EBV-positive mucocutaneous ulcer affecting the bowel

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Abstract

Epstein-Barr virus (EBV)-positive mucocutaneous ulcer (EBVMCU) was included in the latest edition of the WHO classification of tumors of hematopoietic and lymphoid tissues as a distinct clinicopathological entity. The disease is characterized by well demarcated indurated ulcers occurring in cutaneous and mucosal sites including the gastrointestinal tract. Herein, we report two new cases of this peculiar disease. The first case presents as large bowel obstruction mimicking malignancy, the second as acute abdomen due to small bowel perforation. Histology discloses characteristic B cell blasts with Hodgkin/Reed-Sternberg cell like-features, which are positive for EBV on EBER in situ-hybridization. Clinical implications and differential diagnosis, including distinction from classical Hodgkin lymphoma and lymphomatoid granulomatosis are discussed.

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Introduction

Epstein-Barr virus (EBV)-positive mucocutaneous ulcer (EBVMCU) was proposed by Dojcinov et al. in 2010 as a distinct clinicopathological entity [1]. Lesions may be found in oropharyngeal mucosa, skin, and gastrointestinal tract [1, 2].

Since the original description, approximately 100 cases have been described in the literature [3], approximately 20 of them within the gastrointestinal tract [4]. In general, affected individuals are immunocompromised, due to iatrogenic immunosuppression or age-related immunosenescence [1, 5].

On gross inspection, the disease presents as well demarcated indurated ulcer. The histology is characterized by a polymorphous cell infiltrate, containing large B cell blasts with Hodgkin/Reed-Sternberg (HRS) cell like-features, which suggests classical Hodgkin Lymphoma (cHL) as main differential diagnosis [1, 2, 5].

Herein, we report two new cases of EBVMCU that occurred within the gastrointestinal tract of two individuals not receiving immunosuppressive medication. We describe the morphological characteristics of the disease and discuss the differential diagnosis.

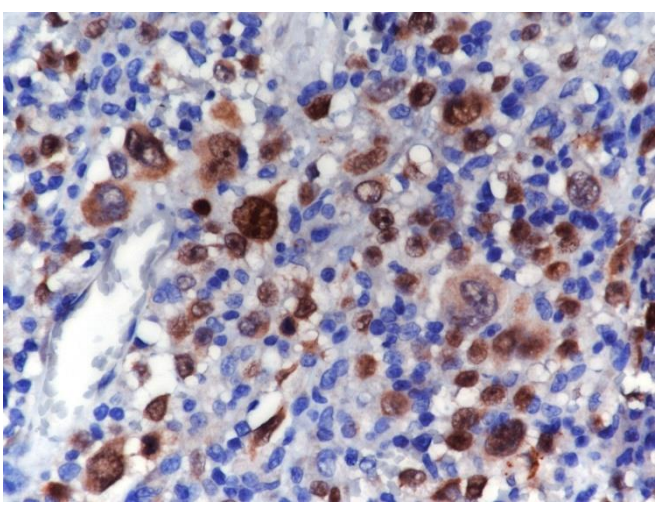
Case 1

A 54-year-old female presented with unspecific abdominal pain, obstipation and iron deficiency anemia. Endoscopy revealed stenosis of the sigmoid colon that was suspicious for malignancy, prompting left-sided hemicolectomy. The resection specimen contained an ulcerated mass lesion, three centimeters in maximum diameter.

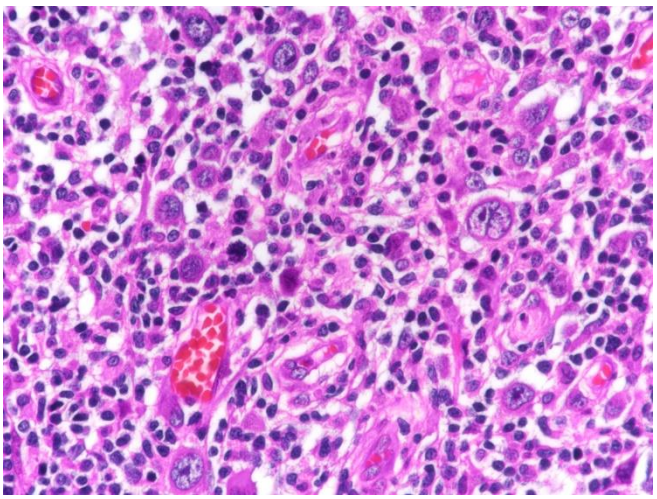
Histology showed a diffuse infiltrate of large cells with immunoblastic morphology, but blasts with HRS cell like-features, including binucleated cells, were also present (Figure 1A). Mitotic figures were frequently observed. Lymphocytes prevailed in the background, admixed with plasma cells and occasional granulocytes. The resected lymph nodes were not involved.

Immunohistochemistry proved the blasts to be diffusely positive for PAX5, CD15, and CD30 (Figure 1B-D), while only occasional cells were positive for CD20. The MIB-1 proliferation rate was 70% (Figure 1E). The infiltrate was strongly positive for EBV applying EBV encoded small RNAs (EBER) *in situ*-hybridization (Figure 1F).

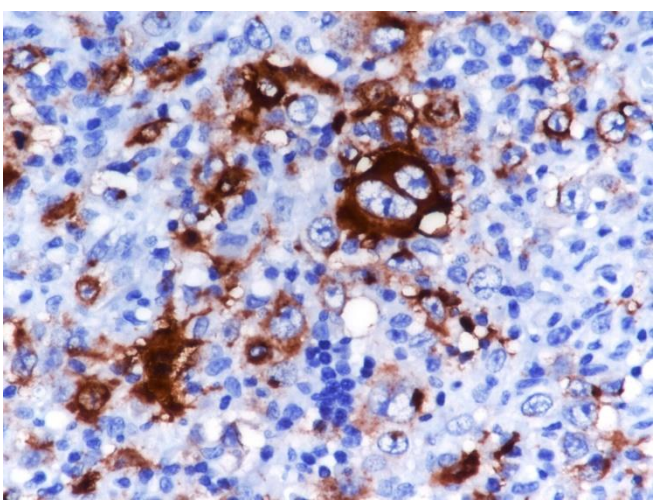
Figure 1: *The large bowel ulcer contains a diffuse infiltrate of large cells with mainly immunoblastic morphology, but also blasts with HRS cell like-features, including binucleated cells, against a background of mainly lymphocytes and rare plasma cells*



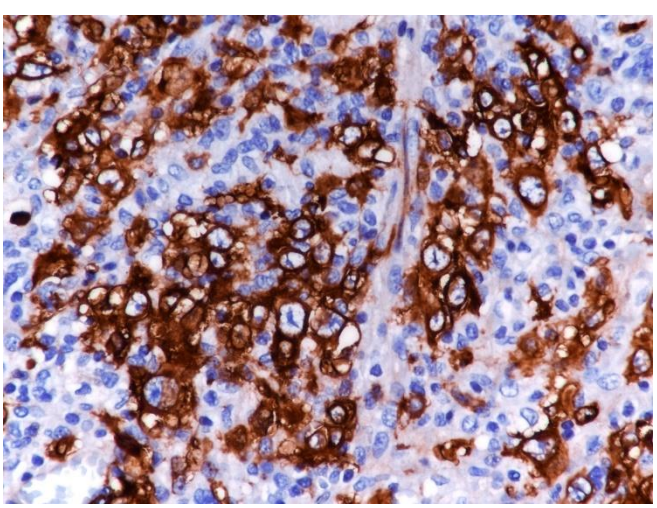
A; *original magnification x400). Immunohistochemistry proves the blasts to be diffusely positive for PAX*



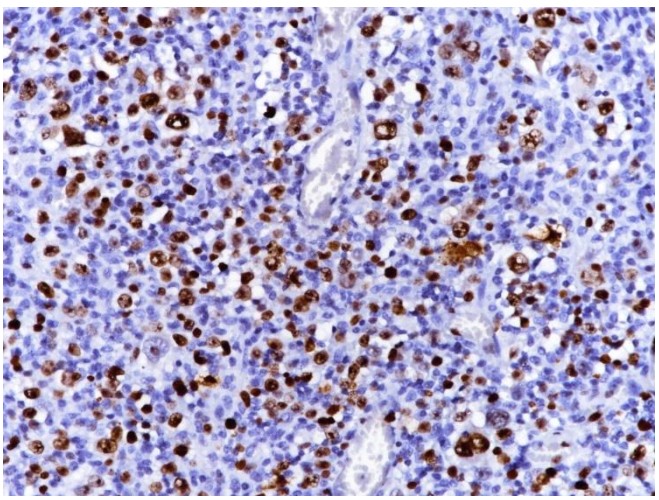
B; original magnification x400), CD1



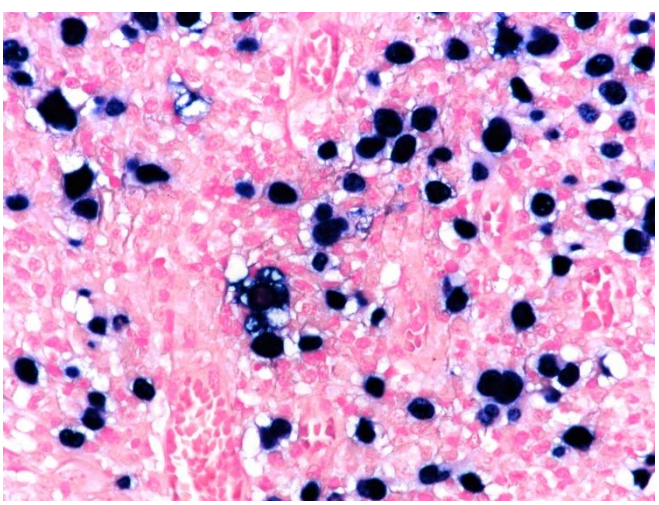
***C;** original magnification x400), and CD30*



***D;** original magnification x400). The MIB-1 proliferation rate is 70%*



***E;** original magnification x400). The blasts are strongly positive for EBV applying EBV encoded small RNAs (EBER) in situ-hybridization*



***F;** original magnification x400).*

Case 2

A 75-year-old female presented with acute severe abdominal pain. CT scan disclosed perforation of the small bowel and segmental resection was performed. The operation specimen demonstrated a deep penetrating ulcer with thickening of the bowel wall and frank perforation.

Upon histology, prominent granulation tissue with mixed cellular infiltrate rich in lymphocytes and plasma cells was identified, extending beyond the bowel wall into the mesenteric adipose tissue. The infiltrate contained scattered polymorphous blasts with HRS cell like-features and high mitotic count. The resected lymph nodes were not involved.

Immunohistochemistry was performed, rendering the blasts positive for CD15, CD20, and PAX5. As in the previous case, EBER *in situ*-hybridization was positive, particularly in the polymorphous blasts with HRS cell like-features.

Discussion

We presented two new cases of gastrointestinal EBVMCU that were diagnosed in patients not receiving immunosuppressive medication. Information regarding other causes of inborn or acquired immunosuppression, including HIV-status was not available. The first lesion mimicked a large bowel malignancy, in the second patient small bowel perforation caused acute abdomen.

EBVMCU represents a newly recognized clinicopathological entity that is characterized by sharply circumscribed indurated mucosal or cutaneous ulcers [1, 2]. The pathogenesis of disease has been related to altered immune function, hence EBVMCU is generally observed in patients under immunosuppressive therapy, e.g. after transplantation [6], in inflammatory bowel disease [1, 7, 8] or rheumatoid arthritis [1, 4, 9]. In patients not receiving immunosuppressive agents, age-related immunosenescence is believed to be the main causative factor [1, 5]. It is of note that the disease has rarely been observed also in HIV-positive individuals [10].

Prognosis is generally favorable, and even spontaneous regression has been reported [1, 5]. Due to the self-limited benign growth potential, conservative management is usually sufficient, and clinical remission can be achieved by modification and/or reduction of immunosuppressive therapy alone [5]. In cases of age-related immunosenescence or lack of response to change of immunosuppressive therapy regimen, additional radio- or chemotherapy may be necessary [1, 5, 10]. In our patients no adjuvant treatment was given after total surgical resection of the lesion and recurrence was not observed.

Two distinct histological patterns of EBVMCU have been described: The first pattern is characterized by a diffuse, predominantly “monomorphic” infiltrate of large cells, most of them with immunoblastic morphology. The second pattern shows a “polymorphic” infiltrate composed of some blast with HRS-like features, and dense accompanying infiltrate with medium-sized lymphocytes, plasma cells, and occasional neutrophils and eosinophils [6, 10].

Upon immunohistochemistry, EBVMCU demonstrates strong expression of CD20, CD30, CD15, and PAX5 in most cases. Crucial for diagnosis is however the proof of association with EBV infection. This can easily be achieved by EBER *in situ*-hybridization [2, 5, 10].

Differential diagnosis mainly includes classical Hodgkin Lymphoma (cHL), but also lymphomatoid granulomatosis (LYG) [2]. Within the gastrointestinal tract, cHL is exceedingly rare and it is conceivable that most cases of EBVMCU have been misdiagnosed as cHL in the past. Our case 1 may in fact serve as a good example since it had initially been labelled as cHL by the referring pathologist. LYG is an angiocentric and angiodestructive lymphoproliferative disease containing EBV-positive B cells, which in grade 3 disease may show atypia reminiscent of Hodgkin cells. The disease involves extranodal sites,

preferably the lungs, yet only rarely the gastrointestinal tract [11, 12]. Table 1 summarizes the morphological features of EBVMCU, cHL, and LYG, including immune profiles and EBV staining results.

In conclusion, EBVMCU is a rare disease that occurs in cutaneous and mucosal sites including the gastrointestinal tract. Pathologists need to be aware of this peculiar lesion, as misdiagnosis, particular as cHL, implies severe clinical implications for the affected individual with respect to potential overtreatment.

Table 1. Morphological features separating EBV-positive mucocutaneous ulcer (EBVMCU) from classical Hodgkin Lymphoma (cHL) and lymphomatoid granulomatosis (LYG)

	EBVMCU	**cHL**	**LYG**
Blasts with Hodgkin/Reed-Sternberg cell like-features	++	++	+/-
Bland-looking mixed inflammatory cell background rich in lymphocytes and plasma cells	++	++	++
Angiocentric and/or angiodestructive pattern	+/-	-	++
Necrosis	+/-	+/-	++
CD15	+	+	+/-
CD20	++	+/-	++
CD30	++	++	+
PAX5	++	+	Not available
MUM1	++	++	Not available
EBER *in situ*-hybridizaion	++	+/-	++

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