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Pembrolizumab-induced cytokine release syndrome in a patient with metastatic lung adenocarcinoma: a case report

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ABSTRACT

Cytokine release syndrome (CRS) is a well-described immune-related adverse event following chimeric antigen receptor T-cell therapy, but has rarely been reported following anti-programmed death ligand-1 therapy. We report the case of a 55-year-old man with metastatic lung adenocarcinoma who presented with fever, chills and hypotension. Initial labs were notable for highly elevated serum ferritin levels and mildly elevated triglyceride levels. He was ultimately diagnosed with pembrolizumab-induced CRS complicated by multiorgan failure. The patient was treated with steroids and tocilizumab with normalization of inflammatory markers and resolution of renal failure. This case not only highlights the importance of considering CRS in patients who have developed multiorgan failure after immune checkpoint inhibitor therapy, but also demonstrates clinical similarities between CRS and other hyperinflammatory states such as hemophagocytic lymphohistiocytosis.

INTRODUCTION

Immune checkpoint inhibitor (ICI) therapy has revolutionized the treatment of non-small cell lung cancer (NSCLC), resulting in improved overall survival in both the first-line and second-line settings in advanced stage disease.[1] While efficacious, such treatments are associated with a variety of immune-related adverse events (IRAEs). In patients receiving chimeric antigen receptor (CAR) T-cell therapy, cytokine release syndrome (CRS) and hemophagocytic lymphohistiocytosis (HLH) are well-described treatment-related complications.[2 3] In rare instances, pembrolizumab, a programmed death ligand-1 (PD-L1) inhibitor, has also been reported to cause CRS and HLH in patients with advanced NSCLC.[4 5] While CRS and HLH are distinct clinical entities, it can be challenging to differentiate the two as ICI therapy-induced HLH has also been recently described in the literature.[6] In this report, we present a challenging case of pembrolizumab-induced CRS successfully treated with steroids and tocilizumab.

CASE PRESENTATION

A never-smoker 55-year-old man with a history of hyperlipidemia presented with hemoptysis accompanied by right shoulder pain and numbness. CT revealed a 5.6 cm right upper lobe spiculated mass with satellite nodularity concerning for lymphangitic spread. Positron emission tomography showed multifocal involvement of the right lung, mediastinal lymphadenopathy and widespread osseous metastases. MRI of the brain demonstrated multiple intracranial metastases. He underwent bronchoscopy and was diagnosed with metastatic lung adenocarcinoma. Tumor PD-L1 expression was >50% by immunohistochemistry. Molecular testing demonstrated an *EGFR* exon 20 mutation (H773_V774insAH), *PMS2* K413E, *KMT2A* Q1033P, *MET* K1262R, *MET* E719D and mutations in *TP53*. He received two cycles of pembrolizumab, pemetrexed and carboplatin. He was premedicated with intravenous dexamethasone 12 mg on day 1 of cycles 1 and 2. For cycle 3, he received pembrolizumab without chemotherapy to allow for stereotactic radiosurgery (SRS) for brain lesions. The patient's cough and shoulder pain improved with treatment. Restaging MRI of the brain and CT of the chest/abdomen/pelvis after cycle 3 demonstrated reduction in size of the brain and lung lesions. Following the brain SRS, he completed a 20-day dexamethasone taper.

Approximately 19 days after cycle 3, he presented to the emergency department with fever and chills. On admission, vital signs were notable for fever 102.0°F, blood pressure 64/44 mm Hg, heart rate 87 beats per minute and respiratory rate 35 breaths per minute with an oxygen saturation of 92% on room air. Physical examination was notable for lethargy and increased work of breathing. Initial labs demonstrated highly elevated inflammatory markers (ferritin, erythrocyte

Table 1 Laboratory values on admission, after the first dose of tocilizumab and at the time of hospital discharge

Laboratory tests					
Inflammatory markers	**Reference values**	**On admission**	**Tocilizumab dose #1 (day 9)**	**Tocilizumab dose #2 (day 16)**	**On hospital discharge (day 27)**
Ferritin (ng/mL)	28–365	>40,000	20,254	10,562	4565
LDH (U/L)	87–241	3465	1515	1079	750
ESR (mm/h)	0–16	85	30	2	NA
CRP (mg/L)	0–3	281	38.1	<2.90	<4.00
sIL-2R (U/mL)	≤1033	23,020	NA	NA	7236
IL-6 (pg/mL)	≤5	75	NA	NA	NA
Liver function tests					
AST (U/L)	3–34	536	119	120	75
ALT (U/L)	15–41	384	151	132	141
ALP (IU/L)	45–117	819	801	627	613
Blood count					
WBC (x10∧9/L)	4000–10,800	2200	9600	12,800	5300
ANC (x10∧9/L)	>1500	658	7000	11,100	3063
ALC (x10∧9/L)	600–4900	579	600	700	1000
Hemoglobin (g/L)	125-165	114	69	70	82
Platelet count (x10∧9/L)	145–400	191	254	113	119
Basic metabolic panel					
Creatinine (mg/dL)	0.66–1.50	1.9	8.4	3.4	1.1

ALC, absolute lymphocyte count; ALP, alkaline phosphatase; ALT, alanine serum aminotransferase; ANC, absolute neutrophil count; AST, aspartate serum aminotransferase; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; sIL-2R, soluble IL-2 receptor; WBC, white blood cell.

sedimentation rate and C reactive protein) as well as elevated lactate dehydrogenase (LDH), serum aminotransferases, acute kidney injury, absolute lymphocytopenia with normal hemoglobin and platelet count, and moderate neutropenia with an absolute neutrophil count of 658 cells/µL (table 1). X-ray of the chest demonstrated known right apical mass without new consolidation. He was admitted to the intensive care unit for vasopressor support, and received intravenous fluid resuscitation and empiric broad-spectrum antibiotics for possible bacterial infection.

The differential diagnoses included COVID-19 infection, tuberculosis, bacterial pneumonia, viral hepatitis, adrenal insufficiency and IRAEs, such as CRS and HLH. The patient tested negative for COVID-19 infection on four separate occasions during the hospitalization. Extensive tests for infectious disease including IFN-gamma release assay (T-SPOT), hepatitis A virus IgM and IgG serologies, hepatitis B surface antigen, hepatitis B surface antibody, Epstein-Barr virus IgM and IgG serologies, Bordatella pertussis antigen, HIV, aspergillus antigen, urine histoplasma, and urine/sputum/blood cultures on multiple occasions were unrevealing. A respiratory viral panel was negative for influenza A/B, parainfluenza 1/2/3/4, adenovirus, coronavirus (not COVID-19), rhinovirus/enterovirus, herpes simplex virus (HSV)-1, HSV-2, human metapneumovirus, mycoplasma pneumoniae and respiratory syncytial virus. Serum cytomegalovirus PCR was 2902 IU/mL, which was felt to represent viral shedding in the setting of acute illness rather than active infection. A morning cortisol level was normal at 19.6 µg/dL. Soluble IL-2R (sIL-2R) and interleukin 6 (IL-6) were found to be significantly elevated (table 1). A bone marrow biopsy could not be obtained due to his critical condition. In light of the negative laboratory workup for infectious disease and other etiologies including adrenal insufficiency, the patient was diagnosed with pembrolizumab-induced CRS and treated with intravenous methylprednisolone 1000 mg once a day for 5 days, followed by methylprednisolone 2 mg/kg daily. Shortly after initiation of steroid treatment, the patient defervesced and was successfully weaned from vasopressors. The patient's serum inflammatory markers also demonstrated marked improvement (figure 1). Since the patient previously lived in Cambodia, he was empirically treated for possible chronic strongyloidiasis with a 2-day course of ivermectin. He developed anuric acute kidney injury and started hemodialysis on day 6, which he received till

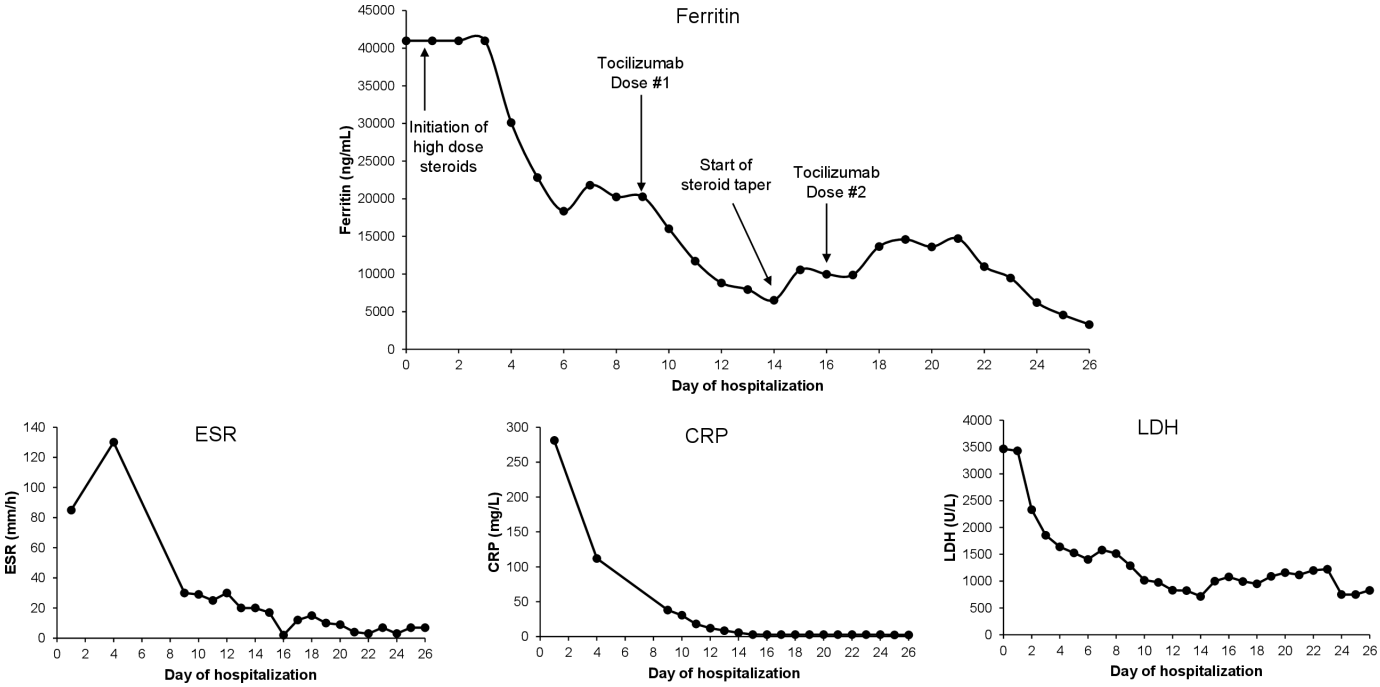

Figure 1 The downward trend of various inflammatory markers including ferritin, erythrocyte sedimentation rate (ESR), C reactive protein (CRP) and lactate dehydrogenase (LDH) during the hospitalization. The graph of serum ferritin over time includes arrows denoting time points for the initiation of steroids, the beginning of the steroid taper and the two doses of tocilizumab administered.

day 14. The patient developed rapidly worsening encephalopathy with somnolence and inability to speak on day 9 and serum ferritin had plateaued around 20,000 ng/mL (figure 1). An electroencephalogram showed findings consistent with non-specific global encephalopathy and did not reveal any evidence of clinical or subclinical seizures. CT of the brain showed unchanged metastatic disease. In light of the patient's clinical deterioration, he was treated with intravenous tocilizumab 8 mg/kg on day 9 with increase in methylprednisolone to 1000 mg once a day for 5 days. Tocilizumab was given again on day 16 of admission given ongoing encephalopathy and uptrending of inflammatory markers (ferritin, LDH). With high-dose steroids and tocilizumab, the patient's serum ferritin as well as his encephalopathy and anuric renal failure improved. With improvement in symptoms and organ function and normal vital signs, he transitioned to oral dexamethasone, which was tapered off over 4 weeks. The patient was successfully discharged from the hospital 27 days after admission.

DISCUSSION

CRS classically presents with fever and, in severe cases, hypotension and multiorgan failure after receiving cancer immunotherapy. Recently, CRS has been described in the literature in patients with metastatic NSCLC treated with pembrolizumab.[4 5] Our patient presented with high fever, hypotension and multiorgan failure, but also had markedly elevated ferritin and sIL-2R levels, raising concern for HLH. He had absolute lymphocytopenia, but no evidence of thrombocytopenia, anemia or organomegaly. He did not meet the HLH 2004 diagnostic criteria and his HScore was 145, denoting a 16%–25% probability of HLH.[7 8] Taken together, his clinical presentation was most consistent with pembrolizumab-induced CRS rather than HLH, although the latter could not be definitively excluded in the absence of a bone marrow biopsy. The elevated ferritin was felt to correlate with the severity of CRS and normalized following treatment of the inflammatory syndrome.

Our patient initially received chemoimmunotherapy but was treated with pembrolizumab alone during cycle 3, as he received brain SRS. He was premedicated with dexamethasone during cycles 1 and 2 and completed a dexamethasone taper following brain SRS. Interestingly, the patient developed CRS at the completion of a prolonged dexamethasone taper whereas most cases of CAR T-cell therapy-related CRS develop within 2–3 days of treatment.[2] We hypothesize that the use of dexamethasone may have contributed to the delayed onset of the CRS in our patient. Also, it is possible that ICI-related CRS may have distinct onset and manifestations compared with CAR T-cell therapy-related CRS.

Management of CRS includes treatment with high-dose steroids with the addition of tocilizumab, an IL-6 inhibitor, for severe cases.[9] Three cases of pembrolizumab-related CRS have been reported in the literature, all of which improved following administration of intravenous methylprednisolone.[4 5 10] Our case was clinically similar to other reported cases of pembrolizumab-induced CRS,

but steroids alone were not sufficient to improve the patient's condition. To our knowledge, this is the first case of pembrolizumab-induced CRS successfully treated with steroids and tocilizumab. Whereas, most cases of severe CAR T-cell therapy-induced CRS usually improve within several days of initiation of immunosuppressive agents such as tocilizumab and high-dose corticosteroids, our patient required a prolonged course of steroids and multiple doses of tocilizumab due to persistent multi-organ failure and neurologic toxicity. The natural history, manifestations and management of ICI-related CRS need to be better understood with future studies. Lastly, we cannot exclude the possibility of CRS related to neo-antigen release following radiation, which has recently been described in the literature.[11]

CONCLUSION

CRS and HLH are distinct hyperinflammatory states with often similar clinical presentations. Our case highlights that an elevated ferritin >10,000 ng/mL may be insufficient to differentiate these conditions. Prompt recognition of CRS is critical as administration of steroids and tocilizumab can reverse multiorgan failure if administered early.

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