Letter to the Editor

Atraumatic splenic ruptures triggered both remission and death in a single case of blastic plasmacytoid dendritic cell neoplasm

Keywords: Blastic plasmacytoid dendritic cell neoplasm, splenic rupture, dendritic cell, cancer vaccination, immunotherapy

A 78-year-old Japanese man presented to our hospital with multiple skin lesions, multiple lymphadenopathies and moderate splenomegaly (Figure 1). Hematological examination revealed a white blood cell (WBC) count of 13100/μL with 63% blasts, hemoglobin concentration of 12.2 g/dL and platelet count of 42000/μL. Blasts in the peripheral blood were medium in size and had scant grey-blue cytoplasm (Figure 2A). On flow cytometry analysis of peripheral blood, abnormal cells expressing CD2, CD4, CD7 and CD56 were observed. Based on these findings, we suspected leukemic transformation of lymphoma. Lymph node biopsy was performed and the specimen exhibited diffuse proliferation of large blastic cells (Figure 2B). These cells were positive for CD4, CD56, CD123 and TCL1 on immunohistochemistry (Figure 2C, D). Infiltration of these abnormal cells was also noted in the specimen from the skin lesion biopsy and bone marrow. The chromosomal analysis demonstrated a normal karyotype. Taken together, a diagnosis of blastic plasmacytoid dendritic cell neoplasm (BPDCN) was established. Fourteen days after the first visit, he returned with fever, anemia and tenderness in the left upper quadrant. We assumed progression of the disease and planned chemotherapy. Two days after admission, the WBC count, including blasts, started to decrease. Computed tomography (CT) demonstrated hematoma around the spleen and hemorrhagic ascites (Figure 3), indicating mild atraumatic splenic rupture (ASR). Serum chemistry revealed the elevation of C-reactive protein (CRP) and uric acid up to 18.58 mg/dL and 11.6 mg/dL, respectively. These findings suggested that strong inflammation and tumor lysis occurred simultaneously after ASR. Chemotherapy was postponed and he was managed conservatively. Afterwards, he developed leukopenia together with slight improvement of skin lesions, but the mechanism of this phenomenon was unclear. His WBC count recovered gradually over 2 months, and blasts were finally undetectable in the peripheral blood. A slight reduction in abnormal blasts was noted in the bone marrow aspirate. Soon afterwards, blasts increased in the peripheral blood, and anemia, thrombocytopenia and skin lesions progressed. One month later, he was admitted again to receive chemotherapy. Three days before the scheduled date of chemotherapy, he developed fever and sudden pain in the left upper quadrant again. Subsequently, the WBC count began decreasing and hemorrhagic ascites was again detected on CT imaging (Figure 4A). The elevation of CRP and uric acid was also observed again. The skin lesions had visibly improved (Figure 4B) and the infiltration of abnormal blasts in the bone marrow markedly decreased. These findings

![Fig. 1. The skin lesions and CT findings at the first visit. (A) Multiple dusky-red colored patches were systemically distributed. (B) Moderate splenomegaly was found on CT. CT, computed tomography.](image-url)
suggested that mild ASRs had repeatedly triggered the spontaneous partial remissions. Two months later, skin lesions started to progress, and thrombocytopenia appeared three months later. We considered disease progression, and started chemotherapy (THP-COP regimen consisting of cyclophosphamide, pirarubicin, vincristine and prednisolone, administered every three weeks). He exhibited immediate improvement of the blood cell count and skin lesions after the first chemotherapy cycle, but the disease gradually became resistant to the treatment during the eight cycles. He developed sudden hypovolemic shock soon after the eighth cycle of chemotherapy, and died within six hours.
Cardiopulmonary resuscitation was not attempted following the previously obtained informed consent. The clinical course is summarized in Figure 5. Marked hemoperitoneum, and the progression of splenomegaly and lymphadenopathy were found on autopsy imaging. Furthermore, autopsy revealed 1550 mL of hemorrhagic ascites and splenomegaly with capsule rupture and hematoma, indicating that ASR was the source of the marked hemorrhage. On microscopic analysis, bone marrow and lymph nodes were packed with tumor cells, demonstrating progression of the disease (Figure 6A, B).
Fig. 6. Autopsy specimens. (A) The bone marrow was packed with tumor cells. The high-power field is shown at the bottom-right. (B) The mediastinal lymph node was packed with tumor cells. The high-power field is shown at the bottom-right. (C) The spleen was packed with tumor cells. The black triangle indicates disruption of the splenic capsule. The parenchyma of the spleen was also disrupted at the same position. The high-power field is shown at the bottom-right. (D) The hematoma was directly attached to the parenchyma of the spleen (black triangles), indicating disappearance of the splenic capsule. (E) The splenic capsule demonstrated thinning and was infiltrated by tumor cells. (F) The vessel walls were also infiltrated by tumor cells. (G) The black triangle indicates the fibrotic tissue and white triangles indicate macrophages engulfing hemosiderin at the splenic capsule. These findings are consistent with prior ASR. (H) Black triangles indicate macrophages engulfing hemosiderin near the hematoma, suggesting that the prior ASR occurred at the same position. ASR, atraumatic splenic rupture.
Table 1. The number of cases of ASR associated with hematological malignancies reported between 1994 and 2018. The cases were extracted from 2 review articles and online sources. ASR, atraumatic splenic rupture.

| Disease                          | Number of cases | References |
|----------------------------------|-----------------|------------|
| Non-Hodgkin’s lymphoma           | 26              | Oinonen et al. Ann Hematol. (1997) |
|                                  |                 | Biswas et al. World J Emerg Surg. (2006) |
|                                  |                 | Dayama et al. Mediterr J Hematol Infect Dis. (2011) |
|                                  |                 | Tan et al. Case Rep Med. (2012) |
|                                  |                 | Mohammed et al. J Surg Case Rep. (2016) |
|                                  |                 | Komeno et al. Intern Med. (2017) |
| Acute lymphoblastic leukemia      | 9               | (1,2) |
| Acute myelogenous leukemia        | 8               | (1,2) |
| Blastic plasmacytoid dendritic cell neoplasm | 5 | Chee et al. Br J Haematol. (2006) |
| Hairy cell leukemia               | 3               | (2) |
| Chronic myelogenous leukemia      | 2               | (2) |
| Multiple myeloma                  | 2               | (2) |
| Chronic lymphocytic leukemia      | 1               | (1) |
| Adult T-cell leukemia/lymphoma    | 1               | (2) |

ASR is a rare complication of hematological neoplasms, including BPDCN. In the present case, the patient with BPDCN experienced three ASRs. The first two were mild ruptures and remission occurred, whereas the last one was severe and fatal. This patient’s course provided two important clinical suggestions.

First, ASR can cause spontaneous partial remission in patients with BPDCN. Previously, 2 BPDCN cases of spontaneous remission were reported, but the triggers and mechanisms were not elucidated. Our patient exhibited spontaneous partial remission after mild ASR. This is the first report describing spontaneous partial remission after ASR. As the mechanism of this phenomenon, we hypothesized that the dissemination of tumor cells in the peritoneal cavity caused some immune reaction resembling the immunotherapy using autologous cells. Recently, a number of cancer vaccinations administering autologous tumor cells are being explored for different neoplasms, and the induction of tumor reactive T cells, and therapeutic efficacy in mouse models and clinical practice were reported. These findings suggested that splenic rupture with the dissemination of tumor cells in the peritoneal cavity evoked some immune reaction that resulted in the systemic eradication of tumor cells.

Second, ASR may be a relatively frequent complication in patients with BPDCN. In rare instances, ASR occurs in a variety of hematological neoplasms. As the disease entity of BPDCN was established in 1994, we extracted and calculated the number of cases of ASR associated with hematological malignancies reported between 1994 and 2018 from 2 review articles and online sources; Case reports were searched on PubMed or Google scholar using the following terms: “splenic rupture leukemia”, “splenic rupture lymphoma”, “splenic rupture myeloma” or “splenic rupture blastic plasmacytoid dendritic cell neoplasm”. The total number of cases of each hematological neoplasm is listed in Table 1. Cases of non-Hodgkin’s lymphoma were the most common, followed by ALL, AML and BPDCN. We must note that our evaluation method contains a publication bias and the incidence of rare diseases may be overestimated. However, the prevalence of BPDCN was much lower than that of the other listed hematological diseases; therefore, it is possible that the incidence of ASR is higher in patients with BPDCN. All five BPDCN cases in Table 1 had accompanying splenomegaly, although this is not a common finding in patients with BPDCN. In addition, ASR occurred at diagnosis in 3 cases, at relapse in one case and during the refractory phase in our
case. These findings suggest that ASR is associated with splenomegaly and disease progression. Autopsy suggested that the disruptive infiltration of tumor cells into the splenic capsule and vessel walls lead to ASR. This infiltration capability may be the cause of the high incidence of ASR. Previously, age above 40, splenomegaly and associated malignancy were reported as risk factors for ASR-related mortality.14 Our patient had all these factors, indicative of a markedly high risk. Thus, we should be aware of the possibility of ASR in elderly patients with BPDCN and splenomegaly, especially at the time of disease progression.

In conclusion, we reported the first case of BPDCN in which spontaneous partial remission was achieved after ASR. Further accumulation of clinical evidence is needed to elucidate the mechanism of this phenomenon. However, fatal ASR should be prevented in order to avoid the sudden death of elderly patients with BPDCN and splenomegaly.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

1. Giagounidis AA, Burk M, Meckenstock G, Koch AJ, Schneider W. Pathologic rupture of the spleen in hematologic malignancies: two additional cases. Ann Hematol. 1996; 73: 297-302.
2. Aubrey-Bassler FK, Sowers N. 613 cases of splenic rupture without risk factors or previously diagnosed disease: a systematic review. BMC Emerg Med. 2012; 12: 11.
3. Hashikawa K, Niino D, Yasumoto S, et al. Clinicopathological features and prognostic significance of CXCL12 in blastic plasmacytoid dendritic cell neoplasm. J Am Acad Dermatol. 2012; 66: 278-291.
4. Yasuda H, Takaku T, Tomomatsu J, et al. Spontaneous regression of cutaneous blastic plasmacytoid dendritic cell neoplasm followed by acute monocytic leukemia evolving from myelodysplastic syndrome. Intern Med. 2014; 53: 2717-2720.
5. Dranoff G, Jaffe E, Lazenby A, et al. Vaccination with irradiated tumor cells engineered to secrete murine granulocyte-macrophage colony-stimulating factor stimulates potent, specific, and long-lasting anti-tumor immunity. Proc Natl Acad Sci USA. 1993; 90: 3539-3543.
6. Maini N, Nishisaka N, Kinoshita Y, et al. Combination of radiation and vaccination with autologous tumor cells expressing IL-2, IFN-gamma and GM-CSF for treatment of murine renal carcinoma. In Vivo. 2003; 17: 119-123.
7. Luiten RM, Kueter EW, Mooi W, et al. Immunogenicity, including vitiligo, and feasibility of vaccination with autologous GM-CSF-transduced tumor cells in metastatic melanoma patients. J Clin Oncol. 2005; 23: 8978-8991.