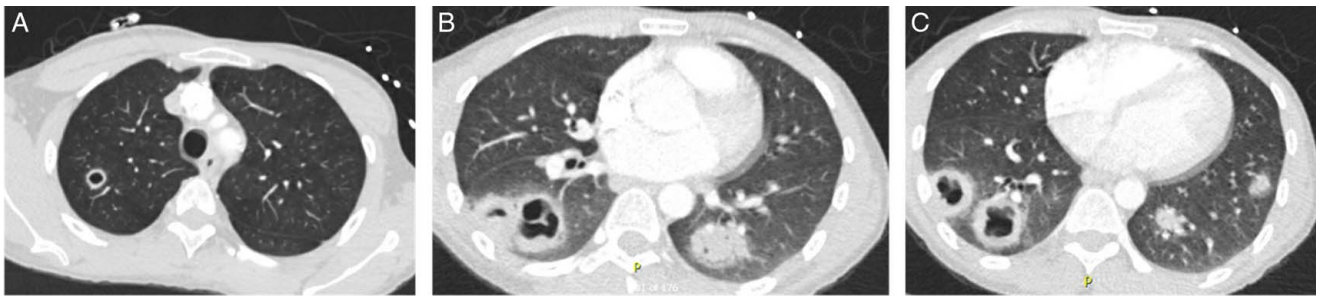

Figure 1. Axial view chest computed tomography scan showing (A) cavitary lesion in the right upper lobe of the lung with diffuse ground-glass opacification. (B, C) Right lower lobe cavitary lesions, and left lower lobe consolidation surrounded with ground-glass opacities (Halo sign) suggesting angioinvasion, seen in invasive pulmonary aspergillosis.

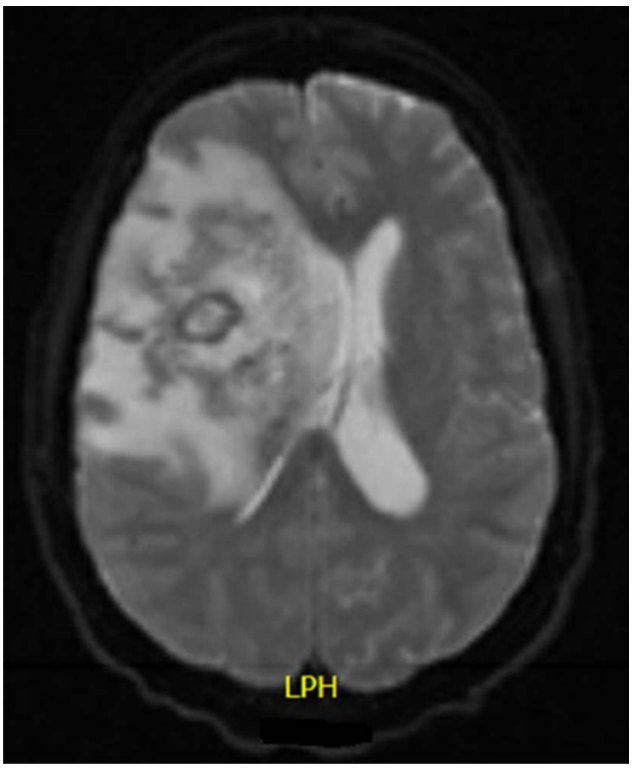

Figure 2. Brain MRI showing a ring-enhancing, right frontal brain lesion with surrounding oedema.

As the patient presented with constitutional symptoms, progressive pulmonary findings, hypoxic respiratory failure, and progressive disseminated KS resistant to chemotherapy, with normalization of CD4 count and undetectable levels of viral load, a diagnosis of KS-induced immune reconstitution syndrome (KS-IRIS) was made.

Despite maximal management that included intubation, haemodialysis, chemotherapy, steroids, broad-spectrum antibiotic therapy, ART, voriconazole, norepinephrine, epinephrine, and phenylephrine, the patient suffered from progressive clinical deterioration with multiorgan failure leading to cardiac arrest and death after failure of resuscitative measures.

Clinical discussion

KS is an angioproliferative disease that remains the strongest stigma of the AIDS epidemic and harbours severe immunodeficiency. It can either affect the skin and mucosal surfaces or metastasize to the viscera, most commonly the lungs and gastrointestinal system[1]. KS develops due to infection with HHV-8, also called KSHV. In HIV patients infected with HHV-8, a low CD4 count promotes the survival and proliferation of this virus within the infected cells, subsequently causing malignant transformation to KS[2]. Although ART has no effect on reducing KSHV, it was found to be effective in reducing HIV viral load and promoting CD4 cell recovery, causing resolution of KS lesions in 60% of patients[3]. However, the initiation of ART in HIV patients with low CD4 counts and opportunistic infections (e.g. TB, CMV, or HHV-8) can be associated with paradoxical clinical worsening as a result of excess cytokine release resulting in IRIS.

IRIS is a well-recognized clinical entity, in which paradoxical worsening of a pre-existing or previously unrecognized opportunistic infection occurs in the setting of ART-induced recovery of the immune system (i.e. rapid decline in HIV viral load and marked increase in CD4 count). Most HIV patients with a low

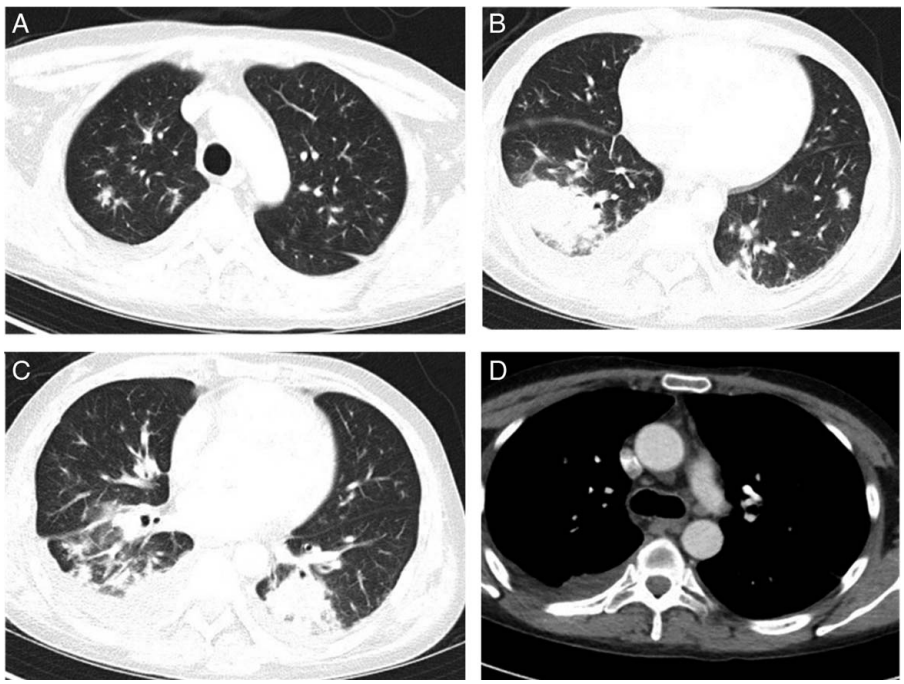

Figure 3. (A–C) Axial view chest computed tomography (CT) scan (lung window) showing resolution of the previous pulmonary cavitary lesions, with the new onset of bilateral nodular opacities in peribronchovascular distribution and mass-like regions of consolidation, involving bilateral lower lobes. (D) Axial view chest CT scan (soft tissue window) showing mediastinal lymphadenopathy (station 4R, RL).

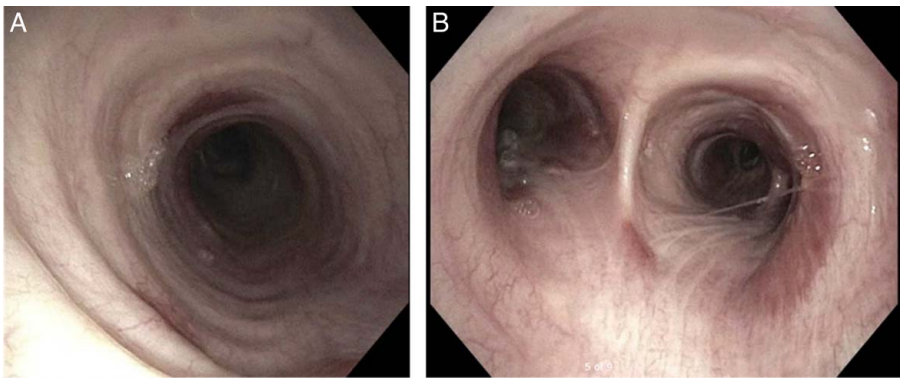

Figure 4. A bronchoscope showing multiple violaceous lesions involving (A) the proximal trachea (B) the carina, left and right main stem bronchi, and the proximal part of the bronchus intermedius consistent with Kaposi sarcoma.

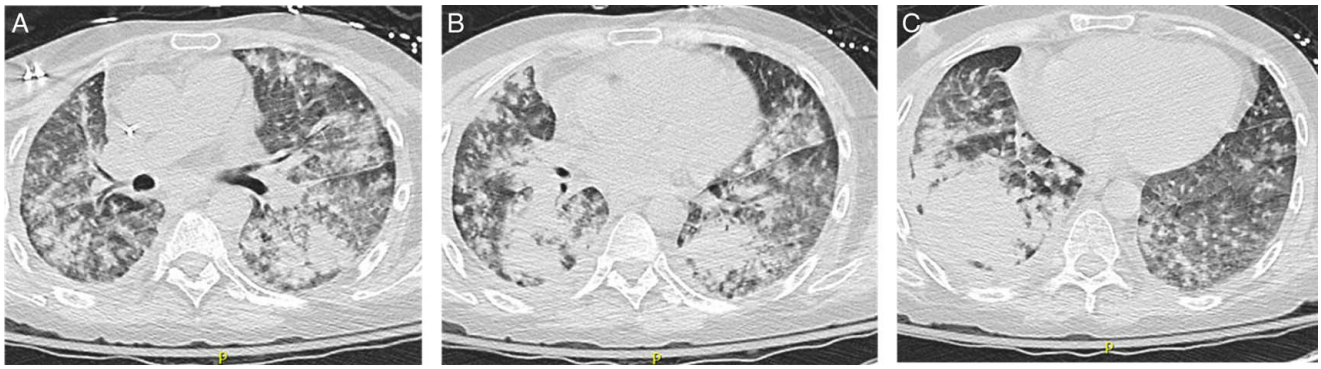

Figure 5. Axial view chest computed tomography scan showing extensive bilateral consolidative and ground-glass pulmonary opacities, with areas of mass-like consolidation in the (A) left upper lobe, (B) lower lobes bilaterally, and (C) right lower lobe.

CD4 count develop IRIS within three months after the initiation of ART[3,4]. The incidence of IRIS was found to be 30% in HIV patients, with mortality ranging from 5 to 30%[5,7]. In a cohort study of 150 therapy-naive HIV patients, ten (6.6%) patients developed new KS lesions and had accelerated progression of established lesions during the first two months of ART initiation, consistent with KS-related IRIS (KS-IRIS)[8]. The criteria for diagnosing IRIS were defined by French and colleagues, in which a diagnosis of IRIS requires both major criteria or criterion A with two minor criteria, as shown in Table 1[9]. The pathogenesis of KS-IRIS is best explained by the rapid increase in CD4+ and CD8+ lymphocytes after ART initiation, resulting in the activation of pro-inflammatory responses (e.g. TNF-α, IFN-γ, and IL-1β) and the suppression of anti-inflammatory ones (e.g. IL-10). This immune dysregulation response is called IRIS. The production of excess inflammatory cytokines causes reactivation of latent HHV-8 in infected cells, resulting in the development or deterioration of KS[10]. In our case, the rapid decline in HIV viral load and the marked increase in CD4 count after ART initiation, along with the transbronchial and lymph node biopsies confirming disseminated KS, led to the diagnosis of KS-related IRIS.

Multiple factors have been identified to be associated with higher risk of IRIS development in KS patients, including clinical pretreatment KS, detectable plasma KSHV DNA, haematocrit less than 30%, high plasma HIV viral load ($\geq 10^5$ Log/ml) and concurrent or recent use of glucocorticoids[11,12]. In addition, a higher median increase in CD4 and CD8 T-cell count was observed in mucocutaneous KS developing KS-IRIS. Such variations in T-cell count were not observed in visceral KS developing KS-IRIS[13]. Although a low CD4 cell count at the start of ART drive the development of IRIS, KS-IRIS can occur at higher levels of CD4[8]. In another study, higher KS disease burden was found to increase the risk of KS-IRIS[3]. The controversy regarding the

Table 1

The criteria to diagnose IRIS in HIV patients on ART

Major criteria

(A) Atypical presentation of opportunistic infections or tumours in HIV patients on ART
- Localized disease
- Exaggerated inflammatory reaction
- Atypical inflammatory response in affected tissues
- Progression of organ dysfunction or enlargement of pre-existing lesions after definite clinical improvement with pathogen-specific therapy prior to the commencement of ART and exclusion of treatment toxicity and new diagnoses

B. Decrease in plasma HIV RNA level by > 1 $\log_{10}$ copies/ml

Minor criteria
- Increased blood CD4 T-cell count after ART
- Increase in an immune response specific to the relevant pathogen
- Spontaneous resolution of disease without antimicrobial therapy or chemotherapy with continuation of ART

ART, antiretroviral therapy; IRIS, immune reconstitution inflammatory response.

risk of IRIS-KS development after the initiation of integrase inhibitors[14,15], seems to be unfounded after the results of a recent meta-analysis[16].

Patients with pulmonary KS seem to have extensive disease with rapid deterioration and poor prognosis. Many fatal cases of pulmonary KS have been reported[17–20], and in a retrospective study, all patients who died of KS-IRIS had pulmonary involvement[4]. In addition, thrombocytopenia (< 100 000 platelets/mm^3) was significantly associated with higher mortality[21]. Our patient was young, had a higher viral load and low CD4 count when ART was started, was treated with an integrase inhibitor (dolutegravir), and had multiple pulmonary and respiratory tract lesions consistent with pulmonary KS, which altogether may have contributed to the development and rapid deterioration of KS-IRIS.

The best therapeutic approach for the prevention of KS-IRIS is still not defined. However, the decision about whether to initiate chemotherapy along with ART to prevent KS-IRIS depends on the extent of the disease and the potential benefits compared with the added toxicities. Furthermore, potential drug-drug interactions between ART and chemotherapy should be assessed[22].

The treatment of KS-IRIS depends on the stage of KS. ART alone is usually adequate in mild cutaneous KS. Chemotherapy and ART are recommended for patients with severe cutaneous and visceral KS. Liposomal anthracyclines and paclitaxel are the gold-standard chemotherapeutic agents for the treatment of severe KS-IRIS[23]. To the best of our knowledge, the optimal therapeutic approach (including the timing of chemotherapy) for KS-IRIS has not yet been identified. In contrast to the usual management of IRIS with other opportunistic infections, glucocorticoid is controversial in KS-IRIS, due to the potential deterioration of KS[12,24,25]. Therefore, glucocorticoids should be limited to cases where steroids are indicated (i.e. anaphylaxis) and a case-by-case risk assessment is needed[26,27]. Recently, many clinical trials have been done on multiple therapies for the treatment of KS, but none of them in patients with KS-IRIS, which makes us unable to define their role in the prevention or treatment of KS-IRIS[28–31].

This case reiterates the importance of close monitoring of HIV patients with KS starting or modifying ART, especially in the first few weeks and in those with visceral and extensive mucocutaneous diseases. Notably, it is advised to continue ART in cases of progressive KS similar to our patient[8]. It is also worth highlighting that the incidence of KS was found to be lower in ART regimens that did not include protease inhibitors[32]. Moreover, we suggest treating opportunistic infections for 8–12 before initiation of ART; this approach might decrease the incidence of KS-IRIS phenomena.

Altogether, an increasing number of reports highlight the risk of KS development in HIV patients after ART initiation. The occurrence of KS in this population is no longer anecdotic and has become a new challenge, given the large number of ART-treated HIV patients worldwide.

Conclusion

- ART is effective in reducing HIV viral load and promoting CD4 cell recovery, but it can paradoxically cause clinical worsening in patients with low CD4 counts and opportunistic infections resulting in a potentially fatal phenomena of immune reconstitution.
- KS-IRIS occurs due to the rapid increase in CD4 + and CD8 + lymphocytes after ART initiation, resulting in immune dysregulation and cytokines storm reactivating latent HHV-8 in infected cells, causing the development or deterioration of KS.
- Our case, who suffered from KS-IRIS phenomena and had an unfortunate outcome, emphasizes a potential treatment approach which might have prevented this fatal outcome. We recommend against initiation of ART simultaneously with opportunistic infection treatment, in fact we believe holding ART for 8–12 weeks while addressing the opportunistic infection would have prevented mortality in such cases.

Ethical approval

Not applicable.

Consent

Consent was taken from the next of kin due to the death of the patient.

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Author contribution

All authors contributed to interpretation and assembly of data and media, drafting or revising the article, gave final approval of the manuscript, and agreed to be accountable for all aspects of the work.

Conflicts of interest disclosure

The author declares no conflict of interest.

Research registration unique identifying number (UIN)

Not applicable.

Guarantor

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Data availability statement

No dataset has been generated and/or analyzed in this article.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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