Case report

Nivolumab-induced myocardial necrosis in a patient with lung cancer: A case report

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ABSTRACT

A 74-year-old man with lung adenocarcinoma recurrence was admitted to our hospital because of dyspnea 7 days after receiving initial immunotherapy with nivolumab. Electrocardiography revealed ST-segment elevation in V1-6 and echocardiography showed a markedly reduced left ventricular ejection fraction of 9% and akinesis of the anteroseptal wall and apex. He died from acute heart failure 3 days after admission. Microscopically, multiple small foci of myocardial necrosis with few inflammatory cells were scattered in both ventricles. Obstruction of the coronary artery was not identified. We believed that the cause of death was acute heart failure possibly due to nivolumab-induced myocardial necrosis.

1. Case report

A 74-year-old man underwent lobectomy and lymph node dissection for a primary lung adenocarcinoma (pT1aN3M0, Stage III B). Computed tomography revealed mediastinal lymph node recurrence 2 months after surgery, and he was treated with 4 cycles of systemic chemotherapy involving carboplatin and pemetrexed. However, as recurrence remarkably progressed after the first-line treatment, he underwent subsequent immunotherapy as second-line treatment and received nivolumab (2 mg/kg body weight) 2 months after the last administration of the chemotherapy drugs. He remained hospitalized for 7 days after the initial nivolumab administration, and blood tests and chest radiography revealed no abnormal findings on the day of discharge. However, he complained of mild general malaise and a decrease in appetite. He was readmitted to our hospital with severe dyspnea 12 hours after discharge. Electrocardiography revealed sinus tachycardia (140 beats/min) and ST-segment elevation in V1-6 (Fig. 1). Echocardiography showed a markedly reduced left ventricular ejection fraction (LVEF) of 9% and akinesis of the anteroseptal wall and apex (Video 1). Chest radiography revealed acute pulmonary edema (Fig. 2). The troponin I level was elevated at 0.40 ng/mL (reference level, < 0.03 ng/mL), creatine phosphokinase level peaked at 251 U/L (reference level, < 5.99 U/L), and brain natriuretic peptide level was elevated at 250 pg/mL (reference level, < 18.4 pg/mL). An extracorporeal circulation-assisting device was necessary to maintain the hemodynamics although large amount of catecholamine was used; however, he did not desire aggressive lifesaving approaches because of cancer progression died from acute heart failure 3 days after admission. No coronary risk factors were noted, normal cardiac function was observed before the immunotherapy, and no new drug, except nivolumab, was administered within the last 2 months.

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Autopsy revealed multiple small foci of myocardial necrosis with few inflammatory cells scattered in both ventricles (Fig. 3A–E). Overexpression of programmed death-ligand 1 (PD-L1) was not found in cardiomyocytes (Fig. 3F). Additionally, atherosclerotic or thrombotic obstruction of the coronary artery and immune-related pathological findings, such as rhabdomyolysis, were not found. Therefore, we believed that the cause of death was acute heart failure possibly due to nivolumab-induced myocardial necrosis.

2. Discussion

Immune checkpoint inhibitors enhance anti-tumor responses, but

Abbreviations: irAE, Immune-related adverse event; LVEF, Left ventricular ejection fraction; PD-1, Programmed death-1; PD-L1, Programmed death-ligand 1

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they can cause unwanted side effects. A previous study reported irAEs in various organs [1]. Cardiotoxicity is not a common irAE, but several recent articles have mentioned the occurrence of myocarditis and acute heart failure in cancer patients treated with immune checkpoint inhibitors shown in Table 1 [2–6]. According to the Bristol–Myers Squibb corporate pharmacovigilance database up to August 2016, 18 drug-related myocarditis were reported among 20,594 patients (0.09%). Additionally, only 1 patients treated with nivolumab alone had fatal myocarditis [7].

Studies on programmed death-1 (PD-1) revealed its involvement in cancer escape from the host immune system [8,9] and the suppression of immune cell-mediated inflammation [10,11]. One study showed fatal myocarditis with infiltration of T cells in the myocardium and a high titer of autoantibodies against cardiac myosin in PD-1-deficient MRL mice [12]. Additionally, a recent case report on immunotherapy-induced myocarditis showed significant infiltration of T cells and macrophages in the myocardium, suggesting that T cells drive the immunotherapy reaction [13].

On the other hand, in our case, multiple small foci of myocardial necrosis with few inflammatory cells (macrophages and lymphocytes) were scattered in both ventricles. The LVEF reduced enough to cause multiple organ dysfunction. These clinical and pathological findings were significantly different from those of previously reported immunotherapy-induced myocarditis, suggesting that the cardiotoxicity in the present patient was caused by a mechanism different from that associated with previously reported myocarditis.

3. Conclusion

We experienced a case of fatal acute heart failure caused by myocardial necrosis possibly associated with nivolumab-induced cardiotoxicity. Cardiotoxicity is a rare irAE, but it sometimes can be fatal. The mechanism of cardiotoxicity should be clarified, and cardiac function should be assessed and monitored following immune checkpoint inhibitor therapies to prevent severe irAEs.

Conflicts of interest

The authors have declared no conflict of interest.

Informed consent

Informed consent was obtained from the patient/family.
Fig. 3. Histopathological findings on autopsy. (A) Hematoxylin-eosin staining and (B, C) Elastica-Masson staining. Multiple small foci of myocardial necrosis are scattered in the left ventricle (B; lower magnification, C; higher magnification). (D–E) Few inflammatory cells infiltrate in the necrotic area of the myocardium (D; CD4 E; CD8). (F) Programmed death-ligand 1 (PD-L1; 22C3) staining. Overexpression of PD-L1 is not seen in cardiomyocytes.

Table 1
Summary of review articles reporting ICI-associated cardiotoxicities.

| Author                  | No. of cases | Cardiac toxicity                  | Time of onset   | Treatment      | Outcome                                      |
|-------------------------|--------------|-----------------------------------|-----------------|----------------|----------------------------------------------|
| Heinzerling (2016)      | 8            | Various                           | 16 weeks (median) | Steroids (63%) | 3 patients (38%) died of a side effect       |
| Escudier (2017)         | 30           | Various                           | 65 days (median) | Not listed     | 8 patients (27%) died of a cardiovascular event |
| Moslehi (2018)          | 101          | Myocarditis                       | 27 days (median) | Not listed     | 46 patients (46%) died of severe myocarditis |
| Mahmood (2018)          | 35           | Myocarditis                       | 34 days (median) | Steroids (89%) | 6 patients (17%) died of a cardiovascular event |
| Yang (Case reports review) (2018) | 13     | Myocarditis, Pericarditis, Takotsubo cardiomyopathy | 15 days- 24 weeks | Steroids (92%) | 2 patients (15%) died of myocarditis         |
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References

[1] J.M. Michot, C. Bigenwald, S. Champiat, et al., Immune-related adverse events with immune checkpoint blockade: a comprehensive review, Eur. J. Cancer 54 (2016) 139–148.
[2] L. Heinzerling, P.A. Ott, F.S. Hodi, et al., Cardiotoxicity associated with CTLA4 and PD1 blocking immunotherapy, J. Immunother. Canc. 4 (2016) 50-5016-0152-y. eCollection 2016.
[3] M. Escudier, J. Castela, N. Malissen, et al., Clinical features, management, and outcomes of immune checkpoint inhibitor-related cardiotoxicity, Circulation 136 (21) (2017) 2085–2087.
[4] J.J. Moslehi, J.E. Salem, J.A. Sozman, B. Lebrun-Vignes, D.B. Johnson, Increased reporting of fatal immune checkpoint inhibitor-associated myocarditis, Lancet 391 (10124) (2018) 933-6736(18)30533-6.
[5] S.S. Mahmoud, M.G. Bradly, J.V. Cohen, et al., Myocarditis in patients treated with immune checkpoint inhibitors, J. Am. Coll. Cardiol. 71 (16) (2018) 1755–1764.
[6] S. Yang, A. Asnani, Cardiotoxicities associated with immune checkpoint inhibitors, Curr. Probl. Cancer 42 (4) (2018) 422–432.
[7] D.B. Johnson, J.M. Ballo, M.L. Compton, et al., Fulminant myocarditis with combination immune checkpoint blockade, N. Engl. J. Med. 375 (18) (2016) 1749–1755.
[8] H. Nishimura, T. Okazaki, Y. Tanaka, et al., Autoimmune dilated cardiomyopathy in PD-1 receptor-deficient mice, Science 291 (5502) (2001) 319–322.
[9] S. Chikuma, S. Terawaki, T. Hayashi, et al., PD-1-mediated suppression of IL-2 production induces CD8+ T cell anergy in vivo, J. Immunol. 182 (11) (2009) 6682–6689.
[10] Y. Iwai, M. Ishida, Y. Tanaka, T. Okazaki, T. Honjo, N. Minato, Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade, Proc. Natl. Acad. Sci. U. S. A. 99 (19) (2002) 12293–12297.
[11] T. Okazaki, Y. Tanaka, R. Nishio, et al., Autoantibodies against cardiac troponin I are responsible for dilated cardiomyopathy in PD-1 deficient mice, Nat. Med. 9 (12) (2003) 1477–1483.
[12] J. Wang, I.M. Okazaki, T. Yoshida, et al., PD-1 deficiency results in the development of fatal myocarditis in MRL mice, Int. Immunol. 22 (6) (2010) 443–452.
[13] T. Tadokoro, E. Keshino, A. Makiyama, et al., Acute lymphocytic myocarditis with anti-PD-1 antibody nivolumab, Circ. Heart Fail 9 (10) (2016) 10.1161/CIRCHEARTFAILURE.116.003514.