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Decoding The Molecular Landscape of Erdheim–Chester Disease: From BRAF to Beyond

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Abstract: Erdheim*-Chester disease (ECD) is a rare, multisystemic non-Langerhans cell histiocytosis that causes clonal proliferation of lipid-laden CD68⁺/CD1a⁻ foamy histiocytes. ECD was formerly misdiagnosed as an inflammatory condition, but current improvements in molecular diagnostics have redefined it as a clonal hematopoietic neoplasm caused mostly by mutations in the mitogen-activated protein kinase (MAPK) pathway. The BRAF^V600E mutation is the most common, accounting for 50-60% of patients. It is linked to systemic involvement and a poor prognosis. Additional mutations in MAP2K1, NRAS, KRAS, and PIK3CA have been discovered, demonstrating the genetic variability and complexity of ECD etiology.This review delves deeply into the pathophysiological underpinnings of ECD, with an emphasis on MAPK and PI3K-AKT-mTOR pathway dysregulation, histiocyte immunohistochemistry profiles, and the significance of a Th1-skewed cytokine milieu. Molecular discoveries have not only increased diagnosis accuracy, but also influenced the development of targeted medicines. BRAF inhibitors (vemurafenib, dabrafenib) and MEK inhibitors (cobimetinib, trametinib) have shown significant effectiveness in mutation-specific cases. Furthermore, emerging resistance mechanisms, such as secondary KRAS mutations, have prompted research into combination therapies and alternative pathway blockade. Diagnostic methods, including as liquid biopsy and next-generation sequencing (NGS), have improved mutation identification, particularly in low-yield or fibrotic tumors. Future directions include the integration of single-cell omics, spatial transcriptomics, and the identification of novel targets such as CSF1R, which would provide a precision oncology framework for ECD. This increasing molecular knowledge identifies ECD as a paradigm for mutation-driven, targeted treatment in uncommon histiocytic neoplasms, stressing the importance of routine genetic sequencing to enhance clinical outcomes and therapeutic methods.*

Keywords: *Erdheim–Chester Disease, BRAF^V600E Mutation, MAPK Pathway, Targeted Therapy, Molecular Diagnostics*

INTRODUCTION

Erdheim–Chester disease (ECD) is a rare, multisystemic type of non-Langerhans cell histiocytosis characterized by the aberrant infiltration of organs by lipid-laden, foamy histiocytes.

Initially misclassified as an inflammatory disorder with uncertain cause, ECD has gained significant awareness over the last decade, partly due to breakthroughs in molecular diagnostics and imaging technology.

[1]. There have been around 1,000 instances recorded in the literature so far. The condition mainly affects individuals in their fifth to seventh decades of life, with a small male preponderance in certain cohorts, however other studies imply an equal gender distribution.[2][3].

The illness was first characterized in 1930 by Austrian pathologists Jakob Erdheim and William Chester. It was originally recognized in two individuals with a distinct presentation of lipoid granulomatosis, which varied from other known histiocytic disorders such as Hand-Schüller-Christian and Niemann-Pick diseases.

It wasn't until 1972 that Jaffe reintroduced the disorder and developed the term "Erdheim-Chester disease," which recognized its specific clinical and pathological characteristics.

Recent molecular findings have dramatically altered our knowledge of ECD pathophysiology.

Although the actual cause remains unknown, genetic investigations have discovered activating mutations in the mitogen-activated protein kinase (MAPK) pathway in over 80% of patients, most notably the BRAFV600E mutant, which is detected in at least half of cases.

[1][2]. Furthermore, around 15% of ECD patients show overlapping characteristics with Langerhans cell histiocytosis (LCH), and roughly 10% are linked with other hematologic malignancies such as myeloproliferative neoplasms or myelodysplastic syndromes.[1][2].

Histiocytes, the primary effector cells in ECD, develop from myeloid progenitors and are members of the mononuclear phagocyte system, which also includes monocytes, macrophages, and dendritic cells.

In 1987, the Histiocyte Society classified histiocytoses into three major classes. (1) Langerhans cell histiocytosis (LCH), formerly known as histiocytosis X; (2) non-Langerhans cell histiocytoses originating from monocytes and macrophages; and (3) malignant histiocytoses.

[3]. Interestingly, ECD was not listed in either the 1987 or the 1998 histiocytosis classifications, delaying its identification as a unique clinical entity.[1]

ECD is currently recognized as a clonal hematopoietic illness with systemic involvement, which causes substantial organ damage.

The condition mostly affects the skeletal system, central nervous system, endocrine glands, orbits, cardiovascular structures, retroperitoneum, lungs, and skin, frequently causing both local and systemic inflammation.

The most common symptoms described at presentation are bone pain, diabetes insipidus, xanthelasmas, and exophthalmos.[1][4]

Because of its diverse clinical presentation, ECD is commonly misdiagnosed, sometimes for months or years.

It involves a multidisciplinary approach that combines clinical evaluation, imaging tests, histopathologic study, and genetic profiling

[1][4].The characteristic radiologic features include bilateral cortical sclerosis of long bones, the so-called "hairy kidney" look on CT owing to perirenal infiltration, coated aorta, and right atrial pseudotumour.

[1][5].

Histological evidence of ECD often displays xanthogranulomatous infiltrates comprised of foamy histiocytes that are CD68+ or CD163+ and CD1a−, helping to differentiate ECD from LCH and other histiocytoses[6].

Despite breakthroughs in diagnosis and therapy, ECD is still a dangerous illness with high morbidity and mortality.

The 5-year survival rate varies between 70% and 80%, depending on the extent and location of organ involvement.

Current therapy options include interferon-α, targeted medicines like BRAF inhibitors (e.g., vemurafenib) and MEK inhibitors (e.g., cobimetinib), especially in instances with MAPK pathway mutations.[7].

Comprehensive Review of Methods

Pathogenesis of Erdheim–Chester Disease (ECD): An Overview

Pathophysiology

Erdheim-Chester disease (ECD) is thought to be caused by the proliferation and migration of CD68-positive, CD1a-negative non-Langerhans histiocytes that are monocyte-macrophage in origin. This distinguishes ECD from Langerhans cell histiocytosis (LCH), which includes CD1a (+), Langerin (+), and S-100(+) Langerhans-type dendritic cells generated from the same CD34 (+) myeloid stem cell lineage.

[8]. Despite sporadic reports of patients presenting with both ECD and LCH, no definite conclusion has been established regarding a common progenitor problem. Some researchers hypothesize a shared malfunction of the CD34 (+) precursor cell.[8].

Histologically, ECD differs from LCH in terms of immunophenotypic profile. ECD histiocytes are normally CD68 (+), CD1a (−), and S-100(−/low), whereas LCH histiocytes test positive for S-100 protein and contain Birbeck granules in more than 20% of cells on electron microscopy.

[9][10]. However, rare cases of S-100 positive in ECD have been described, indicating variability in histiocyte features. Furthermore, factor XIIIa positivity has been documented, especially in pulmonary ECD lesions.[11].

The typical histological environment of ECD lesions includes xanthogranulomatous infiltration, proliferating fibroblasts leading in fibrosis, a noteworthy lack of eosinophils, the presence of lymphocytic aggregates, and Touton giant cells.

[12]. Despite much research, it is still uncertain whether ECD is a monoclonal neoplastic illness or a polyclonal reactive condition. HUMARA tests and cytogenetic studies produced inconsistent results, indicating contradictory data on clonal origin.[13].

Immunological profiling has led to progress. Arnaud et al. (2011) found a distinct cytokine and chemokine profile in ECD, with higher levels of interferon-α, interleukin-12, and monocyte chemotactic protein-1 (MCP-1/CCL2), and lower levels of IL-4 and IL-7.
Interestingly, interferon-α levels remained increased even in individuals undergoing treatment, suggesting that this cytokine may not effectively modify the disease's immunological environment.
The source of interferon-α remains unknown as dendritic cells responsible for its production were lacking in ECD lesions. However, interferon-γ-positive lymphocytes and the chemokine IP-10 (CXCL10), a downstream result of Th1 activation, were also found.
These findings suggest a strong Th1-skewed immune response in ECD pathogenesis.[14].
Stoppacciaro et al. found enhanced chemokine expression and receptor activity in ECD histiocytes and endothelial cells, providing additional evidence for a Th1-dominant milieu.
Notably, Ki-67 staining was negative, and no mitotic figures were seen, indicating that lesion growth may not be due to active proliferation but rather to an inflammatory or immune-mediated mechanism.
This study found high interferon-γ and low interleukin-10 levels, supporting the Th1 profile.
Studies have found elevated levels of TNF-α, IL-6, and IL-1β, indicating these cytokines might be therapeutic targets.
Isolated patients treated with cytokine-targeting drugs like infliximab (anti-TNFα) and anakinra (IL-1 receptor antagonist) showed encouraging results.

Finally, the finding of activating mutations in the BRAF V600E gene in a large number of ECD and LCH patients has transformed our knowledge of ECD's molecular etiology.
This data lends credence to the neoplastic concept and opens the door to targeted therapy with BRAF inhibitors like as vemurafenib, which has demonstrated encouraging clinical results in certain patients.

Clonality and Origin of Erdheim–Chester Disease
Erdheim-Chester disease (ECD) is typically classified as a non-Langerhans cell histiocytosis due to its morphological and immunophenotypic differences from Langerhans Cell Histiocytosis (LCH). However, molecular discoveries in the last decade have transformed our view of ECD, revealing that it is a clonal myeloid neoplasm caused by mutant hematopoietic progenitor cells rather than a reactive or inflammatory condition as previously thought. This has significant consequences for ECD classification, diagnosis, and treatment.
The evidence for ECD's myeloid origin comes mostly from genetic investigations, which show that the illness is caused by somatic mutations seen in neoplastic myeloid diseases. BRAF^V600E is the most often reported mutation in ECD, accounting for 50-60% of patients. This mutation is also commonly found in other myeloid cancers, such as hairy cell leukemia. In key investigations, including those by Diamond et al. and Emile et al., ECD histiocytes were revealed to possess not just BRAF mutations but also changes in other MAPK pathway genes such as MAP2K1, KRAS, NRAS, and PIK3CA, all of which are established oncogenic drivers in hematologic neoplasms.
[20]. Importantly, these mutations are mutually exclusive among individual individuals, indicating a clonal neoplastic origin rather than a polyclonal inflammatory response.
Studies on hematopoietic progenitor cells provide more persuasive data. Mutations like BRAF^V600E have been found not only in lesional histiocytes, but also in peripheral blood mononuclear cells and bone marrow CD34+ hematopoietic stem/progenitor cells (HSPCs).
Berres et al.'s seminal study showed that ECD patients' hematopoietic progenitors have the same BRAF^V600E mutation as their tissue-infiltrating histiocytes.
[32]. These findings indicate that the illness begins early in the hematopoietic hierarchy, with mutant myeloid progenitors producing pathogenic tissue-infiltrating histiocytes. The clonal growth of these progenitors, followed by differentiation into monocytes and macrophages that concentrate in organs, accounts for ECD's systemic and frequently multisystemic appearance.
When compared to Langerhans Cell Histiocytosis (LCH), which was formerly classified as a histiocytic disease alongside ECD, some major molecular and pathogenetic parallels emerge. LCH, like ECD, is caused by MAPK pathway activating mutations, such as BRAF^V600E in 50-60% of cases and MAP2K1 in BRAF-wild type patients. Furthermore, similar to ECD, clonal hematopoietic progenitor cells in LCH patients have these mutations, confirming a common myeloid progenitor origin for both disorders.[16][32].

Despite its genetic similarities, ECD and LCH have different tissue distributions, histology, and immunological markers. ECD histiocytes are generally CD68+, CD163+, Factor XIIIa+, and negative for CD1a and Langerin (CD207), whereas LCH cells are CD1a+, Langerin+, and S100+. Histologically, ECD lesions are distinguished by lipid-laden, foamy histiocytes surrounded by fibrosis, whereas LCH lesions are more cellular and xanthogranulomatous, with eosinophilic infiltrate.
ECD has a specific inflammatory milieu with higher levels of cytokines such IL-6, IFN-α, and TNF-α, which contribute to the disease's fibrosis and systemic inflammation. LCH, while also involving inflammation, is more commonly seen in pediatric patients and can involve discrete lesions in bone, skin, and the central nervous system, whereas ECD usually affects adults and presents with diffuse multi-organ involvement, particularly of the bones, cardiovascular system, retroperitoneum, and CNS.
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These findings support the present idea that ECD and LCH are both inflammatory myeloid neoplasms arising from mutant hematopoietic progenitors with distinct differentiation routes and clinical characteristics. This prompted the World Health Organization (WHO) and the Histiocyte Society to categorize these conditions as "clonal histiocytic neoplasms," with shared MAPK pathway activation serving as the molecular hallmark.[4][21]

Molecular Genetics of ECD
Recent advances in the molecular genetics of Erdheim-Chester disease (ECD) have highlighted the occurrence of mutations in the BRAF gene, particularly the BRAF^V600E mutant.
The BRAF gene produces a protein kinase that is a necessary component of the MAPK (mitogen-activated protein kinase) signaling cascade, commonly known as the RAS-RAF-MEK-ERK pathway.
This route regulates critical biological processes such as cell proliferation, differentiation, apoptosis, angiogenesis, and cell survival. Under normal physiological settings, the RAS protein initiates upstream signals that govern the activation of this signaling pathway.
The BRAF^V600E mutation replaces valine (V) with glutamic acid (E) at position 600 of the BRAF protein, resulting in constitutive activation of the BRAF kinase independent of upstream RAS signals.
This aberrant activation generates persistent signaling through the MAPK pathway, contributing to the uncontrolled development and survival of diseased cells, such as those observed in ECD. [15].
The BRAF^V600E mutation is not unique to ECD and has been found in several human malignancies, with different frequency. For example, it is seen in around 40% to 60% of melanomas, 100% of hairy cell leukemias, and around 5% of papillary thyroid carcinomas.
[15]. This mutation represents a significant step forward in the field of histiocytic diseases. In 2010, Barrett Rollins' group did a mass spectrometry-based genomic study (OncoMap) targeting known cancer genes and discovered the presence of the BRAF^V600E mutant in 57% of 61 archival samples from patients with Langerhans cell histiocytosis.
[16]. This research showed a clear genetic connection and offered strong evidence that LCH is a clonal condition caused by oncogenic mutations, notwithstanding its inflammatory characteristics.
[17]. A large histological study of 127 patients with various histiocytic disorders found the BRAF^V600E mutation by pyrosequencing in 13 out of 24 patients with ECD (54%) and 11 out of 29 patients with LCH (38%). However, the mutation was not found in other histiocytic conditions such as Rosai-Dorfman disease (RDD) or xanthoma disseminatum.
[18]. This specificity highlights the role of BRAF^V600E in the pathophysiology of ECD, distinguishing it from other histiocytic disorders.
Immunohistochemistry utilizing a BRAF^V600E-specific antibody showed the presence of the mutant protein in tissue samples of ECD patients.
The mutant BRAF protein was found mostly in foamy histiocytes and Touton giant cells, which are common histological characteristics of ECD. Notably, the expression was lacking in adjacent non-histiocytic cells such as lymphocytes, fibroblasts, and endothelial cells, demonstrating that the mutation is exclusive to the diseased histiocyte population implicated in ECD.
[18]. Additionally, immunostaining for phosphorylated extracellular signal-regulated kinase (pERK), a downstream marker of MAPK pathway activation, was shown to be positive in virtually all ECD tissue samples, giving further evidence of constitutive MAPK signaling in the condition.[19].
BRAF^V600E is not the sole genetic mutation that activates the MAPK pathway in ECD. Other oncogenic mutations have been discovered in people who lack the BRAF mutation (BRAF-wild type). A comprehensive whole-exome and transcriptome analysis of ECD tissue samples identified recurrent

mutations in genes such as MAP2K1, ARAF, NRAS, and KRAS, as well as translocations involving BRAF, ALK, and NTRK1.
[20][21]. MAP2K1 mutations were particularly frequent, accounting for approximately 30% of cases. Mutations in KRAS or NRAS were found in around 27% of patients. In addition, rare genetic changes such as BRAF deletions, MAP3K1 amplifications, ARAF mutations, and RET fusions have been identified.
ECD is mostly caused by BRAF^V600E, however deregulation of the MAPK pathway is a common molecular feature, independent of the genetic mutation.
Interestingly, the PI3K-AKT pathway has also been linked to ECD etiology. Activating mutations in the PIK3CA gene have been discovered in around 11% of ECD patients
[19]. This route can also be triggered secondary to the MAPK cascade, indicating that both signaling networks interact. In ECD histiocytes, hallmarks of PI3K-AKT-mTOR signaling, such as phosphorylated mTOR and p70S6K, have been found, notably in CD68-positive cells
[22]. These molecular discoveries enhance our understanding of the illness by revealing several oncogenic drivers and signaling pathways that contribute to ECD's clinical phenotype.
Because of the low quantity of mutant alleles in ECD tissue, extremely sensitive detection technologies such as digital droplet PCR are necessary to properly identify BRAF and other alterations.
Traditional sequencing approaches may miss up to 25% of BRAF mutations due to low variant allele frequency (≤5%), highlighting the importance of precision diagnostics in suspected instances of ECD. [23].
The BRAF^V600E mutation in ECD has clinical and prognostic implications, in addition to its molecular characterisation. According to studies, BRAF-mutant ECD is more commonly linked with severe and multisystemic illness. Retroperitoneal fibrosis (RA pseudotumor) was found in 57% of BRAF^V600E-positive individuals compared to only 9% in those with wild-type BRAF. This difference was highly significant (P <.0001).
[11]. The mutation was substantially linked to cardiac and aortic infiltration, with an odds ratio of 4.92 per standard deviation rise in BRAF^V600E burden.
[24]. Furthermore, pericardial involvement was more likely in individuals carrying the BRAF mutation [25]. A study of 97 ECD patients with CNS involvement indicated that 77% had the BRAF^V600E mutant, suggesting a relationship between this mutation and aggressive, systemic illness with neurologic signs.
BRAF^V600E is a significant molecular driver of ECD, impacting etiology, clinical expression, and therapeutic response. Targeted MAPK pathway drugs, notably BRAF and MEK inhibitors, have showed promise in treating ECD patients carrying these mutations, highlighting the translational value of molecular diagnosis in this uncommon histiocytic neoplasm.

Mechanism: MAPK Pathway Activation in Erdheim–Chester Disease

The mitogen-activated protein kinase (MAPK) pathway, also known as the RAS-RAF-MEK-ERK signaling cascade, is critical to the molecular pathogenesis of Erdheim-Chester disease (ECD).
This intracellular signaling system is evolutionarily conserved and plays an important role in regulating cellular functions such as proliferation, differentiation, survival, apoptosis, and migration. Extracellular growth factors and cytokines bind to their respective receptor tyrosine kinases (RTKs) on the cell membrane, activating the MAPK pathway.
This receptor interaction stimulates the small GTPase RAS, which then recruits and activates RAF family kinases (ARAF, BRAF, and CRAF/RAF1). Activated RAF phosphorylates and activates MEK1/2 (MAP2K1/2), which in turn phosphorylates and activates ERK1/2.
Activated ERK moves into the nucleus, where it controls gene expression programs that promote cellular development and survival.[16][18]
In ECD, somatic mutations in the MAPK pathway disrupt the highly regulated cascade, resulting in constitutive activation of downstream signaling independent of external growth signals. The BRAF^V600E mutation is the most well-known of these mutations, found in approximately 50-60% of ECD cases.
This point mutation replaces valine with glutamic acid at position 600, causing a structural shift in the BRAF kinase that mimics phosphorylation-induced activity. As a result, the mutant BRAF kinase is permanently "switched on" and constantly stimulates MEK and ERK, promoting uncontrolled cell proliferation, inflammation, and resistance to apoptosis.

[26]. Immunohistochemical investigations have revealed high nuclear staining for phosphorylated ERK (pERK) in almost all ECD lesions, giving direct evidence of pathway hyperactivation.[21].
In addition to BRAF^V600E, several somatic mutations impacting the MAPK pathway have been discovered in ECD patients, particularly those who are BRAF-wild type. Notably, mutations in MAP2K1 (MEK1) affect up to 30% of these individuals. These mutations also cause constitutive ERK activation by circumventing the requirement for upstream RAF activation.
[20][27].Mutations in KRAS and NRAS, which encode GTPases that function upstream of RAF, have been discovered in around 27% of instances and have comparable downstream consequences. Rare mutations or changes, including as ARAF mutations, MAP3K1 amplification, and BRAF fusions or deletions, have also been documented as contributing to abnormal MAPK signaling.
[20][27]. Furthermore, gene translocations involving BRAF, ALK, and NTRK1 have been discovered in ECD and other histiocytoses, underscoring the genetic variability driving MAPK activation.[20].
The ramifications of activating this route in ECD are numerous. At the cellular level, MAPK signaling stimulates the clonal development of histiocytes, particularly foamy CD68+ and CD163+ histiocytes, which infiltrate bone, cardiovascular tissue, the retroperitoneum, and the central nervous system.
These histiocytes frequently exhibit characteristics of both neoplastic proliferation and chronic inflammation. Hyperactivation of the MAPK pathway also causes the production of pro-inflammatory cytokines and chemokines, which contribute to the inflammatory milieu found in ECD lesions.[21].
Furthermore, crosstalk between the MAPK pathway and other carcinogenic pathways has been observed. For example, activation of the PI3K-AKT-mTOR pathway may arise subsequently via ERK-mediated signaling or independently through PIK3CA mutations, which are seen in around 11% of individuals with ECD.
[21]. The downstream activation of mTOR and p70S6K, indicated via phosphorylated protein labeling in histiocytes, contributes to improved protein synthesis, cellular metabolism, and survival.[4].
The significance of MAPK pathway activation in ECD goes beyond pathophysiology to therapeutic implications. BRAF inhibitors (vemurafenib, dabrafenib) and MEK inhibitors (cobimetinib, trametinib) have shown significant therapeutic benefit in individuals with ECD who have the relevant mutations.
These medicines function by specifically blocking hyperactive kinases while decreasing downstream oncogenic signaling, which frequently results in quick symptom alleviation and disease reversal.
The constitutive activation of the MAPK pathway is now recognized as a molecular signature of Erdheim-Chester illness, which is caused by a number of mutually exclusive somatic mutations affecting various nodes of the circuit.
This insight has not only changed our view of ECD as a clonal myeloid neoplasm, but it has also heralded a new era of precision medicine in the treatment of this hitherto mysterious condition.[4]

NRAS Mutation in Erdheim–Chester Disease:
Erdheim-Chester disease (ECD) additional oncogenic drivers are progressively being identified in BRAF-wildtype ECD.
The NRAS mutation, for example, is an alternative driver that activates the MAPK signaling cascade in a similar manner.
NRAS belongs to the RAS family of small GTPases and functions upstream in the MAPK pathway, sending signals from activated cell surface receptors to downstream effectors including RAF, MEK, and ERK. Mutations that activate NRAS cause constitutive GTP binding and persistent downstream signaling in the absence of external inputs.
In the setting of ECD, such variants can replace BRAF mutations in driving pathogenic histiocytic proliferation and inflammation.
Aitken et al. (2015) described the second documented instance of ECD including an NRAS mutation, broadening the disease's genetic range.
In this instance, a 77-year-old man with various comorbidities reported worsening localized bone discomfort in his right knee. Imaging demonstrated increased bone density in the femur and tibia, and histological evaluation of a sample from the tibial lesion confirmed widespread macrophagic infiltration and bone remodeling, which are consistent with ECD morphology. Because of the patient's fragility and limited presentation, no systemic imaging or active treatment were used.
A next-generation sequencing (NGS) panel targeted hotspot mutations in 11 oncogenes (EGFR, KRAS, BRAF, TP53, PTEN, NRAS, and PIK3CA). A total of 10 ng of DNA from formalin-fixed paraffin-embedded bone tissue was sequenced using the Ion Torrent PGM platform.

A mutation in NRAS at codon 61 (c.182A>G, p.Q61R) was found using the Integrative Genomics Viewer (IGV), verified by a 35% base substitution with over 500 read depth. This Q61R mutation is a well-studied oncogenic alteration that causes loss of intrinsic GTPase function, thus trapping NRAS in an active signaling state. Notably, no mutations were discovered in BRAF or the other genes tested, validating the NRAS mutation as the most likely oncogenic driver in this case.

This discovery is relevant because NRAS-mutant ECD is a separate genetic subtype that may not benefit from BRAF-targeted therapy like vemurafenib, which are beneficial in BRAF^V600E-positive illness. Direct suppression of NRAS has proven difficult in clinical oncology, although downstream effectors in the MAPK cascade, such as MEK, are promising targets. MEK inhibitors have been demonstrated to be effective in NRAS-mutated melanomas and may provide therapeutic benefit in similarly mutated ECD patients.

This work not only emphasizes the diagnostic usefulness of genetic profiling in uncommon histiocytic neoplasms, but it also supports the rising necessity for comprehensive, multi-gene molecular testing in ECD patients. While the appearance of ECD might be confused with reactive or other inflammatory diseases, molecular diagnosis gives objective confirmation and has direct treatment consequences.

Therapies that target MEK or other components of the MAPK and PI3K pathways may be interesting options for people with NRAS-mutated ECD. The study eventually advocates for more thorough research into ECD's genetic variability and the clinical effects of non-BRAF mutations in order to improve patient treatment in this rare and previously difficult-to-treat condition.[28]

MAP2K1 (MEK1) Mutations in Erdheim–Chester Disease

MAP2K1 encodes MEK1 (Mitogen-Activated Protein Kinase Kinase 1), a key dual-specificity kinase in the MAPK signaling cascade. This kinase acts immediately downstream of RAF, directly activating ERK1/2 via phosphorylation. Under normal physiological conditions, MEK1 activation is tightly controlled by upstream signals via receptor tyrosine kinases and RAS-RAF activation in response to growth factors and cytokines. Once activated, ERK1/2 moves to the nucleus and influences transcriptional programs that control cell proliferation, differentiation, metabolism, and survival.

In Erdheim-Chester disease (ECD), somatic mutations in MAP2K1 have emerged as a key mechanism of MAPK pathway activation, particularly in instances that are negative for the more frequent BRAF^V600E mutation. These MAP2K1 mutations, such as the K57N (lysine to asparagine at codon 57) substitution, are gain-of-function changes that result in MEK1 activation regardless of upstream RAF signaling.

This results in persistent ERK phosphorylation and hyperactivation of downstream signaling pathways, which promote the pathological histiocytic proliferation and systemic fibrosis associated with ECD.

A 55-year-old man was characterized in the literature as having a 22-year history of progressive, multi-organ fibrosing illness, which included pericarditis, vascular occlusions, and retroperitoneal and mediastinal fibrosis. Despite thorough clinical examinations, a unified diagnosis could not be made until a liquid biopsy (cell-free DNA next-generation sequencing) was conducted.

This non-invasive technique detected a MAP2K1 K57N mutation at a variant allele frequency of 1.2%, demonstrating MAPK pathway activity in the absence of a BRAF mutation.

The identification of a MAP2K1 mutation was critical for making diagnostic and treatment decisions. Traditional biopsy failed due to the poor cellularity of fibrotic lesions, but molecular testing using plasma DNA overcome this constraint, demonstrating the efficacy of blood-based genomic sequencing in histiocytic illnesses.

Furthermore, MAP2K1-mutant ECD does not react to BRAF inhibitors like vemurafenib, although BRAF-mutant ECD does. Instead, MEK inhibitors like cobimetinib and trametinib, which directly target the abnormal MEK1 activity, have demonstrated therapeutic effectiveness in MAP2K1-positive ECD patients. These medications have been linked to disease control and even remission, including symptom alleviation and radiological improvement on PET-CT scans.

Furthermore, a study of the literature shows that MAP2K1 mutations account for 14% to 30% of ECD patients with wild-type BRAF. These individuals frequently show signs of systemic fibrosis and inflammation, such as "hairy kidneys" (perirenal fibrosis), coated aorta, and stomach involvement.

Unlike BRAF-mutant ECD, which usually affects the central nervous system and has a xanthogranulomatous phenotype with foamy histiocytes and Touton giant cells, MAP2K1-driven ECD often has less lipid-laden cytology and more fibrotic tissue on histology.

Mechanistically, the MAP2K1 K57N mutation alters MEK1's kinase domain, changing the protein structure to promote a persistent active state. This activation can induce ERK phosphorylation without

upstream input, similar to the consequences of other MAPK pathway mutations as BRAF^V600E or NRAS Q61R.

Such redundancy in oncogenic signaling emphasizes the key significance of the MAPK pathway in ECD pathogenesis and the need of thorough genetic testing, including MAP2K1 screening, particularly in BRAF-negative patients.

In conclusion, MAP2K1 mutations define a new genetic subtype of Erdheim-Chester illness, distinguished by autonomous MAPK pathway activation, fibrotic clinical symptoms, and susceptibility to MEK-targeted treatments. Their identification not only validates diagnosis in histologically equivocal situations, but it also allows for precision medicine methods, which provide patients with appropriate therapies based on their unique molecular profile. [4][20][29]

PI3K–AKT–mTOR Pathway Alterations in Erdheim–Chester Disease

In addition to the well-established significance of MAPK pathway mutations in Erdheim-Chester disease (ECD), growing data points to the PI3K-AKT-mTOR signaling axis as a significant factor to its pathogenesis. This route is a key regulator of cellular activities like metabolism, growth, proliferation, and survival.

Under normal circumstances, activation of cell surface receptors, including receptor tyrosine kinases (RTKs), recruits and activates phosphoinositide 3-kinase (PI3K), which transforms phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 serves as a docking site for AKT (also known as protein kinase B), allowing it to be activated by phosphorylation.

Activated AKT phosphorylates several substrates, including mTOR (mechanistic target of rapamycin), a serine/threonine kinase found in the mTORC1 and mTORC2 complexes. These complexes govern protein synthesis, lipid biosynthesis, autophagy, and mitochondrial metabolism, all of which help cells survive and flourish.

In the context of ECD, investigations have revealed activating mutations in PIK3CA, the gene that encodes PI3K's catalytic subunit, in roughly 11% of patients. These mutations cause constitutive activation of the PI3K pathway in the absence of external growth cues, resulting in persistent AKT and mTOR activity.

Notably, immunohistochemical analyses of CD68+ foamy histiocytes in ECD lesions revealed increased expression of phosphorylated mTOR and its downstream target p70S6 kinase, confirming that the pathway is functionally active in disease tissue. [30].

Importantly, the PI3K-AKT-mTOR pathway does not work alone; rather, it interacts extensively with the MAPK signaling cascade, which is regarded as the primary oncogenic driver in ECD. Both pathways are commonly active together and may impact each other's signaling dynamics. For example, ERK activation downstream of MAPK signaling can increase mTOR activity by inhibiting the TSC1/TSC2 complex, which is a negative regulator of mTORC1.

In contrast, PI3K signaling can influence components of the MAPK cascade via feedback loops involving mTORC2 and other intermediates. This bidirectional cross-regulation leads to a synergistic amplification of proliferative and anti-apoptotic signals, promoting the growth and persistence of histiocytic infiltrates in ECD.

Furthermore, mutations in both pathways have been seen to occur concurrently. Patients with BRAF^V600E or MAP2K1 mutations may exhibit PI3K-AKT-mTOR activation, indicating that certain ECD lesions are affected by dual-pathway dysregulation. This might explain therapy resistance or partial responses to MAPK inhibitors alone. These findings have far-reaching implications for treatment, indicating that combination inhibition of MEK and mTOR may be more beneficial in specific genetically determined subgroups of ECD.

Therapeutically, this understanding paves the way for precise treatments that target the PI3K-AKT-mTOR pathway. Although PI3K and mTOR inhibitors are not yet widely used in ECD therapy, preclinical and anecdotal clinical data suggests they may be useful, especially in BRAF-wildtype, MAPK-resistant, or PIK3CA-mutant ECD patients. The use of mTOR inhibitors, such as sirolimus or everolimus, which have been extensively researched in other neoplasms, may open up new paths for treatment refractory or multisystemic illness in ECD.

In summary, the PI3K-AKT-mTOR pathway is a secondary but important carcinogenic signaling pathway in Erdheim-Chester illness. Its activation, whether through PIK3CA mutations, downstream MAPK signaling, or microenvironmental cues, contributes to disease progression by increasing cellular proliferation, survival, and inflammation. The interaction of the PI3K-AKT-mTOR and MAPK pathways

highlights the molecular complexity of ECD and the necessity for extensive molecular profiling to guide individualized treatment. [4][20][21][31]

Molecular Diagnostics in Erdheim–Chester Disease

Molecular diagnostics have become an important part of the diagnostic and treatment framework for Erdheim-Chester disease (ECD), a rare clonal histiocytic neoplasm caused by oncogenic mutations in the MAPK signaling pathway. Molecular discoveries, including somatic mutations like BRAF^V600E, MAP2K1, NRAS, KRAS, and PIK3CA, are crucial for confirming ECD diagnosis, despite its different histopathologic and radiologic characteristics. These molecular discoveries not only confirm the neoplastic origin of ECD, but they also serve as indicators for customized treatment.

Current diagnostic criteria for ECD involve a triad of findings: (1) clinical and radiologic features consistent with ECD (e.g., long bone osteosclerosis, "hairy kidney" sign, coated aorta); (2) histopathologic confirmation through tissue biopsy demonstrating lipid-laden, CD68+ CD163+ CD1a– Langerin– histiocytes with associated fibrosis; and (3) molecular testing confirming oncogenic mutations, most commonly within the MAPK pathway. The addition of molecular testing to the diagnostic algorithm reflects its dual role: as a diagnostic marker separating ECD from non-neoplastic histiocytoses, and as a predictive biomarker directing the use of targeted treatments such as BRAF and MEK inhibitors. [4][21].

Tissue biopsy remains the primary method of diagnosis and molecular testing in ECD. However, it provides distinct problems due to the varied tumor cellularity and fibrotic stroma found in ECD tumors. The best biopsy location is generally determined by FDG-PET/CT imaging, which reveals metabolically active lesions. Bone lesions, perinephric soft tissue tumors, and cutaneous xanthelasmas are typical targets. Whenever feasible, biopsy of the most FDG-avid yet accessible location is desirable, especially when a large cellular yield is required for both histology and subsequent genetic testing. Skin lesions, such as xanthelasmas, may give a less-invasive option for sampling, however sensitivity may be decreased due to restricted tissue volume and cellularity.[31].

The technique of tissue preservation is an important procedural concern in ECD biopsy, particularly when sampling bone. Standard decalcification processes involving strong acids can damage DNA, greatly impeding next-generation sequencing (NGS) or PCR-based mutation analysis.

To address this, EDTA-based decalcification is recommended when obtaining bone samples, as it helps preserve nucleic acid integrity, allowing high-quality molecular analysis. [31].

Recent advances have also shown that liquid biopsy may be used as a minimally invasive alternative or supplement to tissue-based diagnostics. Cell-free DNA (cfDNA) isolated from peripheral blood has been used effectively to find actionable mutations in ECD patients, especially when tissue biopsy is not possible due to anatomical inaccessibility, patient fragility, or inconclusive past histology.

Zhou et al. reported a significant instance in which a MAP2K1 K57N mutation was identified using blood-based next-generation sequencing (NGS) in a patient with a 22-year history of multisystemic fibrosis consistent with ECD. The mutation was detected with a variant allele frequency of only 1.2%, demonstrating the sensitivity of modern cfDNA platforms.

[29]. This result not only verified the diagnosis, but it also affected the treatment decision to target MEK. As such, liquid biopsy is a potential diagnostic method, especially in patients with low-yield biopsy sites, advanced fibrotic illness, or who require quick molecular confirmation to begin targeted therapy.

Tissue-based molecular profiling in ECD is most commonly done with targeted next-generation sequencing panels that look for hotspot mutations in oncogenes linked to histiocytic neoplasms. These panels often comprise genes like BRAF, MAP2K1, KRAS, NRAS, ARAF, PIK3CA, and ALK. Digital droplet PCR (ddPCR) or real-time PCR can effectively identify low-frequency variations, especially when DNA amount is restricted or the mutation spectrum is known (e.g., BRAF^V600E).

Importantly, because to the patchy distribution of neoplastic histiocytes and frequent stromal predominance, several core biopsies are frequently indicated to optimize cellular yield for both morphological and molecular investigation.[31].

To summarize, the incorporation of molecular diagnostics into the standard of treatment for ECD has transformed how the condition is diagnosed and controlled. Tissue biopsy remains the diagnostic gold standard, but molecular profiling—whether via tissue or liquid biopsy—allows for conclusive diagnosis, subclassification, and focused therapy selection. The increasing availability of extremely sensitive cfDNA detection tools, together with ECD's molecular heterogeneity, strongly favors a multimodal diagnosis strategy that includes both histology and precise molecular characterisation.

Therapeutic Implications of Molecular Findings in BRAF-Mutated Erdheim–Chester Disease

The discovery of the BRAF^V600E mutation in 50-60% of patients with Erdheim-Chester disease (ECD) has changed the treatment options for this uncommon histiocytic tumor. The mutation of valine for glutamic acid at codon 600 in the BRAF gene causes constitutive activation of the MAPK signaling cascade, making it an ideal target for pharmacological suppression. Two BRAF inhibitors, vemurafenib and dabrafenib, have emerged as key agents in the treatment of BRAF-mutant ECD, ushering in a new era of molecularly guided precision therapy.

Vemurafenib:

The FDA authorized Vemurafenib, the first BRAF inhibitor, to treat patients with BRAF^V600E-positive ECD. This approval was based on the pivotal results of a phase II, open-label study sponsored by the National Cancer Institute (NCT02281760), where 22 patients with confirmed BRAF-mutant ECD were treated with vemurafenib.

The trial reported a 62% objective response rate based on RECIST criteria and an impressive 100% metabolic response rate as assessed by FDG-PET/CT imaging.

[33]. These findings validated previous case series and cohort studies from centers such as the Pitié-Salpêtrière Hospital in France, which had already observed rapid and dramatic clinical improvements in patients with multisystemic and life-threatening disease manifestations. [31].

However, the first vemurafenib treatment regimen (960 mg twice daily) was found to be poorly tolerated in many patients due to side effects. In the phase II study, most patients required dosage decrease to 480 mg twice daily, which is currently widely used as the recommended beginning dose in clinical practice.

[33]. Despite dosage decreases, responses were long-lasting and powerful, with many patients seeing symptom relief, radiological improvement, and even reversal of organ failure.

Importantly, vemurafenib has demonstrated the ability to save patients from critical sickness caused by severe ECD consequences, such as cardiovascular and CNS involvement, demonstrating its therapeutic potential. However, long-term data do reveal some limitations.

In a retrospective research from the French cohort, over 75% of patients who ceased vemurafenib medication showed recurrence within six months, underlining the possible need for extended or ongoing treatment in most instances.

[34].Interestingly, all patients in that trial reacted again after restarting the BRAF inhibitor, indicating that retreatment is still a successful method after recurrence.

In addition to the risk of recurrence, vemurafenib treatment has been linked to a variety of side effects, including arthralgia, rash, tiredness, photosensitivity, and gastrointestinal problems. More troubling, while rare, are significant toxicities such as sarcoidosis-like granulomatous inflammation, pancreatitis, and the formation of secondary skin neoplasms, potentially due to paradoxical activation of MAPK signalling in BRAF-wild-type cells via RAS overexpression.

[35]. These hazards demand thorough patient counseling and long-term monitoring, particularly when considering medication termination.

Dabrafenib:

Dabrafenib, a selective BRAF^V600E inhibitor, is a viable option to vemurafenib, especially in individuals who are intolerant to the latter. Although the data on dabrafenib in ECD is sparse and primarily based on case reports or short series, its safety and effectiveness profile is positive.

Compared to vemurafenib, dabrafenib may be linked with less cutaneous side effects and less frequent dose-limiting toxicities. In a recent observation, a patient with BRAF-mutated ECD receiving dabrafenib developed a new KRAS-mutant lesion, raising the possibility of rare resistance mechanisms or clonal evolution under therapeutic pressure.

However, such cases are atypical, and resistance to BRAF inhibitors in histiocytoses is uncommon.

Ongoing research attempts to further define the criteria for complete remission (CR), both in terms of depth and duration, as well as to create safe treatment cessation recommendations.

Until then, continued treatment is the traditional method, especially considering the high incidence of recurrence following discontinuation. Future trials may investigate combinatorial techniques, such as dual BRAF and MEK inhibition (for example, with trametinib), to improve response persistence and minimize toxicity, similar to approaches utilized in melanoma and other BRAF-driven tumors.

In conclusion, genetic discovery of BRAF^V600E mutations in ECD has elucidated its pathophysiology as a clonal myeloid neoplasm and changed therapy with the development of targeted BRAF inhibitors.

Vemurafenib is still the most well-studied and extensively used drug, with dabrafenib emerging as a possible option in some instances. These drugs have dramatically improved the prognosis of patients with BRAF-mutant ECD and continue to serve as a paradigm for precision oncology in uncommon inflammatory neoplasms.

MEK Inhibitors in Non-BRAF-Mutated Erdheim–Chester Disease

While BRAF^V600E mutations have led to significant advances in targeted therapy with BRAF inhibitors, a substantial proportion of patients (approximately 40-50%) are BRAF-wild type and instead harbor other activating mutations within the MAPK-ERK pathway. These include somatic mutations in genes including MAP2K1 (which encodes MEK1), KRAS, NRAS, and ARAF.

Despite their diversity, these mutations all have the same downstream effect: constitutive activation of MEK and ERK, which promotes pathological histiocyte proliferation, tissue infiltration, and inflammation.

The treatment approach for these non-BRAF-mutated instances has naturally developed to include MEK inhibition, which targets the final common pathway node shared by upstream oncogenic mutations. Cobimetinib and trametinib are potential MEK inhibitors for ECD patients who do not have BRAF^V600E mutations or are intolerant to BRAF-targeted therapies.

Cobimetinib, an oral MEK1/2 inhibitor originally designed for melanoma, has demonstrated excellent activity in histiocytic neoplasms, including BRAF-wild-type ECD. In a study of five patients with refractory, non-BRAF-mutated ECD, substantial clinical and metabolic responses were achieved with either cobimetinib or trametinib, prompting the start of two phase II clinical studies testing cobimetinib in histiocytosis.

In the first planned analysis of one of these studies (NCT02649972), an 89% overall response rate (ORR) by FDG-PET/CT imaging was seen in patients with histiocytic diseases, including ECD, who were BRAF-wild-type or could not take BRAF inhibitors.

[36]. Responses to cobimetinib were observed across a variety of illness locations, including the skeleton, retroperitoneum, cardiovascular system, and central nervous system, demonstrating the wide applicability of MEK inhibition independent of disease location.

Trametinib, another selective MEK1/2 inhibitor with a somewhat different pharmacokinetic profile, has also been used well in individuals with non-BRAF-mutated ECD. Trametinib, like cobimetinib, was first licensed for BRAF-mutated tumors, but its potential for treating MAP2K1-mutant and other MAPK-driven ECD is becoming more well acknowledged. Case reports and short cohort studies have showed clinical improvement, radiographic responses, and symptom eradication in individuals with MAP2K1 mutations treated with trametinib.

[37][38]. These findings highlight trametinib's potential as a first- or second-line therapy in the treatment of ECD with molecularly characterized non-BRAF mutations.

Despite the obvious usefulness, several restrictions exist. The ideal length of MEK inhibitor medication has yet to be determined, and there is no defined approach for treatment discontinuation. As a result, long-term therapy is frequently used empirically to prevent relapse, despite a lack of data on the risk and timing of recurrence following MEK inhibitor discontinuation. Furthermore, MEK inhibitors are not without side effects.

Common toxicities include rash, diarrhea, tiredness, peripheral edema, and cardiomyopathy, which need close monitoring and possible dosage modifications. However, in the setting of a previously resistant and severe illness, the benefit-risk profile of MEK inhibitors is still very beneficial for correctly chosen patients.

MEK inhibitors like cobimetinib and trametinib have expanded the treatment options for Erdheim-Chester illness, especially for individuals who do not have BRAF^V600E mutations. By targeting the common downstream effector of several MAPK pathway mutations, these medicines provide a logical and successful strategy to disease management in genetically varied instances. Ongoing and future clinical trials are intended to optimize their use, identify the best treatment duration, and investigate combination regimens that may avoid resistance or improve response durability.

Resistance Mechanisms & combination therapies

BRAF inhibitors, including vemurafenib and dabrafenib, have significantly improved patient outcomes with BRAF^V600E-mutant Erdheim-Chester disease (ECD). Nonetheless, as seen in other BRAF-driven malignancies such as melanoma, acquired resistance to BRAF inhibition can develop even after a strong initial response, posing significant challenges in long-term disease management. Although resistance

appears to be unusual in ECD, there is increasing evidence of secondary MAPK pathway-activating mutations, such as KRAS Q61H, emerging during therapy and triggering recurrence.
A prominent case reported in the literature was a patient with BRAF-mutant ECD who responded initially to dabrafenib but then had disease reactivation. Genetic sequencing of a new lesion revealed a somatic KRAS^Q61H mutation, although the initial BRAF^V600E mutation was no longer detected.
The addition of trametinib, a MEK inhibitor, to dabrafenib was able to overcome this acquired resistance, restoring disease control. This case is the first known example of resistance to BRAF inhibition in ECD due to a secondary MAPK driver mutation, and it highlights the potential value of dual BRAF/MEK blocking as a method to prevent or overcome relapse by reducing signaling at multiple pathway nodes.[39].
Adaptive resistance to BRAF inhibition often involves feedback reactivation of RAS-MAPK signaling. In BRAF-mutant tumors treated with specific RAF inhibitors, an initial profound reduction of ERK signaling is frequently followed by a progressive reactivation of pathway activity.
This rebound is triggered by compensatory overexpression of upstream activators such as RTKs (e.g., PDGFRβ, EGFR), or subsequent RAS mutations that restore ERK phosphorylation through RAF-MEK-ERK signaling, bypassing the suppressed BRAF node. Such adaptive resistance is well-established in melanoma and other solid tumors, and comparable mechanisms are anticipated to operate in ECD. [40].
To combat these resistance mechanisms, combined treatment that targets both BRAF and MEK has emerged as a viable strategy. Clinical and preclinical studies in melanoma show that combining BRAF inhibitors (e.g., dabrafenib or vemurafenib) with MEK inhibitors (e.g., trametinib or cobimetinib) slows adaptive MAPK reactivation, increases response rates, extends progression-free survival, and reduces paradoxical activation in wild-type cells.
These combinations have established standards of treatment in BRAF-mutant melanoma, providing proof-of-concept that comparable techniques may be effective in ECD.[40].
Although formal studies of BRAF-MEK combos in ECD are rare, the first clinical data in ECD—a case of KRAS-driven recurrence under dabrafenib—indicates that adding trametinib restored control and stopped progression. Expert consensus recommendations now recommend considering dual MAPK blocking in individuals with significant disease burden or CNS involvement, or where partial response or recurrence occurs with BRAF monotherapy. [39][41][42].

To combat resistance caused by secondary mutations such as KRAS Q61H or overexpression of upstream RTKs (e.g., PDGFRβ, EGFR), RTK or SHP2 inhibitors can be used with BRAF or MEK inhibitors. Such multi-targeted techniques try to inhibit route reactivation via parallel or feedback bypass mechanisms.
[40]. Furthermore, in preclinical studies of melanoma, combining MEK inhibition with mTOR pathway inhibitors (e.g., everolimus) demonstrated enhanced anti-proliferative effects and apoptosis, suggesting that dual targeting of MAPK and PI3K-AKT-mTOR signaling may be beneficial in cases where cross-pathway activation contributes to resistance.[43].
In conclusion, while resistance to BRAF inhibitors is unusual in ECD, acquired secondary mutations (such as KRAS activation) or feedback-driven MAPK pathway reactivation are likely causes of therapy failure. The combination of MEK inhibitors and BRAF-directed treatment offers a promising strategy for overcoming these resistance mechanisms and maintaining long-term disease management. Furthermore, combination strategies targeting upstream RTKs or parallel pathways such as PI3K-AKT-mTOR may provide future avenues for preventing or overcoming resistance, though clinical data in ECD are limited.

Future Directions and Emerging Targets in Erdheim–Chester Disease
Next-generation sequencing (NGS) has greatly improved molecular profiling of Erdheim-Chester illness, detecting both known and unknown genetic changes in MAPK, PI3K-AKT, and receptor tyrosine kinase pathways.
Whole-exome, targeted DNA and RNA sequencing in large cohorts has revealed previously unknown variations in genes including CSF1R, EPHA2, SETBP1, and others. This has expanded our understanding of ECD's genetic landscape and identified possible novel treatment targets.
[44][45]. Among these, CSF1R (colony stimulating factor 1 receptor) has received special attention: activating mutations in CSF1R have been documented in histiocytic disorders, and CSF1R inhibitors—including small molecule kinase inhibitors and monoclonal antibodies—are in clinical development and have demonstrated sustained complete response in at least one ECD case harboring a CSF1R mutation. This provides a viable alternative to MAPK-driven illness, particularly for individuals who lack classical driver mutations.

As precision oncology advances, molecular categorization is increasingly used to guide individualized therapy in ECD. Mutational profiles, such as BRAF, MAP2K1, KRAS/NRAS, and CSF1R mutations, are used to guide therapeutic selection and predict response to BRAF inhibitors, MEK inhibitors, or CSF1R-targeted agents.

The current paradigm emphasizes individualized treatment regimens, shifting away from one-size-fits-all treatments and toward biomarker-guided tactics that maximize efficacy while minimizing toxicity. [46].

Beyond genomics, the combination of proteomics and single-cell transcriptomics/proteogenomics has the potential to reveal ECD's cellular heterogeneity and microenvironmental interactions with unparalleled resolution.

CITE-Seq (simultaneous profiling of surface proteins and mRNA in single cells) and spatial omics technologies (DBiT-seq) can map transcriptomic and proteomic states in tissue architecture, revealing dynamic interactions between histiocyte subpopulations and stromal compartments.

While multi-omics approaches have not yet been widely used in ECD, their success in other hematologic and inflammatory disorders suggests that similar studies could uncover new cellular phenotypes, biomarkers of disease activity or resistance, and potential intervention targets.

The future direction for ECD research and clinical care is to incorporate next-generation genomic profiling, investigate new actionable mutations such as CSF1R, refine molecular subclassification for personalized treatment, and integrate multi-omics at single-cell resolution. These developing techniques have the potential to improve not just diagnostic accuracy but also the rational design of targeted medicines and combination regimens, resulting in better outcomes for patients with this uncommon and complicated histiocytic neoplasm.

CONCLUSION

Erdheim-Chester Disease (ECD) is now a well-known clonal myeloid neoplasm due to advancements in molecular diagnostics and genomic profiling. The disease is caused by abnormal activation of the MAPK signaling pathway, primarily through the BRAF^V600E mutation, but also involving MAP2K1, NRAS, KRAS, and other upstream or downstream effectors.

Furthermore, the discovery of new oncogenic drivers, including those in the PI3K-AKT-mTOR and CSF1R pathways, highlights the genetic variability of ECD and emphasizes the significance of customized molecular testing in each patient. New diagnostic methods, such as liquid biopsy and extremely sensitive NGS platforms, are enhancing accessibility and accuracy, especially in patients with limited tissue availability or fibrotic lesions.

Despite these advances, difficulties persist. Active research is being conducted on acquired monotherapy resistance, the significance of co-occurring mutations, and treatment optimization for BRAF-wildtype patients. Combination treatments that target several routes or resistance mechanisms provide promise for long-term remission and deeper molecular responses.

Moving forward, the combination of next-generation multi-omics, spatial transcriptomics, and single-cell analysis will help to better understand the cellular heterogeneity and immunological landscape of ECD. These findings will improve subclassification, discover new treatment targets, and pave the road for precision therapy in this uncommon and previously underdiagnosed disease.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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All datasets generated or analyzed during this study are included in the manuscript.

ETHICS STATEMENT

Not applicable.

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