

Kaposi Sarcoma Involving the Gastrointestinal Tract

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Kaposi sarcoma is a low-grade vascular tumor associated with human herpesvirus-8 infection (HHV-8). The first description of this tumor dates back to 1872 and was made by Dr. Moritz Kaposi, a Hungarian dermatologist who described 5 cases of “idiopathic multiple pigmented sarcomas of the skin.”¹ In total, 4 forms of this disease have been described. As HHV-8 has been detected in all 4 forms of Kaposi sarcoma,² these forms likely represent different manifestations of the same pathologic process.

The classical variant of Kaposi sarcoma occurs predominantly in elderly men from Eastern Europe and Mediterranean countries.³⁻⁵ This form is not associated with HIV, but it coincides with an altered immune system and malignant diseases. Clinically, this variant is distinguished by multiple red-to-purple nodules on the lower limbs. These nodules slowly grow larger and are subsequently also found in more proximal regions. The tumors are usually asymptomatic and are rarely systemically progressive. The second variant is the lymphadenopathy-associated form of Kaposi sarcoma, also called the endemic or African form. This form is very aggressive⁶ and is often found in South Africa in young Bantu children with local or generalized lymphadenopathy.⁷ Skin lesions are rare in this variant. The third variant is the transplant- or immunosuppression-associated form of Kaposi sarcoma. This form develops between several months to several years after organ transplantation with immunosuppressive therapy. Lesions develop on the skin, but in approximately half of the cases, they are also found in internal organs and lymph nodes.⁸⁻¹⁰ The fourth variant of Kaposi sarcoma is the AIDS-associated (epidemic) form. This form is found in approximately one fourth

of all AIDS patients and is the most common AIDS-associated tumor in the United States. Kaposi sarcoma occurs in AIDS-affected homosexual men 20 times more frequently than in nonhomosexual AIDS patients with the same degree of immunodeficiency. AIDS-associated Kaposi sarcoma has no preferred locations but is widely scattered, and involvement of the lymph nodes and intestine occurs relatively early.^{3,11}

Case Report

A 40-year-old African-American man with a history of anemia and small-bowel thickening on computed tomography scan was referred for single-balloon small-bowel enteroscopy. His past medical history was suggestive of asthma and depression, and his medications included an albuterol inhaler as needed. The patient had a history of unprotected sexual contact but was currently living with his girlfriend of many years. He denied having any history of drug allergies, smoking, alcohol, or intravenous drug abuse, or blood transfusions. On examination, the patient was moderately built and nourished, with stable vitals, a weight of 183 lbs, and no evidence of skin lesions. Laboratory studies revealed a hemoglobin level of 10.5 g/dL, hematocrit of 31.9%, white blood cell count of 7,800/cmm with a differential of 55.6% neutrophils and 28.4% lymphocytes, platelet count of 470 units, and mean corpuscular volume of 82 fL. Computed tomography scan showed 3 small-bowel masses of uncertain etiology. Small-bowel enteroscopy revealed scattered umbilicated nodules with central ulceration extending from the left tonsillar area to the distal jejunum (Figures 1–4). Biopsy specimens were obtained from the small bowel (Figures 5–7) and gastric lesions (Figures 8–11).

Histology is similar in each form of Kaposi sarcoma, with submucosal vascular spindle-shaped cells, and does not allow for distinguishing the 4 forms. In our patient,

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Figure 1. Umbilicated nodule with central ulceration in the mid-jejunum.



Figure 2. Umbilicated nodule with central ulceration in the proximal jejunum.



Figure 3. Umbilicated nodule with central ulceration in the duodenum.



Figure 4. Umbilicated nodule in the esophagus.

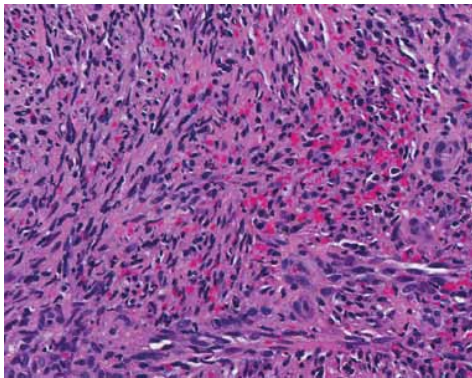


Figure 5. Hematoxylin and eosin stain showing the small intestine with Kaposi sarcoma ($\times 200$).

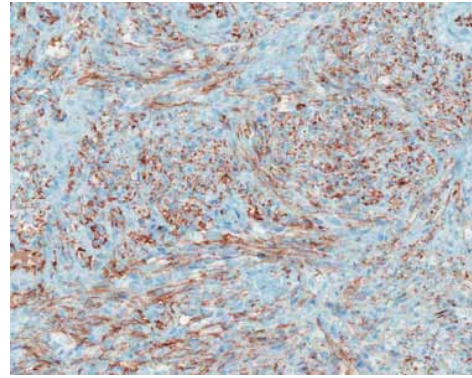


Figure 6. CD31 immunostain revealing the small intestine with Kaposi sarcoma ($\times 200$).

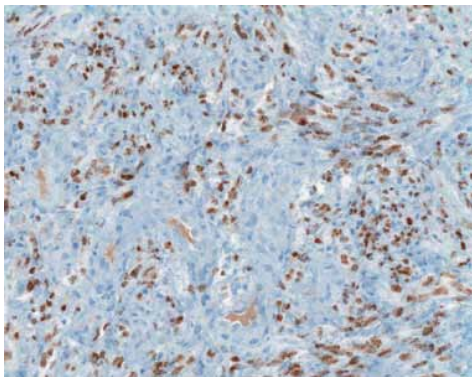


Figure 7. Human herpes virus-8 immunostain showing the small intestine with Kaposi sarcoma ($\times 200$).

the biopsy specimens revealed whorls of spindle-shaped cells and neovascularization with small-vessel proliferation suggestive of Kaposi sarcoma. Immunostains for HHV-8 and CD31 were positive, supporting the above diagnosis. The patient tested positive for HIV, with a CD4 count of less than 50 cells per cubic millimeter of blood. The patient received a referral for an infectious diseases consultation for the initiation of highly active antiretroviral treatment (HAART).

Discussion

Kaposi sarcoma is the most common gastrointestinal malignancy in AIDS (seen in approximately 40% of

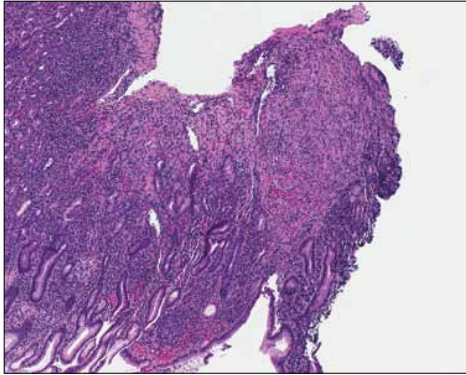


Figure 8. Hematoxylin and eosin stain revealing stomach mucosa with Kaposi sarcoma (×40).

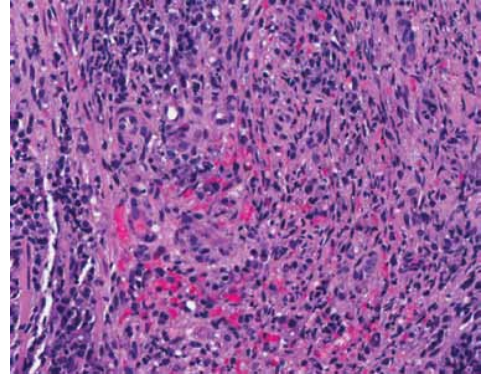


Figure 9. Hematoxylin and eosin stain showing stomach mucosa with Kaposi sarcoma (×200).

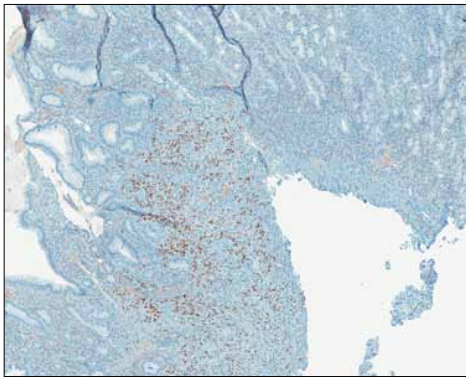


Figure 10. Human herpes virus-8 immunostain revealing stomach mucosa with Kaposi sarcoma (×40).

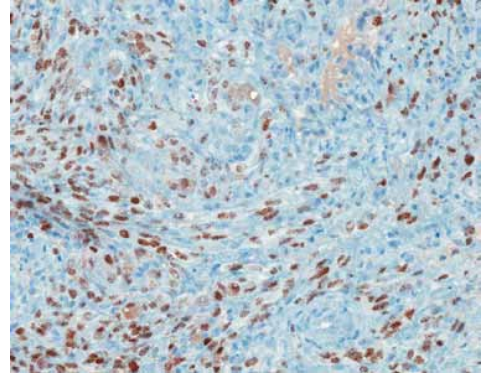


Figure 11. Human herpes virus-8 immunostain showing stomach mucosa with Kaposi sarcoma (×200).

patients) and is often asymptomatic.¹ The presentation of Kaposi sarcoma led to the establishment of an AIDS diagnosis in our patient. A greater-than-50% incidence of Kaposi sarcoma of the gastrointestinal tract has been seen in AIDS patients with cutaneous Kaposi sarcoma.

Although gastrointestinal Kaposi sarcoma is usually asymptomatic, hemorrhages from the oral cavity, esophagus, stomach, and large bowel have been reported in this disease.^{12,13} Some patients present with abdominal pain, weight loss, nausea, vomiting, malabsorption, or diarrhea.² Further complications of gastrointestinal Kaposi sarcoma can be perforation¹⁴ or obstruction¹⁵ of the bowel.

One case of HIV-related Kaposi sarcoma of the appendix and acute appendicitis has been described in the literature.¹⁶ As a differential diagnosis of Kaposi sarcoma, non-Hodgkin lymphomas frequently involve the gut in AIDS patients.¹⁵ Furthermore, tumors of

the gut with spindle-shaped cells such as leiomyomas, rhabdomyosarcomas, high-grade pleomorphic sarcomas, or gastrointestinal stromal tumors have to be considered in the differential diagnosis. The primary diagnosis of Kaposi sarcoma in the stomach or small or large intestine should be considered in elderly men from Eastern Europe, Mediterranean and Arabian regions, and, naturally, in immunosuppressed and AIDS patients with corresponding lesions. The diagnosis of Kaposi sarcoma with a negative HIV test and positive test for HHV-8 should lead to the consideration of other causes such as iatrogenic or tumor-related immunosuppression (lymphoproliferative disorders).

The origin of the proliferating spindle cells in Kaposi sarcoma is uncertain, though these cells are currently believed to be derived from lymphatic endothelium.¹⁷ Immunohistochemistry shows expression of CD34,

CD31, and D2-40.^{18,19} Another lymphatic endothelial cell marker (hyaluronan receptor LYVE-1), expressed by endothelial cells of normal lymphatic vessels but not blood vessels, is positive in angiosarcomas and Kaposi sarcomas.²⁰ A monoclonal antibody (FHI-1) against the carboxyl terminal end of the FLI-1 protein can be reliably applied in the differential diagnosis of tumors of endothelial differentiation. All rhabdomyosarcomas, desmoplastic small round cell tumors, high-grade pleomorphic sarcomas, and colonic adenocarcinomas are negative for FLI-1.²¹ Therefore, FLI-1 can help in the differential diagnosis of nonvascular tumors such as gastrointestinal stromal tumors. Infection with HHV-8 is necessary for the development of Kaposi sarcoma in HIV patients, and, at present, it is considered the definitive cause of Kaposi sarcoma. Over 95% of Kaposi sarcoma lesions, regardless of their source or clinical subtype, have been found to be infected with HHV-8.²² The long-lasting expression of HHV-8 latency genes is important for Kaposi sarcoma spindle-cell progression,²³ and the lesional spindle cells in our patient's biopsies confirmed HHV-8 infection using immunohistochemistry staining.

Overall, the visceral involvement of the Kaposi sarcoma is usually associated with poor prognosis.²⁴ Treatment is usually palliative and aimed primarily at improving symptoms and preventing progression. Options may include antiretroviral medications, radiation therapy, chemotherapy, or combination therapy.³ Depending upon the severity of HIV and the disease burden of Kaposi sarcoma, HAART could be first-line therapy. Antiretrovirals may help decrease the proportion of new lesions, promote regression of existing lesions, and improve survival with or without chemotherapy.³ Systemic chemotherapy is usually reserved for cases with widespread disease. Due to favorable response rates and toxicity profiles, liposomal anthracyclines (eg, doxorubicin) have become first-line systemic agents for treatment of disseminated Kaposi sarcoma.⁴

In conclusion, we suggest that Kaposi sarcoma be included within the differential diagnosis of small-bowel nodules in otherwise asymptomatic patients. Although the era of HAART has significantly decreased the incidence of Kaposi sarcoma and its gastrointestinal manifestations, a high index of suspicion in susceptible populations may increase the likelihood of early diagnosis and aid management of this aggressive disease.

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Review

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Kaposi sarcoma is a mesenchymal tumor that primarily occurs in a mucocutaneous distribution but can potentially affect any tissue in the body. The pathogenesis of Kaposi sarcoma has been linked to human herpesvirus-8.¹ There are 4 clinically distinct manifestations of Kaposi sarcoma: classic Kaposi sarcoma, which occurs most commonly in elderly men of Mediterranean, Eastern European, or Jewish heritage; endemic African Kaposi sarcoma, which is seen in children and young adults in sub-Saharan Africa; iatrogenic or immunosuppression-related Kaposi sarcoma, which primarily occurs in solid organ transplant patients; and AIDS-related Kaposi sarcoma.

Arora and Goldberg² report a case of Kaposi sarcoma occurring in the small intestine without mucocutaneous involvement in a patient with no previous diagnosis or symptoms of HIV or AIDS. Upon further investigation, the patient was found to be HIV antibody-positive, with a CD4 count of less than 50 cells. This case demonstrates several key points regarding AIDS-related Kaposi sarcoma and the gastrointestinal manifestations of this disease.

At one time, Kaposi sarcoma affected up to 40% of men with AIDS in the United States. Kaposi sarcoma is approximately 20–30 times more common among homosexual or bisexual men with AIDS compared to heterosexual individuals with AIDS.³ Although the rate of AIDS-related Kaposi sarcoma has fallen dramatically since the advent of highly active antiretroviral therapy (HAART),^{4,5} Kaposi sarcoma remains the most common malignancy among all patients with AIDS.⁶ Despite increased awareness and screening, improved diagnostic methods, and more advanced treatment for HIV, the diagnosis of HIV or AIDS is not always apparent when a patient presents with Kaposi sarcoma. As demonstrated by Arora and Goldberg,² an AIDS-defining malignancy such

as Kaposi sarcoma can be the initial presentation of HIV infection, particularly in patients with low CD4 counts.⁷ This is of particular concern in the approximately 20% of HIV-infected individuals in the United States population who are unaware of their condition.⁸

Although Kaposi sarcoma primarily manifests as a mucocutaneous disorder, visceral involvement is common and occurs in up to 25% of cases.⁹ Visceral disease tends to be more common in patients with low CD4 counts. Gastrointestinal involvement is usually asymptomatic but can present with a wide array of manifestations, including bleeding, obstruction, enteropathy, and intussusception. More subtle gastrointestinal symptoms can also occur, including abdominal pain, nausea, vomiting, diarrhea, and weight loss. These symptoms can be seen in AIDS patients for multiple other reasons; thus, the clinician must have a high degree of suspicion, particularly in the absence of coexisting cutaneous lesions. Classic (as opposed to AIDS-associated) Kaposi sarcoma commonly presents with anemia, as with the patient in this case study.¹⁰ The finding of anemia, particularly in association with microscopic blood in the stool, should prompt an evaluation for gastrointestinal Kaposi sarcoma in patients with cutaneous Kaposi sarcoma or known AIDS. The most common location in the gastrointestinal tract where Kaposi sarcoma occurs is the small intestine, followed by the colon and the stomach.¹¹ Importantly, as noted by Arora and Goldberg,² AIDS-related Kaposi sarcoma can occur in the gastrointestinal tract in the absence of cutaneous disease.^{12,13}

The diagnosis of Kaposi sarcoma of the gastrointestinal tract is made via endoscopy with biopsies. Endoscopically, the lesions of Kaposi sarcoma can vary from flat maculopapular lesions to large raised polypoid masses. Often, the disease will progress from patches and/or plaques to nodules, as seen in this case.¹⁴ Kaposi sarcoma is often submucosal, which can make obtaining adequate biopsy specimens challenging. Endoscopic access to Kaposi sarcoma has improved with the advent of technology that can provide direct imaging of the entire small bowel. Capsule endoscopy can visualize the entire small bowel, thus increasing the detection of Kaposi sarcoma in this part of the intestine.¹⁵ When coupled with double-balloon endoscopy or single-balloon endoscopy (as with Arora and Goldberg's case²), capsule endoscopy facilitates both endoscopic access to the small bowel as well as tissue sampling. Histologic findings of Kaposi sarcoma include spindle cells with cytologic atypia, blood vessel proliferation, extravasated red blood cells with hemosiderin deposition, and mixed plasma cell and lymphocytic infiltrate.¹⁶ Immunohistochemistry is used to identify human herpesvirus-8 and to differentiate Kaposi sarcoma from other similar-appearing gastrointestinal tumors such

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as high-grade sarcomas, leiomyomas, and gastrointestinal stromal tumors.

Clinical staging is based upon the extent of the tumor, the immune status of the patient, and the overall severity of the patient's systemic illness, with patients being categorized into either a good- or poor-risk group based upon each factor.¹⁷ Survival has been found to directly correlate with these factors, with increased mortality in those placed into each poor-risk category. Even patients who present with gastrointestinal Kaposi sarcoma should undergo a simple staging evaluation, including a close physical examination of the lower extremities, genitalia, face, and oral mucosa. A chest radiograph should be obtained to evaluate for pulmonary involvement, and a bronchoscopy should be used if the patient has respiratory symptoms or an abnormal chest radiograph.

The mainstay of treatment for AIDS-related Kaposi sarcoma includes HAART.^{18,19} Systemic chemotherapy is used for gastrointestinal and other visceral involvement of AIDS-related Kaposi sarcoma, usually either pegylated liposomal doxorubicin or paclitaxel.^{20,21} Although chemotherapy beyond HAART has become the standard of care for Kaposi sarcoma patients with gastrointestinal disease, the HIV viral load, CD4 count, and overall condition of the patient should be considered before starting systemic chemotherapy.²² The combination of HAART and systemic chemotherapy has been shown to prolong the time to treatment failure.¹⁹ Patients who are on HAART before being diagnosed with Kaposi sarcoma have a decreased mortality and the Kaposi sarcoma tends to be less aggressive. In Kaposi sarcoma patients with gastrointestinal involvement who undergo chemotherapy with doxorubicin, relapse is rare, but mortality may still be relatively high secondary to the development of other AIDS-related malignancies, particularly in patients with low CD4 counts.²³ Current 2-year survival rates for AIDS-related Kaposi sarcoma have significantly increased from 35% before 1996 to over 80% at the present time.⁷

Arora and Goldberg² present a case of AIDS-related Kaposi sarcoma involving multiple locations of the gastrointestinal tract in a previously healthy individual without cutaneous lesions. This case demonstrates that Kaposi sarcoma can be the initial presentation of HIV infection and that Kaposi sarcoma can occur anywhere throughout the gastrointestinal tract and can do so without mucocutaneous involvement.

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