

Case Report

Stage 4 Cytokine Release Syndrome Caused by the First Dose of Nivolumab and Ipilimumab Combination Therapy in a Patient with Metastatic Melanoma Successfully Treated with Methylprednisolone, Tocilizumab, and Etanercept

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Keywords

Cytokine release syndrome · Etanercept · Metastatic melanoma · Nivolumab · Ipilimumab

Abstract

The authors report the first case of stage 4 cytokine release syndrome (CRS) (graded by the National Cancer Institute Common Terminology Criteria for Adverse Effects scale) involving a patient with advanced metastatic melanoma who was treated with the combination of two monoclonal antibodies, nivolumab (anti-programmed cell death receptor 1 inhibitor [PD-1]) and ipilimumab (a cytotoxic T lymphocyte-associated antigen 4 inhibitor [CTLA-4]) after her first dose of both. The patient was treated initially with methylprednisolone and tocilizumab but was refractory to treatment. A trial of etanercept was initiated due to her elevated levels of TNF- α which elicited a satisfactory response. Monoclonal antibody therapy is a new tool for the treatment of many cancers, and therefore there may be a subsequent rise in the cases of CRS and this case exemplifies a treatment algorithm. Utilizing levels of cytokines assists in tailoring treatment such as in this case where etanercept, a TNF- α inhibitor, was utilized due to the patient's elevated levels of TNF- α .

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Introduction

Nivolumab is an IgG4 antibody that binds PD1, preventing PD-L1 and L2 from inhibiting the action of T-cells, which in turn restores the patient's T-cell response [1]. Ipilimumab is a human IgG1 that binds to CTLA-4 which prevents the inhibition of the T cell signal pathway [2]. Both anti-CTLA-4 and anti-PD-1 antibodies function by modifying the interaction between T lymphocytes, antigen-present cells, and the tumor [3]. Immune checkpoint inhibitors such as nivolumab and ipilimumab are becoming more widely utilized in the current oncological practice as clinical studies have shown a major benefit in survival. Their addition to the regimen of oncologists has been revolutionary; however, they are not without side effects [4, 5]. The combination of nivolumab and ipilimumab has been shown to be more effective compared to either alone; however, there is an increase in immune-related adverse events (ir-AEs) with combination therapy [6]. One of the most serious of these immune-related adverse events is cytokine release syndrome (CRS).

CRS is defined as an acute potentially life-threatening supraphysiologic systemic inflammatory response to immunotherapy characterized by high-grade fever and multiple organ dysfunction [7]. It is associated with increased levels of inflammatory cytokines and the activation of T lymphocytes, macrophages, and endothelial cells usually after the administration of chimeric antigen therapy (CAR-T) [8]. Rarely, CRS may be associated with immunotherapy such as nivolumab and ipilimumab [3, 9]. CRS can occur immediately, minutes, hours, days, or weeks after the administration of therapy [10]. The authors detail the first reported case of stage 4 CRS after the usage of combination therapy of nivolumab and ipilimumab and subsequent treatment with dexamethasone, tocilizumab, and etanercept.

Case Report/Case Presentation

A 58-year-old female with a newly diagnosed American Joint Committee on Cancer (AJCC) stage IV metastatic melanoma with spread to the lungs was started on combination therapy of 1 mg/kg nivolumab and 3 mg/kg ipilimumab every 3 weeks for four doses. She received both of her first doses 6 days before she arrived at the emergency room. She presented severely altered, hypotensive to 66/41 mm Hg, tachycardic, febrile to 40.1 C, and hypoxic on room air at 84%. She was placed on bilevel positive airway pressure (BiPAP) and in the intensive care unit. On physical examination, significant findings include peripheral edema +3 in the lower extremities extending up to the hips. She did not have any significant past medical history other than the newly diagnosed metastatic melanoma as she had never previously been to a physician.

Laboratory results showed elevated serum creatinine of 2.8 mg/dL with her baseline of 0.7 mg/dL, alanine transaminase and aspartate transaminase were elevated to 180 Units/L and 165 Units/L, respectively, lactate was elevated to 10.9 mmol/L, CRP was elevated to 20.2 mg/L, and mild leukocytosis to 13.7 k/cumm. Chest X-ray showed pulmonary edema. She was suspected to have septic shock as she met systemic inflammatory response syndrome criteria and was started on broad-spectrum antibiotics with piperacillin-tazobactam and vancomycin. She initially required norepinephrine, then epinephrine and vasopressin were added to the regimen. She continued to receive BiPAP and fluids. She did not improve within 24 h and, therefore, was started on 1 mg/kg of methylprednisolone as there was concern her symptomatology was immune-mediated. Her oxygenation saturation was not able to be maintained on BiPAP and she was intubated.

Due to no improvement after 2 days of methylprednisolone, she was started on tocilizumab due to the suspicion of CRS. Before starting tocilizumab, oncology was consulted, and interleukin-6

(IL-6) levels were measured as were tumor necrosis factor-alpha (TNF- α) levels which came back as 21.4 pg/dL (0–16.4 pg/mL) and 1,876 pg/dL (0–29.4 pg/mL), respectively. Due to there not being set guidelines for CRS after the utilization of monoclonal antibodies, tocilizumab was chosen as it has been found to be effective in patients treated with chimeric antigen receptor (CAR) therapy-induced CRS. There have been case reports of tocilizumab working in patients with CRS caused by nivolumab, and consent was obtained from the family. Even after 4 doses of tocilizumab 8 mg/kg with methylprednisolone 1 mg/kg concurrently, her symptoms did not improve. Based on literature, a trial of etanercept was done given its action on the blockade of TNF- α . After the administration of etanercept, her symptoms improved and she was extubated after 3 days with an overall improvement in her laboratory results, mental status, and fever. She was discharged from the hospital in stable condition with close follow-up with both her primary care provider and her oncologist.

Discussion/Conclusion

CRS is an acute systemic inflammatory response that is characterized by fever with or without multiple organ dysfunction, hypoxia, and hypotension triggered by CAR-T cell therapy, other forms of immunotherapy, or haploidentical hematopoietic cell transplantation (HCT) [11]. The term “cytokine release syndrome” was first brought to light in the early 1990s, when the anti-T-cell antibody muromonab-CD3 was introduced as an immunosuppressive treatment for solid organ transplants [12]. CRS has been described after utilizing immunotherapy such as pembrolizumab, alemtuzumab, dacetuzumab, rituximab, as well as nivolumab which was utilized in our case. With the ever-growing utilization of T cell immunotherapies such as in solid tumors, leukemia, and lymphomas, there have been more cases of CRS and clinicians should be aware of the situation as it is one of the most serious adverse effects of therapy.

CRS is a supraphysiological response to immunotherapy that is triggered by the release of interferon-gamma (INF- γ) by activated T cells. The INF-g will in turn activate macrophages and this causes an uprise in the amount of IL-6, TNF- α , and IL-10 [6]. IL-1, IL-5, IL-8, IL-10, and macrophage colony-stimulating factors are also elevated in CRS which may contribute to the pathophysiology as well. A release of massive amounts of cytokines can possibly cause fever, chills, watery diarrhea, activation of the coagulation cascade, vascular leakage, lung injury, cardiomyopathy, and activation of acute-phase proteins [13]. IL-6 is very important in the pathophysiology of CRS. The treatment of CRS with tocilizumab is currently the treatment option of choice for CAR-T-induced CRS due to its ability to interrupt the signaling between IL-6 and IL-6R [14].

The evaluation of a patient with CRS should be prompt and suspicion should be high in patients who develop sudden onset sepsis-like symptoms after the initiation of immunotherapy. It is important that infection be ruled out as most patients will be immunosuppressed and therefore be at high risk for sepsis or neutropenic fever. The initial evaluation should include routine blood cultures, and empiric antibiotic therapy is often started in cases of CRS before the infection is ruled out by microbiological testing. Laboratory studies are not necessary to establish a diagnosis of CRS as it is a clinical diagnosis. However, CRP, ferritin, and/or cytokine levels such as IL-6 may provide supportive data that may be useful to monitor the course of CRS [15]. CRS should be diagnosed in a patient based on a fever greater than 38.0 C, with or without the presence of either hypotension, hypoxia, and/or endo-organ dysfunction that occurs hours to days after the treatment of immunotherapy [16].

The grading of CRS is based on the American Society for Transplant and Cellular Therapy (ASTCT) and is divided into 4 grades (Table 1). Fever must not be attributable to any cause, and if the fever has already been corrected then hypoxia or hypotension is the driving factor

Table 1. ASTCT consensus grading for CRS

Clinical parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	≥38 C	≥38 C	≥38 C	≥38 C
Hypotension	None	No Vasopressors utilized	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
Hypoxia	None	Low flow nasal cannula or blow by	High-flow nasal cannula, non-rebreather, facemask, Venturi mask	CPAP, BiPAP, mechanical ventilation

For stages 2+ patients must have a fever ≥38 C plus hypotension and/or hypoxia.
Patients may have other constitutional symptoms, but they do not affect the grade of CRS.
CPAP, continuous positive airway pressure; BiPAP, bilevel positive airway pressure.

for diagnosis. The grade of CRS is determined by the more severe event of either hypotension or hypoxia. Hypotension is graded on the quantity of different vasopressors excluding vasopressin. Hypoxia is defined by the correction of an oxygen deficit. When the patient requires intubation, it is considered grade 4 only if intubation is done for hypoxia and not for other uses such as protecting the patient's airway [17]. In our patient, she was graded as having CRS stage 4 given that she required 2 vasopressors and was intubated due to her worsening oxygen saturation.

The management of CRS depends on the cause and the severity. Milder cases of CRS require only symptomatic management of specific symptoms such as utilizing intravenous fluids, antihistamines, antipyretics if needed, and close monitoring. More severe cases of CRS require management in the intensive care unit as most require management of hypotension with fluids or vasopressors and oxygenation through supplemental oxygen or mechanical ventilation. The administration of glucocorticoids has been shown to be beneficial with either dexamethasone 10 mg 4 times daily, hydrocortisone 100 mg every 8 h, or methylprednisolone 1 mg/kg/day until improvement occurs [18]. Tocilizumab has been shown to be effective in CAR therapy-induced CRS due to IL-6 blockade by the drug. Tocilizumab should not be administered for more than 4 doses. In our case, we utilized both methylprednisolone and tocilizumab to no avail, and therefore etanercept was chosen given its effect on the blockade of TNF-α which was effective in downgrading the cytokine release with an overall improvement of symptoms in our patient.

This is the first reported case of metastatic melanoma treated with nivolumab and ipilimumab causing a stage 4 CRS. This case brings to light that as the utilization of monoclonal antibodies grows there is also a subsequent rise in the risk of CRS, and therefore clinicians should not only be aware of the stages of CRS but also of the possible treatment options. There are currently no treatment guidelines for the management of CRS due to monoclonal antibodies as currently guidelines are only established for CRS associated with CAR-T. There may be a need for the utilization of steroids and tocilizumab given their mechanism of action; however, in refractory cases such as this case, the possibility of utilizing other agents for the blunting of the cytokine response should be taken under consideration. It may be beneficial to measure cytokine levels in refractory cases to get a grasp on the severity and then tailor management to blunt that response. In the case presented, the authors utilized etanercept due to high levels of TNF-α present. Other possible agents to utilize include anakinra which blocks the receptor to IL-6, siltuximab which is another IL-6 agent, and ruxolitinib and baricitinib which both interfere with cytokine signaling via the Janus kinase pathway [15, 19]. There may be other agents which help treat CRS, and as the use of immunotherapy grows more studies should be done on effective management.

The onset of CRS can occur at the first dose of immunotherapy such as in our case or after cycles of therapy [20]. A low threshold for the diagnosis of CRS must be realized by clinicians,

especially if there is a history of immunotherapy administration or haploidentical hematopoietic cell transplantation. The patients must also be aware that in situations where symptoms related to CRS occur they must be evaluated as soon as possible. There may be cases of CRS that are undiagnosed or misdiagnosed as sepsis given the lack of awareness, and therefore physician education is important. There may be a benefit of measuring IL-6, TNF- α , and other cytokines in cases of CRS as this may help in the management to guide the use of immunosuppressive agents. This case reveals that cytokine levels may be important in treating CRS as treatment can be tailored to a specific agent targeting the elevated cytokine. Given that this case is only one example of treatment with etanercept working in severe CRS with an elevated TNF- α , other cases may or may not respond in a similar way. In the next few years as the usage of immunotherapy grows, we hope that more effective ways of management of side effects such as CRS are brought to the market. The authors conclude that there should be more research on the treatment of CRS, and guidelines should be developed for effective management of monoclonal antibody induced CRS.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Sasmith R. Menakuru saw the case, wrote the case, and did research on the topic. Quirat Azeem, Adelina Priscu, Ibrahim Khan, and Amir Beirat helped with research and editing the case.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author, Sasmith R. Menakuru.

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