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Case Report

Challenges in the treatment of melanoma with BRAF and MEK inhibitors in patients with sickle cell disease: case report and review of the literature

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***Abstract*:** Patients with sickle cell disease (SCD) suffer from complications due to anemia, inflammation, and vaso-occlusion. Factors that trigger sickling and/or inflammation may initiate such complications, while treatment with hydroxyurea (HU) reduces their emergence and prolongs survival. On the contrary, inhibition of the BRAF-MEK-ERK pathway with BRAF and MEK inhibitors (BRAF/MEKi) has revolutionized treatment of melanoma but their use has been correlated with inflammatory adverse events. Thus, treatment of patients with SCD with BRAF/MEKi may be quite challenging and pyrexia in those patients should be managed as a medical emergency. In this article, intrigued by the case of a 36-year-old female patient with S/β-thal under HU who was treated with dabrafenib and trametinib for melanoma, we analyze the mechanisms underlying inflammation and vaso-occlusion in SCD, the mechanisms of pyrexia and inflammation induced by BRAF/MEKi, their potential interconnections, the shared role of the inflammasome in these two entities, and the protective effect of HU in SCD. Since SCD is the most common inheritable blood disorder, the administration of BRAF/MEKi for melanoma in patients with SCD may be a rather common challenge. Thus, proper treatment with HU may pave the way for an uneventful management of such patients.

Keywords: BRAF inhibitor, case report, hydroxyurea, inflammation, MEK inhibitor, melanoma, sickle cell disease

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Introduction

Sickle cell disease (SCD) is the most common inheritable blood disorder worldwide. Patients with SCD present with various acute and chronic complications attributed to anemia, inflammation, and vaso-occlusive crises (VOC). Sickle cell-beta thalassemia (S/β-thal, SBT) results from the double heterozygosity of a sickle hemoglobin (HbS) mutation and a beta thalassemia allele. Hydroxyurea (HU) is the mainstay of SCD treatment, since it has been shown to reduce the emergence of devastating complications and prolong survival.[1,2] Management of the emerging complications, such as VOCs, acute chest syndrome (ACS), thrombotic episodes, and infections is crucial. Red blood cell (RBC) transfusions are indicated for the management and prevention of specific complications.[3] Novel therapies include anti-sickling agents, targeting adhesion molecules and radical approaches such as gene therapy or gene editing, while hemopoietic stem cell transplantation is the only established curative approach.[4–7]

Patient counseling and education are a crucial part of the management of patients with SCD and focuses on appreciating the importance of routine health-care encounters and early intervention for

acute and chronic complications of the disease, as well as on recognizing warning signs of acute illness. Factors that trigger sickling and may cause acute complications such as VOC include dehydration, physical exhaustion, exposure to cold, sudden temperature or altitude changes, fever and infections, and their avoidance and reversal is mandatory. Avoidance of agents that may cause vasoconstriction or initiate an inflammatory process is also considered highly important. In this context, cigarette smoking, and alcohol consumption, use of illicit drugs such as marijuana and cocaine, as well as G-CSF administration should be avoided.[8] Finally, in patients with SCD, fever should be managed as a medical emergency.

Inhibition of the BRAF-MEK-ERK pathway with the use of BRAF and MEK inhibitors (BRAF/MEKi) has proven a valuable treatment option for patients with *BRAF*-mutated melanoma. Their use has revolutionized the management of melanoma but has also been correlated with a series of inflammatory adverse effects affecting almost every organ system. Pyrexia is one of the most common adverse effects of treatment with BRAF/MEKi, while arthralgias/myalgias, acneiform rash, erythema nodosum or other types of panniculitis, uveitis, and, more rarely, cardiomyopathy may complicate treatment. Inflammatory adverse events have been reported to complicate as much as 75% of patients in several studies.[9]

In this context, intrigued by the case of a 36-year-old female patient with SBT diagnosed with metastatic BRAF-mutated melanoma, effectively and uneventfully treated with BRAF and MEK inhibitors, we review the literature on the inflammatory processes in patients with SCD, the protective role of HU, as well as data on the mechanisms underlying the inflammatory complications of BRAF/MEKi. Since, both melanoma and SCD are rather common conditions in the general population, the evaluation and management of melanoma in patients with SCD should not be uncommon, especially since there is available data on the increased risk of cancer and melanoma in particular in patients with SCD.[10] We have followed the CARE case report guidelines when drafting this case report.[11]

Case presentation

A 36-year-old woman was diagnosed with a stage IIA (T2b, N0, M0) melanoma of the right eyelid that had developed on a congenital nevus. Six months from diagnosis, she had a local recurrence and underwent a surgical orbital exenteration along with sentinel lymph node biopsy that was negative for malignant infiltration. Two months later, she underwent a pulmonary wedge resection for a lung nodule that proved to be metastatic.

The patient had been diagnosed with SCD (S/β-thal; genotype, βS/IVSI-1 G > A) at the age of four. She had not experienced any VOCs over the last 5 years. The staging imaging studies for melanoma revealed bilateral humeral head avascular necrosis and a necrotic lesion of the right iliac bone consistent with a bone infarct and she was started on HU at 1 g/day (20 mg/kg/day, moderate fixed dose strategy) despite the absence of VOCs over the last 5 years. Her baseline hematologic profile before HU initiation included a hemoglobin (Hb) level of 10.4 g/dL with a mean corpuscular volume (MCV) of 71.9 fL and fetal hemoglobin (HbF) and HbS levels of 26.9% and 66.1%, respectively. Following HU initiation, she did not have any VOCs or other complication and did not require any RBC transfusions. Her spleen size was measured at 12.9 × 12.6 cm by an ultrasound performed just before her lung surgery. The metastatic lesion was found to be *BRAF*-mutated (BRAFV600E); thus, she was started on dabrafenib at 150 mg BID and trametinib at 2 mg QD (the patient provided informed consented to treatment). Before treatment initiation, a heart ultrasound revealed no findings, while an electrocardiogram did not show a QT segment prolongation. Moreover, an ophthalmological evaluation did not reveal any findings. The Hb level at treatment initiation, while on HU for several months was 11.3 g/dL with an MCV of 95.2 fL and an Hb electrophoresis showing an HbF at 46.7% and HbS at 47.7%. Five days after treatment initiation, she had a pyrexia episode up to 39.8°C (104°F) without any localizing findings or pain. Treatment was temporarily withheld, and the clinical and laboratory evaluation (complete blood count, serum C-reactive protein, biochemical profile, urinalysis, blood and urine culture, chest X-ray) did not reveal any signs of infection thus the episode was deemed as BRAF/MEK inhibitor related (laboratory values presented in Table 1). The fever subsided 48 hours later and treatment with BRAF/MEKi was resumed 48 hours after her last fever wave with

Table 1. Laboratory values of the patient during the febrile episode.

Test (units)	Reference range	Result
Hemoglobin (g/dL)	12–16.5	10.7
White blood cell count ($\times 10^9$/L)	4.0–10.0	5.7
Neutrophil count ($\times 10^9$/L)	2.5–6.0	3.9
Platelet count ($\times 10^9$/L)	140–440	207
Serum CRP level (mg/L)	0–5	7.3
Aspartate aminotransferase (U/L)	13–35	17
Alanine aminotransferase (U/L)	<33	22
Creatinine (mg/dL)	0.51–0.95	0.74
Lactate dehydrogenase (U/L)	135–214	227
Urinalysis	White blood cells, ⩽2–5 Bacteria, none	White blood cells, 0–1 Bacteria, none
Blood culture	Negative	Negative
Urine culture	Negative	Negative

CRP, C-reactive protein.

no dose reduction. No further pyrexia episodes were recorded and the patient continued uneventfully 12 months of treatment with no clinical or radiological signs of progression. A written informed consent for the publication of this case was obtained from the patient.

Discussion

To the best of our knowledge, this is the first case of administration of BRAF/MEKi in a patient with SCD or SBT (or other compound sickle cell syndromes). Treating patients with SCD with agents that may promote inflammation is a challenge for the treating physician, since an inflammatory complication of the treatment may induce a cascade of inflammatory processes leading to the initiation of a painful or thrombotic episode.[12,13] The mechanisms of inflammation in SCD are complex and involve most parts of the immune system. The main aspects of the inflammatory processes developing in patients with SCD as well as data on the mechanisms underlying the inflammatory complications of BRAF/MEKi are presented below.

Mechanisms of inflammation and vaso-occlusion in SCD

Multiple mechanisms are implicated in the emergence of VOC in SCD. Activation of adhesion molecules has been well established in several *in vitro* models and inhibition of adhesion molecules has recently been adopted as a therapeutic target, while inflammation and leukocytosis have a significant role as mediators of VOC. The enhanced interaction of leukocytes with the endothelium during inflammatory processes and the slow passage of the less deformable leukocytes through the microvasculature may enhance adhesion and red cell sickling proximal to the area of retarded flow.[14] It has been shown that neutrophils from patients with SCD are highly sensitive to chemokine activation and adhesion, thus showing a pro-adhesive phenotype.[15,16] Finally, a higher leukocyte count has been correlated with higher mortality rates in patients with SCD,[17] while extreme leukocytosis induced by the use of granulocyte colony-stimulating factor (G-CSF) has been correlated with severe or fatal vaso-occlusion.[18]

Numerous proinflammatory molecules including cytokines, chemokines, growth factors, and other

peptides have been found elevated even in steady-state SCD. Circulating tumor necrosis factor (TNF)-a levels have been consistently reported to be elevated in patients with SCD. TNF-a increases the adhesion of neutrophils to the endothelium[19] by stimulating the expression of surface b2 integrins, leading to interactions with other cells through the NF-κB and MAPK signaling pathways.[20] Inflammatory markers, such as C-reactive protein (CRP) levels, have been correlated with painful or vaso-occlusive events.[21] Furthermore, cytokines such as interleukin 1 (IL-1) and IL-6 have been found increased in patients with SCD. Increases in the level of IL-1a enhances leukocyte recruitment, endothelial cell activation, and production of several inflammatory mediators.[22]

Moreover, IL-6 seems to be responsible for the high levels of acute phase proteins, even in the steady state of the disease,[23] and recent reports suggest that IL-6 levels can be used as a predictor of vaso-occlusive episodes.[24] IL-17, also elevated in SCD, may reflect activation of lymphocytes and may contribute to the production of cytokines and chemokines involved in leukocyte recruitment.[25] Chemokines such as the monocyte chemoattractant protein (MCP)-1, platelet factor 4, macrophage inflammatory protein (MIP)-1a, end eotaxin-1 have also been found activated in SCD.[26–28]

Pyrexia and inflammation induced by BRAF/MEKi

The inflammatory mechanisms of BRAFi-based treatment remain insufficiently studied and poorly understood. Nevertheless, several inflammatory markers have been proposed for the diagnosis and prediction of pyrexia in patients under treatment with BRAF/MEKi. CRP has been consistently reported elevated in patients with BRAF-induced pyrexia, while the neutrophil count has been found normal or elevated.[29,30] IL-6 and IL-1β have been also found elevated in patients with BRAFi-induced pyrexia,[31] possibly through the activation of dendritic cells.[32]

Although the above inflammatory properties represent class effects of BRAF/MEKi, certain individual agents or combinations may predispose more frequently to specific adverse events. In a recent review of the tolerability and adverse event profile of BRAF/MEKi combinations in pivotal and phase III clinical trials, it was reported that fever of any grade was more common in patients treated with dabrafenib/trametinib compared to those treated with vemurafenib/cobimetinib, or encorafenib/binimetinib (51.1% *vs* 28.7% *vs* 18.2, respectively).[33] Interestingly, pharmacokinetic analysis has showed a possible association between pyrexia and exposure to the hydroxy-dabrafenib metabolite and, to a lesser extent to dabrafenib.[34]

The role of the inflammasome

During the past decade, inflammasome pathways have been implicated in the sterile inflammatory processes of SCD. In brief, activation of inflammasomes leads to the release of proinflammatory cytokines such as activated IL-1β and IL-18 that promote a cascade of events toward the activation of neutrophils and platelets and the upregulation of adhesion molecules and chemokines that triggers VOC.[35,36] The products of hemolysis have been shown to be a potent inflammasome activator. On the contrary, BRAF inhibition leads to caspase-1 dependent and independent activation of the inflammasome, leading to upregulation of IL-1β.[32] This finding correlates pyrexia caused by BRAFi with the inflammasome and IL-1β production, when at the same time IL-1β has been identified as a major mediator of pyrexia in mice.[37] These correlations furthermore support the hypothesis that BRAF inhibition in patients with SCD may induce cytokine and chemokine production that may trigger inflammatory processes which may eventually lead to vaso-occlusion.

HbF levels and the protective effect of HU in SCD

It has been well established that elevated HbF levels prevent sickling of HbS and patients with high HbF levels have generally a milder clinical phenotype. Treatment with HU induces HbF production and patients who start HU with a baseline normal level of HbF (<5%) are considered to achieve a good response when HbF levels are elevated to 20%. Our patient, although diagnosed with S/β-thal, had very high baseline HbF levels even before HU initiation; this explains her mild clinical course. Starting HU with elevated HbF levels resulted in an impressively high HbF level leading to a reduction of HbS levels below

50% (the conventional target for HbS is around 30%).

HU has proven effective in changing the course of SCD, mainly by inducing fetal Hb production but also by reducing the expression of adhesion molecules, decreasing the peripheral blood neutrophil counts, ameliorating the inflammatory process, and improving nitric oxide bioavailability. It has been shown that HU reduces granulopoiesis[38] and reverts the high levels of myeloperoxidase, TNF-α, IL-8, IL-10, vascular endothelial growth factor, and e-selectin[39–42] thus reducing both the count and activation of neutrophils. These laboratory findings correlate with the clinical benefit of the use of HU in patients with SCD in reducing inflammation and VOC. Therefore, the highly protective combination of very elevated HbF and reduced HbS levels, along with the beneficial anti-inflammatory effect of HU may have prevented red cell sickling and related clinical acute complications during treatment with dabrafenib and trametinib.

The role of MEKi in vaso-occlusion

The use of MEKi has been correlated with central retinal vein occlusion (CRVO) which is a visually threatening adverse event. Recent studies focus on the identification of clinical risk factors for CRVO in patients with melanoma treated with an MEKi. Hyperhomocysteinemia has been identified as one of them,[43] while hypertension, diabetes, dyslipidemia and glaucoma have also been reported.[44] In this context, SCD may also represent such a risk factor, although there are no relevant preclinical or clinical data. The mechanism of CRVO has been investigated in animal models and an upregulation of genes involved in oxidative stress and inflammatory responses has been found.[45] In contrast to the above, recent reports have highlighted MEK1/2 as a therapeutic target in SCD and have proposed MEKi as a means to reverse vaso-occlusion.[46,47] Nevertheless, these reports in animal models have not yet triggered their use in humans with SCD in the context of clinical trials.

Conclusion

The use of BRAF/MEKi for patients with SCD and melanoma is challenging due to the risk of pyrexia/inflammation which may eventually lead to painful crises and thrombotic complications. BRAF inhibition shares common proinflammatory pathways with SCD, and, although BRAF/MEKi are not officially contraindicated in patients with SCD, vigilance is needed for the early detection and prompt management of pyrexia. Choosing less pyrexia inducing BRAF/MEKi combinations, such as vemurafenib/cobimetinib, or encorafenib/binimetinib, could also be of some importance. The investigation and management of pyrexia and inflammation potentially attributable to BRAF/MEKi in patients with SCD should be aggressive, and pyrexia should be managed as an emergency, since triggering of VOC or other inflammatory complications is a possibility.

Furthermore, it would be prudent to review and optimize the SCD treatment plan before BRAF/MEKi initiation. HU is the gold standard of treatment in SCD and, through the effective induction of HbF and the corresponding reduction in the levels of HbS, may allow patients to receive novel therapies safely with a low risk of inflammatory complications. The multiple actions of the drug on the inflammatory and prothrombotic state of the disease possibly play a protective role, nevertheless this assumption needs further confirmation. Finally, although there are no available data, immunotherapy may be a more prudent choice for patients with SCD and BRAF-mutated melanoma who are not under treatment with HU and have high levels of HbS.

Declarations

Ethics approval and consent to participate

Ethics approval was not required for this case report.

Consent for publication

The patient has provided written informed consent for the publication of data concerning the case presentation included in this review article.

Author contributions

Panagiotis T Diamantopoulos: Conceptualization; Data curation; Methodology; Writing – original draft.

Amalia Anastasopoulou: Conceptualization; Writing – original draft.

Maria Dimopoulou: Investigation; Writing – original draft.

Michalis Samarkos: Conceptualization; Writing – review & editing.

Helen Gogas: Conceptualization; Investigation; Supervision; Writing – review & editing.

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Availability of data and materials
The patient's data are available upon reasonable request.

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Supplemental material
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