Scientific Research Publishing

Case Reports in Clinical Medicine, 2022, 11, 353-357
https://www.scirp.org/journal/crcm
ISSN Online: 2325-7083
ISSN Print: 2325-7075

Epstein-Barr Virus Upper Gastrointestinal Tract Mucocutaneous Ulceration in a Renal Transplant Recipient with Leucopenia and Hypogammaglobulinaemia

Kalpa Jayanatha[1,2*], Jonathan Hsiao[1], Viliami Tutone[1]

[1]Department of Renal Medicine, Middlemore Hospital, Health New Zealand, Auckland, New Zealand
[2]South Auckland Clinical Campus, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand
Email: *kalpa.jayanatha@auckland.ac.nz

How to cite this paper: Jayanatha, K., Hsiao, J. and Tutone, V. (2022) Epstein-Barr Virus Upper Gastrointestinal Tract Mucocutaneous Ulceration in a Renal Transplant Recipient with Leucopenia and Hypogammaglobulinaemia. *Case Reports in Clinical Medicine*, **11**, 353-357.
https://doi.org/10.4236/crcm.2022.119048

Received: July 30, 2022
Accepted: September 2, 2022
Published: September 5, 2022

Abstract

Epstein-Barr virus (EBV) mucocutaneous ulceration is a rare complication of immunosuppression that results in painful ulceration of the tongue or gingiva, and less commonly, refractory ulceration of the gastrointestinal tract. High clinical suspicion is required, as failure to diagnose EBV mucocutaneous ulceration may result in significant morbidity and mortality. We report the case of a 64-year-old female renal transplant recipient requiring admission to hospital for management of severe oral and epigastric pain. Examination revealed a large, superficial, well-circumscribed ulcer at the base of the tongue. Blood tests suggested a secondary immunodeficiency characterised by mild leucopenia, hypogammaglobulinaemia, and low memory B-cells with normal immunophenotype. Endoscopy revealed four, cratered ulcers in the pre-pyloric region of the stomach. A core biopsy of the tongue ulcer confirmed EBV mucocutaneous ulceration. The patient's immunosuppression was optimised, which resulted in complete resolution of the tongue and gastric ulcers at eight and twelve weeks of follow-up respectively.

Keywords

Epstein-Barr Virus, Mucocutaneous Ulceration, Renal Transplant, Immunosuppression, Immunodeficiency

1. Introduction

EBV mucocutaneous ulceration is a rare complication that has previously been described in human immunodeficiency virus (HIV) infection, immunosuppres-

sive therapy for inflammatory arthritis, and age-related immunosenescence [1] [2]. It is most commonly associated with the use of methotrexate, azathioprine, and ciclosporin [2] [3] [4]. Approximately 20% of cases present with painful ulceration involving the gastrointestinal tract, however diagnosis can be challenging and requires clinicopathological correlation [2] [3] [4] [5].

EBV mucocutaneous ulceration affecting the oral mucosa has also been described in immunosuppressed patients, including patients who have undergone haematological and solid organ transplantation [6] [7]. EBV recipient-negative, donor-positive transplantations are at the highest risk, and an association with hypogammaglobulinaemia has been described [3] [8]. Human herpesvirus (HHV) 8 infection is an important differential diagnosis in renal transplant recipients with non-healing mucosal ulcers [6].

2. Case Presentation

A 64-year-old female with a deceased-donor renal transplant, performed for end-stage renal failure secondary to obstructive nephropathy, presented nine months post-transplantation with severe oral and epigastric pain. Her post-transplantation period was remarkable for subclinical vascular rejection on three month protocol biopsy (treated with three doses of intravenous methylprednisolone and change of calcineurin inhibitor from ciclosporin to tacrolimus), cytomegalovirus (CMV) viraemia at seven months post-transplantation (treated with therapeutic-dose valganciclovir), and recurrent gastrointestinal infections (two episodes of *Camplyobacter jejuni* enterocolitis and two episodes of *Clostridium difficile* colitis) necessitating reduction of her mycophenolate mofetil (MMF) dose. At the time of admission, the patient's immunosuppressive regime comprised of prednisone (7.5 mg once daily), MMF (750 mg twice daily), and tacrolimus (trough levels 8 - 10 ug/L).

Examination revealed a large (32 mm by 20 mm), superficial, well-circumscribed ulcer on the left base of the tongue (**Figure 1**) without dental caries, lymphadenopathy or other organomegaly. Her renal function and electrolytes were normal, tacrolimus trough level within target range (9.0 μg/L), and full blood count revealed mild leucopenia (WBC 2.1×10^9/L, neutrophils 1.4×10^9/L). Viral swabs of the ulcer were negative for herpes simplex virus (HSV) 1 and 2, enterovirus, and varicella zoster virus (VZV) by polymerase chain reaction (PCR). She was HIV and hepatitis C virus antibody negative, hepatitis B virus immune, and serum PCR negative for CMV, EBV, parvovirus, HHV-6, and HHV-8. The serum protein electrophoresis and serum free light chains were normal; however, the serum IgG (5.3 g/L) and IgM (0.2 g/L) were suppressed. An orthopantomogram (OPG) was normal and computed tomography (CT) head and neck with contrast showed no evidence of a mass, abscess, or lymphadenopathy.

An oesophago-gastro-duodenoscopy (OGD) revealed four (5 - 7 mm) non-bleeding, cratered ulcers in the pre-pyloric region of the stomach (**Figure 2**), snare-biopsies of which revealed active inflammation without evidence of

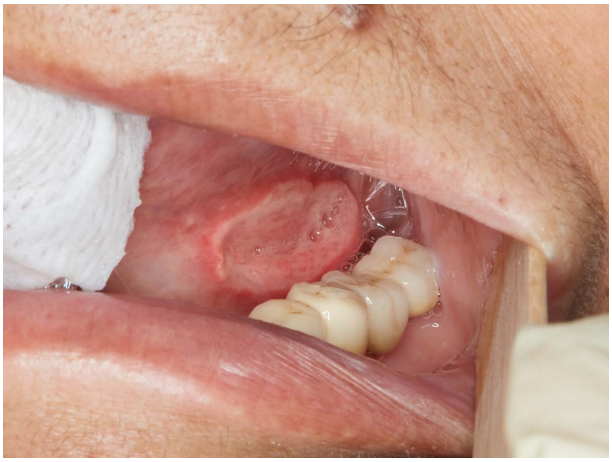

Figure 1. Superficial ulcer (32 mm by 20 mm) at the left base of the tongue in a patient nine months post deceased-donor renal transplantation.

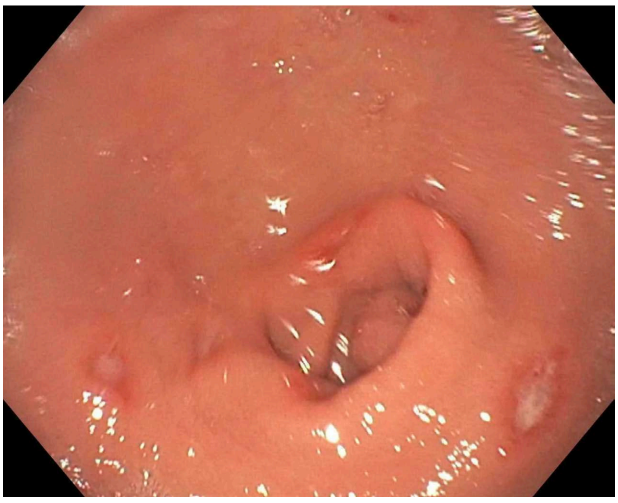

Figure 2. OGD image of gastric ulcers (5 - 7 mm) in the pre-pyloric region of the stomach in a patient nine months post deceased-donor renal transplantation.

Helicobacter pylori, CMV inclusions, or malignant infiltration. Core biopsies of the tongue ulcer revealed intermediate-sized lymphocytes with EBV positivity on immunohistochemical staining in keeping with EBV mucocutaneous ulceration, without evidence of Hodgkin or Reed-Sternberg cells, lymphoma, or carcinoma in situ. These biopsies were PCR negative for CMV, HSV, VZV, and enterovirus. PCR analysis revealed polyclonal pattern of immunoglobulin heavy chain (IgH) and T-cell receptor gamma (TCR γ) PCR primers.

The patient's serum lymphocyte subsets and lymphocyte cell lines were normal. Additionally, B-cell subsets revealed normal immunophenotype with normal naïve and switched memory B-cells, but low memory B-cells of unclear significance. The hypogammaglobinaemia and low memory B-cells were deemed to be in keeping with secondary immunodeficiency. The patient's MMF was reduced to 500 mg twice daily and target tacrolimus trough level lowered to 6 - 8 μg/L. The patient was subsequently followed up at eight weeks in the out-patient

renal transplant clinic, at which time her tongue ulcer had completely resolved. Repeat OGD at twelve weeks confirmed complete resolution of the gastric ulcers.

3. Discussion

This is the first case of EBV mucocutaneous ulceration to be reported in a renal transplant recipient in New Zealand. The pathophysiology of EBV mucocutaneous ulceration is ill defined; however, it is postulated that T-cell mediated immunosurveillance is reduced by immunosuppression, which allows for the proliferation of EBV-infected B-cells [3]. Macroscopically, EBV mucocutaneous ulcers are large, superficial, and well-circumscribed (**Figure 1** and **Figure 2**) [2] [3]. The microscopic appearances consist of a prominent rim of T-cells in the ulcer base with mixed haematolymphoid infiltrate and atypical B-cells positive for EBV by in situ hybridisation [2] [3] [6] [7].

Approximately 40% of cases are clonal for immunoglobulin receptor gene or T-cell gene rearrangement on PCR analysis [2]. EBV mucocutaneous ulceration is postulated to be on the disease spectrum with post-transplant lymphoproliferative disorder (PTLD) and classical Hodgkin lymphoma [1] [2] [9]. Clonality of immunoglobulin receptor gene or T-cell receptor gene rearrangements, serum EBV PCR positivity, and failure to respond to immunosuppression reduction, are associated with aggressive disease and PTLD transformation [2] [3].

At first glance, EBV mucocutaneous ulceration may appear indolent, however it is not currently possible to predict the risk of refractory disease or transformation to PTLD [2] [3]. The mainstay of treatment is reduction of immunosuppression, which leads to resolution of ulceration within four to six weeks in approximately 45% of cases [2] [3] [5] [7]. High clinical suspicion is required as failure to respond to treatment, or transformation to PTLD, results in significant mortality [3] [5] [6]. B-cell depleting chemotherapies have been utilised in cases of refractory EBV mucocutaneous ulceration with varying degrees of success [2] [3] [4] [9].

Conflicts of Interest

The authors declare that they have no competing interests.

References

[1] Swerdlow, S.H., Campo, E., Pileri, S.A., Harris, N.L., Stein, H., Siebert, R., *et al.* (2016) The 2016 Revision of the World Health Organization Classification of Lymphoid Neoplasms. *Blood*, **127**, 2375-2390. https://doi.org/10.1182/blood-2016-01-643569

[2] Dojcinov, S.D., Venkataraman, G., Raffeld, M., Pittaluga, S. and Jaffe, E.S. (2010) EBV Positive Mucocutaneous Ulcer—A Study of 26 Cases Associated with Various Sources of Immunosuppression. *The American Journal of Surgical Pathology*, **34**, 405-417. https://doi.org/10.1097/PAS.0b013e3181cf8622

[3] Hart, M., Thakral, B., Yohe, S., Balfour, H.H., Singh Jr., C., Spears, M., *et al.* (2014) EBV-Positive Mucocutaneous Ulcer in Organ Transplant Recipients: A Localized

Indolent Posttransplant Lymphoproliferative Disorder. *The American Journal of Surgical Pathology*, **38**, 1522-1529. https://doi.org/10.1097/PAS.0000000000000282

[4] Makino, Y., Tani, C., Miyokawa, N., Yoshimoto, R., Mizumoto, K., Eguchi, K., *et al.* (2015) Multiple Intestinal Ulcers Associated with Primary Epstein-Barr Virus Infection in a Patient with Rheumatoid Arthritis Undergoing Methotrexate Therapy. *Internal Medicine*, **54**, 2851-2855. https://doi.org/10.2169/internalmedicine.54.4735

[5] Badham, K., Mirchandani, A., Arumainayagam, N. and West, D.R. (2007) Epstein-Barr Virus Associated with a Post-Transplant Lymphoproliferative Disorder Presenting as Isolated Gastrointestinal Tract Bleeding. *Endoscopy*, **39**, E64-E65. https://doi.org/10.1055/s-2006-944922

[6] Leon, J.E., Takahama, J.A., Vassallo, J., Soares, F.A., de Almeida, O.P. and Lopes, M.A. (2011) EBV-Associated Polymorphic Posttransplant Lymphoproliferative Disorder Presenting as Gingival Ulcers. *International Journal of Surgical Pathology*, **19**, 241-246. https://doi.org/10.1177/1066896909353599

[7] Nelson, A.A., Harrington, A.M., Kroft, S., Dahar, M.A., Hamadani, M. and Dhakal, B. (2016) Presentation and Management of Post-Allogeneic Transplantation EBV-Positive Mucocutaneous Ulcer. *Bone Marrow Transplant*, **51**, 300-302. https://doi.org/10.1038/bmt.2015.245

[8] Kleinman, S., Jhaveri, D., Caimi, P., Cameron, R., Lemonovich, T., Meyerson, H., *et al.* (2014) A Rare Presentation of EBV(+) Mucocutaneous Ulcer That Led to a Diagnosis of Hypogammaglobulinemia. *The Journal of Allergy and Clinical Immunology*: *In Practice*, **2**, 810-812. https://doi.org/10.1016/j.jaip.2014.07.009

[9] Satou, A., Kohno, A., Fukuyama, R., Elsayed, A.A. and Nakamura, S. (2017) Epstein-Barr Virus-Positive Mucocutaneous Ulcer Arising in a Post-Hematopoietic Cell Transplant Patient Followed by Polymorphic Posttransplant Lymphoproliferative Disorder and Cytomegalovirus Colitis. *Human Pathology*, **59**, 147-151. https://doi.org/10.1016/j.humpath.2016.08.001