Hepatic Portal Venous Gas Associated with Severe Graft-versus-host Disease of the Gastrointestinal Tract

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Abstract

We report a 67-year-old woman who was diagnosed with hepatic portal venous gas associated with severe graft-versus-host disease (GVHD) of the gastrointestinal tract. The patient received allogenic peripheral blood stem cell transplantation from a haploidentical son against Philadelphia chromosome-positive acute lymphocytic leukemia. The patient developed grade 3 intestinal GVHD on day 90 from the transplantation. On day 149, she presented septic shock and computed tomography (CT) scan revealed hepatic portal venous gas (HPVG); an ileocecal resection was performed immediately. The damage of gastrointestinal mucosa by GVHD resulted in the invasion of gas-producing bacteria. Although HPVG-associated gastrointestinal GVHD is extremely rare, we should pay special attention to this pathogenesis.

Key words: hepatic portal venous gas (HPVG), graft-versus-host disease (GVHD), acute lymphocytic leukemia, allogenic hematopoietic stem cell transplantation


Introduction

Hepatic portal venous gas (HPVG) was first described for necrotizing enterocolitis in infants by Wolfe and Evans (1). HPVG is induced by various abdominal diseases and is usually detected by computed tomography (CT) scan. The ischemic type of HPVG demands urgent operative intervention and shows a high mortality rate. HPVG-associated gastrointestinal GVHD is extremely rare. We report a case of HPVG after allo-peripheral blood stem cell transplantation (PBSCT) for Ph+ ALL. Our patient presented severe gastrointestinal GVHD, followed by HPVG and pneumatosis intestinalis (PI).

Case Report

A 67-year-old woman was admitted to our hospital for leukocytosis with blast cells as identified at a previous hospital. In her past history, she had received gastric resection for gastric cancer at the age of 45. On admission the white blood cell count was elevated to 9,740/μL, containing 64% blasts. Bone marrow aspiration showed that peroxidase stain-negative blasts had increased to 97%. Flow cytometry showed the blasts were positive for cluster differentiation (CD) 10, 19, 34, KOR-SA3544 and human leukocyte antigen-DR (HLA-DR). Minor breakpoint cluster region-v-abl Abelson murine leukemia viral oncogene homolog 2 (BCR-ABL) transfusion signal was detected by fluorescence in situ hybridization (FISH). The patient was diagnosed with Ph+ ALL. Treatment of the patient was started with a Japan Adult Leukemia Study Group (JALSG) ALL 202-like protocol (2) on day 121, including imatinib administration (Fig. 1). She received induction chemotherapy with cyclophosphamide, daunorubicin, vincristine, prednisolone and imatinib. After a course of induction therapy, biological complete remission (CR) was achieved. On day 71, consolidation therapy #1 containing Methotrexate MTX, Ara-C, methyprednisolone and central nervous system (CNS) prophylaxis was performed. On day 36, consolidation therapy #2 was started, but she had to discontinue imatinib owing to strong nausea and vomiting even after dose reduction. At that time, other tyrosine kinase inhibitors (TKIs) dasatinib and nilotinib were not available in Japan. Allogenic hema-
topoietic stem cell transplantation (allo-HSCT) was expected to be difficult and present a high risk because she was over 65 years old. At first, we considered unrelated bone marrow transplantation or cord blood cell transplantation. However, there were only a few appropriate donors in the Japan Donor Program and the Japanese Cord Blood Bank Network at that time. We discussed treatment with the patient and her family under informed consent. We decided to perform allogenic HSCT from her first son, who was a 2-locus HLA-mismatched donor with 1-locus mismatch for direction of GVHD and 1-locus mismatch for direction of rejection. As for the rejection, PBSCT have advantage of a large quantity of stem cells and were thought to overcome it. On the other hand, allogenic PBSCT from related donors with 1-locus HLA-mismatched donor is thought to be permissible. The conditioning regimen consisted of fludarabine phosphate at a total dose of 180 mg/m$^2$ divided over 6 days and i.v. busulfan at a total dose of 6.4 mg/kg divided over 2 days. Granulocyte colony stimulating factor (G-CSF)-mobilized peripheral blood stem cells were infused on day 0. The number of infused CD34-positive cells was $7.17 \times 10^6$ cells/kg. Prophylaxis against GVHD was performed with a continuous infusion of tacrolimus hydrate (TAC) and short-term MTX at 10 mg/m$^2$ on day 1 and 7 mg/m$^2$ on days 3, 6 and 11. In general, anti-thymocyte globulin (ATG) is an appropriate agent for GVHD prophylaxis on haploidentical hematopoietic stem cell transplantation (HSCT). In the present case, because the donor was just 1-locus mismatch for direction of GVHD, we chose TAC and short-term MTX for GVHD prophylaxis.

On day 20, neutrophil engraftment was confirmed. Although we tried imatinib re-administration, she soon became intolerant again for the same reasons. On day 34, acute GVHD of skin on her neck appeared. On day 58, chimerism test revealed that the proportion of chromosome XY was 98.4%. On day 71, her renal function got worsened and it was necessary to change immunosuppressant from TAC to cyclosporine A (CyA). At the same time, dasatinib became available and was administered. After a while, dasatinib had to be discontinued because of massive pleural effusion. On day 90, she had watery diarrhea of over 1,500 mL per day. Clostridium difficile (C. difficile) toxin was checked several times and not detected. We considered the diagnosis to be grade 3 gastrointestinal GVHD. Although TAC was restarted in place of CyA with 1 mg/kg prednisolone (PSL), the effect on gastrointestinal GVHD was insufficient. Total colonoscopy on day 143 revealed edematous and reddish mucosa. Pathological findings from the biopsy revealed lymphocyte infiltration, erosive change and apoptosis cell of crypt, which were considered as GVHD findings (Fig. 2). There were no findings of cytomegalovirus (CMV) colitis. Although the patient presented low-grade fever, no significant pathogens were detected from the culture of blood and stool. On day 149, she suddenly presented abdominal pain and developed septic shock status. CT scan revealed HPVG and PI (Fig. 3); then, an ileocecal resection and colostomy were immediately performed on the same day. Broad-spectrum antibiotics (doripenem hydrate) were administrated for the septic shock. Mesenteric gas from ileum to ileoce-
Figure 2. Pathological findings from the biopsy revealed lymphocyte infiltration, erosive change and crypt cell apoptosis, which were considered as GVHD findings.

HPVG is induced by various abdominal diseases, from benign causes to lethal diseases that require urgent surgical treatment (3-7). Bowel ischemia, diverticulitis, gastric dilatation, inflammatory bowel diseases, liver transplantation and chemotherapy are known as causes of HPVG. It is extremely rare that GVHD of the gastrointestinal tract is followed by HPVG. Although the mechanism of HPVG and PI is not completely understood, PI and HPVG are associated with three major clinical subgroups, namely, mechanical causes, acute mesenteric ischemia and benign idiopathic causes (8). The mechanical causes mean that HPVG and PI are induced at the site of injury or disease, for example, adhesion-related complications, trauma and radiation. The present patient was classified into this category. There is another simple classification of HPVG and PI, which has two categories. One is a bacterial theory, which refers to gas-producing bacterial invasion into the gastrointestinal wall. The other is a mechanical theory in which defects of mucosa and increased intraluminal pressure cause gas to infiltrate inside the gastrointestinal wall (5, 9, 10).

The five-year estimate of survival from complete remission in Ph+ ALL patients without stem cell transplantation or imatinib was only 0.08 (8). In addition, continuous administration of imatinib after stem cell transplantation brought better outcome (11). However, the present patient was completely intolerant to imatinib because of severe nausea, which is considered as a highly frequent adverse event. Other TKIs were not approved for use in Japan at that time. Although stem cell transplantation for this patient was thought to have a high risk, the patient and her family chose stem cell transplantation to obtain a better outcome, with informed consent.

We supposed that HPVG and PI in the present patient were triggered by GVHD of the gastrointestinal tract at first, and then invasion of gas-producing bacteria to the gastrointestinal wall. Her immunosuppressive status must have promoted the invasion by intestinal bacteria. Then, bacterial translocation led to septic shock status. We needed to perform surgical treatment for the entrance of bacteria. The mechanism was thought to be similar to HPVG in inflammatory bowel disease patients (12, 13). As she was an elderly patient, we chose the reduced intensity conditioning regimen. Though total body irradiation (TBI) 2 Gray (Gy) is beneficial to prevent rejections, we did not think that it would have an effect on GVHD prophylaxis at allogeneic HSCT from the related donor with 1-locus mismatch for direction of GVHD. TAC+MTX are more effective prophylaxis of acute GVHD than CyA+MTX in bone marrow transplantation from an unrelated donor (14). This patient needed to change TAC to CyA for renal dysfunction. Although no comparative studies of CyA and TAC in acute and chronic GVHD of allo-PBSCT have been carried out, this change of immunosuppressant might facilitate the progression of GVHD.

The main causes of severe diarrhea in allo-HSCT patients are associated with pseudomembranous enterocolitis by C. difficile, CMV enterocolitis and GVHD of gastrointestinal tract. C. difficile is associated with severe GVHD and, in a previous study, 13% of patients had C. difficile infections in allo-HSCT recipients (15). C. difficile toxin was checked frequently and the results were negative. CMV antigenemia was negative. Total colonoscopy and biopsy did not show the findings of pseudomembranous enterocolitis or CMV enterocolitis.

Abdominal radiograph, ultrasonography and CT scan are imaging modalities that can demonstrate HPVG and PI. The most sensitive modality is CT scan (16). It is important to distinguish HPVG from biliary gas. CT findings of HPVG show branching lucencies or hypodensities within 2 cm of the liver capsule. The portal gas is transported to small peripheral branches by the centrifugal flow of portal venous blood. On the other hand, biliary gas is found centrally and is located more than 2 cm away from the liver capsule (17). These were also significant findings in the present case.
It is highly possible that GVHD of the gastrointestinal tract occurred, followed by bacterial translocation, which finally led to septic status. The gas-producing bacteria that induced HPVG were not determined. The result of blood culture might not be accurate because this patient was administered broad-spectrum antibiotics after presenting with HPVG.

When a patient with gastrointestinal GVHD after stem cell transplantation presents strong peritoneal signs and a high value of C reactive protein (CRP), HPVG should be considered. CT scan is the most sensitive modality. An appropriate treatment including urgent surgical treatment should be considered immediately because of the high mortality, even in patients with normal immunity.

The authors state that they have no Conflict of Interest (COI).

References

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