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Review Article

Clinicopathology Landscapes And Prediction Evaluation Of Follicular Dendritic Cell Sarcoma (FDSC): A Dreadfully Rare Entity

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ABSTRACT

Follicular dendritic cell sarcoma is an uncommon neoplastic proliferation of spindle to ovoid cells with morphologic and immunophenotypic features similar to normal follicular dendritic cells. While most follicular dendritic cell sarcomas arise from lymph nodes, at least one-third occur in extranodal sites. A broad differential diagnosis can be developed—as this tumor has morphologic features similar to other tumors, hence creating a diagnostic pitfall—but its immunophenotypic profile is quite specific and is diagnostically crucial. Follicular dendritic cell sarcoma (FDSC) is a very rare malignant tumor derived from follicular dendritic cells. Radical resection is the standard therapy for patients with local disease, but an optimal chemotherapy regimen has not been determined for unresectable disease.

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INTRODUCTION

Dendritic cells are immune cells involved in antigen presentation and endocytosis and are classified as T-cell-associated dendritic cells and B-cell-associated dendritic cells. Follicular dendritic cells are B-cell-associated dendritic cells present in lymph follicles¹. Follicular dendritic cells are mesenchymal in origin, and although they play a role in the maintenance of the lymph follicle environment and the activation of B cells in lymph follicles, they have no antigen presenting or endocytosis functions unlike other dendritic cells.

Follicular dendritic cell sarcoma (FDCS) is a very rare malignant tumor derived from follicular dendritic cells. It is not always easy to make the distinction because of histological similarities with non-Hodgkin lymphoma, sarcoma, melanoma, undifferentiated carcinomas, and other dendritic and histiocytic cell disease. The diagnosis is based on morphology and immunohistochemical assay. Morphology is characterized by spindled to ovoid cells forming fascicles, whorls, diffuse sheets, or nodules. Lymphoplasmacytic infiltration is frequently present in tumor tissue². Tumor cells typically express markers of follicular dendritic cell differentiation, including CD21, CD23, and CD35. Clusterin, fascin, and podoplanin are additional markers that are uniformly positive. Radical resection is the standard therapy for patients with local disease, and adjuvant radiotherapy did not have a significant influence on survival outcomes. Chemotherapy is indicated for patients with unresectable disease or multiorgan involvement. An optimal chemotherapy regimen has not been determined for this rare disease and cytotoxic agents for malignant lymphoma or soft tissue sarcoma are commonly used to treat FDCS patients. Therefore, the accumulation of case reports is important to clarify the pathophysiology of FDCS and establish an optimal treatment strategy³.

Follicular dendritic cells (FDC) proliferate in several reactive and neoplastic conditions, including reactive follicular hyperplasia,

follicular lymphoma, mantle cell lymphoma, nodular lymphocyte-predominant Hodgkin's lymphoma and angioimmunoblastic T-cell lymphoma. These tumors were first suspected of being primary tumors of FDCs in 1978, and the first primary neoplasm that arose in a lymph node and exhibited FDC differentiation was characterized in 1986. Tumors of FDCs are called follicular dendritic cell sarcomas (FDCSs), and these tumors are grouped with the histiocytic and dendritic cell neoplasms in the World Health Organization (WHO) classification of tumors. This group also includes histiocytic sarcoma, Langerhans cell histiocytosis, Langerhans cell sarcoma, interdigitating dendritic cell sarcoma and dendritic cell sarcoma not otherwise specified⁴. Herein, we describe a patient with FDCS and extensive lymph node involvement, dry cough and an itching sensation, and the patient was treated with systemic chemotherapy.

FDCS is a rare neoplasm that shows a low-to-intermediate malignant potential. FDCS can lead to enlargement of the cervical, mediastinal and axillary lymph nodes, but approximately one-third of the cases involve extranodal sites such as the tonsils, palate, pharynx, soft tissues, pancreas and mesocolon. FDCS patients most often present with slow-growing, painless masses and they are without systemic symptoms, although patients with abdominal disease may present with abdominal pain. Normal FDCs participate in the immune system by presenting and retaining antigens for B-cell action, and by stimulating B-cell proliferation and differentiation. Although the etiology of FDCS is unknown, the condition has been associated with Epstein-Barr virus. FDCS tumors range from 1~15 cm in size, and the size is dependent on tumor location, with the smallest tumors located in the cervical regions and the largest in the intra-abdominal and mediastinal areas. FDCS affects both genders with no predilection, and the patients have a wide range of ages, but they show an adult predominance. FDCS tumors contain ovoid

elongated cells with a pale eosinophilic cytoplasm that has a syncytial appearance. These cells tend to exhibit a storiform, fascicular, whorled, diffuse, follicle-like or trabecular pattern. FDCS cells generally share the immunophenotype of non-neoplastic FDCs, with CD21, CD35 and/or CD23 being the most specific diagnostic markers⁵. Other positive markers include vimentin, fascin, HLA-DR and EMA. Some tumors are also positive for S-100, CD68, CD45 and CD20, whereas others are not.

Because of the rarity of the condition, there has been no prospective study on the treatments and outcomes of patients with FDCS. The few relevant reports are based on retrospective analyses, which makes it difficult to provide detailed treatment recommendations. As with lymphomas, FDCS may be treated aggressively and often with systemic chemotherapy such as the CHOP or CHOP-like regimens. In contrast, FDCS can also be treated in the manner of soft tissue sarcomas, including wide resection with or without radiotherapy and/or chemotherapy⁶. Most FDCS tumors are localized at the time of diagnosis.

Histopathology

FDC tumor is composed of spindle to ovoid cells that are arranged in fascicles, storiform patterns and whorls. The individual neoplastic cells generally have plump, slightly

eosinophilic cytoplasm with indistinct cell borders. The nuclei are elongated, with vesicular or granular finely dispersed chromatin, small but distinct nucleoli, and a delicate nuclear membrane. Lymphocytes are characteristically sprinkled throughout the tumor. Nonetheless, the recognized morphologic spectrum of FDC sarcoma has broadened over the years, such as endocrine tumor like vasculature, polygonal cells, hyaline cytoplasm, and myxoid stroma; and a definitive diagnosis always requires confirmation by immunohistochemical and/ or ultrastructural studies (Figure:1). More than half the cases are nodal in origin, with cervical lymph nodes as the most common site of involvement. Approximately 30% of the cases have been located at extranodal sites. The tonsil, nasopharynx, pancreas, peripancreatic and peritoneal tissues are the most common extranodal sites.

Systemic symptoms are rare⁷. Patients most often present with a slow growing painless mass. Castleman disease is one clinical setting where hyperplasia and dysplasia of follicular dendritic cells has been implicated as precursor lesions to this neoplasm. Nearly 10-20% of cases are associated with Castleman disease (of hyaline vascular type). EBV genome has been identified in several putative FDC sarcomas that show morphologic resemblance to inflammatory pseudotumor.

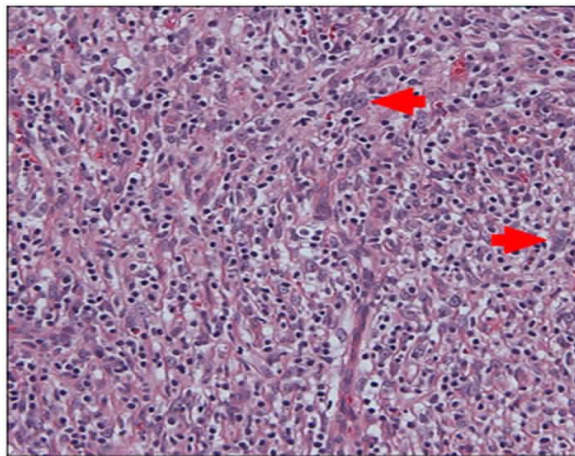


Figure 1: Histopathologic features of a follicular dendritic cell sarcoma (FDCS). Numerous spindle shaped elongated cells are seen with finer nuclear chromatin and frequently prominent nucleoli, some binucleate (red arrows) cells are clearly seen which is typical of FDCS

Gross appearance is similar to that of other sarcomas with a well-circumscribed tan grey cut surface. Necrosis and cystic change may be seen in larger tumors. Histologic appearance is that of a spindled and ovoid cell proliferation forming fascicles and a storiform pattern with whirling, reminiscent of a meningioma. Tumor cells have plump eosinophilic cytoplasm and indistinct cell borders. Nuclei are elongated with vesicular or finely granular chromatin and distinct nucleoli. Although most cases are cytologically bland with a low mitotic rate (0-10/10 HPF), cases with greater cytologic atypia and higher mitotic rates may be seen. Often there is a sparse infiltrate of mature lymphocytes and plasma cells, predominantly in a perivascular distribution⁸. In cases involving the liver and spleen, the tumor cells often do not demonstrate a cohesive proliferation of spindled cells, and have a greater degree of inflammatory infiltrate causing diagnostic confusion with inflammatory pseudotumor.

FDC sarcoma may occur in association with Castleman disease in about 10 - 20% of cases, either concomitantly or after several years. It can occur both in a nodal and extranodal site, usually in the hyaline vascular type. There is a proliferation of FDCs in the interfollicular spaces. In addition, FDC dysplasia with chromosomal abnormality is identified in some follicles of HVCD. These dysplastic FDCs may form tumor-like lesions and have clonality and aberrant expression of cell adhesion molecules and growth factor receptor. Therefore, a hyperplasia-dysplasia-neoplasia sequence was suggested as an explanation for the evolution of FDC sarcoma in the background of Castleman disease⁹.

Pathological diagnosis is essential for FDSCS. FDSCS may be suspected if the tumor exhibits distinct microscopic features, such as a storiform arrangement of spindle-shaped cells and a background of lymphocytes scattered throughout the neoplastic cells. The morphologies of our cases are typical of FDSCS. To confirm the tumor, immunohistochemical

staining is also required. The most widely used FDC markers, including CD21, CD35, and CD23, can be used for confirmation. Other markers including vimentin, CD68, CD45, CD3, CD20, EMA, melanoma (HMB-45), and Ki-67 (MIB-1) can be variably positive, although they lack specificity. The S-100 and certain vascular or muscular markers may also help to distinguish this tumor from other tumors, such as malignant peripheral nerve sheath tumors and gastrointestinal stromal tumors. The diagnosis of an FDC tumor is established based on the findings of morphology and immunohistochemistry¹⁰. Ultrastructural studies may be helpful but are not indispensable for accurate diagnosis. The most distinctive feature is numerous long, slender, interwoven cytoplasmic processes joined by well-formed desmosomes.

Cellular mutations

Biological mutations of the FDSCS tumor have been exploited for diagnostic purposes. Characteristically FDSCS have microtubuloreticular structures (MTRS) and increased levels of intracellular clusterin. MTRS contribute to microtubule formation of many structures including the mitotic spindle during cell division. This contributes to many of the hallmarks of cancer including proliferative signaling, growth activation, and replicative immortality¹¹. Clusterin is a heterodimeric protein that aids in the clearance of cellular debris and is involved with apoptosis. Clusterin can be stained to help distinguish FDSCS and is involved in the many important cancer hallmarks including resistance to cell death and evading growth suppressors.

Cytogenetics Molecular

The genetic alterations that drive tumorigenesis are not well understood in FDSCS. One recent study that assessed the genetic basis of FDSCS reported BRAF V600 mutations in a subset of cases. Another study analyzing somatic alterations, showed loss of

function alterations in tumor suppressor genes (NF- κ B regulatory genes), including bi-allelic loss of CYLD and frameshift mutations in NFKBIA. Alterations in genes that regulate cell cycle include bi-allelic loss of CDKN2A and RB-1. Finally, focal copy-number gains on chromosome 9p24, a well described mechanism of immune evasion, have been observed in the regions containing CD274 (PD-L1) and PDCD1LG2 (PD-L2).

Current Therapies

CHOP

At the time of the follicular dendritic cell sarcoma discovery information on the effect of chemotherapy and radiation on it was nonexistent. The best physicians could do was try existing chemotherapeutic agents. With no evidence of the clinical benefit of chemotherapy, many of the first cases were treated solely with complete resection and/or radiation. However, 12 of 31 patients who had surgery alone as primary treatment relapsed. Of the patients who received surgery and radiation 2 of 8 relapsed. It became apparent that better treatment options were necessary¹². Being so similar to lymphomas, physicians began using a common leukemia and non-Hodgkin's lymphoma chemotherapy regimen on FDCS patients.

The CHOP regimen consists of Cyclophosphamide, Doxorubicin, Oncovin, and Prednisone (CHOP). They all exploit different pathways common in cancer cells. Cyclophosphamide slows or stops cell growth cells. It targets cells that are rapidly dividing which include cancer cells that are self-sufficient in growth signals and insensitive to antigrowth signals. More importantly, the biological actions of cyclophosphamide are dose-dependent. At high doses it is very cytotoxic; its metabolite phosphoramide adds an alkyl group to the N7 position on guanine resulting in arrested growth and cell death. The metabolite is only formed in cells with low levels of cytoplasmic aldehyde dehydrogenase (ALDH) resulting in relatively low chemotherapy toxicity in other non-cancer cells

like bone marrow¹³. It is also an immunosuppressant and decreases the inflammatory response. At low doses, while it is less cytotoxic, it shows some anti-angiogenic properties. The mechanism is not fully understood but it is thought that it interferes with the VEGF growth factors produced in and around the tumor microenvironment.

Doxorubicin interferes with cell growth and replication by intercalating in DNA. This stops topoisomerase II from relaxing the DNA strands and inhibiting transcription. Recent studies have also shown that doxorubicin may be involved in the Akt pathway. An important hallmark of cancer, Akt is part of the cell survival pathways by inhibiting apoptosis. There is also evidence that Akt is involved in angiogenesis and vascular maturation. Activation of PI3-kinase/Akt mediates VEGF production in cells. Therefore, doxorubicin has a dual role in cancer treatment: it inhibits cell survival (causes apoptosis), and decreases angiogenesis.

Oncovin, more commonly known as vincristine, is a mitotic inhibitor. It binds to tubulin dimers, inhibiting the assembly of microtubule structures like the cytoskeleton and mitotic spindle¹⁴. Although this drug still cannot strictly target cancer cells, cancer cells have a higher average turnover of microtubules making them more susceptible to the cytotoxicity of oncovin. Prednisone, the last drug in the CHOP combination therapy is a corticosteroid that acts as an immunosuppressant decreasing inflammation. Although some results were seen in FDCS patients treated with CHOP, they were far from consistent. Using a chemotherapy regimen designed for another cancer is an archaic "guess-and-check" way of treating a disease. In 2008 the largest review of FDCS was published as a retrospective analysis on 98 patients and the authors recommended that surgery with no adjuvant treatment be the standard for FDCS treatment. Patients treated with surgery alone had a recurrence rate of 40% and those treated with adjuvant therapy after surgery did not have a significantly different recurrence rate¹⁵.

Radiation and/or chemotherapy had no significant effect in improving patients' disease-free survival. With developments in our understanding of the hallmarks of cancer, however, novel approaches to specifically targeting and treating FDCS are being developed.

(PEG)-liposomal doxorubicin

One such development is in the delivery of doxorubicin. While it is an effective inducer of apoptosis, doxorubicin is quickly filtered out of the body. By loading a PEG-liposome with doxorubicin the circulation time and localization to tumors greatly increases. Cancerous tumors characteristically have extensive angiogenesis and leaky vasculatures, which causes the PEG-liposomes to naturally accumulate in the tumor¹⁶. This also allows for patients to receive lower and fewer doses of the drug and experience fewer side effects. This is also being attempted with nanoparticles but has not been tested on FDCS. In 2008 COP plus (PEG)-liposomal doxorubicin went into a clinical trial for an FDCS patient to replace the CHOP regimen, and after 5 years the patient remains in CR.

Taxotere And Gemcitabine

Newer cases are also starting to be treated by taxotere and gemcitabine. Taxotere is similar to Oncovin used in CHOP; it irreversibly binds beta tubulin halting formation of microtubules. Taxotere has an added benefit though; it also phosphorylates bcl-2 to halt the anti-apoptotic pathway. The dual effect of taxotere on integral cancer pathways makes it a more potent drug than Oncovin. Gemcitabene is a nucleoside analog and when incorporated into DNA during replication leads to apoptosis; the fluorine on the 2' carbon atom stops other nucleosides from attaching. The most important part of this combination therapy, however, is the synergism between the drugs¹⁷. While researchers are not entirely sure of the mechanism, there is evidence of synergistic effects of taxotere and gemcitabine when used in combination. This allows for decreased

dosages of each single agent with an increased apoptotic response.

Future FDCS developments

All advances in the understanding and treatment of FDCS come from advances made in other cancers. Funding for research is hard to come by and being such a rare cancer FDCS does not receive monetary priority. CHOP, Gemcitabine, and Taxotere were all initially developed for other cancers, but mutually mutated pathways allow for its use in FDCS. The hallmarks of cancer have helped physicians realize that there are biological commonalities between seemingly very different cancer types that can be exploited to develop new and better treatment plans. While standards of care for FDCS patients have progressed rapidly over the last twenty years the process is slowing. When FDCS was "discovered" in 1986 there was no standard of treatment. Now, 25 years later, there are multiple chemotherapeutic agents used, clinical trials available, and a much greater knowledge of its mechanism of action¹⁸. This rapid response occurred because physicians modified the use of pre-existing drugs. Financial restrictions mean that further advances rely on research made on other cancer types. Fortunately with constant progress in research technology this process is becoming much faster. The more we know about acquired capabilities of cancer, the more we can target those pathways, put new drugs on the market, and hopefully bring the word "cure" into view.

CONCLUSION

Although FDCS is a rare neoplasm, the frequency of FDCS is increasing and this disease should be kept in mind when diagnosing those patients who present with lymph node enlargement. It is difficult to provide treatment recommendations, but surgical resection for localized disease remains the mainstay of treatment, and the possible roles for adjuvant radiotherapy and chemotherapy remain undefined. Systemic chemotherapy has been reserved for patients with metastatic disease and/or after failure of

primary treatment. Multicenter clinical trials would help to further understand of this uncommon tumor. FDCS is a rare low to intermediate-grade malignant tumor. Appropriate application of FDC markers, such as CD21, CD35 and D2-40, would be helpful for arriving at a correct diagnosis. Most cases are associated with good prognosis after surgical treatment, with or without chemotherapy and radiotherapy. Patients with paraneoplastic pemphigus carry a less favorable prognosis. Although most of the patients initially responded to treatment, all of them eventually relapsed, which is in contrast to previously reported relapse rates of 16–36%. A better understanding of the biology of FDCS could guide our efforts in the development of new treatment modalities for this rare disease.

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