Follicular Dendritic Cell Sarcoma

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Abstract

Review on Follicular Dendritic Cell Sarcoma, with data on clinics, and the genes involved.

Keywords
Follicular Dendritic Cell Sarcoma; BRAF; CYLD; NFKBIA; CDKN2A; RB1; CD274; PDCD1LG2

Clinics and pathology

Disease
Follicular dendritic cell sarcoma (FDCS) is an extremely rare mesenchymal neoplasm. This tumor was first reported in 1986 by Monda et al. and is classified by the World Health Organization (WHO) under histiocytic and dendritic cell neoplasms.

Phenotype/cell stem origin
The cell of origin is the antigen presenting follicular dendritic cell. Normal (Non-neoplastic) follicular dendritic cells process antigen antibody complexes, and present them to B-cells in lymphoid follicles (Wu et al., 2016).

Etiology
The etiology is unknown. Rare cases have been described in association with the hyaline vascular type of Castleman disease (Youens et al., 2008).

Epidemiology
Follicular dendritic cell sarcomas are extremely rare. The number of reported cases are fewer than 100. Patients as young as 9 up to 82 years old have been described, though it occurs predominantly in adults.

Mean and median age of disease are in the fifth decade of life. Both sexes are equally affected.

Clinics
Most cases of follicular dendritic cell sarcoma present with asymptomatic lymphadenopathy. Cervical and axillary lymph nodes are commonly affected. Extra nodal sites that can be involved include spleen, liver, gastrointestinal tract, skin, lung, mediastinum, pharynx, tonsils and soft tissue. Patients with intra-abdominal tumors may suffer from abdominal pain. Other systemic presentations include fever, night sweats and fatigue. Rarely paraneoplastic myasthenia gravis and pemphigus has been reported in FDCS (Wang et al., 2016). Abnormal levels of alkaline phosphatase as well as anemia are reported with hepatic involvement by FDCS.

Pathology
The tumor shows various histologic patterns of spindle cells in storiform (the most common form), menigioma -like (whorled), fascicles, bundles or diffuse sheets; heterogeneity in growth patterns can also be seen. Tumor cells are plump with indistinct cell borders (syncytial appearance) and show fibrillary slightly eosinophilic cytoplasm. Tumor cells have vesicular nuclei with fine chromatin, sometimes intranuclear pseudoinclusions, and nucleoli; binucleate cells are present. Perivascular B or T lymphocytes can be seen. In some cases TdT+ T-lymphoblasts can be associated with these tumors (Ohgami et al., 2012, 2013, 2014). Tumor necrosis is unusual and the mitotic rate can vary from 0 to 10 per 10 high power fields.
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Figure 1: Histopathologic features of a follicular dendritic cell sarcoma (FDCS). Numerous spindled 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.

High mitotic rates are more common in cases with cytologic atypia and clinically aggressive behavior.

Treatment

Complete surgical excision is the treatment of choice for both primary and recurrent cases. The benefits and advantages of radiotherapy and chemotherapy are not established yet. In cases with a BRAF V600 mutation, a BRAF enzyme inhibitor such as vemurafenib can be a potential choice. Another therapeutic agent are EGFR inhibitors, especially in cases which express moderate to strong EGFR.

Prognosis

Extranodal tumors have a higher risk of metastases than nodal counterparts. Local recurrences are common. Liver, lung and lymph nodes are common metastatic sites. Tumors with larger size (>6cm) significant cellular atypia, coagulative necrosis, intra-abdominal location and high mitotic rate (greater than 5 mitoses in 10 hpf) have unfavorable prognosis.

Cytogenetics

Cytogenetics morphological

No specific chromosomal aberration has been established in FDCS. Non-recurrent types of complex cytogenetic abnormalities have been documented (Udayakumar et al., 2015; Perry et al., 2013).

Cytogenetics molecular

The genetic alterations that drive tumorogenesis are not well understood in FDCS. One recent study that assessed the genetic basis of FDCS reported BRAF V600 mutations in a subset of cases (Go et al., 2014). Another study analyzing somatic alterations, showed loss of function alterations in tumor suppressor genes (NF-kB 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) (Griffin et al., 2016).

Genes involved and proteins

BRAF (v-raf murine sarcoma viral oncogene homolog B1)

Location 7q34

Protein
This gene belongs to the RAF/MAPK family of serine/threonine kinases. The protein product affects cell division, secretion and differentiation through its regulating role in the MAP kinase/ERK signaling pathway. Mutations have been associated with cancers including malignant melanoma, colorectal cancer, non-Hodgkin lymphoma, thyroid carcinoma, non-small cell lung carcinoma, and adenocarcinoma of lung.

**CYLD (cylindromatosis (turban tumor syndrome))**

**Location** 16q12.1

**Protein**

The product of this gene is a cytoplasmic protein. The role of this gene in FDCS is purportedly through negative regulation of NF-κB activation by bi-allelic loss of CYLD gene.

**NFKBIA (NFκB inhibitor alpha)**

**Location** 14q13.2

**Protein**

NFKBIA is a member of the NF-kappa-B inhibitor family and involved in inflammatory responses. The alteration in FDCS is a frameshift mutation or deletion in NFKB1 resulting in altered cytoplasmic sequestration of NF-κB complex.

**CDKN2A (cyclin dependent kinase 2a / p16)**

**Location** 9p21.3

**Protein**

This gene generates several transcripts differing in their first exon. At least three spliced variants encode distinct proteins. The most well-known proteins are p16 (INK4a) and p14 (ARF) which both have tumor suppressor activity.

**RB1 (retinoblastoma)**

**Location** 13q14.2

**Protein**

This gene encodes a protein which is a negative regulator of the cell cycle. Bi-allelic losses of RB1 are seen, as well as nonsense mutations in FDCS.

**CD274 (CD274 molecule)**

**Location** 9p24.1

**Protein**

The protein product of PD-L1 is involved in T-cell proliferation, activation and the production of cytokines like IL-10 and IFN-gamma. It is considered to be prognostic in various types of malignancies, including renal cell carcinoma and colon cancer.

**PDCD1LG2 (programmed cell death 1 ligand 2)**

**Location** 9p24.1

**Protein**

PD-L2 is involved in T-cell proliferation and INF-γamma production. In some cases of FDCS, a copy number gain on chromosome 9p24 in the location of these genes was observed, and believed to contribute to immune system evasion.

**References**


This article should be referenced as such: