Histiocytosis and the nervous system: from diagnosis to targeted therapies

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Abstract

Histiocytoses are heterogeneous hematopoietic diseases characterized by the accumulation of CD68(+) cells with various admixed inflammatory infiltrates. The identification of the pivotal role of the mitogen-activated protein kinase (MAPK) pathway has opened new avenues of research and therapeutic approaches. We review the neurologic manifestations of three histiocytic disorders with frequent involvement of the brain and spine: Langerhans cell histiocytosis (LCH), Erdheim-Chester disease (ECD) and Destombes-Rosai-Dorfman disease (RDD). Central nervous system (CNS) manifestations occur in 10-25% of LCH cases, with both tumorous or neurodegenerative forms. These subtypes differ by clinical and radiological presentation, pathogenesis, and prognosis. Tumorous or degenerative neurologic involvement occurs in 30-40% of ECD patients and affects the hypothalamopituitary axis, meninges, and brain parenchyma. RDD lesions are typically tumorous with meningeal or parenchymal masses with strong contrast enhancement. Unlike LCH and ECD, neurodegenerative lesions or syndromes have not been described with RDD. Familiarity with principles of evaluation and treatment both shared among and distinct to each these three diseases is critical for effective management. Refractory or disabling neurohistiocytic involvement should prompt the consideration for use of targeted kinase inhibitor therapies.

Keywords: Central nervous system, Langerhans cell histiocytosis, Rosai-Dorfman disease, Erdheim-Chester disease, MAPK pathway

Introduction

Histiocytoses are rare diseases in adults and children, characterized by the accumulation of cells belonging to the mononuclear phagocyte system in various tissues and organs [1,2]. The common histopathological features of histiocytoses are the presence of CD68(+) cells, accompanied by various degrees of tissue infiltration by inflammatory cells and/or fibrosis. In 2016, the classification of histiocytoses was revised by the Histiocyte Society based on histology, clinical and imaging phenotypes, and molecular alterations, was revised, broadly defining five groups of histiocytic disorders [3]. More than 100 different types of histiocytoses have been described within these groups, with a wide range of organ manifestations and clinical phenotypes. When present, histiocytic infiltration of the nervous system and adjacent structures is an important cause of clinical symptomatology, functional impairments, and potentially morbidity and mortality. Here we review the neurologic manifestations of three histiocytic diseases with frequent and heterogeneous involvement of the brain and spine: Langerhans cell histiocytosis (**LCH**), Erdheim-Chester disease (**ECD**) and Destombes-Rosai-Dorfman disease (**RDD**). We present the recent advances that molecular and genomic investigations have brought to the pathogenesis and therapy of the histiocytoses, and we review management strategies of these three entities.

Molecular pathogenesis of histiocytoses

Research conducted in the last decade has offered key new insights into the pathogenesis of the histiocytoses and shifted the understanding of these diseases from autoimmune to clonal hematopoietic disorders. The first discovery came from an analysis of 61 LCH samples, which revealed the presence of the *BRAF*^{V600E} mutation, an oncogenic driver in several human cancers, in 57% of them [4]. Moreover, the detection of *BRAF*^{V600E} mutations in CD34+ bone marrow cells of some LCH patients provided evidence that LCH is likely derived from hematopoietic progenitor cells. Several subsequent studies confirmed the presence of *BRAF*^{V600E} in 50-60% of LCH samples [5]. Another critical step in understanding of histiocytoses pathogenesis came from the evidence that,

although the *BRAF*^{V600E} mutation was found in almost 60% of LCH patients, 100% had activation of the MAPK pathway [4], with the description of other *BRAF* activating mutations or gene rearrangements, or other kinase mutations involving the MAPK pathway [6,7]. Mutations in *MAP2K1*, which activate MEK1's kinase activity, are the next most prevalent mutations in LCH after those of *BRAF* and occur in about 25% of cases [8-10]. Other mutations in *ARAF* and *MAP3K1* were also been reported [11]. The presence of *BRAF* mutations was then investigated in ECD, and found in up to 65% of ECD cases, exclusive with other less frequent mutations or rearrangements of genes of the MAPK pathway (*MAP2K1, NRAS, KRAS,* and *ARAF*) also detected in ECD [11,12]. ECD and LCH were subsequently classified together as clonal L-group histiocytoses by virtue of their shared dependence upon MAPK pathway mutations [3]. The etiology of RDD, by contrast designated as R-group in the above classification, is currently not as clearly defined. Unlike the L-group histiocytoses, recurrent kinase mutations have not been found to be invariably present in RDD. However, recent studies have identified *BRAF, NRAS, KRAS, MAP2K1,* or *ARAF* mutations in a subset of patients with RDD [11,13-15]. This may reflect the notion that RDD is a heterogenous entity with both immune and neoplastic forms. For ECD, LCH, and RDD, the identification of the pivotal role of the MAPK pathway has opened new avenues of research and therapeutic approaches (see **Figure 1**).

Langerhans cell histiocytosis

Overview

LCH is characterized by organ infiltration by histiocytes that share characteristics with the epidermal dendritic Langerhans cells, but derive from misguided differentiation of myeloid dendritic cell precursors [16]. The diagnosis of LCH is based on appropriate clinical and radiological findings and a pathological demonstration of tissue infiltration by $CD1a^{+}/CD207^{+}$ histiocytes (**Table 1**). Biopsy is necessary in all virtually cases for confirming diagnosis and molecular analysis. The disease predominantly affects young children, with a peak age of 1–3 years, and with male predilection. The clinical course varies from a self-limiting disease to a

rapidly progressive one, leading to death [1]. LCH is classified by number of organ systems involved (single versus multisystem) and number of disease sites (single versus multiple). "Risk-organ" involvement in LCH refers to involvement of the bone marrow, spleen, or liver and is associated with worse prognosis. The concept of "risk-organ" related prognostication is considered relevant to the pediatric LCH context, not the adult setting in which this has not been examined. Clinical presentation of LCH includes variable constitutional symptoms (fever, weight loss), and local signs and symptoms depending of the involved organs, including bone pain, mucosal or cutaneous lesions, lymphadenopathy, or cytopenias. Estimated frequencies of site involvement in LCH vary by report. In adults, infiltration of bone is most frequent (60-80% of cases), then lungs (15%-50%--associated with smoking in adults), skin (15-40%), liver or spleen (15%), and lymph nodes (5-10%) [2,17]. In children, in a compiled analysis of 1741 patients[18], bone is also most frequently involved (77%), then skin (39%), lymph nodes (19%), liver (16%), spleen (13%), oral mucosa (13%), and lung (10%).

Tumorous LCH of the nervous system

Estimates of neurologic involvement of LCH, and other histiocytoses as well, vary in relation their inclusion of non-parenchymal sites (e.g., dura, base of skull) as "neurologic" (**Table 2**). True infiltration of the brain parenchyma is rare, occurring in ~5% of both adults and children, but considering all sites involving neurologic structures, these manifestations occur in 10-25% of LCH cases[2,17,18]. Neurologic involvement of LCH can be considered distinctly in its (1) tumorous or (2) neurodegenerative forms [19,20]. These subtypes differ by clinical and radiological presentation, pathogenesis, and prognosis. Tumorous manifestations are characterized by one or more infiltrative lesions in cranial or spinal structures. The hypothalamic-pituitary axis (HPA) is among the most commonly infiltrated site, occurring in up to 20% of patients. HPA infiltration presents clinically as diabetes insipidus, and in some cases deficiency of anterior pituitary hormones; in adults, DI can precede an LCH diagnosis by months or even many years [21]. Other sites of neurologic disease include the pachymeninges, choroid plexus, pineal gland,

and brain parenchyma (**Figure 2**). Parenchymal lesions are typically located in the posterior fossa including the brainstem and cerebellar peduncles. Clinical manifestations of CNS tumorous LCH reflect the site of the lesion but include headache, focal pain or swelling for calvarial disease, motor or sensory deficits for spinal lesions, or ataxia, dysarthia and bulbar deficits for posterior fossa LCH. Special note should be made of LCH infiltration of the mastoid sinus which leads to otalgia, otorrhea, swelling, and fullness, and can masquerade as chronic/recurrent otitis media [22,23]. Upon MRI evaluation, intracranial LCH lesions are expansile, T1-hypointense, T2-hyperintense, and strongly enhancing after gadolinium [24].

Treatment of LCH with neurologic involvement depends on the extent and severity of disease (**Figure 3, Table 3**). Solitary lesions of the calvarium or dura can be treated with surgical resection or low-dose radiotherapy and these interventions can frequently be curative. Multifocal disease or LCH involving the brain parenchyma is treated systemically with a variety of conventional (chemotherapeutic and/or immunosuppressive) agents. Current guidelines for conventional therapies [25-27], mainly based on the results of 4 prospective trials and a large cohort study [28-32], can be summarized as follows. The most frequently used first-line chemotherapy regimen for LCH in children is a combination of vinblastine with prednisolone, with treatment for up to 12 months [30]. In a nationwide retrospective study of 20 LCH patients (median age 11.5; range 1-50) with CNS manifestations, vinblastine with (n=9) or without (n=11) steroids was efficacious and well tolerated for treating CNS LCH [33]. In this study, 15 patients achieved an objective response, including 4 out of 6 who did not receive steroids (complete response in 5 cases and partial response in 10 cases), while 4 had stable disease and one patient progressed. Nonetheless, there is lack of consensus about the role of vinblastine in adults with LCH, particularly in the setting of neurologic disease. Purine-analogue chemotherapies cytarabine and cladribine given as monotherapies are effective for neurologic LCH; some specialists use these agents as first-line therapy while others reserve them for relapsed or refractory disease [25,34,35]. The implications of *BRAF* and other *MAPK* pathway mutational status upon LCH

treatment remain largely unclear. BRAF or MEK inhibitors have demonstrated efficacy in prospective trials of histiocytosis patients, although with a small proportion of LCH participants [36,37]. In our view, this reflects the modest proportion of LCH patients who do not respond to conventional treatments, however this specific population is in dire need of effective treatments. Therefore, the dramatic and well-established efficacy of targeted therapies in ECD leads us to recommend that LCH patients with refractory or clinically severe neurologic disease be treated with BRAF of MEK inhibitors to salvage neurologic function.

Neurodegenerative LCH

Neurodegenerative LCH (ND-LCH) is a highly rare but devastating form of disease, occurring in fewer than 5% of patients [19]. ND-LCH refers to a syndrome of progressive multi-domain neurologic deterioration that often arises many years after tumorous LCH is treated and presumed to be cured. Some patients have both tumorous and ND-LCH. Clinically, ND-LCH in children and adolescents manifests most commonly as a progressive cerebellar syndrome, accompanied by cognitive dysfunction and behavioral disturbances [38]. Adult ND-LCH patients suffer predominantly from cerebellar deficits with variable cognitive impairment. Radiologic abnormalities can be observed throughout the brain parenchyma but are most prevalent in the posterior fossa. ND-LCH lesions are characterized by non-expansile, T2 and fluid attenuation inversion recovery (**FLAIR**) intense lesions in the cerebellar peduncles, medial cerebellar structures (peri-dentate region), basal ganglia, and/or brainstem. It should be noted that MRI changes can be seen in patients without clinical symptomatology, although many such patients will develop symptoms eventually [39]. In a study of 13 ND-LCH patients[40], posterior fossa was involved in 12 patients (92%), showing a symmetrical T2 hyperintensity of the cerebellar white matter areas (n=7), a circumscribed T1 hyperintensity of the dentate nuclei (n=5), definite hyperintense T2 areas in the adjacent pontine tegmentum white matter (n=9), and/or hyperintensity of the pontine pyramidal tracts (n=4). Cerebellar atrophy was noted in 8 cases, and diffuse atrophy in 3 cases.

Cerebrospinal fluid (CSF) profile is typically unremarkable in LCH without pleocytosis or elevated protein. Osteopontin was the only consistently elevated CSF protein in patients with ND-LCH compared with patients with other brain pathologies, among 121 unique proteins associated with inflammation and/or neurodegeneration that were assessed in CSF samples from 40 patients [41]. The *BRAF*^{V600E} mutation can be detected in cell-free DNA in the CSF in 10% of patients with ND-LCH, at a lower frequency than in blood [41].

Given the clinical morbidity of ND-LCH, significant efforts have been made to better understand its epidemiology, pathogenesis, and risk factors. In a national prospective registry of pediatric LCH patients, 36/1897 (1.9%) were ultimately diagnosed with a ND-LCH [42]. The 10-year cumulative incidence was 4.1%. ND-LCH typically affected (in 69% of cases) patients previously treated for a multisystem LCH without risk organ involvement. This study also showed that pituitary gland, skin, base skull or orbit tumoral lesions, and *BRAF*^{V600E} mutation, were frequently associated with neurodegenerative phenotype.

The etiology and pathogenesis of ND-LCH are still undefined, and both immunologic and neoplastic mechanisms have been postulated. Brain biopsies of patients with ND-LCH are rare, although in one neuropathologic series, infiltrating T cells without characteristic CD1a+/CD207+ LCH lesional cells were observed, and histopathology was noted be reminiscent of immune encephalitis [20]. This finding has led to an enduring notion of paraneoplasia driving ND-LCH, although this has never been demonstrated directly. More recently, several avenues of research have indicated that mutational events likely underlie ND-LCH. In the post mortem analysis of one patient who died from ND-LCH, *BRAF*^{V600E}+ cells were identified in brainstem (13% of cells), including the pons (8%) and cerebellum (5%), with aggregates of perivascular mutated cells in areas of active demyelination. These areas enriched for BRAFV600E+ cells corresponded to characteristic areas of T2 hyperintensity illustrated in a brain MRI from the same patient. Additionally, *BRAF*^{V600E}+ cells with monocyte phenotype (CD14+ CD33+ CD163+ P2RY12-) were found in perivascular area of 3 brain specimens of ND-LCH patients [41]. In the same study, patients with ND-LCH were found to have BRAF^{V600E}+ circulating peripheral blood

mononuclear cells. These data suggest the possibility that ND-LCH lesions arise from CNS-infiltrating BRAF^{V600E}-mutated hematopoietic (myeloid/monocytic) cells. However, a different line of research suggests that in ND-LCH is driven not by mutated hematopoietic cells, but rather by somatic mutations occurring during organogenesis in yolk-sac erythro-myeloid progenitors, leading to mutated tissue-derived macrophages (i.e. microglia in the CNS). In a mouse model, mosaic expression of *BRAF*^{V600E} in yolk-sac erythromyeloid precursors resulted in clonal expansion of tissue-resident macrophages and a severe late-onset neurodegenerative disorder [43]. Neurobehavioural signs, astrogliosis, deposition of amyloid precursor protein, synaptic loss and neuronal death were driven by ERK-activated microglia. In these mice, neurodegeneration was ameliorated by BRAF inhibitor administration [43]. Further research is necessary to provide clarity about these disparate conceptualizations of the pathogenesis of ND-LCH.

Treatment of ND-LCH is challenging, and conventional therapies have yielded modest results. Disease stabilization has been observed in patients treated with *all-trans* retinoic acid in one report [44], treated with IVIG alone [45], or with IVIG and chemotherapy[46]. Clinical and radiologic improvement was reported in a small series of patients receiving cytarabine-based chemotherapy regimens[47]. Recently, 3 of 4 patients with ND-LCH treated with BRAF inhibitor following worsening despite conventional chemotherapy experienced significant clinical and radiologic improvement [41]. This has led to increased enthusiasm about targeted therapies for ND-LCH, and further studies and clinical experience are still needed. Our view is that early implementation of BRAF and MEK inhibitors, for BRAFV600E-mutated and BRAFV600-wildtype or undefined respectively, will gain traction in the coming years.

Erdheim-Chester disease

Overview

First described in 1930 [48], Erdheim-Chester disease (ECD) is a rare, multi-systemic non-Langerhans cell histiocytosis, characterized by an infiltration of various organs by xanthomatous histiocytes, Touton giant cells, lymphocytes, and scattered plasma cells with surrounding fibrosis. The histiocytes are positive by immunohistochemistry for CD68, and CD163, negative for CD1a and Langerin, and have a variable expression of S-100 protein. Clinical and radiological presentations of ECD differ strongly from those of LCH [49]. ECD mainly affects adults around 50-60 years of age, with a slight male predominance (2-3/1), although rare pediatric cases have been reported. ECD diagnosis relies on consistent clinic-radiological features, presence of long-bone involvement, compatible histopathology, and exclusion of differential diagnoses (**Table 1**) [49,50].

ECD clinical phenotypes are widely heterogenous, ranging from indolent and minimally symptomatic to progressive, disabling, and life-threatening forms. Disease infiltration of the long bones of the legs is an iconic feature of ECD, occurring in up to 96% of cases, and is characterized by symmetric osteosclerosis of the diaphyseal and metaphyseal regions of the femora and tibia [49]. Other manifestations suggestive of ECD are cardiovascular infiltration, occurring in 50% of patients, seen around the aorta or large vessels, pericardium, right coronary artery, and interatrial wall. Also, retroperitoneal fibrosis visualized as contrast-enhancing peri-nephric sheathing (“hairy kidneys”) seen on abdominal CT is a common finding. ECD-like xanthogranulomatous histiocytosis that is limited to the nervous system, i.e. neurologic juvenile or adult xanthogranuloma (in children and adults, respectively) is an ultra-rare form of non-Langerhans cell histiocytosis with similar neurologic manifestations to ECD.

Neurologic ECD

Neurologic involvement occurs in 30-40% of ECD patients, and typically affects the hypothalamic-pituitary axis, meninges, and brain parenchyma **(Figure 2, Table 2**)[51]. Hypothalamic-pituitary axis involvement can lead to various neuro-endocrinopathies (including diabetes insipidus in 17-47%), hypersomnia, and visual impairment if there is extension to the optic chiasm. Pachymeningeal thickening can mimic a nodular meningioma or cause a diffuse plaque-like expansion of dural structures. These lesions may be asymptomatic, or cause compression of cranial nerves, spinal cord, or brain parenchyma. Intraparenchymal ECD lesions have a proclivity for the posterior fossa like LCH, but can involve the cerebral hemisphere as well. Additionally, retro-orbital lesions are seen in 20-30% of cases, diabetes insipidus in 17-47%, and both are associated with other neurologic manifestations [51-53]. An additional feature suggestive of ECD is the sheathing of intracranial vessels that can lead to ischemic stroke or compression of adjacent structures [54]. In a study of 40 patients, radiographic evidence of CNS involvement (i.e., dural, brain, including Fazekas score >1, or spinal cord) occurred in 22 (55%). The MRI lesions were mainly seen in dura (6/41), brainstem (9/39), cerebellum (8/39), spinal cord (2/16), spinal epidural region (2/16), hypothalamopituitary axis (17/39), and orbits (13/42). T2 white matter abnormalities (Fazekas score ≥1) were present in 21/34 patients [55]. The same characteristics were observed in another study of 33 patients, in which the hypothalamopituitary axis was involved in 16/33 (53%), with 6 cases of micronodular or nodular masses of the infundibular stalk, meninges in 5, bilateral symmetric T2 high signal intensity in the dentate nucleus areas in 3, and intracranial periarterial infiltration in 3 patients [56]. Non-tumorous atrophic changes in the brainstem and cerebellum have been observed in ECD, although neurodegenerative phenomena have not been characterized as they have been in LCH [53]. In a study of self-reported symptoms in 50 ECD patients, 26 (52%) reported memory impairment and 17 (34%) reported difficulty with concentration [57]. In a volumetric neuroimaging study comparing 11 ECD

patients without tumorous neurologic involvement to age-matched controls, patients had diffuse bihemispheric reduction in cortical thickness and subcortical gray matter volumes [58].

Neurologic ECD Treatment

Neurologic involvement of ECD is associated with poor prognosis [53], but the prognosis is closely linked to CNS phenotype, with neurodegenerative forms having the worst prognosis. Treatments options (**Table 3**) in ECD include anti-neoplastic agents (interferon (IFN)-α and pegylated IFN-α (PEG-IFN-α), cladribine), anti-inflammatory agents (anakinra, sirolimus, infliximab, and tocilizumab), and, since the discovery of the major role of the MAPK pathway, therapies targeting BRAF or MEK (**Figure 3**). As a general rule, neurologic ECD requires more intensive therapy than non-neurologic forms of disease in order to prevent morbidity and mortality. The first established ECD treatment was IFN-α [59], and this was associated with better overall survival compared with other therapies in a cohort study of 46 ECD patients [60]. Responses in the nervous system to IFN-α have been mixed, and in one study prolonged treatment with higher doses was needed to achieve responses [61]. Anakinra, an interleukin (IL)-1 receptor antagonist, has been studied in a small number of ECD patients with variable efficacy and only anectodal neurologic responses [62,63]. Additional biological agents that have been investigated in ECD, including infliximab and tocilizumab, have not had efficacy in neurologic forms of disease [64,65]. Cladribine demonstrated an overall response rate of 53% of 21 patients in one retrospective analysis, including 5 patients with CNS involvement [66]. Vemurafenib has achieved robust and durable responses with both systemic and neurologic ECD in one prospective trial and in numerous case reports and series [67-70 71,72], including patients with severe and life-threatening neurologic illness. This led to the United States Food and Drug Administration approval of vemurafenib for treating BRAFV600E-mutated ECD [73]. Similarly favourable responses have been seen with dabrafenib[74]. However, chronic treatment may be needed as one prospective study demonstrated that ECD relapsed upon cessation of vemurafenib in 75% of cases [68]. MEK inhibitors (cobimetinib and trametinib) have shown dramatic efficacy in BRAFV600-wildtype ECD, also in one

prospective trial and several case series [69,75]. Given the morbidity posed by neurologic ECD, BRAF and/or MEK inhibitors should be considered first-line therapy in cases of tumorous parenchymal disease and in neurodegenerative forms of ECD. *BRAF*^{V600E} mutated patients can be treated with BRAF inhibitor monotherapy, or combined with MEK inhibitors as is done in other *BRAF*^{V600E}-mutated cancers to reduce toxicities [68], although the benefit of combination therapy in ECD has not been clearly shown. BRAF-wild type patients with neurologic involvement, or even neurologic ECD patients with unknown mutational status, should be treated with MEK inhibitor monotherapy [69]. In one retrospective series of 30 patients with neurologic ECD, targeted (BRAF, MEK, or ALK inhibiting) therapies led to partial or complete response by MRI in 24 (89%) of cases versus 20% for chemotherapy or immunosuppressive therapies. Mutations outside of the MAPK pathway, including alterations in NTRK, ALK, and CSF1R, have been recently documented[76], and these should be pursued if MEK inhibition is not efficacious and an alternative therapeutic target is identified.

Destombes-Rosai-Dorfman disease

Overview

RDD is another rare non-Langerhans cell histiocytosis, first described by the French pathologist Destombes in 1965 [77], then recognized as a distinct clinicopathological entity by Rosai and Dorfman in 1969 [78]. RDD mainly occurs in children and young adults but can affect all ages. It is characterized by the accumulation of large pale CD68^{+}, S100^{+}, and CD1a^{-} histiocytes, with frequent histological finding of emperipolesis, referring to the trafficking of intact leukocytes through the cytoplasm of histiocytes, and varying proportions of IgG4/IgG plasma cells [14]. RDD belongs to the R-group of the revised classification, and several subtypes have been described, including inherited forms, overlap with immunoglobulins (Ig)-G4 related disease, or association with autoimmune disorders [3]. The predominant clinical presentation of RDD is a massive, bilateral and painless cervical lymphadenopathy. However, extranodal localizations have been documented in 43% of patients [14], most frequently involving the skin, ear-nose-throat, CNS, soft tissue, and bones [80].

Neurologic RDD

Neurologic RDD involvement has been described in both adults and children, with a mean age at presentation of 39 years and a male prevalence (male: female ratio: 1.8: 1.0) [81]. Neurologic RDD can be isolated or associated with extra-neurological manifestations, and clinical presentation is typically indolent in its pace [82]. Conversely to nodal forms of the disease, CNS manifestations of RDD mainly occur in older adults [81]. In a review of 210 cases of the literature published until 2014, RDD was isolated to the CNS in 174 cases, while in 36 patients it was part of a systemic disseminated disease [81]. In the same study, 167 patients (80%) had intracranial lesions, 24 (11%) had spinal involvement, and 19 (9%) had both intracranial and spinal involvement. Tumorous lesions, predominantly of the pachymeninges, can lead to compression of neurologic structures, leading to various neurological signs. Intraparenchymal lesions are quite rare but can occur. Presenting symptoms include headaches, motor or sensory abnormalities, cranial nerve deficits, and less frequently seizures or gait difficulty. A large variety of presentations have been described: spinal cord compression, conus cauda syndrome, hydrocephalus, cognitive dysfunction, or seizures [81]. Radiological presentation of CNS RDD includes nodular meningioma-like lesions, diffuse thickening of the dura, or masses in the parenchyma, orbits, or cavernous sinuses (**Table 2**). RDD lesions typically present as homogenous, T1 isointense lesions, T2 hypo or isointense, with contrast enhancement. Perilesional edema can also be seen. Unlike LCH and ECD, neurodegenerative lesions or syndromes have not been described with RDD.

Treatments and outcomes of CNS RDD are widely heterogeneous, and little published data exists to guide treatment. Therapeutic options include observation, surgery, radiotherapy, steroids, and various immunosuppressive or chemotherapeutic agents **(Figure 3**). Surgical resection can be curative for unifocal disease, and debulking surgery may be warranted in case of spinal cord compression or other lesions causing an immediate risk of neurologic deterioration [69]. Long-term remissions with resection alone have been reported in isolated intracranial disease. Steroids are

usually helpful in reducing lesional size and improving symptoms, although responses have been variable and are not thought to be durable [83]. Also, high doses are usually required for brain lesions. Variable responses with some success have been observed with cladribine [84], rituximab [85], lenalidomide and dexamethasone [86]. Little is known about the efficacy of targeted therapies in neurologic RDD, as has been observed in L-group histiocytoses. Few reports have shown the response of RDD lesions to MEK inhibitors, but no patient had CNS manifestations [11,69].

Mixed histiocytosis

Patients with overlapping forms of histiocytosis have been described in many instances, primarily mixed ECD and LCH [87-91], and this entity is characterized almost invariably by *BRAF*^{V600E} mutations. Recently, mixed forms of ECD and RDD have been described [79], predominantly harbouring mutations in *MAP2K1*. Neurologic presentations of these mixed histiocytoses have not been characterized, however it is our experience of the overlap entities that their clinical phenotype, as well as responses to treatment, are more representative of ECD rather than the co-occurring disease. From the standpoint of treatment, it is suggested that therapy is formulated along the lines of treating ECD in these very rare cases.

Challenges and future directions for neurohistiocytosis

Despite the insights and therapeutic advances gained with the identification of targetable MAPK pathway mutations in the histiocytoses, there continue to be challenges and knowledge gaps in the evaluation and management of patients with neurohistiocytic disease. First, achieving a diagnosis of neurologic ECD, LCH, or RDD can be a protracted process, punctuated by misdiagnoses. Pathology studies have demonstrated that biopsies of neurologic structures frequently do not demonstrate typical LCH, ECD, or RDD morphology, rather they can mimic non-neoplastic inflammatory [20,52,92] or fibroinflammatory[93,94] processes. Specifically, cases of isolated HPA LCH pose a vexing diagnostic challenge as lesions are radiologically minimal, and difficult to sample surgically. Molecular advances

have allowed for diagnosis of neurologic histiocytosis by way of identification of MAPK pathway mutations in cases with clinical suspicion for histiocytosis but non-specific biopsy findings [95]. Difficulty in diagnosing neurohistiocytosis underscores the importance of awareness among clinicians of these diseases, their clinical spectrum, and the role of detailed molecular analysis, even of equivocal biopsies. Another emerging challenge is suboptimal CNS penetration of existing kinase inhibitor therapies. BRAF and MEK inhibitors are both substrates of P-glycoproteins[96] and their efflux by the blood-brain-barrier leads to limited drug levels within the nervous system. There are limited reports of unfavorable CNS responses to BRAF inhibitor monotherapy in *BRAF*^{V600E}-mutated ECD that are salvaged with combined BRAF/MEK inhibitor therapy[97]. Our collective clinical experience reflects a related phenomenon of differential systemic versus neurologic responses to targeted therapies, with neurologic sites of disease responding to a lesser degree than systemic sites. In some cases, suboptimal response can be augmented by higher dosing or combined treatment, but a price is paid with toxicity and tolerability. Last, patients with isolated neurohistiocytosis also present an unmet need for effective and durable local therapies in order to spare systemic treatment. There is a recent report of intra-arterial chemotherapy as highly effective in three such cases, including HPA neurohistiocytosis (cite in-press), and further investigation of other creative local interventions is needed.

Conclusions

Neurologic manifestations of LCH, ECD, and RDD are fascinating and heterogeneous clinical entities with disabling forms in some patients. Treatment outcomes have historically been variable, and particularly dismal with severe and degenerative neurologic forms of disease. The molecular advances in the understanding of histiocytic neoplasms, however, and the advent of targeted therapies have profoundly modified the management and outlook for these diseases. Awareness of the spectrum of these clinical entities and the diagnostic and therapeutic potential of molecular analysis is critical to improving identification and management of these patients.

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Figure legends

Figure 1. Magnetic resonance imaging of histiocytoses of the nervous system

A. Axial T1 post gadolinium MRI demonstrates calvarial-dural Langerhans cell histiocytosis (LCH)

B. Axial T2 FLAIR MRI demonstrates Erdheim Chester disease (ECD) of the brainstem, and cerebellum.

C. Sagittal T1 post gadolinium mixed histiocytosis (ECD with Destombes-Rosai-Dorfman disease, RDD) of the spine

D. Sagittal T1 MRI demonstrates profound cerebellar atrophy in neurodegenerative LCH.

E. Sagittal T1 post-gadolinium MRI with enhancement and thickening of the infundibulum in a patient with LCH.

F. Axial T1 post gadolinium MRI with RDD involving dura and bifrontal lobes.

Figure 2: Overview of MAP Kinase and PI3K-AKT signaling and the diverse kinase alterations discovered in select histiocytic neoplasms. (A) Diagram of the MAP Kinase and PI3K-AKT signaling pathways with description of the activation of the RAS proteins (HRAS, KRAS, and NRAS) with annotation of the signaling proteins affected by genetic alterations in the histiocytic neoplasms. **(B)** Pie chart illustrating a composite of the known kinase alterations in Langerhans cell histiocytosis. **(C)** Pie chart showing a composite of the known kinase alterations in Erdheim-Chester disease. **(D)** Pie chart demonstrating the published kinase alterations in Destombes-Rosai-Dorfman disease.

Figure 3. Management of Langerhans cell histiocytosis (A), Erdheim-Chester disease (B), and Destombes-Rosai-Dorfman disease (C) with nervous system involvement

Table 1. Diagnosis criteria, clinical and radiological presentations, molecular biology, and central nervous system manifestations in histiocytoses

	Langerhans cell histiocytosis	Erdheim-Chester disease	Destombes Rosai Dorfman
Distinctive clinical manifestations	• Constitutional symptoms (fatigue, night sweats), bone pain, skin lesions, anemia, and lymphadenopathy. • Cough, dyspnea, and apical-predominant nodular and/or cystic lung disease with interstitial changes. • Lytic lesions in the calvarium, base of skull, and axial skeleton. • The disease course is variable (from slowly progressive to acute or subacute presentations)	• Osteosclerosis in the legs (96% of cases). May be asymptomatic and only detected by radiotracer uptake in the distal ends of the femurs and the proximal and distal tibia. • Dense infiltration of perinephric fat, described as a "hairy kidney" on computed tomography, is a highly prevalent (68% of cases) finding. • Other organs involvements vary depending on *BRAF* status [56]. Right atrium pseudo-tumor and cardiac involvements are more prevalent in *BRAF* mutated patients. • The disease course is usually slow (over several years), but some symptoms and signs may be not clinically detected.	• Bilateral, massive, and painless cervical lymphadenopathy with or without intermittent fevers, night sweats, and weight loss. • Extranodal involvement (skin, head and neck, CNS, soft tissues, kidneys, ophthalmic manifestations) is present with or without lymphadenopathy. • Association with autoimmunity (e.g. cytopenia, lupus). • The disease course is usually slow, over several months or years.
Distinctive pathological features	• Histopathological analysis demonstrates inflammatory lesions containing abundant CD68(+), CD163(+), CD1a+ Langerin+ S100+ histiocytes	• Tissues are infiltrated by foamy CD68(+), CD163(+), Factor XIIIa(+), CD1a(-), and Langerin(-) histiocytes with fibrosis. • Touton giant cells are often present. • Positivity for S100 and emperipolesis have been rarely	• Typical findings include large pale histiocytes. with cytoplasmic and nuclear S100 and fascin positivity, CD68 positivity, and variable CD163 and CD14 positivity. The cells are CD1a−/CD207− in contrast to LCH

		observed (2).	• Emperipolesis is frequently present but may be variable, especially in extranodal sites.
Molecular features	• *BRAF*^{V600E} mutation is present in 50% of cases. And can be detected in lesional tissue or cell-free DNA extracted from plasma. • *BRAF*V600-wild-type cases are characterized by activating mutations in the MAPK pathway	*BRAF*^{V600E} mutation is present in 50% of cases The presence of *BRAF* mutation is useful to confirm ECD in ambiguous cases. *BRAF*^{V600E} mutations can be detected in lesional tissue cell-free DNA extracted from plasma. Ultrasensitive techniques are often needed for *BRAF*^{V600E} determination because of low VAF in tissues [53]. *BRAF*V600-wild-type cases are characterized by activating mutations in the MAPK pathway as well as *ALK*, *NTRK*, and others.	Typically BRAFV600-wildtype although few cases of BRAFV600E reported. *NRAS, KRAS, MAP2K1*, and *ARAF* mutations may be found in a subset of cases [15]

LCH Langerhans-cell histiocytosis

ECD Erdheim-Chester disease

RDD Destombes-Rosai-Dorfman disease

DNA desoxyribonucleic acid

CNS central nervous system

Table 2: Sites and clinical features of neurologic histiocytosis

Site of tumorous disease	LCH	ECD	RDD	Sign and symptoms
Osseous and sinuses	+++	++	+++	
Calvarium	+++	++	+++	• Focal pain • Swelling
Facial sinuses	+	++	+++	• Chronic congestion • Airway obstruction • Facial fullness
Cavernous sinuses	-	++	+	• Facial pain or numbness
Maxilla, mandible	++	+	+	• Pain • Dental decay • Multiple tooth extractions
Mastoid	+++	+	+	• Otalgia • Hearing loss • Pain and fullness
Meningeal structures	+	++	++	
Dura	+	++	++	• Headache • Dementia (rare, large bulky lesions)
Leptomeninges/CSF	+	+	+	• Cranial nerve deficits (e.g. blindness, deafness) • Elevated intracranial pressure (i.e. headache, nausea) • Radiculopathy
Hypothalamic-pituitary axis	+++	++	+	• Diabetes insipidus • Visual impairment (i.e. via chiasmatic extension of hypothalamic lesions) • Hypogonadotropic hypogonadism
Brain/spine parenchyma	+	+++	+	
Cerebral hemispheres	+	+	+	• Focal deficits • Cognitive impairment
Basal ganglia and thalamus	+	+	+	• Movement disorders, sensory disturbance (very rare)
Cerebellum	+	+++	+	• Dysarthria • Truncal ataxia • Mood instability

Brainstem	+	++	+	• Diplopia • Limb weakness • Spasticity • Bulbar affect
Spinal cord	+	+	+	• Myelopathy • Spasticity
Neurodegeneration	+	+	NA	• Ataxia • Dysarthria • Cognitive impairment • Spasticity • Mood dysregulation

LCH Langerhans-cell histiocytosis

ECD Erdheim-Chester disease

RDD Destombes-Rosai-Dorfman disease

+++ Most frequent site(s) of neurologic involvement

++ Common but not frequent site of neurologic involvement

+ Rare but described site of neurologic involvement

NA Not applicable

Table 3: Systemic Treatments for Neurologic Histiocytosis

Treatment	Regimen	Neurodegenative LCH	Tumorous LCH	ECD	RDD	Comment
Corticosteroid monotherapy	Prednisone 1mg/kg day (or equivalent) until optimal response followed by 2-3 month taper	NR	NR	NR	+/-	Variable and non-lasting responses in RDD
Chemotherapy						
Vinblastine/Prednisone	Vinblastine 6 mg/m^2 (10 mg maximum) IV weekly x 6, followed by maintenance phase dosing every 3 weeks x 6-12 months; Prednisone 40 mg/m^2 PO daily x 4 weeks, then taper, followed by 40 mg/m^2 PO maintenance phase dosing days 1-5 every 3 weeks x 6-12 months	NR	+	NR	NR	Reasonable first-line treatment in LCH
Cytarabine	100-150 mg/m^2 IV days 1-5 (6-12 cycles; 28 days/cycle)	+/-	+	AD	AD	Reasonable first-line treatment in LCH, or if refractory to vinblastine Previously given for

						ND-LCH, however has been replaced with BRAF/MEK inhibitors
Cladribine	0.14 mg/kg IV days 1-5 or 5 mg/m^2 IV days 1-5 (total of 6 cycles; 28 days/cycle)	NR	+	+/-	+/-	Reasonable first-line treatment in LCH or if refractory to vinblastine; modest evidence in ECD; anecdotal in RDD
Melphalan (intra-arterial)	0.4mg/kg	AD	AD	AD	+/-	Small series in three patients, 2/3 RDD
IVIG	0.4 g/kg/day x 5 days	+/-	NR	NR	NR	Previously given for ND-LCH, however has been replaced with BRAF/MEK inhibitors
Interferon-alpha	Pegylated 135 µg SC/week (standard dose) or 180 µg SC/week (high dose) or Standard 3 mIU SC TIW (standard dose) or 6-9 mIU SC TIW (high dose)	NR	NR	+	NR	Reasonable treatment for clinically mild ECD, without parenchymal brain involvement

Anakinra	100mcg SC daily	NR	NR	+/-	NR	2 cases of neurologic response in ECD
Targeted Therapy						
Vemurafenib	480-960 mg twice daily	+	+	+	NR	Recommended for refractory or clinically severe symptomatic BRAFV600E-mutated disease*
Dabrafenib	75-150 mg twice daily	+	+			
Cobimetinib	20-60 mg daily for 21 of 28-day cycle	+	+	+	+/-	Recommended for refractory or clinically severe BRAFV600-wildtype or BRAFV600E-undefined disease
Trametinib	1-2 mg daily					

LCH Langerhans-cell histiocytosis

ECD Erdheim-Chester disease

RDD Destombes-Rosai-Dorfman disease

+ Recommended

+/- Recommended in the context of modest evidence

NR Not recommended

AD Absent data

SC Subcutaneous

TIW Three times per week

*Rosai-Dorfman disease is nearly invariably BRAFV600-wildtype. Rare exceptions would be appropriate for BRAF inhibitor therapy

Figure 1

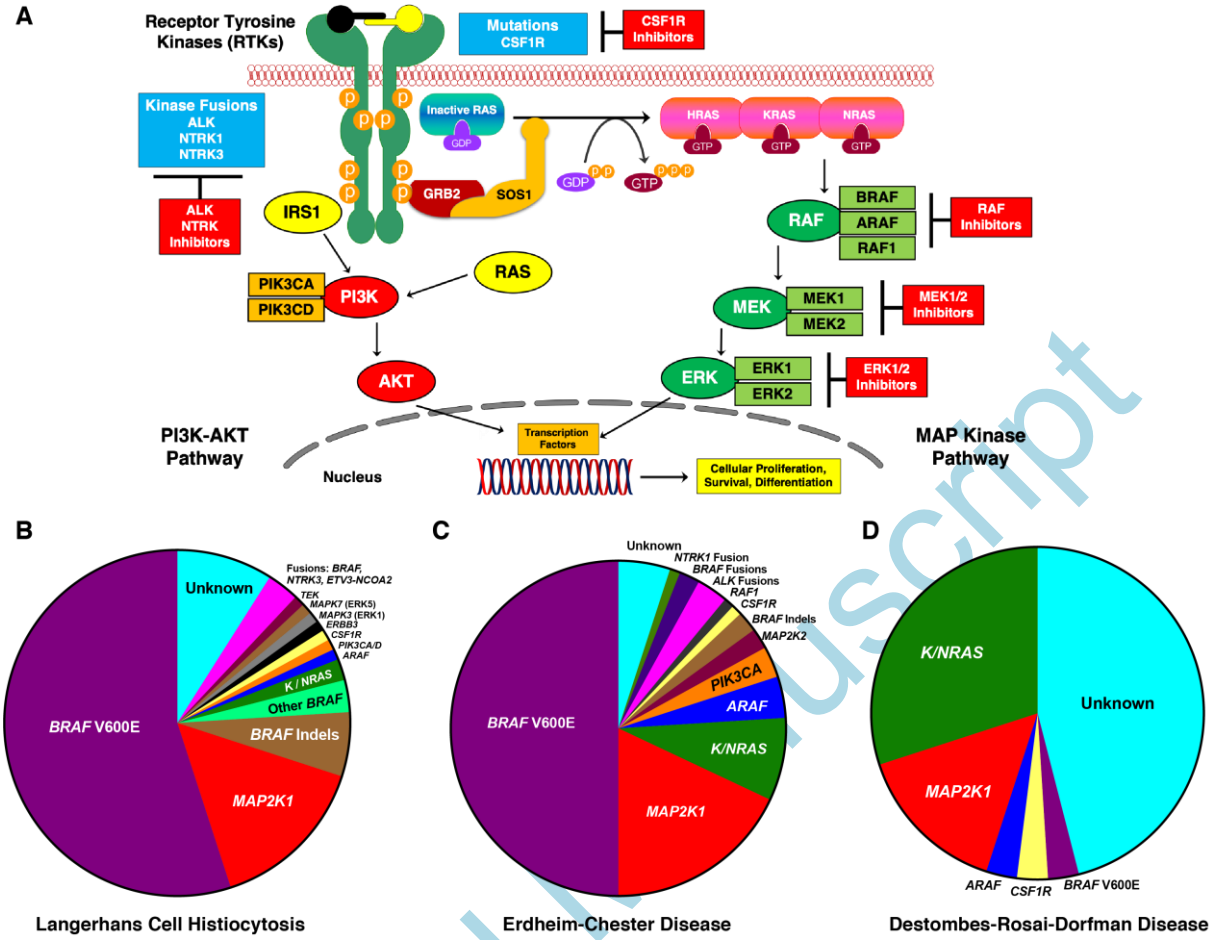

Figure 2

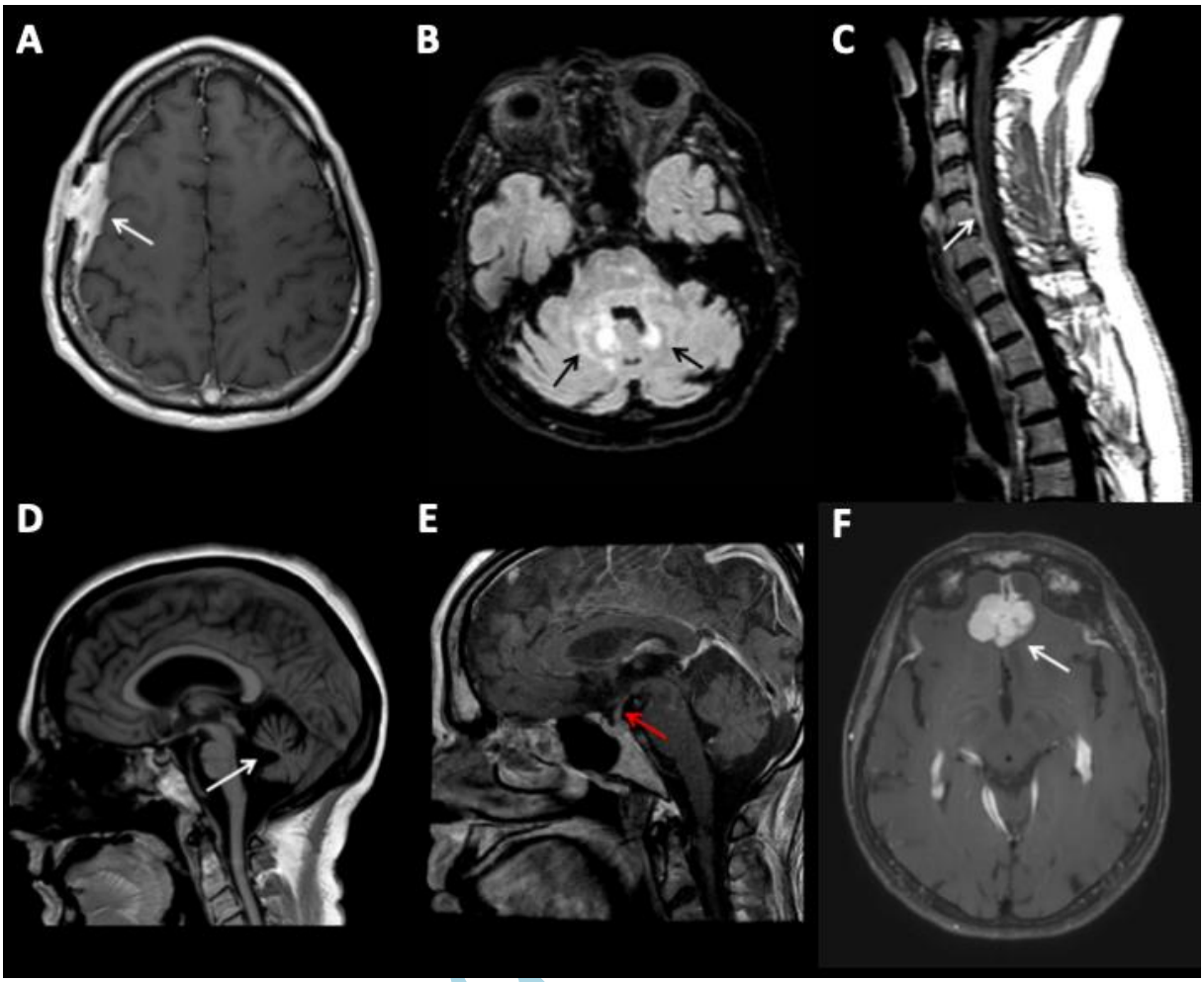

Figure 3