Received: 8 September 2020 | Revised: 28 October 2020 | Accepted: 29 October 2020

DOI: 10.1002/cia2.12148

CORRESPONDENCE

Journal of Cutaneous Immunology and Allergy

WILEY

Tumor lysis syndrome and collateral immune activation in dual checkpoint blockade

Immune checkpoint inhibitors (ICIs) that target programmed cell death 1 or cytotoxic T lymphocyte-associated protein-4 brought about a revolution in the field of malignant melanoma (MM) treatment. Notably, compared with single regimens, the combination regimen confers higher risk of immune related adverse events (irAEs),[1] as well as better treatment efficacy.[2] Accordingly, dual checkpoint blockade efficiently increments immunological memory and could cause acute tumor lysis. Tumor lysis syndrome (TLS) is an oncologic emergency, which is caused by a sudden rapid death of cancer cells that form bulky tumors in solid organs, such as the liver.[3,4] Herein, we reported a case of TLS in a patient with metastatic MM treated with the dual checkpoint blockade.

A 69-year-old man was diagnosed as MM of the left choroid, pT3aN0M0, Stage IIb, for which ophthalmectomy was performed (Figure 1A and Table S1). One year after the initial diagnosis, regular computed tomography revealed multiple tumors in the liver (Figure 1B), and the serum level of lactate dehydrogenase (LDH) was elevated (Table S1). After three weeks from the first dose of nivolumab (NIVO, 80 mg)/ ipilimumab (IPI, 3 mg/kg), the serum LDH decreased to 822 IU/L, indicating partial tumor eradication. However, three weeks after the third dose, he developed progressive jaundice, epigastric pain, and diarrhea. The blood test revealed typical TLS features: hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and renal failure (Table S1).[5] Serum levels of alanine aminotransferase, aspartate transaminase, alkaline phosphatase, and total bilirubin were elevated (Table S1). TLS was successfully managed with supportive care, including rasburicase administration and hemodialysis.[5] Later on, despite the treatment with corticosteroids, he developed thyroid dysfunction and thrombocytopenia (Table S1), which could be interpreted as a sequence of immune related adverse events (irAEs). Thereafter, the tumor burden appeared to have decreased, based on the serum LDH level of 193 IU/L (Figure 1C). However, persistent liver inflammation, which could also be the consequence of persistent off-target effects of ICIs, eventually resulted in decompensated liver cirrhosis (Figure 1C), and he died three months after the onset of TLS.

Bulky cancer mass and lytic potential are important risk factors for severe TLS,[5] and most reported cases of TLS in patients with MM comprised large metastatic tumors in the liver.[3,4] Theoretically, ICIs evoke pre-existing cytotoxic T lymphocyte memory cells and achieve durable antitumor immune responses.[2] In the present case, TLS became clinically apparent 3 months after the first dose of NIVO/ IPI. However, the off-target effects of ICIs likely hampered the recovery and led to the dismal outcome. Although the high therapeutic potential makes the combination of NIVO/IPI a reliable treatment option for advanced MM cases,[2] clinical oncologists need to be aware of the triple-edged sword aspect of dual checkpoint blockade in high-risk cases.[5]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DECLARATION SECTION

Approval of the research protocol: Yes

Informed Consent: The written informed consent was obtained from the subject and guardian.

Registry and the Registration No. of the study/trial: NA

Animal Studies: NA

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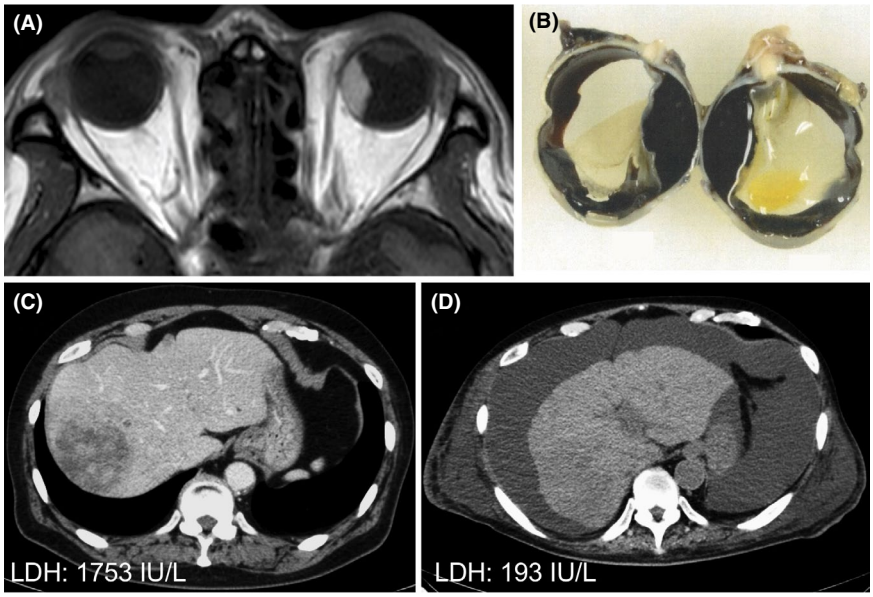

FIGURE 1 A, Magnetic resonance imaging on T1W1 shows a 16 × 12 × 17-mm tumor attached to the choroid of the left eyeball. B, Gross pathological finding of the extirpated left eyeball. C, Before treatment with dual checkpoint blockade, computed tomography (CT) reveals multiple low-density areas in the liver, with the largest measuring 52 × 63 mm and located in the S6. D, Two months after the onset of tumor lysis syndrome (TLS), CT shows a blurred tumor shadow. Note the large amount of ascites surrounding a shrunken liver and decreased serum lactic acid dehydrogenase level

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REFERENCES

1. Almutairi A, McBride A, Sundararajan S, Abraham I. Immune related adverse events (irAE) of mono-, combination, and sequential therapy regimens of ipilimumab (IPI), nivolumab (NIV), and pembrolizumab (PEM) for advanced melanoma. American Society of. Clin Oncol (R Coll Radiol). 2019;37(15_suppl):e21011.
2. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob J, Rutkowski P, Lao C, et al. 5-year survival outcomes of the CheckMate 067 phase III trial of nivolumab plus ipilimumab (NIVO+ IPI) combination therapy in advanced melanoma. Ann Oncol. 2019;30:v904–v905.
3. Nakamura Y, Nakamura Y, Hori E, Furuta J, Ishii Y, Takahashi T, et al. Tumor lysis syndrome after transcatheter arterial infusion of cisplatin and embolization therapy for liver metastases of melanoma. Int J Dermatol. 2009;48(7):763–7.
4. Masson Regnault M, Ofaiche J, Boulinguez S, Tournier E, Rochaix P, Paul C, et al. Tumour lysis syndrome: an unexpected adverse event associated with ipilimumab. J Eur Acad Dermatol Venereol. 2017;31(2):e73–e74.
5. Elinoff JM, Salit RB, Ackerman HC. The tumor lysis syndrome. N Engl J Med. 2011;365(6):571–573. author reply 3–4.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Konishi R, Ishitsuka Y, Imai H, et al. Tumor lysis syndrome and collateral immune activation in dual checkpoint blockade. *J Cutan Immunol Allerg*. 2021;4:39–40. https://doi.org/10.1002/cia2.12148