Role of Adjuvant Chemotherapy in Extranodal Follicular Dendritic Cell Sarcoma

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ABSTRACT

Extranodal follicular dendritic cell sarcomas (FDCSs) are an uncommon entity, commonly misdiagnosed because of the morphologic similarities with other neoplasias. Previously, FDCSs were not considered a differential diagnosis because of the limited use of immunohistochemistry. Surgical excision is the treatment of choice for localized FDCS. The role of chemotherapy has not been determined for this rare disease. We report 2 cases of metastatic extranodal intra-abdominal FDCS, initially misdiagnosed as gastrointestinal stromal tumor, their clinicopathological features, literature review, and the role of adjuvant chemotherapy.

INTRODUCTION

Extranodal follicular dendritic cell sarcomas (FDCSs) are a rare entity, first reported in 1994 in head and neck cases.¹ Extranodal FDCSs are commonly underreported, as the immunohistochemistry (IHC) markers for FDCSs are not included among the routine antibody panel used for the investigation of poorly differentiated neoplasms.²

CASE REPORT

Patient 1: A 28-year-old man presented in 2013 with a history of surgery done elsewhere for a mesenteric mass in 2011. Histopathology of that mass was reported as gastrointestinal stromal tumor (GIST) based only on microscopic findings, and accordingly, he was started on imatinib 400 mg for 2 years. In 2013, he was detected to have a local recurrence and underwent right hemicolectomy at another center, which was again reported as GIST. However, review of the pathology report at our center showed negative IHC results for C-kit (CD117) and DOG-1, ruling out the diagnosis of GIST. Subsequent IHC revealed CD21 and CD23 positivity, suggestive of FDCS.

The patient completed 6 cycles of adjuvant gemcitabine and docetaxel in January 2014. In May 2017, follow-up computed tomography (CT) reported a solitary metastatic segment VII liver lesion. In view of disease-free interval of 40 months, the patient underwent nonanatomical resection of the liver lesion, which was consistent with metastatic FDCS with clear margins based on IHC markers. In the multidisciplinary meeting, it was decided to keep the patient under observation only (Figure 1).

Patient 2: A 63-year-old man presented in February 2013 with abdominal pain. The patient had similar complaints 1 year prior in September 2012, for which he was evaluated with CT, which showed a 12 × 9 cm retroperitoneal mass involving the second part of the duodenum, the lower pole of the right kidney, and the psoas muscle. Biopsy was reported as...
lymphoplasmacytic inflammatory cells with interspersed spindle-shaped cells. Because GIST is the most common differential diagnosis of retroperitoneal tumor with spindle cells on microscopy, the patient was started on imatinib 400 mg based on a presumed diagnosis of malignant GIST. However, after 2 months of imatinib, the patient had no improvement, and repeat CT showed radiological progression with right hydronephrosis. Therefore, repeat biopsy of the mass was performed, which was suggestive of FDCS based on histomorphologic features and expression of IHC marker CD23. The mass was deemed unresectable upfront, in a multidisciplinary meeting, and decision was taken to administer neoadjuvant radiotherapy. The patient received external beam radiotherapy of 50.4 Gy/28# over 28 days. Response assessment CT showed marginal regression of an exophytic mass. The patient underwent surgery entailing excision of the retroperitoneal mass with right hemicolectomy, right nephrectomy, and pancreas-preserving duodenectomy. Final histopathology was consistent with FDCS with clear margins based on IHC markers. The patient completed 6 cycles of adjuvant gemcitabine and docetaxel. In June 2017, follow-up abdominal ultrasonography showed a suspicious hypoechoic segment III liver lesion measuring 3.9 × 3 cm. The patient underwent positron emission tomography–contrast-enhanced CT (Figure 2), which showed uptake in liver segment III and ruled out extrahepatic disease. In view of a good disease-free interval of 48 months, the patient underwent left lateral hepatectomy, which showed metastatic FDCS with clear margins. Diagnosis of FDCS was based on histomorphologic features (Figure 3) and expression of IHC marker CD23 (Figure 3). Further adjuvant chemotherapy (gemcitabine and docetaxel) was planned but discontinued in view of drug toxicity. At the time of the final follow-up, both patients were free from any recurrence.

DISCUSSION

FDCS is an exceedingly rare neoplasm with very few cases reported in the literature. FDCSs are described as abnormal proliferation of accessory cells in the lymphatic system having low malignant potential.3,4 FDCS most commonly involves cervical nodes. However, one-third of cases are extranodal in origin, mainly involving the head and neck sites, gastrointestinal tract, soft tissue, and mediastinum.4,15 Extranodal intra-abdominal FDCS is an extremely rare entity, involving the liver and spleen, and it is rarer with tumors of the gastrointestinal tract and mesentery/omentum.5,6 FDCS typically affects middle-aged adults with no sex predilection. The most common clinical presentation is that of a painless, slow growing swelling.4 Imaging can be an initial tool for diagnosis and staging. Smaller homogeneous masses are usually seen on CT scan; however, heterogeneity as a result of necrosis or hemorrhagic areas have been reported in 80% of cases.7 Grossly, FDCSs are well-circumscribed pink or tan-gray nodular to bossed solid masses with size ranging from 1 to 20 cm. Intra-abdominal tumors can measure up to 20 cm.8 Pathological diagnosis cannot be based solely on morphological grounds but must be confirmed by IHC and preferably supported by ultrastructural studies. Most widely used FDCS markers are CD21, CD23, CD35, and D2-40 (podoplanin), which can distinguish FDCS from other spindle-cell neoplasms.1,9–11 FDCSs have been regarded as low-grade indolent malignant neoplasms with local recurrences and low risk of metastasis, behaving like a low-grade soft-tissue sarcoma. Extrahepatic abdominal/pelvic lesions showed high recurrence and also higher mortality rates.12 Chan et al13 considered FDCS to be of intermediate grade with a substantial risk of metastasis.
to the lung, liver, peritoneum, and lymph node and also showed a higher recurrence rate in intra-abdominal locations. However, Perez-Ordonez et al8 considered FDCS to be more aggressive.

FDCS can often be misdiagnosed. There are reports of 30% to 58% misdiagnosed cases, especially when arising from extranodal sites. FDCS arising in the gastrointestinal tract commonly may be mistaken for kit-negative GIST, but dense lymphocytic infiltrates are uncommon in GIST; GIST is also negative for CD21 and CD35, whereas FDCS is negative for CD34 and DOG-1 (Table 1).10,14 Two most reliable IHC markers are CD21 and CD23, which have led to improve the accuracy of this rare entity underlying the importance of IHC in diagnosis. Recently, 2 novel, highly sensitive and specific markers for FDCS, follicular dendritic cell–secreted protein and serglycin, have been identified.15

Figure 3. Photomicrographs showing (A) tumor cells in sheets and focal nodular arrangement infiltrating liver parenchyma. Residual portal tracts with bile ductular structures can be seen (H&E ×100). (B) High-power view shows sheets of cells with abundant eosinophilic cytoplasm, indistinct cell membranes, and vesicular nucleus with distinct to prominent nucleolus. Interspersed lymphoid cells are noted (H&E, ×400). (C) Immunohistochemistry was positive for CD23 (×200).

Table 1. Differential Diagnosis of FDCS Based on IHC Markers

| Pathology Characteristics | FDCS | GIST | MPNST | Leiomyosarcoma | Inflammatory Myofibroblastic Cell Tumor |
|---------------------------|------|------|-------|----------------|--------------------------------------|
| Microscopic               |      |      |       |                |                                      |
| Spindle to ovoid cells    |      |      |       |                |                                      |
| arranged in fascicles,   |      |      |       |                |                                      |
| storiform pattern         |      |      |       |                |                                      |
| Spindle cells arranged    |      |      |       |                |                                      |
| in whorls and fascicles   |      |      |       |                |                                      |
| with stromal hyalinization|      |      |       |                |                                      |
| Spindle cells arranged    |      |      |       |                |                                      |
| in fascicles and          |      |      |       |                |                                      |
| whorls with               |      |      |       |                |                                      |
| mitotic figures           |      |      |       |                |                                      |
| Spindle cells with        |      |      |       |                |                                      |
| cigar-shaped nuclei       |      |      |       |                |                                      |
| arranged in long and      |      |      |       |                |                                      |
| short intersecting fascicles. |    |      |       |                |                                      |
| Necrosis is usually seen. |      |      |       |                |                                      |
| Mitotic activity is high. |      |      |       |                |                                      |
| Spindle cells arranged    |      |      |       |                |                                      |
| in fascicles and          |      |      |       |                |                                      |
| whorls with               |      |      |       |                |                                      |
| abundant plasma cells,    |      |      |       |                |                                      |
| lymphocytes, and          |      |      |       |                |                                      |
| eosinophils               |      |      |       |                |                                      |

| IHC |      |      |       |                |                                      |
| CD21|    + |      |       |                |                                      |
| CD23|    + |      |       |                |                                      |
| D2-40|  + |      |       |                |                                      |
| CD117(C-kit)|  + |      |       |                |                                      |
| DOG-1|  + |      |       |                |                                      |
| S100p| ± |      |       |                |                                      |
| SMA | ± |      |       |                |                                      |
| Desmin| ± |      |       |                |                                      |
| H-Caldesmon|  + |      |       |                |                                      |
| ALK | ± |      |       |                |                                      |

ALK1, anaplastic lymphoma kinase; DOG-1, discovered on gastrointestinal stromal tumours protein 1; FDCS, follicular dendritic cell sarcoma; GIST, gastrointestinal stromal tumor; IHC, immunohistochemistry; MPNST, malignant peripheral nerve sheath tumor; SMA, smooth muscle actin.
prognosis. Surgical excision is the treatment of choice for localized FDCS.\textsuperscript{6,10,15,17} Chemotherapy is indicated for patients with unresectable disease or multiorgan involvement.\textsuperscript{5,6,17–20} Conry published a case series of 2 patients in which combination chemotherapy with gemcitabine and docetaxel was tried for the first time in metastatic FDCS with good response rates.\textsuperscript{19} Response of FDCS to this commonly used sarcoma regimen supports the mesenchymal nature of this malignancy and suggests a role for other agents such as pazopanib approved for soft-tissue sarcoma therapy.

**DISCLOSURES**

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