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Immunohistochemical analysis of potentially targetable markers in histiocytic disorders

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Histiocytosis describes a heterogenous group of rare disorders of the mononuclear phagocyte system. These disorders can clinically present in any organ with varying severity and age of onset. They can manifest in form of a single self-healing lesion or as a severe therapy-resistant disseminated disease. Such systemic forms often require salvage therapy when first- and second-line treatment fail. Recently, targeted therapy with BRAF inhibitors can be used for patients with verified BRAF mutations. The aim of this study is to find more targetable markers that increase the range of possible treatment for patients with Langerhans cell histiocytosis (LCH) and non-Langerhans cell histiocytosis (NLCH) by analysing druggable key signalling pathways and molecules. The analysed parameters were mitogen-activated protein kinase (MAPK) pathway components, proteins of the neurotrophic tyrosine receptor kinase (NTRK) family and immunorelevant programmed cell death-ligand 1 (PD-L1). Clinicohistopathological and tissue microarray (TMA) data from 69 patients with a diagnosed form of histiocytosis were acquired and evaluated within the scope of a multicentric and retrospective study. Data and tissue samples of patients with LCH, xanthogranuloma (XG), necrobiotic xanthogranuloma (NXG), xanthoma disseminatum (XD), Rosai-Dorfman disease (RDD), Erdheim-Chester disease (ECD) and generalized eruptive histiocytosis (GEH) were collected. Only tissue samples with histopathologically confirmed diagnoses were utilized, further validated through specific immunohistochemical (IHC) stainings against diagnostic markers after generating TMAs. XG and LCH were each grouped in high- and low-risk subtypes. They were evaluated using a semiquantitative multiplicative quickscore method (IHC score), which considers staining intensity and the percentage of immunopositive cells, in order to identify potential therapeutical targets and correlations with clinicohistopathological data. Antibodies of significant value were the following: anti-PD-L1, anti-ERK2, anti-MEK2, anti-pMEK1/2, anti-MEK1/2 and anti-ERK1/2.

This study appears to be the first to detect significant PD-L1 overexpression in XG, especially in disseminated XG. It implies the involvement of PD-L1 in XG pathobiology and indicates a potential role of XG cells in immune evasion and tumour progression. Patients with higher levels of PD-L1 expression are likely to benefit from therapy with immune checkpoint inhibitors (PD-1/PD-L1-blockade therapy). Further results confirm the known association between MAPK pathway proteins and histiocytoses. Firstly, there were findings of significant MEK overexpression in high-risk LCH and XG. High MEK expression can be synonymous with a possible MEK mutation and can (over)activate ERK1/2. The use of MEK inhibitors in MEK-positive LCH and NLCH without BRAF overexpression or in severe LCH and NLCH cases can be suggested in order to improve clinical outcome. Secondly, the analysis of ERK undertaken here showed a significant ERK overexpression in multifocal and multisystemic LCH and in XG. This is most likely due to an (over)activation of upstream MAPK pathway components. These results indicate that histiocytosis cases with ERK overexpression might profit from treatment with ERK inhibitors in the future, although these are not yet clinically established.

Taken together, this work represents a significant step forward in understanding histiocytic disorders and identifying potentially targetable markers for LCH and NLCH patients.