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Langerhans-Cell Histiocytosis

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LANGERHANS-CELL HISTIOCYTOSIS (LCH), THE MOST COMMON HISTIOCYTIC disorder, encompasses conditions characterized by aberrant function and differentiation or proliferation of cells of the mononuclear phagocyte system. "Histiocyte" is an archaic term (meaning "tissue cell") used to describe phagocytic cells with mononuclear morphologic features.[1,2] In the case of LCH, granulomatous lesions comprising langerin-positive (CD207+) histiocytes and an inflammatory infiltrate can arise in virtually any organ system but have a particular affinity for bone, skin, the lungs, and the pituitary (Fig. 1). LCH has a widely variable clinical presentation, ranging from single indolent lesions to explosive multisystem disease. Children with liver, spleen, or bone marrow involvement are at highest risk for death from LCH and are therefore classified as having high-risk LCH.[3]

Although clinical outcomes have steadily improved over the past decades, standard-of-care chemotherapy (vinblastine, prednisone, and mercaptopurine) fails to cure more than 50% of children with high-risk disease,[4] and the majority of patients have long-term consequences,[5] including a devastating neurodegenerative syndrome that can arise years after a patient is presumed to be cured.[6,7] In a 1998 review, Arceci and colleagues captured the plight of stalled progress in LCH therapy by calling empirical treatment a "roulette wheel" and noting that the "lack of consensus is derived from a persisting ambivalence as to whether LCH is primarily a neoplastic disorder, an immunodysregulatory disorder, or a disorder with characteristics of both."[8] The benign histologic appearance of the CD207+ cell, the accompanying inflammatory infiltrate, and the characteristic local and systemic cytokine storm support an inflammatory origin of LCH, whereas clonality, somatic activating gene mutations in the mitogen-activated protein kinase (MAPK) pathway, and shared mutations with hematopoietic precursors favor reclassification of LCH as a myeloid neoplastic disorder. The incidence of LCH is similar to that of pediatric Hodgkin's lymphoma, raising

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the question of whether LCH is an “orphan disease” or one of the most common pediatric cancers.[9] This identity crisis not only has limited the development of rational therapeutic strategies for patients with LCH but also has hindered access to funding and organizational resources that have catalyzed advances in other pediatric neoplastic disorders.[10] Here we review the history of LCH and discuss recent biologic insights that are poised to propel the treatment of LCH beyond an empirical roulette wheel into the era of personalized medicine.

A Brief History

ORIGINS OF LCH

The first descriptions of what we now recognize as LCH appeared in the early 1900s as case reports and case series. Hand–Schüller–Christian disease was described as eosinophilic granulomatous lytic bone lesions, diabetes insipidus, and exophthalmos in young children.[11-13] Letterer–Siwe disease was described in infants with aggressive and generally fatal systemic disease, including skin, liver, spleen, and bone marrow infiltration by reticuloendothelial cells[14,15] (Fig. 1). In the mid-1900s, Farber and Lichtenstein noted that biopsy specimens from cases of fatal Letterer–Siwe disease and specimens from cases of clinically mild eosinophilic granuloma were indistinguishable, and the two pathologists hypothesized that these conditions represent manifestations of a common disorder.[16,17] Lichtenstein proposed a common diagnosis, histiocytosis X, with the *X* indicating an uncertain cell of origin. Two decades later, with the advent of electron microscopy, Nezelof and colleagues identified a unique intracellular organelle, the Birbeck granule, in histiocytosis X lesions[18] (Fig. 2). At this point, Birbeck granules were thought to be exclusive to epidermal Langerhans cells, skin-restricted cells of the mononuclear phagocyte system. Histiocytosis X was renamed Langerhans-cell histiocytosis, reflecting the concept that LCH cells represented dysfunctional epidermal Langerhans cells. Over the next decades, reviews debated whether LCH was a disorder of transformed Langerhans cells or of normal Langerhans cells rendered pathologic by inappropriate stimuli.[8]

LANGERIN, INFLAMMATION, AND LCH

Langerhans cells are named after Paul Langerhans, a bright, young medical student who worked with the new technique of gold colloid staining in the mid-19th century. In 1868, Langerhans described an epidermal cell population, accounting for approximately 1% of epidermal cells, with characteristic dendrites that he described as extracutaneous nerves.[20] We now know that epidermal Langerhans cells are not nerves but dendritic cells, a heterogeneous group of hematopoietic cells enriched in interface tissues and lymphoid organs. In the 1970s, Steinman and Cohn distinguished dendritic cells from macrophages on the basis of specific morphologic features of dendritic cells and their superior capacity to present antigens to and activate antigen-specific T cells.[21,22] Epidermal Langerhans cells are unique among dendritic cells in that they arise not from myeloid progenitor cells in bone marrow[23] but rather from yolk-sac progenitors and fetal liver–derived monocytes that populate the skin before birth and are maintained locally under steady-state conditions.[24,25] However, on severe injury or inflammation, monocyte-derived cells in peripheral blood have the potential to migrate to the epidermis and differentiate into Langerhans cell–like cells.[26] Activated Langerhans cells mobilize through chemo-kine receptor CCR7–dependent

migration to draining lymph nodes, where they present antigen to T cells and are eventually cleared through apoptosis and other mechanisms[27] (Fig. 3A). Immature epidermal Langerhans cells express high levels of langerin (CD207), a lectin required for the formation of Birbeck granules that was initially considered to be exclusive to Langerhans cells.[30]

Histiocytic disorders are generally characterized by cellular phenotype: LCH shares surface markers with epidermal Langerhans cells (CD1a+/CD207+), whereas surface markers of juvenile xanthogranuloma and Erdheim–Chester disease are more characteristic of macrophages (CD14+/CD68+/CD163+/factor XIIIa–positive). The lesions in patients with histiocytic sarcoma or malignant histiocytosis are more aggressive than LCH lesions, with histologic features of macrophage–monocyte lineage, including CD68 and CD163 positivity, and a higher mitotic index.[31] In some cases, a mixed disorder arises in which separate lesions have distinct phenotypes or a single lesion has a mixed phenotype[32] (Fig. 2). In LCH lesions, the pathologic dendritic cells constitute less than 1% to more than 70% of the granulomatous lesion (median, approximately 8%).[33] The remainder of the lesion is composed of inflammatory infiltrate, including activated T cells on the background of a cytokine storm.[34-36] Immune dysregulation clearly characterizes aspects of the pathogenesis of LCH, although the mechanisms driving inflammation remain uncertain.

In the 1990s, Willman and colleagues investigated nonrandom inactivation of X chromosome loci and found that the percentage of clonal cells approximates the percentage of CD1a+ histiocytes in lesions from female patients with LCH.[37] Although this finding foreshadowed the characterization of LCH as a myeloid neoplastic disorder, its biologic importance remained uncertain for decades. Despite suggestions of Langerhans-cell clonality,[37,38] there was no evidence of proliferation within the lesion,[34,36]and no gross genomic alterations were identified.[39]

CURRENT UNDERSTANDING OF LCH

SOMATIC MAPK PATHWAY MUTATIONS AND LCH

Improved genomic technology heralded a breakthrough in LCH biology. Using the OncoMap pyrosequencing platform, Badalian-Very and colleagues identified the *BRAF* V600E mutation in a remarkable 57% of LCH lesions,[40] a finding that was subsequently verified in other series and attributed to the pathogenic LCH cell.[33,41-44] BRAF is a central kinase of the RAS–RAF–MEK signal-transduction pathway that is involved in numerous cell functions (Fig. 4A). The *BRAF* V600E mutation renders the MAPK pathway constitutively active.[46] Although somatic *BRAF* V600E mutations occur in 7% of all human cancers, they are also frequently found in benign conditions such as melanocytic nevi and colon polyps.[46,47] Whole-exome sequencing has revealed mutually exclusive MAPK-pathway activating mutations in an otherwise quiet genomic landscape, with no significant difference in mutation frequency between low-risk and high-risk lesions.[48,49] In addition to BRAF V600E, other activating mutations in *BRAF*, including in-frame deletions, fusions, and duplications, have been reported in LCH lesions. Additional MAPK-pathway gene mutations with proven in vitro function include insertions or deletions in exons 2 and 3 of *MAP2K1* and rare ARAF mutations.[44,48-52] Activating somatic mutations in receptor tyrosine kinase genes *(ERBB3), NRAS,* and *KRAS* have also been reported in LCH lesions

in adults.[44,49,53,54] In an institutional series, a somatic activating mutation in a MAPK-pathway gene was identified in more than 85% of cases,[51] a finding that is in line with universal extracellular signal-regulated kinase (ERK) activation observed in LCH cells[40,49] (Fig. 4B).

LCH AS A CONSEQUENCE OF MISGUIDED MYELOID DIFFERENTIATION

Advances in dendritic-cell ontogeny and descriptive studies of LCH CD207+ cells were difficult to reconcile with the model of LCH cells representing transformed or activated epidermal Langerhans cells. Alternative dendritic-cell subsets with the potential to express langerin and form Birbeck granules were discovered that survey tissues in steady-state conditions and with increased recruitment from blood to tissue during inflammation.[25] The broad tissue distribution of CD207+ dendritic cells includes organs at risk for LCH lesion formation, in contrast to the restricted tropism of Langerhans cells to the epidermis and skin-draining lymph nodes. In addition, gene-expression profiling of CD207+ LCH lesions showed minimal overlap with epidermal Langerhans cells but showed relatively increased expression of genes associated with immature myeloid dendritic-cell precursors.[36] Closer investigation of the differentiation status of LCH cells within lesions identified heterogeneous CD1a+ subpopulations with variable CD207+ expression.[55,56] Together, these findings suggested that LCH cells were more likely to arise from dysregulated differentiation or recruitment of bone marrow–derived precursor cells than from transformed or activated epidermal Langerhans cells.

BRAF V600E provided a critical biomarker with which to mine hematopoietic cells in order to define the origins of the pathologic LCH cell. Surprisingly, mutated *BRAF* V600E–positive cells were consistently identified in peripheral-blood mononuclear cells (PBMCs) from high-risk LCH patients with *BRAF* V600E–positive lesions, though the mutated cells constituted a very low percentage of these cells (typically <0.5%). By comparison, *BRAF* V600E–positive PBMCs were almost always absent from patients with active, low-risk LCH. The *BRAF* V600E mutated cells in blood localized to CD11c+ dendritic-cell precursors and CD14+ monocytes. In addition, *BRAF* V600E was identified in CD34+ hematopoietic stem cells in bone marrow aspirates from some high-risk patients, including many cells that were reported as morphologically normal.[33] Induced expression of *BRAF* V600E in langerin-positive cells generated LCH-like lesions in otherwise asymptomatic mice, whereas *BRAF* V600E expression in mononuclear phagocyte precursors (which give rise to monocytes and dendritic cells) drove aggressive and rapidly fatal disease, with diffuse infiltration of the spleen, liver, and bone marrow by dendritic cell–like cells that expressed CD207+.[33] We therefore hypothesized that the state of differentiation of the precursor cell in which somatic MAPK activating mutations arise defines the clinical extent and severity of disease.[57] In the proposed “misguided myeloid differentiation” model, activating MAPK mutations in pluripotent hematopoietic stem-cell precursors may give rise to high-risk LCH, whereas these same mutations in more committed or tissue-restricted precursors can give rise to multifocal low-risk LCH, and mutations in a local precursor can give rise to a single lesion (Fig. 3B). In patients with activating MAPK mutations in hematopoietic stem cells, the percentage of cells carrying the mutation remains relatively low and stable over time,

with skewed differentiation toward pathogenic LCH cells,[33] an observation that provides further support for the misguided-myeloid-differentiation hypothesis.

Patterns of LCH in the skin and brain offer insights into ontogeny. In the case of skin disease in infants, some patients have skin-limited disease that frequently resolves spontaneously over a period of several months. However, skin lesions, along with other systemic lesions in infants, can develop into progressive, life-threatening disease that requires chemotherapy. In a study involving infants with skin lesions, *BRAF* V600E–positive PBMCs were undetectable in almost all cases of skin-limited disease (including those with *BRAF* V600E–positive skin lesions), whereas *BRAF* V600E–positive cells were frequently detected in the peripheral blood of patients with systemic as well as skin lesions. These findings may explain the phenomenon of self-resolving lesions in some infants with skin-limited disease.[45] Like the transient myelodysplastic syndrome in children with trisomy 21 that coincides with persistent fetal hematopoiesis, skin-limited LCH may arise from mutated epidermal Langerhans-cell precursors derived from fetal liver that resolve with the transition to bone marrow hematopoiesis, so that precursors are undetectable in the circulation (Fig. 3).

In approximately 5% of patients, progressive neurodegeneration develops initially, with characteristic signal changes in the brain stem, basal ganglia, and cerebellum on magnetic resonance imaging, followed by clinical symptoms of ataxia, dysarthria, dysmetria, learning problems, and behavioral abnormalities.[7] For years, it has been thought that LCH-associated neurodegeneration arises from immune dysregulation, on the basis of biopsy studies showing infiltrating T cells and the absence of characteristic LCH CD1a+/ CD207+ cells.[58] However, despite low or absent expression of CD207, *BRAF* V600E–positive cells were recently identified in brain-biopsy specimens from patients with LCH and neurodegeneration,[19,29] with an extraordinarily high level of infiltration (>12%) in affected regions.[19] Microglia are resident myeloid cells of the central nervous system that may arise from the yolk sac during gestation. Mass et al. reported that yolk-sac erythromyeloid progenitors with enforced expression of BRAF V600E could populate the brain with *BRAF* V600E–positive microglia in mice, with the development of progressive neurodegeneration in adults.[29] Somatic mutations in the fetal yolk sac were therefore hypothesized to represent the origin of neurodegenerative LCH. In a study involving patients with LCH, the persistence of *BRAF* V600E–positive cells in the peripheral blood after chemotherapy in the absence of systemic LCH lesions was specific to patients with neurodegenerative LCH. Furthermore, examination of brain-biopsy specimens from such patients showed perivascular infiltration by *BRAF* V600E–positive cells with a monocytic phenotype (CD14+CD33+CD163+P2RY12–), supporting circulating precursors as the origin of pathogenic *BRAF* V600E–positive cells[19] (Fig. 2). This observation is consistent with a model in which a hematopoietic clone causing the original LCH lesions persists (or reemerges) after a presumed cure and serves as a reservoir for future neurodegenerative LCH (Fig. 3B). As in the case of skin LCH, multiple origins (e.g., yolk sac and bone marrow) may be possible.

EPIDEMIOLOGIC FEATURES OF LCH

The annual incidence of LCH has been reported to be 4.6 cases per 1 million children under 15 years of age, with a male-to-female ratio of 1.2:1.[59] The estimated incidence among adults is 1 to 2 cases per million, though LCH is probably underdiagnosed in this population.[60] Race and ethnic background appear to influence the risk that LCH will develop. Registry studies in the United States have shown an increased incidence among Hispanics and a decreased incidence among black children.[61,62] Furthermore, a study involving patients with LCH in Texas showed that Hispanic mothers were more likely to have children with LCH than were non-Hispanic mothers.[63] LCH can present before, after, or along with other histologic cancers, frequently with shared mutations suggesting clonality, though it is not clear whether a history of LCH confers an increased risk of cancer in children.[64,65]

CURRENT CLINICAL APPROACHES

CHEMOTHERAPY

Despite advances in unraveling the pathogenetic mechanisms of LCH, the current standard of frontline care for multifocal LCH remains empirically derived chemotherapy. Overall outcomes have improved in LCH clinical trials over the past decades, though progression-free survival among high-risk patients remains at less than 50% (see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[3,4,28,66,67] Our willingness to tolerate initial treatment failure probably stems from historical uncertainty about whether to consider LCH a cancer or an autoimmune disorder, which is also reflected in the tendency to refer to “reactivation” rather than “relapse.” However, even with low-risk patients, for whom the short-term rate of death is low, treatment failure is associated with an increased long-term risk of complications, including neurodegeneration.[5] In the LCH-III trial, children with low-risk LCH treated with frontline vinblastine and prednisone for 12 months had higher rates of progression-free survival than patients treated for 6 months (5-year relapse rate, 37% vs. 54%; P = 0.03).[4] The potential for prolonged chemotherapy (12 months vs. 24 months) to improve progression-free survival for patients with high-risk LCH is currently being tested in the LCH-IV trial of frontline therapy conducted by the Histiocyte Society (ClinicalTrials.gov number, NCT02205762). In another multicenter trial, frontline treatment with vinblastine and prednisone is being compared with cytarabine, on the hypothesis that LCH precursor cells, much like myeloid precursors in cancers such as acute myeloid leukemia, may be sensitive to nucleoside analogues (NCT02670707).

A paucity of data exist to guide therapy after frontline treatment has failed. Nucleoside analogues may be a reasonable class of drug for LCH, though optimal dosing remains to be defined. In a phase 2 trial, low-dose cladribine rarely resulted in a cure after 6 months of therapy.[68] By contrast, salvage treatment with cladribine and cytarabine, similar to that used for acute leukemia, resulted in very high rates of cure among high-risk patients but was associated with prolonged hospitalization and high rates of treatment-related death.[69,70] Allogeneic hematopoietic-cell transplantation may also be curative for patients with refractory or relapsed LCH: U.S. and European registry data from 2000 through 2013 showed a 3-year overall survival rate of 71 to 77%.[71] Data from institutional series have also

shown promising results with a less aggressive approach in which cytarabine or clofarabine monotherapy is administered at moderate doses in the outpatient setting[72,73] (Table S2 in the Supplementary Appendix).

Data to guide clinical care of adults with LCH and those with neurodegenerative LCH are limited to case studies and series. Adults may present with mixed-phenotype lesions, which may coexist with other myeloid neoplasms. Isolated pulmonary LCH may develop in adult smokers. Vinblastine and prednisone may be associated with unacceptable side effects in adults, and in general, responses to chemotherapy are less robust in adults than in children.[74,75] Clinical approaches to neurodegenerative LCH have historically been limited by the interpretation of neurodegeneration as an autoimmune or paraneoplastic phenomenon. Intravenous immune globulin has been reported to stabilize symptoms.[76] However, if neurodegenerative LCH is a manifestation of inflammation driven by clonal, MAPK-activated myeloid cells in the central nervous system, LCH-directed therapy may be more appropriate.[19,29] In fact, some patients with neurodegenerative LCH have dramatic responses to cytarabine or targeted therapy with vemurafenib.[19,77]

TARGETED THERAPY

Despite the discovery of the *BRAF* V600E mutation in LCH in 2010 and substantial evidence that LCH is driven by pathologic MAPK activation in myeloid precursors, few studies have been completed to guide the development of targeted therapy in children. Early trials involving adults with LCH or the related Erdheim–Chester disease showed promising responses to MAPK-pathway inhibition. In a phase 1–2 “basket” trial (VE-BASKET) involving 14 adults with *BRAF* V600E–positive LCH or Erdheim–Chester disease that could be evaluated, treatment with vemurafenib resulted in a 41% response rate according to Response Evaluation Criteria in Solid Tumors (RECIST).[78] By contrast, a retrospective study of vemurafenib in 12 adults with Erdheim–Chester disease showed that the metabolic response rate (i.e., the proportion of patients with positive uptake on positron-emission tomography [PET] before treatment and negative uptake with treatment) was 100%.[79] The difference in these study results probably reflects the effect of *BRAF* V600E inhibition on metabolic activity versus the effect on cytotoxicity (Table S3 in the Supplementary Appendix). In a follow-up report from the VE-BASKET trial, all patients with LCH or Erdheim–Chester disease that could be evaluated had a metabolic response.[80] How a metabolic response translates into improved survival is not yet defined. A limited number of pediatric case reports also suggests the potential for clinical responses in children with refractory LCH (Table 4 in the Supplementary Appendix). Similarly, early case reports and series support a potential benefit of MEK inhibition (Tables S3 and S4 in the Supplementary Appendix).[44,54,81]

The potential for MAPK-targeted therapy to cure LCH is not known. In the Long-Term Outcome after Vemurafenib/BRAF Inhibitors Interruption in Erdheim–Chester Disease (LOVE) study, relapse occurred in 75% of patients (adults with Erdheim–Chester disease) after *BRAF* V600E inhibitor therapy was stopped.[81] Although *BRAF* V600E–positive peripheral-blood cells and circulating extracellular *BRAF* V600E DNA in patients with high-risk disease are generally undetectable with a complete response to therapy, these

biomarkers may remain detectable in patients treated with a *BRAF* V600E inhibitor, despite dramatic clinical responses.[19,33,82,83] This observation suggests that targeted MAPK inhibitors may stun rather than kill the mutated LCH precursor cells. Collecting peripheral-blood cells prospectively in clinical trials will be valuable to determine the clinical usefulness of detecting minimal residual disease for the treatment of LCH.

The undefined toxicity profile of agents still undergoing early-phase evaluation in children is another factor that has challenged implementation of treatment with MAPK inhibitors in pediatric LCH. In studies involving adults with LCH or Erdheim–Chester disease, the toxic effects of MAPK inhibitors have been consistent with those observed in other cancer trials. Rash, arthralgias, pyrexia, nausea, vomiting, diarrhea, fatigue, and a potential for a second cancer (most often cutaneous squamous-cell carcinoma) have been reported with BRAF-V600E inhibitors, and rash, ophthalmologic inflammation, drug reaction with eosinophilia and systemic symptoms (DRESS), rhabdomyolysis, and pneumonitis have been observed with MEK inhibitors.[78,81,84,85] Once the safety and efficacy of MAPK-inhibitor monotherapy have been established for children, these studies may lay the platform to explore the safety and efficacy of combinations of targeted agents or chemotherapy combined with MAPK inhibitors.

MOLECULAR RISK STRATIFICATION

Mutually exclusive MAPK-pathway mutations and activated (phosphorylated) ERK have been identified in almost all LCH lesions.[40,43,49,51] Are there predictable clinical differences in cases of LCH driven by different MAPK mutations? Although MAPK is generally considered a linear pathway (at least below the level of RAF),[86] it is possible that specific mutations have unique downstream consequences. In vitro assays of CD207+ cells in primary LCH lesions show a mutation-specific effect on ERK activation.[49] Two institutional studies showed that patients with the *BRAF* V600E mutation had increased risks of frontline treatment failure and neurodegenerative LCH, though the results varied according to the relationship between *BRAF* mutation status and the extent of disease at presentation.[33,87] Prospective trials, including LCH-cell genotype assessment, will probably be necessary to definitively determine the relative risk of different driver mutations on clinical outcomes in LCH.

Differences among U.S. ethnic groups in the risk of acquiring LCH suggest that inherited risk factors may play a role in susceptibility to LCH and the response to therapy.[61] In addition, a genomewide association study identified a variant of *SMAD6,* encoding an inhibitory SMAD for signaling by bone morphogenetic protein, transforming growth factor β (TGF-β), or both, that is associated with an increased risk of acquiring LCH and is more likely to be present in Hispanic populations than in other ethnic groups.[88] Whether SMAD6 or TGF-β signaling plays a role in the pathogenesis of LCH is not known, but these data, along with a predisposition to LCH, point to pathogenic mechanisms beyond somatic mutations in MAPK genes.

ADDITIONAL THERAPEUTIC TARGETS

Current therapies for LCH remain suboptimal. Frontline treatment with vinblastine and prednisone performs poorly, and although salvage therapy with high-dose nucleoside analogues may be effective, it is also highly toxic. Early reports and trials of BRAF and MEK inhibitors are promising, though the side effects are not trivial and the potential for a cure is uncertain. As the outlines of pathogenetic mechanisms beyond ERK activation are filled in, additional therapeutic opportunities may be identified. The MAPK signaling pathway has a critical role in cell functions, including cell differentiation, proliferation, and survival in a cell-specific manner.[47,89] Although early studies identified mitotic figures in some LCH lesions and reported high levels of expression of Ki67 (a marker for cell proliferation),[90] more recent studies have shown that normal epidermal Langerhans cells and CD207+ cells in LCH lesions have similar rates of proliferation.[36,41,91] *BRAF* V600E–positive cells generally account for less than 1% of total PBMCs and bone marrow aspirates in high-risk patients, suggesting that a hyperproliferative precursor is also unlikely. In the absence of augmented proliferation, it is plausible that the accumulation and persistence of pathologic dendritic cells constitute a mechanism for lesion formation. BRAF V600E in CD207+ LCH lesions strongly inhibits the expression of *CCR7,*[91] which encodes a chemokine receptor required for dendritic-cell migration.[92] Furthermore, BRAF V600E drives the expression of *BCL2L1,* resulting in resistance to apoptosis.[91] Pathologic activation of MAPK signaling therefore results in suppressed migration and enhanced survival of dendritic cells, with CD207+ cells trapped in LCH lesions and resistant to cell death (Fig. 3C). Therapeutic strategies that target dendritic-cell migration and survival may represent promising new approaches.

The percentage of CD207+ cells in LCH lesions is highly variable but generally represents a minority of the lesion cells, with a median of 8% in one study.[33] Under normal circumstances, dendritic cells interact with T cells to stimulate antigen-specific responses. The functional interactions between CD207+ cells and tumor-infiltrating T cells in LCH lesions is unclear, though the CD207+ cells express high levels of programmed death ligand 1 (PD-L1), the infiltrating T cells express high levels of the coinhibitory receptor programmed death 1 (PD-1) protein,[93] and the infiltrating lymphocytes are enriched for activated CD4+ regulatory suppressor T cells.[36,41] As mechanisms driving T-cell recruitment and activation are elucidated, therapy targeting drivers of local and systemic inflammation may provide some clinical benefit. An early trial of thalidomide and a case series in which patients were treated with indomethacin suggest a potential for clinical responses to antiinflammatory agents.[94,95] Disruption of the immune microenvironment could also explain the potential for local glucocorticoid injection or even simple curettage to cure isolated LCH bone lesions.[96]

CLASSIFICATION

Is LCH a cancer? The answer carries important implications. Twenty years ago, Arceci and colleagues speculated that the uncertainty about whether LCH was a cancer or an immune disorder led to the “ambivalent” immunochemotherapeutic approach to LCH.[8] Frontline treatment with vinblastine and prednisone remains the standard of care, providing improved

overall survival but still with high rates of treatment failure.[4] We believe that the presence of activating somatic MAPK mutations in resilient myeloid precursor cells provides the basis for defining LCH as a myeloid neoplastic disorder.[33,57] The Histiocyte Society also supports reclassification of histiocytic disorders on the basis of mutation and hematopoietic lineage.[97] This reinterpretation of LCH opens up opportunities for additional clinical trials conducted by cooperative research organizations in pediatric oncology to complement the ongoing efforts of the Histiocyte Society.

CONCLUSIONS

Biologic perspectives on LCH have evolved from notable case reports describing a spectrum of disease patterns to a histologically unified diagnosis (histiocytosis X) to shared cytoplasmic structures with epidermal Langerhans cells (Langerhans-cell histiocytosis). Clinical advances have historically been hindered by undefined mechanisms of pathogenesis. Accelerated advances in the past decade have defined LCH as a disorder driven by misguided myeloid differentiation, with the extent of disease determined by the cell of origin in which activating MAPK somatic mutations arise. The challenge we now face is to translate biologic discovery into improved outcomes for children and adults with LCH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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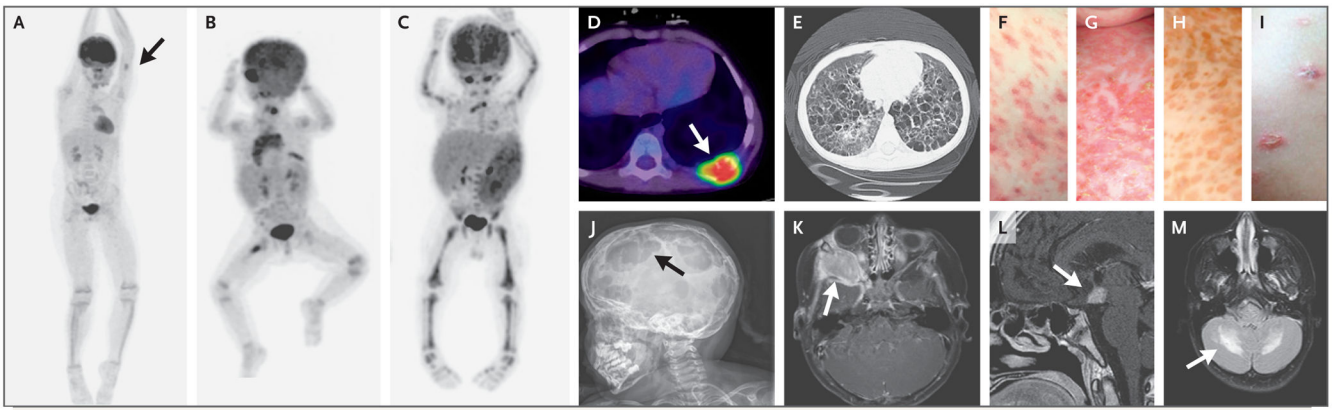

Figure 1. Clinical Spectrum of Langerhans-Cell Histiocytosis (LCH).

Positron-emission tomographic (PET) images show a single bone lesion involving the humerus (Panel A, arrow); low-risk lesions involving the orbit, lymph nodes, bone (multifocallesion), and thymus (Panel B); and high-risk lesions involving the liver, spleen, and bone marrow (Panel C). Other classic presentations include a lytic bone lesion (Panel D, arrow), cystic lung lesions (Panel E), and various skin lesions (Panels F through I). Examples of LCH lesions involving the skull and brain include multifocal skull lesions (Panel J, arrow), an orbital lesion (Panel K, arrow), a pituitary lesion (Panel L, arrow), and LCH-associated neurodegeneration (Panel M, arrow).

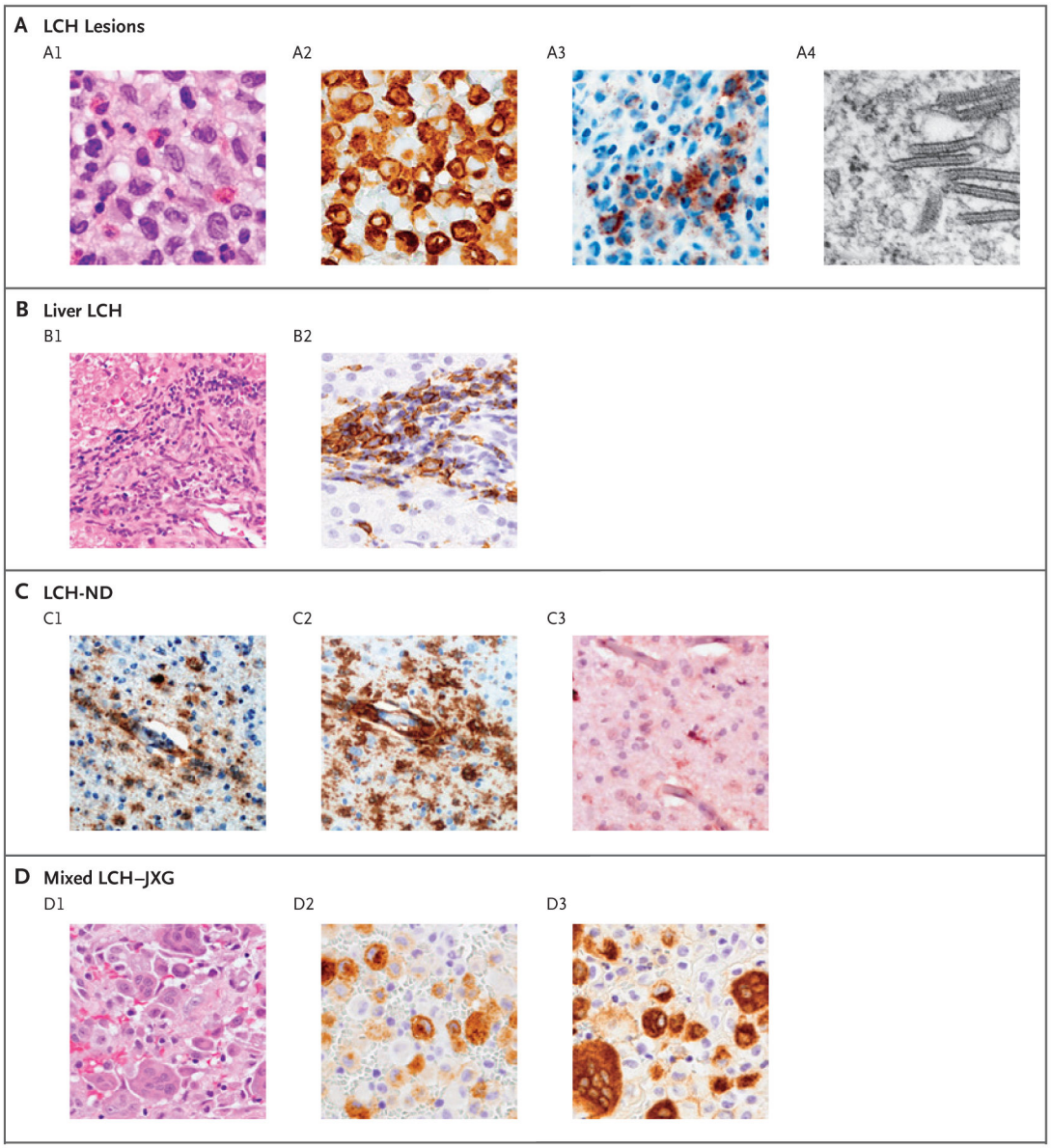

Figure 2. Histologic Features of LCH.

Panel A shows typical LCH lesions with large cells, pale cytoplasm, and reniform nuclei on hematoxylin and eosin staining (A1); CD207-positive immunostaining (A2); VE1-positive immunostaining for BRAF V600E protein (A3); and Birbeck granules visualized with electron microscopy (A4). Panel B shows liver involvement, which is frequently characterized by periportal infiltration by histiocytes (B1) and variable CD207-positive staining (B2). Panel C shows biopsy specimens from a patient with severe LCH-associated neurodegeneration (LCH-ND),[19] characterized by perivascular VE1-positive staining (C1), CD163-positive staining (C2), and a P2RY12 infiltrate with occasional P2RY12-positive, tissue-resident microglia (C3). Panel D shows histiocytic lesions that are characteristic of both LCH and juvenile xanthogranuloma (JXG), with heterogeneous histologic features on

hematoxylin and eosin staining (D1), including distinct cell populations that are CD207-positive (D2) and CD68-positive (D3).

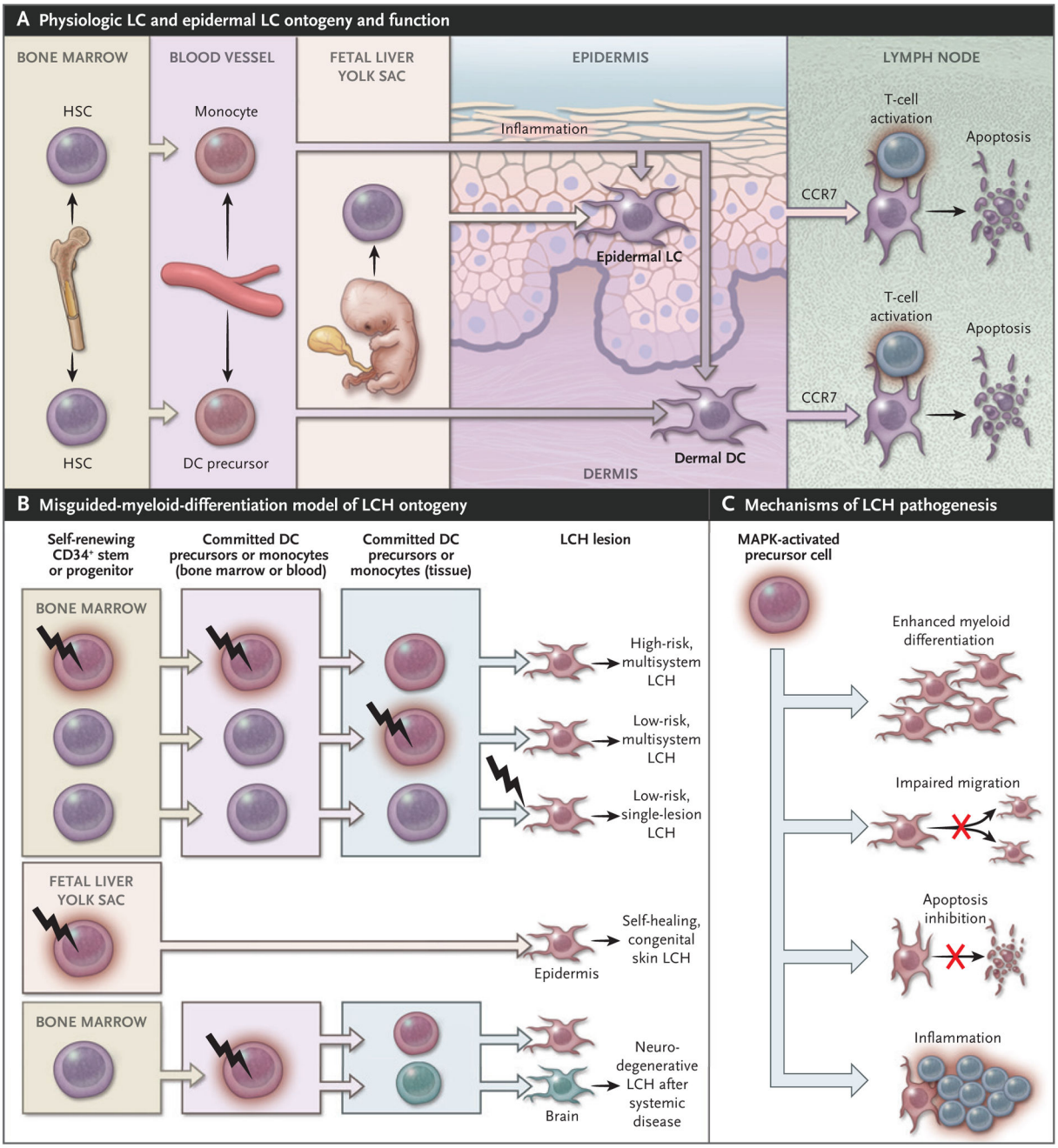

Figure 3. Models of LCH Ontogeny and Pathogenesis.

Panel A shows physiologic Langerhans-cell (LC) and dermal dendritic-cell (DC) ontogeny and function. Under normal conditions, LC precursors arise from yolk-sac progenitors or fetal liver monocytes that seed the epidermis and are maintained locally by radioresistant epidermal LC precursors in the steady state. Circulating DC-restricted precursors are constantly recruited to the skin to replenish dermal DCs. During injury or inflammation, bone marrow–derived monocytes can differentiate into epidermal CD207+ LC-like cells or dermal DC-like cells that replenish the damaged LC and dermal DC pool. CCR7 is required for activated epidermal LCs and dermal DCs to migrate through the lymphatics to the lymph

node, where they recruit and activate T cells and are ultimately cleared through various mechanisms, including apoptosis. Panel B shows the misguided-myeloid-differentiation model of LCH ontogeny. According to this model, the stage of differentiation in which the myeloid cell acquires activating MAPK mutations determines the extent of LCH. High-risk, multisystem LCH arises from self-renewing stem or progenitor cells from bone marrow; low-risk, multisystem LCH arises from MAPK activation of committed DC precursors or monocytes; and a low-risk, single lesion arises from a regional DC precursor. Clinical data support a fetal-liver origin for self-healing, congenital skin LCH and a hematopoietic origin for clonal cells that infiltrate the brain after systemic disease[28]; a mouse model also suggests that it is possible for cells derived from the fetal yolk sac to drive neurodegeneration.[29] Panel C shows mechanisms of LCH pathogenesis. MAPK activation in precursor cells contributes to the formation of LCH lesions through the following mechanisms: differentiation toward the LC phenotype, impaired migration through abrogation of CCR7 expression, and resistance to apoptosis, resulting in the accumulation of pathologic DCs and the development of an immune infiltrate that contributes to local and systemic inflammation.

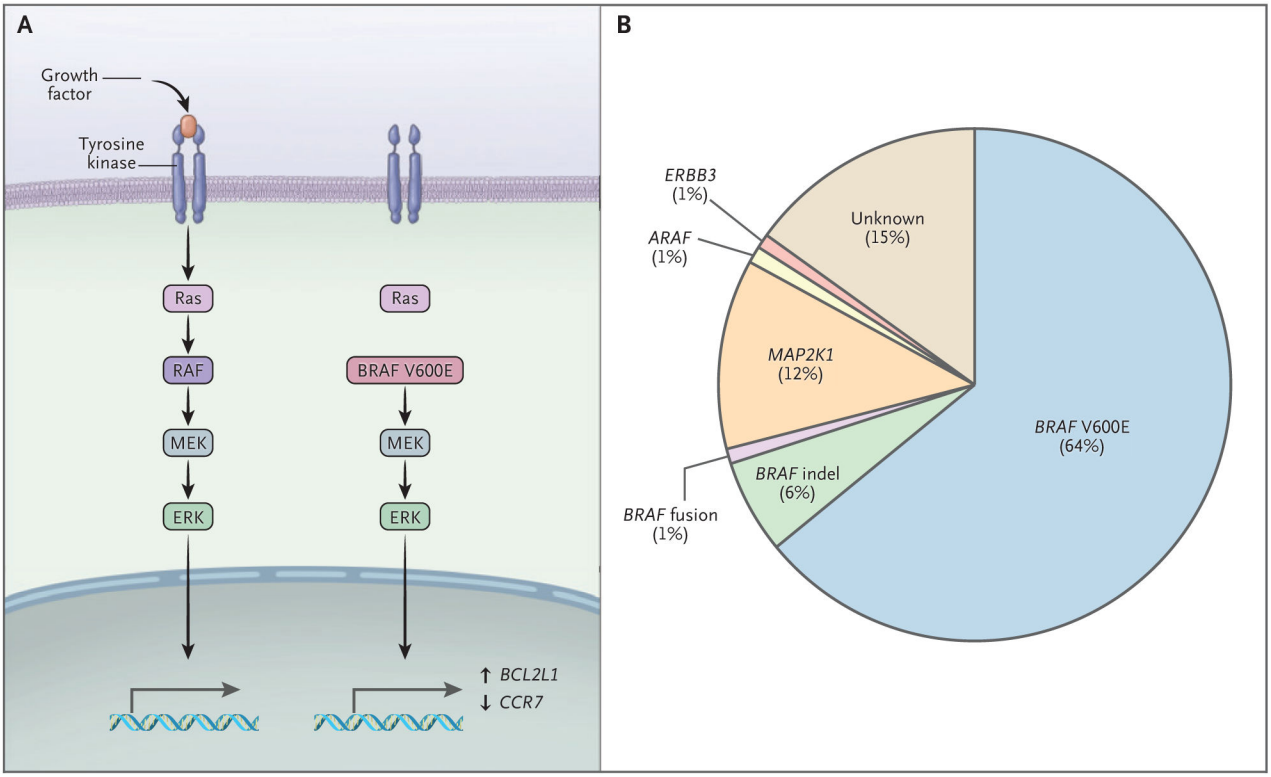

Figure 4. Activating MAPK Pathway Mutations in LCH.

As shown in Panel A, canonical MAPK signaling transduces extracellular signal through receptor tyrosine kinase (RTK), which activates Ras, then RAF, then MEK, and then extracellular signal-regulated kinase (ERK) proteins, which in turn regulate cell-specific nuclear targets and gene transcription programs. Activating mutations such as *BRAF* V600E drive constitutive ERK activation and downstream transcriptional targets, including *BCL2L1* (up-regulated) and *CCR7* (down-regulated). The pie chart in Panel B shows the proportions of cases with specific activating MAPK mutations in a primarily pediatric series from one center.[45]