Follicular Dendritic Cell Sarcoma: Ultrastructural and Immunohistochemical Studies


Abstract

A rare case of follicular dendritic cell (FDC) sarcoma is reported. A 71-year-old woman was admitted for evaluation of constipation. Computerized tomography showed cervical, supraclavicular, retroperitoneal, and paraaortic lymphadenopathies. Histological findings from a cervical lymph node revealed Hodgkin's disease at first. But tumors that arose both in the cervical and the left interscapular regions during the chemotherapy were immunohistochemically confirmed to be of follicular dendritic cell origin. The ultrastructural findings were consistent with those of FDC sarcoma. FDC sarcoma is a rare nonlymphoid cell-derived malignant tumor originating from the lymphoid tissue. The diagnosis of FDC sarcoma is most accurately established by immunohistochemical methods, using its specific markers.

Key words: lymphadenopathy, FDC tumor, reticulum cell tumor, lymphoma, lymphoproliferative disorder

Introduction

The dendritic cells (DC) are nonlymphoid antigen-presenting cells (APC) (1–3). Follicular dendritic cells (FDC) are one of DC which are in the lymphoid follicle associated with B lymphocytes, and function as antigen-presenting cells (1–3). The FDC can be recognized histologically by their oval to triangular nucleus, delicate violaceous nuclear membrane, almost empty nucleoplasm, small but distinct central nucleolus, and indistinct cellular outline; some cells can be binucleated or multinucleated (1–3). Ultrastructurally, they possess delicate interwoven cell processes connected by desmosomes. Immunohistochemically, they can be highlighted by staining with CD21, CD35, R4/23, Ki-M4, CNA.42, CD68 (Kp-1), and/or EMA (1–4).

FDC tumor/sarcoma is rare. To date there are few reports of FDC sarcoma, but in fact there probably are many FDC sarcoma cases that are diagnosed as other diseases such as large cell lymphoma. Here, we report such a case and review this rare disorder based on the previous reports.

Case Report

A 71-year-old woman patient noted intermittent constipation. About two weeks before admission constipation became worse. One week before admission she presented nausea and abdominal distension, and vomited occasionally. Because these symptoms continued, she entered our hospital on August 13, 1996 for the evaluation of constipation.

Her past medical history was cholecystectomy due to cholelithiasis 5 years before admission. At that time there was no lymphadenopathy on abdominal computed tomography (CT). She never smoked, drank, and took any kind of drugs. On physical examination, body temperature was 37.0°C. Blood pressure was 123/76 mmHg and heart rate was 96/min. One elastic hard lymph node was palpable without tenderness in the right neck and two in the left neck. There was no lymphadenopathy in the axillar or inguinal region. The abdomen was distended and soft. No fluctuation was detected. The liver and spleen were not palpable. But there was a slightly hard mass in the umbilical region. The lung was clear to percussion and auscultation. Laboratory data are summarized in Table 1. A complete blood count showed leukocytosis (11,900/µl) with monocytosis (17.4%), mild anemia (hemoglobin 11.6 g/dl, hematocrit 33.6%), and thrombocytopenia (106,000/µl). Blood chemistry showed a mild to moderate increase in alkaline phosphatase (456 IU/l) and serum transaminase (AST 44 IU/l, ALT 32 IU/l). An immunoserological examination showed an elevation of C reactive protein (15.4 mg/dl). Viral markers for HTLV-I, hepatitis B virus, and hepatitis C virus were negative. Chest and abdominal X-rays showed no abnormal findings. Electrocardiogram was normal. Abdominal ultrasound and CT

From the Department of Internal Medicine, Fukuoka Tokusyuukai Hospital, Fukuoka, *the Department of Hematopoietic, Kyusyu-Gan Center, Fukuoka and **the Department of 1st Pathology, Fukuoka University School of Medicine, Fukuoka

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Reprint requests should be addressed to Dr. Kentaro Toyoda, the Department of Internal Medicine, Fukuoka Tokusyuukai Hospital, 4-22, Sukukita, Kasuga-shi, Fukuoka 816-0864
scan revealed marked paraaortic lymphadenopathy (Fig. 1A). Upper gastrointestinal and colonic fiberoscopic studies showed no abnormality. Gallium scintigraphy disclosed abnormal uptake in the left supraclavicular region, mediastinum, and umbilical region (Fig. 1B). Bone marrow aspiration revealed hypercellular bone marrow. No abnormality in lymphoid cells was found and maturation of hematopoietic cells were reserved, but morphologic abnormalities in trilineage hematopoietic cells were noted. Urinalysis was not abnormal.

After admission, constipation improved spontaneously, but a high fever developed. She experienced daily periodic attacks of high fever with afebrile and asymptomatic intervals between. There were no symptoms or physical findings which let us suspect infection. On the 9th hospital day, left cervical lymph node biopsy was performed.

Biopsy specimen showed diffuse proliferation of suggestive reticulum cells with spindle nuclei and some scattered Reed-Sternberg (RS) like cells and picknotic giant cells. Mitotic features were rare in number. Lymphocytic cells were decreased in number (Fig. 2). Giant cells showed positive stain-
Figure 3. Magnetic resonance imaging (MRI) of the back mass shows the tumor within the muscle layer (A). The sagittal T1-weighted scan reveals a low signal tumor, whereas the sagittal T2-weighted scan exhibits a high signal tumor (B). The axial T1-weighted scan with contrast shows enhancement of the outer side of the tumor.

Table 2. Immunohistochemical Findings of the Cervical Lymph Node and the Back Tumor

<table>
<thead>
<tr>
<th>Cervical LN</th>
<th>Back tumor</th>
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<tbody>
<tr>
<td></td>
<td>G* R**</td>
</tr>
<tr>
<td>CD2 (T11)</td>
<td>– –</td>
</tr>
<tr>
<td>CD3 (Leu4)</td>
<td>– –</td>
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<tr>
<td>CD4 (OKT 4)</td>
<td>– +</td>
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<tr>
<td>CD5 (Leu1)</td>
<td>– –</td>
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<tr>
<td>CD8 (OKT 8)</td>
<td>– –</td>
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<tr>
<td>CD15 (LeuM1)</td>
<td>+ –</td>
</tr>
<tr>
<td>CD19 (B4)</td>
<td>– –</td>
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<tr>
<td>CD20 (B1)</td>
<td>– –</td>
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<tr>
<td>CD21</td>
<td>± ±</td>
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<tr>
<td>CD25 (Tac)</td>
<td>+ +</td>
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<tr>
<td>CD30 (Ki-1)</td>
<td>+ –</td>
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<tr>
<td>Ki-67</td>
<td>+ +</td>
</tr>
<tr>
<td>CD35 (BerMacDRC)</td>
<td>– +</td>
</tr>
<tr>
<td>CD68 (KP-1)</td>
<td>– +</td>
</tr>
<tr>
<td>S-100</td>
<td>– –</td>
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<tr>
<td>NSE</td>
<td>– –</td>
</tr>
<tr>
<td>C45RO (UCHL-1)</td>
<td>– –</td>
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*GIant cells, **Reticulum cells, ***+/-: Weakly or scattered positive.

FDC is one type of DC. DC are nonlymphoid antigen-presenting cells (APC) distributed widely throughout the body. There are two major hypotheses in the cellular origin of DC: (I) bone marrow-derived and (II) stromal cell-derived theories (1, 5, 6). DC are classified into two groups: B- and T-cell associated DC. The former is identical to FDC. FDC are mainly restricted to the primary follicles and germinal centers of the secondary lymphoid tissue, where FDC are in close association with B lymphocytes with its dendritic processes. FDC func-
FDC Tumor/Sarcoma

...tion as follows: (I) supporting the construction of lymph nodes, (II) immune complex trapping and retention, (III) antigen presentation, and (IV) activation of B cell proliferation (1-5).

FDC sarcoma is the tumor of FDC. Since the first report of FDC sarcoma in 1978, only about 51 cases of FDC sarcoma have been described in the English-language literature (3). In Japan there are only 3 case reports from 1996 (7). FDC sarcoma is very rare, because the identification of FDC sarcoma has remained unknown until recently. In fact, there probably are more cases than the reported number of cases (1, 5, 7, 8-13). FDC sarcoma occurs mostly in adults and from many studies the mean age of this disease onset is about 45 years old ranging from the 20s to 70s. The present case did develop rather in her advanced age. There seems to be no difference between sex (1, 3, 5, 6, 8, 9, 14).

Similar to the present case, the most common clinical presentation is lymph node enlargement (about 60%) and the tumor frequently occurs in extranodal lymphoid tissues, such as the mediastinum, spleen, liver, small intestine (mucosal associated lymphoid tissues), and tonsils (7, 10-12, 14-16). The present case showed mild liver damage with an elevation of alkaline phosphatase; the subsequent improvement after chemotherapy indicate the possibility of liver invasion.

The microscopic appearance of FDC sarcoma shows that the sarcoma cells are composed of oval to spindle cells grown in whorls, fascicles, sheets, and sometimes a storiform pattern, as seen in the present case. The neoplastic cells are intimately admixed with small lymphocytes, which show a prominent perivascular cuffing (10-12, 17).

On electron microscopy, FDC sarcoma cells are almost the same as normal FDC. The tumor cells have few organelles, numerous mitochondria, and cytoplasmic processes which carry electron-dense deposits, and these processes are joined by scattered mature desmosomes. Tonofilaments, myofilaments, and basement membranes are not identified (Fig. 4), and small foci of lymphocytes and plasma cells are found throughout the tumor cells, as observed the present case (3, 11, 12, 14).

Diagnosis, however, is made by immunohistochemical analysis of the biopsy specimen. FDC sarcoma cells have immunohistochemical characteristics the same as and different from normal FDC. The CD21 (C3d receptor) and CD35 (C3b receptor) are the most widely used FDC markers. Other FDC specific markers such as R4/23, KiM4, KiM4p, and KiFDC1p can also be used, in addition to Ki-67 and Kp-1 (CD68). CD4, CD19, CD45 (common leukocyte antigens), CNA.42. Desmoplakin (desmosome-associated protein) is positive in more than 50% cases of FDC sarcoma. Epithelial membrane antigen (EMA) is positive in more than 85% of cases of FDC sarcoma.

Figure 4. Back tumor biopsy specimen: HE stain shows diffuse proliferation of large and medium-sized lymphoid cells in the fascicular arrangement. Large lymphoid cells possess irregular and vesicular nuclei with distinct nucleoli and amphophilic cytoplasm. Medium-sized lymphoid cells have irregular nuclei with inconspicuous nucleoli. Mitosis is occasionally encountered \( \times 200 \) (A), \( \times 400 \) (B). Immunohistochemical staining of reticulum cells with CD35 (C), CD68 (D), CD4, CD25, are positive. Those of CD5, CD8, CD20, S-100 (E) are negative. That of KI-67 (F) is positive.
sarcoma. Occasionally weak expression of S-100 protein is positive. Some studies showed the presence of myosin, actin, and vimentin. In the present case, the tumor cells showed the positive FDC-specific marker staining of CD35, CD21, Ki-67, Kp-1, CD4 (Leu3), and CD25 indicating the origin of FDC. CAN.42, Desmoplakin and EMA staining were not performed. S-100 was negative in staining (3, 6, 7, 10–18).

EB virus (EBV) has been found to be present in malignant cells, especially in lymphoproliferative disorders. From many studies EBV can infect and transform resting human B lymphocytes. EBV does not appear to play a significant etiologic role in the usual form of FDC sarcoma. By in situ hybridization for EBV RNA sequences many studies have shown that FDC sarcoma cells are negative (3, 6, 10–15, 17). But in the present case giant cells were positive for latent membrane protein of EBV (EBV-LMP) and in-situ hybridization of EBV (ISH-EBV). Giant cells can be the tumor cell that EBV infected and produced a large size with transformation (Fig. 3).

Some literature reported cases of FDC tumor are complicated with hyaline-vascular Castleman’s disease. It is characterized histologically by the presence of structurally abnormal lymphoid follicles, where FDC is present and some dysplastic FDC may transform to neoplastic tumor (8–10, 16).

The differential diagnosis of FDC tumor includes ectopic meningeoma, ectopic or orthotopic thymoma, carcinoma, malignant melanoma, malignant fibrous histiocytooma, large cell lymphoma, and another uncommon dendritic cell tumor (interdiginating cell sarcoma). Immunoreactivities for CD21, CD35, Ki-M4p, and KiFDC1p are negative for all of these tumors. The ultrastructural profiles are substantially different from those of FDC tumor (3, 8–11, 16).

Complete excision, if feasible, is the most common treatment for both primary and recurrent FDC sarcoma. Current study has shown that intraabdominal tumors are invariably aggressive (3, 8–13). Therefore, with aggressive cases like the present patient, intraabdominal tumors require adjuvant chemotherapy. Whether adjuvant therapy is necessary for tumors occurring outside the abdominal cavity remains to be proven. The role of radiotherapy is unclear, but might be of some benefit for residual or locally recurrent tumors (9–13).

The natural history of FDC sarcoma is variable and often difficult to predict. FDC sarcoma has traditionally been viewed as an indolent tumor with a substantial risk of metastases (more common sites are the lung, liver, peritoneum, and another lymph node). Now, FDC sarcoma should be considered to be at least of intermediate grade malignancy (4, 6, 7, 14). Although cure can be achieved in about 60% of cases, the tumor is sometimes highly aggressive, causing death within 2 years. The present case showed progressive lymphadenopathy associated with the recurrence by systemic metastasis during chemotherapy, indicating that this case was a very aggressive type. One reason for this aggressiveness is considered due to the long duration of the FDC sarcoma, resulting in multiple metastases and invasion.

In conclusion, FDC sarcoma is a rare disorder of nonlymphoid malignant tumor. The diagnosis is made by biopsy specimen that shows positive staining for CD21, CD35, R4/23, KiM4, KiM4p, KiFDC1p, Ki-67, CD68 (Kp-1), CAN.42, CD4, CD19, CD45, and EMA, and also desmoplakin and S-100. By using the specific immunohistochemical staining pattern for FDC sarcoma, more cases are expected to be recognized in the future. The electron microscopic findings are suggestive of the diagnosis of FDC sarcoma, but not confirmative.

Such cases will provide not only further characteristics of clinical behaviors, but also contribute to the etiological understanding of the tumor for development of new diagnostic procedures and effective therapies.
Figure 6. Electron microscopic finding of the back tumor shows fine clumped and well marginated chromatin in the irregular nuclei, well developed rough endoplasmic reticulum in the cytoplasm and well developed thin cytoplasmic processes (like labyrinth structure). These findings are consistent with that of follicular dendritic cell. Desmosome-like structures were not clearly identified (x10,000).

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