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REVIEW ARTICLE

FOLLICULAR DENDRITIC CELL SARCOMA, ITS DIAGNOSTIC DIFFICULT, CLINICAL BEHAVIOUR, AND MANAGEMENT – WITH REVIEW OF LITERATURE

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ABSTRACT

Follicular dendritic cell sarcoma is a rare mesenchymal neoplasm arising from follicular dendritic cells and accounts for only 0.4% of soft tissue sarcomas. Most of the follicular dendritic cell sarcomas arise from lymph nodes. However, at least one third cases occur at extranodal sites. Clinico-pathological misdiagnosis is common in this disease because of its similarity in clinical presentation, histopathological findings and immunohistochemical markers in initial evaluation to many malignancies. The genetic alterations leading to tumourigenesis in follicular dendritic cell sarcoma are unknown. The disease is considered under intermediate grade malignancy, but it has significant locoregional recurrence and distant metastatic potential. The clinical history, different pattern of treatments, and response to treatments is unclear due to insignificant data. But to advance in diagnostic assays and few chemotherapeutic agents helps in accurate diagnosis and better treatment of follicular dendritic cell sarcoma.

INTRODUCTION

Definition

Follicular dendritic cell sarcoma (FDCS) is defined as a neoplastic proliferation of spindled to ovoid cells with morphologic and immunophenotypic features similar to those of normal follicular dendritic cells (FDC). It is classified under histiocytic and dendritic cell neoplasms by the WHO classification of tumours.[1] It is a rare mesenchymal neoplasm of FDC that are antigen-presenting cells of the B-cell follicles in lymph nodes and extranodal lymphoid tissue. FDCS was first described by Rosai and colleagues.[2]

Cells of origin

FDCs are accessory cells of the lymphoid system locating in the germinal centres of lymphoid follicles. FDCs are also widely distributed in extranodal locatons. In the liver, FDCs are located around the portal spaces.[3] Previously, FDCs believed to be of hematopoetic origin, but ultrastructure, cytology and immunophenotype favouring mesenchymal origin.[4] FDC have a humoral immune response cooperating with dendritic cells and Langerhans cells. These cells play a role in regulation of the germinal centre reaction and present antigens to B cells without any lymphocytic or phagocytic property of its own. Tumours arising from FDC are classified by WHO as FDCSs.[5]

Interdigitating cell sarcoma arises from Interdigitating dendritic cells (IDC). These cells are arachnoid nonlymphoid accessory cells acting as potent antigen-presenting cells responsible for initiating primary T-lymphocyte immune response. These cells are found in the T-cell areas of peripheral lymphoid tissue including the paracortex and deep cortex of lymph nodes, the splenic periarteriolar lymphoid sheaths, and the interfollicular areas of mucosa-associated lymphoid tissue.

FDCS and IDCS are the two subtypes of dendritic cell sarcomas (DCS) and are rarely found. These are difficult to diagnose with poor outcomes on standard therapy.[6]

Incidence and sites of involvement

FDCS is a very rare malignancy and majority cases were reported from East Asia showing a predilection for certain ethnicities or in certain geographic locations. Majority cases found as primary in the lymph node and one third or approximately 30% cases found in extranodal sites.[7] FDCS was first described in 1986 in a series of four cases of lymph node origin.[2] According to Francisca EMML *et al*, about 31% being nodal disease, 58% being isolated extranodal involvement, and 11% being combined diseases.[2] In spite of large number of extranodal sites involvement, cervical lymph nodes remain the most common site of FDCS.

Nodal FDCS: It is commonly found in cervical, mediastinal, and axillary areas.[8]

E-FDCS (Extranodal-FDCS): E-FDCS can present elsewhere in the body such as: Head and neck, gastrointestinal tract, spleen, liver, soft tissue, lung, skin, breast, retroperitoneum, mesentry, mesocolon, mediastinum, etc.[1,9] In 1994, 2 cases were first reported in the literature with oropharynx primary such as: soft palate and tonsil.[10] Only 13 cases with mesentery primary were reported.[11] Few extranodal sites had been reported with extremely rare incidence such as: stomach, colon, appendix, small bowel, and liver.[12] However, extranodal disease shows a predilection for head and neck locations. A data showed out of 19 cases of E-FDCS of head and neck areas, 6 cases were from tonsil, 5 cases from pharynx, 2 from hard palate, 5 in soft tissue, and 1 from thyroid.[9]

Risk factors and aetiology

Risk factors or aetiology are not clearly defined in FDCS due to lack of significant data. A study found no definitive cause linked to FDCS.[13] However some evidence shows previous exposure to EBV or diagnosis of Castleman's disease are the possible risk factors.[8] Approximately 10% to 20% of FDCS cases are associated with Castleman disease, mostly the hyaline vascular variant.[14-16] Castelman disease is a benign lymphoproliferative disorder. Hyperplasia and dysplasia of FDC are found in Castleman disease considering it as precursor lesions for FDCS.[5] Few cases of antecedent Castleman disease demonstrate areas of FDC proliferation showing a hypothesis to arise of FDCS in these areas.[15] Clonal expression of FDC in Castleman disease have been reported in literature.[17] Over expression of p53 protein and increased number of weakly p53-positive spindle cells were reported in a Castleman disease specimen showing a possible role of p53 in the transformation process.[16] EGFR positivity also found in FDCS and FDCs in Castleman disease, but the role is not clearly mentioned.[15] FDCs express the EBV receptor CD21.[18] Data showed approximately 12% of FDCS cases are associated with EBV, but its role in development of FDCS is not clear and also does not play a role in the transformation process of Castleman's disease to FDCS.[9] Most of the EBV association found in IPT-like FDCS and also found in liver and spleen primary.[19,20] But in majority cases of FDCSs EBV is absent showing controversy in relation of EBV to FDCS. Association of FDCS with autoimmune diseases were reported in paraneoplastic pemphigus and myasthenia gravis.[21] According to Wu A *et al*, at least 6 reports of FDCS found in concurrent with myasthenia gravis.[14]

Clinical presentation

FDCS mostly affect young to middle-aged adults with mean age being 44 years for both the sex.[14] The median age of presentation is 41 year for FDCS with no predilection of sex.[7,13] Sign and symptoms vary widely depending on site of the body or organ involved. FDCS have an indolent clinical course. Majority cases present with an asymptomatic, slow-growing, painless cervical lymphadenopathy.[21] Fever and weight loss may present in 10% cases. Neck is the most common site of nodal FDCS. Sore throat, difficulty in swallowing, cough, weight loss and tiredness are other symptoms may present.

A study showed majority cases presented with cervical and axillary lymphadenopathy, and 17 out of 51 cases presented in extranodal sites including liver, spleen, bowel and pancreas.[13] A study on DCS (including FDCS and IDCS) at MDACC showed the median was age at diagnosis was 50 years, 58% of the patients were female, 60% cases presented with localized disease, 40% cases presented with systemic involvement, abdomen was involved in 17/35 patients and spleen was involved in 7/35 patients (as the most common extranodal site).[6]

Data on E-FDCS showed the age range of presentation from 2 to 82 years, mean and median age found in the fifth decade of life with a slight female predominance (1.2:1).[22] A study showed, out of 19 cases of E-FDCS of head and neck regions, 11 cases were found in female, and 8 cases were found in male, and the mean age of presentation was 42.2 years with mean tumour size in greatest dimension was 4.8 cm.[9] Abdominal pain is the most common symptom in abdominal primary and fever, weight loss, fatigue, intestinal obstruction, rectal bleeding, and dyspepsia are the possible systemic symptoms. Patient may present as slow-growing painless mass with nonspecific abdominal pain. Inflammatory pseudo tumour (IPT)-like FDCS of intra-abdominal location is a separate entity in terms of different clinical and pathological features than those of classical FDCS.[3] IPT-like FDCS have a female predominance with frequent systemic symptoms.[1,19] According to Cheuk *et al*., 11 cases of intra abdominal IPT-like FDCS were reported and EBV association were found in these cases.[19]

Imaging and other investigations

Clinical examination, imaging, and pathological assessment are the initial modes of diagnosis for FDCS. Radiological findings confirm the presence of space-occupying lesion and provide delineation of the extent of the lesion and staging. Ultrasound and CT scan are the initial imaging procedures. Common imaging findings for abdominal-FDCS are a well defined mass with regional lymphadenopathy and homogenous enhancement with interal necrosis and calcifications.[23] GIST and primary GI lymphomas are the differential diagnoses. CT scan commonly shows homogeneus areas in the mass, but heterogeneity may be due to necrosis or hemorrhagic areas.[24] PET scan in one case showed moderate uptake by tumour to FDG and high thymidine kinase 1 actiity by the tumour.[25] Alkaline phosphatise level may rise in hepatic FDCS.[26] In situ hybridization for EBV-encoded RNA and Southern blot studies may detect the presence of EBV.[19]

Histopathology

Pathological diagnosis of FDCS is difficult. It requires a combination of morphological, immuophenotypical, cytochemical, and electron microscopic analyses for the confirmation of diagnosis.[21] E-FDCS are with more probability of under recognized than nodal primary.[3] Gross appearance of FDCS shows a round-to-ovoid, well-circumscribed or even encapsulated, bosselated or fleshy solid masses, pink or white to tan gray cut surface, but hemorrhage, necrosis and cystic changes may be found in larger tumours.[5,14,19] Size for FDCS can range from 1 to 15 cm depending on the tumour location, with a median of approximately 5 cm.[21] Whereas, size of the E-FDCS can range from 1 to 20 cm with a median of 7.4 cm.[22] According to Youens KE *et al*., for intra-abdominal tumour the median size is 11 cm, whereas it is 3 cm outside the abdominal cavity.[18] Histologic appearance of FDCS shows spindled and ovoid cell proliferations forming a varied architectural patterns in storiform (most common) or whirling (reminiscent of a

meningioma), fascicles, trabecular, or diffuse sheets.[12] Plump eosinophilic fibrillary cytoplasm and indistinct cell borders imparting a syncytial appearance are found in tumour cells with elongated or ovoid nuclei, presence of vesicular or finely granular chromatin inside nuclei and distinct nucleoli with a delicate thin nuclear membrane.[18] Scattered multinucleated cells in small number can be seen resembling Warthin-Finkeldey giant cells. Nuclear pseudoinclusions are rarely seen with frequency increased after radiotherapy.[27] Cytology features show epithelioid to spindled cells both in syncytial groups as well as single cells, with oval-to-cigar-shaped nuclei containing vesicular chromatin, intranuclear inclusions, nuclear grooves and distinct nucleoli.[28] Majority cases are cytologially bland with a low mitotic rate (0-10/10HPF), but greater cytologic atypia and higher mitotic rates may be seen. A sprse infiltration of mature lymphocytes and plasma cells present, predominantly in a perivascular distribution. The perivascular distribution of small lymphocytes within the tumour is the key histologic feature for FDCS. A study of 16 cases of FDCS showed 75% cases with classical features of whorls, fascicular or storiform pattern, 15 cases with lymphoplasmacytic infiltration, one case with nuclear pseudo inclusions, 18.7% cases with epithelioid cells, and 25% cases with presence of giant cells.[4]

Tumour involving liver and spleen shows absence of spindled cells, but have a greater degree of lymphoplasmacytic inflammatory infiltrate causing histological dilemma with inflammatory pseudotumour (IPT) and considering as a separate entity of IPT-like FDCS.[3] Spindle cells are usually dispersed showing a loose fascicular and sheet-like growth pattern with vescicular nuclei and scattered by a prominent lymphoplasmacytic infiltrate and nuclei are variably atypical containing prominent nucleoli, reminiscent of Reed-Sternberg cells.[19] A review of 31 cases of E-FDCS on mitotic count showed a median value of 3/10 HPFs and a range of 0-50/HPFs.[22] Coagulative necrosis was reported in 30% of cases of E-FDCS.[22]

Immunohistochemistry

Immunophenotyping findings are similar for both nodal and extranodal FDCSs. CD21, CD23 and CD35 are specific markers for FDCS differentiation.[21] Vimentin, fascin, HLA-DR, EMA, S100, R4/23, Ki-M4, Ki-M4p, Ki-FDC1p and CD68 may positive without specificity.[29] CD1a, desmin, CD45, lysozyme, CD34, CD3, CD79a, CD30, HMB45, myeloperoxidase, and cytokeratin are consistently negative.[5,30] However, FDCS of liver and spleen show only weak and focal positivity of the markers. Clusterin, fascin, and podoplanin are three recent markers positive in majority cases of FDCSs.[21] Clusterin is found strongly positive in FDCSs with high specificity and sensitivity and weak to no expression in other dendritic cell tumours.[21] Podoplanin have high sensitivity for FDCS with strong membrane staining.[21] A recent marker c-Synuclein has shown strongly staining for FDC meshwork and it may help in identifying FDCS.[31] Podoplanin helps in distinguishing FDCS from histiocytic sarcoma.[21] Microtubuloreticular structures (MTRS) and increased levels of intracellular clusterin are the characteristic features of FDCSs.[32] MTRS involved in many cancer hallmarks such as: proliferating signalling, growth activation, and replicative immortality, whereas, clusterin is involved in resistance to cell death and evading growth suppressors.[33] According to Lima FEMM *et al*., at least 18.6% cases were erroneously diagnosed at presentation.[30] One study showed CD21, CD23, and CD35 were positive in 83%, 90%, and 44% of the cases, respectively.[34,35] A report on 3 cases of FDCS showed CD21, CD35, and fascin markers were positive in all the cases and S100, cytokeratin, EBV-LMP-1, EBER, and LCA markers were negative.[9] A report on liver-FDCS showed CD21, and CD35 were positive, S100, EMA, vimentin, and CD117 were focally positive.[7] Ki-67 labelling usually ranges from 1% to 25%.[1] Ultrastructural features of FDCS on electron microscopy shows long, slender, interdigitating cytoplasmic processes, with few labyrinth-like pattern and desmosome-like junctions without Birbeck granules or lysosomes.[8] In overall, CD21, and CD35 are commonly used in FDCS.

Genetic alterations

The genetic alterations causing tumourigenesis in FDCS are largely unknown. B-cell or T-cell rearrangements are absent in FDCS, whereas, only occasional cytogenetic abnormalities have been reported. Karyotypic alterations were identified in few case reports. BRAFV600E mutation found in 18.5% of all FDCS cases (5 of 27) and it was found in 40% (2 of 5) of IPT-like FDCS types.[14,36] BRAF mutations could help in differentiating IPT-like FDCS from inflammatory myofibroblastic tumour.[36] A recent study on 13 cases of FDCS

Table-1 Cases of E-FDCS initially misdiagnosed

Literature	Actual diagnosis with site specific	Initial histological misdiagnosis	Further IHC study confirming diagnosis
Biddle DA *et al*.	Case-1:Tonsil Case-2: Nasopharynx	Case-1: IPT Case-2: Malignant Schwanoma	Both cases: CD 21, CD35: +ve S-100, CK, LCA: -ve
Desai S *et al*.	parapharyngeal	Ectopic meningioma	CD 21, CD35: +ve
Chan JK *et al*.	palate	Acinic cell carcinoma	CD 21, CD35: +ve
Galati LT *et al*.	thyroid	Poorly-differentiated non small cell carcinoma	CD 21, CD35: +ve
Araujo VC	palate	Fibrous histiocytoma	CD 21, CD35, CD23, S-100 protein, CD68, and actin: +ve LCA, CD20, EMA, CK, HMB45, and CD34: -ve
Choi PC *et al*.	mediastinum	Malignant ectopic thymic tumour	CD 21, CD35, CD23: +ve Cytokeratin: -ve
Kaur A *et al*., Schulz-Bischof K *et al*., and Muller-Hermelink HK *et al*.	tonsil	Ectopic mengioma	CD 21, CD35: +ve
Huszar M *et al*.	retroperitonium	Ectopic meningioma	CD 21, CD35, vimentin, keratin, EMA: +ve
Shek TW *et al*.	intraabdominal	Intraabdominal stromal tumour	CD 21, CD35: +ve
Fonseca R *et al*	liver	Diffuse large cell lymphoma	CD 21, CD35,S-100, CD45, CD14, vimentin: +ve
Moriki T *et al*.	mesentry	Unclassified nonepithelial low grade malignant neoplasm	CD 21, CD35: +ve

showed recurrent alterations in tumour suppressor genes critical for the negative regulation of NF-k B activation found in 5 cases (38%), recurrent alterations in cell cycle regulatory genes(CDKN2A and RB1) noted in 4 cases (31%) and immune evasion (CD274 and PDCD1LG2) also seen.[37] However, there was absence of any BRAF V600E mutations in the cohort. A novel translocation of t(5;9)(p15;q22) involving SYK and EXOC3 was reported as a first case till date.[37] However, pathogenic loss of function alterations in NF-k B regulatory genes reported in 5 of 13 cases were also reported in 2 of the 3 metastatic tumours suggesting a possible correlation with more aggressive disease course.[37] One case showed highest mutational burden (involving altered functions of CYLD, CDKN2A, and RB1, copy-number gain of 9p24), suffered with most aggressive disease course and died from metastatic disease 37 months after initial diagnosis.[37] Larger study analyses are required to confirm the association of molecular features with clinical aggressive behaviour of the FDCS.

Differential diagnosis

About one third FDCS cases are initially misdiagnosed due to not considering FDCS as the initial pathology evaluation and also, FDC markers are not included in the routine panel for investigation of undifferentiated neoplasms.[22] Ten cases of E-FDCS of the head and neck region and 4 cases of abdominal E-FDCS were initially misdiagnosed (table-1).[9,10,38-48]

FDCS should be differentiated from other tumours because of the indolent course with unusual recurrences or distant metastasis. IPT, malignant fibrous histiocytoma, ectopic meningioma, mesenchymal tumour with neural differentiation, schwannoma, stromal tumour, thymoma, GIST, lymphoma (both Hodgkin's and non-Hodgkin's), melanoma, peripheral nerve sheath tumour, granulomatous inflammation, undifferentiated carcinoma/sarcoma, and IDCS are the possible differential diagnoses.

However, IHC staining showing negativity of cytokeratin rules out possibility of carcinoma of spindiled or sarcomatoid morphology. CD21 and CD35 markers positivity in FDCS rules out the possibility of meningioma, thymoma, malignant fibrous histicytoma, and interdigitating reticulum cell sarcoma.[5,27] Also, positivity of clusterin in FDCS rules out the possibility of other dendritic cell neoplasms.[21] IPT-like hepatic FDCS not contain cells with marked pleomorphism, and the spindle cells not express FDC markers.[3]

In IDCS cells are large and polygonal, and express S100 protein and CD68, lacking FDC markers.[49] Langerhans' cell tumour, a type of dendritic cell neoplasm, express staining for CD1 and S100 protein and Birbeck granules are found in cells on electron microscopy.[3] In hepatocellular carcinoma (HCC) cells are large, granular cytoplasm, centrally placed nuclei, with variable pleoorphism, but spindle cells are absent.[3] In metastatic adenocarcinoma of liver, tumour cells are large with eccentrically placed nuclei. However, in metastatic small cell tumour of liver, cells may be spindled and with little cytoplasm, but with absence of nucleoli and lack of a prominent inflammatory component like in IPT-like FDCS.

Treatment

The real treatment guidelines for FDCS are not clear till date due to insufficient study. Some physician treat FDCS in line of lymphoma (with chemotherapy CHOP regimen), whereas, some treat in line of soft tissue sarcomas (with wide resection and adjuvant radiotherapy). Complete resection is the treatment of choice for both primary and recurrent FDCS with better overall survival in comparison to other treatment modalities.[4,21] The role of radiation and chemotherapy, and best chemotherapeutic agent is not clear. Previous data showed adjuvant treatments had no significant effect on disease free survival after a radical surgery.[50] However, adjuvant radiotherapy or chemotherapy is indicated in presence of adverse pathological features (postoperative surgical margins and extra-capsular extension), advanced disease, and incompletely resected lesions.[7,30] A retrospective analysis on 98 patients showed patients treated with surgery alone had a recurrence rate of 40%, whereas those treated with adjuvant treatment did not have a significant difference in recurrence rate suggesting surgery with no adjuvant treatment be the standard of treatment.[51] A study showed 12 out of 31 patients who had treated with surgery alone relapsed, but 2 out of 8 patients who had treated with surgery and radiation relapsed.[13] Treatment with combination chemotherapy as CHOP regimen produces some degree of response by increased tumour necrosis and decreased uptake on PET.[52] Chemotherapy drugs in line of sarcomas treatment (doxorubicin, ifosfamide, gemcitabine, and vinorelbine) can be used in FDCS.[7] Polyethelene glycol-liposomal doxorubicins can be used with a favourable response, are more accumulated in the tumour, and the patient will receive lower and fewer doses of the drug with fewer side effects.[53]

Table-2 Differential diagnoses for FDCS[13]

Differential points	FDCS	IDCS	Thymoma	MM	GIST	IMT	SCC	LCT	MUSC
Cell origin	FDC	IDC	Epithelial cells of the thymus	Melanocytes	Cells of Kazal	Myofibroblasts	Long spindle-shaped cells (connective tissue)	Langerhan's cells	NA
Histology	spindled/ovoid cell proliferation with storiform or whirling patterns with absence of reticulin	Presence of reticulin	Hassall corpuscles may +	NA	Dense lymphocytic infiltration is uncommon	NA	NA	NA	NA
IHC +ve markers	CD21, CD35, CD23, fascin, clusterin, podoplanin	S100, CD68	CK, p63	HMB45, Melan-A	CD34, DOG1	SMA, desmin, ALK	CK	CD1, S100	CK
IHC –ve markers	CD34, DOG1, HMB45, Melan-A	CD21, CD35	CD21, CD35	CD21, CD35	CD21, CD35	CD21, CD35	CD21, CD35	CD21, CD35	CD21, CD35
Electron microscopy	Desmosome +ve	Desmosome -						Birbeck granules +ve	

IHC = Immunohistochemistry, + = positive, - = negative, MM = Malignant melanoma, SCC = Spindle cell carcinomas, MUSC = Metastatic undifferentiated or sarcomatoid carcinomas, CK = Cytokeratin, SMA = Smooth muscle actin, NA = not applicable

In a clinical trial (2008), COP plus PEG-liposomal doxorubicin was taken as a regimen to replace CHOP regimen, and after 5 years the patient remains in complete response.[53] Taxotere and gemcitabine can be used alone or as combination therapy in FDCSs because of strong effect on cancer pathways and synergistic effects in combination. A report on liver FDCS showed partial response to ifosfamide and platinum based regimen, CHOP regimen, single agent gemcitabine and single agent vinorelbine.[7] Treatment with Vemurafenib, a BRAF enzyme inhibitor, showed dramatic effect in other dendritic and histiocytic neoplasms such as: Erdheim Chester disease and Langerhans'cell histiocytosis and can be used as a targeted therapy in BRAF6000E mutated FDCS cases.[14,54] EGFR inhibitors can be used in moderate to strong expression of EGFR cases.[7]

Prognosis

FDCS have an indolent course and have a tendency for local recurrence but with a low risk of metastasis. The behaviour is almost similar to that of a low-grade soft tissue sarcoma.[21] FDCS have a unpredictable clinical course with some patients remain disease free for a prolonged period and some patients die due to disease progression.[7] Further studies with longer follow up periods with recognization of increased cytologic atypia suggested that, the disease is more aggressive and should be considered as intermediate grade malignancy.[27] Nodal FDCS are having low rate of metastasis (approximately 10%) in comparison to E-FDCS especially with abdominal locations where it is approximately 20%.[2]

According to Soriano AO *et al*., lung, lymph node, liver, and bone are the common sites of distant metastasis with percentage of 9.4%, 8.9%, 9.4%, and 3% respectively.[34] E-FDCS have a worse prognosis in comparison to nodal FDCS. Intrabdominal-FDCS are presented with a larger tumour size (on average 9.5cm) with delayed diagnosis which may be a strong factor for worse prognosis than other FDCS than a true difference in FDCS biology. A tumour diameter greater than 6 cm, intra-abdominal presentation, coagulative necrosis, significant nuclear pleomorphism, greater cytologic atypia, abnormal mitosis, and increased mitotic activity (>5 of 10 HPF) are associated with more aggressive clinical course.[14,18] Younger age and sparse inflammatory infiltrate are the other possible poor prognostic factors.[29] A case of breast-FDCS with high-grade features survived for 19 years after initial treatment without any recurrence or distant metastasis. A report showed spontaneous regression suggesting an incomplete understanding of the pathophysiology.[55] A study showed recurrence, metastasis and mortality rates were 35%, 35%, and 17.6% respectively.[27] According to Khalid T *et al*, 36% of the cases showed local recurrence and 28% cases showed metastasis.[7] Study showed local recurrence at a median time of 15 months, and distant metastasis at a median of 18.5 months were 28.1%, and 27.2% respectively.[30] A data showed the 2- and 5-year disease free survival rates were only 57% and 32% respectively, whereas, another study showed findings with 62.3% and 27.4% respectively.[22,35] Even after good response to therapy in FDCS, the relapse rate can be as high as 80% with mortality rate approximately 20%.[14,34]

Table-3 Difference between FDCS and IDCS

Points	FDCS	IDCS
Cells of origin	FDC	IDC
About cells of origin	Lymhoid accessory cells Located in germial centres of the lymphoid follicles	Nonlymphoid accessory cells Found in T-cell areas of peripheral lymphoid tissue
Role of the cells	Regulation of the germinal centre reaction and present antigens to B cells	Responsible for initiating primary T-lymphocyte immune responses
IHC staing	CD21, CD23, CD35 positive CD1a, desmin, CD45, lysozyme, CD34, CD3, CD79a, CD30, HMB45, myeloperoxidase, and cytokeratin are consistently negative	S100, vimentin, HLA-DR, CD68 positive CD21, and CD35 negative
Incidence	Rare	More rarer than FDCS
Median age of presentation	41	52
Sex	No sex predilection	Male:female = 1.5:1
Histology	Absence of reticulin	Collagenous or hyalinised background with increased reticulin may be positive
Mitotic rate	Usually low	Usually intermediate
Differential diagnosis	Langerhans cell sarcoma and histiocytosis X are notincluded	As in FDCS including Langerhans cell sarcoma, malignant histiocytosis X
Behaviour	Less aggressive	More aggressive
Response to conventional therapy	Response to therapy	Generally unresponsive
Widespread disease	Less	More

Table-4 Difference between nodal FDCS and E-FDCS

Points	*Nodal FDCS*	*E-FDCS*
Incidence	More	Less
Sex	No sex predilection	Female:male = 1.2:1
EBV association	Less	More
Gross tumour size range	1-15 cm	1-20 cm
Median tumour size	5 cm	7.4 cm
IPT-like pathology	uncommon	common
Mitotic activity	Comparatively less	Comparatively more
Systemic symptoms	Comparatively less	Comparatively more
Misdiagnosis	Less in comparison to E-FDCS	More
Distant metastasis after treatment	10%	20%
Prognosis	Better than E-FDCS	Worse

A study showed mortality rates for low-, medium-, and high risk FDCS over a 120-month surveillance period were 0%, 4%, and 45% respectively.[35] This risk stratification mortality rate data needs further evaluation with large number of studies to conclude regarding which patients will receive adjuvant treatment after surgery.

CONCLUSION

FDCS of both nodal and extranodal sites are poorly described in the literatures. Misdiagnosis and delayed diagnosis is common due to rarity of the disease and challenging in the pathology confirmation. Proper histopathology and immunohistochemical analysis is necessary for early diagnosis and to avoid misdiagnosis. Standard labrotaries should have immunohistochemical makers for FDCS such as CD21, CD23, and CD35 along with S100, EMA, CD68, vimentin, LCA, CD1a, fascin, clusterin, podoplain, etc. Surgical resection is the preferred treatment. Role of adjuvant chemotherapy and radiotherapy is not clear. CHOP regimen is commonly used as adjuvant chemotherapy. Second line chemotherapy with docetaxel plus gemcitabine combination and PEG-liposomal doxorubicin can be tried in recurrence or metastatic settings. Large number of studies is necessary for evaluation of such a rare disease to draw a standard guideline for treatment and to know survival status of the disease.

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