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Review Article

Interdigitating Dendritic Cell Sarcoma and Follicular Dendritic Cell Sarcoma : Histopathological Findings for Differential Diagnosis

Hiroya Ohtake and Mitsunori Yamakawa

Both interdigitating cell sarcoma (IDCS) and follicular dendritic cell sarcoma (FDCS) are rare neoplasms derived from dendritic cells in lymphoid organs. IDCS is defined as a neoplastic proliferation of spindle-shaped to ovoid cells with phenotypic features similar to those of IDCs. FDCS is a malignant neoplasm derived from FDCs that possess and present antigens to B cells in the follicular (germinal) centers of lymphoid organs. They often occur in lymph nodes, although they can also arise at extranodal sites. In this review, we have highlighted the morphological and immunohistochemical properties of these neoplasms, which could help in unequivocal and accurate diagnosis. 〔*J Clin Exp Hematop 53(3) : 179-184, 2013*〕

Keywords: interdigitating dendritic cell, follicular dendritic cell, interdigitating dendritic cell sarcoma, follicular dendritic cell sarcoma

INTRODUCTION

Both interdigitating cell sarcoma (IDCS) and follicular dendritic cell sarcoma (FDCS) are rare neoplasms derived from dendritic cells in lymphoid organs. They often occur in lymph nodes, although they can also arise at extranodal sites. IDCS and FDCS are seemingly difficult to diagnose. In this article, we summarize the characteristics of these entities and illustrate the essential points for diagnosis.

INTERDIGITATING DENDRITIC CELL SARCOMA (IDCS)

Definition

IDCS is defined as a neoplastic proliferation of spindle-shaped to ovoid cells with phenotypic features similar to those of IDCs.[1] Although IDCS is thought to be derived from IDC present in T-cell areas of lymphoid organs, other dendritic cell tumors without Langerhans cell or follicular dendritic cell (FDC) phenotypes are also placed in this category.

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Department of Pathological Diagnostics, Yamagata University Faculty of Medicine, Yamagata, Japan
Corresponding author: Dr. Hiroya Ohtake, Department of Pathological Diagnostics, Yamagata University Faculty of Medicine, 2-2-2 Iida-Nishi, Yamagata 990-9585, Japan
E-mail: hootake@med.id.yamagata-u.ac.jp

Clinical features

IDCS is an extremely rare tumor with only approximately 70 cases documented in the English literature. The median age of occurrence is 51 years, with a wide range of 2 to 88 years, although IDCS rarely occurs in children. The male to female ratio is 1.18 : 1.[2] Solitary lymph node involvement (especially of the cervical lymph nodes) is often seen, although systemic lymphadenopathy, hepatosplenomegaly, and bone marrow involvement have also been documented. In approximately one-third of cases, IDCS occurs at extranodal sites including the skin, kidney, lung, breast, salivary gland, pleura, urinary bladder, testis, alimentary canal, and uterus. Patients usually present with no symptoms, although general symptoms such as fever, fatigue, and night sweat have been documented. Cases associated with B-cell lymphomas (chronic lymphocytic leukemia/small lymphocytic lymphoma and follicular lymphoma) or T-cell lymphoma (lymphoblastic lymphoma) have also been reported.[3-6]

Histopathological, immunophenotypic, and cytogenetic features

Tumor cells in the lymph nodes are often located in paracortical areas ; they are mainly polygonal, ovoid to spindle-shaped, and arranged in storiform or whorled patterns. In some cases, tumor cells are round and occur in a sheath-like arrangement. They have abundant and slightly eosinophilic cytoplasm and indistinct cell borders. The nuclei are often vesicular and can present deep irregular invaginations, and

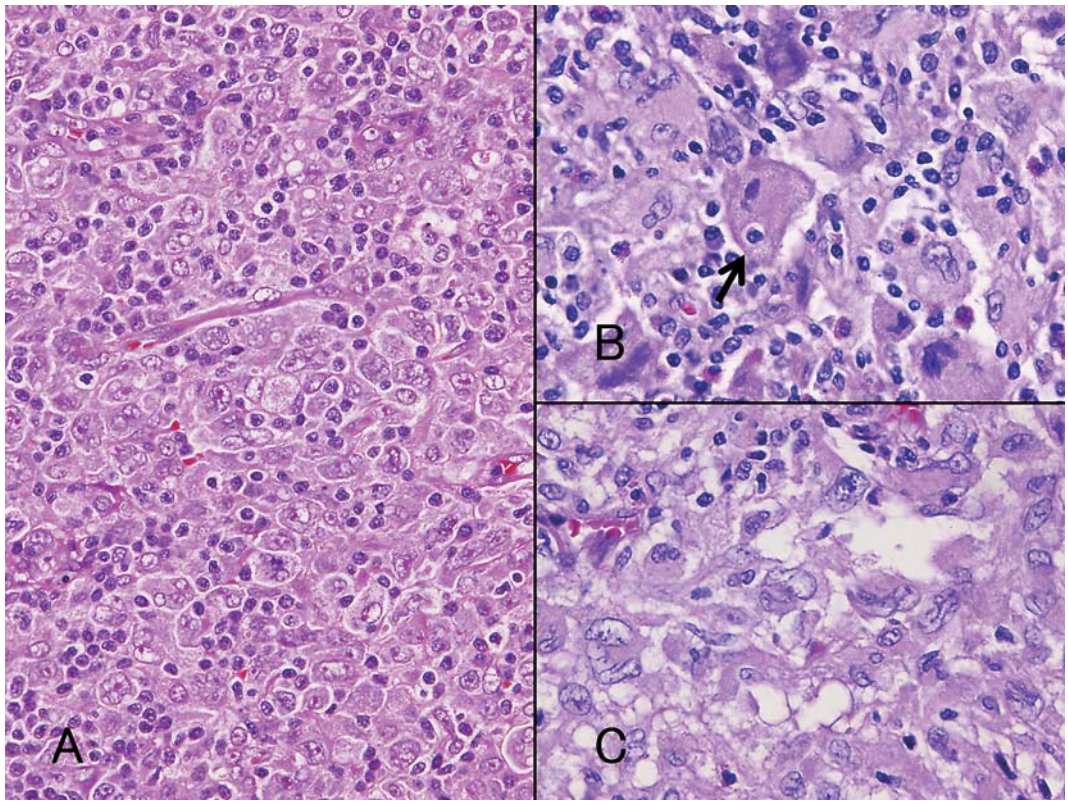

Fig. 1. Histopathological findings of 3 different cases of interdigitating dendritic cell sarcoma. Tumor cells are arranged in a diffuse pattern with numerous intermingled lymphocytes (*1A*). Some non-neoplastic cells show emperipolesis (*arrow*) (*1B*). Nuclei with complex invaginations are sometimes observed (*1C*).

nucleoli vary in size from small to large and conspicuous. Multinucleated or syncytial tumor cells are observed. Tumor cells sometimes infiltrate lymphatic sinuses. Usually, reactive inflammatory cells such as lymphocytes, plasma cells, and eosinophils are intermixed with tumor cells. Emperipolesis can also be observed (Fig. 1). Mitotic figures are usually less than 5/10 high-power fields (HPF).[1]

Immunohistochemically, tumor cells show negative staining for CD1a, although exceptional cases with positive staining have been reported,[7,8] and positive staining for S-100 protein, vimentin, and fascin. Several studies have reported positive staining for CD4, CD11c, CD14, CD45, CD68, HLA-DR, lysozyme, and epithelial membrane antigen, and negative staining for markers such as langerin ; FDC markers (CD21, CD23, and CD35) ; and other T-cell, B-cell, and myeloid cell markers. MIB-1 index measured in these tumors ranges between 10% and 20%. Intermingled lymphocytes found within IDCS are predominantly T cells, whereas B cells are quite rare. *Ig* and *TCR* gene rearrangements are usually not detected, although t(14;18) was reported in a case that developed from follicular lymphoma,[4] and chromosome 12 trisomy with *IgH* rearrangement was reported in a case that developed from chronic lymphocytic leukemia.[3]

Ultrastructurally, IDCSs are characterized by the presence of nuclear membrane indentations and a heterochromatin pattern. The cytoplasm is rich in cellular organelles and presents complex interdigitation. Birbeck granules and adhesive structures such as desmosomes are usually not present.[9]

Treatment and prognosis

The clinical course is generally aggressive, although surgical excisions tend to be curative when lesions are localized.[10] Overall median survival is 30 months.[11]

FOLLICULAR DENDRITIC CELL SARCOMA (FDCS)

Definition

FDCS is a malignant neoplasm derived from FDCs that possess and present antigens to B cells in the follicular (germinal) centers of lymphoid organs.

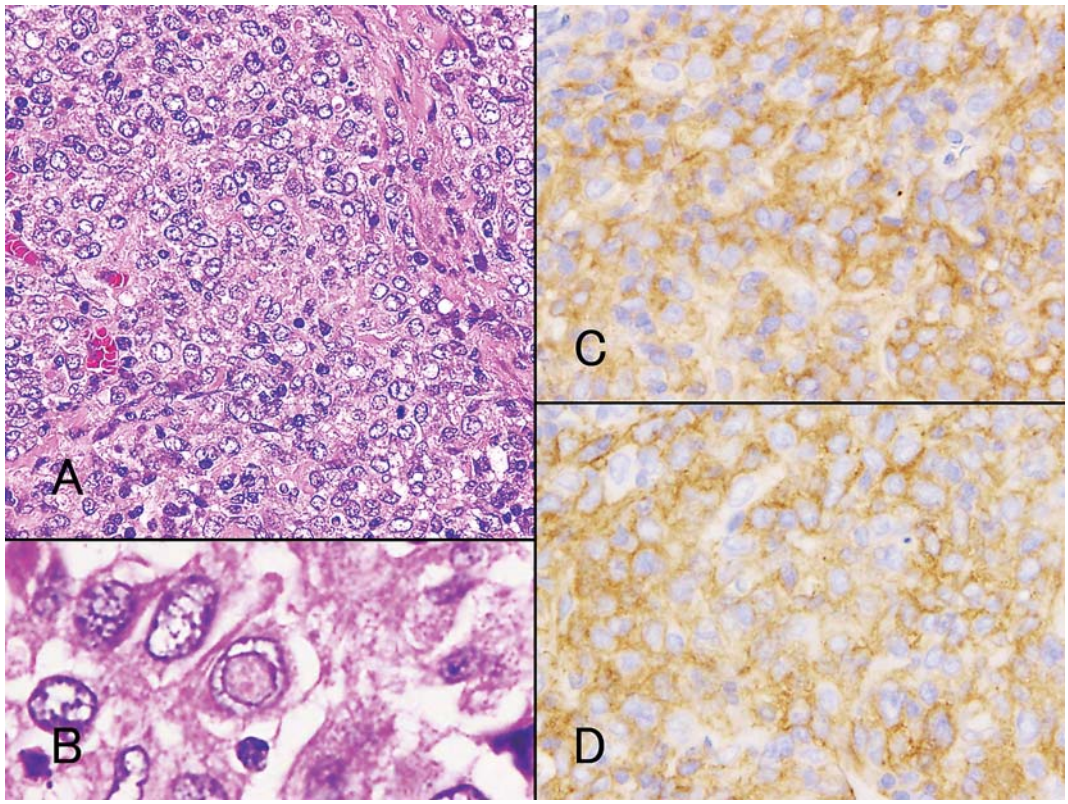

Fig. 2. Histopathological findings of follicular dendritic cell sarcoma. Tumor cells show a diffuse arrangement with indistinct cell borders (*2A*). Intranuclear pseudoinclusions are sometimes observed (*2B*). Tumor cells are positive for clusterin (*2C*) and CD23 (*2D*) antibodies. (*2C*) & (*2D*), Counterstained with hematoxylin.

Clinical features

FDCS is a rare tumor, with approximately 160 review and original articles having been published so far. Ages of the patients at presentation range widely, with FDCS occurring predominantly in adults (mean age, 46 years).[12] No gender preference is observed, although the inflammatory pseudotumor (IPT)-like variant is more common in female patients. Involvement of lymph nodes, in particular cervical lymph nodes, is common. Extranodal lesions have been reported in the tonsils, oral cavity, liver, spleen, alimentary canals, omentum, lungs, breasts, skin, and mediastinum.

FDCS associated with Castleman disease, usually the hyaline vascular type, has been reported. Usually, Castleman disease precedes or coexists with FDCS.[13] The IPT-like variant seems to be related to the presence of Epstein-Barr virus infection.[14] Rarely, paraneoplastic pemphigus occurs.[15] Moreover, recently, paraneoplastic myasthenia gravis has been reported.[16,17]

Histopathological, immunophenotypic, and cytogenetic features

Histologically, 2 major FDCS subtypes have been described : the common type with sarcomatoid appearance and the IPT-like variant. In the former subtype, spindle-shaped tumor cells with multinucleated giant cells are arranged in storiform, fascicular, or whorled patterns. A biphasic pattern with perivascular lymphoid infiltration has also been observed. Nuclei of tumor cells are vesicular or have a fine chromatin pattern, have small nucleoli, and have thin nuclear membranes. Intranuclear inclusions are occasionally seen. Tumor cells have unclear cellular borders and a moderate amount of eosinophilic cytoplasm (Fig. 2A, 2B). Binucleated or multinucleated cells are frequently observed. Mean mitotic rates are 3/10 HPF.[18] In the IPT-like variant, spindle-shaped tumor cells with vesicular nuclei and conspicuous nucleoli are scattered in the background and marked infiltration by lymphocytes and plasma cells is seen. The composition of lymphocytes is variable : sometimes T cells predominate and sometimes B cells predominate. Cases associated with myasthenia gravis showed proliferation of immature T cells.[16, 17]

Table 1. Immunohistochemical properties of dendritic cell and histiocytic neoplasms

Antibody	IDCS	FDCS	LCH/LCS	HS	IDCT
S-100 protein	+	+/−	+	+/−	+
CD68	+/−	+/−	+/−	+	+/−
CD1a	−	−	+	−	+
Langerin	−	−	+	−	−
FDC markers	−	+	−	−	−
D2-40	−	+ (membranous)	−	+/− (cytoplasmic)	ND
clusterin	+/− (weak)	+ (strong)	+/− (weak)	ND	ND

IDCS, interdigitating dendritic cell sarcoma; FDCS, follicular dendritic cell sarcoma; LCH, Langerhans cell histiocytosis; LCS, Langerhans cell sarcoma; HS, histiocytic sarcoma; IDCT, indeterminate dendritic cell tumor; −, negative; +/−, often positive; +, positive; ND, no data

Ultrastructurally, intertwined cellular projections and cellular adhesions mediated by desmosomes are observed.[19]

Immunohistochemically, several FDC markers (CD21, CD23, CD35, KiM4p, and CNA.42) are detected on tumor cells.[13] Staining for clusterin is always positive (Fig. 2C, 2D), and D2-40 staining is characterized by a membranous pattern.[20, 21] Tumor cells are positive for desmoplakin, vimentin, fascin, epidermal growth factor receptor, and HLA-DR. Positive staining for CD4, CD11a, CD14, CD20, CD45, CD68, epithelial membrane antigen, HLA-DR, nerve growth factor receptor (low affinity), S-100 protein, and muscle actin have also been reported. Staining for CD1a, CD3, CD34, CD79a, myeloperoxidase, lysozyme, and HMB45 is negative. The MIB-1 index is 1–25% (mean, 13%).[13] *Ig* or *TCR* gene rearrangement is not detected.

Treatment and prognosis

In general, FDCS has low to intermediate malignant potential and usually progresses slowly. Although complete surgical excision with or without radiotherapy and/or chemotherapy is employed, local recurrence occurs in approximately half of the patients, and distant metastasis after therapy in one-quarter of patients.[22] Intra-abdominal lesions, high-grade atypia, coagulative necrosis, high mitotic activity (mitotic figures 5/10 HPF), and large tumor size (> 5 cm) are indicators of poor prognosis. Li *et al*. classified FDCS according to tumor size and atypia into high-risk and low-risk cases.[12] In cases of extranodal lesions, 5-year disease-free and overall survival rates are 32% and 79%, respectively. FDCS has favorable prognosis compared with IDCS.[23]

CLUES TO DIFFERENTIAL DIAGNOSIS

Both IDCS and FDCS are difficult to distinguish from other dendritic cell or histiocytic tumors. The morphological characteristics indicative of IDCS and FDCS are a storiform or whorl-like arrangement of tumor cells with indistinct cellular borders and the associated presence of multinucleated cells. In IDCS cases, cellular proliferation is predominantly restricted to the paracortical areas, and emperipolesis is sometimes observed. On the other hand, FDCS shows intranuclear inclusions.

Immunohistochemically, the intermingled lymphocytes in IDCS are predominantly T cells ($CD3^+$ and $CD5^+$). FDCS shows membranous positive staining with D2-40 antibody and strong positivity for clusterin, staining patterns that are not observed for other dendritic cell neoplasms. The immunohistochemical properties of dendritic cell and histiocytic neoplasms are summarized in Table 1. A diagnostic algorithm is shown in Fig. 3. For correct immunohistochemical analyses, excessive formaldehyde fixation must be avoided.

CONCLUSIONS

IDCS and FDCS are rare neoplasms, which are seemingly difficult to diagnose. In this paper, we have highlighted the morphological and immunohistochemical properties of these neoplasms, which could help in unequivocal and accurate diagnosis.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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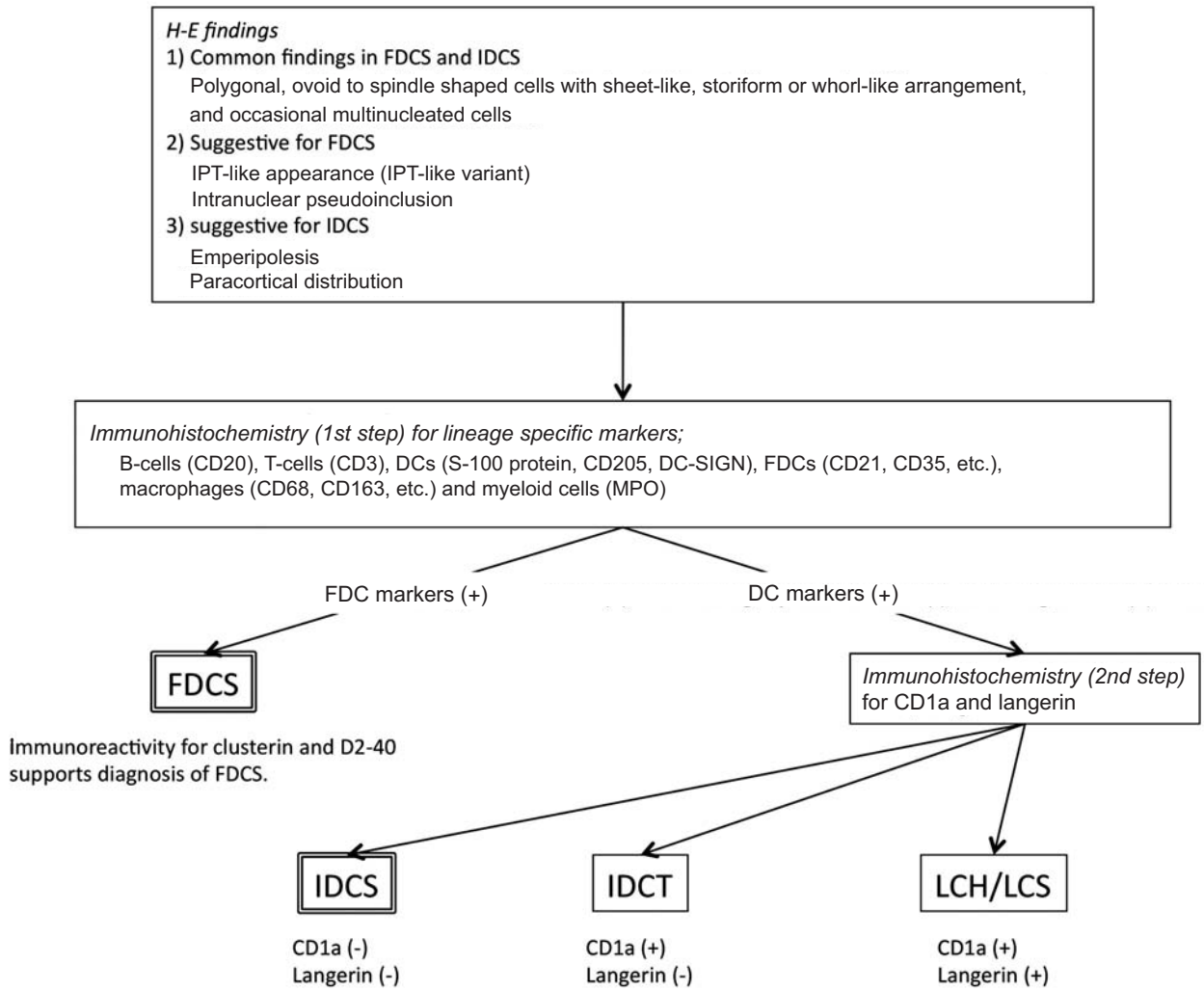

Fig. 3. A diagnostic algorithm of interdigitating dendritic cell sarcoma and follicular dendritic cell sarcoma. FDCS, follicular dendritic cell sarcoma; IDCS, interdigitating dendritic cell sarcoma; IPT, inflammatory pseudotumor; DCs, dendritic cells; FDCs, follicular dendritic cells; MPO, myeloperoxidase; IDCT, indeterminate dendritic cell tumor; LCH/LCS, Langerhans cell histiocytosis/Langerhans cell sarcoma.

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