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Impact of surgery, radiation and systemic therapy on the outcomes of patients with dendritic cell and histiocytic sarcomas

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Abstract ***Background:*** Neoplasms of histiocytic and dendritic cell origin, including follicular dendritic cell sarcoma (FDCS), histiocytic sarcoma (HS) and interdigitating dendritic cell sarcoma (IDCS), are extremely rare, and data on their natural history and treatment outcomes are sparse. We evaluated the impact of surgery, radiation and systemic therapies on overall survival (OS).

Methods: We conducted a retrospective chart review of patients with FDCS, IDCS and HS treated at Memorial Sloan Kettering Cancer Center between 1995 and 2014.

Results: We identified 31, 15 and 7 patients with FDCS, HS and IDCS, respectively. Median age was 48.7, 42.3 and 58.8 years for FDCS, HS and IDCS, respectively. Only a slight disparity in gender distribution existed for FDCS and HS; however, IDCS predominantly affected males (6:1). The most common sites of presentation were abdomen and pelvis (42%), extremities (33%) and head and neck (57%) for FDCS, HS and IDCS, respectively. At diagnosis, 74%, 40% and 86% of patients presented with localised disease in FDCS, HS and IDCS, respectively. Patients with localised disease had significantly improved OS than

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those with metastatic disease in FDCS ($P = 0.04$) and IDCS ($P = 0.014$) but not in HS ($P = 0.95$). In FDCS and HS, adjuvant or neo-adjuvant therapy was not associated with improved OS compared with observation. In IDCS, surgery alone provided a 5-year overall survival rate of 71%.

Conclusions: Adjuvant or neo-adjuvant treatment in FDCS and HS did not affect OS. Patients with IDCS had an excellent outcome with surgery. In the metastatic setting, chemotherapy and small molecule inhibitors may provide benefit.

1. Introduction

Histiocytic and dendritic cells play critical roles in the immune system, contributing to phagocytosis, antigen processing and presentation to B and T cells [1–3]. The broad term histiocytic neoplasms as used by pathologists refers to neoplasms derived from monocytes/macrophages and dendritic cells [1]. Monocytes/macrophages and dendritic cells are derived from a common precursor known as the macrophage-dendritic cell progenitor (MDP). MDP is of myeloid origin and gives rise to the monocytes and a common dendritic cell precursor (CDP), which is a dendritic cell-restricted precursor. The CDP then differentiates into two broad categories of human dendritic cells: plasmacytoid dendritic cells (pDC) and classical dendritic cells (cDC) (Supplementary Fig. 1 and Table 1).

Monocytes/macrophages express the CD14 lineage marker. pDC and cDC constitutively express major histocompatibility complex II proteins (MHC-II) and lack lineage-specific markers (CD3, CD14, CD19, CD20, CD56, and glycophorin A) [4]. Follicular dendritic cells are the exception; these cells are mesenchymal in origin and express CD21, CD23 and CD35 [1]. Neoplasms that arise from these cells are exceedingly rare: they are estimated to make up <1% of neoplasms that arise in lymph nodes, extranodal lymphatic tissues or soft tissues. Since they arise in sustentacular cells in lymph nodes but not from lymphocytes, they are historically classified as "sarcoma". Haematopoietic tumours arising from CD34+ myeloid progenitor cells include histiocytic sarcoma (HS), Langerhans cell histiocytosis/sarcoma (LCH) and interdigitating dendritic cell sarcoma (IDCS). In contrast, stromal or mesenchymal derived tumours include follicular dendritic cell sarcoma (FDCS) and the rarer fibroblastic reticulum cell tumours. While these are conveniently classified as histiocytic and dendritic neoplasms, their biology, natural history and treatment appear to be distinct [1].

Follicular dendritic cells (FDC) are mesenchymal in origin and found in the germinal center of lymph nodes where they are involved in antigen presentation, proliferation and differentiation of B-cells [1,5]. Although mesenchymal in origin, there have been reports of FDCS sharing clonality with co-existent follicular lymphoma, possibly through trans-differentiation or a common progenitor cell [6]. Tumours usually occur sporadically, but a subset of cases are associated with Castleman disease [7]. FDCS typically presents in middle-aged adults as a slow growing mass in the head and neck or abdominal lymph nodes [1]. For localised disease, surgical resection is the mainstay of treatment and adjuvant chemotherapy and radiation remains controversial. For disseminated disease, lymphoma-type regimens (cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), ifosfamide and etoposide+/-carboplatin (ICE), adriamycin, bleomycin, vinblastine and dacarbazine (ABVD)) are often employed although no prospective data on outcomes are available [5].

Histiocytic sarcoma is an extremely rare tumour of mature tissue histiocytes (non-Langerhans), with fewer than 40 cases reported in the literature [3,5,8–10]. HS typically presents in the gastrointestinal tract, skin, and soft tissues, but lymph node involvement has also been observed. Age varies widely at diagnosis (range, 6 months–89 years) and has a bi-modal distribution with a slight male predominance [11]. A treatment standard for HS does not exist. Localised disease is surgically resected and may additionally receive adjuvant radiation or chemotherapy with non-Hodgkin lymphoma regimens such as CHOP, ICE or ABVD.

Interdigitating dendritic cells are found in the paracortex of lymph nodes and involved in antigen presentation to T cells [1,2,5]. Neoplasms of interdigitating dendritic cells have been reported in less than 100 cases, and may be associated with low grade B-cell neoplasms, mycosis fungoides, and other solid tumours [12]. IDCS is typically diagnosed in middle-aged adults and presents as a solitary lymph node mass, and surgical resection is the mainstay of treatment [5,12]. A pooled-analysis of published case reports reported 2-year survival rates for localised and disseminated disease of 68.1% and 15.8%, respectively [12]. These reports showed conflicting outcomes on the impact of multi-modal therapy following surgery [5,12]. Disseminated disease is often treated with lymphoma-like regimens with variable success.

In an effort to improve the current understanding of the natural history and treatment outcomes of FDCS, HS, and IDCS, we conducted a retrospective analysis of patients evaluated at our institution. In this study, we evaluated patient demographics, pathological and

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