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Review Article

Internal Medicine Section

Erdheim-Chester Disease: Therapeutic Challenges, Multidisciplinary Management, and Emerging Targeted Treatment Strategies in Rare Histiocytosis

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ABSTRACT

Erdheim-Chester Disease (ECD) is an uncommon non-Langerhans Cell Histiocytosis (LCH) characterised by histiocytic organ infiltration and subsequent multisystemic fibrosis and chronic inflammation. The disease primarily affects the skeleton, cardiovascular system, Central Nervous System (CNS), kidneys, and lungs, and is extremely hard to diagnose and treat. Though the treatment modalities have been reformed in the last few years, the disease is still complex due to resistance to standard treatments and its heterogeneity. This review explains the therapeutic challenge of ECD and the latest developments with targeted therapies. We conducted a comprehensive review of recent clinical guidelines, case reports, and literature on the treatment modalities, such as targeted therapies, immunomodulators, and the role of multidisciplinary therapy. Identification of the BRAF V600E mutation in more than 50% of cases of ECD has been the primary reason for the activity of BRAF and MEK inhibitors, which were capable of enhancing survival. However, the challenges are still there, such as resistance to drugs, side effects, and the unavailability of standardised therapeutic regimens. For BRAF-negative ECD, other therapeutic agents such as PI3K inhibitors, JAK inhibitors, and immunomodulatory treatments are being studied. The management of ECD with multidisciplinary therapy, with the assistance of oncologists, neurologists, radiologists, and pathologists, is needed to provide optimal patient care. Though the targeted therapies have been optimised, ECD treatment remains non-standardised. Further studies should be conducted to formulate standardised treatment algorithms and provide optimal long-term treatment with the assistance of a collaborative, multidisciplinary centre.

Keywords: Autoimmune disease, Clonal histiocytosis, Cytokine inhibitors, Neuroinflammatory disease, Oncogenic mutations, Systemic fibrosis

INTRODUCTION

The ECD is a rare, systemic non-LCH with multisystemic involvement characterised by the invasion of organs by foamy histiocytes and the development of chronic inflammation, fibrosis, and organ dysfunction. First described by Jakob Erdheim and William Chester in 1930, the disease remained poorly characterised for a few decades due to its heterogeneity of presentation and rarity [1]. Historically, an idiopathic inflammatory disease, molecular pathology, and genetic analysis have reclassified the disease as a clonal neoplastic disorder, and the BRAF V600E mutation is identified as a key pathogenic driver in more than 50-68% of the population. Despite the recent developments in diagnostics and treatment, ECD remains a challenging disorder, typically misdiagnosed as an autoimmune, metabolic, or infectious disorder and thus treated late [2].

Background, History, and Awareness of ECD

Reports of ECD were early in the first half of the 20th century. However, due to its rarity and partially overlapping clinical presentation with inflammatory and neoplastic conditions, it remained a diagnosis of suspicion. With time, sophisticated histopathology and imaging facilitated the diagnosis of certain features of ECD, including symmetrical sclerotic long-bone disease and retroperitoneal fibrosis [3]. ECD was a chronic inflammatory histiocytic condition, similar to LCH, until clonal mutations of the MAPK pathway, like BRAF V600E, were discovered. This finding placed ECD on the map as a myeloid neoplasm and has led to a change in the paradigm of therapeutic approaches, like the use of targeted kinase inhibitors like vemurafenib and cobimetinib [4].

Epidemiology: Prevalence and Incidence

The ECD is a rare condition with a rough incidence estimate of less than one case per million per annum. While there is no definite epidemiological estimate, only 800 reported cases exist. However, with increasing awareness and molecular diagnosis, many cases have been reported in recent years. The condition occurs in middle-aged individuals with a mean age at presentation of 55 years, with male preponderance (~70-75%). Paediatric presentations are uncommon, though a few have been described [5].

Due to its pleomorphic presentation and lack of specific, uniform diagnostic criteria, most cases go undiagnosed or misdiagnosed for years. False diagnoses, such as sarcoidosis, lymphoma, or autoimmune disease, are provided to patients prior to histopathological diagnosis of ECD. Due to the multisystemic nature of the disease, increased physician awareness and early screening in these patients with such suggestive features as pain in long bones, retroperitoneal fibrosis, or neurological deterioration should be practiced [6].

Pathogenesis and Aetiology of ECD

The pathogenetic mechanisms of ECD have remained obscure for a long-time. Recent molecular studies have defined ECD as a clonal neoplastic histiocytic disorder mediated through activating MAPK pathway mutations. The BRAF V600E mutation, an effective oncogenic driver, is present in over 50% of cases [7]. Through the activation of the RAF-MEK-ERK cascade, this mutation results in uncontrolled proliferation of the histiocytes and cytokine-dependent inflammation. In BRAF-negative cases, other genetic mutations such as MAP2K1, NRAS, ARAF, and PIK3CA

have been reported, suggesting alternative oncogenic pathways to disease [8].

Genetic and Molecular Mechanisms

Targeted treatment with BRAF inhibitors (vemurafenib, dabrafenib) and MEK inhibitors (cobimetinib, trametinib) has significantly improved survival and symptom control in BRAF-mutated ECD. However, targeted treatment resistance and toxicity side-effects represent a daunting challenge to treatment. In the BRAF-negative subgroup, other molecular targets, including the JAK-STAT and PI3K-AKT pathways, are targeted for potential therapeutic intervention. Clonal somatic mutations detected in myeloid progenitor cells are utilised to emphasise further ECD's neoplastic nature and its differentiation from reactive histiocytic diseases [9].

Chronic Inflammatory Component in ECD

Genetic mutations are responsible for the neoplastic underpinnings of ECD, whereas the chronic inflammation aspect plays a key role in the pathogenesis of ECD. To some degree, an elevation of pro-inflammatory cytokines Interleukin-1 (IL-1), IL-6, Tumour Necrosis Factor-alpha (TNF-α), and Interferon-gamma (IFN-γ) leads to chronic histiocytic activation, fibrosis, and organ damage. Immune dysregulation features in a few patients are attributed to a concomitant paradoxical immune-modulating response to treatment. These all indicate that ECD is not a purely neoplastic process but a multifaceted interplay of oncogenesis and immune-mediated inflammation, and hence deserves multidisciplinary therapy [10].

Diagnostic Challenge, Clinical Presentation, and Need for Multidisciplinary Management

The ECD is an excellent diagnostic puzzle with its overlap in presenting clinically with inflammatory, autoimmune, and neoplastic diseases, with frequently delayed, accurate diagnosis. It has multiple organs and multiorgan involvement, with some having isolated organ disease and others having a multisystem presentation, with the necessity for high levels of suspicion in making the accurate diagnosis [11].

Skeletal involvement is most frequent (96% of cases), typically in bilateral femur, tibia, and fibula osteosclerosis. Radiological features with X-ray, MRI, and Positron Emission Tomography-Computed Tomography (PET-CT) show osteosclerosis and tracer uptake, even in asymptomatic patients, and thus, early diagnosis is difficult. Neurological involvement (50%) is seen in the form of mental impairment, ataxia, cranial neuropathies, and pyramidal tract dysfunction, with MRI findings of white matter lesions, atrophy, and demyelination, mimicking multiple sclerosis [12].

Cardiovascular involvement (75%) is the most important cause of mortality, observed as pericardial fibrosis, myocardial infiltration, and the "coated aorta" sign, with the potential to lead to vascular stenosis, ischaemia, and arrhythmias [13]. Renal and retroperitoneal involvement (68%) is observed as perinephric fibrosis ("hairy kidney" sign), hydronephrosis, and renal insufficiency, and pulmonary involvement (30-50%) is observed as interstitial lung disease and pleural effusions, leading to progressive dyspnoea and respiratory dysfunction. Endocrine dysfunction (30%), particularly Central Diabetes Insipidus (CDI), adrenal insufficiency, and hypogonadism, is secondary to hypothalamic infiltration [14].

Histopathology and molecular studies depend on correct diagnosis. Foamy histiocytes (CD68+, CD163+, Factor XIIIa+, but CD1a–, S100–) are employed to separate ECD from LCH, and BRAF V600E mutation study guides targeted treatment. PET_CT and MRI remain useful in monitoring disease and therapeutic response [15].

The Need for Multidisciplinary Management

Because of the multisystemic nature of ECD, early intervention and multidisciplinary care are necessary to prevent irreversible organ damage and maximise long-term outcomes. Evaluating CNS involvement involves neurologists, coordination of chemotherapy and targeted therapy in refractory disease by oncologists and hematologists, diagnostic imaging, and follow-up of disease by radiologists, particularly for skeletal, cardiovascular, and pulmonary involvement [16]. Cardiologists are required to evaluate aortic and myocardial infiltration, endocrinologists pituitary and adrenal dysfunction, and nephrologists renal complications. Multidisciplinary care improves patient survival, symptom control, and facilitates individualised therapeutic intervention. Standardisation of diagnostic criteria and treatment protocols will be necessary in maximising outcomes in ECD patients [17].

This review aims to highlight the issues in the treatment and diagnosis of ECD. The author wishes to stress the recent advancement in targeted therapy, multidisciplinary management, and the need for standardised treatment protocols. With this review, the author stresses the ongoing need for better management and multidisciplinary integration of medical specialties to attain optimum results in patients with ECD.

Review of Literature

Literature has widely discussed ECD in detailing its diagnostic difficulty, pathogenesis, and new treatment strategies. Mazor RD et al., (2014) reported a series of cases of difficulty in diagnosis and multimodal treatment, with a specific interest in imaging and histopathologic distinction from other histiocytosis [18]. Mazor RD et al., (2013) discussed the pathogenesis, clinical presentation, and treatment strategies in a review article, emphasising the role of inflammation and oncogenic mutations in the development of ECD [19].

Goyal G et al., (2020) reported consensus guidelines for diagnosis, assessment, and treatment in the era of molecular, reaffirming the significance of MEK and BRAF inhibitors in targeted therapy [20]. Likewise, Diamond EL et al., (2014) defined clinical guidelines for treating ECD, stating that using uniform diagnostic criteria and treatment protocols was crucial [21].

Boyd LC et al., (2020) investigated the neurological presentation of ECD. They experienced a high incidence of CNS involvement in the form of pyramidal tract dysfunction and cognitive impairment, rendering it challenging to predict [22]. Cavalli G et al., (2017) also spoke about possible target therapy, where JAK inhibitors, PI3K inhibitors, and immune checkpoint inhibitors were effective in BRAF-negative ECD [23].

[Table/Fig-1] outlines significant findings, research priorities, challenges, and future directions of pioneering studies of ECD [18-23].

Authors (Year)	Key finding	Research focus	Challenges	Future scope
Mazor RD et al., (2014) [18]	Highlighted diagnostic challenges and the need for multidisciplinary care.	Case series on ECD diagnosis and management.	Limited cases and diverse presentations.	Expand case studies and validate treatments.
Mazor RD et al., (2013) [19]	Comprehensive review of ECD's pathogenesis and treatment.	Pathogenesis, inflammatory vs. neoplastic nature of ECD.	Lack of molecular insights and targeted therapies.	Integrate molecular findings into treatment.
Goyal G et al., (2020) [20]	Consensus on diagnosing and treating ECD with a focus on targeted therapies.	Molecular evaluation and treatment guidelines.	Need for long-term evaluation and real-world effectiveness.	Refine precision medicine for ECD.
Diamond EL et al., (2014) [21]	Established clinical guidelines for ECD.	Diagnostic and therapeutic criteria.	Variability complicates standardisation.	Create standardised protocols globally.

Boyd LC et al., (2020) [22]	Explored neurological manifestations, including cognitive impairment.	Neurological impact of ECD.	Difficulty distinguishing from other neurodegenerative diseases.	Develop CNS-specific therapies.
Cavalli G et al., (2017) [23]	Reviewed emerging therapies, such as JAK and PI3K inhibitors.	New therapies for BRAF-negative cases.	Need for clinical trial validation.	Validate new treatments in clinical trials.

[Table/Fig-1]: Literature review: previous work on Erdheim-Chester Disease (ECD) [18-23].

RESULTS

Erdheim-Chester Disease (ECD) Incidence and Demographics

The ECD is a sporadic histiocytic disorder of estimated prevalence of fewer than one case per million people globally. Due to underdiagnosis and misclassification, prevalence may be higher [24]. A total of 800 cases have been documented globally, with increasing numbers of detection following the recognition of BRAF V600E mutations and improved diagnostic techniques [25].

ECD occurs predominantly in middle-aged to old individuals with a mean age at diagnosis of 55 years. It is primarily male (~70-75%), though some cases have been reported in females [26]. While cases have been reported from around the globe, no typical geographic preference has been noted. Most reported cases are from Europe and North America, likely secondary to greater healthcare access and availability of molecular diagnosis [27].

Due to its multisystemic presentation, ECD is frequently misdiagnosed as sarcoidosis, lymphoma, or autoimmune disorders. This makes the delays in diagnosis and treatment initiation exceedingly important, making epidemiological assessments even more challenging, as seen in [Table/Fig-2] [24-28].

Author et al.,	Year	Prevalence	Age Range	Gender	Geographic Distribution	Key Findings
Benson JC et al., [24]	2023	CNS involvement in 50% of cases	40-70 years	Male (~75%)	Mainly Europe and North America	Highlights CNS imaging features
Riso V et al., [25]	2022	Low prevalence in small cohorts	40-70 years	Predominantly male	Global, concentrated in the West	Focus on neurological and ataxic presentations
Aswani A et al., [26]	2024	Prevalence unknown, rare condition	50-70 years	Slight male predominance	Europe, USA, Asia	Discusses CNS and cardiac imaging techniques
Cives M et al., [27]	2015	Limited population-based data	45-70 years	Male > Female	More cases in Western countries	Review of 400+ cases, multiorgan involvement
Shekhar S et al., [28]	2020	Endocrine involvement in 52.8% of cases	45-65 years	Higher in males	Mostly in developed nations	Identified hypothyroidism as a key feature

[Table/Fig-2]: Erdheim-Chester Disease (ECD) prevalence and demographics [24-28].

Significant Clinical Features and Organ Involvement

ECD is a multisystem disorder with a varied clinical presentation, and hence is hard to diagnose in the early stages. The skeletal system is the most commonly affected, in 96% of the patients, and is characterised by bilateral osteosclerosis of the long bones, which is often a cause of bone pain but is asymptomatic in a small percentage of patients [29]. Neurological involvement (~50%) includes cognitive impairment, ataxia, cranial neuropathies, and pyramidal tract dysfunction, with demyelination and white matter lesions on MRI, typically mimicking multiple sclerosis. Cardiovascular complications (~75%) are pericardial fibrosis, myocardial infiltration, and the "coated aorta" sign, and result in high mortality [30].

Kidney and retroperitoneal fibrosis (~68%) is followed by hydronephrosis and renal failure, while pulmonary involvement (30-50%) is in the interstitial lung disease and pleural effusion pattern and presents as dyspnea. Endocrine dysfunction (30%), particularly CDI, is caused by hypothalamic and pituitary infiltration. The severity of symptoms is variable, with some developing mild disease while others come with acute organ failure and poor prognosis [31].

Advances in Diagnostic Techniques and Molecular Understanding

Role of PET-CT, MRI, Histopathology, and Molecular Testing

Early and accurate ECD diagnosis combines molecular testing, histopathology, and imaging. The test of choice for diagnosis is PET-CT, which shows hypermetabolic lesions at characteristic sites such as long bones, periaortic spaces, perinephric spaces, and the CNS. MRI is helpful in the diagnosis of neurological disease at presentation with brain atrophy, demyelination, and white matter lesions, differentiating ECD from neurodegenerative disease or multiple sclerosis [32].

Histopathological examination of involved tissues establishes the presence of foamy histiocytes, CD68+ and CD163+, but they are CD1a and S100 negative, differentiating ECD from LCH. Molecular analysis has transformed ECD diagnosis by identifying BRAF V600E mutations (~50-68% of cases). Secondary mutations in MAP2K1, NRAS, ARAF, and PI3K are identified in BRAF-negative patients, affecting the treatment option [33]. ECD should be differentiated from sarcoidosis, lymphoma, and IgG4-related disease, with overlapping features. Development of diagnostic criteria has resulted in the routine use of BRAF mutation analysis, enhancing the validity of treatment. The association of genetic mutation and response to treatment has allowed targeted therapy, such as BRAF and MEK inhibitors, significantly enhancing the prognosis and preventing disease progression [34].

Targeted Therapy Results and New Treatment Models

BRAF and MEK Inhibitors: Efficacy and Resistance Cases

Detection of the BRAF V600E mutation (~50-68% of ECD cases) has led to breakthroughs in targeted therapy. BRAF inhibitors (vemurafenib, dabrafenib) have been successful, considerably improving disease progression-free survival and symptom relief. Clinical response has been rapid in vemurafenib-treated patients, somewhat more so in neurological and cardiovascular presentations. However, resistance to BRAF inhibitors has been reported, resulting in relapse of disease in some patients. In BRAF-negative ECD patients, MEK inhibitors (cobimetinib, trametinib) have been effective alternatives, inhibiting the MAPK pathway and histiocytic proliferation. These drugs are combined with BRAF inhibitors to avoid resistance and allow long-term remission [35].

Long-Term Targeted Therapy Challenges

While efficacious, long-term targeted therapy with BRAF and MEK inhibitors is not without problems. Side-effects are cutaneous toxicity, hepatic injury, secondary malignancy, and cardiovascular disease. Moreover, relapse upon discontinuation is a testament to the necessity of other long-term maintenance regimens. Emerging immunotherapy drugs are under study for BRAF-negative or refractory ECD patients. IL-1 inhibitors (Anakinra, Canakinumab) and JAK inhibitors (Ruxolitinib) are promising in the suppression of systemic inflammation and histiocytic activity, particularly in resistant cases to conventional targeted therapy [36].

In addition, novel drug combinations are undergoing clinical research, e.g., PI3K inhibitors and immune checkpoint inhibitors, to modulate immune response and tumour growth. Although chemotherapy and corticosteroids were used before, they are now less toxic and less potent, with reduced long-term gain. Lastly, precision medicine approaches and combination therapy are revolutionising the landscape of ECD therapy in the future with the prospects of improved tolerability, lower relapse rate, and better survival gain, as shown in [Table/Fig-3] [32-37].

Author et al.,	Therapy	Efficacy	Resistance/ Challenges	Emerging Alternatives
Kulkarni AM et al., (2024) [32]	BRAF inhibitors (Vemurafenib)	High response in BRAF V600E+ cases	Resistance over time, risk of secondary cancers	Combination with MEK inhibitors
Starkebaum G and Hendrie P (2020) [33]	MEK inhibitors (Cobimetinib, Trametinib)	Effective in BRAF-negative ECD cases	Toxicity, high cost	PI3K and JAK inhibitors
Diamond EL & Durham BH (2018) [34]	IL-1 Inhibitors (Anakinra, Canakinumab)	Reduces systemic inflammation	Limited response in BRAF-mutant cases	JAK-STAT pathway inhibitors
Huang LC et al., (2023) [35]	TNF-α Inhibitors (Infliximab)	Suppresses the inflammatory response	Uncertain long-term benefits	IL-6 blockade, immune checkpoint inhibitors
Tran TA et al., (2014) [36]	Canakinumab (IL-1 Inhibitor)	Improves inflammatory markers in ECD	Limited long-term efficacy evidence	Combination with targeted therapies
Riancho JA et al., (2023) [37]	Cobimetinib for NRAS-mutant ECD	Response in rare NRAS-mutant cases	limited patient cohort, unknown long-term benefit	New MAPK pathway inhibitors

[Table/Fig-3]: Targeted therapy outcomes and emerging treatment approaches for ECD [32-37].

Multidisciplinary Treatment Strategies

The ECD is a multisystemic, complicated disease that demands a multidisciplinary, interdisciplinary approach to optimal therapy. Due to its multifaceted organ involvement, an interdisciplinary team of neurologists, oncologists, cardiologists, nephrologists, endocrinologists, and radiologists is needed for early diagnosis, individualised treatment planning, and long-term disease management [38].

Neurologists play a central role in treating cognitive impairment, cerebellar ataxia, and pyramidal tract dysfunction, which are characteristics of CNS-involvement ECD. Oncologists and hematologists treat targeted therapy with optimal dosing and monitoring of BRAF and MEK inhibitors for drug resistance or relapse. Cardiologists evaluate and treat aortic fibrosis, myocardial infiltration, and pericardial effusion, the most common causes of ECD-related mortality [39]. Nephrologists evaluate renal function and retroperitoneal fibrosis, and endocrinologists treat pituitary dysfunction, diabetes insipidus, and adrenal insufficiency. Multidisciplinary treatment optimises patient outcomes to a great extent by reducing diagnostic delay, allowing early treatment, and avoiding complications by organ-specific monitoring. Follow-ups, imaging procedures, and multidisciplinary case conferences facilitate optimisation of individualised treatment regimens, leading to improved symptom control and survival [40].

Recent developments in targeted therapies have transformed the prognosis of ECD. The survival rate at five years was previously thought to be ~50-60%, but with BRAF and MEK inhibitors, survival is currently >80% in treated patients. Patients with earlier diagnosis and treatment have a better quality of life in the long term, mostly when treated with multidisciplinary treatment [41]. Recurrence is still an issue, particularly in patients losing targeted therapy or developing resistance to BRAF inhibitors. Progression of the disease is based on CNS and cardiovascular involvement, extent of fibrosis, and type of genetic mutation. BRAF-negative ECD cases generally have a poorer prognosis, again highlighting the use of other treatments like JAK inhibitors and immunotherapy [42].

Standardised treatment regimens and followup schedules are becoming more imperative for the best long-term disease control. PET-CT and MRI follow-up at intervals and genetic testing for treatment selection will be crucial in preventing relapses and maximising therapeutic interventions. More clinical trials and real-world data assessment will continue to shape precision medicine approaches to maximise patient survival and quality of life, as described in [Table/Fig-4] [38-43].

Research Gaps and Future Directions

Despite remarkable diagnostic and therapeutic advancements, some lines of investigation lag in ECD. Molecular pathogenesis in BRAF-negative ECD is not yet elucidated and requires further investigation to study other oncogenic pathways (MAP2K1, NRAS, ARAF, PI3K) and disease progression. There are no biomarkers to optimise treatment strategies rationally, to maximise targeted therapy selection and resistance development monitoring [44]. Expansion of clinical trials is needed to evaluate new drugs in the pipeline, like JAK inhibitors, PI3K inhibitors, and immunotherapy combinations. Future research areas should include relapse, long-term survival rate, and optimisation of maintenance therapies to determine standard treatment regimens and improve patient outcomes globally [45].

DISCUSSION

THE ECD presents a rare multisystem histiocytic neoplasm with extensive clinical heterogeneity. Misinterpreted in the past as a chronic inflammatory disease, the condition comes under the rubric of clonal myeloid neoplasms because of recurrent mutations in the MAPK pathway, the most prominent one, namely the BRAF V600E mutation, seen in more than 50% of the cases [46]. Even today, apart from difficulty in early recognition, the problem of resistance to treatment and the absence of protocols has arisen.

Authors et al.,	Role in ECD management	Key responsibilities	Treatment goals	Benefits	Challenges
Girschikofsky M et al., (2013) [38]	Primary disease management	Diagnosis, molecular testing, targeted therapy	Disease control, prevent progression	Successful targeted therapy	High cost, resistance to treatment
Chetritt J et al., (1999) [39]	Tissue diagnosis	Histopathological and molecular analysis	Confirm diagnosis, differentiate from LCH	Accurate histiocytosis classification	Limited tissue availability, overlap
Gong L et al., (2009) [40]	Imaging and monitoring	MRI, PET-CT interpretation, disease extent	Early detection, treatment, and monitoring	Improves diagnosis and treatment response	Non-specific imaging findings
Vencio EF et al., (2007) [41]	Molecular analysis of mutations	Identify BRAF and MAPK mutations	Personalise therapy, predict response	Guides targeted therapy	Mutation heterogeneity limits treatment
Badalian-Very G et al. (2010) [42]	Immune dysregulation evaluation	Assess immune pathways and inflammatory markers	Reduce inflammation, immunomodulation	Identifies novel targets	Limited long-term clinical data
Arnaud L et al., (2012) [43]	Whole-body MRI-based assessment	Evaluate systemic involvement, predict prognosis	Improve early intervention strategies	Provides comprehensive disease mapping	Variability in imaging interpretation

[Table/Fig-4]: Multidisciplinary treatment strategies for ECD [38-43].

Diagnostic Complexity and Clinical Spectrum

The incidence of ECD, below one case per million worldwide, results in frequent misdiagnosis and underreporting. The middle-aged men are typically the patients who experience nonspecific symptoms imitating autoimmune, neoplastic, or infectious diseases [47,48]. The multisystemic pattern typically involves the skeletal, neurological, cardiovascular, renal, pulmonary, and endocrine systems. This pattern attracts a high degree of clinical suspicion for diagnosis at the correct time.

Skeletal involvement occurs in ~96% of patients, and most typically presents as bilateral long-bone osteosclerosis. Neurological manifestations develop in ~50% of patients and are sinister because they are potentially permanent [49]. CNS involvement may masquerade as multiple sclerosis on imaging and may develop ataxia, peripheral neuropathies, and cognitive dysfunction. Pericardial effusion, myocardial infiltration, and the characteristic "coated aorta" sign are significant causes of death [50,51].

The diagnosis depends on a triumvirate of imaging studies, histopathology, and molecular testing. PET-CT and MRI provide localisations of disease, and histopathology identifies CD68+, CD163+, Factor XIIIa+ histiocytes that are CD1a and S-100 –. Molecular testing for mutations in the BRAF, MAP2K1, NRAS, and PIK3CA genes then directs the decision for therapy [52,53].

Therapeutic Developments and Limitations

Therapeutic targeting has transformed the treatment of ECD. The rapid response agents in BRAF-mutant disease are the BRAF inhibitors (e.g., vemurafenib, dabrafenib), which enhance progression-free survival and symptom control. The alternatives or additions in such patients or in patients who develop resistance are the MEK inhibitors (e.g., cobimetinib, trametinib) [54,55].

Although such progressions do exist, long-term toxicity (e.g., hepatotoxicity, dermatologic toxicities, secondary neoplasias) and resistant disease continue to be significant issues. Recurrence following treatment interruption does exist and necessitates continued maintenance therapy and follow-up [56]. For the refractory or BRAF-negative diseases, the new therapies encompass the IL-1 inhibitors (anakinra, canakinumab) and JAK inhibitors (ruxolitinib), and new agents focusing on PI3K and immune checkpoint targeting. The therapies attempt to suppress the inflammatory microenvironment accompanying neoplastic proliferation [57,58].

Importance of Multidisciplinary Management

Due to the multiorgan involvement in ECD, management necessitates interdisciplinary collaboration. Neurologists manage CNS involvement; oncologists and haematologists manage systemic and target therapies; cardiologists, nephrologists, endocrinologists, and radiologists offer organ-specific monitoring and intervention [46].This multidisciplinary approach refines early recognition, allows individualised intervention, and maximises outcomes. Regular follow-up by PET-CT, MRI, and molecular markers helps assess disease activity and response to treatment. Targeted therapy has also advanced 5-year survival rates from ~50-60% to >80% in optimally treated patients [59].

Future Outlook

There are research gaps beyond progress. BRAF-negative ECD needs more extensive molecular characterisation to delineate other driver mutations and therapies by design. Mechanisms for resistance to available target therapies must be defined and combination regimens optimised for stability and tolerability [60]. Efforts should be made in future research to identify predictive biomarkers that allow for better long-term tolerability and tailoring precision medicine practices. Clinical trial extensions, especially among minority patient populations, will be valuable for deriving worldwide treatment guidance.

CONCLUSION(S)

The ECD is a life-threatening, rare histiocytic neoplasm with multifold therapeutic and diagnostic challenges. In the past, it was thought to be inflammatory. However, with recent advances in molecular diagnostics, i.e., BRAF V600E mutation, ECD has been classified as a clonal neoplastic disease, and therapy has changed. BRAF and MEK inhibitors have been successful, but resistance, toxicity, and Relapse are critical concerns, reflecting the need for long-term therapy optimisation. Because of its multisystemic presentation, interdisciplinary management by neurology, oncology, cardiology, nephrology, endocrinology, and radiology is warranted for early diagnosis, tailored therapy, and improved outcomes. New immunotherapies and novel targeted agents are promising in BRAF-negative and refractory patients, but clinical trials must prove their efficacy. Subsequent studies must clarify resistance mechanisms, develop predictive biomarkers, and extend personalised medicine strategies. Uniform treatment protocols, regular follow-up schedules, and international collaboration will be the pillars of optimising the care of ECD. Though the present advances have optimised survival, continuous precision medicine strategies and multidisciplinary paradigms of care will be the hallmark of future successful, long-term disease control, with better prognosis and quality of life for patients with ECD.

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REFERENCES

[1] Adawi M, Bisharat B, Bowirrat A. Erdheim–Chester disease (ECD): Case report, clinical and basic investigations, and literature review. Medicine (Baltimore). 2016;95(42):e5167.
[2] Oweity T, Scheithauer BW, Ching HS, Lei C, Wong KP. Multiple system Erdheim-Chester disease with massive hypothalamic-sellar involvement and hypopituitarism. J Neurosurg. 2002;96:344-51.
[3] Davies AM, Colley SP, James SL, Sumathi VP, Grimer RJ, Dagna L, et al. ECD literature search (found with GoPubMed). Clin Radiol. 2010;65(3):265-71.
[4] Vital C, Bioulac-Sage P, Tison F, Rivel J, Begueret H, Gomez C, et al. Brain stem infiltration by mixed Langerhans cell histiocytosis and Chester-Erdheim disease: More than an isolated case? Clin Exp Pathol. 1999;47:71-76.
[5] Cavalli G, Guglielmi B, Berti A, Campochiaro C, Sabbadini MG, Dagna L, et al. The multifaceted clinical presentations and manifestations of Erdheim–Chester disease: Comprehensive review of the literature and of 10 new cases. Ann Rheum Dis. 2013;72(10):1691-95.
[6] Killu AM, Liang JJ, Jaffe AS. Erdheim-Chester disease with cardiac involvement successfully treated with anakinra. Int J Cardiol. 2013;167:e115 17.
[7] Monti L, Haroche J, Sciarra A, Balzarini L, Fiamengo B, Amoura Z, et al. Interferon-alpha in cardiac Erdheim-Chester disease. J Am Coll Cardiol. 2011;58:2695.
[8] Merli E, Savelli F, Lovato L, Zompatori M. Cardiac involvement in Erdheim-Chester disease: Echocardiographic appearance and value of cardiac MRI. Eur Heart J Cardiovasc Imaging. 2012;13:198.
[9] Protopapadakis C, Antoniou KM, Nicholson AG, Voloudaki A, Tzanakis N, Karantanas A, et al. Erdheim-Chester disease: Pulmonary presentation in a case with advanced systemic involvement. Respiration. 2009;77:337-40.
[10] Yelfimov DA, Lightner DJ, Tollefson MK. Urologic manifestations of Erdheim-Chester disease. Urology. 2014;84:218-21.
[11] Wimpissinger TF, Schernthaner G, Feichtinger H, Stackl W. Compression of kidneys in Erdheim-Chester disease of retroperitoneum: Open surgical approach. Urology. 2005;65:798.
[12] Sanchez JE, Mora C, Macia M, Navarro JF. Erdheim-Chester disease as a cause of end-stage renal failure: A case report and review of the literature. Int Urol Nephrol. 2010;42:1107–12.
[13] Lee HJ, Lee KY, Shin DY, Lee YG, Choi SY, Moon KC, et al. A case of Erdheim-Chester disease with asymptomatic renal involvement. Cancer Res Treat. 2012;44:146-50.
[14] Heller MT, Haarer KA, Thomas E, Thaete FL. Neoplastic and proliferative disorders of the perinephric space. Clin Radiol. 2012;67:e31-e41.
[15] Dion E, Graef C, Haroche J, Renard-Penna R, Cluzel P, Wechsler B, et al. Imaging of thoracoabdominal involvement in Erdheim-Chester disease. AJR Am J Roentgenol. 2004;183(5):1253-60.

[16] Haroutunian SG, O'Brien KJ, Estrada-Veras JI, Yao J, Boyd LC, Mathur K, et al. Clinical and histopathologic features of interstitial lung disease in Erdheim–Chester disease. J Clin Med. 2018;7(9):243.
[17] Kobic A, Shah KK, Schmitt AR, Goyal G, Go RS, Guo R, et al. Mayo Clinic Histiocytosis Working Group. Erdheim-Chester disease: Expanding the spectrum of cutaneous manifestations. Br J Dermatol. 2020;182(2):405-09.
[18] Mazor RD, Manevich-Mazor M, Kesler A, Aizenstein O, Eshed I, Jaffe R, et al. Clinical considerations and key issues in managing patients with Erdheim-Chester Disease: A seven case series. BMC Med. 2014;12:72.
[19] Mazor RD, Manevich-Mazor M, Shoenfeld Y. Erdheim-Chester Disease: A comprehensive literature review. Orphanet J Rare Dis. 2013;8:137.
[20] Goyal G, Heaney ML, Collin M, Cohen-Aubart F, Vaglio A, Durham BH, et al. Erdheim-Chester disease: Consensus recommendations for evaluation, diagnosis, and treatment in the molecular era. Blood. 2020;135(22):1929-45.
[21] Diamond EL, Dagna L, Hyman DM, Cavalli G, Janku F, Estrada-Veras J, et al. Consensus guidelines for the diagnosis and clinical management of Erdheim-Chester disease. Blood. 2014;124(4):483-92.
[22] Boyd LC, O'Brien KJ, Ozkaya N, Lehky T, Meoded A, Gochuico BR, et al. Neurological manifestations of Erdheim–Chester disease. Ann Clin Transl Neurol. 2020;7(4):497-506.
[23] Cavalli G, De Luca G, Dagna L. Advances in potential targeted therapies for Erdheim-Chester disease. Expert Opin Orphan Drugs. 2017;5(3):253-60.
[24] Benson JC, Vaubel R, Ebne BA, et al. Erdheim-Chester Disease: CNS involvement and imaging features. Am J Neuroradiol. 2023;44(5):505. Available from: https://www.ajnr.org/content/44/5/505.abstract.
[25] Riso V, Nicoletti TF, Rossi S, Vita MG, Alessia P, Di Natale D, et al. Neurological Erdheim-Chester disease manifesting with subacute or progressive cerebellar ataxia. Brain Sci. 2022;13(1):26. Available from: https://www.mdpi.com/2076-3425/13/1/26.
[26] Aswani Y, Patel A, Zhan X, Ansari S, Marcelino LG, Aswani N, et al. Imaging in Erdheim-Chester Disease. Radiographics. 2024;240(1):011. Available from: https://pubs.rsna.org/doi/abs/10.1148/rg.240011
[27] Cives M, Simone V, Rizzo FM, Dicuonzo F, Cristallo Lacalamita M, et al. Erdheim-Chester disease: A systematic review. Crit Rev Oncol Hematol. 2015;95(1):01-11. Doi: 10.1016/j.critrevonc.2015.02.004. Epub 2015 Feb 17. PMID: 25744785.
[28] Shekhar S, Sinaii N, Irizarry-Caro JA, Gahl WA, Estrada-Veras JI, Dave R, et al. Prevalence of hypothyroidism in patients with Erdheim-Chester disease. JAMA Netw Open. 2020;3(10):e202340. Available from: https://jamanetwork.com/journals/jamanetworkopen/article-abstract/2772340.
[29] Mirmomen SM, Sirajuddin A, Nikpanah M, Symons R, Paschall AK, Papageorgiou I, et al. Thoracic involvement in Erdheim-Chester disease: Computed tomography imaging findings and their association with the BRAF V600E mutation. Eur Radiol. 2018;28(11):4635-42.
[30] Parks NE, Goyal G, Go RS, Mandrekar J, Tobin WO. Neuroradiologic manifestations of Erdheim-Chester disease. Neurol Clin Pract. 2018;8(1):15-20.
[31] Shah MV, Call TG, Hook CC, et al. Clinical presentation, diagnosis, treatment, and outcome of patients with Erdheim-Chester disease: The Mayo Clinic experience [abstract]. Blood. 2014;124(21):1405.
[32] Kulkarni AM, Gayam PKR, Aranjani JM. Advances in Understanding and Management of Erdheim-Chester Disease. Life Sci. 2024. Available from: https://www.sciencedirect.com/science/article/pii/S0024320524002820.
[33] Starkebaum G, Hendrie P. Erdheim-Chester Disease. Best Pract Res Clin Rheumatol. 2020;34(4). Available from: https://www.sciencedirect.com/science/article/pii/S1521694220300279.
[34] Diamond EL, Durham BH. Erdheim-Chester Disease. In: histiocytic disorders. Springer; 2018. Available from: https://link.springer.com/chapter/10.1007/978-3-319-59632-7_18
[35] Huang LC, Park JK, Kossler AL. Erdheim–Chester disease and vemurafenib: A review of ophthalmic presentations and clinical outcomes. Orbit. 2023;42(1). Available from: https://www.tandfonline.com/doi/abs/10.1080/01676830.2022.2087232.
[36] Tran TA, Pariente D, Guitton C, Delwail A, Barat-Houari M, Meinzer U. Treatment of Erdheim–Chester disease with canakinumab. Rheumatology. 2014;53(12):2312-14.
[37] Riancho JA, Hernández JL, González-Vela C, López-Sundh AE, González-Lopez MA, Gomez de la Fuente F, et al. Erdheim–Chester Disease Due to a Novel Internal Duplication of NRAS: Response to Targeted Therapy with Cobimetinib. Int J Mol Sci. 2023;24(20):15467.
[38] Girschikofsky M, Arico M, Castillo D, Chu A, Doberauer C, Fichter J, et al. Management of adult patients with Langerhans cell histiocytosis: Recommendations from an expert panel on behalf of Euro-Histio-Net. Orphanet J Rare Dis. 2013;8:72.
[39] Chetritt J, Paradis V, Dargere D, Adle-Biassette H, Maurage CA, Mussini JM, et al. Chester-Erdheim disease: A neoplastic disorder. Hum Pathol. 1999;30(9):1093-96.
[40] Gong L, He XL, Li YH, Ren K-X, Zhang L, Liu X-Y, et al. Clonal status and clinicopathological feature of Erdheim-Chester disease. Pathol Res Pract. 2009;205(9):601-07.
[41] Vencio EF, Jenkins RB, Schiller JL, Huynh TVT, Wenger DD, Inwards CY, et al. Clonal cytogenetic abnormalities in Erdheim-Chester disease. Am J Surg Pathol. 2007;31(2):319-21.
[42] Badalian-Very G, Vergilio J-A, Degar BA, MacConaill LE, Brandner B, Calicchio ML, et al. Recurrent BRAF mutations in Langerhans cell histiocytosis. Blood. 2010;116(11):1919-23.
[43] Arnaud L, Bach G, Zeitoun D, Drier A, Cluzel P, Grenier PA, et al. Whole-body MRI in Erdheim-Chester disease. Rheumatology (Oxford). 2012;51(5):948-50.
[44] Volpicelli ER, Doyle L, Annes JP, Murray MF, Jacobsen E, Murphy GF, et al. Erdheim-Chester disease presenting with cutaneous involvement: A case report and literature review. J Cutan Pathol. 2011;38:280-85.
[45] Veyssier-Belot C, Cacoub P, Caparros-Lefebvre D, Wechsler J, Brun B, Remy M, et al. Erdheim-Chester disease. Clinical and radiologic characteristics of 59 cases. Medicine (Baltimore). 1996;75:157-69.
[46] Clerico A, Ragni G, Cappelli C, Schiavetti A, Gonfiantini M, Uccini S. Erdheim-Chester disease in a child. Med Pediatr Oncol. 2003;41:575-77.
[47] Song SY, Lee SW, Ryu KH, Sung SH. Erdheim-Chester disease with multisystem involvement in a 4-year-old. Pediatr Radiol. 2011;42:632-35.
[48] Adam Z, Szturz P, Buckova P, Cervinkova I, Koukalova R, Rehak Z, et al. Interleukin-1 receptor blockade with anakinra provided cessation of fatigue, reduction in inflammation markers, and regression of retroperitoneal fibrosis in a patient with Erdheim-Chester disease: Case study and literature review. Vnitr Lek. 2012;58:313-18.
[49] Dagna L, Corti A, Langheim S, Guglielmi B, De Cobelli F, Doglioni C, et al. Tumor necrosis factor alpha as a master regulator of inflammation in Erdheim-Chester disease: Rationale for treatment with infliximab. J Clin Oncol. 2012;30:e286-e290.
[50] Ivan D, Neto A, Lemos L, Gupta A. Erdheim-Chester disease: A unique presentation with liver involvement and vertebral osteolytic lesions. Arch Pathol Lab Med. 2003;127:e337-e339.
[51] Gundling F, Nerlich A, Heitland WU, Schepp W. Biliary manifestation of Erdheim-Chester disease mimicking Klatskin's carcinoma. Am J Gastroenterol. 2007;102:452-54.
[52] Pan A, Doyle T, Schlup M, Lubcke R, Schultz M. Unusual manifestation of Erdheim-Chester disease. BMC Gastroenterol. 2011;11:77.
[53] Tan AP, Tan LK, Choo IH. Erdheim-Chester disease involving breast and muscle: Imaging findings. AJR Am J Roentgenol. 1995;164:1115-17.
[54] Barnes PJ, Foyle A, Hache KA, Langley RG, Burrell S, Juskevicius R. Erdheim-Chester disease of the breast: A case report and literature review. Breast J. 2005;11:462-67.
[55] Provenzano E, Barter SJ, Wright PA, Forouhi P, Allibone R, Ellis IO. Erdheim-Chester disease presenting as bilateral clinically malignant breast masses. Am J Surg Pathol. 2010;34:584-88.
[56] Ambrosini V, Savelli F, Merli E, Zompatori M, Nanni C, Allegri V, et al. F-18 FDG PET/CT detects muscle involvement in Erdheim-Chester disease. Clin Nucl Med. 2012;37:196-97.
[57] Sheu SY, Wenzel RR, Kersting C, Merten R, Otterbach F, Schmid KW. Erdheim-Chester disease: Case report with multisystemic manifestations including testes, thyroid, and lymph nodes, and a literature review. J Clin Pathol. 2004;57:1225-28.
[58] Joo CU, Go YS, Kim IH, Kim CS, Lee SY. Erdheim-Chester disease in a child with MR imaging showing regression of marrow changes. Skeletal Radiol. 2005;34:299-302.
[59] Tsai JW, Tsou JH, Hung LY, Wu HB, Chang KC. Combined Erdheim-Chester disease and Langerhans cell histiocytosis of skin are both monoclonal: A rare case with human androgen-receptor gene analysis. J Am Acad Dermatol. 2010;63:284-91.
[60] Al-Quran S, Reith J, Bradley J, Rimsza L. Erdheim-Chester disease: Case report, PCR-based analysis of clonality, and review of literature. Mod Pathol. 2002;15:666-72.

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