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CASE REPORT

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Epstein-Barr Virus-related mucocutaneous ulcer lymphoma associated with Crohn's disease, treated with monoclonal antibody anti-CD30

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Abstract

Epstein-Barr virus-related mucocutaneous ulcer lymphoma is a rare entity promoted by immunosuppression. It is less described in inflammatory bowel diseases, and mostly these are refractory diseases. CD30 acts to Epstein-Barr virus (EBV) local proliferation and thus could be an interesting target. Brentuximab vedotin could become a new helpful tool.

KEYWORDS

brentuximab vedotin, CD30, epstein-barr virus, immunosuppression, lymphoma

1 | INTRODUCTION

Epstein-Barr virus-positive mucocutaneous ulcer (EBVMCU) is a new entity in the 2016 review of the World Health Organization (WHO) classification of lymphoid neoplasms. It is a rare condition promoted by immunosuppression, well described in patients exposed to long-term immunosuppressive therapies.[1,2] EBVMCU is characterized by sharply circumscribed ulcers, localized in mucosa (gastrointestinal tract and oropharynx mainly). Cytologic analysis describes polymorphous infiltration of lymphocytes and immunoblasts with Reed-Sternberg like morphology, and a strong positivity of CD30+ lymphocytes and Epstein-Barr virus (EBV) presence into cells.

Epstein-Barr virus reactivation in state of immunosuppression often occurs and can evolve to lymphoma diseases, like in Burkitt lymphoma or post-transplant lymphoproliferative disease.[3,4] Immune system depression allowed viral replication and amplification into lymphoid cells. CD 30, present in many inflammatory conditions, could be an activator of EBV replication and helps local proliferation.[5] CD 30 could be an interesting target in EBVMCU, as we described it herein.

2 | CASE PRESENTATION

We present here the case of a 34 years old man suffered from a Crohn's disease for 14 years old, without any other medical and hematological histories. He was first treated for 4 years by azathioprine monotherapy, and then in combination with infliximab. Patient relapsed in 2006, and left colectomy was then performed. Azathioprine with adalimumab was initiated until his third relapse in 2014. Afterward, golimumab, another anti-TNF drug, was initiated with a limited response until 2016, when Ustekimab

was tested in monotherapy. No macroscopic or microscopic improvement were observed at each colonoscopy and biopsy samples under these treatments (Figure S1).

In May 2017, the patient was hospitalized for fatigue, fever, and rectal pain. Colonoscopy highlighted rectum's deep ulcerations, covered by adherent membranes (Figure 1). Rectal biopsy showed a completely ulcerated mucosa, capillary neoangiogenesis, and inflammatory fibrinous exudate. There were many polymorphic inflammatory elements with many large lymphoid cells, with a hyperchromatic nucleus, expressing CD30 demonstrated by the immunohistochemical study (Figure 2). These lymphoid cells also expressed MUM1 (Multiple Myeloma 1) and PAX5 (Paired Box 5) and not CD15, rejecting a Hodgkin lymphoma diagnosis. Finally, a significant number of these cells were marked by the EBER probe in in situ hybridization (Figure 2). These lymphoid elements CD30+ and EBV+ were present in varied proportions on all biopsy samples retrospectively analyzed since 2015. EBV polymerase chain reaction (PCR) done during this hospitalization was >4log in serum.

A first-line therapy by rituximab was administered 4 times, once weekly, and was associated with local steroids. Unfortunately, it did not reduce symptoms and did not decrease the blood EBV PCR. A second-line therapy with brentuximab vedotin, a composed monoclonal antibody anti–CD-30, was then initiated monthly. After 4 infusions, we observed dramatically clinical and biological improvements, with reduced amount of stool by day, general status improvement, blood EBV PCR, and systemic inflammation markers negativation. Colonoscopy brought to light a reduction of both the pseudomembranous aspect and ulcerations (Figure 1). Biopsies showed cells CD30+ and EBV+ clearance (Figure 3).

Sadly, two months after the first course end, the patient had relapse. Colonoscopy showed resurgence of macroscopic ulcerations and anal stenosis. Blood EBV PCR was once again positive. Lymphoid cells, CD30+, and EBV+ were again highlighted on rectal biopsies. Therefore, further management consisted on maintenance therapy with brentuximab vedotin, one infusion every two months. At this time, the patient still going through maintenance therapy. Clinical improvement is already back with macroscopical remission on colonoscopy.

3 | DISCUSSION AND CONCLUSION

Epstein-Barr virus is an endemic virus infecting 90%-95% of the whole population, mainly in childhood. Virus infection first occurs in the oropharyngeal cells and rejoins B-cells circulating nearby, via viral attachment to CD21. EBV integrates the B-cells' nucleus and viral genome use nuclear mechanisms to express EBV nuclear antigen leader protein (EBNA-LP) and EBNA-2, leading to cell growth and transformation. Evasion of host surveillance is due to decreased viral protein expression on B-cells' surface. Also, EBV expresses nuclear antigens, small noncoding RNA and transcripts that contribute to viral genomic maintenance.[6] Reduced stock and activity of cytotoxic T lymphocytes is a major issue in auto-immunity diseases like inflammatory

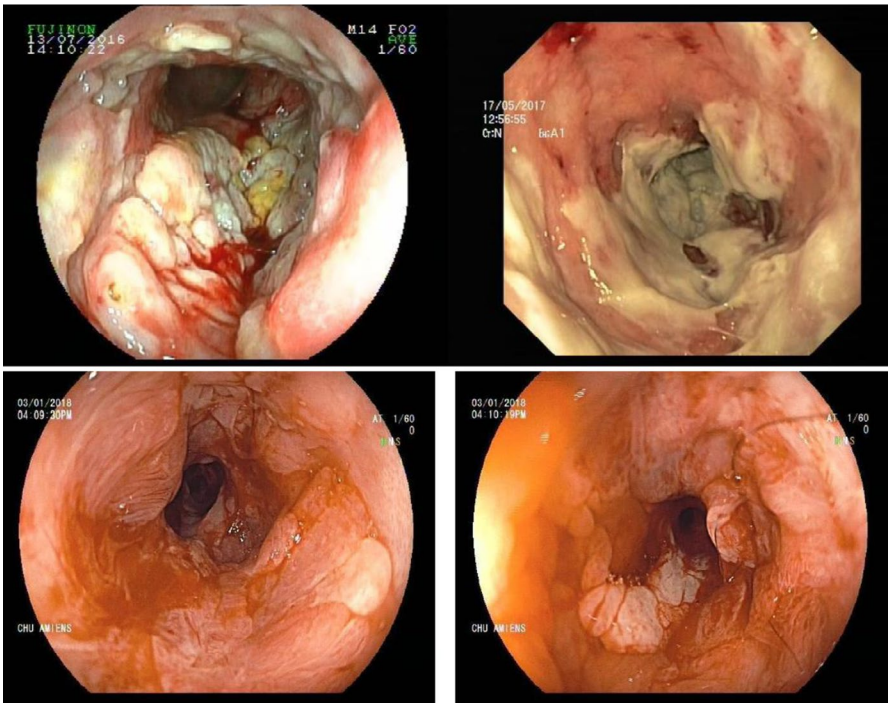

FIGURE 1 Colonoscopy images: large and deep ulcerations and pseudomembranes before treatment (images above). macroscopical improvement after treatment with Brentuximab vedotin (images below)

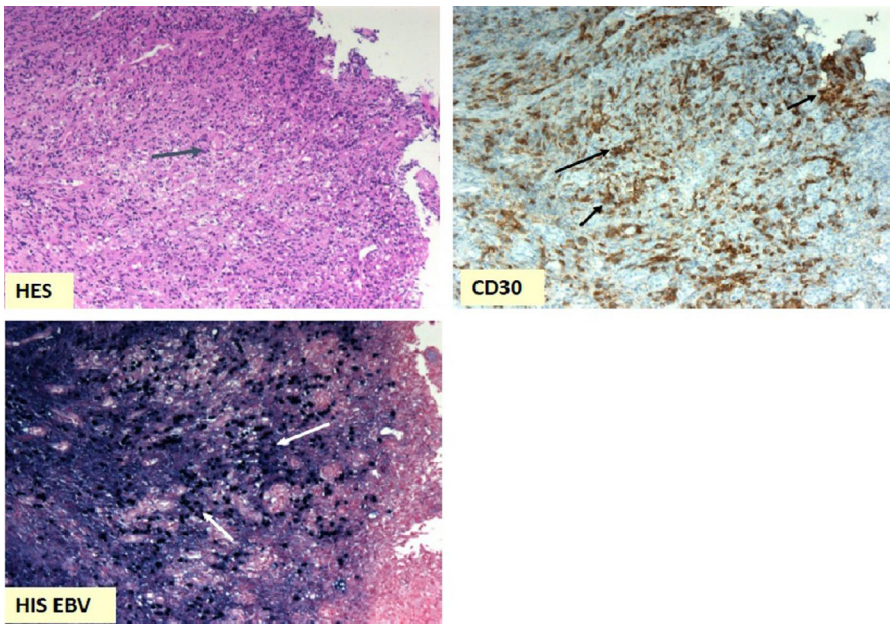

FIGURE 2 Rectal biopsies at diagnosis: large lymphoid cells seen in HES coloration (blue arrow) (×20 magnification); large lymphoid cells marked by CD30 antibody (black arrows); lymphoid cells nucleus marked by EBER probe in in situ hybridation, highlighting EBV presence (white arrows) (×10 magnification)

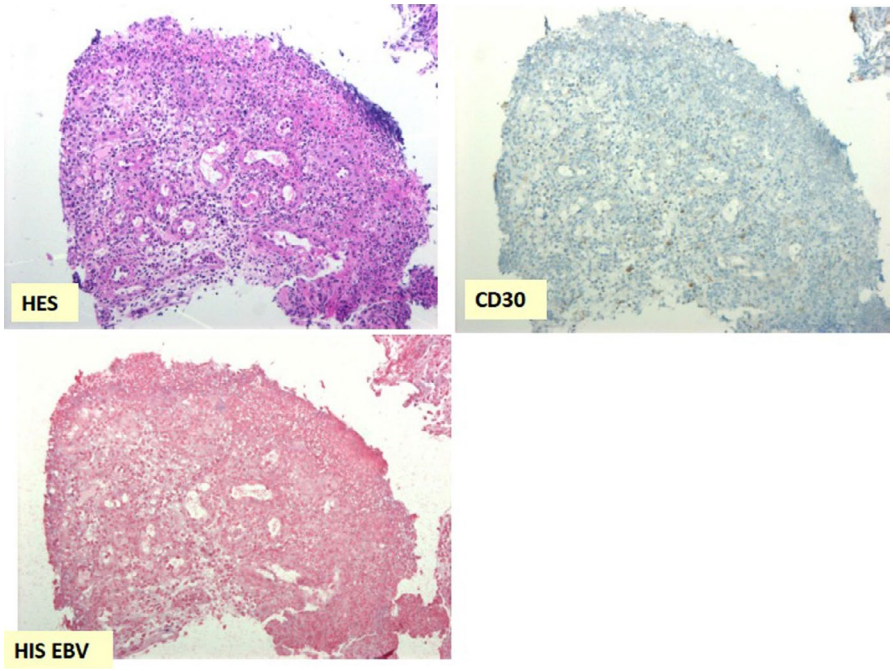

FIGURE 3 Rectal biopsies after treatment with Brentuximab vedotin: disappearance of large lymphoid cells in HES coloration (×20 magnification); clearance of lymphoid cells marked by CD30 antibody (×20 magnification); disappearance of lymphoid cells nucleus marked by EBER probe in in situ hybridation (×10 magnification)

bowel diseases, allowing B-cell—EBV mediated—proliferation.[7] It is compounded by therapeutic strategy using immunosuppressive therapies as ciclosporin, methotrexate or more recently, anti-TNF drugs treated with thiopurines are also at increased risk of EBV-associated lymphomas.[7-11] Whether risk of lymphoma in patients treated with anti-TNF agents alone remains controversial.[10] Lemaitre et al have reported in 2017, an increasing risk of lymphoma in patients treated with thiopurines (HR, 2.6 [2.0-3.4]), anti-TNF monotherapy (HR, 2.4 [1.6-3.6]), and combination of thiopurines and anti-TNF (HR, 6.1 [1.3-4.2]).[12]

Epstein-Barr virus-positive mucocutaneous ulcer was first described in a case series of 26 patients suffering from different inflammatory diseases, treated with immunosuppressive therapy (azathioprine, cyclosporine, or methotrexate) in 2010 by Dojcinov et al[1] EBVMCU is then characterized by sharply circumscribed ulcers, localized in mucosa (gastrointestinal tract and oropharynx), polymorphous infiltration of lymphocytes and immunoblasts with Reed-Sternberg like morphology, angioinvasion, and variable tissue necrosis. The immunophenotypage shows a strong positivity for CD10, CD30, MUM1, PAX5, and variable expression of CD20, CD45, CD15, and Bcl-6. EBER positivity demonstrates EBV proliferation.[2] Affirm the diagnosis in patients suffering from inflammatory bowel diseases is not easy since EBVMCU could mimick their usual

symptoms and some patients could have both affections.[4] Clinical evolution is often indolent but some damages are possible: absorption dysfunction, fatigue, colic distension, perforation… Observing several biopsies at each relapse, and looking for CD30 and EBER positivity, seem to be relevant in those patients management.[5]

The first step of EBVMCU therapeutic strategy is based on immunosuppression reduction.[2,4] Rituximab could be tried in order to reduce lymphocytes CD20+ and also lymphoproliferation, but lacks efficacy in this indication. Recently, composed monoclonal antibody brentuximab vedotin was developed to target CD30. Brentuximab vedotin binds to CD30 on cell surface and then vedotin is transported into nucleus cell, leading to cell cycle dysfunction and to apoptosis.[13-15]

To our knowledge, here is the first case of EBVMCU treated by anti-CD30 antibody that allowed to clinical, biological, and endoscopic efficacy. These interesting results attest that CD30 could be a new target in EBVMCU.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

LM and DL wrote the manuscript; ET and DC realized histology analysis; CY, CD, MF, and JPM revised the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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