Hepatic Follicular Dendritic Cell Sarcoma Favorably Controlled by Transcatheter Arterial Chemoembolization

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Abstract

A 78-year-old woman with multiple tumors in the liver and spleen was diagnosed with follicular dendritic cell (FDC) sarcoma based on the histological picture of splenectomized specimen and its expression of CD21 and CD23. As a paraneoplastic immune disorder, Coombs’ test was positive although hemolysis was not obvious. Since systemic chemotherapies were ineffective for residual liver tumors, transcatheter arterial chemoembolization (TACE) was performed with subsequent tumor reduction. Currently, the patient is alive 27 months after the diagnosis with residual hepatic tumors favorably controlled by repeated TACE. Our experience suggests that TACE is useful for the management of hepatic FDC sarcoma.

Key words: follicular dendritic cell sarcoma, transcatheter arterial chemoembolization, Coombs’ test, Epstein-Barr virus

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Introduction

Follicular dendritic cell (FDC) sarcoma is rare neoplasm and was first described in 1986 by Monda et al in a report of four cases of non-lymphomatous primary lymph node malignancy (1). FDC normally act as antigen-presenting cells for B cells and promote B-cell proliferation and differentiation (2, 3). Approximately 200 cases of FDC sarcoma have been reported to date. FDC sarcoma primarily arises from lymph nodes, while one-third of the cases develop in extra-nodal sites, most frequently in the oral cavity, spleen, liver, small bowel, pancreas, and peritoneum (2). The median age of FDC sarcoma patients is 41.5 years, but it ranges widely from 9 to 82 years old with a slight female predominance (4). The treatment modality has not been well established due to limited experience and the poor response to conventional chemotherapy. Surgical resection followed by radiotherapy seems to be standard for localized disease. For advanced disease, combination chemotherapies that act against both lymphoma and sarcoma have generally been employed; however, the response is generally poor, and thus the optimal treatment regimen has not yet been established (5, 6).

In this report, we present a case of FDC sarcoma of the spleen and liver. After splenectomy, conventional chemotherapies that act against both lymphoma and sarcoma were ineffective for residual liver tumors. However, favorable disease control was achieved by transcatheter arterial chemoembolization (TACE).

Case Report

A 78-year-old woman was referred to our hospital in September 2007 because of multiple tumors in the liver and spleen, which were found in a preoperative examination for total hip arthroplasty. She was asymptomatic and had no superficial lymphadenopathy. In terms of medical history, the patient had malum coxae senile, diabetes mellitus, and hypertension. Laboratory tests showed a white blood cell count of 7.7×10^9/L with normal differential count, a hemoglobin concentration of 9.1 g/dL, a red blood cell count of 277×10^10/L, a hematocrit level of 26.6% and a platelet count of 278×10^9/L. The serum concentration of lactate dehydroge-
nase (LDH) was 230 IU/L (normally 120 to 230) and that of soluble interleukin-2 receptor (sIL-2R) was elevated to 2,760 U/mL (normally 220 to 530). Serum hepatitis B virus antigen and anti-hepatitis C virus antibody were negative. Serum levels of alpha-fetoprotein (AFP) and carcinoembryonic antigen (CEA) were within normal ranges. Both direct and indirect Coombs’ tests were positive and antinuclear autoantibody (ANA) was positive with a titer of ×160. The indirect bilirubin level was slightly increased to 0.9 mg/dL (normally below 0.8). A bone marrow aspirate showed no erythroid hyperplasia and atypical cells with a normal karyotype. Body CT scanning showed a large mass in the enlarged spleen and multiple tumors in the liver, of which the largest measured 2.5×2.7 cm (Fig. 1A, B). Fluorine-18 fluorodeoxyglucose-enhanced positron emission tomography (FDG-PET) also revealed abnormal accumulation in the splenic and hepatic nodular lesions (C).

After splenectomy, blood sIL-2R level decreased to 536 U/mL, whereas hepatic tumors increased from 2 to 3 lesions and enlarged the size, with the largest measuring 3.4×3.6 cm. Furthermore, abdominal ultrasonography revealed 2 additional small tumors in the liver. The patient was serially treated for hepatic tumors with 2 cycles of combination chemotherapy (650 mg/m² gemcitabine on days 1 and 8 and 60 mg/m² docetaxel on day 8), 1 cycle of another combination (1,000 mg/m² gemcitabine on day 1 and 30 mg/m² cisplatin on days 1-3), and 2 cycles of THP-COP (500 mg/m² cyclophosphamide on day 1, 30 mg/m² pirarubicin on day 1, 1.0 mg/m² vincristine on day 1, and 30 mg/m² oral prednisolone.
Since the tumors were multiple and localized in the liver, and blood flow of the tumors were predominantly supplied from the hepatic artery when evaluated by dynamic CT scanning, the treatment was changed to transcatheter arterial chemoembolization (TACE) in March 2008. The angiography showed the tumor stain pattern and ring enhancement in segments 7 and 6, respectively (Fig. 3). In TACE, a mixture of lipiodol and Gelpert (Nippon Kayaku, Japan) containing 30 mg of epirubicin and 4 mg of mitomycin-C was infused. After one week of TACE, CT scanning showed the accumulation of lipiodol in these hepatic tumors. FDG-PET performed three months after the first TACE showed a clear reduction of the size from 3 cm to 1 cm in the largest tumor, and decreased accumulation in the all hepatic tumors (Fig. 4). Consequently, the patient safely underwent total hip arthroplasty in July 2008. Since the size of hepatic tumors was enlarged to the initial level 5 months after the first TACE, this procedure was performed again and was repeated thereafter every 5 months (total five times) with a modest reduction of the size of tumors. The patient is currently alive 27 months after the diagnosis with residual hepatic tumors favorably controlled by repeated TACE.

**Discussion**

The World Health Organization (WHO) classified den-
dritic cell neoplasms into five groups: Langerhans’ cell histiocyotosis, Langerhans’ cell sarcoma/tumor (LCS/T), interdigitating dendritic cell sarcoma/tumor (IDCS/T), follicular dendritic cell (FDC) sarcoma/tumor, and dendritic cell sarcoma (7). Typical histological characteristics of FDC sarcoma is the proliferation of spindle-like or ovoid cells forming whorled, storiform, or fascicular pattern. Often there is sparse infiltrate of mature lymphocytes and plasma cells, predominantly with perivascular distribution. The neoplastic cells in FDC sarcoma generally demonstrate the immunophenotype of non-neoplastic FDC and are positive for the follicular dendritic cell markers, CD21 and CD23, but negative for S100, CD1a, CD20, and CD34. On the other hand, IDCS/T cells show consistent expression of S100, lacking the expression of CD1a, CD21 and CD35. LCS cells are positive for both CD1a and S100, but negative for CD21 and CD23 (2, 6). The splenic tumor in the present patient was compatible with FDC sarcoma in terms of both histological picture and surface phenotype.

FDC sarcoma has been considered as an indolent tumor; however, recent reports have shown that this neoplasm is more aggressive and should be considered as an intermediate-grade malignancy. The overall rates of recurrence, metastasis, and mortality are 43%, 24%, and 17%, respectively (8). A review of extranodal FDC sarcoma cases that have been reported in the literature showed that the rate of 5-year recurrence-free survival was only 27.4% and that an intra-abdominal location is associated with an aggressive clinical course (4).

The therapeutic modality for FDC sarcoma is varied. The majority of patients have been treated with surgical resection, radiotherapy, chemotherapy, or a combination of these treatments (9). The combination chemotherapies that have been most commonly employed are CHOP or CHOP-like regimens that are effective for non-Hodgkin’s lymphomas (2, 5). Soriano et al reported that 4 of 8 patients treated with CHOP regimen achieved a complete response, although all 4 of these patients subsequently relapsed (5). The relapsed and CHOP-resistant patients were treated with regimens that act against sarcomas, which included gemcitabine and taxane, as a salvage therapy, and they showed an objective response (5). In addition, Azim et al reported that a patient with c-kit-positive FDC sarcoma involving the liver and the lung was successfully treated with a combination of gemcitabine and imatinib, a tyrosine kinase inhibitor (10). EGFR is also a possible therapeutic target in the treatment of FDC sarcoma. Sun et al reported that EGFR was expressed in FDC sarcoma but not in FDC, the normal counterpart of FDC sarcoma, which resides in reactive lymph nodes or in several types of malignant lymphoma, forming the FDC networks (11). The expressions of c-kit and EGFR were examined in the present case, but both were negative in tumor cells. However, currently, it is difficult to find an alternative treatment modality because of the very small number of patients with advanced FDC sarcoma. Further experience is needed to identify active chemotherapeutic agents for the treatment of FDC sarcoma.

TACE is a local therapeutic option for unresectable intrahepatic tumors. This treatment can selectively deliver chemotherapeutic agents to target tumors and may be combined with vascular embolization of the tumor, exerting selective ischemic and chemotherapeutic effects on hepatic tumors with reduced systemic toxicity by chemotherapeutic agents (12). Mitomycin-C and epirubicin are dose-dependent agents with broad-spectrum anti-cancer effects. TACE with these agents has been employed for unresectable hepatocellular carcinoma and metastatic liver tumors. To the best of our knowledge, this is the first report of hepatic FDC sarcoma treated with TACE. Kang et al described that the imaging findings of FDC sarcoma of the abdomen manifested as a well-enhancing homogenous mass with internal necrosis (13). In the present patient, hepatic tumor was mostly hypervascular but it was hypovascular in some portion. This hypovascular lesion may have reflected the internal necrosis. From this experience, TACE may be a useful strategy of management for FDC sarcoma of the liver and should be taken into consideration when intrahepatic FDC sarcoma is refractory to chemotherapies effective for both lymphoma and sarcoma.

It has been reported that FDC sarcoma is associated with paraneoplastic pemphigus that is considered to be an autoimmune disease (14). Autoimmune disease might manifest itself in the process of certain immune regulation by FDC sarcoma cells, possibly through the presentation of antigen

Figure 4. FDG-PET showed abnormal accumulation in the liver tumors (A). FDG-PET performed 3 months after TACE showed that the abnormal accumulation was reduced with a clear decrease in the size of tumors (B).
to B cells and subsequent B-cell activation, because the normal counterpart of FDC sarcoma performs this immune regulation. In the present patient, Coombs’ tests were positive as a paraneoplastic immune disorder, although hemolysis was not obvious.

Although the pathogenesis of FDC sarcoma is not well understood, there have been some interesting observations. It is known that FDC sarcoma expresses EBV receptor CD21 and that most hepatic and some splenic FDC sarcomas have been associated with EBV infection and EBER was positive in these cases (4, 15, 16). On the other hand, EBV is negative in nodal and most extranodal FDC sarcomas other than hepatosplenic sarcomas. This finding suggests a pathogenetic difference between hepatosplenic FDC sarcomas and other types of FDC sarcomas. From this point of view, EBV appears to play an important role in the pathogenesis of hepatosplenic FDC sarcomas including the present case that showed a positive EBER test in the tumor cells and an EBV reactivation pattern in the serum antibody examination. Nevertheless, the profiles of serum EBV-specific antibodies have not been described in patients with EBV-associated FDC sarcoma. Therefore, to confirm the pathogenic role of EBV in FDC sarcomas, precise studies on EBV infection using both pathological techniques including in situ hybridization and serological methods are needed in forthcoming cases.

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References