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【 CASE REPORT 】

Atraumatic Splenic Rupture Due to Ectopic Extramedullary Hematopoiesis after Autologous Stem Cell Transplantation in a Patient with AL Amyloidosis

Shuku Sato[1], Yotaro Tamai[1], Satomi Okada[1], Emiko Kannbe[1], Kotaro Takeda[2] and Eri Tanaka[1]

Abstract:
A 50-year-old man was diagnosed with multiple myeloma complicating AL amyloidosis. Splenic rupture was complicated during autologous stem cell transplantation (auto-SCT). Granulocyte colony-stimulating factor (G-CSF) was not administered. A pathological examination of the spleen revealed that CD34-positive cells were concentrated in the ruptured part of the splenic capsule. Hematopoietic cells were engrafted in the small gap between the capsule and amyloid protein deposition area of the spleen, which might have caused the splenic rupture in the absence of G-CSF administration. Special attention is thus required for amyloidosis patients undergoing auto-SCT, even when G-CSF is not administered.

Key words: AL amyloidosis, splenic rupture, autologous stem cell transplantation, granulocyte colony-stimulating factor

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Introduction

AL amyloidosis is characterized by the progressive deposition of fibrillar amyloid proteins in tissues; these proteins are derived from immunoglobulin light chains produced due to clonal plasma cell disorder (1). Amyloid fibrils are mainly deposited in the heart, kidneys, liver, spleen, gastrointestinal tract, peripheral and autonomic nerves, skin, joints, and blood vessels of virtually all organs (2). Splenic amyloid infiltration is a common finding in systemic amyloidosis cases. Although extremely rare, atraumatic splenic rupture can be a serious complication and can sometimes even prove to be life threatening. Cases have been reported wherein the spleen ruptured during or after administering high melphalan doses with auto-SCT. Such amyloidosis cases where myeloid engraftment was achieved were supported by the short-term daily administration of G-CSF injections (3). Splenic rupture can occur at any time during the auto-SCT. Causes of rupture aside from G-CSF injection are diverse and include coagulation deficiency (4), loss of vascular integrity owing to previous chemotherapies, and thrombocytopenia (5). To our knowledge, however, no report has pathologically demonstrated that extramedullary hematopoiesis causes splenic rupture.

We herein report a case of a fragile spleen during stem cell engraftment after auto-SCT, during which pathologically reseeded hematopoietic cells were observed only in a tiny gap between the capsule and amyloid protein-deposited spleen.

Case Report

A 50-year-old man was admitted to our hospital because of anorexia and an approximately 15-kg weight loss over the previous 6 months. The patient's height and weight were 170 cm and 45.5 kg, respectively (BMI, 15.7 kg/m^2). On admission, he was alert, and his blood pressure, heart rate, and body temperature were 106/62 mmHg, 68 beats/min, and 36.8 °C, respectively. A physical examination revealed an enlarged tongue but no hepatosplenomegaly. Furthermore, neurological findings revealed no abnormalities, although the

[1]Division of Hematology, Shonan Kamakura General Hospital, Japan and [2]Department of Pathology, Shonan Kamakura General Hospital, Japan
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Correspondence to Dr. Yotaro Tamai, y_tamai@shonankamakura.or.jp

patient was extremely thin. Laboratory-based tests revealed the following: leukocyte count, 6,200 cells/μL; hemoglobin (Hb) levels, 12.5 g/dL; and platelet count, 215×10^3 cells/μL. Serum biochemical parameters were as follows: levels of total protein, 7.9 g/dL; albumin, 4.8 g/dL; blood urea nitrogen, 26.3 mg/dL; creatinine, 1.93 mg/dL; and beta 2-microglobulin, 2.8 mg/dL. The estimated glomerular filtration rate was 30.9 mL/min/1.73 m^2. The immunological workup results were as follows: levels of immunoglobulin (Ig) G, 1,774 mg/dL (normal: 820-1,740 mg/dL); IgA, 153 mg/dL (normal: 90-400 mg/dL); and IgM, 36 mg/dL (normal: 31-200 mg/dL). The patient's serum free light chain ratio (κ/λ) was 0.168 (normal: 0.248-1.80), and serum immunofixation electrophoresis revealed monoclonal protein.

He underwent upper gastrointestinal endoscopy, colonoscopy, and duodenal and rectal biopsies; amyloid deposition was observed in all tested organs. In addition, myocardial hypertrophy was observed, and a subsequent myocardial biopsy revealed amyloid myopathy. Bone marrow aspiration revealed 11% plasma cells; immunohistochemical staining revealed predominantly λ light chains, and fluorescence *in situ* hybridization of the bone marrow revealed IgH-BCL1 at 7.8%. We made a diagnosis of multiple myeloma mainly complicating AL amyloidosis.

The patient was treated with three cycles of bortezomib (1.3 mg/m^2/week) and dexamethasone (40 mg/week) therapies. He initially received high-dose melphalan as a part of the SCT treatment protocol. According to this protocol, daily subcutaneous G-CSF injections (filgrastim, 600 μg/day) were initiated for stem cell mobilization before collection by leukapheresis. From day 4 of G-CSF administration, allergic urticaria was observed throughout his body; however, the urticarial lesions subsided after administering an anti-allergy medication, and stem cell mobilization and leukapheresis were performed. We successfully harvested 3.4×10^6/kg CD34-positive cells.

The patient was subsequently admitted to our hospital for high-dose melphalan therapy (140 mg/m^2) and auto-SCT (all CD34-positive cells were harvested). Diarrhea was observed as an adverse event of high-dose melphalan therapy. On day 11 after SCT, the patient experienced febrile neutropenia. Despite the patient having neutropenia with a fever, G-CSF injection was not administered because of his allergy history. On day 17 after SCT and 2 days after myeloid engraftment, he developed sudden chest pain and fainted while standing without an earlier traumatic episode. Laboratory-based examination results revealed anemia, as his Hb levels had decreased from 8.3 to 5.3 g/dL in 2 days. Simultaneously, the platelet count was 34×10^3 cells/μL. Computed tomography revealed massive ascites and a capsular splenic hematoma consistent with splenic hemorrhaging and rupture. The patient underwent emergency open splenectomy. During laparotomy, several hematomas and relatively fresh hemorrhaging were observed on the spleen. The splenic capsule had ruptured, and the ruptured parts were fragile; hematoma formation was observed. Emergency splenectomy was successful, and hematopoiesis recovered, but he died of sepsis from an *Enterobacter cloacae* infection four months after autologous transplantation.

A pathological examination revealed the spleen size to be 8×6×4 cm. On the external surface of the spleen, adherent hematoma and multiple subcapsular hematomas were observed (Fig. 1a). Amyloid deposition was observed throughout all the red pulp of the spleen; these deposits were positive on Congo red staining and appeared apple green in color when observed using polarizing microscopy (Fig. 1b-d). White pulp was rarely observed because it had atrophied. The spleen with amyloid deposits in the red pulp appeared bright red and shiny, resembling ham; it was therefore referred to as a "ham-like spleen." In addition, numerous CD34-positive cells were concentrated in the ruptured part of the splenic capsule (Fig. 2a-c). In addition to CD34-positive cells, CD71-positive cells presumed to be of erythroid lineage were also found to be concentrated because of extramedullary hematopoiesis (Fig. 2d, e). These may have become engrafted in the spleen during auto-SCT.

Discussion

Primary systemic AL amyloidosis is characterized by increased protein production by plasma cells and amyloid deposition in organs such as the kidney, heart, liver, and spleen (6). Owing to amyloid protein deposition in the red pulp and marginal zone of the spleen, the follicular dendritic cells of the spleen are enlarged. The division of the spleen due to this amyloid deposition and its subsequent resemblance to ham has led to this condition being referred to as a "ham-like spleen."

Splenic rupture is relatively common both immediately and as a delayed condition following significant blunt abdominal injury (7). Atraumatic splenic rupture, which can be caused by neoplastic diseases, hematological disorders, infection, and chronic inflammation, is uncommon; however, it is associated with a high mortality rate (8, 9). Infiltration of the spleen with amyloid proteins has been identified in 41% of cases of systemic amyloidosis, and splenic rupture might occur as a subsequent complication; however, spontaneous splenic rupture in systemic amyloid deposition cases has an incidence of approximately 2% (3), suggesting that splenic rupture is a rare phenomenon that likely contributes to the vulnerability underlying infiltration by amyloid (3).

Treating AL amyloidosis patients with high-dose melphalan and SCT induces complete hematologic remissions and reverses amyloid-related disorders (10). G-CSF administration is widely used to mobilize peripheral progenitor cells for collection by leukapheresis before treatment with high melphalan doses and auto-SCT. However, ectopic extramedullary hematopoiesis can occur in the peritransplant period.

Splenomegaly has been attributed to red pulp infiltration by granulocytes owing to G-CSF administrations (11). In mice, increased mRNA expression of the DNA-synthesizing enzymes thymidylate synthase and thymidine kinase in

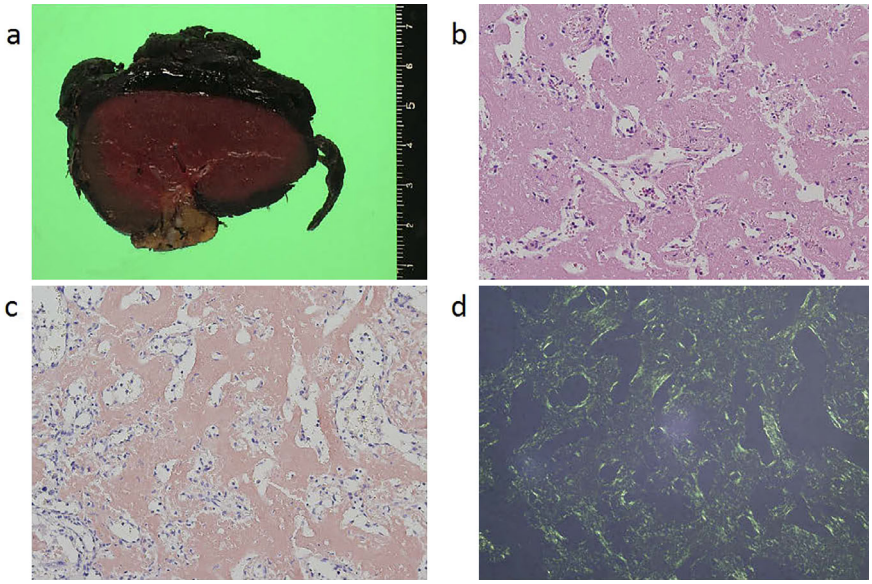

Figure 1. **On the external surface, the spleen showed adherent blood clots and multiple subcapsular hematomas. There was no evidence of splenomegaly. Amyloid-deposited red pulp of the spleen, with the spleen-divided surface showed a "ham-like" appearance (a). Hematoxylin and Eosin staining showed amyloid deposits throughout the red pulp of the spleen (b: ×200), which was positive on Congo red staining (c) and appeared apple green under polarizing microscopy (d).**

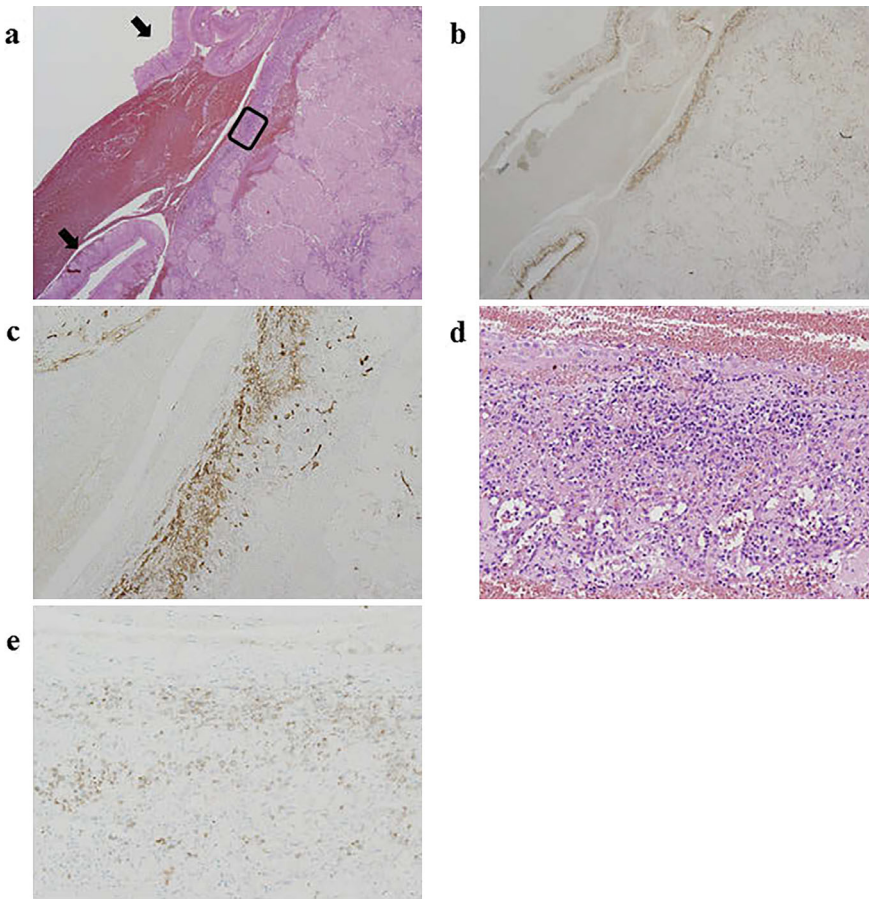

Figure 2. **The ruptured part of the splenic capsule (arrow) showed adherent hematoma [a: Hematoxylin and Eosin (H&E) staining, ×40], and numerous CD34-positive cells were concentrated beneath the splenic capsule (b: CD34 immunostaining, ×40; and c: ×100). The square box in Fig. 2a shows the concentration of hematopoietic cells other than CD34-positive cells (d: H&E staining, ×200; and e: CD71 immunostaining, ×200).**

splenic cells has been observed in splenic cells 6 hours after a single G-CSF injection, indicating reseeding of hematopoietic cells from the bone marrow in the spleen, followed by an increase in the splenic weight (12).

In the present case, amyloid proteins deposited in the spleen caused the splenic capsule to become fragile, and the hematopoietic cells were reseeded into the spleen after SCT. O'Malley et al. reported morphological and immunohistochemical evaluations of splenic hematopoietic proliferation in post-bone marrow transplant patients (13). In those cases, although the hematopoietic cells were predominantly composed of myeloid elements, erythroid elements were often prominent, and a one case showed a mild increase in the CD34 expression (13). Splenic rupture in our patient may have occurred because of the concentration of CD34-positive cells and extramedullary hematopoiesis just under the capsule in an extremely small gap. The spleen with amyloid deposition was fragile, and on performing auto-SCT, ectopic extramedullary hematopoiesis was observed in the splenic capsule. Granulocytes generally infiltrate the red pulp; however, this was precluded by the amyloid depositions in the "ham-like spleen," and extramedullary hematopoiesis might have ruptured the spleen in the absence of G-CSF administration. Therefore, special attention is required in such cases.

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

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