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Brief Communications

Successful Treatment of Cytokine Release Syndrome with IL-6 Blockade in a Patient Transitioning from Immune-Checkpoint to MEK/BRAF Inhibition: A Case Report and Review of Literature

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Abstract

There are now multiple targeted and immunotherapies available for the treatment of metastatic melanoma. Although these agents have dramatically improved the survival of patients, the appropriate sequencing and the safety during the transition between these drugs remains unknown. Recently two cases of cytokine release syndrome (CRS) following transition from immune-checkpoint inhibitors to BRAF and MEK inhibitors (BRAFi/MEKi) in patients with metastatic melanoma have been reported. CRS is a systemic cytokine-driven inflammatory reaction, previously well reported in chimeric antigen receptor T-cell therapies for hematologic malignancies. Here, we report a third case in which severe CRS resistant to glucocorticoid therapy following transition to a MEKi/BRAFi was treated successfully with tocilizumab, an interleukin-6 (IL-6) inhibitor. CRS should be on the differential diagnosis of immune-related adverse events of immunotherapies or targeted cancer therapies for metastatic melanoma, and clinicians in multiple disciplines should be aware of this rare complication and the potential benefits of IL-6 blockade. ***The Oncologist*** 2020;25:e1120–e1123

Introduction

Targeted and immunotherapies have transformed the landscape in the adjuvant and advanced melanoma treatment settings [1]. How these drugs should be optimally sequenced and the potential toxicities during the transition remain unknown [2]. Recently, two cases of cytokine release syndrome (CRS) were reported in patients who were treated with immune-checkpoint inhibitors followed by BRAF and MEK inhibitors, one of whom did not respond to high doses of glucocorticoids and required a single dose of IV tocilizumab [3]. We present a third case of CRS following a transition from immune-checkpoint inhibitor therapy to treatment with BRAF/MEK inhibitors (BRAFi/MEKi) successfully treated with tocilizumab.

Case Presentation

A 58-year-old man with a history of metastatic melanoma to his lungs presented to hospital in distributive shock. He had been diagnosed with metastatic melanoma 18 months prior to his presentation. Initial treatment included Interferon for induction followed by maintenance (15 months prior to current presentation, total duration 6 months). He developed a left axillary recurrence that was completely excised and then he was treated with nivolumab (8 months prior to current presentation, duration 6 months). Subsequently, he developed lung metastases, and as such, he was transitioned to trametinib (MEKi) and dabrafenib (BRAFi) (2 months prior to his presentation, duration 1.5 months). He had difficulty with dabrafenib and trametinib, developing fever, arthralgia, thrombocytopenia, hand and foot syndrome, transaminitis, and an increased creatine kinase. He recovered with discontinuation of therapy and supportive care. Eleven days prior to his presentation, he was started on cobimetinib (MEKi) and vemurafenib (BRAFi). Five days after initiation of this treatment he began to develop fatigue, malaise, and chills, and he discontinued therapy. Over the next 24 hours, he developed severe nausea, vomiting, diarrhea, fever of 39°C, and a purpuric eruption on his lower extremities, which progressed to involve his buttocks, trunk, arms, hands, nose, and left eyelid (Fig. 1A).

He presented to hospital 3 days later in distributive shock unresponsive to 7 L of intravenous crystalloid. He was found to have transaminitis, atrial fibrillation, an

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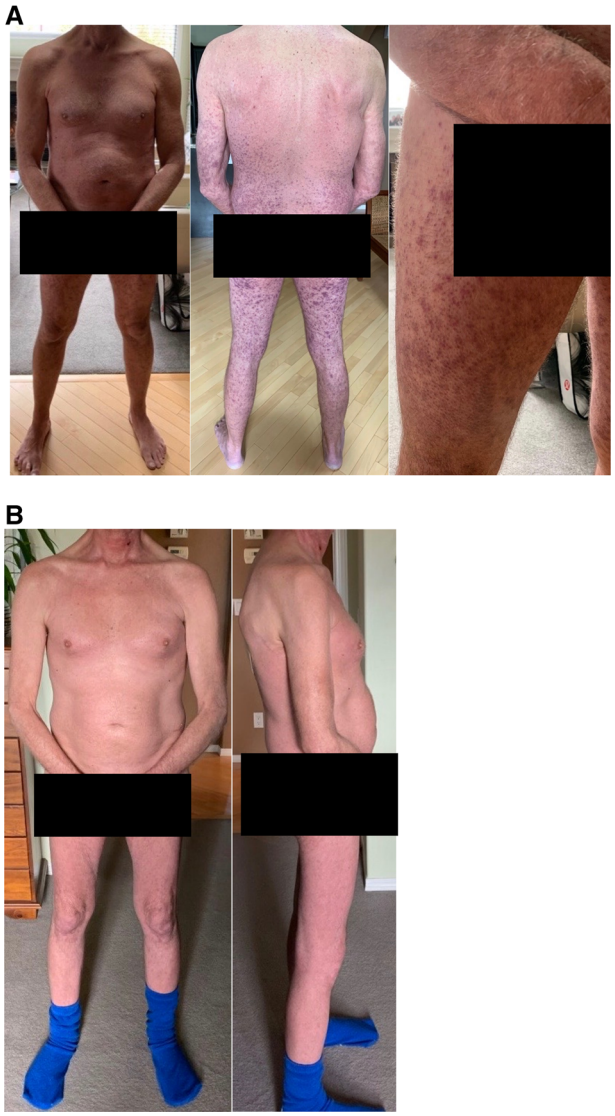

Figure 1. Pictures of patient's rash. **(A)**: Rash prior to hospital admission. **(B)**: Resolution of rash upon discharge from hospital.

oliguric acute kidney injury, worsened anemia and thrombocytopenia, and confusion. His presenting lab work is shown in Table 1. He was initially treated with broad spectrum antimicrobials for presumed septic shock and admitted to the intensive care unit. His skin biopsy showed an interface dermatitis with eosinophils suggestive of a drug reaction, and intraluminal thrombi in keeping with a coagulopathy on deeper sections, with no evidence of a vasculitis (online supplemetal Fig. 1). His bone marrow biopsy was not consistent with hemophagocytic lymphohistiocytosis. As no infection was found, he was started on treatment with intravenous methylprednisolone 1 g daily for 5 days on admission day 2, followed by 50 mg every 8 hours.

After 5 days of treatment, his purpura began to resolve. Additionally, his urine output improved and his creatinine clearance began to recover; however, his encephalopathy worsened, as did his thrombocytopenia and transaminitis, and he developed hypofibrinogenemia. At this point, the favored diagnosis was CRS, and thus IV tocilizumab 4 mg/kg was administered. Within hours of tocilizumab administration, the patient's encephalopathy resolved, and he was given a second dose after 12 hours. Both his transaminitis and thrombocytopenia began to improve within 4 days.

Table 1. Key initial laboratory results on presentation to the emergency department

Lab	Value[a]	Normal range
Hemoglobin	**96 g/L**	137–180 g/L
WBC	5.7×10^9	$4–11 \times 10^9$
Platelets	**80×10^9**	$150–400 \times 10^9$
Creatinine	**375 µmol/L**	50–120 µmol/L
LD	**999 U/L**	100–235 U/L
Haptoglobin	1.53 g/L	0.3–2 g/L
Fibrinogen	3.0 g/L	1.6–4.1 g/L
Total bilirubin	**36 µmol/L**	0–24 µmol/L
ALT	**107 U/L**	1–60 U/L
AST	**228 U/L**	8–40 U/L
Calcium	**1.89 mmol/L**	2.1–2.6 mmol/L
Phosphate	**1.55 mmol/L**	0.8–1.5 mmol/L
Magnesium	**0.62 mmol/L**	0.65–1.05 mmol/L
Urate	420 µmol/L	210–490 µmol/L
Albumin	**29 g/L**	33–48 g/L
INR	**1.9**	0.9–1.1
CRP	**331.4 mg/L**	0–8 mg/L
Ferritin	**15,273 µg/L**	30–500 µg/L
CK	**670 U/L**	0–195 U/L

Additional negative tests: antinuclear antibody, extractable nuclear antigen, anti–double-stranded DNA, antiphospholipid antibodies, antineutrophil cytoplasmic antibody, rheumatoid factor, complement C3, complement C4, serum protein electrophoresis, cryoglobulins, blood, urine cultures, repiratory viral panel, hepatitis B panel, hepatitis C, and cytomegalovirus IgG.
[a]Abnormal values bolded.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; CRP, C-reactive protein; INR, international normalized ratio; LD, lactate dehyndrogenase; WBC, white blood cell count.

His stay was further complicated by atrial fibrillation and an acute aspiration event requiring intubation for 24 hours. His biochemistry continued to improve, and his glucocorticoids were tapered to oral prednisone 40 mg daily, and he was discharged home in stable condition on day 25 with a prednisone taper with resolution of his rash (Fig. 1B). A cytokine profile drawn before tocilizumab infusion (not available at the time of clinical decision making) did confirm that the expected cytokines in CRS (interleukin [IL]-6, IL-10, interferon [IFN]-γ, and tumor necrosis factor [TNF]-α) were elevated (online supplemental Table 1).

Discussion

To our knowledge, this is the third case of a patient with CRS during the transition from immunotherapy to targeted therapy with a BRAFi/MEKi and the second case successfully treated with tocilizumab.

CRS is a systemic cytokine-driven inflammatory response described as a consequence of multiple antibody and non–protein-based cancer therapies [4, 5]. In the era of cancer

Table 2. Comparison of subject patient with other published cases of cytokine release syndrome with MEKi/BRAFi

Characteristic	Subject patient	Case 1	Case 2A	Case 2B
Age (years)	58	47	48	48
Sex	Male	Male	Female	Female
Melanoma stage	IV	IV	IV	IV
Previous Treatment	Interferon, anti–PD-1, MEKi/BRAFi	anti–PD-1	anti–PD-1, T-VEC, anti-LAG3	anti–PD-1, T-VEC, anti–PD-1 again, anti-LAG3, MEKi/BRAFi
MEKi/BRAFi	Cobimetinib/ Vemurafenib	Cobimetinib/ Vemurafenib	Trametinib/ Dabrafenib	Cobimetinib/ Vemurafenib
Time to CRS onset[a]	11 days	21 days	10 days	10 days
Fever	Yes	Yes	Yes	Yes
Hypotension	Yes	Yes	No	No
Cardiac	SVT, atrial fibrillation	Tachycardia, ventricular extrasystoles	Tachycardia	Tachycardia
Dermatologic	Purpura, blisters/bullae, Mucositis	Diffuse maculopapular	Generalized macular rash, erosive mucositis	Blisters/bullae, erosive stomatitis
Renal Insufficiency	Yes	Yes	No	No
Neurologic	Confusion	No	No	No
Gastrointestinal	Nausea, vomiting, diarrhea	No	No	No
Transaminitis	Yes	Yes	No	No
Cytopenias	Anemia, thrombocytopenia	Unknown	Leukopenia	Unknown
↑ inflammatory markers	Ferritin, CRP	CRP	Unknown	Unknown
↑Cytokines	IL-1, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, IFN-γ, TNF-α	IL-6, IFN-γ, TNF-α	IL-6, IFN-γ, TNF-α	IL-6, IFN-γ
Treatment	Systemic CS, TCZ 400 mg × 2 doses	Local and systemic CS	Systemic CS	Systemic CS, TCZ 400 mg
Outcome	Discharged home	Developed tolerance to MEKi/BRAFi	Switched to cobimetinib/vemurafeni, had relapse of CRS (Case 2B)	Dramatic improvement following TCZ

[a]Time to CRS following MEKi/BRAFi treatment.
Abbreviations: BRAFi, BRAF inhibitor; CRP, C-reactive protein; CRS, cytokine release syndrome; CS, corticosteroids; IFN, interferon; IL, interleukin; LAG3, lymphocyte activation gene 3; MEKi, MEK inhibitor; PD-1, programmed cell death protein 1; SVT, supraventricular tachycardia; TNF, tumor necrosis factor; T-VEC, talimogene laherparepvec, TCZ, tocilizumab.

immunotherapy, CRS has recently gained significant attention as a frequently observed and serious adverse effect among immunotherapies, including chimeric antigen receptor (CAR) T-cell therapies used in the treatment of hematologic malignancy [4, 5]. Patients with CRS can present with a wide range of symptoms, varying from mild flu-like symptoms to severe multiorgan failure, multifactorial shock, and disseminated intravascular coagulation [4, 5]. CRS is classically characterized by the release of a variety of cytokines, most notably IL-6, IL-10, IFN-γ, and TNF-α [4, 5].

The pathophysiology of CRS among patients treated with CAR T-cell therapies is thought to be related to activation of bystander immune and nonimmune cells, such as endothelial cells, resulting in a massive release of cytokines [4]. The pathophysiology of CRS among patients with melanoma who are sequentially treated with immunotherapies followed by targeted therapies remains unclear but has been recently hypothesized to be a result of simultaneous exposure to immune-checkpoint and MAPK inhibition due to the long half-life of immune-checkpoint inhibitors, resulting in T-cell activation and release of multiple cytokines including IL-6 [2, 4]. IL-6 causes a positive feedback loop and at high levels initiates a proinflammatory cascade through the *trans*-signaling pathway [4–6]. Notably, our patient as well as both published cases of this were exposed to T-cell stimulating therapies prior to initiation of MEK and BRAF inhibition (Table 2).

There is a paucity of guidance with regard to management of patients such as ours in the long term. From our experience, ongoing management with tocilizumab was not necessary, and we also recommend tapering the glucocorticoids rapidly, given the potential for complications in some nonhematologic malignancies [7]. With respect to further cancer therapies, rechallenging patients with the same agents has been described [2, 4]. We suggest that the decision to rechallenge should be shared between the patient and health team based on risks and benefits of other therapeutic options.

As the use of targeted and immunotherapies becomes more commonplace, clinicians need to be aware of CRS, and tocilizumab should be considered in cases unresponsive to corticosteroids.

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