International Rare Histiocytic Disorders Registry (IRHDR)

Protocol Version: 12-DEC-2024

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LIST OF ABBREVIATIONS

non-LCH, non-Langerhans cell histiocytoses

RHD, rare histiocytic disorders

HLH, hemophagocytic lymphohistiocytosis

DC, dendritic cell

JXG, Juvenile Xanthogranuloma

BCH, benign cephalic histiocytosis

XD, xanthoma disseminatum

MRH, multicentric reticulohistiocytosis

ECD, erdheim-chester disease

RDD, multi-system rosai-dorfman disease

GEH, generalized eruptive histiocytoma

PNH, progressive nodular histiocytosis

JMML, juvenile myelomonocytic leukemia

IRHDR, international rare histiocytic disorders registry

CRA, clinical research associate

HS, histiocyte society

1.0 BACKGROUND

The non-Langerhans cell histiocytoses (non-LCH) or "Rare Histiocytic Disorders" (RHD) are a diverse group of disorders defined by the accumulation of histiocytes that do not meet the criteria for the diagnosis of Langerhans cell histiocytosis (LCH) or hemophagocytic lymphohistiocytosis (HLH) [1]. The normal human dermis contains immunostimulatory myeloid CD45+ HLA-DR+ dendritic cells (DCs) identified by CD11c and CD1c, as well as an additional population of poorly stimulatory macrophages that are positive for CD163, FXIIIa and CD14, and negative for CD1a [2]. Most of the RHD's are thought to arise from either a DC or a macrophage cell line [3].

The RHD's are proliferative disorders which can be divided clinically as follows[1]:

The Xanthogranuloma (XG) family includes cutaneous, ocular, and systemic XG. Cutaneous XG includes benign cephalic histiocytosis (BCH), generalized eruptive histiocytoma (GEH), progressive nodular histiocytosis (PNH), xanthoma disseminatum (XD), giant XG, and reticulohistiocytoma. The majority of XG **occurs** in young children, and usually resolve spontaneously. The pathogenesis is unknown[4]. XG can be associated with neurofibromatosis type 1 and juvenile myelomonocytic leukemia (JMML)[5]. Extra-cutaneous involvement occurs in 5-10% cases of JXG and the commonest site is deeper soft tissues. Liver, spleen, CNS and lung involvement can also occur, most of which undergo spontaneous resolution[4]. However, fatalities have been reported in systemic XG due to progressive CNS disease or hepatic failure[6]. **Ocular XG** occurs in the very young child and may occur without any skin lesion[1]. **GEH and PNH** occur mainly in adults and have been reported rarely in childhood. GEH lesions can disappear completely or progress to JXG, PNH or xanthoma disseminatum (XD). PNH is usually progressive with no tendency to spontaneous involution and can cause severe disfigurement[1]**. Xanthoma Disseminatum (XD)** is a disorder with widespread cutaneous xanthomatous lesions with prominent systemic component. XD is considered a variant of XG, most often occurring in young adult males. Ocular, CNS and meningeal involvement can cause significant morbidity[1]. **XG in adults** occurs usually as solitary lesions and do not undergo spontaneous involution. The majority of these lesions are cured by excision. Generalized lesions in adults are less common and do not respond to chemotherapy or radiotherapy[3].

Erdheim-Chester Disease (ECD) is a rare histiocytic disorder with histopathologic overlap with XG. The typical skeletal involvement and radiologic findings distinguish ECD (predominantly middle-aged adults) from systemic JXG (mainly young children)[1]. Pediatric cases of ECD have rarely been reported. The most common presentation is bone pain due to bilateral symmetrical long bone involvement. Fifty percent have extraskeletal disease including kidney, retroperitoneum, skin, brain, lung and heart. Pituitary involvement with DI occurs in 30% of cases[1]. Responses to vinblastine/prednisone, cyclophosphamide/prednisolone, 2-CDA and to interferon-α therapy have been reported[1]. The prognosis of ECD is significantly worse than that reported in other histiocytoses. Nearly 36% of ECD patients die of their disease within 6 months. The mean survival is less than 3 years. Cardiac, pulmonary, or renal failures are the primary causes of mortality[1].

The non - XG cutaneous histiocytoses include **multicentric reticulohistiocytosis (MRH)** which is a rare multisystem histiocytic disorder with cutaneous involvement and destructive osteoarthropathy. MRH is a disease of older adults although rare cases in children have been reported[1]. It can be associated with underlying malignancy, hyperlipidemia and autoimmune disease. Fifteen to 50% of adults progress to a mutilating osteoarthropathy, while most children have self-limited disease with non-deforming arthritis. Treatment responses with methotrexate, cyclophosphamide, prednisone and azathioprine have been reported[1].

Rosai-Dorfman Disease (RDD) or sinus histiocytosis with massive lymphadenopathy (SHML) is a non-neoplastic, polyclonal, usually self-limited histiocytic disorder due to accumulation of S100+, CD1a- histiocytes[7]. RDD can occur in any age group but is most frequently seen in children and young adults. It has been reported to occur in patients with Hodgkin's and non-Hodgkin's lymphoma[8]. Systemic RDD-like histopathology has been described with ALPS, Faisalabad Histiocytosis[9] and "H" syndrome[10]. The most frequent clinical presentation of RDD is a massive bilateral and painless cervical lymphadenopathy. Extranodal involvement has been documented in 43% of cases, mostly skin, soft tissue, upper respiratory tract, bone and eye[11]. Intracranial RDD can occur with

lesions attached to the dura. In the majority of cases, RDD has a benign course and treatment is not necessary. Since results with chemotherapy have not been encouraging, the use of chemotherapy is restricted to patients with life-threatening disease or multiply relapsing cases[1].

The Malignant Histiocyte Neoplasm (MHN) is also considered among the rare histiocytic disorders. These disorders may present as localized or as disseminated disease. Limited information is available on the incidence of these conditions. Histiocytic and dendritic cell neoplasms as a group has an estimated crude incidence of less than 1/100 000 per year.[12] The 'Surveillance of Rare Cancers in Europe' project estimate the incidence of histiocytic sarcoma, interdigitating dendritic cell sarcoma and follicular dendritic cell sarcoma each to be <0.01/100 000 per year.[13] Due to the rarity of malignant histiocytoses, treatment regimens have not been standardized and the optimal treatment for these conditions are not known. Histiocytic sarcoma, Langerhans cell sarcoma and interdigitating dendritic cell sarcoma are usually aggressive malignancies with >50% mortality while follicular dendritic cell sarcoma often has a more indolent course.[14] One report of histiocytic malignancies for instance reported that 6 out 12 histiocytic sarcoma patients for whom follow up data was available died of progressive disease without responding to treatment. In total 7 of the 12 patients died due to the disease. The same report had follow up data available on 8 out of 9 Langerhans cell sarcoma patients and 4 of these patients died due to the disease. One out of the 11 evaluable patients with follicular dendritic cell tumours died due to the disease.[15]

1.1. Rationale

RHDs are characterized by the infiltration of one or more organs by non-LCH histiocytes. They can range from localized disease that resolves spontaneously, to progressive disseminated forms that can be sometimes life-threatening. Since they are extremely rare, there is limited understanding of their causes and best treatment options. Physicians, patients and parents of children with RHDs frequently consult members of the Histiocyte Society regarding the best management of these disorders. Very often, no specific recommendation can be made due to the lack of prospective outcome data, or even large retrospective case series. The creation of an international rare histiocytic disorders registry (IRHDR) could facilitate a uniform diagnosis of the RHDs, as well as the collection and analysis of the clinical, epidemiological, treatment and survival data of patients with RHD. The registry may also lead to future therapeutic recommendations, provide a framework for future clinical trials and create excellent research opportunities.

2.0 OBJECTIVES (SCIENTIFIC AIMS)

2.1 Primary Objectives

- Collect retrospective and prospective clinical, treatment and outcome data about patients with RHDs worldwide.
- Use the validated cases to improve the scientific categorization of histiocytic lesions and understand their distinguishing features and possible relationships.

2.2 Secondary Objectives

- To use the registry data in order to develop future clinical trials.

3.0 STUDY ENROLLMENT PROCEDURES AND ELIGIBILITY CRITERIA

3.1 Study Enrollment

Evaluable research participants are defined as those who provide demographic, clinical and treatment data for research purposes, as well as pathology samples for central review.

Research participants may be enrolled at the Hospital for Sick Children, Toronto, Canada and at any collaborating institution which seeks ethics approval for this registry. Please contact Arnelle Lardizabal, Registry CRA (Toronto, arnelle.lardizabal@sickkids.ca, 416-813-6431 Ext. 406431) to complete registration. Any participating institution must have local ethics approval prior to enrolling patients. Small/remote centers may seek local institutional approval to have a phone call for consenting by the submitting MDs or CRAs.

3.2 Informed Consent

Informed consent or assent will be obtained according to institutional standards and local laws.

For Canadian sites, obtaining assent/consent from a patient will be determined based on the patient's capacity as assessed by a delegated health care practitioner.

The potential subject will be identified by the responsible physician who will review the study and consent form with the patient/patient representative. Consent will then be obtained by the study CRAs or from the submitting physician. In cases of non-English speaking participants at both the Canadian sites and/or international sites, the consent can be obtained by an individual at the respective site that speaks the same language of the patient/patient representative.

Participating sites will be required to provide a copy of the de-identified signed consent forms containing the institutional study IDs.

3.3 Telephone Consent

For small and remote centers with a very rare occurrence of these RHD subtypes, telephone consenting (by the local treating MD/team who is submitting the data) with the parent or participant would be acceptable if the submitting institution would allow it.

The local treating MD/team will provide an informational letter to the patient/parent. If interested, the patient/parent will contact the CRAs through the Registry email (irhdr.registry@sickkids.ca). The designated Registry CRA in Toronto will then contact the treating local MD/team to notify that the patient/parent is interested. The treating local MD/team will explain the study and consenting procedure via telephone to the interested patient/parent. If the patient/parent agrees to participate, the local treating MD/team will send the informed consent form via email or provide a hardcopy consent form to be completed. A copy of the signed informed consent form will be sent to the patient/parent and a copy will be saved at the local site for documentation purposes. The local site will be responsible for all data entry for small and remote site participants enrolled.

3.4 Consent Procedures

- Study coordinators will review consent forms directly with local patients/parents and will obtain their consent.
- In case of non-local patients or non-English-speaking participants, the consent can be obtained with the help of an international delegate.
- Participating centers submit de-identified signed consents/assents containing only the study ID (i.e., all PHI redacted and only sections that participants mark off for the main registry and biobank portion to be included) and medical records release forms to the study coordinators via email (irhdr.registry@sickkids.ca)

3.5 Non-English-Speaking Participants

The Protocol and Data Collection Forms (CRFs) will remain in English, while consent forms can be translated by the respective international delegates.

3.6 Enrollment Timing and Patient Registration

Evaluable research participants are defined as those who provide demographic, clinical and treatment data for research purposes, and pathology samples for central review.

Screening procedures for eligibility must be performed prior to enrollment.

Informed consent/parental permission must be signed prior to enrollment.

Once screening for eligibility and consent is signed, patients will be assigned to an IRHDR patient ID number. This number will be provided by the PI institution once consent obtained. The ID number is used to identify the patient and patient samples in all future interactions with the IRHDR.

For international (non-Canadian) participating institutions, a copy of the signed consent must be submitted (anonymized with no identifiable sensitive patient information) to the study coordinators via secure/encrypted e-mail. **Non-English participants are eligible and must sign a translated copy of the study consent form (a translated consent to the patient primary language will be provided by the respective international site and all translations will be reimbursed by the Registry)**.

3.7 Patient Eligibility Criteria

3.7.1 Inclusion Criteria

The inclusion criteria listed below are interpreted literally and cannot be waived. Subjects must meet all the following inclusion criteria to be eligible to enroll in this study:

1. Any age at diagnosis.
2. Diagnosis of a rare histiocytic disorder, established before or after the opening of the registry.
3. Cases diagnosed from January – 01- 1995 until the present time and prospectively.
4. Signed informed consent by a patient, or parent/legal guardian.
5. Cognitively impaired patients can be included after consent by legal guardian/parent.
6. Deceased patients can be included if they are contacted at least 6 months after the death of their child and not on their child's birthday or anniversary of death.

In these cases of retrospective enrollment, telephone consent or other consent documentation must be sent to The Hospital for Sick Children for approval/confirmation.

As of this protocol version 12-DEC-2024, pathology samples available for central review is an optional component of the registry and is no longer a requirement for eligibility.

3.7.2 Exclusion Criteria

1. Informed consent has not been signed.
2. Diagnosis other than RHD.
3. Cases diagnosed before the year 1995.

4.0 DATA COLLECTION, PATHOLOGY REVIEW AND BIOBANK OVERVIEW

This study has the following primary components:

- Retrospective and prospective clinical, treatment and outcome data
- Pathology specimens for review by the registry designated pathologist. **(Optional as of protocol version 12-DEC-2024)**
- Pathologist's report on diagnostic pathology specimens. **(Optional as of protocol version 12-DEC-2024)**

There are no specific evaluations or visits required for participation in the IRHDR. Patients are evaluated and treated as per the treating physician's standard of practice. Data captured in the Registry reflects what is standard of practice for patients with RHD. Patient's data will be entered by the submitting physician/clinical research associate (CRA) directly on the REDCap database.

4.1 Data Collection and Confidentiality

Once the patient has signed consent for participation, and enrollment is completed, the institutional physician or CRA will be required to complete the CRFs and send pathology samples to the designated central pathology lab. Submission of documents (i.e., de-identified consent/assent forms) will be emailed to the study coordinator. Data entry is the responsibility of each site and will be done directly into the REDCap dataset. Internal SickKids monitoring will be done routinely to verify data entered into REDCap.

Each patient will be assigned a study identification number (ID); identifying information such as patients' names and medical record numbers will then be stripped from the medical documents, and no identifying information other than the patients' ID will be stored in the database. A separate record which links patient identifiers with their ID will be maintained in a secure protected environment by the project PI. Patients' data will be entered directly on REDCAP website by the submitting physician; subsequently the study PI and CRA will check the data before loading them permanently into the database.

5.0 MAIN REGISTRY DATA COLLECTION AND PATHOLOGY REVIEW

1. Demographics and Clinical Data

- Date of Diagnosis (dd/mmm/yyyy)
- Partial Date of Birth (mmm/yyyy)
- Gender (Male, Female, Not Reported)
- Personal/Family History
- IRHDR Disease Classification
- Symptoms/Signs and Organ Specific Symptoms Present at Diagnosis
- Diagnostic Radiologic Testing
- First/Second/Third/Fourth Line Therapy Details

2. Laboratory and Pathologic Data

Erythrocyte sedimentation rate, hemoglobin, platelet and white blood cell count, IgG, creatinine, bilirubin

Spinal fluid, bone marrow aspirate, bone marrow biopsy, mutational analysis

3. Central Pathology Review (Optional as of protocol version 12-DEC-2024)

Primary Aim

- To learn more about the clinical aspects, treatment modalities and outcome of patients with RHD based on registry data.

Secondary Aim

- To ultimately develop treatment guidelines for the RHD based on solid clinical trial data.

Central review of the diagnostic pathologic slide will be performed **if suitable pathology samples are available and consented to by the patient/family**. This review is not intended for clinical care but only for the integrity of the database. Cases will be deemed "appropriate" or "not appropriate for inclusion" by the path reviewer.

1. Material for review is to be sent by courier directly from the submitting center to the reviewer identified by the registry. It must include the Institutional Pathology Report, a clinical summary and glass slides (mandatory): 1 H&E and 10 unstained slides for immunostains (or a tissue block).

2. The reviewer will get additional stains if needed for diagnosis and prepare a report which will be faxed to the registry. (It may not be necessary to repeat the stains done at source).

3. In addition, the reviewer will scan the slides, and the digitized files can be submitted to the registry.

4. Original slides will be returned directly (via courier) from the reviewer to the submitting center.

5. Shipping charges and immunostaining fees will be reimbursed by the registry.

Specimen Types
Representative sample (paraffin embedded material, 1 or 2 blocks) from tumor biopsy at original diagnosis. If blocks are unavailable, submit 10 unstained slides from one representative block and 1 H&E slide.

Pathology Report
All corresponding pathology reports for each case must be submitted. This is a study requirement and should include:

- Final pathology reports of all diagnostic biopsies, bone marrow specimens, and cerebrospinal fluid specimens including all immunophenotyping reports at diagnostic biopsy, bone marrow specimens, and cerebrospinal fluids specimens (if available).
- Results of any genotypic studies (e.g. gene rearrangements or FiSH)
- Results of any cytogenetic (G-banding) analysis.
- Label all review materials with the patient's study ID number and the surgical pathology ID and block number form the corresponding pathology report

4. Central Pathology Review Shipping Addresses

For North American Sites:

Dr. Jennifer Picarsic
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Combate de los Pozos 1881 CP 1245
Buenos Aires, Argentina
Phone: 541143084300 (int 1402/1403)
Email: lauragalluzzoch@yahoo.com.ar

Shipping charges, slides processing/immunostaining fees (at the submitting site), and pathology review will be reimbursed by the Registry.

Legal issues related to pathology review: For patients who are still on treatment, in the event that the initial diagnosis is not the same as that reported by the pathology reviewer (i.e. not a rare histiocytic disorder), the pathologist will inform the study primary investigator (Dr. Oussama Abla) of the new finding. The study primary investigator will recommend to the submitting MD, a second pathology review to be performed outside of the IRHDR, and the case will be deemed not acceptable for database inclusion. If the right diagnosis was another rare histiocytic disorder. For retrospective patients who are not on treatment anymore, and in case of a major discrepancy between initial diagnosis and the one diagnosed by the pathology reviewer, the case will be deemed "not acceptable for the database". A minor discrepancy, such as a minor change in rare histiocytosis category, will not exclude the case from the registry.

All discrepant cases will be discussed between IRHDR pathology reviewers prior to any data publication.

5. Annual Follow-Up

All sites will be reminded to fill out the annual follow-up forms by the study CRAs.

6.0 BIOBANKING FOR FUTURE RESEARCH (OPTIONAL)

6.1 Biobanking Background and Rationale

The RHDs are very heterogeneous disorders that can range from localized disease that resolves spontaneously, to progressive disseminated forms that can be sometimes life-threatening. While 60% of cases of LCH and 70% of ECD (which is an RHD disorder) are known to harbor the BRAF-V600E mutation, the biology and genomics of RDD, JXG and malignant histiocytoses are largely unknown. Most cases of RDD are benign but at least 5% of cases can be fatal and non-responsive to any treatment. The survival of patients with malignant histiocytoses, particularly those with histiocytic sarcoma, is extremely poor. Further improvements in outcome will depend on

the identification of new therapeutic targets for which better tolerated targeted therapies can be developed. The understanding of the biology of the RHDs has been greatly limited by the scarcity of pathological samples, the fact that the pathological histiocytic cells are usually surrounded by a large number of reactive eosinophils and lymphocytes making up the bulk of the histiocytic lesion and by the lack of funding for large cooperative biology studies. By banking pathology samples on patients registered on the IRHDR will allow us to correlate biological with clinical and outcome features of these patients. This may enable us in the recognition of new prognostic factors that can identify patients for whom more aggressive therapy may be required, and other patients for whom mild or no treatment may be justified.

The goal of this optional component of the registry is to establish a repository of biological samples of RHDs. This biobank will provide biological samples for research aimed at further understanding of the biology and etiology of RHDs, which could potentially help developing novel targeted therapies for these rare disorders. Samples will include pathology samples taken at diagnosis and/or at relapse.

Biospecimens will be utilized for banking for future research. The same pathology samples used by the central pathology review will be sent for biobanking at the Biobank site, The Hospital for Sick Children, Toronto, ON. Research utilizing samples from the Registry biobanks will follow all applicable local and regulatory guidelines. Future research may include a broad range of technologies. Access to the Biobank specimens for any potential research will be granted by the Review Steering Committee after research proposal review approval.

If patients decline participation in the biobank but agree to participate in the registry, only samples for central pathology review will be shipped. Previously consented patients can be re-approached for biobank consent at the site's discretion.

6.2 Biobank Enrollment and Patient Criteria

Patients must meet the eligibility criteria for IRHDR and have been consented for participation in the IRHDR as per institutional guidelines. If patients agree to participation in the biobank component, samples will be shipped to the SickKids CRA to store in the SickKids Biobank. If patients decline participation in the biobank component but agree to participate in the main registry, samples sent for central pathology review will be shipped back to the submitting center.

All previously consented patients should be approached and re-consented for their participation in the Biobank at the discretion of the participating center.

6.3 Biobank Materials and Methods

Samples will be collected from previously collected tissue samples taken at the time of diagnosis or at relapse. No new biopsy will be scheduled for participation in the IRHDR or its biobank.

6.4 Sample Collection and Shipment

Tissue samples from the initial diagnosis or relapse are requested for the biobank. As this is a retrospective sample collection, specimens stored in any of the methods below are accepted. Please provide one of the following:

1) Slides: 10 unstained slides from paraffin blocks (10µM sections)
2) OCT embedded tissue: 0.5 g of frozen OCT block
    - ***Packing***: The OCT embedded tissue must be sent on dry ice. Paraffin and slides will require ambient shipment. No shipping supplies will be provided.
3) Paraffin embedded material: Block from initial diagnosis

If participants consent to the biobank component, the following will occur:

1) The SickKids CRA will contact the central pathology reviewer to notify which participants have consented to the biobank component.
2) The central pathology reviewer will ship the same specimens that were reviewed for the main registry component to the SickKids Biobank.
3) In the event that the specimens sent to the central pathology reviewer are not usable to be biobanked, the SickKids CRA will contact the submitting center to ask for one of the three options listed above.

If participants do not consent to the biobank component, the following will occur:

1) The SickKids CRA will contact the central pathology reviewer to notify which participants have not consented to the biobank component.
2) The central pathology reviewer will ship the specimens back to the submitting center upon completing the review for the main registry component.

6.5 How To Ship Samples

Specimen Transmittal Form: Please label the sample as per the IRHDR sample labeling and complete the provided Biobank transmittal form.

Shipping Information:

- Please include the correct shipping labels
- For Dry Ice Shipments: Dry ice label (UN1845)
- Diagnostic Specimen label, UN3373 label and the Biohazard label.

Please use Federal Express pick-up per your institutional guidelines. All shipping charges will be reimbursed by the IRHDR. Include the biobank transmittal form in the shipment and email a copy to irhdr.registry@sickkids.ca on the day of shipment with the tracking number. The SickKids CRA will notify the submitting center when the shipment has been received.

If there are questions about the available tissue sample for biobank, please contact irhdr.registry@sickkids.ca

The Hospital for Sick Children Shipping Address:

ATTN: Arnelle Lardizabal
The Hospital for Sick Children
72 Elm Street
Patient Support Centre – 10th Floor
Toronto, Ontario
M5G 1H3
Canada
Phone: 416-813-6431 Ext.406431
Email: arnelle.lardizabal@sickkids.ca

7.0 STATISTICAL CONSIDERATIONS

This is a registry; thus, all eligible patients who provide informed consent will be entered into the study, and no limits regarding accrual are provided. The statistical design of the analyses to be performed is dependent upon the nature of the analyses and will be determined at the time of the planned analyses for each condition.

8.0 AUTHORSHIP AND PUBLICATIONS GUIDELINES

The authorship of the study report will consist of the study PI (first author) followed by the study steering committee and statistician and study Co-PI (as senior author). Individuals who had a significant contribution to the registry, by contributing data on several patients, will also be considered for authorship. All authors are expected to contribute to the writing and reviewing of the research papers that will come out from this registry, and to be willing to assume responsibility for the study.

9.0 Request for Banked Specimens for Research

Histiocytosis researchers or participating sites may request biology specimens by submitting a research proposal to the Histiocyte Society (HS) scientific committee. The submission should include proposed research, including background, proposed studies, preliminary data and significance. After the approval from the HS Scientific committee, the proposal must be approved by the Rare Histiocytoses Steering committee. Please contact the IRHDR PI (Dr. Oussama Abla) or the chair of the RHD steering committee to submit proposal and request samples. Abstracts and manuscripts that present the results of studies utilizing material from the IRHDR biobank must include as coauthors the PI (Oussama Abla) and Co-PI (Dr. James Whitlock) of the IRHDR and must credit the HS RHD steering committee regardless of the affiliation of the principal investigators or authors.

10.0 Regulatory Access

The Histiocyte Society (HS) Rare Histiocytoses Steering Committee & Scientific Committee will control access to the information held in the registry. Members of the Rare Histiocytoses Steering Committee, HS researchers and researchers outside the HS can have access to the data in the registry after approval by the HS Scientific and Rare Histiocytoses Steering Committees.

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APPENDIX

CLASSIFICATION: RARE HISTIOCYTIC DISORDERS

- **Xanthogranuloma Family (XG)**
  - Cutaneous
    - Benign cephalic histiocytosis (BCH)
    - Generalized eruptive histiocytosis (GEH)
    - Progressive nodular histiocytosis (PNH)
    - Xanthoma disseminatum (XD)
    - Giant XG
    - Reticulohistiocytoma
  - Ocular
  - Systemic

- **Erdheim-Chester Disease (ECD)**

- **Rosai-Dorfman disease (RDD)**
  - Single system
    - Nodal
    - Extranodal
      - Skin
      - CNS
      - Bone
      - Orbit
      - Other
  - Multisystemic

- **Indeterminate Dendritic Cell Histiocytosis**

- **Malignant Histiocytic Neoplasm (MHN)**
  - Histiocytic
  - Langerhans cell
  - Interdigitating dendritic cell
  - Indeterminate dendritic cell
  - Primary MHN
  - Secondary to:
    - ALL
    - Follicular lymphoma
    - Other B-cell lymphoma
    - Other hematologic malignancy
    - Histiocytosis

- **ALK-positive Histiocytosis**

- **Mixed Histiocytosis (MXH)**
    - ECD/LCH
    - RDD/LCH
    - RDD/ECD
    - LCH/JXG
    - Other

- **Other**
    - Multicentric reticulohistiocytoma (MRH)
    - Necrobiotic xanthogranuloma (NX)
    - Not otherwise specified (NOS)