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Opinion

Multimodal Approach in Histiocytic and Dendritic Cell Neoplasms

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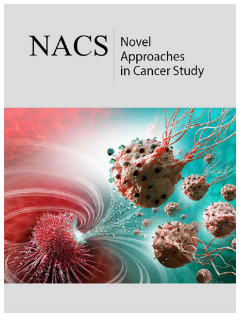

Abstract

Histiocytic and dendritic cell neoplasms are rare but extremely aggressive tumors that represent less than 1% of all neoplasms arising in lymph nodes or soft tissues. Often the tumor is detected lately, and diagnosis is challenging both for pathologists and for clinicians. Based on the multiplicity of resembling tumors a final diagnosis is often difficult to find. Furthermore, structured therapy algorithms do not exist. Here we show our experience in diagnostics and treatment of these tumors.

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Opinion

Histiocytic and dendritic cell neoplasms are rare but aggressive tumors that represent less than 1% of all neoplasms arising in lymph nodes or soft tissues. They may arise de novo or in association with T-cell, B-cell or myeloid neoplasms. These malignancies can be placed into two main groups based on their derivation from mesenchymal or bone marrow cells [1]. While Follicular Dendritic Cell Sarcoma (FDCS), Indeterminate Dendritic Cell Sarcoma (INDCS), Fibroblastic Reticular Cell Tumors (FRCT) and Disseminated Juvenile Xanthogranuloma (DJX) evolve from mesenchymal or stromal-derived dendritic cells, Histiocytic Sarcoma (HS), Langerhans Cell Histiocytosis (LCH) and Interdigitating Dendritic Cell Sarcoma (IDCS) are derived from bone marrow precursors [1,2].

Often the tumor is detected lately, and diagnosis is challenging both for pathologists and clinicians. Based on the multiplicity of resembling tumors a final diagnosis is often difficult to find. Previous case reports and case series as well as expert opinions suggest that diagnosis should be supported by imaging including CT and PET-CT followed by bioptic confirmation as well as bone marrow biopsy [3,4]. However, the diagnostic value of tumor-biopsy should be related to the risk of tumor expansion, especially in large ulcerating tumors. Hence the alternative of primary resection for large, ulcerating tumors without preoperative histological assessment should be discussed. Tumor-biology is not completely understood. Based on the work of the International Lymphoma Study Group we know that immunohistochemistry seems to be effective to differ the malignancies [5]. The difference between these tumors and the complexity of diagnosis is shown in Figure 1. The partial aggressive and fast growth combined with a high rate of local relapse, e.g., for HS, aggravate the decision of therapy. Prognosis of each tumor-type is different. Hence, therapy strategies have to be most individual but should start quickest possible.

	FDCS	IDCS	INDCS	HS	FRCT	DJX	LCH
Clinical finding	Slow growing	Solitary lymphatic mass, aggressive	Papules or nodules on the skin	Solitary mass, fast growing	Solitary mass	Small papule	Paediatric patient's solitary/multifocal bone/ adjacent soft tissue
Cytomorphology	Spindle/ ovoid cells with whorls	Spindle/ ovoid cells with whorls	Resembles Langerhans cells, irregular nuclear grooves/ clefts	Large, round, focal spindling areas	Spindle/ ovoid cells with whorls in paracortical areas	Small, oval, bland round/oval nucleus, no grooves	Large ovoid epitheloid histiocytes, nuclear grooves
IHC- markers	CD4 + CD21 + CD23 + D2-40 + CD35 + CD68 +/- Fascin + Clusterin + CD 34 – CD1a – S100 – Cytokeratin – HMB 5 – MSA –	CD4 + CD45 +/- CD 68 + S100 + Fascin + CD1a –	CD4 + CD68 +/- S100 + Fascin + CD1a – Birbeck granules -	CD68 + CD 163 + Lysozyme+ S100 + CD1a – CD21 – CD35 – CD33 -	Vimentin + Desmin + Smooth muscle actin + FXIIIa + CD21 – CD35 – CD1a – S100 -	Vimentin + sCD14 + CD68 + Stabilin-1 + CD 163 + FXIIIa + CD1a -	CD1a + S100 + Iangerin + Birbeck granules +
BRAF mutation	19 %	possible	possible	63 %	unclear	none	50% - 60%
Treatment	Surgical resection + adjuvant chemotherapy/ radiotherapy	Surgical resection or radiotherapy	Surgical excision	Surgical resection and chemotherapy/ radio- therapy	Surgical resection and radiotherapy	Resection, none, if asymptomatic	Surgical excision
Prognosis	40-50% recurrences, 20 % mortality	50% recurrence within 1 year	spontaneous regression or rapid progression	Overall survival 6 months	Median survival 13 months	good	Systemic or CNS affection

Figure 1: Pathological and clinical findings of histiocytic and dendritic sarcoma [10,14,15].

Surgery, radiation and chemotherapy are the therapeutic options. Unfortunately, because of the rareness of these malignancies, structured therapy algorithms do not exist. Even the problem of primary surgery, radiation, chemotherapy, or combined therapy is not solved. Many chemotherapy- schemes are reported in former studies, although the therapeutic value is not known as well. Saygin et al. [6] show in a pooled analysis of 462 case reports about dendritic cell sarcoma no benefit for adjuvant modalities. However, the tendency for using the CHOEP-scheme (Cyclophosphamide, Hydroxydanuorubicin, Vincristine, Etoposid, Prednisolone) seems to be effective especially in HS [7-9].

New molecular genetic studies discovered mutations in the RAS-RAF-MEK-ERK pathway which induced new diagnostic and therapeutic options. Hence, new BRAF- inhibitors such as cobimetinib (Cotellic®) vemurafenib (Zelboraf®), dabrafenib (Tafinlar®), and encorafenib (Braftovi®) seem to be a promising approach before or after surgery/ radiation if mutational analysis is positive [10-13]. Therefore, choosing the first line treatment for histiocytic or dendritic cell neoplasms remains a high individual decision that should take into account tumor growth, location, infiltration in vessels or nerves, patients' co-morbidities, and presence of mutations in the RAS-RAF-MEK-ERK pathway. Primary surgical therapy followed by a chemotherapy or MEK inhibitor therapy might be a useful strategy. However, prospective well-designed research is urgently needed to understand the tumor-biology and to improve the therapy. We recommend that patients with Histiocytic and Dendritic sarcoma should be treated in a specialized sarcoma and cancer center to get an early and sufficient diagnosis and therapy [14,15].

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