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Severe Complication of a Recently Recognized Condition: Epstein-Barr Virus Positive Mucocutaneous Ulcer

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Abstract

The incidence of EBV positive mucocutaneous ulcer is likely highly underestimated, given its self-limiting course, in addition to its rarity amongst the spectrum of EBV positive lymphoproliferative disorders with only a limited number of reported cases in the literature. It was first identified in 2010 and is associated with immunosuppression, iatrogenic, primary and age related. A slight female predominance has been reported with a median patient age of 66.4 years. Disruptions in the balance of this interaction are believed to result in the lymph proliferation of various cell derivatives. EBV positive Mucocutaneous Ulcer (EBVMCU) is an indolent condition on this spectrum of LPDs, which localizes to the skin and mucosal surfaces. It is a rare lymph proliferation that gained recognition as a new entity in the 2016 revisions to the World Health Organization classifications.

Keywords: Blood pressure • Inhibitors • Chemotherapy • Prognosis

Introduction

Epstein-Barr Virus (EBV) positive B-cell Lymphoproliferative Disorders (LPDs) are a spectrum of diseases that range from self-limiting, localized conditions to aggressive lymphomas. The Epstein-Barr virus is a ubiquitous organism, achieving asymptomatic lifelong carrier status in a large proportion of the world's population. The pathophysiology of this latent infection is due to the interaction of EBV with the memory B cells of a healthy, immunocompetent individual. This activity reviews the pathophysiology of EBV positive mucocutaneous ulcer and highlights the role of the interprofessional team in its management.

Objectives

- Review the presentation of a patient with EBV positive mucocutaneous ulcer.
- Describe the evaluation of a patient with EBV positive mucocutaneous ulcer.
- Summarize the treatment of EBV positive mucocutaneous ulcer.
- Explain modalities to improve care coordination among interprofessional team members in order to improve outcomes for patients affected by EBV positive mucocutaneous ulcer.

Etiology

Epstein-Barr Virus (EBV), also known as human herpesvirus 4, is transmitted *via* saliva and has a propensity to infect B-cells. The virus can persist in humans asymptomatically throughout their lifetime; however can also result in delayed complications such as lymphoproliferative disorders. One of the most noteworthy risk factors for the development of EBV positive mucocutaneous ulcer is immunosuppression. This condition has been reported in the setting of iatrogenic immunosuppression (56%), advanced age-associated immunosenescence (40%) and primary immunosuppression (4%). Many commonly used immunosuppressive drugs have correlations with the development of EBVMCU, including methotrexate, cyclosporin A, azathioprine, tacrolimus, TNF inhibitors, mycophenolate and topical steroid treatment. Reports also suggest that immunosenescence is a significant predisposing factor for patients who are also on immunomodulating drugs.

Case Presentation

A 52-year-old female diagnosed with ulcerative pancolitis after a severe flare-up in 2014, currently under treatment with infliximab 5 mg/kg every 4 weeks and mercaptopurine 50 mg OD, was admitted to the emergency department of our hospital with a 7-day history of diarrhea, abdominal pain and fever.

Emergency surgery was performed. Intraoperative findings included pelvic fecal peritonitis and a big perforation of the anterior sigmoid wall in intimate contact with the bladder. A subtotal colectomy with end ileostomy was performed based on the previous diagnosis of ulcerative colitis. Enterovesical fistula was ruled out. Histopathological findings in the perforation area

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showed wall necrosis and ulceration of the mucosa with an underlying inflammatory polymorphous infiltration with lymphocytes, immunoblasts, hodgkin-like cells and vasculitis. Immunohistochemical analysis revealed small CD3 T-cells, forming a peripheral band around the lesion and medium to big CD20-positive cells in the central area. Atypical cells showed CD30 and Epstein Barr Virus (EBV) positivity. Reactive lymphadenopathy was found in the eight lymph nodes that were analyzed [1].

These findings are consistent with the diagnosis of a complicated Epstein-Barr Virus-positive Mucocutaneous Ulcer (EBVMCU). After being reviewed by a multidisciplinary team, immunosuppressive therapy was discontinued and outpatient follow-up with a PET-CT scan was planned [2].

Results and Discussion

EBV is a member of the *Herpesviridae* family that can behave as an opportunistic pathogen infecting both enterocytes and B-cells present in intestinal mucosa. Its replication cycle is the main factor in its etiopathogenesis. Immunosuppression favors infection by EBV and the development of lymphoproliferative syndromes [3]. First reported in 20102, EBVMCU was categorized in 2018 as a new independent pathological entity among mature B-cell lymphoproliferative syndromes by the World Health Organization-European Organization for Research and Treatment of Cancer (WHO-EORTC) update on primary cutaneous lymphomas (Figure 1).

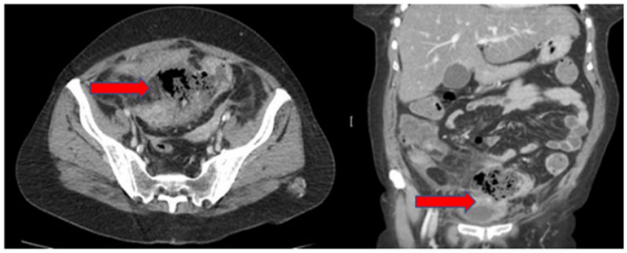

Figure 1. Axial view showing disruption of colonic wall (arrow) coronal view showing an abscess adjacent to the urinary bladder.

Up to 60% of the cases are related to immunosuppressive therapy, specially azathioprine and TNF inhibitors, but it is also associated with HIV infection and chemotherapy. It has been recently reported in elderly patients, probably due to a diminished T-cell response. The most frequently described clinical presentation is solitary ulcer of the oropharynx (58%), gastrointestinal tract (20%) and skin (19%). The largest case series only included two patients with uncomplicated colonic involvement. EBVMCU is most likely an underdiagnosed condition, as it can resemble methotrexate-induced cutaneous ulcers, malignant intestinal lesions or Inflammatory Bowel Disease (IBD) reactivation [4,5].

EBV prevalence in IBD patients is reported to be 33% and even higher when severe illness is present. This is probably due to intestinal mucosa being more susceptible to viral infection and larger doses of immunosuppressant therapy. However, no colonic perforation has been reported yet as far as we know Figure 2 [6]. EBVMCU is more frequent in women, with more than 20% of the cases presenting in females undergoing treatment for rheumatoid arthritis. Diagnosis requires histopathological examination, in which CD20, CD30, EBER-1, MUM-1, OCT-2, PAX-5 positivity can be found as well as CD3 T-cells [7,8]. Lymphocytes show similar morphology to Reed-Sternberg cells, expressing CD15 and CD309. They share histological and epidemiological features with diffuse B-cell non-Hodgkin lymphoma. Unlike other EBV related diseases, viremia is usually undetectable.

Figure 2. Macroscopic image of the surgical resection piece showing a perforated ulcer arrow.

Because of the recent recognition of this entity, a universally accepted treatment is still lacking. In a review of the first hundred cases described, 50% had their immunosuppressive therapy reduced or stopped, 20% were treated with rituximab, 20% received radiation therapy and 10% required surgery. The 2018 WHO-EORTC update recommends stopping immunosuppressive treatment as a first step [9,10].

Conclusion

In conclusion, EBVMCU is an infrequent entity that can worsen prognosis. A high degree of clinical suspicion is necessary in patients with risk factors, performing an endoscopy and biopsy when needed, since it can resemble an acute IBD flare-up. Therefore, stablishing a therapeutic and follow-up strategy by a multidisciplinary team is required. Prognosis is generally favorable, with at least 15 cases reported of complete remission after discontinuing immunosuppressive agents and 65 after local or systemic treatment. Nonetheless, patients receiving chemotherapy should be closely monitored due to increased risk of developing lymphomas.

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