Sarcoid-like reaction in a child following prolonged therapeutic exposure to dabrafenib and trametinib for BRAF V600E mutated hypothalamic/ chiasmatic glioma

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LETTER TO THE EDITOR

TITLE: Sarcoid-like reaction in a child following prolonged therapeutic exposure to dabrafenib and trametinib for BRAF V600E mutated hypothalamic/ chiasmatic glioma

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ABBREVIATIONS
Limited data exist in children regarding the long-term use of agents inhibiting the RAS/MAP-kinase pathway including both BRAF and MEK-inhibitors (BRAF/MEKi). We report a 7-year-old girl with low-grade glioma presenting with BRAF/MEKi induced sarcoidosis/sarcoid-like reaction (S/SLR).

Our patient’s initial diagnosis at 2-months of age with a BRAF-V600E mutant hypothalamic-chiasmatic glioma, and her dramatic response to dabrafenib after failure of chemotherapy were previously reported. Progression at 5-years of age mandated addition of trametinib. Following two uneventful years on dual BRAF/MEKi, the child presented with significant swelling of her right eyelid (Fig.1A). Bilateral dacryoadenitis (Fig.1B,C) elevated ACE levels (115 U/L; normal range: 8-76), and bilateral pulmonary nodules (Fig.1D) with enlarged bilateral hilar and axillary lymph nodes on CT chest were suggestive of S/SLR. Though initially started on antibiotics, she was shifted to prednisone (0.5 mg/kg/day) after withholding BRAF/MEKi, resulting in complete resolution of symptoms within 10-days. PET-CT and pulmonary function tests were normal, with no evidence of additional organ involvement. Work-up for genetic predisposition did not reveal any deleterious variants in the nucleotide binding oligomerization domain-2 (NOD2) gene. A novel frameshift variant in the nucleotide-binding leucine-rich repeat-containing receptor 12 (NLRP12) gene (c.654_656delinsAGGA; p.Ala219Glyfs*27) was detected. This was predicted to cause premature protein translation and has not been described in population databases.

Within 2-weeks of stopping BRAF/MEKi, there was glioma progression (Fig.1E) that mandated a carefully considered re-challenge of BRAF/MEKi with rapid tumor control. Inflammatory biomarkers were closely monitored, in addition to surveillance for clinical symptom flare.Persistently elevated ACE (310 U/L) indicating S/SLR burden, and significantly elevated SAA levels (15,280 ng/ml; normal range: 1000-5000) consistent with subclinical long-term biochemical inflammation, warranted reinstitution of low-dose steroids (0.1 mg/kg/day) following multi-disciplinary consensus after 6-months of reinitiating BRAF/MEKi. Interestingly, an elevated SAA level can upregulate Th17-cell proliferation and cytokine production, and has been linked to a higher risk of pulmonary fibrosis in sarcoidosis. The child is currently doing well on low-dose steroid, dabrafenib and trametinib.

The immune effects of BRAF/MEKi are increasingly appreciated. BRAF/MEKi are associated with increased intra-tumoral T-cell infiltration, immunogenic antigen expression, upregulation of HLA class I, suppression of M2-type macrophages, myeloid derived suppressor cells and T-regulatory cells, and increased TNF-α and INF-γ levels. Sarcoidosis is a multisystem, granulomatous disease rarely diagnosed in children. However, both sarcoidosis and sarcoid-like reactions (that do not fulfill all the diagnostic criteria) are reported in adults treated for cancer, most frequently in patients with melanoma.
treated using BRAF/MEKi. The reported incidence was 5.7%, and 11% for vemurafenib monotherapy and dabrafenib/trametinib combination, respectively. Onset following BRAF/MEKi initiation was at 9-months (median) (range: 1-21). Most patients had mild manifestation, with the skin reported as a commonly involved site. Discontinuation of BRAF/MEKi was not needed in the majority, except for vital organ involvement. Only one fatality with granulomatous myocarditis was reported. For those needing discontinuation, usually lesions resolved soon after stopping BRAF/MEKi and initiating steroids. Anecdotal reports on re-challenge support that S/SLR may not always recur on reinitiating BRAF/MEKi. Additionally, limited data suggest that oncologic outcomes of patients who develop S/SLR can be superior to those without such immune adverse events.

In drug-induced S/SLR, whether the medication acts as trigger in patients with genetic predisposition, or exacerbates subclinical sarcoidosis, or just causes a similar granulomatous reaction, remain unknown. In contrast, in young children, early-onset sarcoidosis is linked to deleterious variants in NOD2, also termed caspase recruitment domain–containing protein 15 (CARD15), mapped on chromosome 16q12. Genome-wide association studies in adults have linked sarcoidosis to multiple genes affecting immune function, including BTN2, C100RF67, ANXA11, XAF1, IL23R and specifically, autophagy-related genes and two regulatory hubs, mTOR and Rac1. Our patient did not harbor mutations in any of these genes, but did have a novel frameshift variant in NLRP12 gene. Interestingly, NLRP12 is a negative regulator of innate immune activation and type-1 interferon production. The spectrum of the rare and relatively novel, monogenic NLRP12-related autoinflammatory disease syndrome has currently evolved beyond the classical presentation of cold-induced periodic fever, polyarthralgia and rash. Not only can NLRP12 mutations lead to varied systemic autoimmune manifestations, reduced NLRP12 expression has been linked to more severe phenotypes of other autoimmune disorders like lupus in preclinical models. Though no reports of S/SLR have been reported, it is intriguing to postulate whether the novel variant in NLRP12 could have contributed to the risk of a drug-induced S/SLR in our patient.

In conclusion, to the best of our knowledge, no reports exist on BRAF/MEKi-induced S/SLR in children. In our patient, a very young age of initiation and prolonged exposure could have exacerbated the risk of S/SLR, especially in the backdrop of a possible genetic aberration involving the innate immune pathway. She had to be restarted on her oncologic treatment following the well-known phenomenon of rebound glioma growth after sudden termination of BRAF/MEKi. Subclinical inflammation mandated prolonged treatment with low-dose steroids. These observations highlight that pediatric oncologists need to be aware of relatively rare, immune toxicities that may manifest in young children following prolonged therapeutic exposures and may need complex multi-disciplinary management. Collaborative studies are needed to optimize a weaning strategy for targeted therapies, including use of combinatorial approaches, to mitigate such long-term immune toxicities.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. Informed consent was obtained.

FIGURE AND LEGEND

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Fig.1. (A) Clinical presentation with bilateral eyelid swelling. (B) MRI suggesting bilateral dacryoadenitis (white arrows) and (C) detailed ophthalmological examination confirming the same. (D) CT chest showed
multiple bilateral pulmonary nodules (white arrow) along with mediastinal lymphadenopathy. (E) MRI brain at the time of diagnosis of S/SLR, 2-weeks after stopping BRAF/MEKi, and 3-months after reinitiating targeted therapy

REFERENCES


