Follicular Dendritic Cell Sarcoma or Not? A Series of 5 Diagnostically Challenging Cases

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ABSTRACT: Imperfect or unusual presentation, morphology, or immunophenotype can make the diagnosis of follicular dendritic cell sarcoma (FDCS) very challenging. To illustrate this, we present 5 unique cases from the archives of our tertiary care academic medical center that presented a diagnostic challenge wherein FDCS was the top differential diagnostic possibility. The workup of these cases, including multiple expert consultations, highlights the importance of avoiding specific pitfalls in the diagnosis of FDCS.

KEYWORDS: FDCS, follicular dendritic cell sarcoma, pitfalls in diagnosis, review, tumors of the accessory immune system

Introduction

Follicular dendritic cell sarcoma (FDCS) is a neoplasm of cells that demonstrate the morphologic and immunophenotypic features of follicular dendritic cells (FDCs).1 Confirming the cell of origin for these rare tumors can sometimes create diagnostic difficulties for surgical pathologists and hematopathologists alike. The plasticity of FDCs and the ubiquity of lymphoid tissue throughout the body can render the differential diagnosis broad and complicated.2 FDCS can occur at any age; however, it typically presents in adults and demonstrates no sex predilection. Most of the patients present with isolated adenopathy, but extranodal disease can also occur. These masses tend to grow slowly, are usually painless, and typically devoid of systemic symptoms (sans the inflammatory pseudotumor-like variant). Microscopically, typical cases of FDCS are composed of spindled to ovoid cells that demonstrate a range of architectural features such as fascicle formation, storiform arrays, whorls, diffuse sheets, and even vague nodules (Figure 1). The sarcoma cells can be oval or elongated and usually demonstrate finely dispersed chromatin, small but distinct nucleoli, and a delicate nuclear membrane. Multinucleated (giant) tumor cells can often be seen. Sarcoma cells can have varying degrees of cytologic atypia and mitotic activity. Immunophenotyping typically reveals the lesional cells to express markers of FDC origin such as CD21, CD23, CD35, CXCL13, and clusterin, as well as desmoplakin, vimentin, fascin, epidermal growth factor receptor (EGFR) and HLA-DR. Follicular dendritic cell sarcoma usually demonstrates variable positivity for EMA and only rarely other cytokeratins. There is variable immunoreactivity for S-100, CD68, and only rarely positivity for the B-cell marker CD20 and leukocyte common antigen, CD45. Stains for other hematopoietic (myeloid, lymphoid, monocytic, immaturity, etc.) markers including lysozyme, myeloperoxidase, CD34, CD3, CD79a, CD30, CD1a, and HMB-45 are negative. The Ki-67 proliferation fraction can be variable, but is usually less than 30%. On ultrastructural examination, the neoplastic cells display long processes connected by scattered desmosomes, devoid of Birbeck granules, a very important diagnostic feature. The clinical course of usual FDCS is variable, with some patients achieving complete remission after surgery and others with persistent disease after adjuvant therapy.

Case 1

The first case is of a 29-year-old woman who was evaluated for recalcitrant hypertension of unknown cause. A 2.3-cm solid right renal mass was discovered by ultrasound and a partial nephrectomy was performed. The tumor was well-circumscribed and composed of mainly spindled cells with vesicular cytoplasm and focally round cells with eosinophilic cytoplasm (Figure 2A). The lesion demonstrated variable cytologic atypia without necrosis and prominent vasculature (Figure 2B). Morphologically, FDCS was one of the top considerations. Given the patient’s age and this morphologic presentation, a broad differential diagnosis was entertained, which included Ewing Sarcoma/PNET, Wilm tumor, sarcoma NO, sarcomatoid carcinoma, melanoma, and hematopoietic malignancy. A panel of immunohistochemical markers revealed tumor cell immunopositivity for the FDC marker CXCL13 and clusterin, supporting FDCS; however, staining for CD21 and CD23 was negative. Additional immunohistochemistry demonstrated positivity for CD34, Bcl-2, vimentin, renin, CD117, and SMA (focal). The neoplastic cells were negative for CD31, CD99, HBM-45, Melan A, S-100, and pancytokeratin (Table 1). Although the differential diagnosis was narrowed significantly; a final diagnosis was difficult to. For expert opinion on the case, material was sent to 2 other academic institutions in North America. Based on the morphology and clusterin positivity, 1 expert favored a diagnosis of FDCS. However, interestingly, the second consulting institution performed electron microscopy (EM) and immunohistochemical staining for renin. The

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immunohistochemical results for renin were positive. A final diagnosis of juxtaglomerular cell tumor (JCT) was subsequently favored.

In this case, the clinical history heavily favored a diagnosis of JCT; however, the tumor cells were mostly spindled with a brisk lymphocytic infiltrate, which is not typical for this very rare neoplasm. Furthermore, the tumor cells were positive for clusterin and CXCL13, which along with the morphology would favor a diagnosis of FDCS. Clusterin is a highly conserved glycoprotein with a broad range of functions, which, in many studies, has been shown to distinguish FDCS from other dendritic cell neoplasms. CXCL13 is a chemokine that is responsible for the generation of germinal centers. Mainly produced by FDCs, CXCL13 has also been used as a marker to differentiate FDCS from other neoplasms. However, as this case proves, immunostaining for clusterin and CXCL3 is not specific, and the clinical history, renin positivity, and EM findings were most consistent with JCT (Figure 2C). The patient recovered promptly after surgery with resolution of her hypertension.

JCTs are very rare, benign tumors of the kidney that usually present in young adults as a cause of secondary hypertension and are more common in women. Grossly, they are well-circumscribed tumors within the renal parenchyma with a yellow/tan and firm cut surface. They are composed of round to oval cells with abundant eosinophilic cytoplasm. The key diagnostic finding is the ultrastructural discovery of renin granules in the cytoplasm. This case illustrates how both morphologically and by phenotyping (CXCL13 and clusterin positivity) this rare tumor could be a potential pitfall in the diagnosis of FDCS.

Case 2
The second case is of a 41-year-old man with an enlarging, painless, left-sided neck mass. Imaging revealed a 4-cm enhancing, solid mass associated with multiple enlarged lymph nodes. A left neck dissection specimen revealed a solid, white-tan, focally hemorrhagic, well-circumscribed mass with a necrotic center. Microscopically, the mass was composed of pleomorphic cells ranging in shape from spindled to round cells, some of which had prominent nucleoli and binucleation (Figure 3A). There was a prominent inflammatory background composed mainly of small lymphocytes and focal areas of necrosis (Figure 3B). Thirty-nine lymph nodes were additionally dissected, none of which were involved by tumor. Immunophenotypically, the tumor cells revealed positivity for vimentin, CD68, caldesmon (focal), and AE1/AE3 (focal). They were negative for CD21, CD23, CD30, CD31, CD34, CD45, CD99, CD1a, CD5, PAX5, ALK-1, MUM1, BCL-2, lysozyme, Ulex, Factor VIII, S-100, HBM-45, Cam 5.2, Mart-1, CK34BE12, SMA, CD20, and myogenin (Table 1). Given the age of the patient, the bizarre morphology of the cells, and the absence of a clear suitable primary origin for a carcinoma, the differential was broad and all-encompassing.
Table 1. Immunophenotype of the 5 cases.

| FDCS MORPHOLOGY | CASE 1 | CASE 2 | CASE 3 | CASE 4 | CASE 5 |
|-----------------|-------|-------|-------|-------|-------|
| Immunostains    |       |       |       |       |       |
| CD21            | −     | −     | −     | −     | +     |
| CD23            | −     | −     | −     | −     | −     |
| CD35            | n/a   | −     | −     | −     | −     |
| CD68            | n/a   | −/+   | −     | −     | +     |
| D2-40           | n/a   | n/a   | −     | +     | n/a   |
| Clusterin       | +     | n/a   | +     | n/a   | n/a   |
| CXCL13          | +     | n/a   | n/a   | n/a   | n/a   |
| Fascin          | n/a   | n/a   | +     | +     | n/a   |
| Renin           | +     | n/a   | n/a   | n/a   | n/a   |
| AE1/AE3         | −     | +     | −     | −     | −     |
| EBER ISH        | n/a   | n/a   | +     | −     | n/a   |
| TTF-1           | n/a   | n/a   | n/a   | +     | n/a   |
| p63             | n/a   | n/a   | n/a   | n/a   | −     |
| Bcl-2           | +     | −     | n/a   | n/a   | n/a   |
| CD34            | +     | −     | n/a   | −     | n/a   |
| CD117           | +     | n/a   | n/a   | n/a   | n/a   |
| EMA             | −     | −     | n/a   | n/a   | +     |
| S-100           | −     | −     | n/a   | −     | +     |
| HMB45/MART-1    | −     | −     | n/a   | n/a   | −     |
| Vimentin        | +     | +     | n/a   | n/a   | +     |

Abbreviation: FDCS, follicular dendritic cell sarcoma.

Figure 3. Sarcomatoid carcinoma with pleomorphic tumor cells (A) with a background of inflammatory cells (B) weak keratin positivity (C).
The case was sent out for expert opinion to 2 leading international pathologists with expertise in soft tissue pathology and lymphoid pathology. The soft tissue pathology expert favored a diagnosis of high-grade form of FDCS relying heavily on morphology and the staining pattern of pancytokeratin. This pathologist noted that the tumor cell positivity for cytokeratin was dendritic in configuration, namely, that it stains long processes that anastomose and create a meshwork (Figure 3C). On the contrary, the lymphoid pathology expert favored a diagnosis of a sarcomatoid carcinoma, concluding that the keratin positivity favored a sarcomatoid carcinoma of unidentified origin.

Pan-keratin stains have shown to be positive in FDCS and located to the cytoplasmic extensions. Sarcomatoid carcinomas of the head and neck region are generally considered to be de-differentiated squamous cell carcinomas (SCCs). However, this patient was young and did not have any predisposing factors. Moreover, the location was not common for an SCC primary. Nevertheless, the lack of dendritic cell markers and the presence of high-grade features made the diagnosis of a sarcomatoid carcinoma more likely. This case illustrates the morphologic promiscuity of such cases. A dendritic configuration of cytokeratin may raise the suspicion for FDCS; however, absence of all follicular dendritic markers is suspect. The patient died a few months later despite surgery and adjuvant therapy.

Case 3

The third case is of a 77-year-old woman who presented with incidental microscopic hematuria on routine workup by her primary care physician. As part of the workup, a computerized tomography (CT) urogram was performed revealing a solid, splenic mass confined to the hilum. Radiologically, this mass was not consistent with a hemangioma. A splenectomy was performed revealing a solid, well-circumscribed mass measuring 6.2 cm in greatest dimension and with a variegated cut surface. Microscopically, the mass demonstrated a lobulated tumor with pushing borders composed mainly of spindle cells admixed with a prominent lymphoplasmacytic infiltrate (Figure 4A). The tumor was composed of various components including spindle cells with large elongated nuclei, admixed lymphoplasmacytic cells, focally hyalinized stroma with fibrosis (Figure 4B), and vascular structures. Immunohistochemical analysis revealed that the spindle cell proliferation to be positive for FDC marker, clusterin; however, other dendritic markers CD21, CD23, CD35, and D2-40 were negative. The tumor cells were strongly and diffusely positive for Epstein-Barr virus-encoded RNA (EBER) by in situ hybridization. The overall findings were consistent with splenic inflammatory pseudotumor-like FDC tumor. The exact demarcation between Epstein-Barr virus (EBV)-related splenic inflammatory pseudotumors and splenic inflammatory pseudotumor-like EBV-related dendritic cell tumor was difficult in this case, due to the variable expression of dendritic cell markers. It was noted that surgery was likely curative in this case regardless of the latter distinction.

Follicular dendritic cell neoplasms associated with EBV are known as inflammatory pseudotumor-like follicular dendritic cell tumor (IPT-FDCT). The differential includes (a) inflammatory myofibroblastic tumor (IMT), which is associated with ALK translocation, and (b) inflammatory pseudotumor of the spleen (IPS), which is associated with EBV, but is not composed of FDCs. Distinct from these 2 entities is IPT-FDCT, which is morphologically similar to splenic inflammatory pseudotumor, but the tumor cells have the immunophenotype of FDCs, thus making it a variant of FDCS. This tumor is considered a low-grade sarcoma, very different from the known aggressive behavior of conventional intra-abdominal FDCS. The patient recovered promptly after surgery and has had no sequelae of the disease.
Case 4
The fourth case is of an 18-year-old girl with an enlarging, painless, left-sided neck mass, initially treated as mononucleosis. Imaging revealed an enhancing, solid mass and multiple reactive enlarged lymph nodes. Left neck dissection revealed a 2.4-cm, white-tan, well-circumscribed mass. Microscopically, the mass was composed mostly of atypical spindled cells with nuclear pleomorphism forming fascicles (Figure 5A and B). Areas with cells revealing prominent nucleoli, binucleation, and vesicular chromatin were present, as well as a background of a brisk lymphoplasmacytic infiltrate (Figure 5C). The tumor cells were positive for CD21, CD23 (focal), fascin, TTF-1, and D2-40 (focal). They were negative for AE1/AE3, CK8/18, p63, EMA, CD68, S-100, EBER ISH, and LCA (Table 1). The morphology and phenotype with positivity for FDC markers and absence of keratins, despite positivity for TTF-1, suggested a diagnosis of FDCS with TTF-1 was favored.
Although TTF-1 is not commonly positive in FDCs, there have been reported cases. The biologic justification of nuclear staining with TTF-1 in FDCs has not been elucidated and seems counterintuitive to the known functions of TTF-1 in lung and thyroid. However, FDCs are known to have a high degree of plasticity in morphology and immunophenotype. The possibility of a lung or thyroid primary could not be totally ruled out on morphologic grounds; however, the young age of the patient and the absence of a known primary tumor made FDCS more likely. The patient recovered promptly after surgery with no recurrences on follow-up.

Case 5
The fifth case is that of a 46-year-old, 20-pack-year male smoker with progressive dysphagia. His symptoms progressed to the point of being unable to swallow. During examination by an ENT surgeon, the patient was noted to have a polypoid mass at the base of the tongue. Partial glossectomy revealed a 4.1-cm, exophytic, fungating mass. Microscopic sections showed a population of ovoid to spindled cells with abundant eosinophilic cytoplasm forming sheets that were not connected to the overlying squamous mucosa (Figure 6). The nuclei were monomorphic with prominent nucleoli. The tumor cells were positive for CD21, vimentin, CD68, EMA, and S-100. Pankeratin, CAM 5.2, p63, and CD138 were negative. Interestingly, likely influenced by the patient’s clinical history of smoking, the initial frozen section diagnosis was consistent with SCC. On histologic examination of the permanent section, it was noted that the tumor cells were not connected to the overlying squamous mucosa, which was benign. Furthermore, the cellular morphology was inconsistent. Given the CD21 positivity, a diagnosis of FDCS was made.
SCCs can have variable morphology, including spindle cell, and can have brisk lymphocytic infiltrates as those normally seen in FDCS. The clinical history and location made the diagnosis of SCC very likely. However, morphology on permanent sections and immunohistochemical stains lead to the diagnosis of FDCS. This case presents a pitfall because the
morphology, location, and history suggested the pitfall of SCC. The patient is currently being managed with active surveillance and is in clinical remission.

Discussion
FDCS was first described in 1986 by Monda et al, who described 4 cases of non-lymphocytic tumors in lymph nodes. These tumors were composed of spindled cells arranged in whorls with associated inflammatory infiltrates. Necrosis and high-grade cytology were absent, and lymph node structures were obliterated. Using electron microscopy, they discovered that the tumor cells had an ultrastructure most similar to the dendritic reticular cells of normal lymph nodes, namely, they had long processes with well-formed desmosomes. In 2002, Pileri et al described 61 cases of accessory dendritic cells and histiocytic tumors of the lymph nodes. In this study, they constructed an immunophenotypic approach for the differentiation of various tumors of accessory cells and histiocytes present in lymph nodes. These were histiocytic sarcoma (HS), Langerhans cell tumor (LCT), FDCS, and interdigitating dendritic cell tumors (IDCT). The main immunohistochemical stains used for phenotyping and differentiating the cell types were CD68 (positive in HS), CD1a (positive in LCT), S-100 (positive in IDCT), and CD35/CD21 (positive in FDCS). Overall, with their scheme, they were able to accurately diagnose most of the cases presented in their study. Also in 2002, Biddle et al described 3 cases of extranodal FDCS and performed a review of the literature. They too recommended basing the diagnosis of FDCS on immunophenotyping with CD23/CD35 being positive in most of FDCS cases. In 2007, Soriano et al described 14 cases of FDCS and presented subsequent treatment and response of these cases. They demonstrated that FDCS is an aggressive neoplasm that, although initially therapy responsive, recurs in the great majority of cases. They proposed that the cases that show high-grade cytologic atypia could have unfavorable prognosis and should be treated as a high-grade malignancy with surgery and adjuvant therapy.

When clinical history, presentation, morphology, and phenotype line-in appropriately, a diagnosis of FDCS may not be hard; however, in this review, we highlight that, in some settings, diagnosing FDCS relies heavily on immunohistochemistry, and additionally, correlation with clinical presentation is of critical importance. Such is Case 1, where the unexplained hypertension in a young woman with a renal mass needed to be weighed against the favored diagnosis in the end, despite 2 international expert pathologists disagreeing on the interpretation of the same stain.

It should be kept in mind that a less aggressive variant of FDCS exists, as shown in Case 3. This needs to be considered because it has a much more indolent course, especially for intra-abdominal tumors. Finally, we showed in Case 4 that FDCS tumor cells have broad immunophenotypic plasticity, such as few rare cases in the head and neck region showing TTF-1 nuclear staining.

The molecular footprint of FDCS may be helpful in avoiding potential diagnostic pitfalls. Go et al probed histiocytic and FDCSs for BRAF V600E mutations. They found that in the 27 cases of FDCS in their study, 5 had the BRAF V600E mutations. In 2016, Fletcher et al used targeted sequencing of more than 300 genes associated with carcinogenesis in 13 cases of FDCS. They showed that there is a diversity of somatic genetic alterations in these tumors. However, loss of function in NF-κB regulatory genes was the most common, seen in 5 of the 13 cases (38%). They also showed that the few cases with a multitude of genetic abnormalities seemed to have worse prognosis. Due to the rarity of these tumors, molecular studies have not been able to elucidate a common abnormality to characterize them. Overall, a role of molecular pathology in cases of FDCS has not been established either in diagnosis or prognostic indications, yet. However, with the frequency of next generation sequencing panels and ease of availability, the likelihood of more extensive studies being performed in the future is high.

For now, given the lack of definitive molecular findings, we wanted to illustrate the complexity in the differential diagnosis of this rare entity using 5 unusual cases from our institution that presented challenges based on clinical presentation, morphology, or immunophenotype.

Author Contributions
NLH performed the case search, retrieved the cases for review, acquired histologic images, reviewed the cases, did the literature review, and wrote and edited the manuscript. KM performed the case search, retrieved the cases for review, edited the manuscript, did the literature review, and wrote and edited the manuscript. RO edited the manuscript. SP edited the manuscript.

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