Follicular Dendritic Cell Sarcoma Presenting as a Submucosal Tumor of the Stomach

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• Follicular dendritic cell (FDC) sarcomas, especially those of extranodal origin, are extremely rare, and this entity could easily be missed without a high index of suspicion. We report a case of FDC sarcoma presenting as a submucosal tumor of the stomach in a 45-year-old man. The mass was a spindle and epithelioid mesenchymal tumor with many individually scattered and perivascular aggregates of lymphocytes. Immunohistochemical and ultrastructural studies confirmed the diagnosis. Although more than 50 cases of this tumor have been documented in the English literature, to our knowledge the presentation of FDC sarcoma as a submucosal tumor of the stomach has never been recorded. This case highlights the occurrence of FDC sarcoma as a submucosal tumor of the gastrointestinal tract. We believe that FDC sarcoma should be included in the differential diagnosis of spindle or epithelioid cell tumors of the gastrointestinal hollow viscus to prevent this still underrecognized tumor from being overlooked.

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Follicular dendritic cell (FDC) sarcoma is an uncommon tumor of FDC origin, although more than 50 cases have been reported in the English literature to date.[1] Follicular dendritic cells are antigen-presenting cells that normally form meshworks in lymphoid follicles, and FDC sarcomas in general recapitulate both the histologic and ultrastructural findings and the immunophenotypic profile of FDCs. This tumor affects mainly the lymph nodes, but it also involves extranodal sites in about one third of cases.[2,3] The intra-abdominal organs are the predominant sites of extranodal forms,[2,3] but hollow viscus is rarely involved and only 1 case of FDC sarcoma primarily involving the small intestine has been described to date.[4] As a result, FDC sarcoma has rarely been listed in the differential diagnosis of spindle cell neoplasms of the gastrointestinal tract. We report a case of FDC sarcoma presenting as a submucosal mass of the stomach to highlight its occurrence as a submucosal mass in the intra-abdominal hollow viscus and to discuss its differential diagnosis.

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REPORT OF A CASE

A 45-year-old man presented with melena and dizziness of 3 weeks' duration. Physical examination and laboratory tests were unremarkable except for mild anemia; his serum carcinoembryonic antigen level was normal. Fiber-optic gastroscopy and an abdominal computed tomographic scan revealed a 4-cm fungating mass with a central ulceration on the antrum of the posterior wall of the stomach. Radical subtotal gastrectomy was performed, based on the pathologic diagnosis of spindle cell sarcoma from gastroscopic biopsy specimens. The patient was well without evidence of disease 10 months after surgery.

PATHOLOGIC FINDINGS

The specimen received was a resected stomach containing a 5 × 4.5-cm fungating mass. The mass was located on the antrum of the posterior wall, and a deep, central ulceration coated by necrotic tissue was present (Figure 1). On cut sections, the mass was well demarcated and had a grayish-white flesh cut surface. The tumor was almost wholly located in the submucosa abutting the muscle proper.

Microscopically, the well-demarcated tumor, which was mainly located in the submucosa but had focal infiltration into the mucosa, was composed of plump, oval to spindle-shaped cells arranged in sheets and interlacing fascicles (Figure 2). Although areas of short fascicles of spindle-shaped cells that formed a vague storiform pattern were present, most of the tumor cells had plump eosinophilic cytoplasm with ill-defined cell borders forming a patternless diffuse growth. The tumor cell nuclei were oval to round and had a vesicular chromatin pattern (Figure 3); some multinucleated tumor cells were also present. Focal nuclear pleomorphism and scattered mitotic figures (average, 3 mitoses/10 high-power fields) were observed.

The tumor cells characteristically were intermingled with many lymphocytes, and in some areas a perivascular cuff of lymphocytes was also present (Figures 2 and 3). Tumor metastasis was present in 1 of the resected perigastric lymph nodes.

Sections from the routinely processed paraffin-embedded tissue were examined immunohistochemically using the labeled streptavidin-biotin peroxidase method (LSAB 2 kit, Dakopatts, Glostrup, Denmark). The antibodies tested included CD21, CD23, CD35, CD45, CD68 (KP1), CD68 (PG-M1), CD3, L26, α-smooth muscle actin, vimentin, desmin, S100 protein, epithelial membrane antigen, HMB-45, CD31, and neuron-specific enolase (Dakopatts); cytokeratin (AE1/AE3), synaptophysin, and factor XIIIa (BioGenex, San Ramon, Calif); CD34 and CNA.42 (Immunotech, Westbrook, Me); and c-*kit* (C-19; Santa Cruz Biotech-

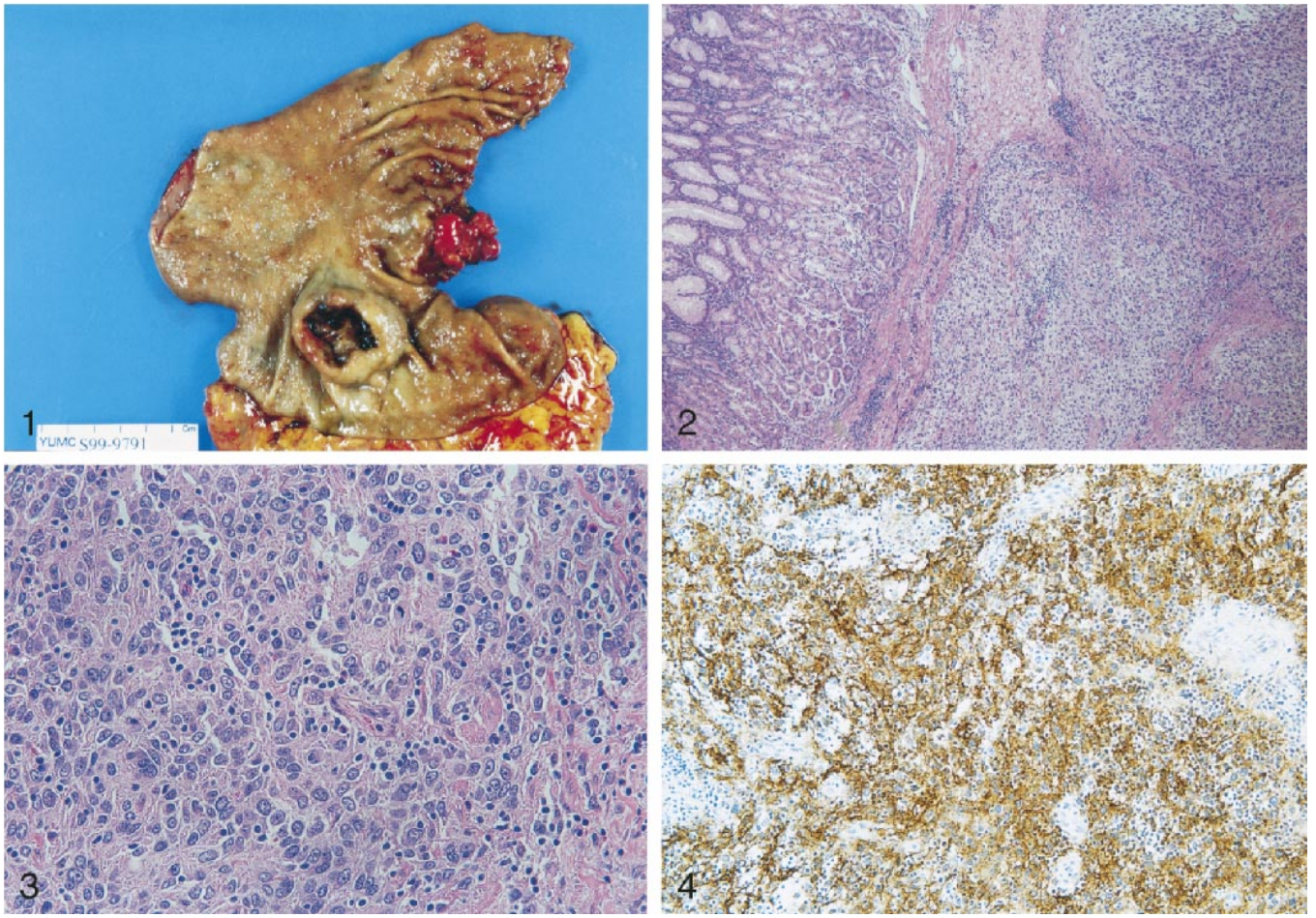

Figure 1. *The radical subtotal gastrectomy specimen showing the 5 × 4.5-cm fungating tumor mass with central ulceration on the posterior wall of the antrum.*

Figure 2. *Low-power view of the well-demarcated submucosal tumor composed of plump ovoid cells (hematoxylin-eosin, original magnification ×40).*

Figure 3. *Plump spindly tumor cells with vesicular nuclei forming a sheetlike growth pattern associated with sprinkling of small lymphocytes (hematoxylin-eosin, original magnification ×200).*

Figure 4. *Strong cell membrane and cytoplasmic immunoreaction in the tumor cells to CD21 and CD35 cocktail (DAB chromogen with hematoxylin counterstain, original magnification ×200).*

nology, Santa Cruz, Calif). Antigen retrieval by trypsin for CD21, CD35, and cytokeratin, and by microwave for other antibodies except for α-smooth muscle actin, synaptophysin, S100 protein, and neuron-specific enolase were performed before incubation with antibodies. An in situ hybridization study for Epstein-Barr virus-encoded (EBER1) mRNA was performed using the probe and detection system from Novocastra (Newcastle upon Tyne, United Kingdom). Tumor cells expressed membrane and cytoplasmic immunoreactivity for FDC markers (CNA.42, CD21, CD23, and CD35) (Figure 4). Cytoplasmic expression of epithelial membrane antigen, CD68 (KP1), α-smooth muscle actin, vimentin, and factor XIII were also present, and focal nuclear and cytoplasmic immunoreactivity for S100 protein was detected. Most of the lymphoid cells were T cells expressing polyclonal CD3, with a minor population of B cells expressing L26. No immunoreactivity was demonstrated for CD45, CD3, L26, desmin, HMB-45, neuron-specific enolase, synaptophysin, cytokeratin, CD31, CD34, and c-*kit* in the tumor cells. CD68 (PG-M1) was expressed only in reactive dendritic cells within the tumor. The nuclear signal for EBER1 mRNA was not detected by the in situ hybridization method.

Ultrastructural examination of the paraffin-embedded tissue demonstrated long and thin interdigitating cytoplasmic processes and desmosomal cell junctions between adjacent cell processes (Figure 5).

COMMENT

In this report, we describe a hitherto unreported presentation of a rare tumor, which was identified as FDC sarcoma by the results of histopathologic, immunohistochemical, and ultrastructural studies. Follicular dendritic cells, interdigitating dendritic cells, and Langerhans cells are the major nonphagocytic antigen-presenting accessory cells of the immune system. They reside in different compartments of the immune system and differ in their functional, morphologic, and immunophenotypic aspects. Each of these cells can give rise to proliferative lesions. Among these, Langerhans cell histiocytosis is the most common and well known, whereas FDC and interdigitating den-

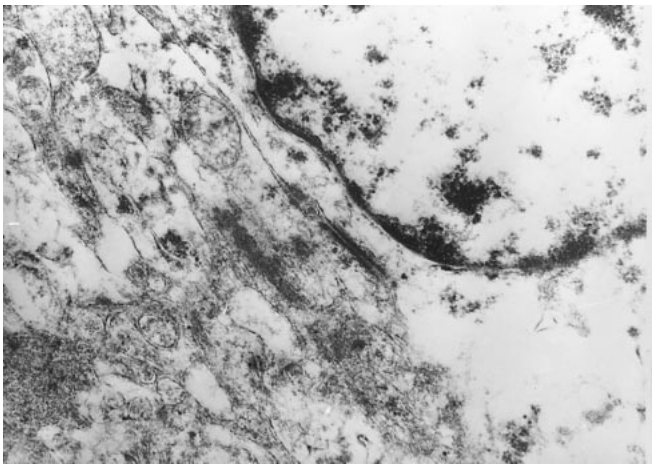

Figure 5. *The long, slender, interweaving cytoplasmic processes focally connected by desmosomal cell junctions (uranyl acetate–lead citrate, original magnification ×42 000).*

dritic cell sarcomas are relatively recently established, rare, and underrecognized.

Although Lennert[5] suggested the existence of FDC tumor in 1978, the first report of FDC sarcoma was described by Monda et al[6] in 1986. They reported 4 cases of nodal spindle cell neoplasms with features suggestive of dendritic reticulum cell differentiation based on the expression of a dendritic reticulum cell marker (R4/23) and the presence of long, complex cytoplasmic extensions and numerous macula adherens–type cell junctions. The extranodal presentation of this tumor was first demonstrated by Chan et al,[7] who reported 2 cases of FDC sarcomas arising from the palate and tonsil 8 years after the first report of this tumor. Currently, more than 50 FDC sarcomas have been described in the English literature.[1] The most common location is the cervical lymph nodes, but in about one third of cases FDC sarcoma presents as an extranodal mass. Interestingly, intra-abdominal organs (retroperitoneum, mesentery, spleen, pancreas, and peripancreatic tissues) and the upper aerodigestive tract (tonsil, palate, and pharynx) are the sites of predilection for this tumor.[2,3] However, mural involvement of the hollow gastrointestinal viscus is extremely rare, and only 1 case primarily involving the small intestine and the adjacent mesentery has been described.[4] Consequently, FDC sarcoma is seldom listed in the differential diagnosis of spindle cell tumors of the gastrointestinal tract.

Because FDC sarcoma occurs rarely in the hollow viscus, several tumors should be excluded before diagnosis. Follicular dendritic cell sarcoma can show diverse histologic patterns, the most common of which is fascicular or storiform proliferation of the spindle cells.[2,3] Sometimes, epithelioid cells with plump cytoplasm predominate, as they did in our case. As in nontumorous FDCs, the cell borders are indistinct irrespective of the cytologic features, causing a syncytial appearance. Another important diagnostic clue is the intimate admixture of tumor cells and lymphocytes, and in a few cases lymphocytes can far outnumber the tumor cells, giving a false impression of small lymphoid cell malignancy.[8] Although FDC sarcoma has fairly characteristic histologic features, confirmation of the cell lineage by immunohistochemical staining is mandatory for a definitive diagnosis. The immunophenotype and ultrastructure of FDC sarcoma recapitulate those of FDCs, so numerous interdigitating cytoplasmic processes joined by desmosomes are invariably present, as in our case. The most widely used practical FDC markers are the CD21 and CD35 antibodies. They are commercially available, and some of antibodies work on paraffin-embedded tissue sections, following meticulous antigen retrieval by enzymes. CD23 antibodies can be used as relatively specific markers of FDC sarcoma, and they are easier to handle than CD21 and CD35 because they work well after heat-induced antigen retrieval. Low-affinity nerve growth factor receptor[9] and CNA.42[10] have been described as sensitive markers for FDCs, but they lack specificity. In addition, actin, epithelial membrane antigen, CD68, S100 protein, and desmoplakin have been reported to be expressed in some FDC sarcomas.[2,3] However, these markers lack specificity, and their use without specific FDC markers can even lead to erroneous typing of spindle cell tumors. Positive immunostaining for factor XIIIa, as found in our case, has not been reported previously. The antibody against factor XIIIa labels dermal dendrocytes, and some of the spindle cell tumors, including dermatofibroma, malignant fibrous histiocytoma, fibrosarcoma, leiomyosarcoma, neurofibroma, malignant peripheral nerve sheath tumor, and Kaposi sarcoma, have been reported to express this marker.[11,12] Follicular dendritic cell sarcoma does not usually express CD45, and no report to date has described a convincing expression of cytokeratin, desmin, CD31, CD34, c-*kit*, or HMB-45.[2,3]

Mesenchymal tumors of the gastrointestinal tract are uncommon compared to epithelial tumors, and most are gastrointestinal stromal tumors (GISTs) composed of uncommitted spindle cells. The tumor cells of GISTs usually have less eosinophilic cytoplasm compared to the cells of spindle cell tumors, which show more specific differentiation, as in smooth muscle and neurogenic tumors. However, GISTs can show diverse histologic features, including epithelioid and myxoid forms, and the distinction is not always possible without the help of immunohistochemical and ultrastructural studies.[13,14] CD34 immunoreactivity has been used as a useful diagnostic marker of GIST,[15] but c-*kit* immunoreactivity recently has been accepted as a highly sensitive and biologically relevant marker of GIST.[16] We could not make a definite histologic diagnosis on the basis of the gastroscopic biopsy specimens and initially considered the possibility of an unusual morphologic variant of GIST in the resected specimen, until the results of c-*kit* and CD34 immunostaining proved negative. The epithelioid variant of leiomyosarcoma, malignant peripheral nerve sheath tumor, and gastrointestinal autonomic nerve tumor were also included in the differential diagnosis; however, the sprinkling of lymphocytes throughout the tumor, coupled with the storiform or whorled growth pattern of the spindle tumor cells in some areas, and the syncytial appearance of the tumor cells were important indications of an FDC sarcoma. Eventually, the results of our immunohistochemical and ultrastructural studies confirmed the diagnosis of FDC sarcoma, and we could exclude these diagnostic possibilities.

The location and morphology of our case suggested a diagnosis of sarcomatoid carcinoma.[17] Sarcomatoid carcinoma usually presents as a fungating mass in the hollow viscus and demonstrates a wide morphologic spectrum. However, it can be distinguished by its tendency to have an infiltrative margin and by the presence of more obvious nuclear pleomorphism. In addition, areas of cytokeratin-

positive carcinoma should be present, and immunoreactivity to FDC markers (CD21, CD23, and CD35) has not yet been reported in sarcomatoid carcinoma. Lymphocyte-rich undifferentiated carcinoma was excluded in a similar way.

Although malignant fibrous histiocytoma is unusual in the stomach,[18] the presence of spindle cells in a storiform pattern and multinucleated tumor giant cells raised the possibility of malignant fibrous histiocytoma. The lack of marked cytologic atypia and the expression of lineage-specific markers precluded this diagnosis.[19] Malignant melanoma could be excluded by the expression of FDC markers and the absence of melanosomes and HMB-45 expression.

Interdigitating reticulum cell (interdigitating dendritic cell) sarcoma is another type of neoplasm of reticular dendritic cell origin, and it shares some histologic, immunophenotypic, and ultrastructural features with FDC sarcoma. Fewer cases of interdigitating dendritic cell sarcoma have been reported than for FDC sarcoma,[1] and this lesion can also present as an extranodal mass, including in the gastrointestinal tract.[20,21] Although there is some overlap of immunophenotypic profiles, the presence of FDC markers and the lack of CD45 expression excluded the diagnosis of interdigitating dendritic cell sarcoma. Sparse intracytoplasmic organelles and interdigitating cytoplasmic processes are common ultrastructural features, but interdigitating dendritic cell sarcoma does not show desmosomes.

The majority of the reported cases of FDC sarcomas have no known etiologic or predisposing factors. Hyaline-vascular Castleman disease sometimes demonstrates proliferating and dysplastic FDCs, and a number of cases of FDC sarcomas complicating Castleman disease have been reported, which suggests a hyperplasia-dysplasia-neoplasia sequence of FDC sarcoma in some cases.[2,8,22,23] Scattered mucosa-associated lymphoid tissue with secondary lymphoid follicles (probably induced by *Helicobacter pylori* infection) was present in the resected stomach, but dysplastic FDCs were not observed in the follicles. Although Epstein-Barr virus has been demonstrated in selected cases of FDC sarcomas,[2,3,23–25] it is unlikely that this virus plays an important role as an etiologic agent, and our case did not reveal any nuclear signal on EBER1 mRNA in situ hybridization, which is the most specific and sensitive method for the detection of Epstein-Barr virus.

The biological behavior of this tumor is difficult to predict, but in general it is more akin to that of an intermediate-grade soft tissue sarcoma than a malignant lymphoma.[23] An intra-abdominal location was reported to be associated with a particularly aggressive course, along with a high mitotic count (≥5 mitoses/10 high-power fields), coagulative necrosis, and significant cellular atypia.[2,3,23] Our case interestingly demonstrated perigastric lymph node metastasis, despite the early stage of the primary tumor. The patient was doing well 10 months after curative surgery, but his clinical course is uncertain because he has already demonstrated regional lymph node metastasis.

In summary, we have described the unusual case of an FDC sarcoma presenting as a gastric submucosal tumor in a 45-year-old man. This case highlights the occurrence of FDC sarcoma as a submucosal tumor of the gastrointestinal tract and demonstrates that FDC sarcoma should be considered in cases of c-*kit*– and CD34-immunonegative spindle or epithelioid cell tumors of the gastrointestinal hollow viscus, particularly if lymphocytes are intimately admixed intratumorally.

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