Received: 16 March 2017 | Revised: 24 April 2017 | Accepted: 24 April 2017

DOI: 10.1002/pbc.26642

BRIEF REPORT

WILEY Pediatric Blood & Cancer

SIOP INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY

aspho The American Society of Pediatric Hematology/Oncology

Severe cytokine release syndrome in a patient receiving PD-1-directed therapy

Seth J. Rotz[1] | **Daniel Leino**[2] | **Sara Szabo**[2] | **Jennifer L. Mangino**[1] | **Brian K. Turpin**[1] | **Joseph G. Pressey**[1]

[1]Cancer and Blood Diseases Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

[2]Department of Pathology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

Correspondence:
Joseph G. Pressey, Cancer and Blood Diseases Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH 45229-3026.
Email: joseph.pressey@cchmc.org

Abstract

Cytokine release syndrome (CRS) is a phenomenon of immune hyperactivation described in the setting of cellular and bispecific T-cell engaging immunotherapy. Checkpoint blockade using anti-programmed cell death 1 (anti-PD-1) inhibitors is an approach to antitumor immune system stimulation. A 29-year-old female with alveolar soft part sarcoma developed severe CRS after treatment with anti-PD-1 therapy. CRS was characterized by high fevers, encephalopathy, hypotension, hypoxia, hepatic dysfunction, and evidence of coagulopathy, and resolved after infusion of the interleukin-6 inhibitor tocilizumab and corticosteroids.

KEYWORDS

cytokine release syndrome, IL-6, nivolumab, PD-1 inhibitor, tocilizumab

1 | INTRODUCTION

Cytokine release syndrome (CRS) is a phenomenon of immune hyperactivation typically described in the setting of chimeric antigen receptor modified T-cell (CAR-T) therapy, bispecific T-cell receptor engaging (BiTE) immunotherapy, and other immunotherapies.[1,2] The severity of CRS ranges from mild, requiring only symptomatic management of fever, myalgias, and malaise (stage 1), to life-threatening symptoms including grade four organ toxicity, potentially requiring ventilator support (stage 4) and even death (stage 5).[2] The immune hyperactivation of CRS is associated with elevated levels of interleukin (IL)-6, interferon-gamma, and other cytokines.[2]

Immune checkpoint blockade using programed cell death 1 (PD-1) inhibitors is an approach to activate the immune system against malignant cells.[3] Severe side effects of PD-1 inhibitors are typically related to autoimmunity and include pneumonitis, hypophysitis, colitis, thyroiditis, adrenal insufficiency, and vitiligo.[4] Fevers, chills, and fatigue have also been reported from PD-1 inhibitors, although severe CRS has not been described in the literature. We describe a young adult female with widely metastatic alveolar soft part sarcoma (ASPS) who developed severe CRS after two doses of the PD-1 inhibitor nivolumab.

Abbreviations: BiTE, bispecific T-cell receptor engaging; CAR-T, chimeric antigen receptor–modified T-cell; CRS, cytokine release syndrome; IL, Interleukin; PD-1, programed cell death- 1; SIRS, systemic inflammatory response syndrome

2 | CASE REPORT

A previously healthy 29-year-old woman originally presented with extremity masses, cough, and headaches. Biopsy revealed ASPS with characteristic t(X;17) ASPS-TFE3. Histology demonstrated peritumoral T-lymphocytic foci and rare intratumoral foci. Of these T-cells, 10–25% demonstrated positive staining for PD-1, although staining for programmed cell death 1 ligand on tumor cells was negative. Imaging identified widely metastatic disease including leg, shoulder, pelvis, chest wall, lungs (innumerable metastases), and brain (>20 metastatic lesions). She was initially treated with the tyrosine kinase inhibitor sunitinib after gamma-knife radiation was delivered to known brain metastasis. After 3 months of therapy, she was found to have progressive disease and treatment was changed to the tyrosine kinase inhibitor pazopanib in combination with the PD-1 targeting antibody nivolumab. The patient tolerated an initial infusion of 3 mg/kg nivolumab without side effects and received palliative radiation to a painful tibial lesion prior to the second infusion of nivolumab 2 weeks later. Prior to the patient's second nivolumab infusion, vital signs, a complete blood count, comprehensive metabolic profile, and coagulation studies were documented to be within normal limits.

Four days after the second infusion of nivolumab, the patient presented with 3 days of severe fatigue, myalgias, fever, diffuse maculopapular rash, and subsequent encephalopathy. On presentation, the patient had a temperature of 41.0 °C, heart rate of 160–170 beats per minute, blood pressure of 83/44 mm Hg, pulse oximetry of 88%, and was disoriented. She received resuscitation with 4 l of normal saline

TABLE 1 Patient abnormal laboratory values on presentation with CRS and subsequent values

Laboratory test	Value at presentation	Subsequent values and notes
Platelet count	127,000/mcl	Nadir of 35,000/mcl on day 8 postinfusion before normalizing
Absolute neutrophil count	3,270/mcl	Nadir of 1,340/ mcl on day 7 postinfusion before normalizing
Sodium	131 mmol/l	Normalized within 12 hr with fluid resuscitation
Creatinine	1.09 mg/dl[b]	Normalized within 12 hr with fluid resuscitation
Blood urea nitrogen	21 mg/dl	Normalized within 12 hr with fluid resuscitation
Lactic acid	3.1 mmol/l	Normalized within 12 hr with fluid resuscitation
Aspartate transaminase	134 units/l	Increased over 4–8 days postinfusion and peaked at 447 units/l before normalizing; note: bilirubin and alkaline phosphatase remained unchanged
INR	1.6[a]	Prolonged from days 4 to 11 postinfusion before normalizing
aPTT	49.2 sec (reference: 22.9–36.0)[a]	Prolonged from days 4 to 11 postinfusion before normalizing
Fibrinogen	194 mg/dl (reference: 200–400 mg/dl)[a]	Nadir of <60 mg/dl on day 8 postinfusion requiring fresh frozen plasma therapy, before ultimately normalizing
Interleukin-1b	16 pg/ml (reference: ≤58 pg/ml)	None
Interleukin-2	3 pg/ml (reference: ≤9 pg/ml)	None
Interleukin-4	8 pg/ml (reference: ≤17 pg/ml)	None
Interleukin-5	2 pg/ml (reference: ≤4 pg/ml)	None
Interleukin-6	45 pg/ml (reference: ≤7 pg/ml)	None
Interleukin-8	125 pg/ml (reference: ≤47 pg/ml)	None
Interleukin-10	128 pg/ml (reference: ≤7 pg/ml)	None
Interferon-γ	660 pg/ml (reference: ≤8 pg/ml)	None
Tumor necrosis factor-α	3 pg/ml (reference: ≤16 pg/ml)	None
GM-CSF	1 pg/ml (reference: ≤11 pg/ml)	None

[a]Obtained +24 hr from admission.
[b]Previously 0.65 mg/dl.
CRS, cytokine release syndrome; INR, international normalized ratio of prothrombin time; aPTT, activated partial thromboplastin time; GM-CSF, granulocyte macrophage colony stimulating factor.

and mentation improved. Due to initially refractory hypotension and tachycardia, she was started on stress-dose hydrocortisone. Blood cultures were obtained and broad-spectrum antibiotics were administered.

Initial laboratory assessment was notable for thrombocytopenia, lactic acidosis, evidence of acute kidney and liver injury, and abnormal coagulation studies (Table 1). Lactic acid and kidney injury improved within 12 hr with fluid resuscitation. A chest X-ray was unchanged and urinalysis and ammonia were normal. C-reactive protein, which has been shown to be a surrogate marker for IL-6 in CRS,[5,6] was also elevated to 4.97 mg/l (reference <0.30 mg/l) (Fig. 1). A cytokine profile was obtained and results eventually demonstrated elevated levels of IL-6, IL-8, IL-10, and interferon-gamma.

Given the patient had no central line, was not considered significantly immunocompromised, had serial negative blood cultures, and had no obvious source of infection, a diagnosis of immune hyperactivation due to nivolumab was considered. In addition to continuing broad-spectrum antibiotics, the patient received high-dose corticosteroids and the IL-6 inhibitor tocilizumab[1,2] Over the initial 48 hr of targeted CRS therapy, fevers improved and C-reactive protein (CRP) declined. A second dose of tocilizumab was given 72 hr after the first, when the patient again became febrile. The patient's diffuse rash improved over the following week and she was discharged from hospital on a corticosteroid taper 11 days nivolumab postinfusion.

At follow-up visit 14 days postinfusion, coagulation studies, complete blood count, and liver function were all normal and patient was asymptomatic. However, 25 days postinfusion patient reported new headaches, double vision, and nausea. An magnetic resonance imaging (MRI) was undertaken and demonstrated no additional lesions, but increased edema surrounding multiple brain metastasis. Additionally at this time, repeat laboratory evaluation demonstrated a platelet count of 98,000/mcl and fibrinogen of 106 mg/dl. Patient was started on dexamethasone and symptoms resolved over 48 hr and laboratory values again normalized. The patient was restarted on and remains on pazopanib monotherapy at this time and is doing well 2 months post-CRS.

3 | DISCUSSION

To our knowledge, this is the first report of severe CRS in a patient treated with a PD-1 inhibitor. CRS has been associated with BiTE and cellular immunotherapy, as well as anti-CD20 antibody therapy.[7] The temporal manifestation of the patient's symptoms was quite similar

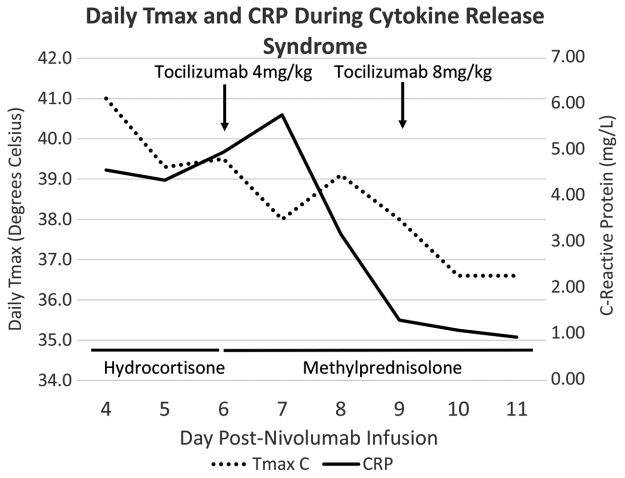

FIGURE 1 **Patient body temperature over time.** On the *x*-axis is time of nivolumab Infusion, on the primary *y*-axis (left) is temperature in degrees Celsius, and on the secondary *y*-axis (right) is C-reactive protein. Arrows indicate initiation of tocilizumab. Horizontal bars represent time frame of ongoing treatment with corticosteroids; hydrocortisone 50 mg/m^2 per day divided every 6 hr, and methylprednisolone 1 mg/kg every 12 hr

to those seen after CAR-T therapy, starting with a systemic inflammatory response syndrome (SIRS) like phase manifested by hypotension and fever, followed by encephalopathy and coagulopathy after the SIRS resolves. Patients with a high tumor burden are at particularly high risk of BiTE and autologous T-cell transfer therapy associated CRS.[8,9] Given the patient's high tumor burden, our patient may have been at a particularly elevated risk of experiencing a dramatic systemic inflammatory response in an analogous manner. Other host factors associated with a higher risk of CRS, including baseline cytokine levels and host cytokine gene polymorphisms, are unknown in our patient but may have contributed.

In addition, a potential risk of severe CRS may be the result of the use of radiotherapy between the first and second nivolumab course. The abscopal effect is an immune-mediated phenomenon of tumor regression at a site distant from radiated lesions[10,11] and has been seen with immune checkpoint inhibitors combined with radiotherapy in melanoma patients.[12] It is possible that radiation contributed to and augmented this patient's systemic immune response. Immune activation as a result of radiation has been shown to be related to the induction of tumor-associated antigens in a context of endogenous adjuvants that facilitates priming of antitumor cytotoxic T lymphocytes, as well as inducing an altered microenvironment that promotes an immune response.[13,14] An additional contribution to our patient's immune response may be related to concurrent pazopanib. Tyrosine kinase inhibitors may alter immune antitumor response in other malignancies by decreasing the number and effectiveness of regulatory T-cells and myeloid-derived stem cells, although the immunologic effects of tyrosine kinase inhibitors are complex and not completely understood.[15–17] Further investigation of combining checkpoint inhibitors with targeted therapy is warranted.

Tocilizumab and corticosteroids appear efficacious in treating the CRS associated with PD-1 inhibitors. The patient's brain MRI postdischarge with increased edema suggests an ongoing immune response, but lack of long-term follow-up and subsequent discontinuation of anti-PD-1 therapy makes drawing conclusions about efficacy difficult.[18] Whether treatment with tocilizumab and corticosteroids abrogate an antitumor immune response with PD-1 inhibition is an area in need of further investigation.

As the use of PD-1 inhibitors increase, clinicians will need to be aware of this potentially fatal complication. This case also highlights the efficacy of tocilizumab in combination with systemic steroids as effective management for CRS, and therapy with these agents should be considered in future patients with CRS secondary to PD-1 inhibitors.

CONFLICT OF INTEREST

The authors declare that there is conflict of interest.

REFERENCES

1. Teachey DT, Rheingold SR, Maude SL, et al. Cytokine release syndrome after blinatumomab treatment related to abnormal macrophage activation and ameliorated with cytokine-directed therapy. *Blood*. 2013;121:5154–5157.
2. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014;124:188–95.
3. Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med*. 2013;369:122–133.
4. Weber JS, Yang JC, Atkins MB, et al. Toxicities of immunotherapy for the practitioner. *J Clin Oncol*. 2015;33:2092–2099.
5. Davila ML, Riviere I, Wang X, et al. Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. *Sci Transl Med*. 2014;6:224ra25.
6. Teachey DT, Lacey SF, Shaw PA, et al. Identification of predictive biomarkers for cytokine release syndrome after chimeric antigen receptor T cell therapy for acute lymphoblastic leukemia. *Cancer Discov*. 2016;6:664–679.
7. Winkler U, Jensen M, Manzke O, et al. Cytokine-release syndrome in patients with B-cell chronic lymphocytic leukemia and high lymphocyte counts after treatment with an anti-CD20 monoclonal antibody (rituximab, IDEC-C2B8). *Blood*. 1999;94:2217–2224.
8. Brentjens RJ, Davila ML, Riviere I, et al. CD19-targeted T cells rapidly induce molecular remissions in adults with chemotherapy-refractory acute lymphoblastic leukemia. *Sci Transl Med*. 2013;5:177ra38.
9. Xu X-J, Tang Y-M. Cytokine release syndrome in cancer immunotherapy with chimeric antigen receptor engineered T cells. *Cancer Lett*. 2014;343:172–178.
10. Mole R. Whole body irradiation—radiobiology or medicine? *Br J Radiol*. 1953;26:234–241.
11. Demaria S, Ng B, Devitt ML, et al. Ionizing radiation inhibition of distant untreated tumors (abscopal effect) is immune mediated. *Int J Radiat Oncol Biol Phys*. 2004;58:862–870.
12. Postow MA, Callahan MK, Barker CA, et al. Immunologic correlates of the abscopal effect in a patient with melanoma. *N Engl J Med*. 2012;366:925–931.
13. Golden EB, Pellicciotta I, Demaria S, et al. The convergence of radiation and immunogenic cell death signaling pathways. *Front Oncol*. 2012;2:88.

14. Shiao SL, Coussens LM. The tumor-immune microenvironment and response to radiation therapy. *J Mammary Gland Biol Neoplasia*. 2010;15:411–421.
15. Porta C, Paglino C, Imarisio I, et al. Immunological effects of multikinase inhibitors for kidney cancer: A clue for integration with cellular therapies. *J Cancer*. 2011;2:333–338.
16. Ko JS, Rayman P, Ireland J, et al. Direct and differential suppression of myeloid-derived suppressor cell subsets by sunitinib is compartmentally constrained. *Cancer Res*. 2010;70:3526–3536.
17. Massari F, Santoni M, Ciccarese C, et al. PD-1 blockade therapy in renal cell carcinoma: Current studies and future promises. *Cancer Treat Rev*. 2015;41:114–121.
18. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: Immune-related response criteria. *Clin Cancer Res*. 2009;15:7412–7420.

How to cite this article: Rotz SJ, Leino D, Szabo S, Mangino JL, Turpin BK, Pressey JG. Severe cytokine release syndrome in a patient receiving PD-1-directed therapy. *Pediatr Blood Cancer*. 2017;00:e26642. https://doi.org/10.1002/pbc.26642