MINIREVIEWS

Hepatic Kaposi sarcoma: A case report and review of the literature

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Abstract

Kaposi sarcoma (KS) is an aggressive cancer caused by human herpesvirus-8, primarily seen in immunocompromised patients. As opposed to the well-described cutaneous manifestations and pulmonary complications of KS, hepatic KS is rarely reported before death as most patients with hepatic KS do not manifest symptoms or evidence of liver injury. In patients with acquired immune deficiency syndrome, hepatic involvement of KS is present in 12%-24% of the population on incidental imaging and in approximately 35% of patients with cutaneous KS if an autopsy was completed after their death. Patients with clinically significant hepatic injury due to hepatic KS usually have an aggressive course of disease with hepatic failure often progressing to multi-organ failure and death. Here we report an unusual presentation of acute liver injury due to hepatic KS and briefly review the published literature on hepatic KS.

Key words: Herpesvirus 8; Acquired immune deficiency syndrome-related Kaposi sarcoma; Acquired immune deficiency syndrome hepatopathy; Human; Kaposi sarcoma

Core tip: Hepatic Kaposi sarcoma (KS) is a clinical presentation that disproportionately affects the human immunodeficiency virus/acquired immune deficiency syndrome (AIDS) population. Up to 34% of patients with AIDS and KS have hepatic involvement. Usually hepatic KS is clinically indolent and diagnosed during autopsy. When clinically significant, hepatic KS presents with evidence of liver injury with elevation in bilirubin and liver enzymes, has characteristic findings on imaging and may progress to liver failure and death. Treatment is indicated in patients with progressive and symptomatic hepatic disease in the absence of other etiologies.

CASE PRESENTATION

A forty-eight years old African American male with HIV and CD4 count of 8/μL presented with conjunctival icterus. Physical exam showed cachexia, icterus, a violaceous 1 cm plaque on the soft palate and similar lesion on the chest wall, and a soft, non-distended, non-tender abdomen. He denied prior treatment with antiretroviral medications. Laboratory studies were significant for AST (SPGT) 172 U/L, ALT (SGOT) 201 U/L, total bilirubin of 20.0 mg/dL, direct bilirubin 14.9 mg/dL, alkaline phosphatase 947 U/L, INR 2.5, and platelet count 52000/μL. Acute and chronic serologies for hepatitis A, B and C, histoplasma, and cytomegalovirus as well as a toxicology screen were negative. Patient did report taking cotrimoxazole for five days which he completed a month prior to presentation. Magnetic resonance imaging (MRI) of the Abdomen showed innumerable 10 mm T2 intense hepatic nodules without enhancement (Figure 1). Liver biopsy was positive for Cytokeratin 7 and human herpes virus-8, consistent with infiltrative Kaposi sarcoma (KS) (Figures 2 and 3). There was no evidence of drug induced liver injury on histopathology. There was no lymphadenopathy indicative of hemophagocytic lymphohistiocytosis or Castleman's disease. The diagnosis was most consistent with acute liver injury (ALI) secondary to infiltrative hepatic KS, stage T1, I1, S1. The patient was not a candidate for cytotoxic therapy given progressive liver injury and was started on rituximab and ganciclovir. Liver injury progressed and was further complicated by acute kidney injury, hypoxic respiratory failure, consumptive coagulopathy and septic shock. The patient received broad-spectrum antibiotics, blood products, vasopressors and ventilator support but unfortunately expired.

BACKGROUND

KS is an angioproliferative low-grade neoplasm that is associated with human herpesvirus-8 (HHV-8). KS can be codified into different clinical variants depending on the patient cohort and the presentation of the disease[1]. The "classical" form primarily affects men of Ashkenazic Jewish or Mediterranean background and follows an indolent cutaneous course. The "African endemic" form of the disease commonly affects Africans as the name implies, presents with lymphadenopathy and is usually fatal within 1-3 years. The "iatrogenic" form is due to HHV-8 activation caused by medical immunosuppression from treatment of autoimmune disorders or post-organ transplantation. The fourth and most common variant, acquired immune deficiency syndrome (AIDS)-related KS,

is rapidly progressive and holds the highest rate of hepatic involvement[2].

The most common presentation of KS is a cutaneous papular disease with lesions on the legs, oral cavity, and genitalia. However, the most common site of visceral organ involvement is the gastrointestinal tract[3]. First described by Moritz Kaposi in 1872, hepatic KS was an autopsy diagnosis that rarely resulted in clinically significant disease or ALI[4]. To further understand hepatic KS, a systematic search of the literature was conducted on PubMed (1954 to 2015), EBSCO HOST (1956 to 2015), the Cochrane Database of Systematic Review, and the OVID interface (1946 to 2015) with comprehensive search terms as documented in Table 1.

EPIDEMIOLOGY

While most herpesviruses are widespread in the adult population, the prevalence of HHV-8 varies with human immunodeficiency virus (HIV) status and exposure risk factors. In the United States, only 5% of HIV uninfected men are seropositive for HHV-8 compared to 25%-60% of HIV-positive men who have sex with men (MSM)[5]. These rates are reflective of HHV-8 and HIV co-infection in MSM in other countries as well[6].

AIDS-patients have 20000 times greater risk of developing KS than the general population. Patients on HAART with a CD4 count of < 200 cells/μL are 18.9 times more likely to have KS than those with CD4 $\geqslant$ 500 cells/μL[7]. In the era of ARV therapy, improved control of HIV viremia and preserved CD4 T-cell function has lead to an 80% decreased incidence of AIDS-associated KS[8], AIDS-related KS currently affects < 1% of AIDS patients, compared to 15% in the pre-HAART era[9].

MODES OF TRANSMISSION

Behavioral risk factors for HHV-8 transmission are incompletely understood. Saliva exchange appears to an important factor with HHV-8 DNA detected in the saliva of 61% of HHV-8-infected MSM[10,11]. With HHV-8 seropositivity higher in the MSM population, commercial sex workers and those with other sexually transmitted infections, a sexual route of transmission has also been proposed. HHV-8 DNA can be isolated from semen and vaginal secretions, but viral load is lower than that found in saliva, calling into question the clinical significance of sexual transmission[12]. HHV-8 seroprevalence in HIV-infected injection drug users is substantially lower than hepatitis B and C rates in HIV-infected MSM[13]. This finding is suggestive that blood exchange through contaminated needle sharing is a less significant route of HHV-8 transmission compared to salivary or sexual contact[14].

HEPATIC INVOLVEMENT

Hepatic KS is typically asymptomatic and rarely diagnosed in life. Therefore the true incidence of hepatic KS is not
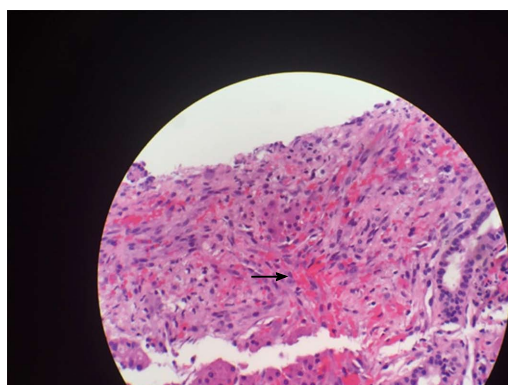
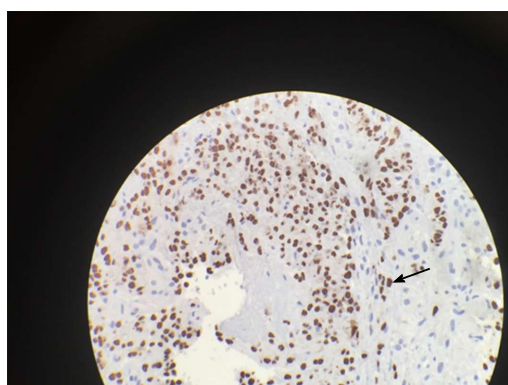**Figure 1 Spindle cells with cytokeratin 7 staining positive.**

Figure 2 Positive human herpersvirus-8 immunohistochemical staining.

well-documented and is limited to small case series and reports. Prevalence of hepatic KS has primarily been determined from autopsy series with small sample sizes, which accounts for the wide variation in prevalence reported. In one autopsy series, approximately 34% of AIDS-related KS cases involved the liver while in another report, 8.3% had liver involvement[15,16]. In another retrospective review, hepatic involvement was present in 9 of 41 patients or 22% of cases of AIDS-related KS in post mortem dissection[17]. In this study ante-mortem hepatic KS was suspected in only one patient, in whom a computerized tomography (CT) scan demonstrated hepatosplenomegaly with a confluence of hypodense lesions in the left hepatic lobe. Autopsy confirmed disseminated KS. Schneiderman *et al*[18] found KS on liver biopsy in 18.6% of AIDS patients making KS the most common hepatic pathological diagnosis caused by AIDS. All of these patients already had a diagnosis of extrahepatic KS at time of biopsy. In contrast, 66% of patients with extrahepatic KS did not manifest hepatic involvement.

As mentioned above, most cases of hepatic KS were not clinically significant. In the study by Schneiderman *et al*[18], there were no statistically significant differences in transaminases, lactic dehydrogenase, alkaline phosphatase or bilirubin based on liver involvement with KS. However, in the few reported patients with clinically significant disease, a rapid progression to liver and multi-organ failure has

Table 1 MeSH search terms
Liver
Hepatopathy
Hepatitis
Hepatology
Cholestatic injury
Hepatocellular injury
Kaposi sarcoma
Herpesvirus 8, human
AIDS-related Kaposi sarcoma
Non-AIDS-related Kaposi sarcoma
Liver neoplasms

AIDS: Acquired immune deficiency syndrome.

been reported, usually with fatal outcomes (Table 2).

In the non-HIV population, the incidence of KS is 0.2% in liver transplant patients from the United States, but the prevalence is higher in patients from Africa, the Middle East or the Mediterranean[19]. KS affected 4.7% of renal transplant patients in Saudi Arabia, 2.4% of recipients in Israel and 0.52% of recipients in France. While there is a well described clinical burden of post-transplant lymphoproliferative disorder including cutaneous and visceral manifestations of KS, there is no described literature of post-transplant hepatic KS.

PATHOGENESIS OF HHV-8 ASSOCIATED TUMORS

HHV-8 consists of a large double stranded DNA genome that includes approximately 145 kilobases (kbases) long region encoding all the expressed viral genes, flanked by approximately 20-30 kbases that encode a number of mimicked human genes, several of which have immunologic or angiogenic properties[20,21]. HHV-8 has a tropism for both hematopoietic and non-hematopoietic cells including monocytes, B cells, endothelial cells and also hepatocytes[22]. Endothelial cells appear to be the most important host cells for oncogenic transformation as HHV-8 infection of these cells leads to their long-term proliferation and survival[23]. Similar to other herpesviruses, HHV-8 alternates between two metabolic cycles: Latent infection, where few genes are expressed, and the active lytic infection, where viral replication and multiple gene expression occurs. Lytic replication can be induced by oxidative stress, hypoxia, inflammatory cytokines, chemical exposure or concomitant infections, including HIV[24-27].

In hepatocytes infected with HHV8 genome by DNA polymerase chain reaction amplification, immunohistochemistry demonstrates expression of the transcriptional regulator, latency-associated nuclear antigen-1 (LANA-1)[28]. It has also been directly implicated in oncogenesis because of its ability to bind to the tumour-suppressing protein p53[29]. Furthermore, hepatocyte growth factor/scatter factor, a kinase that mediates epithelial cell proliferation and angiogenesis[30] has been demonstrated to induce HHV-8 lytic replication, providing a means of KS pro-

Table 2 Outcomes in patients with clinically symptomatic hepatic Kaposi sarcoma

Age (yr)	Sex	HIV status	CD4 count (cells/mm³)	Liver chemistry profile	Pathology	Treatment	Hospital course + complications
45[63]	M	(+)	192	T Bil 19.35 ALP 1309 AST 204 ALT 188 GGT 827	HHV-8 PCR VL (+) 24000 copies/mL. Liver biopsy revealed features of KS with spindle cells, extravasation of red blood cells and haemosiderin deposition. IHC staining HHV8 (+)	Paclitaxel, Montelukast	Continued on chemotherapy. Subsequently developed respiratory and renal failure, anemia and thrombocytopenia from aggressive metastatic KS
36[64]	M	(+)	17	PTT 70 (s) ALT 185 T Bil 23	Necroscopy showed bile duct proliferation with diffuse fibrosis with lymphohistiocytic infiltration	Liposomal doxorubicin	Jaundice, renal failure, fulminant liver failure
28[65]	M	(+)	NR	NR	Biopsy residues of spindle cells lining portal tracts. Immunoperoxidase staining factor Ⅷ (+)	Palliative care	Liver function continued to decline and patient died from respiratory failure two weeks later
38[66]	M	(+)	< 200¹	AST 147 ALT 180 ALP 573	Gross specimen with fibrous thickening of portal tracts and dark red nodules in periportal areas and diffusely infiltrating liver parenchyma	Chemotherapy, NOS	Partial cutaneous response, died several weeks later
40[4]	M	(+)	NR	Reportedly, "normal"	KS present on biopsy of lymph nodes. US with three 7-12 mm hyperechoic nodules. Periportal groups of dilated blood filled cavernous spaces lined by flat endothelial cells and interspersed of spindle cells. Extravasated erythrocytes and minimal hemosiderin deposits	Combination Chemotherapy, NOS	Complete remission of cutaneous lesions and reduction in size of two of the lesions with the third not visible. Readmitted six months later for severe relapse of cutaneous KS. Reinitiated chemotherapy with rapid deterioration and death within one month
48[67]	M	(+)	8	TBili 20.0 ALP 947 AST 186 ALT 155 INR 1.9	Liver biopsy was Cytokeratin-7 and HHV-8 staining positive	Ganciclovir and Rituximab	Presented with jaundice and acute liver injury with a cholestatic pattern, progressed to fulminant hepatic failure and ultimately death
44[68]	M	(+)	CD4/CD8 ratio 0.08	AST 153 ALT 124 ALP 1228	Laproscopy demonstrated enlarged liver with multiple purple 2-3 mm nodules Biopsy demonstrated spindle cells, vascular slits, extravasated red cells and lymphocytic infiltration	Platinum based chemotherapy, NOS	Primary hepatic manifestations without cutaneous lesions. Persistent abdominal pain after treatment. Progressed to cutaneous lesions six weeks after treatment. Lost to follow-up

¹Less than 200, not otherwise reported. M: Male; F: Female; TBili: Total Bilirubin (units, mg/dL); ALP: Alkaline phosphatase (units, IU/L); AST: Aspartate transaminase (IU/L); ALT: Alanine transaminase (IU/L); GGT: Gamma glutamyl transpeptidase (units, IU/L); HHV-8: Human herpes virus-8; PCR: Polymerase chain reaction; VL: Viral load; IHC: Immunohistochemistry; NR: Not reported; NOS: Not otherwise specified; US: Ultrasound; KS: Kaposi sarcoma.

gression in the liver[31].

DIAGNOSIS OF KS

A full integumentary survey including oral and rectal examination quantifying extent of disease should be completed in patients with suspected KS. Cutaneous or visceral biopsy is required for diagnosis. On gross pathology, there are usually multiple, grossly irregular, variable sized red-brown spongiform nodules seen in the periportal connective tissue[32]. Histopathologic features of disease include thin walled vascular formations and inflammatory infiltration. Spindle cell formation is also characteristic of angioproliferative HHV-8-infected cells that have undergone reprogramming of vascular endothelium and tumorigenesis[33]. Immunohistochemical staining is characteristic for HHV-8 LANA expression within the spindle cell formation[34]. Immunohistochemistry staining for endothelial cell markers factor Ⅷ, CD31, CD34 and lymphatic vessel endothelial receptor 1 further corroborate a diagnosis of KS[35].

Further investigation of visceral KS is warranted in the presence of adenopathy or occult bleeding. Patients with cutaneous KS and iron deficiency anemia, fecal occult blood or gastrointestinal symptoms warrant GI endoscopic evaluation. Patients with cutaneous KS and concurrent adenopathy should receive CT of the chest, abdomen, and pelvis to evaluate for visceral KS and HHV-8-related lymphoproliferative disorders including primary effusion lymphoma, Castleman disease, and plasmablastic lymphoma[36].

KS STAGING AND PROGNOSIS

As KS is a disseminated angioproliferative virally mediated malignancy, classic tumor, node, metastasis staging as used in other cancers does not accurately prognosticate disease or dictate treatment. AIDS Clinical Trials Group (ACTG) Oncology Committee has codified staging of AIDS-associated KS[37]. The ACTG staging system risk stratifies patients low risk (0) or high risk (1) based on three criteria: Tumor burden (T), immune status (I), and systemic illness (S). For tumor burden, poor risk (T1) is defined by presence of extensive cutaneous, oral disease or visceral disease. For immune status, poor risk (I1) is defined by CD4 count of less than 150 cells/μL. For
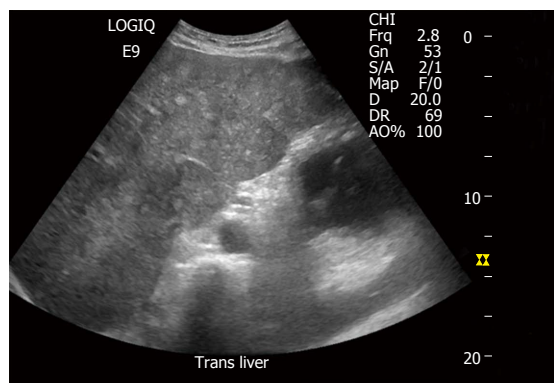
Figure 3 Ultrasound image with multiple small round hyperechoic nodules.

Figure 4 Computerized tomography scan enlarged inhomogeneous liver with multiple hypodense lesions.

systemic illness, poor risk (S1) is defined by the presence of constitutional symptoms, poor performance status, or other opportunistic infections. While these criteria were validated in the pre-ART era, post-ART therapy, a CD4 cutoff of 100 cells/mm^3 has an unclear role in predicting mortality[38,39].

IMAGING IN HEPATIC KS

Hepatic KS has characteristic findings on individual imaging modalities that can help delineate clinically significant disease. Abdominal ultrasound imaging of the liver can demonstrate inhomogeneous cystic lesions with hyperechoic bands and nodules along the peripheral branches of portal veins. Likewise, computed tomography of the abdomen is characteristic for inhomogeneous hepatomegaly with multiple small hypodense nodules, often in the periportal area[40] (Figure 4). Mild hepatomegaly is a non-specific finding in 19% of patients with AIDS-related KS[41]. MRI shows hyperintense nodules on T1-weighted in-phase imaging and hypointense nodules on T1- weighted out-of-phase imaging (Figure 5). Neither T2-weighted imaging nor late hepatobiliary volumetric interpolated breath hold examination have any specific findings in hepatic KS[42].

Image guided biopsy of hepatic nodules in patients suspected to have liver involvement demonstrate hyaline globules, hemosiderin accumulation, macrovaculoar steatosis, large fibrotic portal spaces, bile duct ectasia, neoductogenesis and spindle cells with large, irregular nuclei. Staining of the perinodular tissues is positive for CD31, CD34 and factor Ⅷ as can be seen in extrahepatic KS as well.

TREATMENT

As shown in Table 2, hepatic KS is predominantly manifested in patients with HIV/AIDS. While overall HIV mortality is improving in the era of ARV therapy, patients with AIDS-associated KS have an increased risk of death, compared to HIV controls, irrespective of CD4 count[43]. HIV-infected patients initiating ARV commonly have progression of their KS lesions[44]. However, long term

ARV therapy is associated with a reduced incidence of KS. Guidelines currently recommend correcting underlying immunodeficiency by treating AIDS with ARV therapy. Studies indicate that control of KS progression is related to the degree of control of HIV, rather than the specific cART regimen utilized[45]. Beyond ARVs, a variety of systemic therapies may be used in KS. Usually systemic therapy is indicated in progressive disease, with symptomatic visceral involvement, in the presence of immune reconstitution inflammatory syndrome (IRIS) or with extensive cutaneous involvement. These strategies are not specific to hepatic dysfunction in the setting of KS.

Radiotherapy is a well-established treatment and has a robust clinical response for classic nodular KS but tends to be a palliative approach. While it may be a good modality for superficial lesions, electron beam radiation therapy (EBRT) has limited penetration below the dermis; deeper or unresponsive KS may be treated with standard non-EBRT approaches[46].

Retinoid products appear to inhibit IL-6, a cytokine implicated in KS pathogenesis, and have an antiproliferative effect on KS lesions[47]. Application of alitretinoin can reduce cutaneous lesions of both classic and HIV-KS but has no role in systemic disease[48].

The role of chemotherapy in addition to standard antiretroviral therapy has been explored. A meta-analysis of studies demonstrated that although chemotherapy in addition to ARVs did not have a mortality benefit, it did reduce disease progression[49]. Current first-line therapy for advanced AIDS-KS is liposomal anthracyclines, including pegylated liposomal doxorubicin (PLD). In a randomized control trial (RCT), PLD demonstrated superiority to previous conventional chemotherapy, bleomycin and vincristine with 58.7% *vs* 23.3% ($P < 0.001$) response rate and a decreased adverse event rate (10.7% *vs* 26.7%)[50]. Another RCT of liposomal daunorubicin verses doxorubicin, bleomycin and vincristine showed no statistical difference in response rate or disease progression (25% *vs* 28%)[51]. When the analysis was restricted to patients receiving prior zidovudine, however, survival was improved in the liposomal daunorubicin group. Another non-randomized study showed a trend
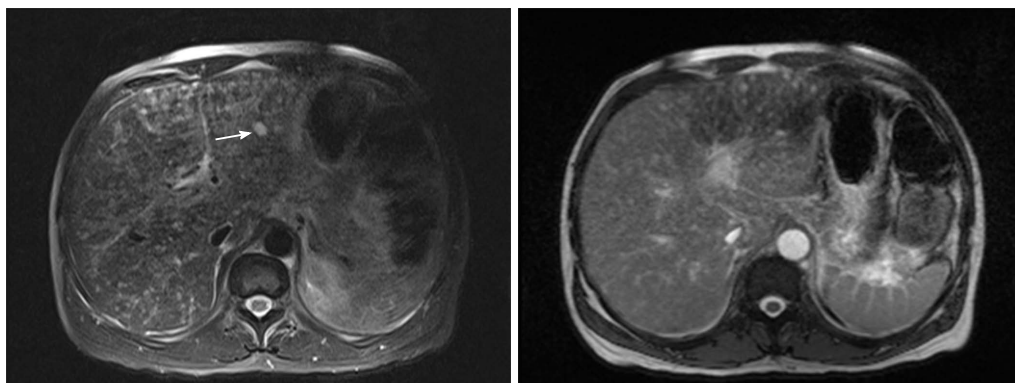
Figure 5 SPAIR and T2 images Kaposi sarcoma on magnetic resonance imaging.

toward mortality benefit with liposomal doxorubicin as compared to bleomycin plus vinblastine, vincristine or ARV monotherapy alone, although this did not reach statistical significance[52].

Interferon-alpha, has an array of antiviral and antiangiogenic properties with efficacy in AIDS-KS, but its use is limited due to hepatotoxicity[48].

Paclitaxel has systemic response rates from 59%-71% and is approved as second-line treatment for KS. In randomized controls, paclitaxel does not demonstrate benefit over PLD in complete or partial remission and no mortality data were available according to KS staging[53]. Less well tolerated than doxorubicin, adverse events include peripheral neuropathies, cytopenias, and gastrointestinal upset. Third line agents for AIDS related visceral KS include etoposide, bleomycin, vinblastine, and vincristine with overall response rates ranging from 23% to 36%. The median survival times are 11 (6 to 20) mo in the bleomycin only group and 13 (7 to 36) mo in the ABV group. With extensive side effect profiles, including secondary malignancies, these treatment modalities are maintained in resource-limited settings[54,55].

Although HAART with or without chemotherapy is the current recommended treatment, novel targets are being explored including inhibitors of angiogenesis and matrix metalloproteinases. These drugs are currently in various phases of clinical trials[56]. Inhibition of HHV-8 replication with agents such as foscarnet and ganciclovir have also been explored[57].

Finally, it bears mentioning that treatment for HIV/AIDS in patients co-infected with HHV-8 can cause a paradoxical worsening of disease. In the KS AIDS AntiRetroviral Therapy Trial, 23/112 (21%) of co-infected patients receiving ARV therapy developed KS-IRIS, which was defined as a rapid worsening of KS beyond its natural course within 12 wk of initiating ARV therapy. Of those 23 patients, 10 died, 9 of which had visceral KS. Eighteen patients in the study overall (16%) had worsening elevation in their liver enzymes and two patients (1.8%) died of liver failure. In this study, exclusion criteria included HIV-KS patients with direct serum bilirubin > 85 μmol/L or aspartate aminotransferase or alanine aminotransferase > 2.5

times the normal range[39].

Biologic and targeted molecular therapies may have a supplementary or alternative role in AIDS-KS, but are currently in early stages of clinical trials. In the AIDS Malignancy Consortium, a phase Ⅱ trial of imantinib with a small sample size showed a partial response in approximately one third of patients[58]. In another study focusing on patients who did not respond to chemotherapy and chimeric antigen receptor T cell therapy, bevacizumab, an anti-vascular endothelial growth-factor monoclonal antibody, had a response rate in again approximately one third of patients[59]. The cytokine, interleukin-12 had a response rate of 71% in small phase Ⅰ and phase Ⅱ trials. However, patients were ineligible if they had transaminitis or a history of hepatic disease[60]. Ongoing studies include a phase Ⅱ trial for the utility of combined PLD and bevacizumab in the treatment of advanced AIDS-KS[61] and a phase Ⅰ study for dosing and side effect profile of combination therapy with ipilimumab, a cytotoxic T-lymphocyte antigen 4 antibody and nivolumab, an antibody against programmed cell death 1 for the treatment of advanced KS solid tumors[62]. These trials show that biologic and molecular therapies may have a role in the future as alternative treatment therapy for some patients with AIDS-KS.

Currently, HHV-8 infection cannot be eradicated but long-term remission is feasible. Treatment is indicated in patients with progressive hepatic disease in the absence of other etiologies.

CONCLUSION

Hepatic KS is a clinical presentation that disproportionately effects the HIV/AIDS population. Up to 34% of patients with AIDS and KS have hepatic involvement. It is rarely clinically significant and often diagnosed during autopsy, but can cause liver injury or even fatal liver failure, as demonstrated in the case presentation above and case series in Table 2. In an immune compromised patient with ALI or failure, a thorough skin exam in addition to abdominal imaging and biochemical testing should be pursued and a diagnosis of hepatic KS should be considered. Treatment of hepatic KS does not differ

from systemic treatment of other KS manifestations with HAART and chemotherapy, and should be considered within the context of medical comorbidities and severity of disease. Due to wide population prevalence, a lack of clinically significant disease and variable presentations, there is little clinical data or dedicated clinical trials for liver specific disease, and further investigation is warranted.

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