Received: 29 December 2023 | Revised: 12 February 2024 | Accepted: 26 February 2024

DOI: 10.1002/jha2.879

eJHaem

British Society for Haematology

SHORT REPORT

Graft-versus-host disease after autologous stem cell transplantation in a recipient who underwent allogeneic stem cell transplantation 20 years earlier

Osamu Imataki | **Shunsuke Yoshida** | **Tomoya Ishida** | **Haruyuki Fujita** | **Makiko Uemura**

Department of Internal Medicine, Division of Hematology, Faculty of Medicine, Kagawa University, Kagawa, Japan

Correspondence
Osamu Imataki, Department of Internal Medicine, Division of Hematology, Faculty of Medicine, Kagawa University, 1750–1 Ikenobe, Miki-town, Kita-county, Kagawa 761–0793, Japan.
Email: imataki.osamu@kagawa-u.ac.jp

Funding information
JSPS KAKENHI, Grant/Award Numbers: JP22K06768, JP23K11850

Abstract

A literature review does not provide information about the safety of autologous hematopoietic stem cell transplantation (HSCT) in a recipient who has previously received allogeneic HSCT. We treated a 69-year-old woman with diffuse large B cell lymphoma. The patient received autologous stem cell transplantation (ASCT) in the second complete remission of malignant lymphoma. The patient had undergone allogeneic hematopoietic SCT (allo-HSCT) for chronic myeloid leukemia 20 years ago. Chronic myeloid leukemia had been in complete remission for the previous 20 years. Thus, the patient received autologous and allogenic HSCT 20 years apart. ASCT involves the patient receiving "self" hematopoietic cells from an allogeneic donor. In other words, this is immunologically the second allo-HSCT. The allo-HSCT 20 years ago was undergone by a related healthy brother, a human leukocyte antigen (HLA) 8/8 full matched donor. The conditioning regimen was reduced-intensity consisting of fludarabine and busulfan. The patient did not experience acute or chronic graft-versus-host disease (GVHD) after allo-HSCT. The second transplantation, ASCT was performed to the MEAM conditioning regimen. Engraftment was uneventful, and complete donor chimerism had been achieved even after ASCT. She suffered from an acute gastric mucosal lesion 52 days after ASCT. Pathological finding of gastric mucosa was nonspecific acute gastritis with significant neutrophil infiltration. Sex chromosome analysis of gastric mucosa demonstrated that mucosal cells had XX signals, whereas infiltrating neutrophils had XY signals. We speculated the patient onset of an acute gastric GVHD in this recipient after the second transplantation. This case remarked infiltration of neutrophils triggered GVHD reaction by resetting allogeneic immune reaction after the second transplantation. We describe a rare occurrence of GVHD reaction in a recipient of ASCT following allo-HSCT.

List of Abbreviations: AGML, acute gastric mucosal lesion; Allo-HSCT, allogeneic hematopoietic stem cell transplantation; ASCT, autologous stem cell transplantation; CML, chronic myeloid leukemia; FISH, fluorescence in situ hybridization; GVHD, graft-versus-host disease; HLA, human leukocyte antigen; SCT, stem cell transplantation.

KEYWORDS
allogeneic transplantation, autologous transplantation, chimerism analysis, graft-versus-host disease, hematopoietic stem cell transplantation

Dear Editor,

We treated a 69-year-old woman with relapsed malignant lymphoma using autologous stem cell transplantation (ASCT). This was hematoimmunologically autologous allogeneic stem cell transplantation. The patient had undergone allogeneic hematopoietic SCT (allo-HSCT) for treating chronic myeloid leukemia (CML) in the chronic phase at the age of 49 years (20 years ago) because the standard treatment for CML was allo-HSCT before the era of tyrosine kinase inhibitors [1]. Therefore, we anticipated that an allogeneic reaction would occur following this ASCT.

Clinical data from the previous allo-HSCT were as follows. The patient's 50-year-old healthy brother was the donor. Donor genetic disparity was a completely 8/8 matched donor for human leukocyte antigen (HLA). We treated the patient with a low-intensity conditioning regimen of 30 mg/m^2/day fludarabine for 5 days and 3.2 mg/kg/day busulfan intravenously for 4 days. The patient's treatment course following stem cell infusion was uneventful, and the patient did not experience acute or chronic graft-versus-host disease (GVHD) after transplantation. Neutrophil recovery was observed on day 23, indicating engraftment. The patient has been in remission from CML for 20 years after allo-HSCT.

However, 19 years after allo-HSCT, she was diagnosed with intestinal malignant lymphoma, diffuse large B-cell lymphoma, due to chronic abdominal pain. The clinical stage was Lugano II, with the intestine as the primary site and invasion of the local mesenteric lymph nodes. Her intestine was partially resected. According to sex chromosomal fluorescence in situ hybridization (FISH) analysis of the resected tumor tissue, the lymphoma was derived from donor hematopoietic cells [1]. The patient was administered six standard courses of rituximab and CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone). After a 14-month complete response, the patient's lymphoma relapsed retroperitoneally. She underwent salvage chemotherapy, which included three courses of rituximab and DeVIC (dexamethasone, etoposide, ifosfamide, and carboplatin), followed by ASCT with MEAM (ranimustine, etoposide, cytarabine, and melphalan) conditioning regimen. The recipient developed nonspecific acute gastritis 52 days after ASCT, the cause of which was unknown, including cytomegalovirus (CMV). Repeated blood and stool cultures, as well as CMV antigenemia, revealed no causative pathogens. The endoscopic diagnosis was an acute gastric mucosal lesion (AGML) (Figure 1A). Pathological diagnosis of gastric mucosa was nonspecific acute gastritis with significant neutrophil infiltration (Figure 1B). We performed a sex chromosome analysis of gastric mucosa [2]. Mucosal cells displayed XX signals, whereas infiltrating neutrophils displayed XY signals (Figure 1C). We checked a chimerism analysis of the patient's buccal cells and peripheral blood cells by short tandem repeat (STR) polymorphism method [3]. The result of chimerism analysis showed STR pattern of the patient's cells derived from buccal and peripheral blood were completely different. This disclosed that the patient's peripheral blood was fully donor chimerism. A small frequency of apoptotic bodies in the gastric mucosa was shown pathologically in Figure 2.

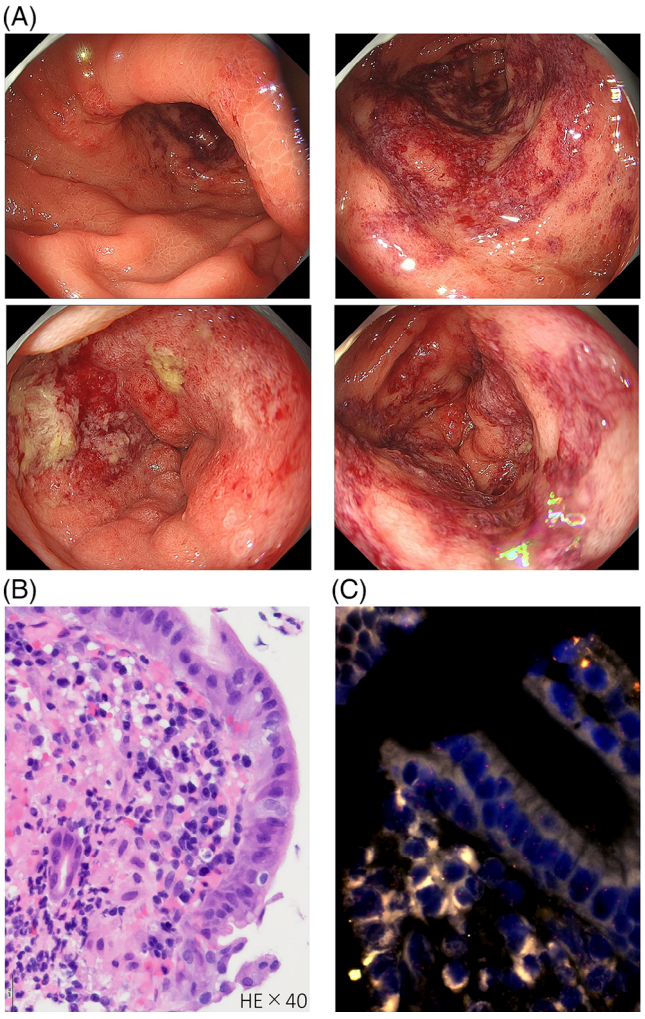

FIGURE 1 Gastric mucosal lesion analyzed by endoscopy, pathology, and cellular genetics. (A) Gastroesophageal endoscopy revealed semi-circumferential gastric lesions near the antrum and duodenum. The gastric mucosa was edematous red with a visible vascular pattern. Mucosa was brittle and easily bled. (B) A mucosal biopsy was performed on the antrum verruca. Pathological examination revealed erosive epithelium with massive immune cell infiltration, including neutrophils and lymphocytes. Submucosal bleeding and capillary proliferation were also observed. (C) Submucosal chromosomal analysis revealed XX signals in the mucosa and XY signals in infiltrating inflammatory cells (primarily neutrophils).

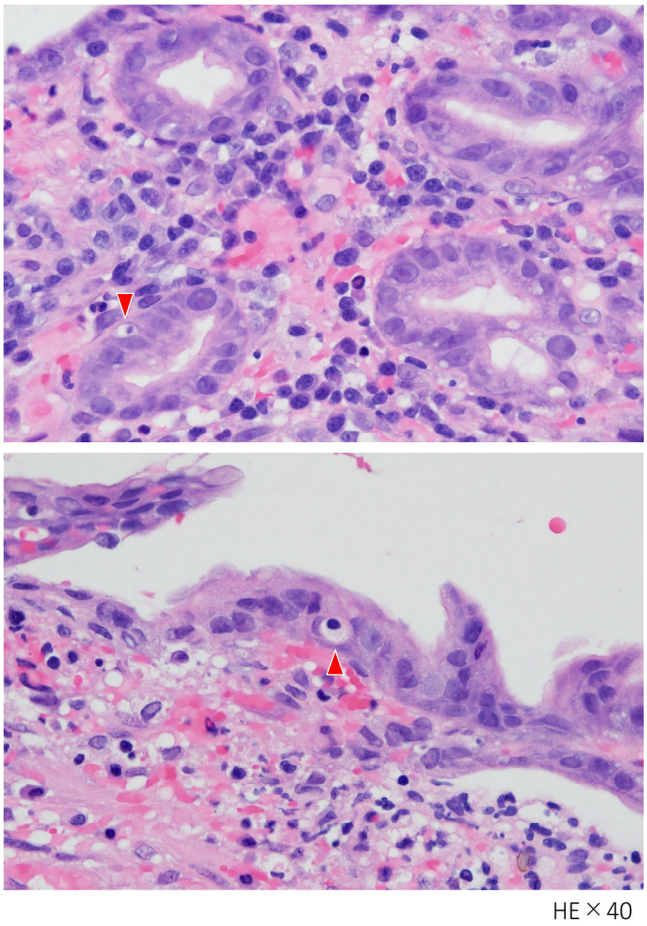

FIGURE 2 Apoptotic body in gastric mucosa. A low frequency of apoptotic findings in gastric mucosa was shown (red arrowhead).

Immunologically, infiltrating immune cells stem from original donor blood cells reacting with allogeneic recipient mucosa. This gastric reaction was clinically similar to gut acute GVHD. However, pathologic findings did not prove a typical GVHD reaction in the patient's mucosa. We could not obtain clear evidence to use corticosteroids in order to suppress the recipient's autologous neutrophils derived from the original allogeneic donor. We did not use corticosteroids to treat this gastritis. The patient was treated with a proton pump inhibitor, lansoprazole, and an antiviral agent, valganciclovir. The mucosal lesion was resistant to these treatments. AGML lesions were monitored by followed-up endoscopy every 2 weeks. The first look (18 days after treatment) and second look (30 days) endoscopy illustrated a remained A2 stage duodenal ulceration. The third look (46 days) endoscopy showed an S2 stage gastric ulcer scar. Thus, gastric mucosal lesion needed 6 weeks to cure by itself recovering mucosa.

Autologous HSCT in a recipient who has previously received allogeneic HSCT should be considered a second allogeneic SCT. In our case, the patient received an infusion of 'currently self' stem cells mobilized in the patient's peripheral blood as an ASCT, which had been gifted from an allogenic donor 20 years earlier. In this setting, there are no clinical reports to determine whether GVHD reaction can occur at clinical risk. We observed an AGML reaction 60 days after SCT, which was immunologically deciphered as acute gastric GVHD. Pathologically, the gastric mucosa revealed massive neutrophil infiltration [4, 5] with lymphocytes. Neutrophils may contribute to the pathogenesis of intestinal GVHD by activating donor effector T cells [5]. According to some studies, bacterial infection causes an inflammatory response that results in pathogenic neutrophil infiltration [6, 7]. Our observation after allogeneic followed by autologous HSCT indicated neutrophil dominant GVHD reaction can be primitively and unspecifically induced by an allo-auto HSCT setting.

Recently, immunology after HSCT has revealed a novel important role for neutrophils in GVHD [4]. Pathogenic neutrophils play a pro-inflammatory role in acute GVHD. The donor's neutrophils provide cellular contact with mesenteric lymph nodes, to activate the donor's T cells for recognizing alloantigen [6]. Finally, we had a gastric immune reaction after ASCT after 20 years of allo-HSCT. This is classified as a newly occurring GVHD caused by ASCT. We present an acute GVHD reaction following allo-HSCT with ASCT.

AUTHOR CONTRIBUTIONS

Osamu Imataki, Shunsuke Yoshida, and Tomoya Ishida managed the patient's case, contributed to the literature search, and wrote the manuscript. Makiko Uemura and Haruyuki Fujita made substantial contributions to the concept and design of this report. Makiko Uemura was involved in the supervision of the manuscript. Makiko Uemura and Haruyuki Fujita managed the research. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This work was supported by JSPS KAKENHI Grant Numbers JP22K06768 and JP23K11850.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article. Data are available on request due to privacy/ethical restrictions.

ETHICS STATEMENT

We obtained approval from the Kagawa University Hospital Institutional Review Board (H23-023). This research was conducted ethically following the World Medical Association Declaration of Helsinki. The patient provided written informed consent to publish their case (including the publication of images).

PATIENT CONSENT STATEMENT

Written informed consent was obtained from the patient for the publication of this study.

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

ORCID

Osamu Imataki https://orcid.org/0000-0001-5332-1316

REFERENCES

1. Imataki O, Kubo H, Kida JI, Uemura M, Fujita H, Kadowaki N. Donor-derived lymphoma harboring a mosaic sex chromosome in a female stem cell transplantation recipient from a male sibling. EJHaem. 2021;3(1):228–30. https://doi.org/10.1002/jha2.347
2. Clark JR, Scott SD, Jack AL, Lee H, Mason J, Carter GI, et al. Monitoring of chimerism following allogeneic haematopoietic stem cell transplantation (HSCT): technical recommendations for the use of short tandem repeat (STR) based techniques, on behalf of the United Kingdom National External Quality Assessment Service for Leucocyte Immunophenotyping Chimerism Working Group. Br J Haematol. 2015;168(1):26–37. https://doi.org/10.1111/bjh.13073
3. Turkiewicz D, Gorczynska E, Toporski J, Kalwak K, Rybka B, Noworolska D, et al. Monitoring of hematopoietic chimerism after sex-mismatched allogeneic stem cell transplantation (alloSCT) by dual-color FISH analysis of X and Y chromosomes. Leuk Res. 2003;27(11):993–98. https://doi.org/10.1016/s0145-2126(03)00077-8
4. Schwab L, Goroncy L, Palaniyandi S, Gautam S, Triantafyllopoulou A, Mocsai A, et al. Neutrophil granulocytes recruited upon translocation of intestinal bacteria enhance graft-versus-host disease via tissue damage. Nat Med. 2014;20(6):648–54. https://doi.org/10.1038/nm.3517
5. Tecchio C, Cassatella MA. Uncovering the multifaceted roles played by neutrophils in allogeneic hematopoietic stem cell transplantation. Cell Mol Immunol. 2021;18(4):905–18. https://doi.org/10.1038/s41423-020-00581-9
6. Martin PJ. Pathogenic neutrophils in acute GVHD. Blood. 2018;131(16):1774–75. https://doi.org/10.1182/blood-2018-03-836353
7. Hülsdünker J, Ottmüller KJ, Neeff HP, Koyama M, Gao Z, Thomas OS, Follo M, et al. Neutrophils provide cellular communication between ileum and mesenteric lymph nodes at graft-versus-host disease onset. Blood. 2018;131(16):1858–69. https://doi.org/10.1182/blood-2017-10-812891

How to cite this article: Imataki O, Yoshida S, Ishida T, Fujita H, Uemura M. Graft-versus-host disease after autologous stem cell transplantation in a recipient who underwent allogeneic stem cell transplantation 20 years earlier. eJHaem. 2024;5:383–86. https://doi.org/10.1002/jha2.879