



Diagnostic value of endothelial markers and HHV-8 staining in gastrointestinal Kaposi sarcoma and its difference in endoscopic tumor staging

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nohistochemical (IHC) staining in gastrointestinal Kaposi's sarcoma (GI-KS) in relation to endoscopic tumor staging.

METHODS: Biopsy samples ($n = 133$) from 41 human immunodeficiency virus-infected patients were reviewed. GI-KS was defined as histologically negative for other GI diseases and as a positive clinical response to KS therapy. The receiver operating characteristic area under the curve (ROC-AUC) was compared in relation to lesion size, GI location, and macroscopic appearances on endoscopy.

RESULTS: GI-KS was confirmed in 84 lesions (81.6%). Other endoscopic findings were polyps ($n = 9$), inflammation ($n = 4$), malignant lymphoma ($n = 4$), and condyloma ($n = 2$), which mimicked GI-KS on endoscopy. ROC-AUC of HE, D2-40, blood vessel markers, and HHV-8 showed results of 0.83, 0.89, 0.80, and 0.82, respectively. For IHC staining, the ROC-AUC of D2-40 was significantly higher ($P < 0.05$) than that of HE staining only. In the analysis of endoscopic appearance, the ROC-AUC of HE and IHC showed a tendency toward an increase in tumor staging (*e.g.*, small to large, patches, and polypoid to SMT appearance). D2-40 was significantly ($P < 0.05$) advantageous in the upper GI tract and for polypoid appearance compared with HE staining.

CONCLUSION: The diagnostic value of endothelial markers and HHV-8 staining was found to be high, and its accuracy tended to increase with endoscopic tumor staging. D2-40 will be useful for complementing HE staining in the diagnosis of GI-KS, especially in the upper GI tract and for polypoid appearance.

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Abstract

AIM: To clarify the diagnostic values of hematoxylin and eosin (HE), D2-40, CD31, CD34, and HHV-8 immu-

Key words: Gastrointestinal Kaposi's sarcoma; Hematoxylin and eosin; CD31; CD34; D2-40; Human herpesvirus-8

Core tip: Diagnosis of gastrointestinal Kaposi sarcoma (GI-KS) is important because treatment specifics depend on the extent of the disease. Endoscopic biopsy is a definitive diagnostic method for GI-KS, but its diagnostic accuracy has not been fully studied. In the current study, receiver operating characteristic area under the curve of hematoxylin and eosin (HE) staining, lymphatic and blood vessel endothelial cell markers, and HHV-8 was found to be high (> 0.80), and its accuracy tended to increase with endoscopic tumor staging. D2-40 will be useful for complementing HE staining in the diagnosis of GI-KS, especially in the upper GI tract and for polypoid appearance.

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INTRODUCTION

Kaposi sarcoma (KS) is a rare cancer that was highly prevalent in the early stages of the acquired immune deficiency syndrome (AIDS) endemic^[1]. Although the rate of KS has shown a marked reduction since the introduction of highly active antiretroviral therapy (HAART)^[1-3], KS remains the most common malignancy in patients with AIDS^[4].

KS primarily involves the skin but can also involve the viscera^[5-7]. Because the need for treatment and choice of treatment depend on visceral involvement^[1-3,8-11], diagnosis of the gastrointestinal (GI) tract, a common site of visceral involvement^[11-13], is important. Definitive diagnosis of GI-KS requires endoscopic biopsy^[6,7,14-16], but GI-KS often presents on endoscopy with submucosal or small protruded appearance^[17,18], which can lead to false-negative biopsy results^[14-16].

Recently, immunohistochemical (IHC) staining with D2-40, CD31, CD34, and HHV-8 has been reported as useful for distinguishing cutaneous KS from other diseases^[19-28]. However, no IHC studies have reported on the utility of KS diagnosis in the GI tract. In addition, it is not known how well such staining methods provide additive effects compared with HE staining alone.

With regard to the diagnosis of cutaneous KS, there may be subtle differences in the staining patterns for endothelial markers between different histologic stages (patch, plaque, and nodular) of KS^[19,21,22,25]. In the GI tract, KS has various macroscopic presentations^[13-15,17,18,29] and KS may affect any part of the GI tract^[7,13,14,17,18]. However, the effect of IHC-positive staining in the diagnosis of GI-KS on the basis of lesion appearance has not been fully investigated.

The purpose of this study was to clarify the diagnostic value of IHC staining in the diagnosis of GI-KS and to assess the difference in accuracy between HE and IHC

staining in relation to endoscopic tumor staging.

MATERIALS AND METHODS

Subjects

We retrospectively reviewed histologic slides from 103 consecutive lesions for which IHC staining was performed between 2006 and 2012 at the National Center for Global Health and Medicine (NCGM). Lesions were obtained from 41 human immunodeficiency virus (HIV)-infected patients who had not received anti-KS therapy. The institutional review board at NCGM approved this study.

Clinical factors

Sexual behavior was classified subjects into two groups: men who have sex with men (MSM); and heterosexual. CD4⁺ cell counts and HIV-RNA viral load (VL) determined by real-time quantitative polymerase chain reaction (PCR) were reviewed within 1 mo of endoscopy. A positive result for real-time HIV-RNA was defined as ≥ 40 copies/mL. History of HAART was collected from medical records prior to endoscopy. GI symptoms were assessed by the physician who interviewed each patient. Those without GI symptoms and negative screening endoscopy were considered to be symptom-free.

Diagnosis of GI-KS

Confirmed GI-KS lesions were defined as those that fulfilled with following criteria. (1) Histologically negative biopsy for other GI diseases; (2) A positive response to KS therapy (HAART or systemic therapy of liposomal anthracycline); and (3) partial or complete resolution was confirmed on follow-up endoscopy after KS therapy (Figure 1). We usually perform endoscopy after 1 mo, 2 mo, or 6 mo of KS therapy to evaluate GI-KS regression.

All 103 lesions were suspected to be GI-KS on endoscopy, as they exhibited properties such as reddish with patches, polypoid appearance, submucosal tumor (SMT)-like lesions, and ulcerative SMT, as previously reported^[13-15,17,18,29]. Therefore, IHC staining in addition to HE staining was performed.

Endoscopic assessment

Endoscopic images were taken using a high-resolution scope (model GFH260, CFH260AI; Olympus Optical, Tokyo, Japan) in all patients. We performed a biopsy using biopsy forceps (FB-240U, FB230-K, Olympus Co., Tokyo, Japan).

Size (< 10 mm or ≥ 10 mm), GI location, and macroscopic findings were assessed endoscopically. Locations of GI involvement were classified as upper GI (esophagus, stomach, and duodenum) and lower GI (ileum, colon, and rectum).

Macroscopic findings were evaluated as the presence of reddish mucosa with patches (Figure 2A), polypoid lesions (Figure 2B), submucosal tumor (SMT) (Figure 2C), and ulcerative SMT (Figure 2D), as previously reported^[13-15,17,18,29]. Ulceration was defined endoscopically as a distinct, visible crater > 5 mm in diameter with a slough base.

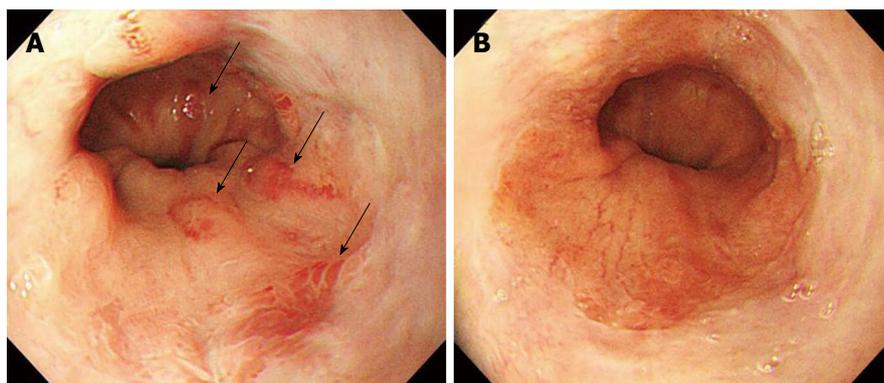


Figure 1 Confirmation of clinical response on follow-up endoscopy before and after Kaposi's sarcoma therapy. A: Gastrointestinal Kaposi sarcoma (arrows) in the esophagogastric junction before Kaposi's sarcoma (KS) therapy; B: After four months of KS therapy with liposomal anthracycline.

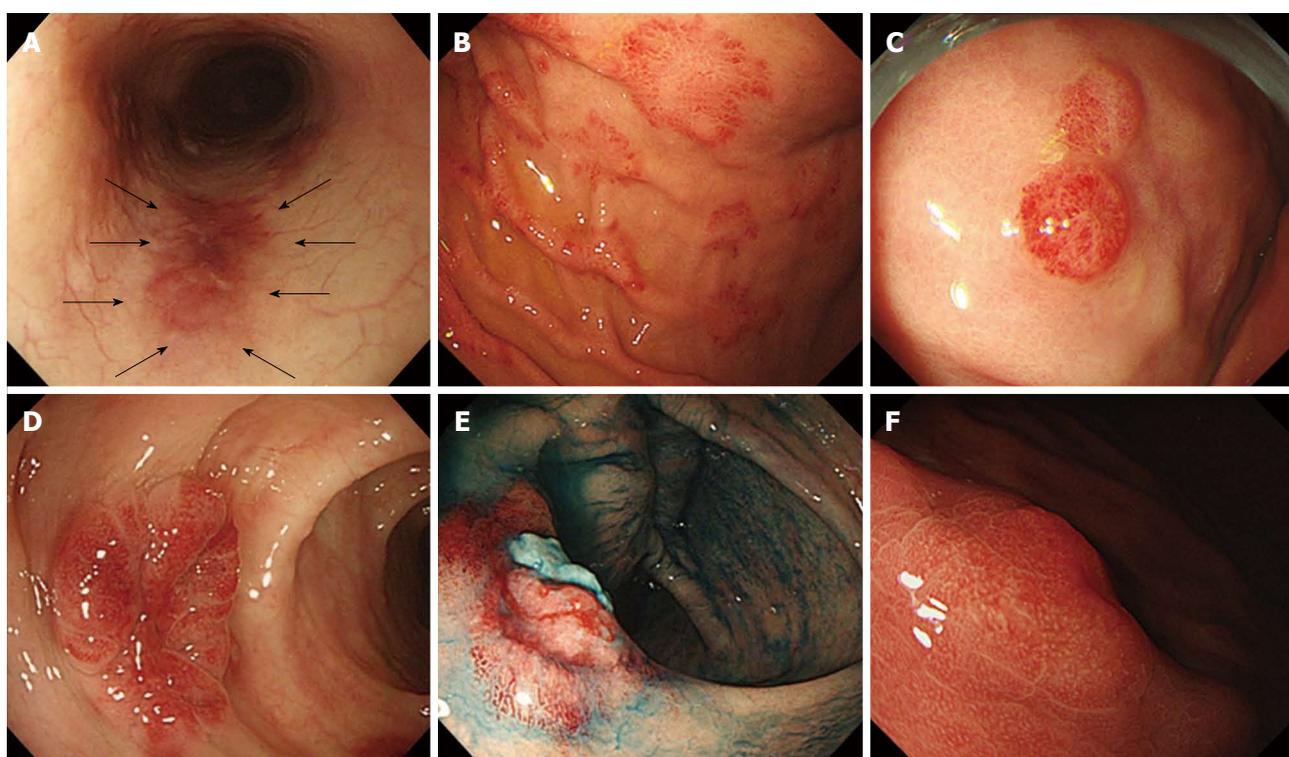


Figure 2 Gastrointestinal Kaposi sarcoma and mimicking lesions on endoscopy. A: Kaposi sarcoma, dark reddish patch (arrows) in the esophagus; B: Kaposi sarcoma, multiple patch appearance in the stomach; C: Kaposi sarcoma, small (< 10 mm) and polypoid appearance in the stomach; D: Kaposi sarcoma, submucosal tumor (SMT) appearance with large size (≥ 10 mm) in the sigmoid colon; E: Kaposi sarcoma, submucosal tumor (SMT) appearance with ulceration in the ileo-cecal valve with indigo-carmin dye; F: Hyperplastic polyps mimicking Kaposi sarcoma with small size (< 10 mm) in the stomach.

Histological assessment

The presence of proliferating spindle cells with vascular channels filled with blood cells (Figure 3A) from biopsy specimens was evaluated with HE staining by an investigator blinded to IHC staining results. IHC staining for the lymphatic vessel endothelial cell marker D2-40 (Dako North America, Carpinteria, CA) (Figure 3B) and the blood vessel endothelial cell markers CD31 (Dako North America) or CD34 (Dako North America) (Figure 3C), and the use of the mouse monoclonal antibody against HHV-8 LNA-1 (Novocastra Laboratories Ltd, Newcastle upon Tyne, United Kingdom) (Figure 3D), were also evaluated on formalin-fixed, paraffin-embedded tissue sections as previously reported^[19-28]. IHC slides were

evaluated at $\times 200$ and $\times 400$ magnification by expert GI pathologists.

Statistical analysis

To elucidate the accuracy of HE and IHC staining for the diagnosis of GI-KS, the sensitivity, specificity, positive and negative likelihood ratio (LR+ and LR-, respectively), and area under the receiver operating characteristic curve (ROC-AUC) were calculated and estimated with a 95%CI.

The difference of the ROC-AUC of the four specific stains (HE, D2-10, vessel markers, and HHV-8) was compared. Subgroup analysis was performed to identify differences in four specific stains according to gross ap-

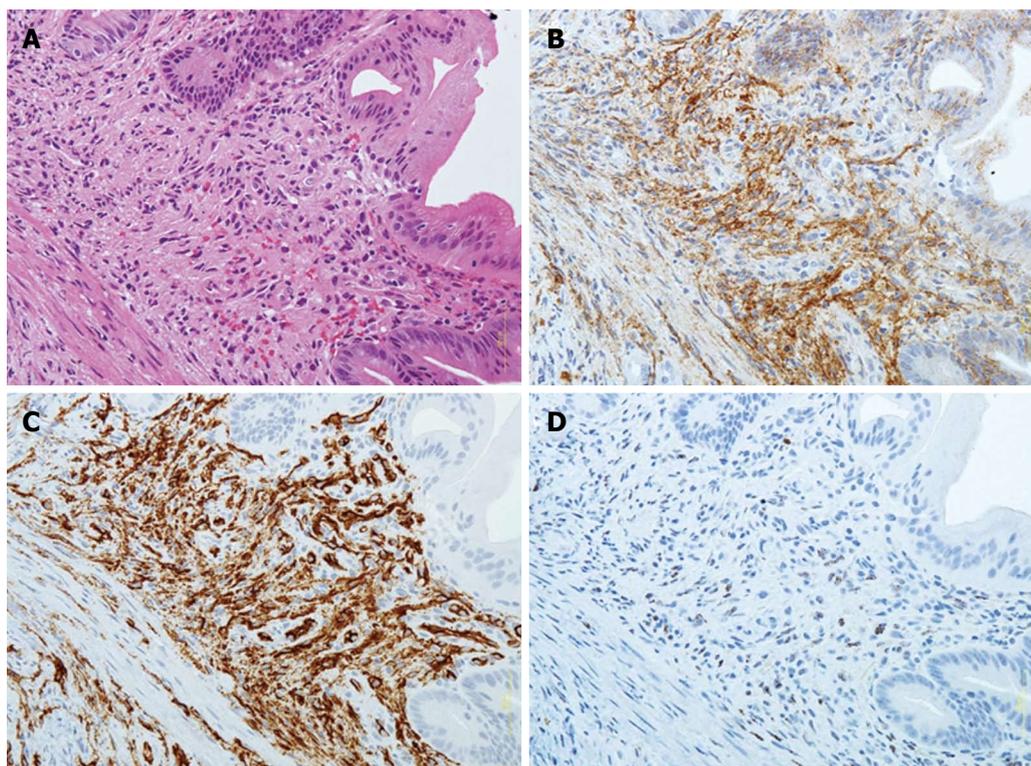


Figure 3 Pathological features of gastrointestinal Kaposi sarcoma. A: Spindle cell proliferation in the submucosa on hematoxylin and eosin (HE) staining; B: Vascular gaps are lined with endothelial cells when staining with D2-40; C: Vascular gaps are lined with endothelial cells when staining with CD34; D: Some endothelial cells are positive for human herpesvirus 8.

Table 1 Definitive diagnosis of gastrointestinal lesion from endoscopic biopsy samples ($n = 103$) n (%)

Diagnosis	No.
GI-KS	84
Upper GI tract	57 (67.9)
Esophagus	7 (8.3)
Stomach	38 (45.2)
Duodenum	12 (14.3)
Lower GI tract	27 (32.1)
Cecum	8 (9.5)
Ascending colon	1 (1.2)
Transverse colon	2 (2.4)
Descending colon	1 (1.2)
Sigmoid colon	7 (8.3)
Rectum	8 (9.5)
Non-KS lesion	19
Hyperplastic polyp	8
Fundic gland polyps	1
<i>Helicobacter</i> -associated gastritis	1
Malignant lymphoma	4
Anorectal condyloma	2
Non-specific colitis	3

GI-KS: Gastrointestinal Kaposi sarcoma.

pearances, and the ROC-AUC was compared in each group. ROC-AUC differences between HE staining and specific IHC staining in each groups were also compared.

Values of $P < 0.05$ were considered significant. All statistical analysis was performed using Stata version 10 software (StataCorp, College Station, TX).

RESULTS

Baseline clinical characteristics

All 41 HIV-infected patients were male and the HIV infection route was MSM in all cases. The median CD4 cell count (interquartile range; IQR) was 77 (33, 157) cells/mL and the median HIV viral load (IQR) was 48500 (< 40, 150000) copies/mL. There were 18 (43.9%) patients with a history of HAART. GI symptoms were noted in 10 patients (24.4%). No notable gastrointestinal bleeding or perforation, either spontaneously or after endoscopic biopsy, was noted.

Table 1 provides details on the definitive diagnosis of GI lesions. Of the 103 lesions, 84 (81.6%) were confirmed as GI-KS while the remainder were other GI lesions (19) consisted of hyperplastic polyps (8), fundic gland polyps (1), *Helicobacter*-associated gastritis (1), malignant lymphoma (4), anorectal condyloma (2), and non-specific colitis (3).

Diagnostic value of specific staining for the diagnosis of GI-KS

Sensitivity, specificity, LR+, LR-, and ROC-AUC of specific staining for the diagnosis of GI-KS are shown in Table 2. The ROC-AUC values of four specific stains (HE, D2-40, blood vessel marker, and HHV-8) were significantly different ($P < 0.01$) in the diagnosis of GI-KS (Table 2). The ROC-AUC of D2-40 staining was only significantly higher ($P < 0.05$) than that of HE staining (Table 2).

Table 2 Diagnostic value of endoscopic biopsy in gastrointestinal Kaposi sarcoma (n = 103)

KS/non-KS (84/19)	Sensitivity, % (95%CI)	Specificity, % (95%CI)	Positive LR (95%CI)	Negative LR (95%CI)	ROC area ¹ (95%CI)
HE (59/1)	70.2 (59.3-79.7)	94.7 (74.0-99.9)	9.33 (1.99-43.8) ²	0.32 (0.23-0.46) ²	0.83 (0.75-0.90)
D2-40 (65/0)	77.4 (67.0-85.8)	100 (82.4-100)	30.8 (1.99-477) ²	0.24 (0.16-0.35) ²	0.89 (0.84-0.93) ^a
Blood vessel marker (68/4)	81 (70.9- 88.7)	78.9 (54.4- 93.9)	3.85 (1.6-9.24)	0.24 (0.15-0.40)	0.80 (0.70-0.90)
HHV-8 (53/0)	63.1 (51.9-73.4)	100 (82.4-100)	25.2 (1.62-391) ²	0.38 (0.29-0.51) ²	0.82 (0.76-0.87)

LR: Likelihood ratio; HE: Hematoxylin and eosin; HHV: Human herpesvirus. ¹Receiver operating characteristic (ROC) area is significantly ($P < 0.01$) different in this category; ²LR estimated using the substitution formula. A value of 0.5 was added to all cell frequencies before calculation; ^a $P < 0.05$ for comparisons of lesions by HE staining.

Table 3 Diagnostic values of gastrointestinal Kaposi sarcoma in relation to size, location, and macroscopic appearances on endoscopy (n = 103)

Subgroup	Specific stain	No. of lesions (KS/non-KS)	ROC-AUC (95%CI)	P value ¹
Size	Size < 10 mm	26/7		
	HE	14/0	0.77 (0.67-0.87)	
	D2-40	16/0	0.81 (0.71-0.90)	
	Blood vessel marker	18/4	0.56 (0.34-0.78)	
	HHV-8	10/0	0.69 (0.60-0.79)	< 0.05
	Size > 10 mm	58/12		
	HE	45/1	0.85 (0.75-0.94)	
	D2-40	49/0	0.92 (0.88-0.97)	
	Blood vessel marker	50/0	0.93 (0.89-0.98)	
	HHV-8	43/0	0.93 (0.89-0.98)	< 0.01
Location	Upper GI tract	57/9		
	HE	36/0	0.82 (0.75-0.88)	
	D2-40	42/0	0.87 (0.81-0.93) ^a	
	Blood vessel marker	44/4	0.66 (0.48-0.84)	
	HHV-8	36/0	0.82 (0.75-0.88)	< 0.01
	Lower GI tract	27/10		
	HE	23/1	0.88 (0.76-1.00)	
	D2-40	23/0	0.93 (0.86-0.99)	
	Blood vessel marker	24/0	0.94 (0.88-1.00)	
	HHV-8	17/0	0.82 (0.72-0.91)	< 0.01
Macroscopic appearance	Patches	23/4		
	HE	12/1	0.64 (0.37-0.90)	
	D2-40	14/0	0.80 (0.70-0.91)	
	Blood vessel marker	15/0	0.83 (0.73-0.93)	
	HHV-8	8/0	0.67 (0.57-0.77)	< 0.01
	Polypoid	9/3		
	HE	5/0	0.78 (0.61-0.95)	
	D2-40	8/0	0.94 (0.84-1.00) ^a	
	Blood vessel marker	8/3	0.44 (0.34-0.55) ^a	
	HHV-8	4/0	0.72 (0.55-0.89)	< 0.01
SMT	37/7			
HE	32/0	0.93 (0.88-0.99)		
D2-40	33/0	0.95 (0.90-0.10)		
Blood vessel marker	33/1	0.88 (0.73-1.00)		
HHV-8	30/0	0.91 (0.84-0.97)	0.15	
SMT with ulcer	15/5			
HE	10/0	0.83 (0.71-0.96)		
D2-40	10/0	0.83 (0.71-0.96)		
Blood vessel marker	12/0	0.90 (0.80-1.00)		
HHV-8	11/0	0.87 (0.75-0.98)	0.34	

¹P values of receiver operating characteristic (ROC) area in each category were compared. ^a $P < 0.05$ for the comparison with lesions by hematoxylin and eosin (HE) staining. GI-KS: Gastrointestinal Kaposi sarcoma; ROC-AUC: ROC area under the curve; SMT: Submucosal tumor.

Diagnostic value of GI-KS according to size, location, and macroscopic appearance

The ROC-AUC of four specific stains showed a tendency toward an increase in tumor staging on endoscopy (e.g., small to large, flat, protruded, and SMT appearance) (Table 3). The ROC-AUC of blood vessel marker in polypoid appearance was extremely low compared with other lesions (Table 3).

The ROC-AUC of four specific stains was significantly different in size, GI tract location, appearance of patches, and polypoid lesion for the diagnosis of GI-KS (Table 3). No significant differences were noted in the ROC-AUC of four specific stains for SMT lesions ($P = 0.15$) or ulcerative SMT lesions ($P = 0.34$) (Table 3).

Comparison of the ROC-AUC between HE staining and specific staining

The ROC-AUC of the D2-40 stain was higher than that of the HE stain for lesions < 10 mm, lesions ≥ 10 mm, upper GI tract, lower GI tract, patches, polypoids, and SMT (Table 3). Of these, upper GI tract and polypoid appearance were statistically significant ($P < 0.05$). The ROC-AUC of blood vessel marker or HHV-8 stain was higher than that of HE staining for lesions ≥ 10 mm, patches, and ulcerative SMT (Table 3), with no statistical significance ($P > 0.05$).

DISCUSSION

Previous IHC studies have shown the utility of differential diagnosis between cutaneous KS and vascular tumors such as hemangioma, lymphangioma, hemangioendothelioma, and angiosarcoma^[19-28]. However, development of vascular tumor in the GI tract is extremely rare^[30]. Therefore, differential diagnosis for GI-KS can be different for cutaneous and GI tract sites. In the present study, lesions that were difficult to distinguish from GI-KS are inflammation-associated protruded lesions with reddish color. The reason for this is that GI-KS can appear as a strong reddish mucosa and vary from flat maculopapular or polypoid masses to SMT, ulceration, or bulky tumor masses on endoscopy^[14,17,18,29,31].

Previous studies investigated only GI-KS cases, and

only sensitivity can be elucidated^[14-16]. In the current study, the ROC-AUC values of the four IHC stains and HE stain were > 0.8, demonstrating that all had good diagnostic accuracy. However, it is not feasible in clinical practice to diagnose KS using all stains. Based on the results of this study, we conclude that D2-40 is the only stain capable of complementing HE staining.

We found that the ROC-AUC of four specific stains tended to increase with endoscopic tumor staging (*e.g.*, small to large, flat, protruded, and SMT). Previous studies, particularly those on cutaneous KS, have also shown that diagnostic accuracy varies according to tumor staging^[19,21,22,25]. Although it is not feasible to apply staging classification of cutaneous KS to the evaluation of the macroscopic appearance of GI-KS, it is important--based on their results and our findings--to take tumor appearance and staging into consideration for the pathological diagnosis of KS.

We further performed subgroup analysis of four stains to reveal differences in diagnostic accuracy. No significant differences were noted in the ROC-AUC of four specific stains in SMT lesions ($P = 0.15$) and ulcerative SMT lesions ($P = 0.34$), indicating that HE staining alone is sufficient for diagnosing lesions with SMT appearance. Although we attempted to find lesions that can be better diagnosed with the addition of other IHC stains, polypoid lesions, and location of upper GI tract attained significant ROC-AUC ($P < 0.05$) scores with D2-40. The ROC-AUC of D2-40 was always > 0.8, regardless of the size, location, or macroscopic appearance of lesions, indicating its utility as an additional staining modality.

One of the characteristic findings of this study is that the ROC-AUC of the blood vessel marker for polypoid appearance was extremely low compared with other lesions. This was due to the presence of hyperplastic polyps, meaning that CD34 staining produces positive results due to vessel proliferation. This can result in higher false-positive cases ($n = 38$) and lower diagnostic accuracy of KS.

There are several limitations of the present study. First, we assessed IHC staining as positive or negative instead of using a scoring system; a semi-quantitative system might provide more accurate or available results in clinical practice. Second, positive vessel marker staining was defined as CD31- or CD34-positive because CD31 or CD34 was used by each pathologist. However, because 80% (82/103) of the lesions were examined using CD34, and because CD34 is reportedly a more accurate marker than CD31^[25], we believe the results of the vessel marker staining in the present study are reliable.

In conclusion, endoscopic biopsy for diagnosing GI-KS can be performed safely. The diagnostic accuracy of HE staining, lymphatic and blood vessel endothelial cell markers, and HHV-8 was found to be high. Among these, D2-40 had the highest accuracy. The diagnostic accuracy of four specific stains tended to increase with endoscopic tumor staging. In particular, polypoid lesions and those in the upper GI tract respond well to HE staining complemented by D2-40 staining.

ACKNOWLEDGMENTS

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COMMENTS

Background

Diagnosis of Kaposi sarcoma (KS) involving the gastrointestinal (GI) tract is important because treatment specifics depend on the extent of the disease. Definitive diagnosis of GI-KS requires endoscopic biopsy with hematoxylin and eosin (HE) or immunohistochemical (IHC) staining. IHC staining for the differential diagnosis of cutaneous disease has been extensively studied, but the diagnostic value of GI-KS remains unknown.

Research frontiers

GI-KS often presents various endoscopic appearances, which can lead to false-negative biopsy results. Furthermore, the difference in accuracy of IHC staining in relation to endoscopic appearances has not been fully investigated. In the current study, the authors demonstrate the diagnostic value of IHC staining for GI-KS and to assess the difference in accuracy between HE and IHC staining in relation to endoscopic tumor staging.

Innovations and breakthroughs

Previous reports have highlighted the accuracy of IHC for diagnosing cutaneous KS. This is the first study to report that the receiver operating characteristic area under the curve (ROC-AUC) of HE staining, lymphatic and blood vessel endothelial cell markers, and HHV-8 for diagnosing GI-KS was found to be high (> 0.80), and its accuracy tended to increase with endoscopic tumor staging. In particular, polypoid lesions and those in the upper GI tract respond well to HE staining complemented by D2-40 staining.

Applications

In the current study, the ROC-AUC values of the four IHC stains and HE stain were good, but it is not feasible in clinical practice to diagnose KS using all stains. Based on the results of this study, the authors conclude that D2-40 is the only stain capable of complementing HE staining.

Terminology

The ROC is a diagnostic testing modality that presents its results as a plot of sensitivity vs 1-specificity (false-positive rate). The ROC-AUC indicates the probability of a measure or predicted risk being higher for patients with disease than for those without disease.

Peer review

This is an excellent paper describing novel findings of IHC in diagnosing GI-KS.

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