Primary Pulmonary Follicular Dendritic Cell Neoplasm

A Case Report and Review of the Literature

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• **Follicular dendritic cell tumor (FDCT) is an uncommon neoplasm that typically presents as a slow-growing, painless mass without systemic symptoms. Histologically, FDCT is characterized as a proliferation of spindle to ovoid cells having plump eosinophilic cytoplasm with indistinct borders and nuclei with vesicular or granular chromatin and small distinct nucleoli. The immunohistochemical profile of FDCT includes positive staining for CD21, CD23, CD35, vimentin, fascin, HLA-DR, epithelial membrane antigen, clusterin, and D2-40. Follicular dendritic cell tumor occurs primarily in lymphoid tissue; however, involvement of extranodal sites such as the tonsils, spleen, and gastrointestinal tract has been reported. Lung involvement typically represents metastatic disease with, to our knowledge, only 2 prior cases of extranodal primary FDCT of the lung reported. We report the third case of primary pulmonary FDCT arising in a 64-year-old woman.**

(*Arch Pathol Lab Med.* 2009;133:643–647)

Follicular dendritic cell tumor (FDCT) is an extremely rare neoplasm of dendritic cell origin.[1] Most FDCTs involve lymphoid tissue but represent less than 1% of all lymphoid neoplasms. In the latest edition of the World Health Organization's *Classification of Tumours of Hematopoietic and Lymphoid Tissue*, FDCT is classified in the category of neoplasms of histiocytic or dendritic origin, which also includes histiocytic sarcoma, Langerhans cell histiocytosis, Langerhans cell sarcoma, interdigitating dendritic cell sarcoma (IDCS), and dendritic cell sarcoma, not otherwise specified.[2] All of these neoplasms are derived from phagocytes or accessory cells that have benign counterparts with major roles in processing and presenting antigens to lymphocytes.[3]

Accepted for publication August 15, 2008.

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The authors have no relevant financial interest in the products or companies described in this article.

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Follicular dendritic cell tumor is morphologically characterized by a neoplastic proliferation of spindle to ovoid cells having histologic and immunohistochemical (IHC) features characteristic of follicular dendritic cells. Other synonyms include reticulum cell sarcoma/tumor and dendritic reticulum cell sarcoma/tumor.[2,4] Descriptions of this rare neoplasm are limited to isolated case reports or small series.[1,5–10] Follicular dendritic cell tumors occur predominantly in adults with a wide age range and with equal sex distribution. Some FDCTs, especially the hyaline-vascular type, are associated with Castleman disease.[5] There are also reports of an increased incidence of FDCT in patients treated for long-standing schizophrenia.[6]

Follicular dendritic cell tumor predominantly involves the cervical lymph nodes; however, it can also involve axillary, mediastinal, mesenteric, and retroperitoneal lymph nodes and extranodal sites such as tonsils, spleen, oral cavity, gastrointestinal tract, liver, soft tissue, skin, and breast. Metastatic FDCTs most often involve lymph nodes, lung and/or liver.[1,2,6–10] Herein, we report what is, to our knowledge, the third case of primary pulmonary FDCT.[7,11]

REPORT OF A CASE

A morbidly obese, 64-year-old woman was hospitalized one month prior to admission at an outside hospital with a history of cough and shortness of breath that was diagnosed as pneumonia. She was treated with antibiotics and steroids with minimal improvement. The patient was then referred to our institution one month later for further evaluation. Chest x-ray and computed tomography scan demonstrated a 1.7-cm nodule in the right lower lobe of the lung. A positron emission tomography scan performed at an outside hospital was only positive at this site. The patient's medical history revealed a questionable history of asthma but no evidence of hemoptysis, prior pneumonia, tuberculosis exposure, deep vein thrombosis, or pulmonary emboli. The patient stated she had lived in a home with high radon levels for approximately 6 years. Following the initial evaluation, the patient underwent a right video-assisted thoracoscopic surgery procedure with a right lower lobectomy and mediastinal lymph node sampling. At the time of surgery, the nodule was shelled out from the lung parenchyma. The patient made an uneventful recovery and has remained asymptomatic for 2 years.

PATHOLOGIC FINDINGS

The well-circumscribed pulmonary nodule grossly measured 1.1 cm in maximum dimension, having a rubbery consistency and yellowish-to-white color. It was approximately 4.5 cm from the bronchial margin and 0.5 cm from the pleural surface, and it clinically abutted the bronchus. Microscopically, the neoplastic cells were spindle to stel-

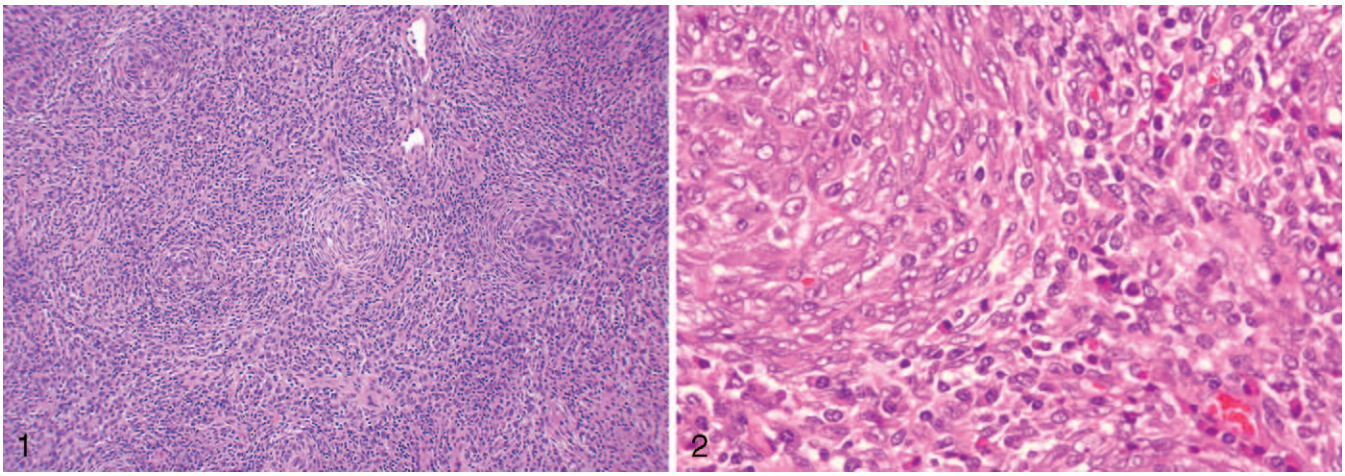

Figure 1. *Primary follicular dendritic cell tumor of the lung showing neoplastic cells which are spindle to stellate in shape, arranged in ill-defined fascicles with a focal whorling pattern (hematoxylin-eosin, original magnification ×100).*

Figure 2. *Primary follicular dendritic cell tumor of the lung showing tumor cells with irregular nuclear borders, slight to abundant pale eosinophilic cytoplasm, and occasional small nucleoli (hemotoxylin-eosin, original magnification ×400).*

late shape, arranged in ill-defined fascicles with a focally whorling pattern (Figure 1). The tumor cells had irregular nuclear borders with occasional small nucleoli and slight to abundant pale eosinophilic staining cytoplasm (Figure 2). The neoplastic cells were relatively bland with minimal cytologic atypia. There was only a very rare mitotic figure and no coagulative necrosis present. Admixed throughout the neoplastic cells were scattered lymphocytes and plasma cells. Eight benign lymph nodes were also sampled, including 4 peribronchial lymph nodes and one each at level 7, 11, 12, and 13.

A panel of IHC stains (Table) demonstrated positive staining of the neoplastic cells for CD35, CD68, clusterin, D2-40 and focal staining for CD23 (Figure 3, A through D). The tumor cells were also positive for vimentin and focally positive for S100 protein but were negative for pancytokeratin, AE1/3, epithelial membrane antigen, desmin, HHF-35, CD1a, ALK, CD31, CD34, CD163, and CD21. In situ hybridization performed at Mayo Clinic (Rochester, Minn) was negative for Epstein-Barr virus RNA (Figure 3). Based on histology and IHC staining, a diagnosis of follicular dendritic cell tumor (sarcoma) was rendered.

COMMENT

The usual clinical presentation of FDCT is that of a slow growing, painless mass. Systemic symptoms are unusual, although patients with abdominal disease may present with abdominal pain.[10] Follicular dendritic cell tumor can grossly measure from 1 to 20 cm; however, size is primarily dependent on tumor location. Histologically, it is characterized by a proliferation of spindle to ovoid cells having plump eosinophilic cytoplasm with indistinct borders and nuclei with vesicular or granular chromatin and small distinct nucleoli. The follicular cells can be arranged in fascicles, whorls and/or a storiform pattern. Fluid-filled cysts and necrosis may also be present. Occasional multinucleated cells may demonstrate pseudonuclear inclusions. Although FDCTs usually have cells with a relatively bland appearance, cytologic atypia may be present. The mitotic rate is usually between 0 and 10 per 10 high-power

Technical Data of Immunohistochemical Staining*

Antibody	Company†	Clone	Dilution	Retrieval Method
AE1/3	Zymed	AE1/AE3	Neat	Protease 1, 8 min
ALK	Ventana	ALK01	Neat	CCI standard
CD1a	Ventana	JPM 30	Neat	CCI standard
CD21	Ventana	2G9	Neat	CCI standard
CD23	Ventana	1B12	Neat	CCI standard
CD31	Cell Marque	1A10	Neat	CCI standard
CD34	Ventana	QBend-10	Neat	Zymed citrate, steam 45 min
CD35	Dako	Ber-MAC-DRC	1:10	Dako citrate, steam 45 min
CD68	Dako	KP-1	1:150	Zymed citrate, steam 10 min
CD163	Novocastra	10D6	1:20	CCI standard
D2-40	Signet	D2-40	1:50	Zymed citrate, steam 45 min
Desmin	Ventana	DE-R-11	Neat	Protease 1, 8 min
EMA	Ventana	E29	Neat	CCI mild
HHF-35	Dako	HHF35	1:100	None
Pancytokeratin	In-house cocktail	AE1/3, CAM 5.2, MAK-6	NA	Protease 1, 8 min
S100	Dako	Polyclonal	1:500	Zymed citrate, steam 20 min

* A Ventana machine was used for all stains. EMA indicates epithelial membrane antigen; NA, not applicable.

† Zymed Laboratories, Inc, South San Francisco, Calif; Ventana Medical Systems, Tucson, Ariz; Cell Marque, Rocklin, Calif; Dako, Carpinteria, Calif; Novocastra Laboratories Inc, Newcastle upon Tyne, United Kingdom; and Signet Laboratories, Inc, Dedham, Mass.

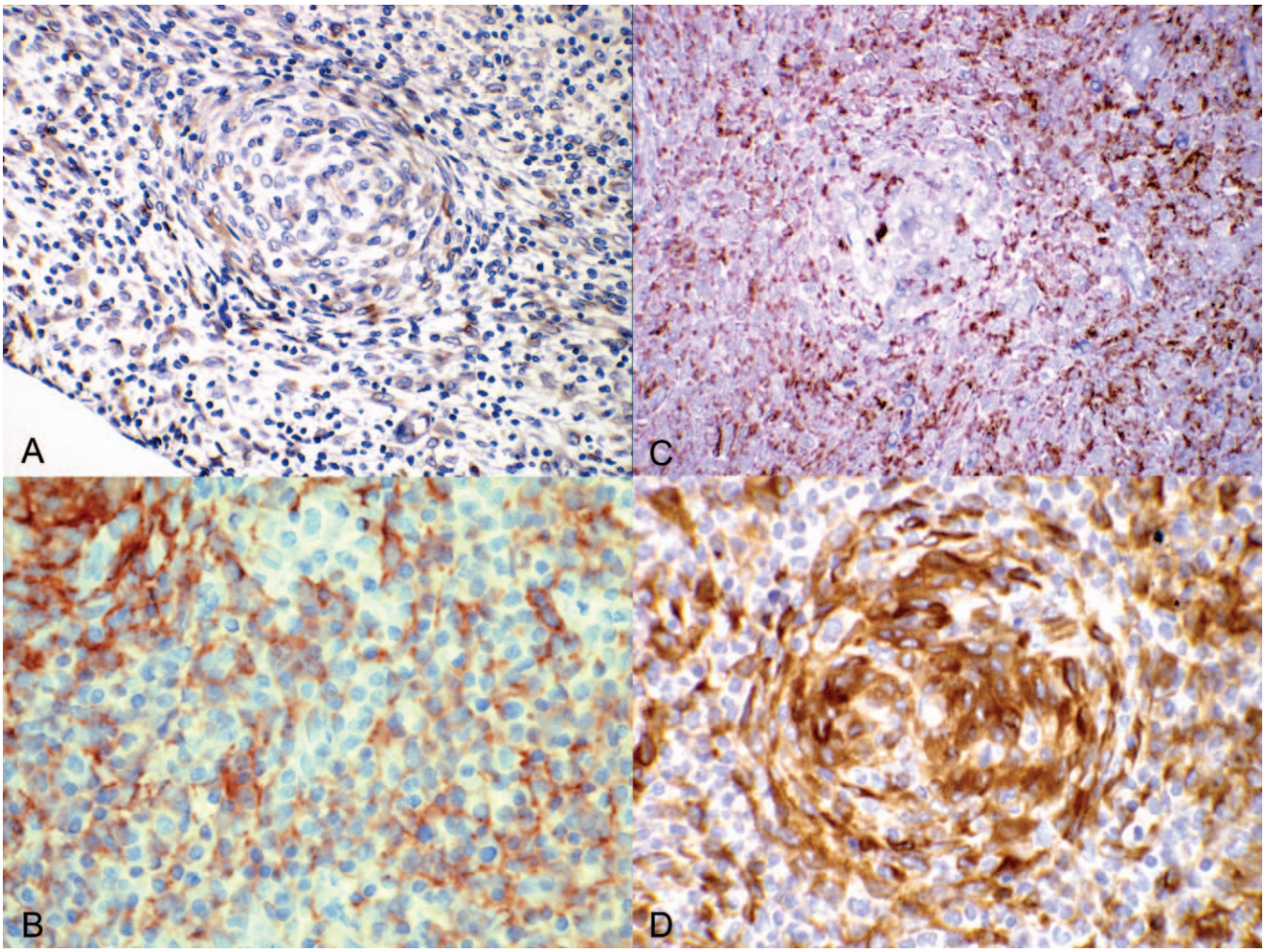

Figure 3. *Positive immunohistochemical staining of primary follicular dendritic cell tumor (FDCT) of the lung. Tumor cells showing focal positive staining for CD23 (A) and diffuse positive staining for CD68 (B) (original magnifications ×200). D2-40 (C) and clusterin (D) are both strongly expressed in neoplastic cells of FDCT of the lung (original magnifications ×400).*

fields, although atypical cases can have mitotic counts greater than 30 per 10 high-power fields, including atypical mitotic figures. Uninvolved residual lymphoid tissue is usually present as well as admixed mature lymphocytes within the neoplastic foci.[2]

The diagnostic IHC profile of FDCT consists of positive staining of the neoplastic cells for CD21, CD35, and/or CD23.[2] Other reported positive IHC markers include vimentin, fascin, HLA-DR, and EMA.[2,12] The tumor cells variably stain for S100, CD68, CD45, and CD20.[1,2,8,13] Recently, D2-40 and clusterin, a glycoprotein involved with a number of cellular functions including apoptosis, have been shown to be strongly expressed in FDCT and absent or weakly expressed in other dendritic cell tumors.[12,13] Our case was strongly positive for both D2-40 and clusterin.

Primary FDCT uncommonly occurs in extranodal sites. Lung involvement usually represents metastatic disease, with, to our knowledge, only 2 prior cases reported of extranodal primary pulmonary FDCT. The first case was in a 33-year-old man whose tumor measured 9.5 cm in maximum dimension and consisted of spindle cells arranged in interlacing fascicles with intermixed small lymphocytes and plasma cells.[7] One of 4 peribronchial hilar lymph nodes was also involved. The second case was a 65-year-old man whose tumor measured 4 cm in greatest dimension and consisted of spindle cells arranged in short fascicles and whorls with focal atypical nuclei and small nucleoli and a few foci of necrosis.[11] The neoplastic cells in both cases stained positively for CD21 and CD35. Therefore, we report the third primary FDCT of the lung.

Follicular dendritic cell tumor is considered to be a low-grade sarcoma with an indolent course.[8] Most patients are treated by complete surgical excision with or without radiotherapy or chemotherapy. However, local recurrences can occur in approximately a third of cases and metastatic disease in approximately a quarter of cases. Patients having intra-abdominal disease, significant cytologic atypia, extensive necrosis, high proliferation rate, and large tumor size (greater than 6 cm) have a poor prognosis.[8] It is estimated that approximately 10% to 20% of patients die, usually after a prolonged course. Although our patient had a relatively small neoplasm (approximately 1 cm) with no significant cytologic atypia, mitotic activity, or necrosis, the natural history of this rare neoplasm occurring in an unusual site is difficult to predict.

The differential diagnosis of FDCT includes other tumors of histiocytic or dendritic origin. Histiocytic sarcoma is a malignant proliferation of cells showing morphologic

and immunophenotypic features of mature histiocytes.[2] This neoplasm is characterized by diffuse proliferation of large round to oval neoplastic cells demonstrating mild to significant atypia. The malignant cells have large eccentric nuclei with vesicular chromatin and surrounding abundant eosinophilic cytoplasm. Associated admixed reactive cells including small lymphocytes, plasma cells, benign histiocytes, and eosinophils can be present, which can contribute to the polymorphic appearance of the tumor in contrast to FDCTs, which may only show the presence of mature lymphocytes. Most cases have an appearance similar to a diffuse large B-cell lymphoma or an anaplastic large cell lymphoma, although the cells of histiocytic sarcoma are generally larger with more abundant cytoplasm.[2] Therefore, IHC markers will be critical in making a correct diagnosis of this rare neoplasm. The tumor cells characteristically express histiocytic markers such as CD68 (PG-M1 and KP-1), lysozyme, CD11c, CD14, and the more recently reported histiocytic marker, CD163.[2] In addition, CD45, CD45-RO, and HLA-DR are usually positive, along with focal to weak S100 expression. There should be no positive staining for specific B- or T-cell markers.[2] In addition, accessory/dendritic cell IHC markers and specific myeloid markers such as myeloperoxidase, CD33, and CD34 give negative results.[2] The prognosis is generally poor with most patients presenting with an advanced clinical stage with a poor response to therapy.

Langerhans cell histiocytosis is a neoplastic proliferation of Langerhans cells, demonstrating immunohistochemical expression of CD1A and S100 as well as ultrastructural evidence of Birbeck granules.[2,14] The diagnosis is made when a proliferation of Langerhans cells is present, characterized by cells with characteristic grooved, folded, indented, or lobulated nuclei. The cells have a slight amount of eosinophilic cytoplasm and are usually admixed with eosinophils, histiocytes, neutrophils, and mature lymphocytes. The presence of atypia and mitotic activity is variable. However, the diagnosis needs to be confirmed by demonstrating positive staining of the cells for CD1A and S100 protein and/or the ultrastructural evidence of Birbeck granules.[2] Langerhans cells are also positive for vimentin, HLA-DR, and placental alkaline phosphatase and may show weak positivity for CD45, CD68, and lysozyme. Langerhans cells are negative for most B- and T-cell markers, CD30, myeloperoxidase, CD4, and EMA.[2,6]

Langerhans cell sarcoma is the cytologic and clinical malignant counterpart of Langerhans cell histiocytosis.[2] This rare neoplasm has cells with malignant cytologic features, has a high mitotic rate, and demonstrates IHC staining consistent with Langerhans cells.[2]

Interdigitating dendritic cell sarcoma/tumor (IDCS) is a neoplastic proliferation of spindle to ovoid cells demonstrating immunohistochemical features similar to benign interdigitating dendritic cells.[2] This is an extremely rare neoplasm, mostly seen in adults. Solitary lymph node involvement is most common, although there are case reports of extranodal presentations involving skin, intestine, soft tissue, and/or spleen and liver. The histologic appearance is indistinguishable from FDCT.[2,4] The neoplastic cells can form fascicles or whorls or have a storiform pattern. Sheets of round cells can occasionally be seen. Tumor cells have abundant cytoplasm with spindle to oval nuclei. The chromatin pattern is vesicular with distinct nucleoli. The cytologic atypia is variable and mitotic count is usually low (lower than 5 per 10 high-power fields). Necrosis is usually not present. Admixed numerous lymphocytes are present, and occasionally plasma cells may also be seen. Therefore, IHC studies are needed in order to differentiate IDCS from FDCT. The IHC profile of IDCS includes positive staining for vimentin, S100, CD68, and lysozyme with CD45 showing variably weak positive staining. Characteristically, the tumor cells are negative for markers of follicular dendritic cells (CD21 and CD35) and myeloperoxidase, CD34, B- and T-cell markers, CD30, EMA, and cytokeratins. The Ki-67 index ranges from 10% to 20%. The admixed small lymphocytes are almost exclusively T cells. The prognosis of interdigitating dendritic cell sarcoma is variable, with localized disease usually having a benign course, while widespread disease usually results in death. Organs commonly involved include bone marrow, spleen, liver, skin, kidney, and lung.[2]

Another entity to be given serious consideration in the differential diagnosis is inflammatory myofibroblastic tumor (inflammatory pseudotumor). Inflammatory pseudotumor is usually a solitary lesion consisting of a proliferation of fibroblastic and myofibroblastic cells with varying numbers of chronic inflammatory cells including plasma cells, lymphocytes, macrophages (including foamy histiocytes), and occasional giant cells. Although inflammatory pseudotumor is found most often in the lung, it can occur in almost any organ or site.

Recently, a series of follicular dendritic cell tumors with an inflammatory pseudotumor-like appearance has been reported.[15] This series included 10 women and one man having a wide age range with a median age of 40 years presenting with intra-abdominal tumors. Cases consisted of liver (7), spleen (3), and peripancreatic region (1) involvement. Nine of the 11 patients are alive with follow-up, although one patient developed a recurrence at 9 years and 2 had repeated occurrences. Features distinguishing inflammatory pseudotumor-like follicular dendritic cell tumor from conventional FDCT include a striking female predominance, exclusive intraabdominal site involvement (especially liver and spleen), frequent presence of systemic symptoms, indolent behavior, prominent lymphoplasmacytic infiltration, and strong association with Epstein-Barr virus.

In conclusion, we report the third case of primary FDCT of the lung. It is uncertain what the natural history of this neoplasm will be due to its occurrence at an unusual site. The histology of this neoplasm is quite similar to many other tumors of histiocytic or dendritic origin, making IHC studies critical for the correct diagnosis. In addition to CD23 and CD35 positivity, the application of IHC staining for D2-40 and clusterin, 2 recently described markers for FDCT, was helpful in confirming this rare neoplasm involving a very uncommon site.

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