Histiocytic disorders are rare entities that are becoming more recognized as our understanding of the molecular pathogenesis lead to novel diagnostic tests and targeted drug development. A symposium held at the American Society of Pediatric Hematology/Oncology (ASPHO) 2013 Annual Meeting discussed new insights into histiocytic disorders. This review highlights the symposium presentations, divided into three sections encompassing Langerhans cell histiocytosis (LCH), hemophagocytic lymphohistiocytosis (HLH) and Rosai Dorfman disease (RDD) including subsections on pathogenesis, clinical diagnostic criteria and novel insights into treatment. Details of other histiocytic disorders as well as the standard treatment guidelines have been published elsewhere and are beyond the scope of this discussion [Haupt et al. (2013). Pediatr Blood Cancer 60:175–184; Henter et al. (2007). Pediatr Blood Cancer 2014;61:1329–1335. © 2014 Wiley Periodicals, Inc.]

**Key words:** hemophagocytic lymphohistiocytosis; Langerhans cell histiocytosis; Rosai Dorfman disease; targeted therapeutics

**INTRODUCTION**

Histiocytoses describe a diverse group of proliferative disorders involving dendritic cells and macrophages. They include a spectrum of diseases including a reactive inflammatory accumulation of cells, pathologic immune activation, or neoplastic clonal proliferation. Advanced molecular technologies are resulting in new breakthroughs in understanding the pathophysiology of histiocytic disorders that are changing the field. The purpose of this update report is to aid in understanding the subtle differences in pathogenesis of three most common histiocytic disorders—Langerhans cell histiocytosis (LCH), hemophagocytic lymphohistiocytosis (HLH), and Rosai Dorfman disease (RDD) and how new insights lead to the hope for novel therapeutics (Table I).

**LANGERHANS CELL HISTIOCYTOSIS (LCH)**

**Pathogenesis**

“Langerhans” in LCH refers to Dr. Paul Langerhans (1847–1888) who first described normal epidermal dendritic cells (DCs) that later were recognized as having some similarity to LCH-lesion DCs, though he initially thought those cells were neuronal cells due to their notable dendritic processes. However, despite epidermal DCs having phenotypic features of cutaneous Langerhans cells (LCs), data comparing transcriptomes of purified epidermal LCs to CD207+ cells in LCH lesions found relatively distinct gene expression profiles, with the LCH CD207+ cells having increased expression of genes associated with immature myeloid precursors [1]. Studies of mouse and human DCs also suggest that langerin/CD207 expression is not limited to epidermal LCs, but occurs in many lineages at different anatomic sites [2–4]. Therefore, it is possible that LCH may have an origin distinct from the epidermal LC.

The pathogenesis of LCH remains unresolved. Clonality of LCH was described many years ago [5,6]. Although a key feature of a neoplasm is its clonal derivation from a single cell, clonality does not necessarily mean malignancy. Willman et al. [7] defined the clonal cells in LCH as CD1a+ dendritic cells. Advances in DNA sequencing technology enabled sensitive screening of CD1a+ cells purified from LCH lesions, and it was discovered that BRAF-V600E point mutations were present in the majority of LCH lesions with a frequency ranging from 38% to 57% [8–12]. A novel somatic mutation in BRAF and germline variants of (T599A) BRAF have also been described in patients with LCH, though the significance of these observations remains to be defined [10–12]. The frequency of the somatic BRAF-V600E mutation implies functional significance in LCH pathogenesis, but no clinical correlations with BRAF genotype have been established. BRAF is an intermediate kinase in the RAS-RAF-MEK-ERK pathway that transduces extracellular signals to the nucleus. Phosphorylation of BRAF induces activation of downstream extracellular signal-regulated kinase (ERK) [8]. The V600E mutation renders BRAF constitutively active, impacting several cell functions including cell proliferation and migration. BRAF activation is insufficient to fully transform cells, as BRAF-V600E has been identified in not only malignancies, including melanoma, papillary thyroid carcinoma, and gliomas, but also in skin nevi and colon polyps [13–15].

Malignant transformation versus immune dysregulation has been a major focus of LCH research for the past 40 years, with supporting data for both mechanisms. While molecular mechanisms are being further explored, many studies have investigated inflammation within the LCH lesion. In addition to the pathologic LCs, LCH lesions are characterized by an inflammatory infiltrate typically including macrophages, eosinophils and lymphocytes.
with enrichment of regulatory CD4+CD25+T cells [16]. The lesion-LCs express high levels of T-cell stimulatory molecules as well as pro-inflammatory cytokines. In addition to the intraleional cytokine storm, increased serum levels of pro-inflammatory cytokines and chemokines are documented in active LCH [1,16–18]. Pathogenesis that defines disease subclasses of LCH needs further elucidation. A specific role for IL17A and its receptor in LCH pathogenesis has been reported, though IL17A expression by LCH elicits an inflammatory condition that often occurs with LCH. The clinical symptoms of dysarthria, ataxia, and cognitive defects resembling multiple sclerosis.

**Diagnosis**

LCH, the most common histiocytic disorder in humans, is estimated to occur in approximately five children per million, but may arise de novo in adults [21]. No screening tests are available and the diagnosis is often delayed. While the range of presentations can make LCH a challenging disease to diagnose, tissue biopsy is diagnostic with pathologic CD207+ and/or CD1a+ DCs in a background of inflammatory cells. Clinically, symptoms of LCH depend on the organs involved. Pulmonary LCH might present with dyspnea and cough, or chest pain, and shortness of breath in the case of pneumothorax. Bone lesions may lead to bone pain, abnormal swelling, or pathological fracture. Skin LCH can occur as a dermatitis rash with vesicles and bullae (more in infancy). Often there is a past history of unresolved seborrheic eczema and oozing of the external ear canal. Pituitary involvement with onset of diabetes insipidus will cause increased thirst and polyuria. Fatigue, weight loss and low-grade fevers are signs of the general inflammatory condition that often occurs with LCH. The clinical course of LCH is highly variable from self-healing without therapy to potentially lethal multi-system disease [22].

Clinical stratification for LCH is based on the extent of organ systems involved, localization and organ dysfunction: single system LCH (SS-LCH) with one organ/system involved (uni- or multifocal) and multisystem LCH (MS-LCH) with two or more organs/systems involved, with or without involvement of “Risk Organs.” Risk organs in LCH include liver, spleen, and bone marrow. The lungs have been considered for many decades a risk organ, but clinical data do not support a prognostic implication. Isolated pulmonary LCH can be seen in children but more often in adults, in strong correlation with smoking. LCH is also classified based on the site of initial presentation. Vertebral lesions with intraspinal growth or craniofacial lesions are classified as “special site” lesions and warrant systemic treatment even as single lesions. Neurodegenerative LCH seems to be a separate entity with a clinical presentation of symptoms of dysarthria, ataxia, and cognitive defects resembling multiple sclerosis.

**Treatment**

Due to incomplete understanding of the pathogenesis of LCH, treatment has relied on empiric strategies. Outcomes have improved over the past decades despite few changes in the treatment backbone, possibly due to improved supportive care. In the most recent Histiocyte Society trial, LCH-III, patients with “Low-Risk” LCH had nearly 100% overall survival, while patients with “High-Risk” LCH had 84% 5-year overall survival [23]. Other important factors are the repetition of induction phase of therapy for all patients who did not achieve a very good response after the first 6 weeks of induction, and an early move to salvage therapy for poor responders who have a very high mortality otherwise. In all patients with LCH, optimizing therapy remains a challenge since approximately one-half of all patients with MS-LCH still have refractory/recurrent disease when treated with vinblastine/prednisone-based strategies [23,24], in contrast to single system disease, which has a lower reactivation rate. Disease- and treatment-related long-term effects are also problematic, and are more common in patients with disease recurrence. While modifications in dose, duration and timing of chemotherapy along with improved supportive care may continue to achieve incremental improvements in outcomes for patients with LCH, an optimized therapeutic approach requires understanding of disease pathogenesis.

**Novel Therapeutics in LCH**

**BRAF** targeted therapy has changed the treatment paradigm in refractory melanoma [25]. Two class I BRAF-inhibitors, vemurafenib and dabrafenib, are orally available and now FDA-approved for use in advanced BRAF-V600E+ melanoma [26,27]. In a phase 3 randomized clinical trial comparing vemurafenib with dacarbazine in patients with BRAF-V600E+ metastatic melanoma, vemurafenib produced improved rates of overall and progression-free survival [28]. Non-specific side effects were reported, but the most worrisome is the development cutaneous toxicities like squamous cell carcinoma in up to 30% of patients, usual well-differentiated and easily resectable, but also de novo malignant melanoma, rare but serious [29].
The clinical potential of BRAF inhibition in patients with LCH was revealed when two patients with Erdheim Chester disease (ECD) and biopsy proven BRAF-V600E+ LCH lesions (one in skin, one in lymphnode) showed significant response to vemurafenib after 1 month [30]. Although these data are promising, validation is necessary with well-designed clinical multicenter studies. A multicenter Phase I/IIa pediatric trial for patients with BRAF-V600E+ gliomas, LCH and papillary thyroid carcinoma is currently open for recruitment in Europe, US and Canada (clinicaltrials.gov NCT01677741) (Table II). At the Histiocyte Society meeting 2013, data were presented of a single-arm open label trial to evaluate the efficacy and safety of afuresertib, an oral pan-AKT inhibitor in adult and adolescents with relapsed/refractory LCH. Although 29% patients were reported as better at the 3 and/or 6 months disease assessment, afuresertib did not meet goals for disease responses of this study.

Progressive MS-LCH (non-risk organ) has been successfully treated with 2-chlorodeoxyadenosine (2CdA or cladribine) monotherapy [31]. A nucleoside analogue like cladribine is often recommended as frontline therapy in adult LCH [32]. Adult LCH with bone lesions only might benefit from cytarabine (Ara-C) monotherapy [33]. Progressive MS-LCH with bone marrow involvement can be brought into remission with reduced intensity bone marrow transplantation [22]. Alternatively, good responses in refractory LCH have been obtained by salvage therapy of clofarabine [34,35]. In addition, the combination of 2CdA and Ara-C, although very immunosuppressive, shows promise as a salvage approach in patients with refractory LCH [32] (Table II).

### HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH)

#### Pathogenesis

The histological signature of HLH is accumulation of histiocytes in tissues, such as activated macrophages that engulf erythrocytes (hemophagocytosis) and activated cytotoxic T-lymphocytes (hence lymphohistiocytosis). Different forms of HLH can be distinguished [36] (Table III). Primary (familial) HLH, a familial form of this hyperimmune state, with persistent fever, cytopenias, hepatosplenomegaly, and hemophagocytosis as cardinal symptoms, was first described by Farquhar and Storb in 1970. Many other forms of HLH have been described since then, including secondary HLH, which is associated with a variety of underlying disorders. The pathogenesis of HLH is complex and involves dysregulation of the immune system, with increased production of cytokines and other inflammatory mediators.

#### TABLE II. Newer Therapeutic Options in Histiocytic Disorders

<table>
<thead>
<tr>
<th>Histiocytic disorder</th>
<th>Name</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Langerhans cell histiocytosis (LCH)</td>
<td>Vemurafenib</td>
<td>Evaluation in process (NCT01677741)</td>
</tr>
<tr>
<td>Hemophagocytic lymphohistiocytosis (HLH)</td>
<td>HLH-94 protocol</td>
<td>Standard of care</td>
</tr>
<tr>
<td></td>
<td>Reduced intensity conditioning</td>
<td>HSCT</td>
</tr>
<tr>
<td></td>
<td>ATG-etoposide/dexa (hybrid immunotherapy)</td>
<td>Evaluation in process (NCT01104025)</td>
</tr>
<tr>
<td></td>
<td>Rituximab</td>
<td>EBV-associated HLH</td>
</tr>
<tr>
<td></td>
<td>Alemtuzumab</td>
<td>Refractory disease</td>
</tr>
<tr>
<td></td>
<td>Tocilizumab (anti-IFN monoclonal antibody)</td>
<td>Evaluation in process (NCT02007239)</td>
</tr>
<tr>
<td>Rosai Dorfman disease (RDD)</td>
<td>Imatinib</td>
<td>Validation needed</td>
</tr>
<tr>
<td></td>
<td>Cladribine</td>
<td>Refractory disease</td>
</tr>
<tr>
<td></td>
<td>Clofarabine</td>
<td>Refractory disease</td>
</tr>
<tr>
<td></td>
<td>Rituximab</td>
<td>Validation needed</td>
</tr>
<tr>
<td></td>
<td>Azathiopine</td>
<td>Validation needed</td>
</tr>
</tbody>
</table>

#### TABLE III. Genes Associated With Primary HLH

<table>
<thead>
<tr>
<th>Gene</th>
<th>Syndrome</th>
<th>Inheritance</th>
<th>Required for lymphocyte cytotoxicity</th>
<th>Required for lymphocyte degranulation</th>
<th>Partial albinism</th>
<th>Diagnostic cellular assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRF1</td>
<td>FHL2</td>
<td>AR</td>
<td>Perforin</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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<tr>
<td>UNC13D</td>
<td>FHL3</td>
<td>AR</td>
<td>Munc13-4</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>STX11</td>
<td>FHL4</td>
<td>AR</td>
<td>Syntaxin-11</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>STXB2</td>
<td>FHL5</td>
<td>AR</td>
<td>Munc18-2</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>RAB27A</td>
<td>GS2</td>
<td>AR</td>
<td>RAB27A</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>LYST</td>
<td>CHS1</td>
<td>X</td>
<td>LYST</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>SH2D1A</td>
<td>XLP1</td>
<td>XL</td>
<td>SAP</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>XIAP</td>
<td>XLP2</td>
<td>XL</td>
<td>XIAP</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

FHL, familial hemophagocytic lymphohistiocytosis; GS, Griscelli syndrome; CHS, Chediak–Higashi syndrome; XLP, X-linked lymphoproliferative disease; AR, autosomal recessive; XL, X-linked. *Cellular assays may fail to diagnose disease caused by coding mutations that impair protein function without affecting protein expression.
Claireaux [36–38]. Primary HLH, in which genetic mutations in HLH-associated genes are identified, usually has an early onset triggered by infection. Primary HLH may also be diagnosed in adult patients [39]. Secondary (acquired) HLH often presents later in life. In the absence of a genetic cause or familial inheritance, secondary HLH occurs in response to viral infections or autoimmunity, leishmaniasis, malignancies (particularly lymphoma), as well as metabolic disorders and acquired immunodeficiencies. Macrophage activation syndrome (MAS) is a potentially fatal complication of rheumatic diseases that bears close resemblance to HLH [40].

Many cases of primary HLH are now known to be caused by defects in target cell killing by cytotoxic lymphocytes (CTL). The major subsets of CTL in peripheral blood are CD8+ T-cells and natural killer (NK) cells. CTL can eliminate virus-infected and transformed cells through direct release of cytotoxic granules that contain perforin and granzymes capable of inducing targeted cell death [41]. CTL also contribute to immune homeostasis through killing autologous, activated immune cells, thereby limiting the magnitude of immune responses. Mutations in the genes encoding perforin as well as other proteins required for cytotoxic granule trafficking and release have been associated with HLH. Upon immunological challenge, an inability of CTL to clear pathogens and control immune responses can result in a massive immune activation with excessive production of proinflammatory cytokines and influx of responding activated macrophages, manifesting as systemic inflammation with the classic immunopathology of HLH. Thus, current HLH research, focused on how defects of CTL are related to human diseases, has defined HLH as an immunodeficiency disorder [42].

**Diagnosis**

HLH is characterized by a sepsis-like systemic inflammation. The presence of five out of eight established diagnostic criteria, confirms the diagnosis of HLH (fever, splenomegaly, cytopenias (≥2 cell lineages), hypertriglyceridemia/hypofibrinogenemia, hemophagocytosis, low or absent NK activity, high ferritin (>500 mg/ml) and sCD25 > 2,400 U/ml) [43]. Altered consciousness might indicate central nervous system involvement [44]. Organ-infiltrating macrophages (CD163+/++/S100+/− , Cad1a−) involved in hemophagocytosis as well as organ-infiltrating CD8+ T-cell expansions are often present. Of note, hemophagocytosis typically manifests late in the course of the disease. Thus, a failure to detect hemophagocytosis does not negate a diagnosis of HLH. Hypercytokinemia, with high systemic levels of IL-6, IFN-γ, and TNF, is also a hallmark of HLH [45]. Upon clinical diagnosis of HLH, it is imperative that patients are rapidly evaluated for the possibility of primary HLH, as this may determine the need for performing hematopoietic stem cell transplantation (HSCT). Two complimentary approaches, genetic, and cellular, can be taken to confirm a diagnosis of primary HLH. Loss-of-function mutations in several genes have been associated with HLH (Table III). Autosomal recessive mutations in PRF1, encoding perforin, are linked to familial HLH type 2 (FHL2) [46]. Milder missense mutations in PRF1 may not cause HLH, but are associated with hematologic malignancies later in life. Autosomal recessive mutations in UNC13D, STX11, and STXB2 are associated with FHL3, FHL4, and FHL5, respectively [42]. These genes encode the Munc13-4, syntaxin-11, and Munc18-2 proteins, which regulate critical steps in lytic perforin/granzym granule exocytosis pathway. Mutations in other genes, some of which cause also partial albinism, are also associated with HLH. Because genetic approaches typically are limited to sequencing of the coding regions and splice-sites of HLH associated genes, mutations in non-coding regulatory sequences or genetic aberrations such as inversions or deletions may not be detected [47]. Importantly, cellular assays can provide rapid results to the clinician and can uncover defects missed by conventional genetic analysis. Assays measuring 51Cr-release by K562 target cells sensitive to NK cell-mediated lysis have represented the gold standard for assessment of CTL function and still constitute one component of the clinical diagnostic criteria for HLH. However, this assay cannot distinguish between an absence of NK cells or a defect in NK cell function and thus does not discriminate between primary and secondary forms of HLH. More recently, sensitive flow cytometric assays for assessment of NK cell intracellular perforin content as well as surface expression of CD107a in response to K562 target cells, the latter representing a measure of NK cell degranulation, have demonstrated efficacy for identification of patients with primary HLH [48]. In a prospective study by a pan-European consortium, assessment of NK cell degranulation provided 96% sensitivity and 88% specificity for a primary degranulation disorder in the perforin/granzyme pathway [48]. Elevated granzyme B in CTL and NK cells also represent a general signature of immune activation, and is elevated in HLH [49]. Improved diagnostic early screening tests are under development. A modified assay that provides robust quantification of cytotoxic T-cell degranulation may complement existing assays of NK-cell degranulation and further improve functional diagnostics [50].

Combining cellular phenotypical and functional assessments with genetic analyses of patients with HLH promises to provide a better view of how genetic mutations or variations perturb cellular function and predispose to disease. Future studies may uncover additional genes associated with HLH and provide greater understanding of cases hitherto defined as patients with secondary HLH.

**Treatment**

The basis of HLH therapy is intensive immunosuppression (including corticosteroids, etoposide, cyclosporin, intravenous immunoglobulin, and infliximab) and standard treatment guidelines are available in excellent reviews [51]. The HLH 94 and HLH 2004 protocols represent consensus protocols developed by the Histioyte Society and have helped in formalizing a more standard approach for treatment of HLH [43,52]. Still, therapy is complicated by high treatment-related morbidity and early disease recurrence. Because the risks and benefits of the addition of cyclosporine to induction is not yet established (HLH 2004), the HLH-94 study should be considered standard of care for all patients not enrolled in clinical trials [52]. In HLH-94, cyclosporine was introduced at the beginning of continuation therapy, while in HLH-2004 cyclosporine administration began during induction therapy in an effort to improve remission rates. In primary HLH the 8-week induction is used as a bridge to allogeneic hematopoietic stem cell transplant (HSCT), the only curative treatment available. Transplant-related morbidity in HLH has been reduced significantly with reduced intensity conditioning for HSCT [53]. Antithymocyte globulin (ATG) based immunotherapy of familial HLH, in combination with corticosteroids, cyclosporine A, and intrathecal...
injections of methotrexate, is effective as a first treatment with a 73% rapid and complete response in a single center study. When HSCT was performed early after complete or partial response induction with ATG in primary HLH, it led to a high rate of cure in the same study [54]. Hybrid immunotherapy, combining ATG, dexamethasone, and etoposide is currently in clinical trial (clinicaltrials.gov NCT01104025) (Table II).

**Newer Therapeutic Options in HLH**

In regards to new therapeutic options, when combined with conventional HLH therapies, the anti-CD20 monoclonal antibody, rituximab, improves symptoms, reduces viral load, and diminishes inflammation in patients with EBV-induced HLH if the EBV is proliferating within the B-cell [55]. However, rituximab is of no value in cases with EBV-associated HLH where EBV proliferates in T-cells instead of B-lymphocytes, as shown in Japan [56]. Furthermore, a case report remission in primary HLH was achieved by treatment with the anti-CD52 monoclonal antibody, alemtuzumab, as a bridge to HSCT [57,58]. Alemtuzumab appears to be an effective salvage agent for refractory HLH with 64% partial response rate in a single institution study, leading to survival to undergo HSCT [53,58]. However, commentaries suggested that alemtuzumab therapy may aid development of HLH in certain settings, possibly through elimination of CTL that usually contribute to the maintenance of immune homeostasis [59]. Thus, the efficacy of anti-CD52 monoclonal antibody therapy is not clear. Finally, anti-IFN-γ monoclonal antibody therapy has demonstrated efficacy in mouse models of HLH and a clinical trial is currently under way (NCT01818492) [60].

**ROSAI DORFMAN DISEASE (RDD)**

**Pathogenesis**

The non-Langerhans cell (non-LCH) histiocytoses are a group of disorders defined by the accumulation of histiocytes that do not meet the phenotypic criteria for the diagnosis of LCs [61]. Systemic non-LCH include juvenile xanthogranuloma (JXG), ECD, and RDD. The non-LCH are thought to arise from either a DC or a macrophage cell line, and can be divided clinically into three major groups—those that primarily affect the skin such as the JXG family and reticulohistiocytosis, those that affect the skin but have a major systemic component such as xanthoma disseminatum and multicentric reticulohistiocytosis, and those that predominantly involve systemic sites, although skin may also be affected, such as systemic JXG, ECD, and sinus histiocytosis with massive lymphadenopathy or RDD.

Initially described by Rosai & Dorfman in 1969, RDD is a non-neoplastic, polyonal, and self-limited non-LCH. RDD cells are CD14+, HLA-DR+, CD68++, CD163+, S100+, and fascin+ macrophages, and they are typically negative for CD1a and langerin [62]. Histologically, RDD lymph nodes show massive sinus infiltration of large histiocytes mixed with lymphocytes and plasma cells. The presence of emperipolesis, or the engulfment of intact erythrocytes, lymphocytes and plasma cells by S100+ histiocytes, in the appropriate clinical setting is considered diagnostic but not unique of RDD [63]. RDD lesions have a moderate expression of IL-6, which could be related to the associated polyclonal plasmacytosis and hypergammaglobulinemia. Furthermore, the lesions tend to express strongly IL-1β and TNF-α. Systemic symptoms in RDD may be related to enhanced production of these cytokines [64]. A cytokine-mediated migration of monocytes could be involved in histiocytes accumulation and activation. This functional activation can be triggered by hematological malignancies or autoimmune diseases. Indeed, RDD has been reported following bone marrow transplant for precursor-B acute lymphoblastic leukemia [65], and concurrently or after Hodgkin and non-Hodgkin lymphoma [66]. Similarly, an increased incidence of autoimmune hemolytic anemia, systemic lupus erythematosus and juvenile idiopathic arthritis has been documented with RDD [67,68]. Histopathological features of RDD were recently identified in the lymph nodes of 18/44 (41%) patients with autoimmune lymphoproliferative syndrome (ALPS) type Ia, with TNFRSF6 heterozygous germline mutations affecting the gene encoding Fas, that might classify some of the RDD as an autoimmune disorder [69]. Patients with ALPS type Ia and RDD tend to have more severe manifestations of ALPS, present at an earlier age and are more often males. However, the RDD changes tend to be mainly nodal and self-limited in these cases and only in a small number of patients contribute significantly to the clinical manifestations of ALPS. The transformation of RDD to a histiocytic sarcoma has been reported in a child with ALPS type Ia [70]. Given the central role of defective Fas signaling in ALPS, histiocytes could be another lineage at risk for neoplastic transformation secondary to an apoptotic block.

**Diagnosis**

The most common presentation of RDD is bilateral painless massive cervical lymphadenopathy associated with fever, night sweats, fatigue, and weight loss. Mediastinal, inguinal, and retroperitoneal nodes may also be involved. Extranodal involvement by RDD has been documented in 43% of cases with the most frequent sites being skin, soft tissue, upper respiratory tract, multifocal bone, eye, and retro-orbital tissue [71]. Other reported sites include urogenital tract, breast, gastrointestinal tract, liver, pancreas, and lungs. Head and neck involvement has been reported in 22% of cases, most commonly the nasal cavity followed by the parotid gland [72]. Intracranial RDD usually occurs without extracranial lymphadenopathy, and most intracranial lesions are attached to the dura with only few extending into the parenchyma. Central nervous system disease can present clinically and radiologically as meningioma, but the presence of emperiploisis in the spinal fluid is usually diagnostic of Rosai–Dorfman disease [73,74]. RDD cases presenting with kidney, thyroid, isolated mediastinal, and unfocal skeletal involvement have also been reported [75–78]. Laboratory abnormalities are non-specific with elevated sediment rate and leucocytosis, high ferritin, hypergammaglobulinemia, and autoimmune hemolytic anemia.

**Treatment**

Since results with chemotherapy for RDD have not been encouraging, the use of chemotherapy is restricted to patients with life-threatening disease or multiple relapses. Successful targeted therapy with platelet-derived growth factor-receptor β (PDGFRB)-inhibitors such as imatinib in a recent case report, might suggest a role for PDGFRB and KIT in the pathogenesis of RDD [79]. Newer cytotoxic agents such as cladribine (2-chlorodeoxyadenosine) and clofarabine, have been found to be effective in recurrent, refractory
or severe cases of RDD [80]. Furthermore, the efficacy of the anti-CD20 monoclonal antibody rituximab has been described in one case [81]. Refractory cerebral disease has been successfully treated with azathioprine in one patient [82] (Table II). The clinical course of RDD can be unpredictable with episodes of remission and exacerbation that may last for many years. The outcome is generally good and the disease is usually self-limited, however, approximately 5–11% of patients die from disease. Patients with combined immunologic abnormalities have a less favorable outcome and a higher fatality rate. In summary, due to the rarity of RDD and other non-LCH disorders, prospective treatment studies can be a challenge to conduct. Biology studies for RDD are urgently warranted, and will be essential for discovering more effective targeted therapies.

CONCLUSIONS

New breakthroughs in understanding the pathophysiology of histiocytic disorders are changing the field and giving hope for newer therapeutic approaches. Consortium clinical trials with targeted therapies should help to advance the management of these unique histiocytic disorders.

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