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634.MYELOPROLIFERATIVE SYNDROMES: CLINICAL AND EPIDEMIOLOGICAL

High Prevalence of Vulvar and Hepatic Manifestations in a Series of 18 Histiocytosis with Brafdel Mutations

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Introduction
L-group histiocytosis (Erdheim-Chester disease (ECD) and Langerhans-cell histiocytosis (LCH)) are multi-system diseases characterized by histiocyte infiltration in several organs. These histiocytes frequently harbor activating somatic mutations of the MAP Kinase pathway. Many of these mutations are frequently associated with a specific phenotype: *BRAF* ^{V600E}mutated ECD patients have more frequently cardiac and vascular involvements, *MAP2K1* mutated ECD patients may exhibit overt Rosai-Dorfman Disease (RDD) component, and *ALK*-mutated patients have a high prevalence of neurological involvement. Our objective was to describe characteristics of patients with histiocytosis and a particular *BRAF*-deletion mutation.
Methods
We performed a retrospective multi-center study. Patients were identified through the Histiocytosis national referral center pathology laboratory in Ambroise-Paré Hospital (Boulogne-Billancourt) in which all suspected diagnosis of histiocytosis samples are sent for proofreading and sequencing. Samples are sequenced with a specific panel next generation sequencing. We identified patients with *BRAF*del mutations and contacted the centers for clinical, morphological, and biological datas.
Results
Twenty-four patients with a *BRAF*del mutation were identified. Data were available for 18 of them. Most patients (n=17) had LCH (one with an ECD component) and one had an ECD. Median age at diagnosis was 50 years (IQR 35-78). The most frequent manifestations were hepatic (n=8, 44%) and vulvar (8/10 female gender patients, 80%). Other manifestations were cystic interstitial lung disease (n=6), lytic bone lesions (n=7), diabetes insipidus (n=6), panhypopituitarism (n=3), pachymeningitis (n=2), long bone osteosclerosis (n=1), perirenal infiltration (n=1), salivary gland infiltration (n=1) and digestive track infiltration (n=1). Hepatic manifestation was sclerosing cholangitis in all patients, and 5/6 patients had histiocytic infiltration in liver biopsy. All patients with sclerosing cholangitis had biological cholestasis, elevated aminotransferases, and hyperbilirubinemia. No patient had cirrhosis. Hepatic MRI, when performed, always showed cholangitis (5/5). PET-scan showed liver abnormalities in 4/6 patients (heterogenous liver uptake or uptake in biliary ducts). First line treatments included vinblastine (n=5), aracytine (n=1), methotrexate (n=1), cladribine (n=1) and cobimetinib (n=1). Nine patients did not receive any treatment. Two patients received cobimetinib, that resulted in partial remission and stable disease at 6 months. After a median follow-up of 43 (IQR 11-315 months), one patient had died from unknown cause.
Conclusion
BRAF-deletion mutations in histiocytoses are associated with a specific LCH pattern with high prevalence of hepatic and vulvar involvements. These manifestations should be carefully screened in these patients.

Disclosures No relevant conflicts of interest to declare.

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