

Iatrogenic colorectal Kaposi's sarcoma complicating a refractory ulcerative colitis in a human immunodeficiency negative-virus patient

L. CHTOUROU¹, L. AYEDI², H. REJAB³, M. BOUDABOUS¹, L. MNIF¹, A. GRATI¹, T. BOUDAOUARA², R. MZALI³, A. AMOURI¹, N. TAHRI¹

¹ Gastroenterology department, Hedi Chaker University Hospital, Sfax, Tunisia; ² Histopathology department, Habib Bourguiba University Hospital, Sfax, Tunisia; ³ General surgery department, Habib Bourguiba University Hospital, Sfax, Tunisia

Key words

Kaposi's Sarcoma • Ulcerative colitis • Human Herpes Virus-8 • Iatrogenic • Immunosuppression • Corticosteroids

Summary

Kaposi sarcoma is an unusual tumor associated to a human herpes virus-8 infection involving the skin or internal organs. Iatrogenic Kaposi's sarcoma often occurs in patients receiving immunosuppressive therapy. So far, a few Kaposi's sarcoma cases have been reported in the literature associated with inflammatory bowel diseases. We report a 53-year-old male diagnosed with a

severe refractory ulcerative colitis who was treated with corticosteroids and azathioprine. The patient underwent a colectomy after the failure of medical treatment. Histological examination of the colon showed findings suggestive of Kaposi's sarcoma. Immunohistochemistry for human herpes virus-8 was positive in the colonic lesions.

Introduction

Kaposi's sarcoma (KS), first described by Moritz Kaposi in 1872, is commonly known as an unusual vascular tumor principally involving the skin. However, in some cases, it can also affect any organ system. It is strongly associated to human herpes virus-8 (HHV-8) infection¹⁻⁷. Iatrogenic form of Kaposi's sarcoma often occurs in patients receiving immunosuppressive therapy. Although the association between Kaposi's sarcoma and renal transplant has been well documented, there are less Kaposi's sarcoma cases in the literature associated with ulcerative colitis (UC) or other inflammatory bowel diseases (IBD)³⁻²². We report a case of a human immunodeficiency virus (HIV) negative man, with refractory ulcerative colitis who developed Kaposi's sarcoma, associated with HHV-8, following treatment with azathioprine and additional corticosteroids. This patient underwent a colectomy.

With the present case, we wish to draw the interaction of immunosuppressive therapy used in ulcerative colitis patients with the development of colonic Kaposi's sarcoma.

Case report

A 53-year-old heterosexual man, without personal or familial medical history, was diagnosed with ulcerative colitis for three months ago revealed by chronic bloody diarrhea (6-8 stools daily) with abdominal pain, rectal syndrome and weight loss of 2 kg. He had no smoking or alcohol drinking history. Initially, before admission in our center, oral steroid and local mesalamine was prescribed without a complete relief of rectal bleeding. Upon physical exam, blood pressure was 130/80 mmHg and his body mass index was 18.7 kg/m². Abdominal exam proved to be normal. Mucus and blood soiled finger at DRE. Besides, there was no skin lesion or lymph node swelling. Laboratory investigations showed iron deficiency anemia (10.3 g/dL) and signs of inflammation: white blood cell count of 9 800/mm³, erythrocyte sedimentation rate (ESR) of 60 mm and C - reactive protein (CRP) of 84 mg/L were noted. Albumin level was 28 g/L. Copro-parasitological examinations were negative. Ileocolonoscopy showed pancolitis with mucosal fragility, large superficial ulcerations and pseudo-polyps, without severe endoscopic signs and with normal ileum. Histology found clear signs of active ulcerative colitis with no malignancy signs.

Correspondence

Lassaad Chtourou, Department of Gastroenterology, Hedi Chaker University Hospital, Route el Ain, 3029, Sfax, Tunisia - Tel. +21 698952537 - E-mail: chtourou_lassaad@medecinesfax.org

Fig. 1. Spindle cell proliferation with extravasation of erythrocytes () infiltrating a colonic mucosa. (Hematoxylin and Eosin stain x 400).

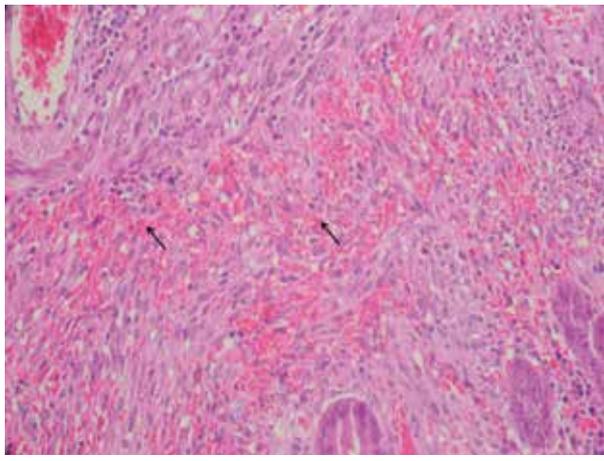


Fig. 2. Marked spindle cell proliferation with vascular channels (). Note architectural distortion of the crypts (). (Hematoxylin and Eosin stain x 400).

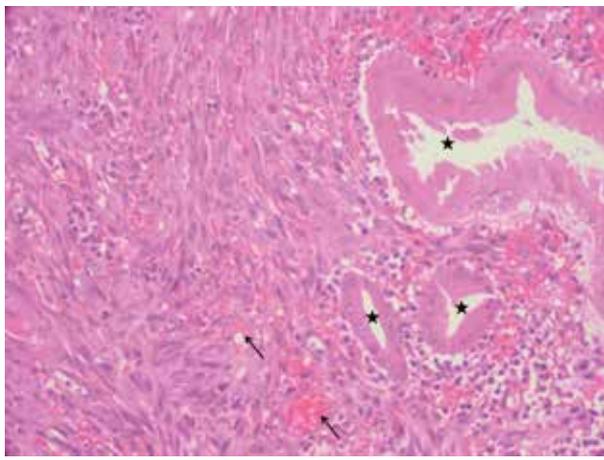
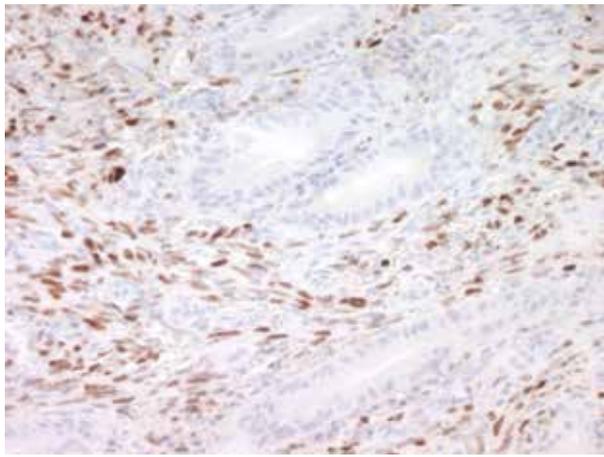


Fig. 3. HHV8 immunohistochemical stain: strong nuclear positivity in spindle tumor cells (x400).



He was initially treated with intravenous steroids (1 mg/kg/day of prednisone), local mesalamine and parenteral nutrition for a severely active disease with a partial relief of diarrhea relayed by oral corticosteroids. At week 4 of corticosteroid therapy decreasing, relapse occurred (6 stools daily, anemia 8.6 g/dL, ESR 40 mm). Dose escalation of steroid was prescribed in association with Azathioprine (2,5 mg/kg/day). After 4 weeks of free steroid treatment, and while patient with Azathioprine (at month 6) another severe relapse occurred (8 stools daily, anemia 6.5 g/dL, ESR 40 mm, CRP 89 mg/L). Copro-parasitological examinations were always negative. Cytomegalovirus and HIV testing was negative too. Detection of *Clostridium difficile* toxins was not conducted. We had considered that it was a refractory severe ulcerative colitis and we suggested a surgical treatment for the patient. A subtotal colectomy with double stoma of the ileum and of the sigmoid colon was performed. Colon macroscopic examination revealed multiple mucosal and submucosal hemorrhagic polypoid lesions that coalesce, associated with large ulcerations. Histologic examination of polypoid lesions (Figs. 1-2) showed sheets of spindle cells interspersed by clusters of extravasated erythrocytes. The spindle cells often run parallel to the mucosae. Many spindle cells show mitoses. Endothelial cells lining the spaces are flattened or more oval, with little atypia, deposits of hemosiderin surrounded the vascular structures. Slit-like spaces, lymphocyte and plasma cell infiltration and extravasated erythrocytes are also observed. There was a partial infiltration of the appendix. No lymph node metastasis was demonstrated. Equally important, histology also found clear signs of active ulcerative colitis. On immunohistochemistry, the spindle cells were positive for vascular markers (CD31, CD34) and HHV-8 (Fig. 3) and were negative for factor VIII, actin, desmin and c-kit. These results were consistent with the diagnosis of Kaposi's sarcoma, associated with typical features of ulcerative colitis. Once again, the patient underwent a total proctocolectomy and ileoanal anastomosis. The patient tolerated the surgery therapy well and recovered after operation.

Discussion

This paper reports a case of iatrogenic colonic KS, associated to HHV-8, in an HIV-negative heterosexual man who had suffered ulcerative colitis. Kaposi's sarcoma developed after starting steroid or immunosuppressive therapy, supporting the theory that colorectal Kaposi's sarcoma associated with ulcerative colitis is iatrogenic. Table I summarizes the main data in literature of KS in association with IBD with or without HIV or HHV-8 infections^{3-7 11 12 14-22}.

Kaposi sarcoma-associated herpes virus (KSHV) occurs in four distinct clinical forms: classic or sporadic KS, endemic KS, HIV-associated epidemic KS and iatrogenic KS associated with immunosuppressor therapy²³. Predominantly, Kaposi's sarcoma is seen in the case of homosexual males suffering from AIDS²⁴.

Tab. I. Main data in the literature on iatrogenic Kaposi's sarcoma and inflammatory bowel diseases (IBD).

Reference	Year of publication	IBD *	Skin lesions	Immunospression	Treatment	Improvement	HHV-8 †	HIV ‡
Gordon ¹⁴	1966	UC [¶]	No		Colectomy			NR **
Weber ¹⁵	1985	UC	Yes	Steroids enemas	Human alpha interferon + Radiotherapy +	initial response with relaps	NR ††	Positive
Biggs ¹⁶	1987	UC	Yes	Steroids	Alpha interferon + Vinblastine + Proctocolectomy	Yes	NR	Positive
Meltzer ¹⁷	1987	UC	Yes	Steroids	Proctocolectomy	Yes	Negative	Negative
Thompson ¹⁸	1989	UC	No	Steroids	Proctocolectomy	Yes	NR	Negative
Puy-Montbrun ¹⁹	1991	CD ††		Steroids AZA ^{¶¶}	Steroids and AZA withdrawal	Yes	NR	Negative
Tedesco ²⁰	1999	UC	No	Steroids	Proctocolectomy	Yes	NR	Negative
Cohen ²¹	2001	CD	No	Steroids	Proctocolectomy	Yes	NR	Negative
Pedulla ²²	2004	UC	No	Steroids AZA	NR	NR	NR	Negative
Bursics ³	2005	UC	Yes	Steroids	Proctocolectomy	Yes	Positive	Negative
Girelli ⁴	2009	UC	No	Steroids Cycosporin	Proctocolectomy	Yes	Positive	Negative
Svrcek ⁵	2009	UC	No	Steroids AZA	Proctocolectomy	Yes	Positive	Negative
Rodriguez-Pelaez ⁶	2010	UC	Yes	Steroids Methotrexate	Colectomy	Yes	Positive	Negative
Cetin ⁷	2011	UC	Yes	Steroids AZA	Radiotherapy of skin lesions and immunosuppressive drugs withdrawal	Yes	Positive	Negative
Pioche ¹¹	2013	UC	No	Steroids AZA Cyclosporin Infiximab	Proctocolectomy	Yes	Positive	Negative
Herculano ¹²	2014	UC	No	Steroids	Immunosuppressive drugs withdrawal	Yes	Positive	Negative
Present study	-	UC	No	Steroids AZA	Proctocolectomy	Yes	Positive	Negative

* Inflammatory bowel disease; † Human herpes virus-8; ‡ Human immunodeficiency virus; ¶ Ulcerative colitis; †† Crohn's disease; ** Not reported; ¶¶ Azathioprine

The association of iatrogenic KS and immunosuppressive therapy in renal or liver transplant patients has been frequently reported ⁸⁻¹⁰. In much less cases in the literature, iatrogenic KS were associated with UC ^{3-7 11 12 14-18 21 22}. In Most of the cases we noticed refractory severe ulcerative rectocolitis on immunosuppressor or immunomodulator therapy ^{4 11}. Our patient has received steroids and immunosuppressor therapy (azathioprine). The link between steroid-therapy and KS is well documented ^{3 12 13 16-18 20 21}. However, there was no evident correlation between the development of KS and dose or duration of steroid therapy ³. Reduction or withdrawal of immunosuppressor therapy often leads to improvement in KS lesions ^{7 10 12 19}.

The diagnosis of colorectal KS may be difficult to establish in the absence of skin lesions, as in the case of our patient. At endoscopy, nodules on the bowel mucosa and polypoid lesions have been reported, as well as some cases of diffuse bowel involvement ^{25 26}. In the case of intraluminal polypoids forms, polyps are red or blue, due to high vascular and conjunctive tissue proliferation. They can be confused with inflammatory pseudo-polyps in inflammatory bowel diseases ²⁷. In accordance with the data provided, our patient has intraluminal pseudo-polyps associated with ulcerations. Biopsies may fail to sample diagnostic tissue before tumor

infiltration of the mucosa ⁴. Large polypoid lesions may frequently undergo ulceration. Thus, superficial biopsies of such lesions may be diagnostically challenging to the histopathologist, and may, therefore, be misinterpreted as an inflammatory polyp ^{3 4}. Upon histological exam, the tumor is made of cellular proliferation of neoplastic spindle cells arranged in fascicles. The tumor cells are relatively monomorphic with some mitoses. Erythrocytes are contained within slit-like channels between the individual spindle cells. Hyaline globules may be seen. The periphery of the tumor may show dilated vascular spaces ²⁸.

Kaposi's sarcoma lesion may be mistaken for several other spindle cell mesenchymal neoplasms such as stromal tumor (GIST) or inflammatory fibroid polyp ²⁹. The diagnosis is confirmed by positive immunohistochemical staining of the tumor cells for HHV-8 ⁴. HHV-8 was positive in our current case. This HHV-8 is the major cause in the development of all epidemiologic variants of KS ³⁰. Rezza et al. have reported a 30% risk of developing KS within 10 years in patients co infected with HHV-8 and HIV ³¹.

The therapeutic approach is challenging. Conservative therapy with immunosuppressive drugs withdrawal has been successfully described ^{12 19}. Proctocolectomy associated to immunosuppressive drugs discontinuation is usually effective to treat both tumor and coli-

tis^{3-5 11 17 18 20 21}. After initial subtotal colectomy, the patient would undergo proctectomy when Kaposi's sarcoma associated to ulcerative colitis is confirmed.

Conclusion

This report has illustrated that it is important to consider a concomitant colorectal Kaposi's sarcoma in patients with refractory ulcerative colitis receiving immunosuppressive drugs. This tumor may be related to immunosuppressor therapy and opportunistic infection with HHV-8, independently of HIV status. Subsequently, in our practice, immunosuppressor therapy should be carefully planned and HHV-8 should be recognized as a possible underlying opportunistic infection in immunocompromised patients with IBD. Surgery and immunosuppressive drugs discontinuation may be indicated to treat both Kaposi's sarcoma and refractory colitis.

References

- Chang Y, Cesarman E, Pessin MS, et al. *Identification of herpesvirus-like DNA sequences in AIDS associated Kaposi's sarcoma*. Science 1994;266:1865-9.
- Antman K, Chang Y. *Kaposi's sarcoma*. N Engl J Med 2000;342:1027-38.
- Bursics A, Morvay K, Abraham K, et al. *HHV-8 positive, HIV negative disseminated Kaposi's sarcoma complicating steroid dependent ulcerative colitis: a successfully treated case*. Gut Jul 2005;54:1049-50.
- Girelli CM, Serio G, Rocca E, et al. *Refractory ulcerative colitis and iatrogenic colorectal Kaposi's sarcoma*. Dig Liver Dis 2009;41:170-4.
- Svrcek M, Tiret E, Bennis M, et al. *KSHV/HHV8-Associated Intestinal Kaposi's sarcoma in patient with ulcerative colitis receiving immunosuppressive drugs: report of a case*. Dis Colon Rectum 2009;52:154-8.
- Rodríguez-Peláez M, Fernández-García MS, Gutiérrez-Corral N, et al. *Kaposi's sarcoma: an opportunistic infection by human herpesvirus-8 in ulcerative colitis*. J Crohn's Colitis 2010;4:586-90.
- Cetin B, Büyükberber S, Yilmaz IB, et al. *Kaposi's sarcoma in patients with ulcerative colitis receiving immunosuppressive drugs: report of a case*. Turk J Gastroenterol 2011;22:621-5.
- Penn I. *Kaposi's sarcoma in transplant recipients*. Transplantation 1997;64:669-73.
- García-Astudillo LA, Leyva-Cobián F. *Human herpesvirus-8 infection and Kaposi's sarcoma after liver and kidney transplantation in different geographical areas of Spain*. Transpl Immunol 2006;17:86-9.
- Duman S, Toz H, Asci G, et al. *Successful treatment of post-transplant Kaposi's sarcoma by reduction of immunosuppression*. Nephrol Dial Transplant 2002;17:892-6.
- Pioche M, Boschetti G, Cotte E, et al. *Human herpesvirus 8-associated colorectal Kaposi's sarcoma occurring in a drug-induced immunocompromised patient with refractory ulcerative colitis: report of a new case and review of the literature*. Inflamm Bowel Dis 2013;19:E12-E15.
- Herculano R, Barreiro P, Hann A, et al. *Drug-induced colonic Kaposi's sarcoma in a HIV-negative patient with ulcerative colitis: a case report and review of the literature*. Int J Colorectal Dis 2014;29:1441-2.
- Bolla G, Disdier P, Swiader L, et al. *Kaposi disease, limited to the skin, in ulcerated hemorrhagic rectocolitis*. Rev Med Interne 1995;16:524-6.
- Gordon HW, Rywlin AM. *Kaposi's sarcoma of the large intestine associated with ulcerative colitis: a hitherto unreported occurrence*. Gastroenterology 1966;50:248-53.
- Weber JN, Carmichael DJ, Boylston A, et al. *Kaposi's sarcoma of the bowel presenting as apparent ulcerative colitis*. Gut 1985;26:295-300.
- Biggs BA, Crowe SM, Lucas CR, et al. *AIDS related Kaposi's sarcoma presenting as ulcerative colitis and complicated by toxic megacolon*. Gut 1987;28:1302-6.
- Meltzer SJ, Rotterdam HZ, Korelitz BI. *Kaposi's sarcoma in association with ulcerative colitis*. Am J Gastroenterol 1987;82:378-81.
- Thompson GB, Pemberton JH, Morris S, et al. *Kaposi's sarcoma of the colon in a young HIV negative man with chronic ulcerative colitis. Report of a case*. Dis Colon Rectum 1989;32:73-6.
- Puy-Montbrun T, Pigot F, Vuong PN, et al. *Kaposi's sarcoma of the colon in a young HIV-negative woman with Crohn's disease*. Dig Dis Sci 1991;36:528-31.
- Tedesco M, Benevolo M, Frezza F, et al. *Colorectal Kaposi's sarcoma in an HIV negative male in association with ulcerative rectocolitis: a case report*. Anticancer Res 1999;19:3045-8.
- Cohen RL, Tepper RE, Urmacher C, Katz S. *Kaposi's sarcoma and cytomegaloviral ileocolitis complicating longstanding Crohn's disease in an HIV-negative patient*. Am J Gastroenterol 2001;96:3028-31.
- Pedulla F, Sisteron O, Chevallier P, et al. *Kaposi's sarcoma confined to the colorectum. A case report*. Clin Imaging 2004;28:33-5.
- Martin RW III, Hood AF, Farmer ER. *Kaposi sarcoma*. Medicine 1993;72:245-61.
- Guinan ME, Thomas PA, Pinsky PF, et al. *Heterosexual and homosexual patients with acquired immune deficiency syndrome*. Ann Intern Med 1984;100:213-8.
- Saltz RK, Kurtz RC, Lightdale CJ, et al. *Gastrointestinal involvement in Kaposi's sarcoma*. Gastroenterology 1982;82:1168.
- Stern JO, Dieterich M, Faust L, et al. *Disseminated Kaposi's sarcoma - involvement of the GI tract in homosexual men*. Gastroenterology 1982;82:1185.
- Tavassolie H, Mir-Madjlessi SH, Sadr-Ameli MA. *The endoscopic demonstration of Kaposi's sarcoma of the colon*. Gastrointest Endosc 1983;29:331-2.
- Arora M, Goldberg EM. *Kaposi sarcoma involving the gastrointestinal Tract*. Gastroenterol Hepatol (NY) 2010;6:459-62.
- Voltaggio L, Montgomery EA. *Gastrointestinal tract spindle cell lesions-just like real estate, it's all about location*. Mod Pathol 2015;28:S47-66.
- Ablashi DV, Chatlynne LG, Whitman Jr JE, et al. *Spectrum of Kaposi's sarcoma-associated herpesvirus, or human herpesvirus 8, diseases*. Clin Microbiol Rev 2002;15:439-64.
- Rezza G, Andreoni M, Dorrucchi M, et al. *Human herpesvirus 8 seropositivity and risk of Kaposi's sarcoma and other acquired immunodeficiency syndrome related disease*. J Natl Cancer Inst 1999;91:1468-74.