International Journal of Infectious Diseases 39 (2015) 110–115

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Upper gastrointestinal Kaposi's sarcoma in HIV-infected patients: ten years of endoscopy observation at a single Brazilian center

Rosamar Eulira Fontes Rezende [a,*], Rafael Lima Kahwage [a], Tarciana Vieira da Costa [a], Alcyone Artioli Machado [a], Mariângela Ottoboni Brunaldi [b], Rafael Kemp [c], José Luiz Pimenta Módena [c]

[a] Department of Clinical Medicine, Division of Gastroenterology, Faculty of Medicine of Ribeirão Preto, University of São Paulo (FMRP–USP), Av. Bandeirantes, 3900, Monte Alegre, CEP 14048-900, Ribeirão Preto, São Paulo, Brazil
[b] Department of Pathology, Faculty of Medicine of Ribeirão Preto, University of São Paulo (FMRP–USP), Ribeirão Preto, São Paulo, Brazil
[c] Department of Surgery, Faculty of Medicine of Ribeirão Preto, University of São Paulo (FMRP–USP), Ribeirão Preto, São Paulo, Brazil

ARTICLE INFO

Article history:
Received 20 April 2015
Received in revised form 1 September 2015
Accepted 3 September 2015

Corresponding Editor: Eskild Petersen, Aarhus, Denmark.

Keywords:
Kaposi's sarcoma
HIV-positive
Upper gastrointestinal endoscopy
Immunohistochemistry
Epidemiology

SUMMARY

Background: Kaposi's sarcoma (KS) is the most common neoplasm among HIV-infected individuals. The frequency of involvement of KS in the gastrointestinal (GI) tract and the associated epidemiological, immune, endoscopic, and histopathological features in HIV-infected patients, were evaluated in this study.

Methods: A review of the medical and endoscopy reports of 1428 HIV-infected patients, who had undergone upper GI endoscopy at the Endoscopy Service, Clinical Hospital, Faculty of Medicine of Ribeirão Preto between January 1999 and June 2009, was performed. Clinical, epidemiological, immunological, endoscopic, and histological data were collected.

Results: Twenty-seven (1.9%) patients were diagnosed with GI KS. Patients were predominantly male (81.5%). Sexual activity was the main route of HIV transmission (81.5%). Cutaneous involvement was noted in 21 patients (78%). Fifteen patients (55%) received highly active antiretroviral therapy for a mean duration of 12.6 weeks (range 2–52 weeks) before endoscopy. GI lesions were mainly found in the stomach (55%). Analysis of the immunohistochemical methods HHV8 LNA-1, CD31, and CD34 for the diagnosis of gastric KS indicated high agreement (kappa = 0.63, 95% confidence interval 0.32–0.94). There was no relationship between CD4 levels ($p = 0.34$) or HIV viral load ($p = 0.99$) and HHV8 LNA-1 positivity in gastric KS.

Conclusions: GI KS is an infrequent finding in patients with HIV infection. Among those with GI KS, 80% had concomitant skin lesions. Immunohistochemical methods for CD31, CD34, and LNA-1 were important tools in the diagnostic assessment of lesions suggestive of KS in the GI tract. Further studies are required to confirm these data, and the need for routine endoscopic investigation of the GI tract in HIV-infected patients with cutaneous KS should be assessed.

1. Introduction

Kaposi's sarcoma (KS) is a vascular tumor associated with human herpesvirus 8 (HHV8) infection and is the most common neoplasm among HIV-infected patients, affecting 15–20% of this population.[1,2] KS usually manifests as nodular lesions on the skin. Visceral lesions are present in nearly 25% of patients with HIV-associated KS.[3]

Gastrointestinal (GI) KS lesions can be present in HIV-positive patients independent of cutaneous disease.[4] GI lesions may be asymptomatic or cause mild symptoms such as nausea and vomiting.[3,4] In some cases, it may lead to hemorrhage, abdominal pain, gastric outlet obstruction, or intussusception.[3,5–7]

KS can be diagnosed at any stage of HIV infection, although it is more commonly related to severe immune suppression, especially with an elevated HIV viral load.[8] Endoscopically, GI KS can vary from erythematous lesions to maculopapular or polypoid lesions.[9] However, the histopathological diagnosis of the tumor may be difficult because of the submucous localization of the lesion. Immunohistochemistry techniques, including the use of

* Corresponding author.
E-mail address: rosamarrezende@uol.com.br (R.E.F. Rezende).

http://dx.doi.org/10.1016/j.ijid.2015.09.006

latency-associated nuclear antigen 1 (LNA-1) anti-HHV8 antibody to detect HHV8 in tissues, have been considered useful tools for the diagnosis of KS.[10,11]

The objective of this study was to evaluate the prevalence and the clinical and pathological presentations of GI KS among HIV-infected patients undergoing upper endoscopy.

2. Methods

2.1. Study design and data collection

An observational, retrospective and descriptive study was conducted of 1428 HIV-infected Brazilian patients who underwent upper GI endoscopy at the Endoscopy Service of the Specialized Unit for the Treatment of Infectious Diseases, Clinical Hospital, Faculty of Medicine of Ribeirão Preto, University of São Paulo (HCFMRP-USP) between January 1999 and June 2009. The upper GI endoscopy was requested for investigation of symptoms related or not to dyspepsia and also for staging of KS.

Inclusion criteria included patients of both sexes, age >18 years, and the presence of lesions suggestive of KS detected by upper GI endoscopy. Twenty-seven (1.9%) HIV-infected patients with KS detected by upper GI endoscopy met the inclusion criteria.

The following data were obtained: age, sex, risk factors for HIV infection, symptoms related to gastrointestinal KS, time elapsed from the HIV diagnosis to first endoscopy, assessment of extra-intestinal manifestations, and use of highly active antiretroviral therapy (HAART).

2.2. Ethics statement

The study was conducted in accordance with the Declaration of Helsinki (1975) and was approved by the Ethics Committee of the Clinical Hospital and Faculty of Medicine of Ribeirão Preto, University of São Paulo (under process 10341/2009; e-mail cep@hcrp.fmrp.usp.br). The Ethics Committee of the Clinical Hospital and Faculty of Medicine of Ribeirão Preto, University of São Paulo, waived the need for consent for upper GI endoscopy and for the use of histopathological samples. The authors used anonymized data from patient medical records. The present data have not been used in previous publications. There are no ethical issues related to the present study and the publication of this manuscript.

2.3. Serum determination of CD4+ T lymphocytes

The CD4 count was measured by flow cytometry, preferably within 6 months prior to or up to 6 months following endoscopy for patients who had not been subjected to a previous CD4 count.

2.4. HIV viral load testing

Viral plasma load was determined by branched DNA assay (Versant HIV-1 RNA 3.0; Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA) within 6 months prior to or up to 6 months following endoscopy for patients with no previous determination of viral load.

2.5. Endoscopic procedure

Upper GI endoscopy was performed using a Pentax EG 2901 endoscope (9.8 mm; Pentax, Tokyo, Japan). During the upper GI endoscopy, photographs and biopsies of the KS lesions were obtained. All endoscopic procedures were performed or reviewed by the same experienced endoscopist (R.E.F.R.).

KS lesions were evaluated on endoscopy and macroscopic findings were characterized using the classification proposed by Ahmed et al.[12] Three different endoscopic appearances of KS lesions were noted: type 1 or maculopapular lesions, characterized by a slight elevation of the mucosal surface, dark pink/scarlet in color, with a diameter of 2–5 mm; type 2 or polypoid lesions, characterized by nodular or papular lesions, darker in color, with a regular or irregular surface ≥1 cm in diameter; type 3 or volcano-like lesions, characterized by nodular lesions with a central depression, generally greater in size (>1 cm diameter).[12] KS lesions were also evaluated in terms of the site of upper GI involvement: esophagus, stomach, or duodenum. A biopsy was performed using multibite biopsy forceps (Multibite Microvasive Endoscopy; Boston Scientific Corp, Natick, MA, USA). The number of biopsy specimens obtained from each individual ranged from 3 to 20.

2.6. Histopathological and immunohistochemical study

A retrospective series of paraffin blocks and histopathology slides of all lesions suggestive of KS identified during endoscopy between 1999 and 2009 were reviewed and selected from the archive of the Service of Pathology at HCFMRP-USP (SERPAT; URL http://www.rpm.fmrp.usp.br/). Hematoxylin and eosin (HE) staining, investigation of HHV8 LNA-1, and immunohistochemistry for CD31 and CD34 were performed for all cases. The histological review was conducted by the same experienced pathologist (M.O.B.).

For the immunohistochemical study, silanisated slides treated with 4% organosilane solution diluted in acetone (3-aminopropyltriethoxysilane; Sigma, St Louis, MO, USA) were prepared from paraffin-embedded sections of 4 μm in thickness. The slides were incubated with the following primary antibodies: mouse monoclonal antibody anti-CD31 (NCL-1A10, 1:400), mouse monoclonal antibody anti-CD34 (NCL-end, QBEnd/10, 1:100) (Novocastra Laboratories, UK), and mouse monoclonal antibody to HHV8 LNA-1 (clone 13B10, 1:100; Cell Marque Corporation, USA).

Histological sections of human skin (known to be HHV8-positive) and human tonsils were used as positive and negative controls for CD34 and CD31. Control specimens were similarly treated, except for no addition of primary antibody for the negative control.

2.7. Statistical analysis

Descriptive statistics were used to summarize the demographic data. The relationships between HIV viral load and CD4 serum levels and the number of upper GI sites affected by KS, and the relationships between CD4 serum levels, HIV viral load, and number of KS lesions confirmed by biopsy and HHV8-associated gastric sarcoma were evaluated using Fisher's exact test. The statistical analyses were performed using SAS version 9.0 software. Values of $p < 0.05$ were considered significant.

The agreement between histological methods for the diagnosis of gastric KS (LNA-1, CD31, CD34, and HE) was calculated using Cohen's kappa coefficient. A kappa >0.61 was considered 'good' agreement, a kappa of 0.41–0.60 was considered 'moderate' agreement, and a kappa <0.40 was considered 'low' agreement.

3. Results

3.1. Demographic and epidemiological characteristics

A total of 1428 endoscopy reports were reviewed and 27 patients (1.9%) were diagnosed with KS. Patients with GI KS

Table 1
Clinical and epidemiological characteristics of 27 cases of Kaposi's sarcoma in the upper gastrointestinal tract

Total	*N* = 27
Age, years, mean ± SD (range)	39.8 ± 10.2 (19–58)
Sex, male/female	22/5
Risk factor for HIV acquisition	
Sexual preference	22 (81.5%)
Heterosexual	13 (48.1%)
Homosexual	6 (22.2%)
Bisexual	3 (11.1%)
Drugs	6 (22.2%)
Other	6 (22.2%)
Absence of gastrointestinal symptoms	22 (81.5%)
Interval between HIV diagnosis and detection of gastrointestinal KS, years	
<1	14 (51.8%)
1–5	6 (22.2%)
5–10	4 (14.9%)
>10	3 (11.1%)
Extra-intestinal KS	
Pulmonary KS	15 (55.5%)
Skin KS	21 (77.7%)
Oral KS	6 (22.2%)
HAART before endoscopy	15 (55.5%)
Duration of HAART before endoscopy, weeks, mean ± SD (range)	12.6 ± 14.9 (2–52)
CD4 lymphocyte count, cells/mm^3 mean (range)	136 (2–676)
HIV-1 viral load, copies/ml, median (range)	117 000 (50–1 400 000)

SD, standard deviation; KS, Kaposi's sarcoma; HAART, highly active antiretroviral therapy.

were predominantly male (81.5%) and the mean age was 39.8 years. The major risk factor for HIV acquisition was sexual activity (81.5%). Twenty-two patients (81.5%) with GI KS had no specific GI symptoms. Cutaneous involvement was noted in 21 (78%) patients. Fifteen patients (55%) received HAART for a mean duration of 12.6 weeks (range 2–52 weeks) before endoscopy.

Clinical and epidemiological features of the study group are given in Table 1.

3.2. Viral and immunological status

The patients with gastrointestinal KS had a median HIV-1 viral load of 117 000 copies/ml (range 50–1 400 000 copies/ml) and a mean CD4 lymphocyte count of 136 cells/mm^3 (range 2–676 cells/μl) (Table 1).

3.3. Upper gastrointestinal endoscopy findings

Gastrointestinal lesions were found in the stomach (55%), esophagus, stomach and duodenum (26%), and stomach and duodenum (7%) (Table 2).

Type 2 (polypoid) and type 1 (maculopapular) lesions were most frequently noted in the stomach (48%) and duodenum (64%), respectively (Figure 1). Concurrence of type 1 and type 2 lesions was most frequently noted in the esophagus (22%) (Figure 1). Type 3 (volcano-like) lesions were noted exclusively in the stomach (8%) (Table 2).

3.4. Histopathological findings

Agreement between histological methods for the diagnosis of gastric KS (LNA-1, CD31, CD34, and HE) was calculated for 23 (85%) patients using Cohen's kappa coefficient. Immunohistochemistry for LNA-1 was considered the gold standard (Figure 2).

A low level of agreement was found between HE and LNA-1 (kappa = 0.21, 95% confidence interval (CI) −0.02 to 0.43), whereas high agreement was observed between LNA-1 and CD31 methods (kappa = 0.63, 95% CI 0.32 to 0.94) and between LNA-1 and CD34 methods (kappa = 0.63, 95% CI 0.32 to 0.94) (Figure 2).

Table 2
Distribution and macroscopic appearance of Kaposi's sarcoma in the gastrointestinal tract on endoscopy, according to the upper gastrointestinal site

Frequency (%)	Esophagus	Esophagus + stomach	Esophagus + stomach + duodenum	Esophagus + duodenum	Stomach	Stomach + duodenum	Duodenum
KS localization	-	3.7	25.9	3.7	55.5	7.4	3.7
Type 1 (Maculopapular lesion)	33.3	-	-	-	24	-	63.6
Type 2 (Polypoid lesion)	33.3	-	-	-	48	-	36.4
Type 3 (Volcano-like lesion)	-	-	-	-	8	-	-
Types 1 and 2	22.2	-	-	-	20	-	-
Types 2 and 3	11.1	-	-	-	-	-	-

KS, Kaposi's sarcoma.

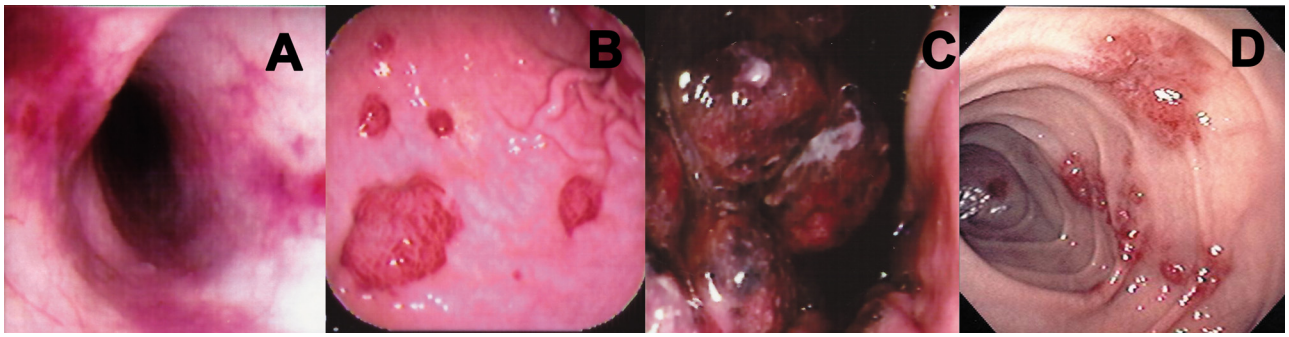

Figure 1. Endoscopic aspects of Kaposi lesions. (A) Esophagus macular lesions; (B) gastric maculopapular and polypoid lesions; (C) U-turn – giant gastric polypoid lesions; (D) duodenum polypoid lesions.

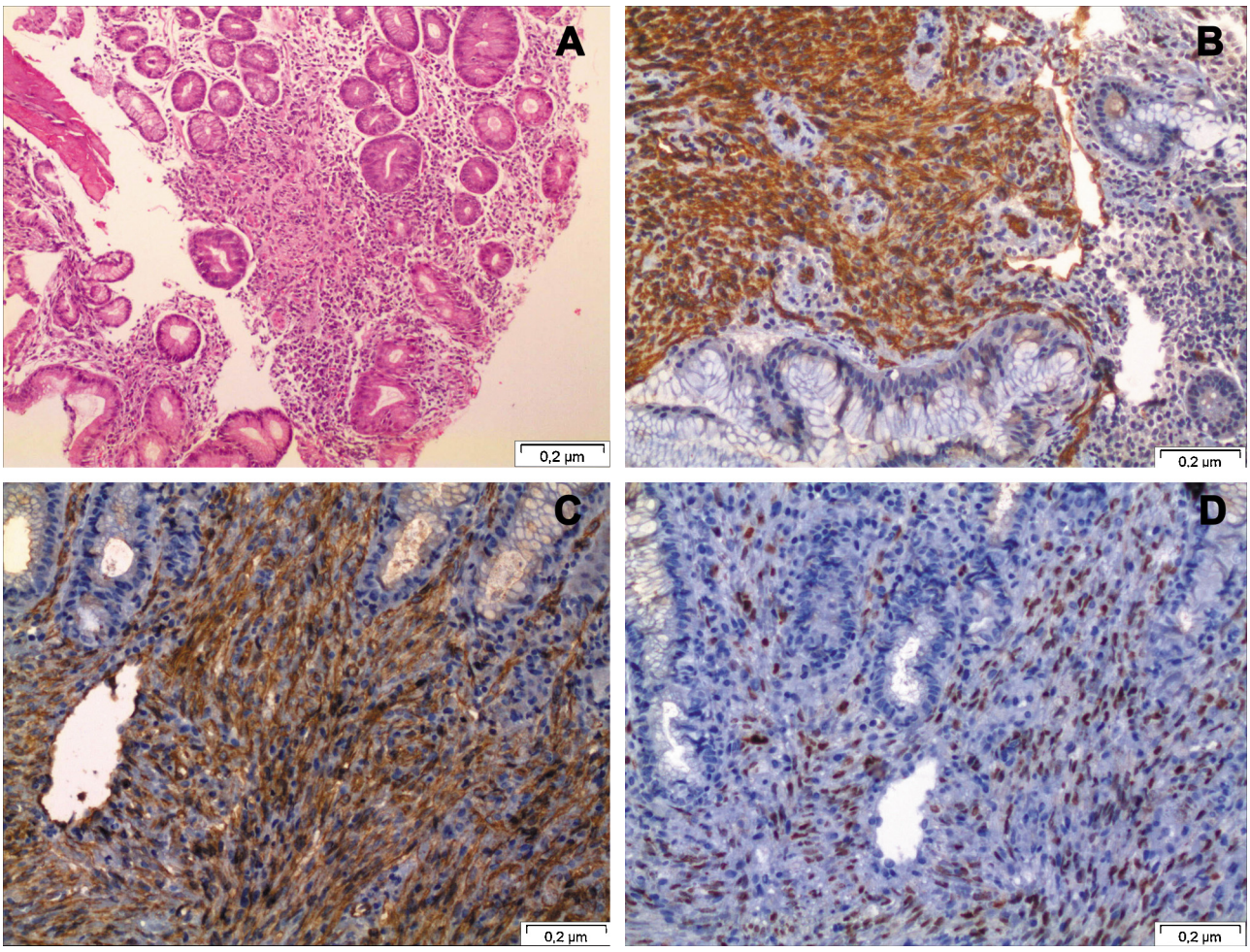

Figure 2. Different gastric histopathological study techniques. (A) Proliferation of fusiform cells at the level of the lamina propria arranged in short fascicles (HE 100×, arrow). Cells with positive immunohistochemical staining are stained brown: CD34 (B), CD31 (C), and HHV8 LNA-1 (D).

3.5. Analyses of CD4 count, HIV viral load, and upper GI sites affected by KS

In regard to CD4 levels and the number of sites affected by KS in the upper GI tract, in the group of patients with CD4 <100 cells/mm^3 (n = 12), nine had KS at one upper GI site and two had KS at two or more sites. In the group of patients with CD4 between 100 and 350 cells/mm^3 (n = 10), five had KS at one site and five had KS at two or more sites. In the group of patients with CD4 >350 cells/mm^3 (n = 4), two had KS at one site and two had KS at two or more sites. No significant differences in CD4 count or number of upper GI sites affected by KS were observed between groups (p = 0.47).

Analysis of the HIV viral load and the number of upper GI sites affected by KS showed that patients with a viral load <50 copies/ml (n = 2) presented KS at one upper GI site. Of the patients with a viral load between 50 and 10 000 copies/ml (n = 7), five presented KS at one upper GI site and two presented KS at two or more sites, and among patients with a viral load between 10 000 and 100 000 copies/ml (n = 6), three presented KS at one upper GI site and three presented KS at two or more sites. No significant differences in HIV viral load or number of upper GI sites affected by KS were observed between groups (p = 0.62).

3.6. Serum CD4, HIV viral load, and HHV8 LNA-1 positivity in gastric KS

In the group of patients with CD4 <100 cells/mm^3, LNA-1 was positive in the gastric tissue in 5/11 patients (45%). In the group of patients with CD4 between 100 and 350 cells/mm^3 (n = 10), LNA-1 was positive in 6/9 patients (67%). In the group of patients with CD4 >350 cells/mm^3, LNA-1 was positive in 2/2 patients (100%). There was no significant relationship between CD4 count and LNA-1 positivity (p = 0.39).

In order to evaluate the relationship between HIV viral load and LNA-1 in the stomach, patients were divided into four groups: in group 1 (HIV viral load <50 copies/ml; n = 1), LNA-1 was positive; in group 2 (HIV viral load between 50 and 10 000 copies/ml; n = 6), LNA-1 was positive in four cases; in group 3 (HIV viral load between 10 000 and 100 000 copies/ml; n = 5), LNA-1 was positive in three cases; and in group 4 (HIV viral load >100 000 copies/ml; n = 9), LNA-1 was positive in five cases. There was no significant relationship between HIV viral load and LNA-1 positivity (p = 0.99).

3.7. Number of biopsy specimens required for KS diagnosis by LNA-1 immunohistochemistry

The relationship between the number of biopsy specimens collected from patients during endoscopy and the investigation of

LNA-1 in the stomach was evaluated. LNA-1 was positive in 5/12 patients (42%) from whom less than five fragments of gastric tissue were collected, and in 8/11 patients (73%) from whom more than six fragments of gastric tissue were collected ($p = 0.21$).

4. Discussion

KS of the upper GI tract can be found in about 24% of individuals with AIDS.[13] The GI tract is the most frequent extracutaneous site of AIDS-KS.

In general, GI KS is asymptomatic, but depending on the stage, many clinical presentations may occur, including nausea, vomiting, abdominal pain, and severe complications such as bleeding, mechanical obstruction, and bowel perforation. In a case series, GI organs frequently involved were the small intestine (30%), colon (17%), and stomach (15%).[14]

The association between KS and infection with HHV8 has been documented since 1994, when the viral DNA sequence of herpesvirus was identified by Chang et al.[2] A higher incidence of HHV8 infection has been reported in homosexual men, particularly among those with male sexual partners. Specific practices including anal–genital and oral–genital contact have been associated with higher HHV8 transmission and seroconversion rates.

Similar to previous reports, the majority of patients in this study were male.[15,16] The great majority of the study group (81.5%) had no GI symptoms, and the skin was the most common extraintestinal site affected by KS, followed by the lungs and oral cavity, similar to results described previously.[17,18] Pulmonary lesions are generally asymptomatic and associated with concurrent cutaneous manifestations of KS.[19]

The role of HAART in the reduction of the incidence of opportunistic infections and malignant neoplasms among HIV-positive individuals is well established.[1,20] In the present study, 55% of the patients were on HAART for a mean 3 months before upper GI endoscopy. Similarly, Nagata et al. reported that 45% of HIV-infected patients diagnosed with KS had undergone HAART for a period of less than 12 months.[17] The duration of HAART may be correlated with KS lesions of less than 1 cm in size (type 1 or 2), as found in the majority of the present study group. These endoscopic findings may be associated with early regression KS induced by treatment, or related to initial stage disease manifestation. Further studies with a larger number of patients are necessary to evaluate this association.

Endoscopic findings in the present study revealed the frequency of KS lesions by site of upper GI involvement. In descending order, KS lesions were noted mainly in the stomach (55%), followed by the esophagus, stomach and duodenum concomitantly (26%), and stomach and duodenum concomitantly (7%). As noted previously,[8,17] a high viral load and low CD4 count are risk factors and predispose patients to the manifestations of the disease, and consequently the spread to multiple sites. The present study population had a mean CD4 count of 136 cells/mm^3 (Table 1) and a median viral load of 117 000 copies/ml. Furthermore, this has already been observed in previous studies, particularly involving individuals with CD4 counts <200 cells/mm^3.[3,21,22] Thus, this finding should alert endoscopists to actively investigate for KS in the GI tract in this particular group of patients.

The risk of acquiring KS is directly related to impaired cell immunity and a low CD4 count, which in turn increases the risk of HIV seroconversion, possibly due to decreased interferon gamma.[23] In the present study, analysis of the relationship between CD4 levels and the number of upper GI sites involved by the disease showed an incidence of 46% of KS lesions at one or more sites, with 25% at two or more sites among patients with a CD4 count <100 cells/mm^3. In contrast, only 15% of patients with a CD4 >350 cells/mm^3 presented KS lesions at one or more gastrointestinal sites, with half of them at two or more sites. Although this suggests the appearance of more lesions in patients with CD4 <100 cells/mm^3, this study was limited by the relatively small number of patients and no statistical significance was identified for this association.

HIV viral load may also be considered a risk factor for KS in patients with AIDS.[8] KS lesions were noted at one or more upper GI sites particularly in patients with an HIV viral load >100 000 copies/ml (40%), and at a limited number of upper GI sites among patients with an undetectable viral load (<50 copies/ml) (8%). Once more, the small sample size may have contributed to the lack of statistical difference between the groups.

Larger and more numerous lesions may be related to the severity of endoscopic findings and may represent a risk factor for a negative clinical outcome of the disease; this is generally associated with the viral load and CD4 count.[17] In the present study, a predominance of lesions <1 cm in diameter was noted. This indicates two possible hypotheses: an initial stage of the disease in the upper GI tract of severely HIV-infected patients, or an early improvement in the lesions during the first months of HAART, as described previously in the present cohort. However, more studies are necessary before conclusions can be drawn. A limitation of this study is the lack of an identified association between the clinical outcome and the presence of lesions <1 cm in diameter. Further studies on this association are to be encouraged, which will probably reveal the rate of complications underlying early KS.

Previous studies have reported that endoscopic biopsy has a low diagnostic yield for KS lesions.[24] In a recent study, the authors investigated causes of false-negative results from endoscopic biopsies of gastrointestinal KS lesions.[25] The esophagus was the main upper GI site significantly associated with false-negative results. Small size (<1 cm) and submucosal localization were also associated with false-negative results. Moreover, it has been suggested that the size of the biopsy forceps may affect the amount or size of sample collected and the diagnostic yield for KS.[26] The number of specimens of gastric lesions collected using endoscopic biopsy was evaluated in the present study and an immunohistochemical method was used for the detection of LNA-1. A slight increase in positive results for the test containing more than six specimens was observed, but with no statistical significance. Other factors such as the type, size, and location of lesions seem to be more relevant for KS diagnosis than the amount of sample obtained from endoscopic biopsy.

Although the exact mechanism of KS pathogenesis has not been clearly elucidated, a number of reports have suggested that chronic endothelial cell proliferation, mediated by cytokines and possibly associated with latent HHV8, causes changes in neoplastic cells.[27] HHV8 is found in the lytic or predominantly in the latent phase in the host, in KS fusiform tumor cells, lymphocytes, monocytes, and keratinocytes.[28] It remains unknown whether KS is derived from vascular or lymphatic endothelium. While some studies have demonstrated the existence of vascular endothelial markers in KS, including CD31 and CD34,[29] others have shown the expression by KS of the specific lymphatic markers VEGFR-3, LYVE-1, and D2-40, supporting a lymphatic origin for KS,[30,31] or an origin from a pluripotent cell type capable of undergoing both vascular and lymphatic differentiation.[27,32]

HHV8 activity can be examined by tests able to detect the virus or the host immune response to the infection. Immunohistochemistry for latency-associated nuclear antigen with anti-HHV8 antibody has been useful for detecting HHV8 in infected tissues and this is considered a sensitive and specific marker of latent infection with HHV8.[10,11] In the present study, high agreement between CD31/CD34 and LNA-1 was found, suggesting a vascular origin of the disease. The expression of these markers is directly

correlated with the late stages of KS. Cells positive for CD34 and CD31 and negative for LNA-1 expression may represent recruited endothelial cells that have not already been infected by HHV8.[32] In fact, this should alert physicians to the necessity of more frequent testing for these specific markers when suspected KS lesions are encountered on endoscopy.

The onset of KS is associated with high viral loads and low CD4 counts,[8] and in vitro and in vivo studies have demonstrated that LNA-1 may be detected at any stage of host cell infection.[33] In the data from the present study, no evidence of a relationship between CD4 levels and LNA-1 positivity on immunohistochemistry was found. Hence, LNA-1 immunoreactivity may not be correlated with the patient's immunological profile, age, tumor recurrence, or site of the lesions.[34]

In conclusion, GI KS is an infrequent finding in patients with HIV infection. Among those with GI KS, 80% had concomitant skin lesions. GI KS lesions were found mainly in the stomach (55%). Immunohistochemical methods for CD31, CD34, and LNA-1 were important tools in the diagnostic assessment of lesions suggestive of KS in the GI tract. Further studies are required to confirm these data, and the need for routine endoscopic investigation of the GI tract in HIV-infected patients with cutaneous KS should be assessed.

Acknowledgements

We thank Professor Sérgio Zucolotto (in memoriam), member of the Pathology Department, FMRP-USP, for supporting this work and providing valuable data.

Conflict of interest: The authors disclose no conflicts of interest.

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