HIV-negative Kaposi's sarcoma overlapping with complicated diabetic foot: A diagnostic challenge in wound care

Kaposi's sarcoma (KS) is a vascular neoplasm classically associated with immunosuppression, particularly HIV infection. Its occurrence in HIV-negative patients, especially in the setting of type 2 diabetes mellitus (T2DM), is uncommon and may pose significant diagnostic challenges when overlapping with more prevalent conditions such as diabetic foot.

Case Presentation: We report the case of an 85-year-old woman with long-standing T2DM and multiple comorbidities who presented with a four-month history of progressive bilateral foot ulcers, purulent discharge, and intermittent fever. Initial evaluation suggested severe diabetic foot infection with a neuroischemic component. However, prior documentation of violaceous macules, and subsequent histopathological and immunohistochemical confirmation established the diagnosis of KS. Laboratory findings revealed severe anaemia, coagulopathy and renal impairment, while HIV serology was negative. Imaging excluded osteomyelitis but demonstrated Charcot arthropathy. Given the patient's frailty and high surgical risk, a conservative, palliative-oriented approach was adopted, resulting in partial local improvement.

Discussion: This case highlights the potential for T2DM-associated immune dysregulation, chronic inflammation and proangiogenic signalling to contribute to the clinical expression of KS in the absence of classical immunosuppression. The overlap between KS and diabetic foot lesions may delay diagnosis and complicate management, particularly in resource-limited settings.

Conclusion: Atypical or refractory diabetic foot ulcers warrant a broadened differential diagnosis, including cutaneous malignancies. Early skin biopsy is essential to avoid diagnostic delay and guide appropriate management. This case underscores the need for a more integrative clinical approach to complex diabetic foot presentations.

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Key words
- Cutaneous lesions
- Diabetic foot
- Kaposi's sarcoma
- Palliative management
- Type 2 diabetes mellitus

Kaposi's sarcoma (KS) is a multifocal, low-grade vascular neoplasm, first described by Moritz Kaposi's in 1872 and is associated with infection by Human herpesvirus 8 (HHV-8), also known as Kaposi's sarcoma – associated herpesvirus (KSHV) (Kaposi's, 1872). Although it is widely recognised in the context of immunosuppression, particularly in patients with HIV/AIDS, classical forms unrelated to immunodeficiency also exist, affecting older individuals, predominantly of Mediterranean or Eastern European origin (Antman and Chang, 2000; Di Lorenzo et al, 2007). In Latin America, cases of classical KS in HIV-negative patients are infrequent and poorly documented. Clinically, it presents with violaceous, cutaneous lesions, although mucosal surfaces, lymph nodes and visceral organs may also be involved, depending on the clinical subtype: classical, endemic African, iatrogenic (associated with transplant-related immunosuppression), or epidemic (HIV-related) (Pantanowitz, 2010). The latter was one of the first malignancies recognised during the AIDS epidemic, and its incidence has declined markedly since the introduction of highly active antiretroviral therapy (HAART) (Bower et al, 2014). The diagnosis is established based on clinical findings and histopathological confirmation, demonstrating spindle cell proliferation and positivity for markers such as CD34 and D2-40 (Dupin et al, 1999).

The KSs varies according to geographic region, epidemiological context and the presence of immunosuppressive factors. Globally, an estimated 34,270 new cases were reported in 2020, with an age-standardised incidence rate of 0.39 per 100,000 inhabitants and a global mortality rate of 0.18 per 100,000

inhabitants (Sung et al, 2021). In the United States, approximately 27,800 cases were reported between 1999 and 2020, with an average incidence of 0.4 per 100,000 persons, the majority corresponding to the epidemic subtype associated with HIV (Shah et al, 2023). However, in populations without known immunodeficiency (i.e., without HIV infection or transplantation), KS is uncommon, with an estimated incidence of 1.53 per 100,000 person-years (95% CI: 0.33–7.08) (Jansen et al, 2018). In Europe, the mean incidence is approximately 0.3 per 100,000, although in southern regions of the continent, such as the Mediterranean area, it may reach up to 0.8 per 100,000, predominantly affecting older men with the classical form of KS (Gatta et al, 2011). In Colombia, according to data from the Cali Population-Based Cancer Registry between 1962 and 2007, a total of 349 KS cases were documented, of which only 20 (5.3%) were diagnosed before the HIV epidemic, suggesting an extremely low incidence of classical KS in the country (Bravo et al, 2014). Most cases reported in Colombia are associated with HIV/AIDS, and contemporary evidence on KS in patients without immunosuppression remains limited and insufficiently characterised.

Although KS is classically associated with immunosuppression related to HIV infection or organ transplantation, non-HIV-related forms also exist, such as classic or sporadic KS, which predominantly affects older men from Mediterranean regions or Eastern Europe (Antman and Chang, 2000; Gatta et al, 2011). In these patients, additional predisposing factors have been identified, including advanced age, chronic kidney disease, and more recently, type 2 diabates mellitus (T2DM). Although the relationship between T2DM and KS is not clearly established, several pathophysiological mechanisms have been proposed to support their coexistence. T2DM is associated with a state of chronic low-grade inflammation, immune dysfunction, oxidative stress and impaired cellular immune response (Donath and Shoelson, 2011; Forbes and Cooper, 2013; Pickup and Crook, 1998), conditions that may promote replication of human HHV-8 and facilitate tumour angiogenesis in predisposed individuals (Angius et al, 2017). Moreover, chronic hyperglycaemia may impair the function of T lymphocytes and macrophages, thereby reducing immune surveillance against oncogenic viral agents (Delamaire et al, 1997; Geerlings and Hoepelman, 1999). In a study conducted in Sicily, T2DM was associated with an increased risk of classic KS, with an odds ratio of 3.3 (95% CI: 0.99-10.9), alongside chronic kidney disease as another relevant factor (Angius et al, 2017). Additionally, prolonged exposure to immunosuppressive therapies, particularly systemic corticosteroids used for autoimmune diseases, has been associated with iatrogenic KS in the absence of transplantation, with regression reported in some cases following reduction or withdrawal of immunosuppressive therapy (Geerlings and Hoepelman, 1999; Andrei et al, 2021). Taken together, the coexistence of T2DM and KS may represent a synergistic interplay between immunosenescence, chronic comorbidities and viral susceptibility.

The coexistence of KS and T2DM in the absence of classical immunosuppression is uncommon and poorly documented in the literature. Although T2DM has been associated with immune dysfunction, chronic inflammation and oxidative stress, mechanisms that may facilitate HHV-8 reactivation and tumour angiogenesis (Angius et al, 2017; Donath and Shoelson, 2011; Geerlings and Hoepelman, 1999), clinical reports describing this association remain limited. In Latin America, and particularly in Colombia, KS has historically been linked to HIV infection, with its occurrence in patients without pharmacological immunosuppression being exceptional.

In this context, the present case illustrates an atypical presentation of KS in a patient with T2DM, highlighting its clinical overlap with diabetic foot lesions and the consequent risk of diagnostic delay. This report provides evidence of a potential interaction between metabolic dysfunction, immunosenescence and viral susceptibility, and underscores the need to broaden the diagnostic approach to atypical chronic ulcers in patients with diabetes.

Case presentation

An 85-year-old female patient from Cali, Colombia, with a history of T2DM of more than ten years duration, hypertension, heart failure and chronic gastritis with intestinal metaplasia, presented to the emergency department with a clinical course of approximately four months characterised by the progressive development of ulcerated lesions on both feet, associated with foul-smelling purulent discharge and intermittent episodes of fever.

She had previously received outpatient management with an unspecified oral antibiotic and local wound care, without clinical improvement. As a relevant antecedent, the development of non-painful violaceous macules on both lower extremities had been documented; these were evaluated by skin biopsy with histopathological and immunohistochemical confirmation consistent with KS, although no specific treatment had been initiated due to economic and administrative barriers.

On physical examination, the patient was

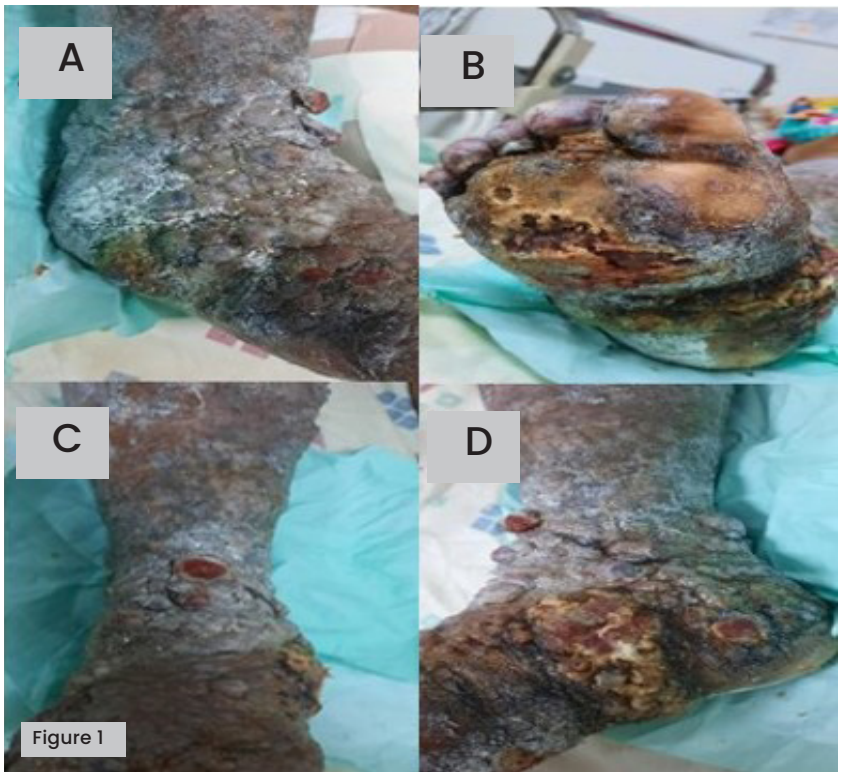




Figure 1. Clinical presentation at admission. (A–D) Extensive ulcerated lesions involving both feet, with areas of necrosis, myiasis and violaceous cutaneous lesions consistent with KS, in the setting of a complicated diabetic foot.

Figure 2. Clinical evolution after treatment, showing partial improvement of ulcerated lesions with persistence of violaceous nodular lesions consistent with KS.

afebrile, with signs of chronic illness and marked bilateral lower-extremity oedema. Extensive ulcerated lesions were observed on the plantar and dorsal aspects of both feet, with areas of necrosis, myiasis and confluence with the previously described violaceous macular lesions [Figure 1]. Dorsalis pedis and posterior tibial pulses were palpable, although diminished. Assessment with the Semmes-Weinstein monofilament demonstrated loss of protective sensation bilaterally, consistent with peripheral neuropathy in the context of diabetic foot.

Initially, a diagnosis of severe skin and soft tissue infection in the setting of diabetic foot with a neuroischemic component was considered, and orthopaedic evaluation was requested for potential surgical management. However, the coexistence of cutaneous lesions previously confirmed as KS introduced diagnostic uncertainty, as the full extent of the cutaneous involvement could not be attributed solely to the infectious process, prompting a comprehensive clinical reassessment.

Histopathological examination of the skin biopsy revealed a proliferation of spindle cells forming irregular vascular spaces, with erythrocyte extravasation and hemosiderin deposition. Immunohistochemistry demonstrated positivity for endothelial markers, findings consistent with KS.

Laboratory studies showed severe normocytic anaemia (haemoglobin 5.8g/dL), moderate thrombocytopenia (78,000/µL), significant coagulopathy (INR 1.44), markedly elevated C-reactive protein levels, and impaired renal function. Blood cultures were negative, and serology for HIV types 1 and 2 was non-reactive.

Radiographic imaging ruled out osteomyelitis but demonstrated findings consistent with Charcot arthropathy. Arterial Doppler ultrasound revealed diffuse atheromatosis without critical hemodynamic compromise. In this context, KS was interpreted as coexisting with the infectious and vascular processes, contributing significantly to the extent and atypical features of the lesions.

Given the patient's clinical frailty, high surgical risk and substantial comorbidity burden, a conservative, palliative-oriented approach was adopted, including multimodal analgesia, advanced wound care and interdisciplinary management. After two weeks of inpatient treatment, partial improvement of the local lesions was observed [Figure 2], without evidence of systemic progression, although the overall prognosis remained guarded.

Overall, the clinical course reflected a complex presentation characterised by the overlap of severe diabetic foot infection and KS in an HIV-negative patient, creating a scenario of clinical convergence that influenced both the diagnostic approach and therapeutic decision-making.

Discussion

The present case illustrates an uncommon clinical scenario of considerable diagnostic complexity: the coexistence of complicated diabetic foot and KS in an elderly, HIV-negative patient with multiple comorbidities. This association is unusual and of particular clinical relevance, as KS in the absence of classical immunosuppression may go unrecognised or be misinterpreted as more common conditions in patients with diabetes, especially when lesions predominantly affect the lower extremities and coexist with ulceration, necrosis and infection (Andrei et al, 2021; Antman and Chang, 2000; Delamaire et al, 1997; Di Lorenzo et al, 2007;

Geerlings and Hoepelman, 1999; Kaposi's, 1872; Pantanowitz, 2010).

From a pathophysiological perspective, this presentation is biologically plausible. T2DM is associated with alterations in both innate and adaptive immunity, chronic low-grade inflammation, oxidative stress, and endothelial dysfunction, conditions that promote the persistence of chronic lesions and increase susceptibility to infections and neoplastic processes (Holt et al, 2024; Shah et al, 2023). In this context, sustained hyperglycaemia may impair the function of macrophages and T lymphocytes, compromising immune surveillance against oncogenic viral agents such as human herpesvirus 8 (HHV-8), the key etiological agent in the pathogenesis of KS (Antman and Chang, 2000; Bower et al, 2014; Kaposi's, 1872; Sung et al, 2021).

Additionally, T2DM is associated with dysregulated angiogenic signalling involving vascular endothelial growth factor (VEGF) and hypoxia-inducible factor-1α (HIF-1α), pathways that play an important role in diabetic vascular complications (Fadini et al, 2019; Catrina and Zheng, 2021). Notably, HIF-1α and VEGF signalling are also involved in the pathological angiogenesis characteristic of KS, where KSHV infection can activate HIF pathways and enhance VEGF expression (Carroll et al, 2006; Ma et al, 2015). Although a causal relationship between T2DM and KS has not been established, the convergence of metabolic dysfunction, impaired immune surveillance and dysregulated angiogenic signalling provides biological plausibility for diabetes acting as a potential pathophysiological cofactor in a predisposed host (Angius et al, 2017; Geerlings and Hoepelman, 1999; Holt et al, 2024).

One of the most relevant aspects of this case is the diagnostic challenge it presents. In clinical practice, ulcerated foot lesions in patients with diabetes are typically attributed initially to neuropathic, infectious or vascular aetiologies, in line with conventional diagnostic algorithms (Senneville et al, 2023). A similar diagnostic challenge has been reported by Khan et al (2024), who described HIV-negative KS presenting as a foot lesion in a patient with diabetes mellitus, highlighting the potential for KS to mimic more common diabetic foot pathology. However, this approach may be insufficient in the presence of atypical, persistent lesions or dermatological findings that are not fully explained by infection or ischemia. In this case, the prior presence of violaceous macules and the histopathological confirmation of KS were decisive elements in broadening the differential diagnosis and avoiding an overly reductionist interpretation of the clinical presentation (Pantanowitz, 2010).

From a therapeutic perspective, the overlap between complicated diabetic foot and KS substantially influenced clinical decision-making. International guidelines recommend an individualised approach to advanced diabetic foot disease based on the severity of infection, ischemia, tissue involvement and limb salvage potential, incorporating surgical debridement, antimicrobial therapy, revascularisation when indicated, and amputation when the limb is considered unsalvageable (Fitridge et al, 2023; Senneville et al, 2023). The concurrent presence of a vascular neoplasm further necessitates individualised management. In this context, the risks and expected benefits of aggressive surgical interventions should be carefully weighed, particularly in a patient with marked frailty, coagulopathy, severe anaemia and multiple comorbidities (Fitridge et al, 2023).

Therefore, the conservative approach adopted, based on multimodal analgesia, advanced wound care and interdisciplinary management, represented a clinically sound and proportionate decision within the patient's context. This strategy is consistent with principles advocated by the International Working Group on the Diabetic Foot (IWGDF) and the European Wound Management Association (EWMA), emphasising individualised wound management and when healing is unlikely or invasive treatment offers limited benefit, prioritising symptom control, prevention of additional complications, comfort and quality of life (Gethin et al, 2025; IWGDF, 2023).

Overall, this case highlights that not all diabetic foot lesions are exclusively infectious, neuropathic or vascular in origin. The presence of atypical features, prolonged evolution or an inadequate response to conventional treatment should prompt a broader diagnostic reassessment, including cutaneous neoplasms within the differential diagnosis. In this context, skin biopsy represents a fundamental tool to reduce diagnostic delay and guide appropriate management (Pantanowitz, 2010). Furthermore, this case suggests a potential interplay between T2DM-associated immune dysfunction, immunosenescence and susceptibility to HHV-8-related disease in the presentation of KS in the absence of classical immunosuppression (Antman and Chang, 2000; Geerlings and Hoepelman, 1999; Holt et al, 2024). These findings highlight the importance of maintaining a high index of suspicion and considering histopathological assessment in atypical chronic ulcers in

patients with diabetes.

Conclusion

The coexistence of complicated diabetic foot and KS in an HIV-negative patient represents an uncommon clinical scenario that highlights the limitations of conventional diagnostic approaches focussed primarily on infectious and vascular aetiologies. This case demonstrates that, in the presence of atypical or refractory chronic ulcers in patients with T2DM, the differential diagnosis must be systematically broadened to include cutaneous neoplasms at an early stage. It also supports the hypothesis that diabetes may constitute a state of immune dysregulation and a proangiogenic microenvironment that facilitates the clinical expression of KS in the absence of classical immunosuppression. In this context, early skin biopsy emerges as a critical diagnostic tool to reduce delays, avoid potentially inappropriate interventions and optimise therapeutic decision-making. Overall, this report highlights the need for a more comprehensive, integrative clinical approach aimed at recognising atypical presentations in the management of diabetic foot.

Ethical considerations

Written informed consent was obtained from the patient and her legal relatives for publication of the clinical information and accompanying images included in this case report. All procedures performed were conducted in accordance with the ethical standards of the institutional and national research committees, as well as the principles of the Declaration of Helsinki and its subsequent amendments. Patient confidentiality and privacy were strictly preserved throughout manuscript preparation by anonymising all identifiable information and clinical photographs. Given the descriptive nature of this report and the absence of experimental interventions, this study was considered minimal risk according to Colombian regulations for health research (Resolution 8430 of 1993). No financial incentives were provided to the patient, and the authors declare that the management described corresponded exclusively to routine clinical care and multidisciplinary decision-making.

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