CASE REPORT

Acute Upper Gastrointestinal Bleeding Secondary to Kaposi Sarcoma as Initial Presentation of HIV Infection

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ABSTRACT

Despite our decades of experience with Kaposi Sarcoma its true nature remains elusive. This angioproliferative disease of the vascular endothelium has a propensity to involve visceral organs in the immunocompromised population. There are four variants of the disease and each has its own pathogenesis and evolution. While the common sources of upper gastrointestinal bleeding are familiar to surgeons and critical care physicians, here we present the exceedingly rare report of upper gastrointestinal bleeding attributable to this malady, explore its successful management, and review the various forms of Kaposi Sarcoma including the strategies in regard to their management.

Key words: Kaposi sarcoma – upper gastrointestinal bleeding – endoscopy – highly active anti-retroviral therapy (HAART) – clinical management

INTRODUCTION

The incidence of hospitalization due to upper gastrointestinal bleeding (UGIB) ranges between 50 and 150 cases per 100,000 [1]. High volume intensive care units (ICUs) have become proficient at resuscitating and managing the common causes of UGIB (Table I). Peptic ulcers are the most common etiology of UGIB, accounting for 30-50% of cases [2]; Mallory-Weiss tears, esophageal and gastric varices, angiodysplasias and arteriovenous malformations, hemobilia, hemorrhagic/erosive gastropathy (e.g., due to NSAIDs or alcohol consumption), and erosive esophagitis are additional etiologies of UGIB [2]. Upper gastrointestinal (GI) hemorrhage associated with neoplasms, however, is less common and within that subset is the exceedingly rare occurrence of bleeding attributable to Kaposi sarcoma (KS) [4].

Kaposi sarcoma is a multicentric neoplasm consisting of multiple vascular nodules appearing on cutaneous surfaces, mucous membranes, and less commonly viscera [5]. Massive GI bleeding from visceral KS is rare, with few cases reported (Table II) [6, 7]. In the United States, KS is most commonly associated with immunosuppression from the Human Immunodeficiency Virus (HIV) or chronic use of transplant anti-rejection medications [8]. Early in the AIDS epidemic the incidence of KS reached >50%, but decreased to 15% by 1989 [9]. A further drop in incidence to <1% occurred in the early

Table I. Common sources and prevalence of upper gastrointestinal bleeding*

Source	Prevalence (%)
Duodenal ulcer	24.3
Gastric erosions	23.4
Gastric ulcer	21.3
Esophagogastric varices	10.3
Mallory-weiss tear	7.2
Esophagitis	6.3
Erosive duodenitis	5.8

*Defined as >5% in American Society for Gastrointestinal Endoscopy bleeding survey of 2225 patients.

2000s with widespread use of the highly active anti-retroviral therapy (HAART) [10].

In the context of the above observations, it is important to note that while approximately 50,000 new HIV infections are diagnosed in the Unites States yearly, more than one million individuals in the United States do not know they are infected [11]. Despite the overall decreasing morbidity and mortality trend in the HIV-infected population, the potential number of patients with advanced opportunistic infections and malignancies continues to be significant, and is further amplified by patients who are non-compliant with HAART or whose virus is resistant to current anti-retroviral regimens [12].

Here we report an unusual case of massive UGIB directly attributable to HIV-associated KS complicated by thrombocytopenia of advanced, undiagnosed HIV infection. We also present a review of the literature for KS-induced UGIB and important aspects specific to the management of the patient with newly-diagnosed, advanced HIV infection.

CASE REPORT

A middle-aged female presented to the Emergency Department (ED) with a chief complaint of facial edema following a visit to a dental clinic three days prior to admission. During that visit, the patient underwent extraction of an infected tooth and was started on penicillin. She continued to have swelling and pain in the left buccal area, and on the morning of hospital admission she noted increased purulent drainage from this area. While en route to the ED she had one episode of hematemesis, approximately 200 mL in volume. Upon further questioning, the patient stated that since the dental extraction, she has also been taking high-dose ibuprofen frequently to help with her severe pain. She denied any past medical or surgical history, although admittedly she rarely sought medical care and felt herself to be generally healthy. She denied tobacco, alcohol or drug abuse.

On initial evaluation, she was a thin-appearing female with notable erythema and edema in the left buccal and periorbital area. On examination her blood pressure was 123/74 mmHg, heart rate 127 beats/minute, respiratory rate 33 breaths/min, temperature 36.3^{0}C, and an oxygen saturation of 100% on room air. Within the middle of the buccal area of erythema was a spontaneously draining abscess containing thick, purulent material. There was no obvious blood in the oropharynx. The remainder of her physical exam was unremarkable. Microbiology culture specimens were sent and broad spectrum antibiotics were started.

Shortly after her initial evaluation the patient experienced a second episode of hematemesis (~250 mL). A nasogastric tube was placed, but it was not possible to clear the lavage output. Large-bore, central venous access was established and fluid resuscitation began. Her initial laboratory evaluation demonstrated hemoglobin of 7.3 g/dl, international normalized ratio (INR) of 1.1, and white blood cell count of 18,800/µL. Concurrent to this most recent episode of hematemesis, her clinical course began to rapidly deteriorate and the patient quickly became hypotensive and increasingly tachycardic. After a third, larger episode of hematemesis occurred (~800 mL), the patient's trachea was intubated for airway protection and emergent esophagogastroduodenoscopy (EGD) was performed. Bright red blood was found throughout the esophagus and stomach. There were numerous (>8) 1-2 cm cratered, nodular gastric ulcers within the gastric body. Some of the ulcers in the distal body of the stomach had a visible vessel with stigmata of recent bleeding. The largest lesion seen in the proximal gastric body was 20 mm in largest dimension with actively blood extravasation visible vessel within the ulcer bed. Multimodality therapy consisting of electrocoagulation, endoscopic clip application, and local epinephrine injections was utilized. The proximal duodenum and antrum appeared to be grossly normal. Biopsies of the lesions were obtained.

Following the upper endoscopy, the patient continued to have sanguineous nasogastric tube output. An arteriogram was performed with intent to perform embolization of any active intragastric bleeding. However, no active bleeding was identified on the study. A repeat upper endoscopy performed approximately 24 hours after the initial EGD demonstrated no active bleeding and re-visualization of the ulcerative lesions (Fig. 1).

The patient was transfused 8 units of packed red blood cells during her first 48 hours in the ICU. The patient gradually stabilized and began to improve. On hospital day four, her pathology results were finalized, showing focal proliferating spindle cells at the edge of the ulcer, granulation tissue positive for CD31, HHV-8 and CD117, and stains negative for S100 and SMA. Overall, these findings were consistent with KS. Upon subsequent testing, the patient's HIV results came back positive, with a viral load of 2,567,006 copies/mL. The patient's CD4 count was 5 cells/mm^3.

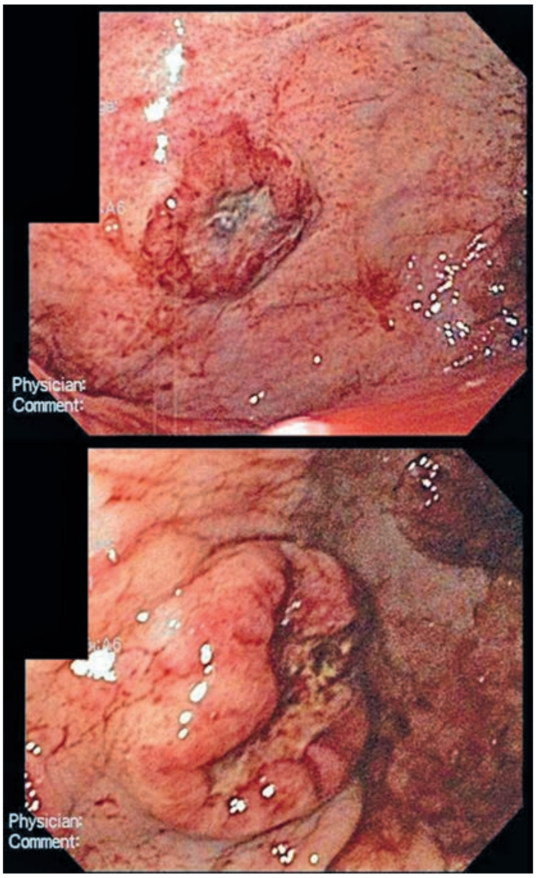

Fig. 1. Esophagogastroduodenoscopy: images of gastric body lesions.

Table II. Literature Review - Gastrointestinal bleeding as a result of Kaposi sarcoma - presentations, treatments and outcomes.

Author	Year	Age/ Gender	Presentation	History	GI Location	Treatment	Outcome
Salako [7]	2007	56 yo / M	melena	H.pylori s/p treatment	jejunum, ileum	small bowel resection	death from rupture of hepatic Kaposi, HIV testing negative
Ablin [23]	1998	73 yo / M	melena, fever	vasculitis on immuno-suppressants	gastric, LI, rectum	vinblastine, cessation of immuno-suppressants	continued hemorrhage, death
Balachandra [24]	2006	61 yo / M	GI bleeding	Inuit, NSAID use	stomach, ileocecal valve	doxorubicin	alive at 2.5 yrs HIV testing negative
Bryk [25]	1978	78 yo / M	weakness, malaise, melena	known cutaneous Kaposi	duodenum, jejunum	local radiotherapy, vinblastine, cyclophosphamide	death from continued bleeding
Calzona [26]	2002	15 yo / F	melena, lymphadenopathy, fever	renal txp	stomach	cessation of immuno-suppressive therapy	bleeding stopped at 16 days, remission at 6 months
Cairncross [27]	2009	5 yo / F	„massive GI bleed”	HIV, CD4 14	unknown	none	death
De Blasio [28]	2005	42 yo / M	anemia, lymphadenopathy	renal txp	gastric, liver, inguinal lymph nodes	sub-total gastrectomy	death few days following surgery
Lin [29]	2002	41 yo / F	lymphadenopathy, tarry stools	renal txp	Esophagus, stomach	none listed	unknown
Kahl [30]	2007	39 yo	hematochezia	none	stomach, SI, LI	none listed	new HIV Dx
Neville [6]	1996	53 yo / M	melena, anemia	HIV, known cutaneous KS	SI	chemo, radiation	resolution of symptoms
Potter [31]	1984	35 yo / M	hematochezia, abdominal distention	known HIV / AIDS	esophagus, duodenum, SI, appendix, LI, liver, GB, pancreas	TPN, bowel rest, vinblastine, adriamycin, bleomycin, vincristine, actinomycin, DTIC	progression of Kaposi, death due to respiratory failure (PCP)
Rodriguez [4]	2012	30 yo / M	anal pain, hematemesis	HIV, known cutaneous KS	stomach, duodenum, rectum	HAART, doxorubicin, radiation	unknown
Stribling [32]	1978	59 yo / M	skin lesions, GI bleed	renal txp	esophagus, stomach, SI, LI, liver, adrenals, retroperitoneum	laparotomy, bowel resection	death
Wien [33]	1991	66 yo / M	upper GI bleed	alcoholic liver disease	stomach	radiation	resolution of gastric lesions
Yildiz [34]	2010	52 yo / M	growing palate mass, melena, hematemesis	known cutaneous classic KS, HIV negative	palate, esophagus, stomach, lung, liver	adriablastine, vincristine, bleomycin	partial remission

PubMed and Google Scholar searches for “*gastrointestinal bleeding AND Kaposi*”. Abbreviations: SI: small intestine; LI: large intestine; GB: gallbladder; KS: Kaposi sarcoma; LAD: lymphadenectomy; txp: transplantation; GI: gastrointestinal.

Over the next several days, she continued to require intermittent packed red blood cell transfusions. In addition, she was diagnosed with HIV-Related Immune Thrombocytopenic Purpura which responded to treatment with intravenous immunoglobulin. The bleeding gradually subsided to the point where she was able to take oral medications, and HAART therapy was initiated consisting of Darunavir, Ritonavir and Emtricitabine/Tenofovir. Her clinical status rapidly improved. Positron emission tomography (PET) revealed multifocal hypermetabolic lesions within the stomach and small bowel (Fig. 2). She received one dose of paclitaxel prior (Taxol) to discharge in order to induce regression of her sarcomas. On hospital day 28 she was discharged to home in stable condition.

The original mouth lesion failed to heal completely, and was thus biopsied. This revealed KS as well. She continued outpatient chemotherapy and HAART, and at her six-month follow-up appointment her viral load was reduced to <40 copies/mL and the CD4 count increased to 46 cells/mm^3. Repeat PET scan after five cycles of Taxol demonstrated significant improvement in hypermetabolic activity in the stomach with mild residual activity (Fig. 2). She completed six doses of paclitaxel and has experienced no additional episodes of GI bleeding. Twenty months after her initial diagnosis, her CD4 count was stable between 190-250 cells/mm^3.

DISCUSSION

Kaposi sarcoma is a low-grade vascular tumor first described in 1872 as a cutaneous „pigmented sarcoma” [5]. Since then the understanding of the different subtypes of

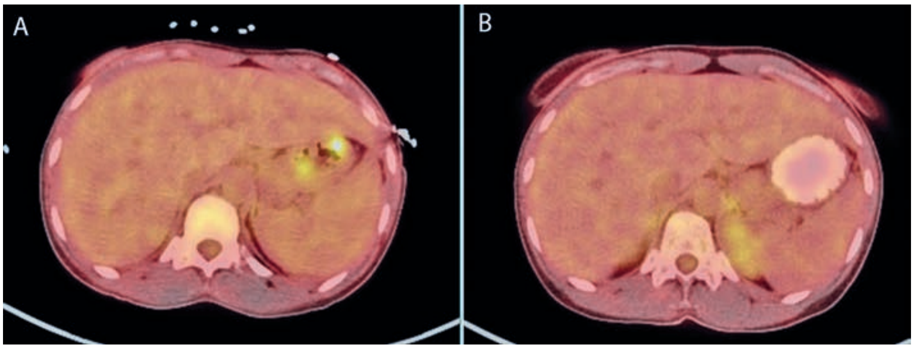

Fig. 2. PET/CT of abdomen: A) Imaging performed prior to treatment (without oral contrast). B) Imaging obtained three months after initiation of medical treatment on the right (with oral contrast).

KS has advanced greatly with the common theme being the involvement of the human herpes virus-8 (HHV-8) infection [13]. The classic variant of KS is found predominantly in older men of Eastern European and Mediterranean origin, presenting with multiple red-to-purple nodules on lower extremities and rare involvement of the GI tract [14]. The second variant is the lymphadenopathy-associated form of KS, also called the endemic or African form. This variant is very aggressive and is often found in South Africa in young Bantu children with local or generalized lymphadenopathy. Skin lesions are rare in this variant [16]. The third variant of KS is the iatrogenic, transplant- or immunosuppression-associated form, which develops in patients on immunosuppressive therapy. Lesions appear on the skin, but in approximately half of the cases they are also found in internal organs and lymph nodes [8]. The fourth variant of KS is the AIDS-associated (epidemic) form. This variant is the most common AIDS-associated tumor in the United States. AIDS-associated KS has no preferred locations and tends to be more scattered, with involvement of the lymph nodes and the GI tract occurring relatively early [13, 17].

In the United States, KS is most commonly associated with immunosuppression from the HIV or chronic use of transplant anti-rejection medications [8]. During the early years of the HIV epidemic, KS was one of the most common clinical manifestations of AIDS. The incidence of KS associated with the early period of the AIDS epidemic (>50%) declined markedly by the late 1980s (15%) [9], and then further dropped to <1% by the early 2000s with the use of HAART [10]. Approximately 80-90% of HIV-associated KS cases are identified in homosexual males, suggesting the HHV-8 as a transmitting agent [18].

Visceral involvement is common in AIDS-related KS but is often asymptomatic. Post-mortem studies suggest that >25% of patients with AIDS-related KS have visceral lesions commonly involving the stomach, bowel, liver, spleen, and lungs [5]. Most of the clinical data regarding the visceral presentation of KS is limited to case reports and series. Rare reports of intussusception, appendicitis, bowel obstruction, and perforation have been reported [19-21]. Table II reviews the reports of KS presenting in the form of GI hemorrhage.

Kaposi sarcoma is usually indolent, and requires no specific treatment with fewer than 10% of patients with KS dying of their malignancy. Many cases of KS regress following the initiation of HAART. Therefore aggressive treatment is reserved for cases with severe cosmetic problems or functional limitations with joint involvement. Recommendations for symptomatic visceral lesions are limited due to the rare nature of the disease. However, there are treatment options, and management of AIDS-associated KS is based on the extent of disease (Table III). Paclitaxel is the most attractive antineoplastic agent with acceptable tolerance. This is also used as rescue therapy for those that fail classical regimens. Neutropenia is the major side effect, occurring in 60% [22].

Essentially, KS therapy is palliative in that it seeks to eliminate tumor-related edema, improve cosmetic results and the functioning of limbs. The management approaches to classic KS, endemic KS, iatrogenic KS, and epidemic will differ as indicated above. Systemic therapy is applicable to the four types of KS. However, side effects, duration of response, and how efficacious the therapy will vary among the different forms of KS. New therapies target prevention of KS-HIV in conjunction with treatment of KS. Gancyclovir, foscarnet, and valgancyclovir have all demonstrated promise. However, anti-herpes drugs alone are inadequate in that their administration with HAART offers the best hope to patients. Other innovative approaches are being brought to bear on KS, such as therapy targetting tyrosine kinase, VEGF, angiogenesis, and matrix metalloproteinases [15].

Table III. Management of AIDS-associated Kaposi Sarcoma (from Fatahzadeh [15])

1. Observation and optimization of antiretroviral therapy
2. Single or limited number of lesions
Surgical excision
Radiation
Intralesional vinblastine
Sclerotherapy
Cryotherapy
Topical alitretinoin, imiquimod cream
3. Antineoplastic agents
Interferon-α
Bleomycin, vinca alkaloids
Adriamycin, bleomycin, vinca alcaloids
Liposomal anthracyclines
Taxol

CONCLUSIONS

Acute upper gastrointestinal bleeding associated with KS is very uncommon. Successful management involves multi-modality approach, including endoscopy and HAART. In some cases, KS lesions have regressed following adequate HIV-targeted therapy. A variety of other therapeutic agents have been described in the management of KS, but there is no universal agreement or standardized approach to this challenging clinical problem.

Conflicts of interest: The authors have no conflicts of interest to report.

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