Long-term Survival of a Patient with Splenic Angiosarcoma after Resection, High-dose Chemotherapy, and Autologous Peripheral Blood Stem Cell Transplantation

Takeshi Hara¹,², Hisashi Tsurumi¹, Senji Kasahara¹, Kengo Ogawa¹, Jun Takada¹, Kenji Imai¹, Koji Takai¹, Jun-ichi Kitagawa¹,², Shigeru Kiyama¹, Naoki Imai³, Masami Oyama², Tsuyoshi Takami⁴ and Hisataka Moriwaki¹

Abstract

A 48-year-old woman was admitted to our hospital in 2003, complaining of weight loss. Complete blood cell count revealed thrombocytopenia. Abdominal CT demonstrated marked splenomegaly. FDG-PET revealed a hot spot in the whole spleen. A splenectomy was performed. Histological examination was typical for angiosarcoma. Adjuvant chemotherapy was given, and high-dose chemotherapy with autologous peripheral blood stem cell transplantation was performed. Thrombocytopenia developed again in 2008. CT scan showed a hepatic tumor. A fine-needle biopsy of the liver revealed the first relapse. Despite hepatic lobectomy, radiofrequency ablations and administration of recombinant interleukin-2, she died from respiratory failure in 2009.

Key words: primary splenic angiosarcoma, autologous peripheral blood stem cell transplantation, splenectomy, recombinant interleukin 2


Introduction

Primary splenic angiosarcoma is a very rare neoplasm with a high metastasis rate and a poor prognosis. This disease entity was reported for the first time in 1879 by Langhans (1). Presentations of splenic angiosarcoma are extremely variable and frequently cause diagnostic difficulties. This disease commonly manifests with anemia, abdominal pain, and splenomegaly. Although splenic angiosarcoma is usually treated with splenectomy (2, 3), the outcome of this disease is typically dismal, with only 20% of patients surviving for 6 months (4, 5). There is no evidence to suggest a clinical benefit of adjuvant chemotherapy (2, 6). Here, we report a 48-year-old woman with splenic angiosarcoma, who achieved long-term, disease-free survival by high-dose chemotherapy with autologous peripheral blood stem cell transplantation (auto-PBSCT) after splenectomy.

Case Report

A 48-year-old woman was admitted to our hospital in August 2003, complaining of weight loss, general fatigue, and left hypochondrial pain. Physical examination disclosed pale conjunctivae and a palpable mass measuring 12×10 cm at the left upper abdominal quadrant. A complete blood cell count revealed severe anemia (6.2 g/dL) and thrombocytopenia (4.8×10⁴/μL). No abnormality was found on the hemogram in a peripheral blood smear. Although biochemical examination revealed increased total bilirubin (3.5 g/dL) and thrombocytopenia (4.8×10⁴/μL). No abnormality was found on the hemogram in a peripheral blood smear. Although biochemical examination revealed increased total bilirubin (3.5 g/dL), predominantly indirect bilirubin, the serum lactate dehydrogenase concentration was normal (161 IU/L). C-reactive

¹The First Department of Internal Medicine, Gifu University Graduate School of Medicine, Gifu, ²Department of Internal Medicine, Kisogawa Municipal Hospital, Ichinomiya, ³Department of Surgery, Kisogawa Municipal Hospital, Ichinomiya and ⁴Department of Immunopathology, Gifu University Graduate School of Medicine, Gifu

Received for publication May 19, 2010; Accepted for publication July 14, 2010

Correspondence to Dr. Hisashi Tsurumi, htsuru@gifu-u.ac.jp
protein was 0.1 mg/dL, soluble interleukin-2 receptor (sIL-2R) 463 U/mL, β2-microglobulin 1.78 mg/L, carcinoembryonic antigen (CEA) 0.4 ng/mL, and CA19-9 14.0 U/mL. Prothrombin and activated partial thromboplastin times were normal. Bone marrow aspiration was performed, and atypical lymphocytes were not found. Abdominal computed tomography (CT) demonstrated huge splenomegaly and mild hepatomegaly (Fig. 1A). Magnetic resonance imaging of the abdomen identified huge, heterogeneous splenomegaly with abnormal enhancement, which was assumed to be malignant (Fig. 1B). FDG-PET revealed high accumulation in the whole spleen (Fig. 1C). A splenectomy was performed for the purpose of both diagnosis and therapy. Grossly, the spleen measured 15×12×12 cm, weighed 990 g (Fig. 2A), and carried a solid tumor (Fig. 2B). The tumor was composed of spindle cells, and several vascular spaces could be identified that were lined by hyperchromatic tumor cells (Fig. 2C, 2D). The phenotypes of the tumor cells were positive for Factor VIII Rag CD31 and CD34 but negative for CD45RO or CD20. A diagnosis of primary splenic angiosarcoma was made. Severe anemia, thrombocytopenia, and increased total bilirubin were improved after splenectomy. Hence, we assumed that hemolytic anemia and thrombocytopenia resulted from a mechanism, a local consumption, like thrombotic thrombocytopenic purpura in splenic tumor. Adjuvant chemotherapy with three courses of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone), in a manner similar to that used for non-Hodgkin lymphoma, was immediately started. Dose reduction for chemotherapy was not required. Since the prognosis of splenic angiosarcoma is generally very poor, we considered the possibility of high-dose chemotherapy with auto-PBSCT for this patient. The patient preferred to have high-dose chemotherapy with auto-PBSCT and provided her written informed consent. This treatment strategy was approved by our institutional review board as required. Furthermore, the stem cells were harvested by the P-IMVP16/CBDCA regimen (methylprednisolone, ifosfamide, methotrexate, etoposide, and carboplatin) (7). High-dose conditioning chemotherapy consisting of ifosfamide (3 g/m²), etoposide (300 mg/m²), and carboplatin (400 mg/m²) from day -5 to day -3 was started in November 2003. Auto-PBSCT was performed on schedule. The patient had normal hematological recovery and was discharged in December 2003. She was followed as an outpatient and maintained complete remission. However, thrombocytopenia and anemia developed again in November 2008, and CT scan showed a hepatic tumor. A fine-needle biopsy of the liver revealed the first relapse of the angiosarcoma. Hepatic lobectomy was performed, but later abdominal CT revealed multiple nodes suggesting metastases. Despite salvage therapy with radiofrequency ablations and recombinant interleukin-2 (rIL-2) administration, she died from respira-
Figure 2. The surgical specimen shows the spleen measuring 15 × 12 × 12 cm, with a tumor (A, B). The tumor is solid and composed of spindle cells. Several vascular spaces, which are lined by hyperchromatic tumor cells, can be identified. (Hematoxylin and Eosin staining, original magnification, C: × 100, D: × 400)

Discussion

Angiosarcoma is thought to account for 2% of all sarcoma, but primary splenic angiosarcoma is quite rare. The clinical features of splenic angiosarcoma are variable, depending on splenic vascular lesions. The main manifestations of angiosarcoma are abdominal pain (75-83%), anemia (75-81%), thrombocytopenia (14-55%), and weight loss (10-40%) (3, 4, 8). Almost all cases have splenomegaly, and acute abdomen due to splenic rupture is often found (13-32%) (3, 4, 8). The pathogenesis of splenic angiosarcoma is still uncertain. Although reported causes include exposure to ionizing radiation (10) and chemotherapy for lymphoma (5), some authors hypothesized that splenic angiosarcoma developed from previously existing benign counterparts, such as hemangioma or hemangioendothelioma (4, 8). However, the present patient had been well until 2 months prior to hospital admission. Fortunately, she did not develop splenic rupture before splenectomy. Early diagnosis with splenectomy before rupture has a favorable survival rate (3, 4). Montemayor and Caggiano (9) found that patients with splenic angiosarcoma had a longer survival time if splenectomy was performed before rather than after rupture (14.4 vs. 4.4 months).

Splenic angiosarcoma is usually treated with splenectomy (2, 3), the optimal treatment methods have not yet been established. There is no evidence to suggest a clinical benefit of chemotherapy, including adjuvant chemotherapy (2, 6). Neuhauser et al reported a clinicopathologic and immunophenotypic study of 28 cases (8, 9). All patients were treated with splenectomy, with adjuvant chemotherapy used in only a small proportion of patients. Although two adults were alive at last follow-up (1 survived with the disease for 8 years, and 1 was disease-free at 10 years), the remaining 26 patients died with disseminated tumor within 29 months (mean, 11 months; median, 5 months) from initial diagnosis. Thus, splenic angiosarcoma has a very poor prognosis due to its very high frequency of metastasis. The rate of metastasis is reported to be 69-100%. The main metastatic sites are the liver (89%), lung (78%), lymph nodes (56%), and bone (22%).

There is no consensus about chemotherapy for splenic angiosarcoma, and there is no standard regimen for this disease. Zwi et al reported the utility of the same chemotherapy regimen as used for follicular lymphoma (5). Rupolo et al reported a case of splenic angiosarcoma that achieved 10-months survival by chemotherapy with epirubicin and ifosfa-
mide (10). In addition, Casper et al reported the utility of paclitaxel (11). However, the efficacy of conventional chemotherapies is limited. To maintain long-term remission after splenectomy, we performed high-dose chemotherapy followed by auto-PBSCT. To the best of our knowledge, this is the first case report showing the utility of high-dose chemotherapy for primary splenic angiosarcoma. This strategy might have been effective at least in the present study.

On the other hand, the possibility of immunotherapy has been reported. Above all, immunotherapy with rIL-2 is effective for angiosarcoma (12, 13). rIL-2 activates the proliferation of antigen-specific killer cells, resulting in the development of an anti-tumor effect. In addition, IL-2 is an activator of T cells, including lymphokine-activated killer (LAK) cells, which damage vascular endothelial cells. It has been reported that angiosarcoma cells are LAK-sensitive, and that LAK cells suppress tumor growth (14). Indeed, Sasaki et al (15) demonstrated that rIL-2 administration appeared to suppress the development of distant metastases. Rosenberg and Lotze (16) suggested that systemic administration of high doses of rIL-2, in combination with LAK cells, is highly effective. Unfortunately, rIL2 was not effective for the recurrent tumor in the present case. However, immunotherapy with rIL2 appears to be promising in combination with other chemotherapies. Recently, anti-VEGF therapy with bevacizumab, which is a recombinant humanized antibody against VEGF, has been reported to be effective in some case reports (17). VEGF is overexpressed in 80% of angiosarcomas (18, 19). VEGF promotes vascular endothelial growth and induces endothelial migration, promotes cell survival, and increases vascular permeability (20, 21). Anti-VEGF therapies have been reported to suppress growth in many human tumor cell lines (22-24). We think that anti-VEGF therapy with bevacizumab could be a more promising treatment in combination with conventional chemotherapies and immunotherapy.

Conclusion

We reported a 48-year-old woman with splenic angiosarcoma, who achieved long-term, disease-free survival by high-dose chemotherapy with auto-PBSCT after splenectomy. Such treatment strategy might be effective for patients with this type of tumor. In the future, high-dose chemotherapy in combination with immunotherapy or monoclonal antibody therapy seems promising. Further study is warranted to improve our understanding of the appropriate indications of this treatment strategy.

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