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CASE REPORT

Human herpesvirus-8 positive iatrogenic Kaposi's sarcoma in the setting of refractory ulcerative colitis

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Abstract

Although Kaposi sarcoma (KS) has been more traditionally considered an AIDS-defining illness, it may also be seen in individuals on immunosuppresive therapy. We report a case of a patient who presented to the hospital in the setting of increasingly refractory ulcerative colitis. Computed tomography scan of the abdomen was consistent with sigmoid diverticulititis and blood cultures were positive for Klebsiella. After a course of antibiotics with resolution of infection, a colonoscopy was performed to evaluate his diverticulitis and incidentally revealed a new rectal tumor. Immunohistochemistry showed the tumor was consistent with KS, with cells staining strongly positive for human herpesvirus-8. This case not only illustrates a rare case of KS found in an HIV-negative individual, but it also highlights the importance of considering an alternative diagnosis in a patient refractory to medical treatment. We discuss the management and care of an ulcerative colitis patient diagnosed with KS on immunosuppressive therapy.

Key words: Kaposi sarcoma; Colorectal cancer; Ulcerative colitis; Inflammatory bowel disease; HIV/AIDS; Human herpesvirus-8

Core tip: Kaposi sarcoma (KS) is associated with human herpes 8 virus infection and is typically an acquired immune deficiency syndrome defining illness. However, KS may also be seen in patients who are on long-term immunosuppression. Review of the literature suggests that isolated gastrointestinal KS is a very rare complication, as there are less than 20 reported cases in the English language literature in ulcerative colitis HIV negative

host. Our findings contribute to a small body of literature illustrating the manifestation of primary gastrointestinal KS without skin manifestations in a patient with refractory colitis to medical management.

Duh E, Fine S. Human herpesvirus-8 positive iatrogenic Kaposi's sarcoma in the setting of refractory ulcerative colitis. *World J Clin Cases* 2017; 5(12): 423-427 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i12/423.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i12.423

INTRODUCTION

Kaposi sarcoma (KS) is a vascular neoplasm caused by human herpesvirus-8 (HHV-8) infection in an immunocompromised host. There are four settings in which KS occurs: The classic form (in elderly men of Mediterranean or Eastern European background), the endemic form (in individuals of African background), the HIV-associated form, and the iatrogenic form[1]. The latter form is most commonly seen after solid organ transplantation. There are, however, several case reports of colonic KS associated with ulcerative colitis, typically in refractory cases requiring either intermittent or continuous corticosteroids. Interestingly, no association has been noted between the development of KS and duration of ulcerative colitis (UC) disease activity[2]. The relationship between KS and corticosteroid dose or duration of therapy has not been deeply explored, though there have been case-control studies that suggest oral corticosteroid use is independently associated with increased risk of classical KS[3]. Clinical manifestations may include characteristic skin lesions (not present in this case) or intraluminal vascular-appearing colonic tumors. The lack of skin lesions in primary gastrointestinal KS makes the diagnosis challenging. We report a case of a HIV-negative patient with refractory ulcerative colitis who was diagnosed with KS on histopathological examination of rectal tissue.

CASE REPORT

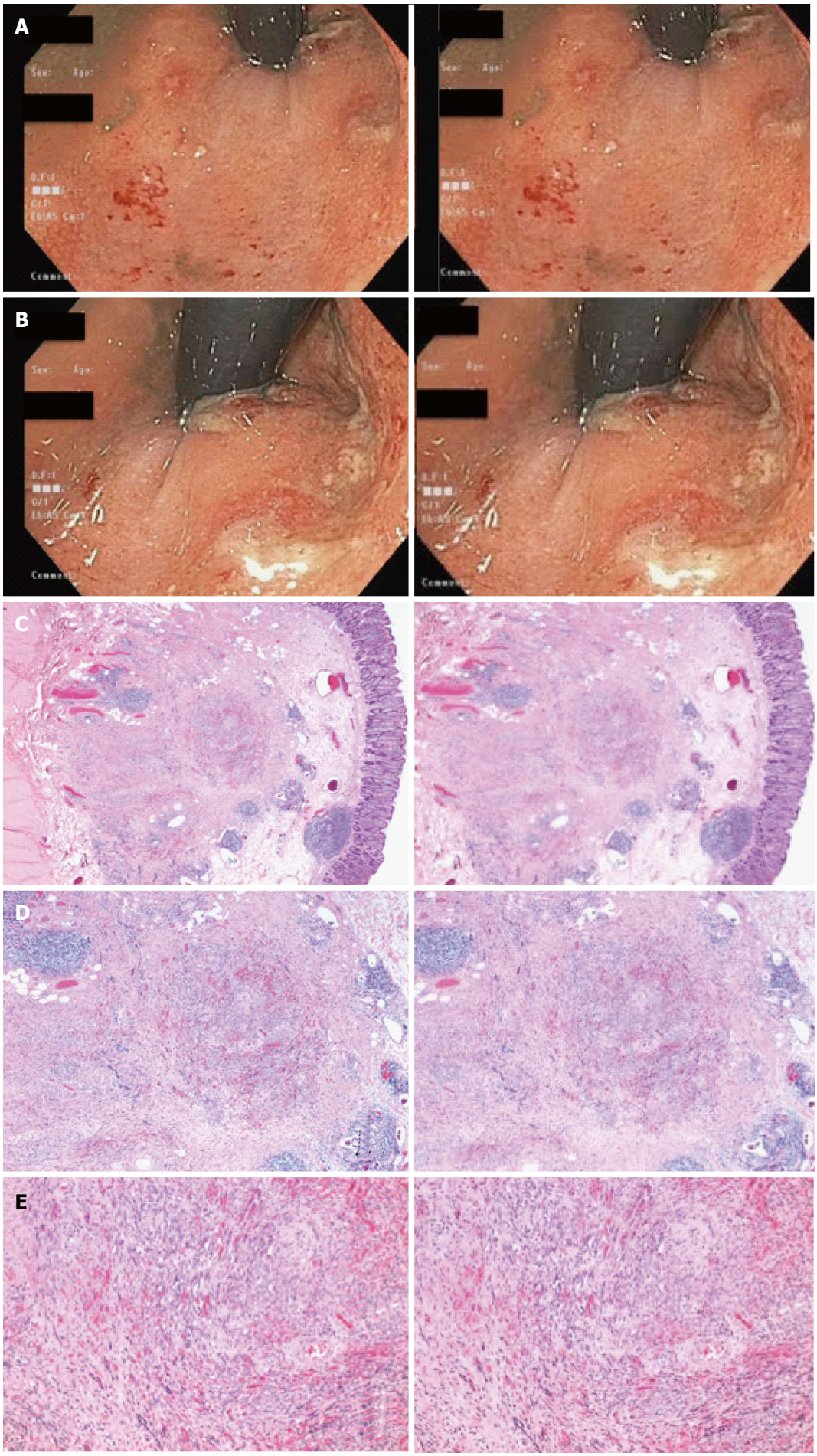
A 48-year-old man with a long-standing history of left-sided UC for 25 years presented to the hospital with fever, nausea, diarrhea and hematochezia for four days. His UC had become increasingly refractory the year prior to presentation with numerous flares that were managed with steroids. Attempts to taper and withdraw steroids had led to multiple relapses. He was started on azathioprine just eight months prior to his presentation and the remainder of his medication at the time of admission included prednisone and pantoprazole.

His exam at the time of presentation was largely unremarkable with a soft, non-tender abdomen without rebound or guarding and no evidence of skin rashes. Vital signs included a temperature of 98.6 °F, a heart rate of 62 bpm, and a blood pressure of 143/84 mmHg. Labs were notable for a hemoglobin of 12.3 g/dL (13.5-16), WBC of 10.1 × 10^9/L (3.5-11) and a negative HIV antibody. A CT scan of the abdomen showed sigmoid wall-thickening, luminal narrowing and surrounding inflammatory stranding with a small fluid collection. He was diagnosed with sigmoid diverticulitis complicated by a 3 cm abscess that was felt to not be amenable to drainage. Blood cultures were positive for Klebsiella and he was treated with a fourteen-day course of antibiotics. A colonoscopy was performed following resolution of acute diverticulitis and revealed a tumor in the rectum (Figure 1A and B). Biopsies of the distal colon revealed focal active colitis and proximal biopsies of the left colon demonstrated crypt architectural irregularities and paneth cell metaplasia consistent with quiescent colitis. Histologic sections of the rectal tumor demonstrated a cytologically bland spindle cell proliferation interspersed by irregular vascular spaces containing extravasated erythrocytes (Figures 1C-E). By immunohistochemistry, the lesional cells were strongly positive for HHV-8 (Figures 1F and G) and consistent with KS. Esophagogastroduodenoscopy and capsule endoscopy demonstrated that tumor involvement was limited to the rectum. In consultation with a sarcoma specialist, the treatment plan involved an attempt at immune reconstitution by withdrawal of steroids. Over the period of a year, attempts to taper the patient off of steroids by introducing alternative agents (including aloe vera, probiotics, phostatidylcholine and Epigallocatechin-3-gallate) were unsuccessful and led to repeated relapses. Surveillance colonoscopies completed four and seven months following diagnosis revealed persistent Kaposi rectal tumor. The patient went on to have a definitive laparoscopic assisted subtotal colectomy with end ileostomy and since has done well.

DISCUSSION

KS is a rare diagnosis and is typically diagnosed when the classic skin manifestations are present. Isolated gastrointestinal KS may occur in patients with ulcerative colitis as a result of the dysregulated immune response seen in IBD or in combination with medications causing immune suppression. Symptoms and signs of gastrointestinal KS may include diarrhea, bleeding, obstruction, and rarely perforation. A misdiagnosis of refractory ulcerative colitis may occur in part because the initial presentation may mimic a IBD flare with diarrhea and rectal bleeding and may be severe to the point requiring blood transfusions[4]. The reason KS lesions are predisposed to bleeding is that they are angioproliferative tumors. Typically, KS lesions in the intestinal tract tend to localize more to the upper intestinal tract and are less frequently encountered in the large bowel[5].

This is one of the few reported cases in the English language literature of large bowel KS associated with ulcerative colitis in an HIV-negative host with positive HHV-8 immunohistochemistry. Infection with HHV-8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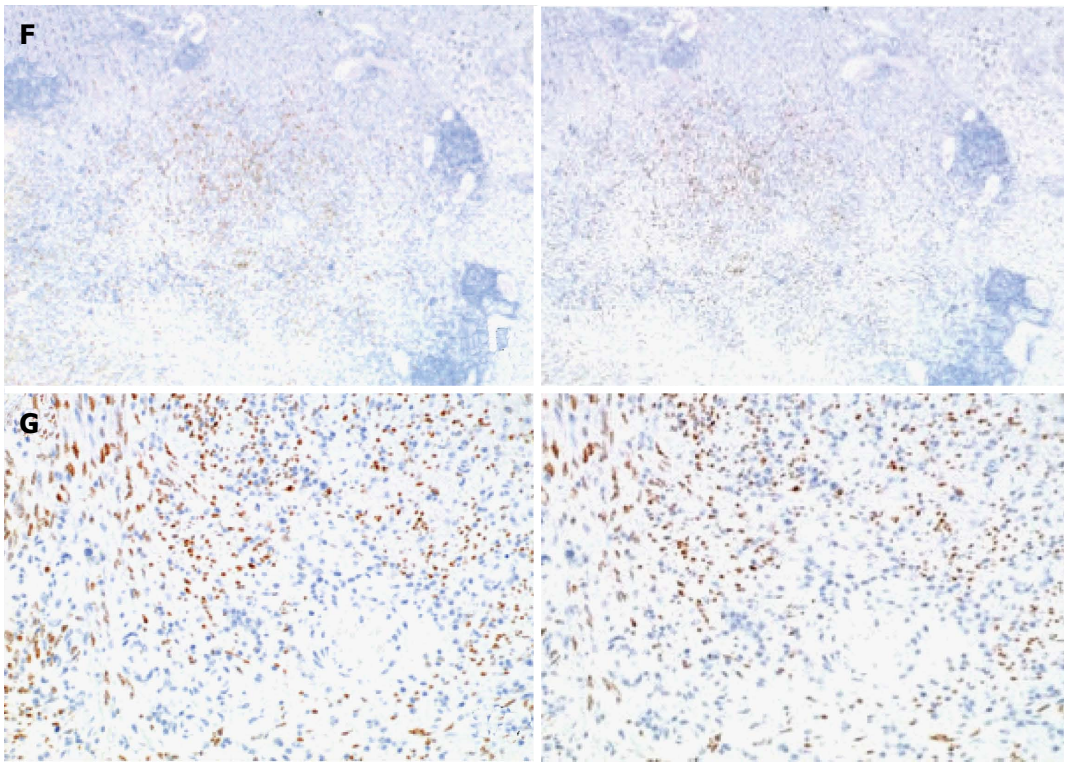

Figure 1 Colonoscopy, histologic and immunohistochemistry. A: A colonoscopy was performed following resolution of acute diverticulitis, revealing a tumor in the rectum. Biopsies of the colon revealed distal focal active colitis as well as more proximal crypt architectural irregularities and paneth cell metaplasia consistent with quiescent colitis; B: A colonoscopy was performed following resolution of acute diverticulitis, revealing a tumor in the rectum. Biopsies of the colon revealed distal focal active colitis as well as more proximal crypt architectural irregularities and paneth cell metaplasia consistent with quiescent colitis; C: Histologic sections of the rectal tumor demonstrated a cytologically bland spindle cell proliferation interspersed by irregular vascular spaces containing extravasated erythrocytes (2 ×); D: Histologic sections of the rectal tumor demonstrated a cytologically bland spindle cell proliferation interspersed by irregular vascular spaces containing extravasated erythrocytes (4 ×); E: Histologic sections of the rectal tumor demonstrated a cytologically bland spindle cell proliferation interspersed by irregular vascular spaces containing extravasated erythrocytes (10 ×); F: By immunohistochemistry, the lesional cells were strongly positive for human herpesvirus-8 and consistent with Kaposi's sarcoma (4 ×); G: By immunohistochemistry, the lesional cells were strongly positive for human herpesvirus-8 and consistent with Kaposi's sarcoma (10 ×).

is a known precedent to the development of all types of KS and has been found in over 95% of cases[5]. The literature shows that only a small proportion of HHV-8 infected people develop Kaposi Sarcoma, suggesting that additional iatrogenic causes such as immunosuppressive drugs could cause viral reactivation, and contribute to the development of KS[6].

Corticosteroid use was first implemented in the 1950's for the management of Ulcerative colitis and has played a pivotal role in decreasing mortality[7]. However, over the years evidence has demonstrated poor outcomes for patients who remain on longterm steroids, notably an increased risk for infections and mortality[8]. In the first population-based field study of classical Kaposi sarcoma, use of oral corticosteroids showed a increased risk for the development of KS (OR = 2.34, 95%CI: 1.23-4.45)[3]. KS has also been reported to be higher in illnesses that are commonly treated with corticosteroids including asthma and rheumatic diseases[9,10]. Studies have shown that glucocorticoids can induce KS and drive progression in multiple different clinical settings through interactions with the gene Transforming growth factor-β (TGF-β). This gene has several effects, one of which is inhibition of cell growth. While glucocorticoids have no effect on the actual transcription of TGF-β, the medication does decrease activation of the TGF-β gene by downregulating plasminogen activator and plasminogen activator receptor, which are known to drive the TGF-β activation pathway[13]. Thus, glucocorticoids reduce levels of plasmin, which prevents activation of TGF-β, and in turn decreases its inhibitory effects on KS cells[11].

Diagnosis of KS in the absence of characteristic skin lesions can be difficult as colonic KS development starts in the submucosa and standard biopsies may not prove diagnostic. Therefore if there is a high suspicion, "bite on bite" biopsies should be taken with large forceps, which may improve the diagnostic yield[6]. When the mucosa is involved, tumors may appear similar to pseudopolyps. Cross sectional imaging may only demonstrate colonic wall thickening. Serum PCR for HHV-8 is an available test that may be useful in the diagnosis and in guiding decision for early surgical management[12]. Treatment consists of immune reconstitution and should be pursued to prevent systemic dissemination of disease[5]. Withdrawal of immunosuppressive agents, which often requires surgical colonic resection, can lead to regression or cure of KS lesions. Lastly, involvement of a multidisciplinary treatment team is vital to coordination of care and ensuring resolution of the disease.

COMMENTS

Case characteristics
Patient's symptoms included fever, nausea, diarrhea, and hematochezia.

Clinical diagnosis
Patient was found to have a rectal tumor consistent with Kaposi sarcoma (KS) after having had surveillance colonoscopies completeded.

Differential diagnosis
Ulcerative colitis flare, vascular transformation of lymph nodes, CMV colitis, infectious colitis.

Laboratory diagnosis
Labs were notable for a hemoglobin of 12.3 g/dL (13.5-16), WBC of 10.1 × 10^9/L (3.5-11) and a negative HIV antibody.

Imaging diagnosis
Esophagogastroduodenoscopy and capsule endoscopy demonstrated that tumor involvement was limited to the rectum.

Pathological diagnosis
Histologic sections of the rectal tumor demonstrated a cytologically bland spindle cell proliferation interspersed by irregular vascular spaces containing extravasated erythrocytes, which on immunohistochemistry were positive for human herpesvirus-8 and consistent with KS.

Treatment
The patient underwent multiple failed attempts to withdraw his regimen of oral corticosteroids, and ultimately received a laparoscopic assisted subtotal colectomy with end ileostomy and since has done well.

Term explanation
Refractory: Resistant to a process or stimulus, in the context of medicine this term often refers to being resistant to treatment. Immunosuppression: Reduction of the activation or efficacy of the immune system

Experiences and lessons
This particular patient's case highlights the importance in considering the diagnosis of KS in the setting of ulcerative colitis patients, as failure to do so delay treatment.

Peer-review
This patient case illustrates the manifestation of primary gastrointestinal KS in a patient with refractory colitis to medical management.

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