Concurrence of a Kinase-dead BRAF and an Oncogenic KRAS Gain-of-function Mutation in Juvenile Xanthogranuloma

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To the Editor

Juvenile xanthogranuloma (JXG) is a very rare benign tumor of histiocytic origin. Being derived from CD14+ dermal dendrocytes, JXG represents the most common type of non-Langerhans cell histiocytosis

(non-LCH) and typically affects young infants[1,2]. Although it is usually confined to solitary, or rarely multiple, yellow-reddish papulous lesions of the skin (monosystemic) that tend to regress spontaneously over the course of a few years, JXG may also extend to ocular, visceral, and central nervous system (multisystem/systemic) disease[2]. Cutaneous lesions generally heal without or sometimes with atrophic scarring, whereas ocular or visceral involvement may result in severe, even life-threatening morbidity and require systemic treatment, historically consisting of agents used in the therapy of LCH (prednisolone, vinca alkaloids, 6-mercaptopurine, cytarabine, cladribine; *see also*LCH-IV protocol of the Histiocyte Society at www.histiocytesociety.org,*ClinicalTrials* identifier: NCT02205762)[2-5]. In analogy to LCH and other non-LCH diseases, recent studies have confirmed the presence of activating mutations in the MAPK signaling pathways in many cases of systemic JXG, or rarely, kinase fusions involving BRAF, ALK, or NTRK in various non-LCH lesions[6,7]. Vemurafenib has been shown to be effective in achieving clinical remissions in refractory multisystem *BRAF* p.V600E-mutated LCH[8]. Consequently, also patients with severe systemic JXG may be offered an effective targeted therapy in the future.

We report on a female infant with multiple cutaneous lesions of JXG affecting her face, upper trunk and proximal upper extremities. A concurrence of a *BRAF* p.D594N and a *KRAS* p.G12V mutation with identical allele frequencies of 12-13% was detected in these lesions. The same constellation of both *BRAF* loss-of-function and*KRAS* gain-of-function mutations occurring simultaneously has been experimentally explained by a mechanism of oncogenic RAS-dependent CRAF binding of BRAF and paradoxical activation of the MAPK pathway via CRAF in the presence of kinase-dead (class III) variants of BRAF or pharmacological inhibition of BRAF *in vitro* and *in vivo*[9,10] . In line, patients treated with BRAF inhibitors are at risk to develop RAS-mutated keratoacanthomas or squamous cell carcinomas[11], and class III BRAF mutations were detected in melanoma, colorectal carcinoma, and non-small cell lung cancer and are typically linked to oncogenic RAS mutations, NF1 deletions, or increased receptor tyrosine kinase signaling (*reviewed in* [12-15]); whereby the exact sequence of these events remains to be elucidated.

The child is clinically stable and neither eyes, nor visceral organs or the CNS are affected as determined by imaging and ophthalmological studies. To date, she is 30 months of age and has been observed without therapy for one year with a mild "waxing and waning" course of the skin lesions. In contrast, three other children diagnosed with unifocal cutaneous JXG within the same year at our institution, did not show any alteration of the genes analyzed (sequencing panel includes *BRAF, GNA11, GNAQ, HRAS, KRAS, RAC1, CDKN2A, KIT, MAP2K1, PIK3CA, PTEN*). This finding and the presence of *MAP2K1* besides *BRAF* p.V600E mutations in a substantial proportion of current local LCH patients analyzed with the same panel (MAP2K1 p.F53_Q58delinsL, n=2; BRAF V600E n=4; total LCH patients analyzed n= 12) highlight the need for detailed tumor genotyping and awareness of the affected stage within the altered signaling pathway prior to initiation of kinase-directed treatment in histiocytosis to identify the precise target and avoid unnecessary adverse effects.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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