Title: Pediatric Erdheim-Chester disease in the molecular era: a multicenter case series

Background: Erdheim-Chester disease (ECD) is a non-Langerhans cell histiocytic disorder that almost exclusively affects adults. Reports of pediatric-onset ECD are only anecdotal. Additionally, a comprehensive clinical and molecular characterization of pediatric ECD is lacking.

Methods: All prevalent and incident cases followed at three ECD referral centers in Italy and France were considered eligible when they had: a) an age <18y at disease onset; b) a clinical presentation consistent with ECD (i.e., at least one of the following localizations: bilateral, sclerotic bone involvement; sclerotic bone lesions of facial sinuses; hairy kidneys; coated aorta; xanthelasma; tumoral atrial involvement); c) pathology consistent with ECD or mixed ECD-Langerhans cell histiocytosis (LCH); d) available data on molecular studies.

Results: Ten patients were included (4 boys and 6 girls); their median age at diagnosis was 4.5 years (IQR 3-9). Bone pain, diabetes insipidus, and exophthalmos were the predominant clinical manifestations at onset. The most commonly involved sites were the hypothalamic/pituitary axis (8/10, 80%), the maxillary/facial structures (8/10, 80%), the bone (6/10, 60%), and the central nervous system (CNS; 7/10, 70%). Other less frequent localizations included the skin (3/10, 30%), the retroperitoneum (2/10, 20%), the lymph nodes (2/10, 20%), the large vessels (1/10, 10%), the heart (1/10, 10%), and the lung (1/10, 10%). The median number of involved sites was four (IQR 4-4).

Four patients (of whom three were younger than nine years) had clinical or pathological features consistent with mixed histiocytosis (ECD-LCH). Molecular analysis of tissue biopsies revealed the BRAFV600E mutation in 6 patients (60%). As compared with adult series, the retroperitoneum, the heart, the lungs, and the skin seemed to be less frequently involved. Conversely, hypothalamic/pituitary and maxillary/facial involvement were apparently more frequent in our pediatric cohort.
Treatments were heterogeneous. First-line regimens mainly consisted of chemotherapy deriving from LCH-based regimens: six out of the eight treated patients received chemotherapy, but only two of them achieved a transient response. Interferon-alpha was used in five patients (as first-line treatment in two and as a rescue treatment in three), with a partial response in two. All but one patient with \(BRAF^{V600E}\) mutation received the BRAF inhibitor vemurafenib at some point (partial responses were obtained in all, in one case requiring a combination with cobimetinib). All patients were alive at last follow up (median 94 months, IQR 12-108). Chronic sequelae included end-stage kidney disease in one patient, growth retardation in two, and endocrine abnormalities in seven.

**Conclusions:** The clinical phenotype of ECD differs between children and adults. The hypothalamic/pituitary axis and the maxillary/facial area are frequently involved in pediatric cases, whereas other localizations typically seen in adults (i.e., retroperitoneum, heart, lung, and skin) are rarer. An overlap with LCH is frequent, especially in younger patients. As for LCH, targeted treatments can be highly effective in children carrying the \(BRAF^{V600E}\) mutation.