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Descriptive Analysis of Histiocytic and Dendritic Cell Neoplasms: A Single-Institution Experience

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Purpose: Histiocytic and dendritic cell neoplasms are rare hematologic tumors. This study aimed to describe the epidemiologic features of the entire spectrum of histiocytic and dendritic cell neoplasms, including clinicopathological variables and patient outcomes.
Materials and Methods: We comprehensively reviewed 274 patients who were diagnosed with histiocytic and dendritic neoplasms at Severance Hospital, Seoul, South Korea between 1995 and 2018.
Results: The most common neoplasm was Langerhans cell histiocytosis (LCH), followed by dermal xanthogranuloma. Among non-LCH sarcomas, histiocytic sarcoma (HS) showed a relatively high prevalence, followed by follicular dendritic cell sarcoma (FDCS). Disseminated juvenile xanthogranuloma (DJG), Erdheim-Chester disease (ECD), indeterminate dendritic cell tumor (IDCT), and interdigitating dendritic cell sarcoma (IDCS) rarely occurred. Generally, these tumors presented in childhood, although the non-LCH sarcoma (HS/FDCS/IDCS/IDCT) group of tumors and ECD occurred in late adulthood. Multiorgan involvement and advanced Ann-Arbor stage, as well as recurrence and death of disease, were not uncommon. The non-LCH sarcoma group had the worst overall survival, compared to the DJG, ECD, and LCH groups.
Conclusion: Our findings indicate that histiocytic and dendritic cell neoplasms exhibit heterogeneous epidemiologic characteristics and that some patients may have unfavorable outcomes, especially those with non-LCH sarcoma.

Key Words: Histiocytic disorders, malignant, dendritic cells, epidemiology

INTRODUCTION

Histiocytic and dendritic cell neoplasms are a rare group of hematologic malignancies. Their cellular origin is the mononuclear phagocyte system, including myeloid (stem cell)-derived monocytes, monocyte-derived macrophages, monocyte-derived dendritic cells, and stroma (mesenchymal stem cell)-derived dendritic cells.[1-3] As the function and phenotype of their normal cellular counterparts vary widely, these histiocytic and dendritic cell neoplasms are classified into a wide range of subtypes. World Health Organization (WHO) classification categorizes these neoplasms into the following subtypes: tumors derived from Langerhans cells, including Langerhans cell histiocytosis (LCH) and Langerhans cell sarcoma (LCS); histiocytic sarcoma (HS); indeterminate dendritic cell tumor (IDCT); interdigitating dendritic cell sarcoma (IDCS); follicular dendritic cell sarcoma (FDCS) and inflammatory pseudotumor-like follicular/fibroblastic dendritic cell sarcoma; fibroblastic reticular cell tumor; disseminated juvenile xanthogranuloma (DJG); and Erdheim-Chester disease (ECD), as well as dermal xanthogranuloma (dermal XG). LCH accounts for the majority of cases of histiocytic and dendritic cell neoplasms and is thought be a typical form of such neoplasms. Therefore, cases with histiocytic and dendritic cell neoplasms are commonly divided into LCH and non-LCH groups.[2-4]

Most histiocytic and dendritic cell neoplasm subtypes are of a malignant nature, designated as "malignant neoplasms of histiocytes and accessory lymphoid cells" by the WHO.[3] However, the dermal XG and DJG subtypes are considered benign

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or "uncertain whether benign or malignant" according to the International Classification of Disease (ICD)-10 or -11.[5,6] Due to their relatively low incidence and the wide range of subtypes, the epidemiologic and clinical features, outcomes, and prognosis-related factors associated with histiocytic and dendritic cell neoplasms have been poorly described. Although some recent studies have described their clinicopathological and prognostic features, these studies focused on only a single subtype, reported results of meta-analyses, or included a relatively small number of LCH and/or other subtypes.[7-20] Comprehensive and comparative analyses have rarely been conducted on the overall spectrum of histiocytic and dendritic cell neoplasms.

Accordingly, the present study aimed to describe the epidemiologic features of the entire spectrum of histiocytic and dendritic cell neoplasms, including clinicopathological variables and patient outcomes.

MATERIALS AND METHODS

Case selection, review, and data acquisition

We retrospectively reviewed the medical records of patients diagnosed with histiocytic and dendritic neoplasms at Severance Hospital (Seoul, South Korea) between 1995 to 2018. The exclusion criteria were 1) diagnosis of myeloproliferative neoplasm and myelodysplastic syndrome, such as acute monocytic leukemia and blastic plasmacytoid dendritic cell neoplasm, and 2) unavailable data from hematoxylin and eosin stain slides or immunohistochemistry findings, as well as molecular test reports. Three pathologists (HM Kim, WI Yang, and SO Yoon) reviewed all available hematoxylin and eosin stain slides, findings of immunohistochemistry and/or in situ hybridization by routine light microscopy, and the molecular test reports. Disagreements in diagnosis were resolved by consensus through a discussion. Details on the diagnostic methods used are summarized in Supplementary Materials 1 (only online). When applicable, the results of ancillary studies transferred from other institutions were used for classification. We re-classified diagnoses according to the recently updated WHO classification,[3,4] and finally, 274 cases of histiocytic and dendritic neoplasms were selected.

We used the algorithm proposed by the Pathology Working Group of the International Lymphoma Epidemiology Consortium (InterLymph).[21,22] Clinicodemographic data were obtained from medical records at initial diagnosis and included information on age; sex; anatomic disease occurrence site; radiologically measured tumor size; bone marrow biopsy and aspiration results; complete blood count results with differential counts, including those of white blood cells, hemoglobin, platelets, neutrophils, lymphocytes, and monocytes; blood chemistry results, including total protein, albumin, lactate dehydrogenase (LDH), erythrocyte sedimentation rate, C-reactive protein (CRP), blood urea nitrogen, creatinine, aspartate aminotransferase, alanine transaminase, total bilirubin, and alkaline phosphatase; and the Eastern Cooperative Oncology Group performance score, Ann-Arbor stage, and B symptoms. Data on treatment modality and follow-up, including recurrence, death of disease, and/or last follow-up visit, were obtained from electronic medical records. This study was approved by the Institutional Review Board of Severance Hospital, Yonsei University College of Medicine (Seoul, South Korea) (Protocol ID, 4-2019-0308). The requirement for informed consent was waived owing to the study's retrospective design.

Statistical analysis

The χ^2 test or Fisher's exact test was conducted to analyze the significance of differences between variables. Overall survival (OS) was measured from the date of initial diagnosis to that of death or the last follow-up visit. Survival rates were determined using the Kaplan-Meier method and compared using the log-rank test. A two-sided p value of <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS 23 software for Windows (IBM Corp., Armonk, NY, USA).

RESULTS

Case distribution and demographic features of the subtypes

LCH was the most commonly observed subtype (56.6%, 155/274), followed by dermal XG (35.0%, 96/274), HS (4.0%, 11/274), FDCS (1.8%, 5/274), DJG (1.1%, 3/274), ECD (0.7%, 2/274), IDCT (0.4%, 1/274), and IDCS (0.4%, 1/274). The distributions of each subtype are summarized in Fig. 1, and representative

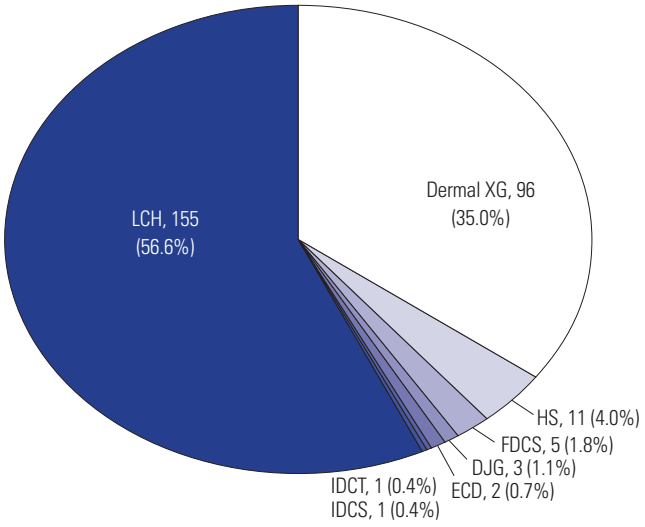

Fig. 1. Distribution of histiocytic and dendritic cell neoplasms in Severance Hospital. LCH, Langerhans cell histiocytosis; XG, xanthogranuloma; HS, histiocytic sarcoma; DJG, disseminated juvenile xanthogranuloma; ECD, Erdheim-Chester disease; FDCS, follicular dendritic cell sarcoma; IDCT, indeterminate dendritic cell tumor; IDCS, interdigitating dendritic cell sarcoma.

images are shown in Supplementary Fig. 1 (only online).

Of the 155 LCH cases in our series, none were histologically compatible with LCS as per the WHO classification.[2-4] Of the five FDCS cases, one showed disease in multiple sites of the retroperitoneum, liver, and iliac bone, suggesting the presence of inflammatory pseudotumor-like follicular/fibroblastic dendritic cell sarcoma. However, Epstein-Barr virus status could not be tested due to a lack of unstained slides transferred from an outside hospital. The five cases of juvenile xanthogranuloma (histologically) showed proliferating CD68-positive foamy histiocytes derived from monocyte-derived macrophages, a histological and immunohistochemical finding compatible with the juvenile xanthogranuloma family. In addition, all five cases revealed systemic involvement compatible with systemic forms of the juvenile xanthogranuloma family. Among them, in two cases, the disease developed in late adulthood (age >60 years) and involved multiple organs (the liver, spleen, spine, and lymph nodes in one case; the skin, lung, pericardium, bones, and lymph nodes in the other case), thus making them compatible with ECD. The remaining three cases involved one infant and two young adults aged 25 years who had systemic, deep visceral organ involvement of the mandible, spine, and nasopharynx. These clinical presentations make the three cases compatible with DJG (Supplementary Table 1, only online). However, the follow-up period of ECD patients was short, and none of the patients experienced death.

To compare the epidemiologic features of the subtypes, the patients were divided into five groups:[2-4] dermal XG, DJG, ECD, and HS/FDCS/IDCS/IDCT as non-LCH sarcoma, and LCH. The demographic features of these five groups are summarized in Supplementary Fig. 2 (only online). In the entire spectrum of histiocytic and dendritic neoplasms, the median age at diagnosis was 6 years (range, 0 to 77 years), and the female: male ratio was 1:1.4. A majority of the LCH cases occurred in pediatric patients (median age, 9 years), with 67.1% (111/155) of these patients aged younger than 15 years. The remaining histiocytic and dendritic cell neoplasm cases showed a wide age range. Dermal XG occurred in very early childhood (median age, 1 year). The ECD group showed the oldest patient age (median age, 64 years) (Supplementary Fig. 2A, only online). Generally, no sex-related predilection was noted (Supplementary Fig. 2B, only online). In most of the cases across the five groups, the affected organs were extranodal in nature (Supplementary Fig. 2C, only online), such as the bone and skin, head and neck, gastrointestinal tract and abdomen, lung and thymus, and brain and pituitary gland. About 13.5% (37/274) of the overall cases revealed multiorgan involvement. Specifically, 20.0% (31/155) of LCH cases, 100% (2/2) of ECD, and 22.2% (4/18, 3 HS and 1 FDCS) of non-LCH cases sarcoma showed multiorgan involvement (Supplementary Fig. 2D, only online). Advanced Ann-Arbor stage (stage III–IV) cases were frequently observed in the LCH (37/155, 23.9%), non-LCH sarcoma (4/18, 22.2%; three HS and one FDCS), and ECD (2/2, 100%) groups (Supplementary Fig. 2D, only online). In the entire spectrum of histiocytic and dendritic neoplasms, the median level of LDH was 245 IU/L (range, 136–2249 IU/L), and the median level of CRP was 5.5 mg/L (range, 0.2–107.4 mg/L). Among the cases for which laboratory data were available, elevated LDH levels were most frequently found in DJG, while elevated CRP levels were observed in all cases of ECD (Supplementary Fig. 2E, only online).

BRAF V600E mutation analysis was performed in 16 LCH cases, 3 DJG, 2 ECD cases, and one IDCT case. Of them, four cases of LCH (4/16, 25.0%) and one case of ECD (1/2, 50.0%) showed *BRAF V600E* mutation (Supplementary Fig. 2F, only online). LCH cases with *BRAF V600E* mutation showed no significant difference in clinicopathologic and prognostic factors from those with wild-type *BRAF* (Supplementary Table 2, only online). Similarly, associations between the disease groups with respect to demographic and laboratory parameters were unremarkable.

Clinical outcomes

The patients in our series underwent various treatments (Supplementary Fig. 3A, only online). Among the 57 patients who underwent chemotherapy, 8 (14%) showed recurrence and 6 (10.5%) died. Among 11 patients who underwent radiation therapy, 2 (18.2%) showed recurrence and 1 (9.1%) died. Among 5 patients who underwent steroid therapy, no patient showed recurrence and 1 (20%) died. One patient underwent chemoradiation therapy, and this patient did not develop recurrence or die. Among the 200 patients who underwent diagnostic biopsy and surgery without any adjuvant therapy, 1 patient, who had HS, developed recurrence and died. One patient with HS and 1 patient with LCH also died. The details are summarized in Supplementary Materials 2 (only online). The median follow-up period was 14.4 months (range, 0–144 months); when dermal XG was excluded, it was 32.3 months (range, 0.03–144 months). The follow-up periods of each group are summarized in Supplementary Fig. 3B (only online). During follow-up, 11 (4.0%, 11/274) patients experienced recurrence, and 11 (4.0%, 11/274) died of disease. Of the 11 patients with recurrence, seven (4.5%, 7/155) had LCH, three (27.3%, 3/11) had HS, and one (20%, 1/5) had FDCS (Supplementary Fig. 3C, only online). Of the 11 patients who died of disease, five (3.2%, 5/155) showed LCH, five (45.5%, 5/11) showed HS, and one (20%, 1/5) showed FDCS (Supplementary Fig. 3D, only online). The clinicopathologic features of the patients who developed recurrence and/or died are summarized in Supplementary Table 3 (only online).

When the Kaplan-Meier survival analysis was performed to compare the prognosis of disease subtypes excluding dermal XG, which has a benign prognosis, the OS rates differed across the subtypes. The non-LCH sarcoma group showed the worst OS values, compared to the DJG, ECD, and LCH groups (p<0.001, respectively) (Fig. 2).

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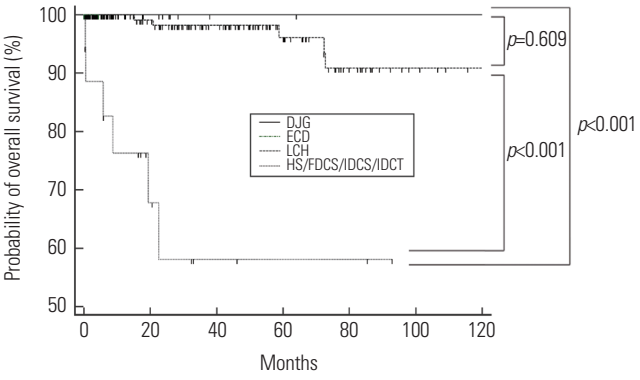

Fig. 2. Kaplan-Meier survival analysis. The HS/FDCS/IDCS/IDCT group showed worse overall survival rates than the DJG, ECD, and LCH groups (p<0.001, respectively). HS, histiocytic sarcoma; FDCS, follicular dendritic cell sarcoma; IDCS, interdigitating dendritic cell sarcoma; IDCT, indeterminate dendritic cell tumor; LCH, Langerhans cell histiocytosis; DJG, disseminated juvenile xanthogranuloma; ECD, Erdheim-Chester disease.

DISCUSSION

In the present series, we comprehensively described the epidemiologic features of histiocytic and dendritic cell neoplasms. The most common subtype was LCH, consistent with previous studies.[2-4] Among the non-LCH type sarcomas, HS showed the highest prevalence, followed by FDCS. IDCS and IDCT were very rarely observed. To our best knowledge, this may be the first comprehensive study focusing on the epidemiologic characterization of the entire spectrum of histiocytic and dendritic cell neoplasms in South Korea according to recent WHO classification.

Dermal XG is a benign disease entity in the juvenile xanthogranuloma family. DJG and ECD do not have an ICD-O-3 code pointing to histologically malignant behavior or are designated as "uncertain whether benign or malignant" according to ICD-10 or -11.[5,6] However, the 2016 WHO classification categorized ECD as a malignancy.[3] The diagnosis of dermal XG, DJG, and ECD as individual entities via histology alone is difficult, as there is no histologic difference between the usual dermal type and systemic type of juvenile xanthogranuloma that shows proliferating CD68-positive foamy histiocytes derived from monocyte-derived macrophages.[1-3] Therefore, we included the entire spectrum of juvenile XG and comprehensively analyzed it to characterize the epidemiologic features of each entity. Dermal XG was the second most prevalent entity following LCH, while DJG and ECD were relatively rarer.

Few comprehensive epidemiologic series to date have included a large number of cases reflective of the overall spectrum of histiocytic and dendritic cell neoplasm. Thus, it may be difficult to compare the subtype proportions observed in our series to those in other series. A recent epidemiologic single-center study of 32 histiocytic and dendritic cell neoplasm cases[7] showed that the most common type was LCH, followed by HS, FDCS, IDCS, and IDCT, consistent with our study.

Data on the general epidemiologic characteristics in our series were in agreement with those described in the literature.[2-4] Histiocytic and dendritic cell neoplasms generally occurred in childhood, despite the wide age distribution range, as previously noted.[2-4] This is due to the large proportion of cases with LCH and dermal XG, which are well-known pediatric malignancies. However, the non-LCH sarcoma group, including HS, FDCS, IDCS, and IDCT, as well as ECD, tended to occur in late adulthood.[2-4] A majority of the histiocytic and dendritic cell neoplasms occurred in extranodal sites like the bone and skin rather than the lymph nodes, and multiorgan involvement was also not uncommon in the LCH, non-LCH sarcoma (HS/FDCS/IDCS/IDCT), and ECD groups. Cases with advanced Ann-Arbor stage (stage III–IV) were also frequently observed in the LCH, non-LCH sarcoma, and ECD groups. Elevated LDH levels were frequently noted, especially in the LCH cases.

Several studies have focused on *BRAF V600E* mutations in histiocytic and dendritic cell neoplasms, and the biologic and prognostic implications of these have been suggested in such tumours.[3,19,23-26] In our LCH cases, *BRAF V600E* mutations were noted in 25% (4/16) of the tested cases, and there was no significant difference in clinicopathologic and prognostic factors between LCH cases with the mutation and those with wild-type BRAF. Most of the samples in the LCH group included the bone and were decalcified in the tissue preparation processes; therefore, we could not comprehensively perform *BRAF V600E* mutation tests. Although such cases account for only a small portion (16/155, 10.3%) of LCH and may not represent the overall number of LCH cases in our series, this mutation rate was lower than that observed previously (57%).[23] A recent meta review of 653 LCH cases showed an overall *BRAF V600E* mutation incidence of 48.5%.[24] In a study using 48 LCH samples from a Western population, the *BRAF V600E* mutation incidence rate was 48%; however, the mutation exhibited no significant implications in terms of clinicopathologic variables or patient prognoses.[24] Our findings are similar to those of another study that tested 27 LCH cases from the same country-based population and found a relatively low rate (22.2%, 6/27) of mutation and a lack of clinicopathologic significance for *BRAF V600E* mutation status.[25] In a recent East Asian study, no *BRAF V600E* mutations were noted.[19] This may be attributed to differences in the *BRAF* testing methods or technical differences, as well as ethnicity-related and regional differences. Although *BRAF V600E* mutation status may predict responses to targeted treatment, the clinical and prognostic implications of this mutation are still controversial, and further research is required.[24] None of the three DJG cases showed *BRAF V600E* mutation, while one of the two ECD cases showed the mutation. Despite the small number of cases in our series, this result is consistent with previous findings.[24,25,27]

Immunohistochemical testing using the BRAF VE1 antibody[28] in this study failed to detect positive immunoexpression in the *BRAF*-mutated LCH or ECD cases. However, *BRAF* immuno-

histochemistry for *BRAF V600E* mutation has been reported to have low sensitivity and specificity in LCH or other histiocytic and dendritic cell neoplasms.[29-31] Therefore, further validation is required to elucidate the accuracy of immunohistochemistry in determining *BRAF V600E* mutation status in histiocytic and dendritic cell neoplasms.

Our outcome analyses showed that most of the histiocytic and dendritic cell neoplasms exhibit indolent clinical behaviours.[2-4] The frequency of disease recurrence or death of disease was not higher than 10%. None of the dermal XG cases revealed death of disease, supporting this entity's benign nature.[2-4] The rate of recurrence or death of disease was also low in the DJG and ECD cases, suggesting the uncertainty of their clinical and biological nature for malignancy.[5,6] As expected,[2-4] the HS cases showed relatively high recurrence and death rates. Of the five FDCS cases, one revealed recurrence and death. The non-LCH sarcoma group showed the worst OS rate, compared to the LCH and DJG and ECD groups. Therefore, more accurate diagnoses and additional treatment may be needed for non-LCH sarcoma, especially HS cases. Despite the limitations associated with the use of single hospital-based data, our series may be used as a surrogate of population-based data, and our findings may be useful in the provision of more accurate diagnoses and formulation of more appropriate patient management strategies.

In summary, the LCH subtype appears to be the most common histiocytic and dendritic cell neoplasm. Among non-LCH type sarcomas, HS was the most prevalent, followed by FDCS. The other subtypes were rare. Generally, these tumors occurred in childhood, although non-LCH sarcoma and ECD occurred in late adulthood. Our findings indicate that outcomes may differ among patients with the same histiocytic and dendritic cell neoplasm subtype, because some may have adverse prognostic factors, such as multiorgan involvement, elevated LDH levels, and advanced Ann-Arbor stage, while others may not. BRAF mutations were noted in the LCH and ECD cases, although the prognostic implications thereof remain uncertain. Most of the patients in our series showed indolent clinical behaviors, while the non-LCH sarcoma group, especially HS cases, showed unfavorable outcomes.

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AUTHOR CONTRIBUTIONS

Conceptualization: Sun Och Yoon. Data curation: all authors. Formal analysis: Hye Min Kim. Funding acquisition: Sun Och Yoon. Investigation: all authors. Methodology: Sun Och Yoon. Project administration: Sun Och Yoon. Resources: Sun Och Yoon. Software: Hye Min Kim. Supervision: Sun Och Yoon. Visualization: Hye Min Kim. Writing—original draft: Sun Och Yoon. Writing—review & editing: Hye Min Kim and Sun Och Yoon. Approval of final manuscript: all authors.

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