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Title Page

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

Running head: Perforated intestinal EBVMCU after alloSCT

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Author Contributions

KH, CS, MT, ES treated the patient

KH, CS wrote the manuscript

TS, BM did 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, SW revised the manuscript

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Case report

A 50-year-old female was diagnosed with Acute Myeloid Leukaemia (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 haematologic 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 from alloSCT, during tapering of immunosuppression (tacrolimus 0,5 mg/d and hydrocortisone 10 mg/d), the patient was admitted to the hospital due to severe abdominal pain, which had developed rapidly within one day and without any further 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 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 abdominal guarding, four days after the first surgery, a second laparotomy was done, however without 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-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 EBVMCU diagnosis. Systemic therapy with rituximab was initiated (4 weekly doses at 375 mg/m² each). Already after the first application, a rapid clinical improvement could be observed, and the patient could be discharged at 19 days from last surgical intervention.

Two months after initiation of rituximab, treatment reevaluation with PET scan and endoscopy including multiple biopsies were performed, without evidence for a persistence of the EBVMCU and without detection of EBV RNA in the mucosa. During an 18-months 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.

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 EBVMCU 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 mucosa or skin, showing a histologically dense polymorphic infiltration with a variable number of plasma cells, macrophages and a high number of EBV positive cells with CD 30 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 usually not detected in the peripheral blood 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].

Lymphoproliferative disorders following allogeneic stem cell transplantation (alloSCT) in general are rare complications with an incidence of 1.1-1.7% [8]. With respect to EBVMCU, 186 clinical cases of have been published until 2020, only very few of them 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]. Consistently, 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 one with psoriasis requiring steroid treatment and EBVMCU in the stomach [13]. In those 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 adjoined in some cases [6,10]. Nevertheless, fatal cases have been described despite systemic treatment [14]. In this regard, a novel second-line therapy

with allogeneic EBV-specific T lymphocytes is nowadays available for patients with refractory disease [15].

In conclusion, EBVMCU is a presumably underestimated manifestation of EBV associated lymphoproliferative disease following alloSCT. 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 positive lesions with characteristic histological findings, absence of typical constitutional symptoms of malignant lymphoma are diagnostic clues, whereas EBV negativity in the peripheral blood 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, beside local therapy like surgery or irradiation.

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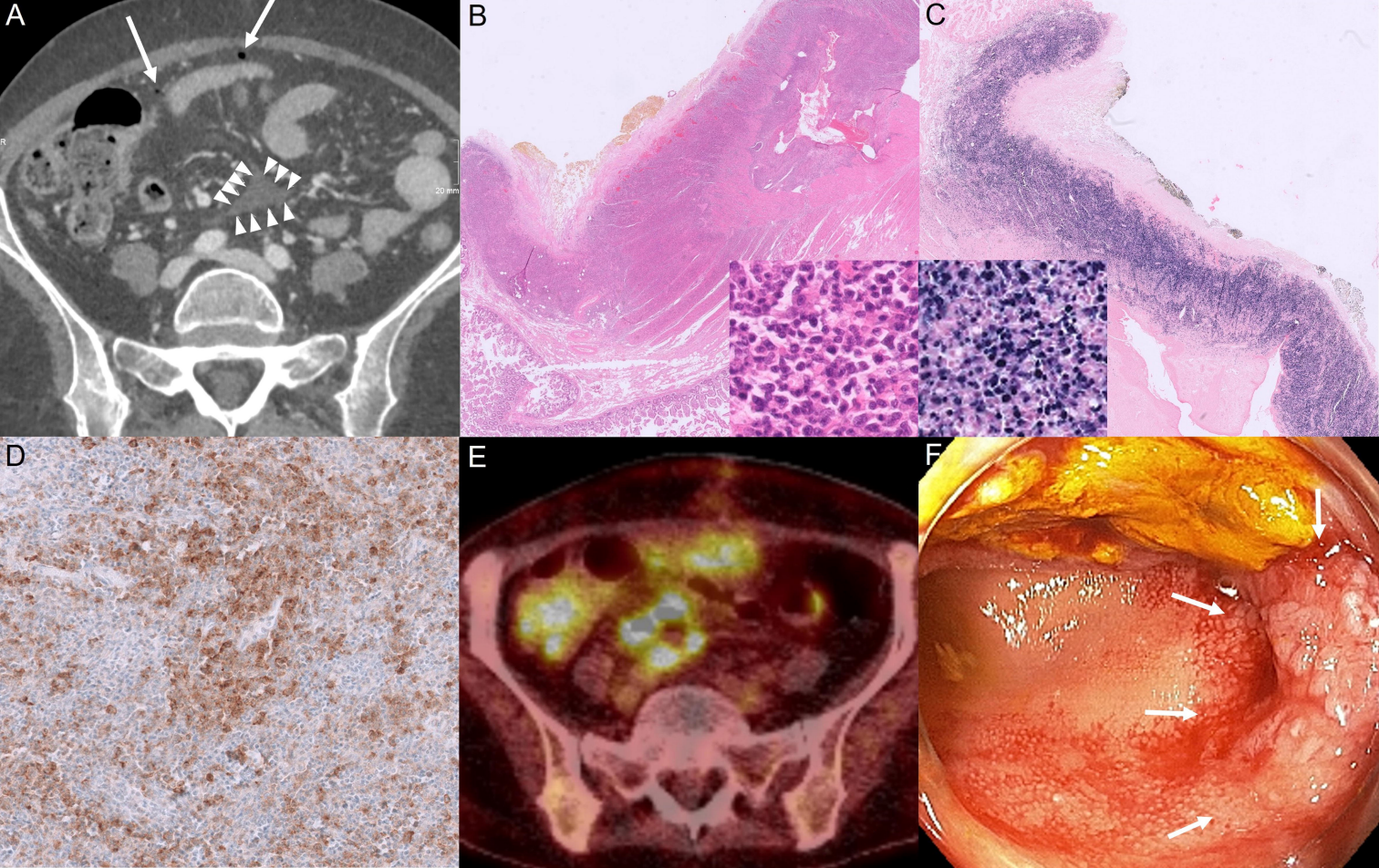
Figure Legends

Figure 1. Imaging, endoscopy and histological processing. (A) CT-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 (inserted magnification); (C) EBV-positivity by in situ hybridization (inserted magnification); (D) CD30-positivity of Epstein-Barr virus-positive mucocutaneous ulcer (EBVMCU). (E) PET-scan with PET- positive foci in colon and ileum corresponding to EBVMCU. (F) Endoscopy shown corresponding lesion in the ileum (see arrows).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