Intestinal perforation following allogeneic stem cell transplantation caused by Epstein-Barr virus-positive mucocutaneous ulcer

Klaus Hirschbühl, Tina Schaller, Bruno Märkl, Adriana Amerein, Michael Gebhard, Georg Braun, Susanne Wasserberg, Elisa Sala, Martin Trepel, Christoph Schmid

Angaben zur Veröffentlichung / Publication details:

Hirschbühl, Klaus, Tina Schaller, Bruno Märkl, Adriana Amerein, Michael Gebhard, Georg Braun, Susanne Wasserberg, Elisa Sala, Martin Trepel, and Christoph Schmid. 2025. "Intestinal perforation following allogeneic stem cell transplantation caused by Epstein-Barr virus-positive mucocutaneous ulcer." *Haematologica* 110 (4): 1038–40. https://doi.org/10.3324/haematol.2024.286488.

Intestinal perforation following allogeneic stem cell transplantation caused by Epstein-Barr virus-positive mucocutaneous ulcer

A 50-year-old female was diagnosed with acute myeloid leukemia (AML) in March 2022. Due to high-risk disease (therapy-related AML following breast cancer in 2015, complex karyotype and MRD positivity after 2 courses of induction chemotherapy) allogeneic stem cell transplantation (alloSCT) was performed in first complete hematologic remission in June 2022. Molecular CR and full donor chimerism were achieved. An episode of intestinal acute graft-*versus*-host-disease (stage 2, overall grade III) was successfully treated with steroids.

Six months after alloSCT, during tapering of immunosuppression (tacrolimus 0.5 mg/d and hydrocortisone 10 mg/d), the patient was admitted to hospital for severe abdominal pain, which had developed rapidly within one day; she had not experienced any other symptoms in the weeks before. As free air on computed tomography suggested intra-abdominal perforation (Figure 1A), meropenem as broad spectrum antibiotic was started and an immediate laparotomy was performed. Several perforated ulcers could be found in the ileum, causing purulent peritonitis. Ileum segmentectomy was performed at two sites (12 cm and 45 cm). Due to persistent abdominal pain, four days after the first surgery, a second laparotomy was carried out; however, there was no evidence of further perforation ulcers or anastomosis insufficiency.

Histopathological work-up of the resected ileum in context with the clinical features revealed an Epstein-Barr virus (EBV)-positive mucocutaneous ulcer post alloSCT (EBVMCU) (Figure 1B-D). Positron emission tomography (PET) scan and endoscopy revealed multiple foci disseminated over the entire ileum and colon, consistent with the diagnosed EBVMCU, but without any further manifestation outside the intestine (Figure 1E, F). Despite strong expression of EBV in the lesions (Figure 1C), EBV-DNA could not be detected at any time in the peripheral blood (PB). However, a vigorous population of EBV-specific T cells could be found in PB at the time of the EBVMCU diagnosis. Systemic therapy with rituximab was initiated (4 weekly doses at 375 mg/m^2 each). Already after the first application, a rapid clinical improvement could be observed, and the patient could be discharged 19 days after the last surgical intervention.

Two months after initiation of rituximab, treatment re-evaluation with PET scan and endoscopy including multiple biopsies were performed, without any evidence of a persistence of the EBVMCU; there was no EBV RNA in the mucosa. During an 18-month follow-up, the patient has so far not revealed any signs of relapse of EBVMCU, whereas AML is still in complete molecular remission with full donor chimerism.

This report fulfils the national ethical standards, and the patient has given written consent for publication.

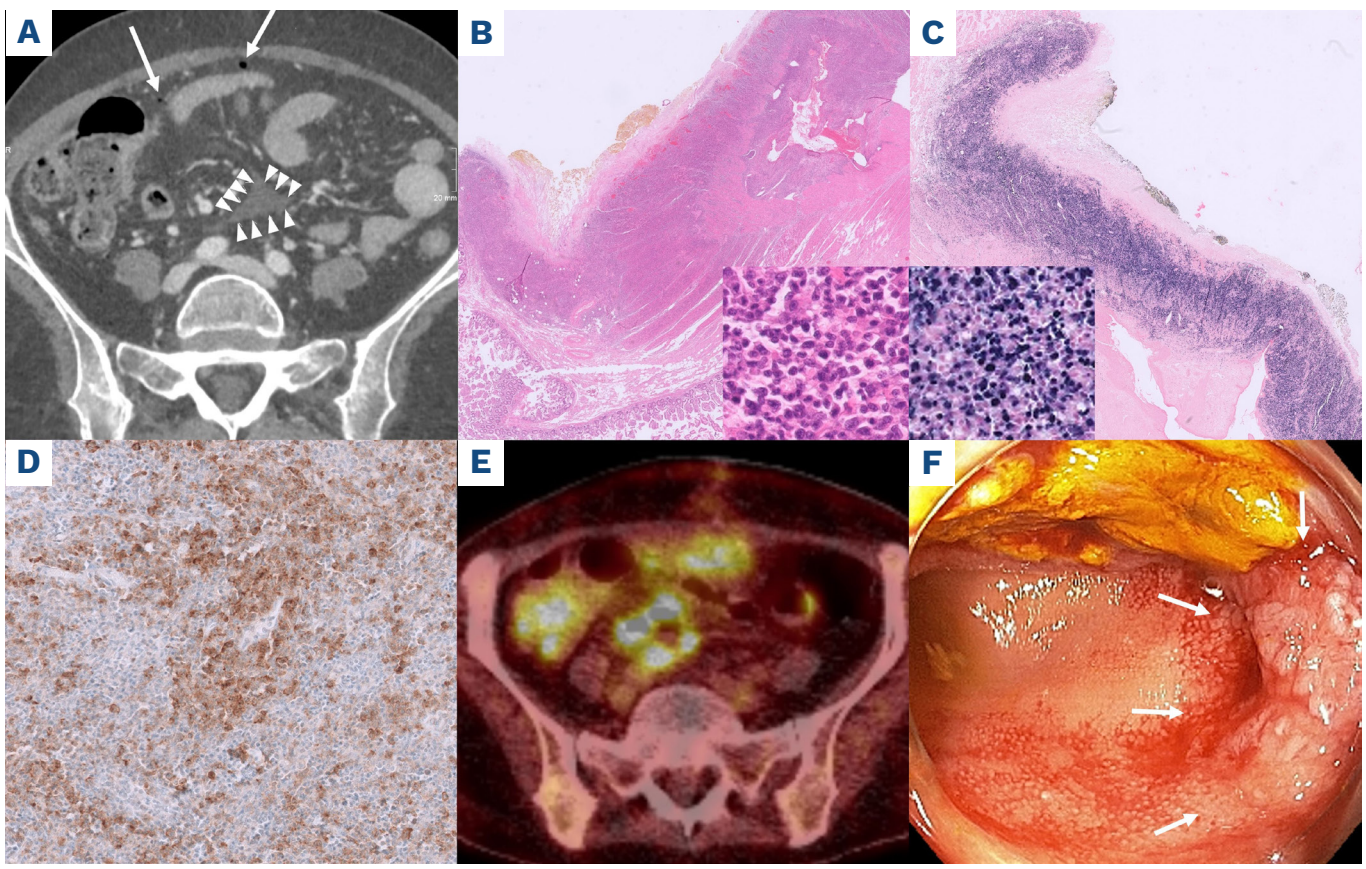

Figure 1. Imaging, endoscopy and histological processing. (A) Computed tomography scan with extraluminal air as sign for perforation (see arrows) and free fluid collection (see arrow heads). (B) Histopathological specimen of resected ileum, showing lymphocyte infiltration (insert: magnification 25x). (C) Epstein-Barr virus (EBV) positivity by *in situ* hybridization (insert: magnification 25x). (D) CD30-positivity of EBV-positive mucocutaneous ulcer (EBV-MCU). (E) Positron emission tomography (PET) scan with PET-positive foci in colon and ileum corresponding to EBV-MCU. (F) Endoscopy showing corresponding lesion in the ileum (see arrows).

EBVMCU was first included in the 4th WHO classification 2017 among "other iatrogenic immunodeficiency-associated lymphoproliferative disorders" and was classified as a distinct sub-entity of "lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation" in the 5th edition in 2022.[1] Distinguishing EBV- MCU from DLBCL EBV+ post alloSCT by histologic criteria is difficult. Therefore, the inclusion of clinical features is crucial to make the final diagnosis.[2] Most commonly, it is localized in the oropharynx, less frequently on the skin and in the gastrointestinal tract, and can occur under various immunosuppressive conditions, both inborn or acquired, including iatrogenic.[3,4] The most important prerequisite for diagnosing EBVMCU is to know the background with existing immunosuppression and the frequently mild or completely missing clinical symptoms. Absence of systemic lymphadenopathy and bone marrow involvement are further clues. At biopsy, sharply circumscribed, isolated ulcers are found in the mucosa or skin, showing a histologically dense polymorphic infiltration with a variable number of plasma cells, macrophages and a high number of EBV+ cells with CD30 positivity, reminiscent of atypical immunoblasts or Hodgkin cells. Immuno-histochemistry reveals expression of markers of an activated B-cell-type: CD20+, Pax5+, OCT2+, MUM1+, CD10-, BCL6-. EBV-DNA is not usually detected in the PB while it is highly positive in the affected tissue itself.[5,6] Therefore, EBVMCU cannot be excluded by negative blood PCR for EBV. In contrast, positivity of EBV blood PCR was reported in a patient developing EBVMCU without underlying immunosuppression.[7]

In general, lymphoproliferative disorders following allogeneic stem cell transplantation (alloSCT) are rare complications with an incidence of 1.1-1.7%.[8] With respect to EBVMCU, of the 186 clinical cases that have been published up to 2020, only a very few of them are in the context of alloSCT.[5,9] In contrast to aggressive EBV-associated post-transplant lymphoma, EBVMCU per se is frequently classified as having a relatively benign disease biology.[3,10-12] The clinical course is often also mild, and self-limitation or regression after reduction of immunosuppressive medication without further treatment was described in some cases.[6,9] However, the severity of clinical symptoms may vary according to the localization. If the intestine is affected, there is a high risk for perforation with the possibility of a dramatic clinical course, requiring urgent surgery, as shown in our patient and in another reported case with psoriasis requiring steroid treatment and EBVMCU in the stomach.[13] In these cases, additional systemic treatment is required to prevent further complications from additional lesions. Rituximab as monotherapy is the most frequently used approach, while chemotherapy was added in some cases.[6,10] Nevertheless, despite systemic treatment, some fatalities have been described.[14] In this regard, a novel second-line therapy with allogeneic EBV-specific T lymphocytes is now available for patients with refractory disease.[15]

In conclusion, EBVMCU is a manifestation of EBV-associated lymphoproliferative disease following alloSCT and its prevalence could be underestimated. Despite its generally benign biology, EBVMCU can lead to a dramatic clinical course depending on the localization, with high potential for secondary complications such as intestinal perforation. In addition to the clinical setting of an immune deficiency and EBV+ lesions with characteristic histological findings, absence of typical constitutional symptoms of malignant lymphoma are diagnostic clues, whereas EBV negativity in the PB does not rule out this diagnosis. Considering the possibility of severe complications with ongoing immunosuppressive conditions, we would recommend systemic treatment at least with rituximab, along with localized therapy like surgery or irradiation.

Authors

Klaus Hirschbühl,[1,2] Tina Schaller,[2,3] Bruno Märkl,[2,3] Adriana Amerein,[4] Michael Gebhard,[5] Georg Braun,[6] Susanne Wasserberg,[7] Elisa Sala,[8] Martin Trepel[1,2] and Christoph Schmid[1,2]

[1]Department of Hematology and Oncology, Faculty of Medicine, University of Augsburg, Augsburg; [2]Bayerisches Zentrum für Krebsforschung (BZKF), Augsburg; [3]Department of Pathology, Faculty of Medicine, University of Augsburg, Augsburg; [4]Department of Nuclear Medicine, Faculty of Medicine, University of Augsburg, Augsburg; [5]Department of Diagnostic and Interventional Radiology, Medical Faculty University of Augsburg, Augsburg; [6]Department of Gastroenterology, Faculty of Medicine, University of Augsburg, Augsburg; [7]Department of General, Visceral and Transplantation Surgery, Faculty of Medicine, University of Augsburg, Augsburg and [8]University Hospital Ulm, Internal Medicine III, Ulm, Germany

Correspondence:
K. HIRSCHBÜHL - klaus.hirschbuehl@uk-augsburg.de

https://doi.org/10.3324/haematol.2024.286488

Received: August 19, 2024.
Accepted: November 28, 2024.
Early view: December 5, 2024.

Disclosures

No conflicts of interest to disclose.

Contributions

KH, CS, MT and ES treated the patient. KH and CS wrote the manuscript. TS and BM carried out the histological processing and analysis. AA performed PET-scan. MG performed CT-scan. GB performed endoscopy. SW performed surgery. MT, ES, TS, BM, AA, MG, GB and SW revised the manuscript.

References

1. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia. 2022;36(7):1720-1748.
2. Dojcinov SD, Quintanilla-Martinez L. How I diagnose EBV-positive B- and T-cell lymphoproliferative disorders. Am J Clin Pathol. 2023;159(1):14-33.
3. Dojcinov SD, Venkataraman G, Raffeld M, Pittaluga S, Jaffe ES. EBV positive mucocutaneous ulcer-a study of 26 cases associated with various sources of immunosuppression. Am J Surg Pathol. 2010;34(3):405-417.
4. Roberts TK, Chen X, Liao JJ. Diagnostic and therapeutic challenges of EBV-positive mucocutaneous ulcer: a case report and systematic review of the literature. Exp Hematol Oncol. 2015;5:13.
5. Nelson AA, Harrington AM, Kroft S, Dahar MA, Hamadani M, Dhakal B. Presentation and management of post-allogeneic transplantation EBV-positive mucocutaneous ulcer. Bone Marrow Transplant. 2016;51(2):300-302.
6. Ishikawa E, Satou A, Nakamura M, Nakamura S, Fujishiro M. Epstein-Barr virus positive B-cell lymphoproliferative disorder of the gastrointestinal tract. Cancers (Basel). 2021;13(15):3815.
7. Schwob E, Szablewski V, Lerisson M, Dereure O. Epstein-Barr virus-related multi-site mucocutaneous ulcer: a previously undescribed clinical subset of a rare disease. Acta Derm Venereol. 2019;99(13):1299-1300.
8. Socié G, Barba P, Barlev A, et al. Outcomes for patients with EBV-positive PTLD post-allogeneic HCT after failure of rituximab-containing therapy. Bone Marrow Transplant. 2024;59(1):52-58.
9. Ikeda T, Gion Y, Nishimura Y, Nishimura MF, Yoshino T, Sato Y. Epstein-Barr virus-positive mucocutaneous ulcer: a unique and curious disease entity. Int J Mol Sci. 2021;22(3):1053.
10. Fei F, Reddy V, Peker D, Patel C, Al Diffalha S. EBV positive mucocutaneous ulcer (EBVMCU): single center series of three cases and review of literature. Ann Clin Lab Sci. 2021;51(1):124-130.
11. Al Hamed R, Bazarbachi AH, Mohty M. Epstein-Barr virus-related post-transplant lymphoproliferative disease (EBV-PTLD) in the setting of allogeneic stem cell transplantation: a comprehensive review from pathogenesis to forthcoming treatment modalities. Bone Marrow Transplant. 2020;55(1):25-39.
12. Hickey CL, Romee R, Nikiforow S, Dorfman D, Mazzeo M, Koreth J. A case of Epstein Barr virus-related post-transplant lymphoproliferative disorder after haploidentical allogeneic stem cell transplantation using post-transplantation cyclophosphamide. Haematologica. 2020;105(7):e379-e381.
13. Falini B, Lazzi S. Epstein-Barr virus-positive mucocutaneous ulcer of the stomach. Blood. 2022;140(15):1743.
14. Shen K, Ma H. Chronic active Epstein-Barr virus infection manifest as extensive mucocutaneous ulceration mimicking Behçet's disease. Br J Haematol. 2022;199(2):167.
15. Mahadeo KM, Baiocchi R, Beitinjaneh A, et al. Tabelecleucel for allogeneic haematopoietic stem-cell or solid organ transplant recipients with Epstein-Barr virus-positive post-transplant lymphoproliferative disease after failure of rituximab or rituximab and chemotherapy (ALLELE): a phase 3, multicentre, open-label trial. Lancet Oncol. 2024;25(3):376-387.