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Case Report
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The Etiology of Gastrointestinal Bleeding with EBV - Associated Hemophagocytic Lymphohistiocytosis in Intestinal EBV-Positive Mucocutaneous Ulcer: A Rare Pathological Entity

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Abstract

Epstein-Barr virus (EBV) positive Mucocutaneous Ulcers (EBVMCU) represent a newly recognized although uncommon disease, especially in children. Here we report an extremely rare case of a 17-month-old girl with intestinally localized EBVMCU EBV-associated hemophagocytic lymphohistiocytosis causing gastrointestinal bleeding without genetic abnormalities. Amongst a range of tests used, pathological examination and immunochemistry proved mandatory for diagnosis. Thus, although rare, it is essential that physicians must be aware of this new disease for both accurate diagnosis and treatment.

Keywords: EBV-positive mucocutaneous ulcer; Gastrointestinal bleeding; EBV-associated hemophagocytic lymphohistiocytosis

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Introduction

Epstein Barr Virus (EBV) positive Mucocutaneous Ulcers (EBVMCU) and EBV-associated Hemophagocytic Lymphohistiocytosis (EBV-HLH) fall within a spectrum of EBV-associated lymphoproliferative diseases. EBVMCUs affect the oropharyngeal mucosa, skin and Gastrointestinal Tract (GIT) with clinical presentations as shallow, sharply circumscribed, unifocal mucosal or cutaneous ulcers. These lesions can occur in immunosuppressed patients, including those with advanced age-associated immunosenescence, iatrogenic immunosuppression and primary immune disorders.

Herein we report the case of a 17-month-old girl presenting with gastrointestinal bleeding with subsequent diagnosis of intestinal EBV positive mucocutaneous ulcers and hemophagocytic syndrome. This represents the first case of EBVMCU occurring with EBV-HLH in children.

Case Presentation

A 17 month old girl was admitted to our hematology department in December 2018 with recurrent fever and bloody stools evident for half a month. She presented with an anemic face with physical examination revealing multiple palpable lymph nodes behind the ears and submandibular region on both sides. Hepatosplenomegaly was evident. The patient had no medical history suggestive of autoimmune disease, HIV, or other infections.

Initial workup revealed anemia (hemoglobin level, 7.8 g/dL [normal: 11 g/dL to 14 g/dL]), thrombocytopenia (platelets 51×10^3/microL [normal: 100-300 $\times 10^3$/microL]), hypertriglyceridemia (triglycerides, 319 mg/dL [normal: 0 mg/dL to 149 mg/dL]), and marked elevations in ferritin (5600.00 ng/mL [normal: 30 ng/dL to 500 ng/mL]) and lactate dehydrogenase (2962 U/L [normal: 140 U/L to 480 U/L]). Extensive lab and radiologic work up to identify infectious agents proved inconclusive. Soluble CD163 (sCD163) levels of 9,394 ng/mL (Reference range: 387 ng/mL to 1785 ng/mL). EB virus antibody analysis provided positive indications with results of EB virus

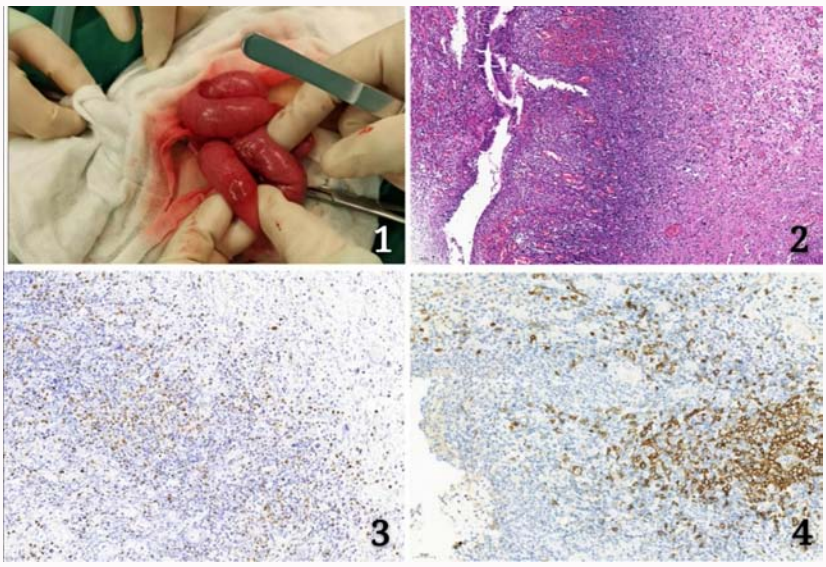

Figure 1: 1) Diffuse segmental patchy ulcer of small intestine. 2) Intestinal mucosal surface ulcer with atypical hyperplasia of lamina propria lymphoid tissue. 3) Low-power view showing diffuse positive staining for CD20. 4) Epstein-Barr virus diffuses positivity in variably sized cells of the infiltrate, by in situ hybridization for EBV-Encoded RNA (EBER).

capsid antigen IgG 95.38 AU/mL (Reference range: <2), EB virus capsid antigen IgM 5.39 AU/mL (Reference range: <3); EBV-TDNA 4.07E+04 copies/mL, EBV-B DNA 2.05E+05 copies/mL, EBV-NK DNA 0 copies/mL and plasma EBV-DNA 2.09E+04 copies/mL. Bone marrow examination showed no hemophagocytic cells; all exons and primary hemophagocytic syndrome-related gene sequencing results indicated no genetic abnormalities. On this basis, EBV-associated hemophagocytic lymphohistiocytosis was diagnosed.

When the child's intestinal bleeding disappeared, abdominal exploration revealed multiple staged ulcers presenting throughout the small intestine (Figure 1.1). Partial resection of the lesions was performed with histological examination indicating mucosal necrosis and shedding in part of the small intestine wall with large numbers of infiltrating lymphocytes in the lamina propria, substratum and part of the muscular layer of the mucosa (Figure1.2). Immunohistochemical analysis revealed large cells positive for LCA (+), CD43 (+), CD2 (partial T cells +), CD3 (T cells +), CD7 (+), CD20 (focal B cells + ; Figure1.3), CD30 (focal activated cells +), PAX-5 (focal B cell +), and Ki-67 (80% +); diffuse positive staining for EBV by *in situ* hybridization for EBV-encoded RNA (EBER) was also present (Figure1.4). Clonal Immunoglobulin (Ig) and T Cell Receptor (TCR) gene rearrangement PCR tests were negative. On this basis we excluded lymphoma and other malignant tumors, diagnosing EBVMCU arising from EBV-related HLH. The patient was treated with 12 weeks of dexamethasone and VP-16 chemotherapy, achieving a complete HLH response and no recurrence of bloody stool after approximately 1 year follow up.

Discussion

Amongst the WHO classification of lymph node hematological tumors published in 2017, EBVMCU represents a new disease entity (tentative type) [1], which is related to age or iatrogenic immunosuppression, and other clinical manifestations. Histologically, EBVMCUs are characterized by the proliferation of EBV-positive, variable-sized, atypical B-cells. It is a benign or self-limiting process similar in morphology and immunophenotype with classic Hodgkin's lymphoma and diffuse large B-cell lymphoma [2]. EBVMCU generally presents as a solitary lesion but can be multifocal as reported in 17% of literature cases. Lesions usually occur in the skin (29%), oral mucosa (52%), or gastrointestinal tract (19% to 40% colon, 30% esophagus, 20% rectum, and 10% terminal ileum) [3].

HLH is a group of clinical syndromes in which a variety of factors cause human immune dysfunction, abnormal activation of cells and ineffective immune responses, producing large amounts of cytokines, causing severe cytokine storm and high systemic inflammation [4,5]. To our best knowledge, no cases of intestinal EBVMCU with HLH have been described in children, making our case the first reported.

Histological examination of EBVMCU usually shows multiple circumscribed ulcers with a polymorphous infiltrate of lymphocytes but without large Hodgkin Reed-Sternberg (HRS) cells. Angioinvasion and necrosis can be observed. The EBV coding region (EBER) in situ hybridization method can be detected; EBV-positive mucosal skin ulcers appear to be caused by isolated and local mucosal EBV-driven lymphatic proliferation, rather than systemic infection or activation, and there may be no viremia [6].

The cause of lower gastrointestinal bleeding in our patient was EBV-positive intestinal ulcer, which is the first such report in children. Although children with EBV infection invading the intestine is relatively rare, it remains necessary to consider the presentation of gastrointestinal bleeding as the possible result from EBV infections. There are potentially many differential diagnoses including systemic Epstein-Barr virus-positive T-cell Lymphoid tissue Proliferative Disease (ASEBV+T-LPD), which has a poorer prognosis than EBVMCU but is also easy to merge with hemophagocytic syndrome [7]. However ASEBV+T-LPD were able to be excluded in our case since the results of PCR-Ig and TCR gene rearrangement tests were negative. EBVMCU can be a benign condition that may not require treatment but where interventions are undertaken; there is some degree of spontaneous regression observed after stopping immunosuppressive treatment. However, rare cases of relapse or progression have been reported [8]. Our patient received 12 weeks

of treatment for dexamethasone and etoposide, and after one year remains in remission, supporting our diagnosis of EBVMCU and not ASEBV+T-LPD.

In conclusion, EBVMCU can be complicated by EBV-HLH and cause considerable lower gastrointestinal bleeding. Clinical history, pathological examination, and immunohistochemistry are necessary to a conclusive diagnosis due to its histopathological similarity with some EBV-associated malignant lymphoproliferative disorders. The correct recognition of EBVMCU is very important for subsequent patient's management.

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