Iatrogenic Immunodeficiency-Associated Lymphoproliferative Disorder in a Pediatric Patient

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Abstract

It is estimated that approximately 90% of the adult population is infected with the Epstein Barr Virus (EBV). In states of immunosuppression, the disruption in immune regulation can manifest as lymphoproliferative disease that classically presents as a lymphoma. Rarely, EBV-driven lymphoproliferative disease can present as a mucocutaneous ulcer. While this phenomenon is becoming well documented in the adult population, cases affecting pediatric patients are lacking. In this report, we describe a case of a pediatric immunosuppressed patient presenting with an EBV-positive mucocutaneous ulcer. EBV-positive mucocutaneous ulcer in an immunosuppressed patient is an entity within the spectrum of iatrogenic immunodeficiency-associated lymphoproliferative disorders (LPD) which closely resembles the better-categorized post-transplant lymphoproliferative disorder (PTLD). Though the concept of lymphoproliferative disorders in immunosuppressed patients has been well established, this is a unique case in a pediatric patient.

Key words: Mucocutaneous ulcer, Epstein Barr Virus, mixed connective tissue disorder, mycophenolate mofetil, atypical lymphocytes

Introduction

It is estimated that approximately 90% of the adult population is infected with the Epstein Barr Virus (EBV). Oropharyngeal transmission of this virus leads to lytic infection with subsequent infection of circulating B cells. Latent infection follows as viral DNA of the EBV persists within the nuclei of these cells. Through a host of complex mechanisms, it appears that EBV infected cells are able to evade typical apoptotic processes leading to their ability to remain latent. [1] Within an immunocompetent host, these latent EBV-infected B-cells remain dormant as a result of controlled surveillance of cytotoxic T-cells.[1,2]

In states of immunosuppression, homeostasis of the immune system is disrupted. In the immunosuppressed population, the EBV is often unregulated and becomes free to induce B-cell proliferation due to a lack of T-cell regulation. This disruption in immune regulation can manifest as lymphoprolif-
erative disease that classically presents as a lymphoma. Rarely, EBV-driven lymphoproliferative disease can present as mucocutaneous ulcerations. While this phenomenon is becoming well documented in the adult population, cases affecting pediatric patients are lacking. In this report, we describe a case of a pediatric immunosuppressed patient presenting with an EBV-positive mucocutaneous ulcer.

Case Report

A 17-year-old African-American female with a seven year history of mixed connective tissue disorder (MCTD) presented with a four month history of progressively worsening oral ulceration. She had been on mycophenolate mofetil (1000 mg daily) for two and a half years and prednisone (between 5 and 20 mg daily) for seven years. Prior to starting mycophenolate mofetil, she was treated with azathioprine for four and a half years. A biopsy of the lesion was obtained and initially showed granulation tissue and oral flora. Out of concern for a possible infectious etiology, the patient was treated with a seven day course of antibiotics. The patient’s mycophenolate mofetil dosage was also increased to 3000 mg daily due to worsening joint pain. The patient was readmitted as the ulceration had increased in size from 1.5 cm to 5 cm in diameter. A repeat biopsy was obtained and showed scattered positivity of EBER-1 (EBV viral RNA) in large atypical cells (Figures 1 and 2) with immunohistochemical stains for CD20, CD30, and CD45 also positive in the large atypical cells (Figure 3). Immunohistochemical stains for CD10 and

Figure 1. H&E stain of ulcer showing large atypical lymphocytes in a background of granulation tissue with mixed inflammatory infiltrate.

Figure 2. Positive immunoperoxidase stain showing EBER-1 positivity in large atypical lymphocytes.

Figure 3. Positive immunohistochemical staining for CD20 (A) and CD30 (B) in large atypical lymphocytes.
CD15 were negative. The diagnosis of iatrogenic immunodeficiency-associated lymphoproliferative disorder, Hodgkin-like subtype was made. CT scans of her neck, chest, abdomen, and pelvis along with bilateral bone marrow biopsies revealed no additional sites of disease. She was treated with a reduction of immunosuppression by discontinuing her mycophenolate mofetil. The patient received a course of rituximab (375 mg/m²/dose weekly for 4 weeks) under the direction of rheumatology to allow treatment of her underlying MCTD without T-cell immunosuppression. At the end of this treatment, the ulcer had completely resolved. Eight months later, the patient suffered from a recurrence of ulceration at the same site. The biopsy showed acute inflammatory exudate with granulation tissue. No atypical lymphocytes were seen, and the EBER-1 stain was negative.

**Discussion**

EBV-positive mucocutaneous ulcer in an immunosuppressed patient is an entity within the spectrum of iatrogenic immunodeficiency-associated lymphoproliferative disorders (IM-LPDs) which closely resembles the better-categorized post-transplant lymphoproliferative disorder (PTLD). The pathogenesis behind these processes is quite complex. In an attempt to explain it simply, immunosuppressive agents are used to block T-cell activity. In post-transplant patients, this is essential to preventing rejection of transplanted organs or bone marrow. In patients such as the one describe in our case, these drugs are required to keep symptoms of their underlying disease under control. In either scenario, by suppressing these T-cells, the EBV-infected B-cells are allowed to expand and proliferate, leading to these lymphoproliferative states. [3]

IM-LPDs have been associated with a classical Hodgkin lymphoma (cHL) form consisting of large atypical B-cells with Reed-Sternberg (RS) morphology combined with a CD30 and CD15 positive, CD20 variable, and CD45 negative immunophenotype. Our case’s atypical B-cell population demonstrated similar morphology but did not meet immunophenotypic criteria for cHL as they expressed CD20, CD30, and CD45 without CD15 expression [4,5]. Because of the immunohistochemical results, a diagnosis of iatrogenic immunodeficiency-associated lymphoproliferative disorder, Hodgkin-like subtype was warranted. EBV+ mucocutaneous ulcer would also be an appropriate diagnostic term and should be included in the spectrum of IM-LPDs.

Though the concept of lymphoproliferative disorders in immunosuppressed patients has been well established, it appears that EBV-associated mucocutaneous ulcerations are quite rare. These lesions are on the spectrum of EBV-related lymphoproliferative disorders; however, it’s interesting to note that though highly atypical cells are present within these lesions, progression to disseminated disease does not occur, as the overall course is typically indolent. In fact, the reduction of immunosuppressive therapy was generally all that was required in order to resolve these mucocutaneous lesions. [2] Similar lesions resembling EBV mucocutaneous ulcers have been seen in patients taking methotrexate, though in most of these cases the lesions were thought to be secondary to drug toxicity. [6,7,8,9] The article by Dojcinov et al. is one of the first to identify EBV-positive mucocutaneous ulcers as distinctive lesions resulting from disruption of immune regulation of EBV, though recently other cases have been published as well. [2,10]

While the majority of cases reported have been in elderly patients, our case shows that this pathological process may be seen in the setting of immunosuppressed pediatric patients as well. Awareness of this phenomenon in the pediatric population may allow for prompt diagnosis, as resolution of such lesions is linked to conservative measures with reduction of immunosuppressive therapy.

**Disclosures:** None

**References**


