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From inflammation to cancer: entering a new frontier in the management of Erdheim–Chester disease

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See article by Bhatia et al in this issue, pp. 979–992.

Since its initial description in 1930 by William Chester and Jakob Erdheim as lipoid granulomatosis, the classification of Erdheim–Chester disease (ECD) has been a topic of debate. On histopathology, it is characterized by xanthogranulomatous infiltration by foamy mononucleated histiocytes positive for CD68 and CD163 and negative for CD1a, and someTouton giant cells (multinucleated histiocytes). In the early 1990s, it was increasingly being recognized that Langerhans cell histiocytosis (LCH) and ECD were clonal proliferations of pathologic histiocytes, thereby suggesting a neoplastic process, but it wasn't until 2010 that recurrent *BRAF*^{V600E} mutations were identified in association with these diseases.[1] Due to their clinical and genomic similarities, LCH and ECD are now both included in the "L" (Langerhans) group of histiocytoses.[2] Approximately 50–60% of ECD cases have been shown to harbor *BRAF*^{V600E} mutations. Additionally, mutations of *NRAS, KRAS, MAP2K1*, as well as translocations involving *ALK* and *NTRK1* have been identified.[3] In addition to mitogen-activated protein kinase (MAPK) pathway, activating mutations of *PIK3CA* have also been noted. As a result, in 2016, the World Health Organization classified ECD along with other histiocytic diseases, as neoplastic disorders.

The clinical spectrum of ECD can be quite broad; most cases are progressive, involving multiple organs, including the nervous system, causing significant morbidity and mortality, and rarely self-limiting. It is a rare disease of adults with a median age at diagnosis of 48–56 years and a male preponderance.[4] Based on most reports, the nervous system can be involved in up to 50% of patients, but there is limited literature focusing specifically on neurologic manifestations of ECD. Moreover, central nervous system (CNS) involvement may be associated with worse prognosis.[5] In this issue of *Neuro-Oncology*, Bhatia et al report on their experience of treating 30 patients with CNS involvement of ECD in the molecular era.[6] The authors' findings supported that CNS involvement of ECD is variable with no pathognomonic manifestations, either clinically or radiographically. Cognitive impairment, previously thought to be an uncommon presentation, was noted in 33% of patients in the reported series in addition to volume loss on MRI brain, further emphasizing the value of comprehensive neuropsychiatric testing in patients with ECD. Cerebellar atrophy, another sign of neurodegeneration, in the absence of other overt lesions, was noted in 4 patients. Of note, in a recent series of 62 patients, 52% reported cognitive deficits.[7] In that study, 28% of patients had age-inappropriate cerebral atrophy, which correlated with the presence of *BRAF*^{V600E} mutation ($P = 0.047$). These important findings require further evaluation.

The authors noted that the median time from development of symptoms to ECD diagnosis was approximately 22 months, reflecting a delay in diagnosis, which is not uncommon.

Due to the rarity of the disease, diverse clinical presentations often mimicking other conditions, and difficulty in pathologic confirmation, ECD and other histiocytic neoplasms are extremely challenging to identify, requiring a high index of suspicion. Often, multiple biopsies are required, and definitive diagnosis can be delayed, especially when it involves the brain and the nervous system. In this study, 8 patients underwent neurosurgical biopsies, and the classic histopathologic hallmark of foamy histiocytes was not as evident, highlighting the fact that diagnosis of ECD, particularly from brain biopsies, can be difficult, and molecular studies are immensely valuable in the context of diagnostic dilemma.

Treatment is recommended for all symptomatic patients with ECD. Until recent molecular discoveries, there have been few prospective therapeutic trials in ECD.The majority of retrospective data supported the use of pegylated interferon-alpha (IFN-α), found to be an independent predictor of survival compared with other therapies, and is generally recommended as first-line therapy.[4,5] Biologic therapies targeting cytokines such as anakinra, infliximab, and tocilizumab have been investigated. But, so far, anti-cytokines are not typically used as first-line agents and are recommended in the context of severe inflammatory symptoms and failure of other therapies like IFN-α.

The identification of *BRAF*^{V600E} mutations in >60% of patients with ECD and additional recurrent activating mutations in the MAPK/ERK (extracellular signal-regulated kinase) pathway led

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to investigation of BRAF and MEK inhibitors in this disease. A basket study of vemurafenib in non-melanoma cancers enriched for *BRAF*^{V600E} mutations enrolled 22 patients with ECD, of whom 55% had objective responses.[8] All patients had a metabolic response on 2-fluoro-2-deoxy-D-glucose (FDG)-PET and the 2-year progression-free and overall survival rates were 83% and 95%, respectively. These results led to FDA approval of vemurafenib for treatment of *BRAF*^{V600E} mutant ECD in November 2017. In a large retrospective series of 54 patients with ECD, treatment with vemurafenib/dabrafenib and/or cobimetinib demonstrated high response rates of 88%, specifically 91% in those with *BRAF*^{V600E} mutations.[9] BRAF inhibitors were stopped in 20 patients, of whom 75% recurred. Remarkably, re-treatment that was initiated in 10 patients was successful. The current study reported by Bhatia and colleagues adds relevant data to the literature describing similar efficacy of BRAF and MEK inhibitors in a large cohort of patients, specifically with neurologic involvement of ECD. In this series, 83% of patients received targeted therapy at some point during their disease course, of whom 28% did not undergo prior conventional therapy. Clinical, radiographic, and metabolic responses to conventional therapy were poor compared with responses to targeted agents. The authors note that response assessment in patients with multisystem involvement, including the CNS, can be challenging and appropriately includes both MRI and FDG-PET evaluation. Neurologic damage from neurodegeneration and atrophy are difficult to measure using standard radiographic response criteria. Moreover, this may result in permanent and irreversible deficits. Clinical and neurologic assessment, as employed in this study, in addition to comprehensive neuropsychiatric evaluation, are equally essential. In this cohort of patients, the authors reported no progression on BRAF and/or MEK inhibitors and the responses seemed durable.

One of the main challenges in rare diseases is the lack of adequate historical controls, thereby making interpretation of data difficult. Nonetheless, the critical role of *BRAF*^{V600E} mutation in pathogenesis of ECD, emerging data that patients harboring these mutations may have worse outcomes including cognitive decline, along with the encouraging data from this study and others support the utilization of BRAF or MEK inhibitors as first-line therapy based on mutational status. As the authors indicate, exact duration of therapy particularly given the side effect profile of these drugs remains to be determined. The ECD Global Alliance recommends BRAF inhibitors as first-line therapy for treatment of patients with multisystem *BRAF*^{V600E} mutant ECD with life-threatening cardiac or neurologic involvement.[10] The autopsy performed in this study points to the fact that even in the absence of clinical and radiographic features, microscopic involvement of the nervous system can still exist. This raises a question regarding the optimal timing of treatment with BRAF inhibitors. While the mechanisms underlying neurodegeneration in ECD are currently unknown, long-term data will identify if early initiation of treatment with BRAF inhibitors delays or prevents overt neurologic involvement, neurocognitive decline, and cerebral atrophy. Further, studies to elucidate the mechanisms of resistance to BRAF and MEK inhibitors and appropriate therapeutic combinations require evaluation in the context of clinical trials. Evaluation of molecular markers with cell-free DNA over the disease course, which may guide decisions on treatment duration, is likely on the horizon, although more data are necessary on adequate utilization of this approach.[11] As our knowledge regarding the biology of ECD is evolving, ongoing efforts will likely bridge these gaps and overcome the barriers in the optimal management of this disease.

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