



Case report

De novo myasthenia gravis in a patient with malignant melanoma after concurrent SARS-CoV-2 vaccination and immune checkpoint inhibitor therapy: Case report and literature review

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ABSTRACT

In recent years, the advent and increasingly common use of immune checkpoint inhibitors (ICIs) in cancer treatment have been notable. While ICIs have shown relatively better toxicity profiles compared to traditional chemotherapy agents, they are linked to a unique range of toxicities known as immune-related adverse events (irAEs), stemming from immune system dysregulation. Following the coronavirus disease 2019 (COVID-19) pandemic, cancer patients were universally categorized as the highest priority subgroup for vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), despite being excluded from vaccine trials. The exclusion of cancer patients from vaccine trials has raised concerns within the scientific community about the potential for a hyperactive autoimmune response, which could lead to severe irAEs in patients receiving concurrent ICIs and anti-SARS-CoV-2 vaccines. Retrospective studies have indicated subtle safety concerns for mRNA vaccines in cancer patients who have undergone ICI treatment, with none of these studies encompassing inactivated anti-SARS-CoV-2 vaccines. Here, we present a case of a patient with malignant melanoma who developed fatal myasthenia gravis (MG) following concurrent vaccination with Sinopharm's inactivated COVID-19 vaccine (BBIBP-CorV) and initiation of pembrolizumab. Additionally, we examine current research on the relationship between anti-SARS-CoV-2 vaccination and irAEs in patients treated with ICIs and propose a potential mechanism responsible for the fatal MG in our patient.

1. Introduction

The emergence of immune checkpoint inhibitors (ICIs) has transformed cancer treatment, with their utilization becoming more prevalent in recent years. ICIs encompass cytotoxic T-lymphocyte antigen 4, programmed cell death 1 (PD-1), and programmed cell death ligand 1 (PD-L1) inhibitors. PD-1, targeted by pembrolizumab, serves as the checkpoint that governs the effector stage of the immune system [1]. Despite their favorable toxicity profile, ICIs' upregulation of the immune system is linked to various immune-related adverse events (irAEs) that

can impact any organ system. The most common irAEs associated with PD-1 inhibitors include cerebritis, pneumonitis, hepatitis, nephritis, colitis, myositis, and dermatitis [1]. While neurologic irAEs may occur in up to 5 % of patients treated with PD-1 inhibitors, myasthenia gravis (MG) is a rare complication [2]. Although MG is typically manageable and not highly fatal, ICI-induced MG can be more severe, potentially leading to fatalities from respiratory failure [2].

Following the COVID-19 pandemic and the rapid development of anti-SARS-CoV-2 vaccines, concerns have arisen regarding the potential of these vaccines to trigger irAEs in patients undergoing ICI treatment

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[3]. While small-scale studies have been conducted to assess the safety of anti-SARS-CoV-2 vaccines in conjunction with ICIs, these studies have exclusively focused on Pfizer and Moderna's mRNA vaccines, with no investigations involving inactivated virus vaccines [4–11].

Here, we report the initial case of de novo MG onset in a patient with metastatic melanoma following the commencement of concurrent pembrolizumab therapy and BBIBP-CoV vaccine administration.

2. Case presentation

A 65-year-old woman presented with a rapidly enlarging mass in her posterior neck over two weeks. Initially noticed five years ago, the mass was asymptomatic until recently. MRI revealed a $7 \times 5.5 \times 3.5$ cm enhancing soft tissue tumor in the posterior neck without brain metastasis. Surgical excision and microscopic examination showed large epithelioid to spindle cells with necrosis, consistent with undifferentiated malignant large cell tumor. Immunohistochemical studies were positive for S100, HMB45, and Melan A, with 25 % Ki67 positivity, indicating malignant melanoma. A subsequent FDG-PET scan revealed an FDG-avid mass near the surgical bed and an FDG-avid subhepatic nodule, suggesting residual malignancy and metastasis (Fig. 1). Core-needle biopsy confirmed metastatic undifferentiated melanoma. A follow-up surgery for the residual neck mass showed deep skull

penetration, leading to partial resection. Tumor genomic DNA testing detected no BRAF somatic variants, indicating a wild-type tumor. The patient was deemed suitable for systemic treatment with pembrolizumab.

Just before starting immunotherapy, the patient received the BBIBP-CoV vaccine, experiencing mild soreness at the injection site. She then received her first 200 mg pembrolizumab infusion without immediate adverse effects. Three weeks later, after her second pembrolizumab cycle and second BBIBP-CoV dose, she developed bilateral diplopia and ptosis, worsening throughout the day. Imaging showed no brain metastases and a significant reduction in the neck tumor size.

Laboratory tests revealed elevated creatine kinase (CK) at 4704 U/L (normal range 26–192 U/L) and aldolase at 98.6 U/L (normal range 1.0–7.5 U/L). Echocardiogram showed an ejection fraction of 57 %, and the CK-MB to CPK ratio was 4 %. The electromyography (EMG) revealed notable decremental changes in the compound muscle action potentials during repetitive nerve stimulation, particularly at low stimulation rates of 2–4 Hz. This decremental response is characteristic of MG, as the facilitation of transmitter release that occurs at higher rates partially counteracts the rundown after several stimuli. The patient was hospitalized with a primary diagnosis of MG.

During hospitalization, the patients developed severe bulbar symptoms, including dysphagia and dysarthria. Although anti-acetylcholine receptor antibodies were not measured, the multidisciplinary team diagnosed MG based on the clinical scenario and EMG findings, which showed characteristics typical of MG. The decision not to perform antibody testing was due to the urgency of the patient's symptoms and the immediate need for treatment. While elevated CK levels are atypical for MG, this finding raised a differential consideration for accompanying myositis or myocarditis, both of which can manifest with elevated CK resulting from potential irAEs associated with ICIs [12]. In the absence of a muscle biopsy or specific antibody testing for myositis, we cannot definitively rule out an overlap syndrome involving both MG and myositis. However, myocardial involvement was considered less likely due to a preserved ejection fraction of 57 % on echocardiogram and a CK-MB to total CK ratio of less than 6 %, both of which argue against significant myocardial injury [13].

The elevated CK level was, therefore, attributed to skeletal muscle damage, which could plausibly arise from muscle inflammation related to the patient's heightened immune response, likely triggered by concurrent SARS-CoV-2 vaccination and immune checkpoint inhibitor therapy. Although CK elevation is not a classical feature of isolated MG, it may occur in cases of MG with secondary muscle inflammation. Additionally, other conditions associated with immune activation, such as inflammatory myopathies or rhabdomyolysis, can result in elevated CK and should be considered in the differential [14].

Treatment comprised pyridostigmine and intravenous immune globulin (IVIG) for five days, resulting in moderate symptomatic improvement and discharge after five days. Meanwhile, an abdominal CT scan indicated the disappearance of the hepatic lesion. However, she was readmitted two days later due to acute exacerbation of bulbar symptoms, neck muscle weakness, and respiratory insufficiency. Two rounds of plasmapheresis were administered within two days, along with subsequent intubation due to worsening hypoxia. Additional IVIG doses were given, but unfortunately, she suffered a cardiac arrest the following day and passed away. No muscle biopsy or autopsy was performed.

3. Discussion

The COVID-19 pandemic has disproportionately affected cancer patients, significantly increasing morbidity and mortality, especially in those undergoing chemotherapy [15,16]. Consequently, cancer patients are prioritized for SARS-CoV-2 vaccination [3]. However, large-scale trials on the safety and efficacy of these vaccines in cancer patients are lacking. Additionally, the exclusion of cancer patients from trials

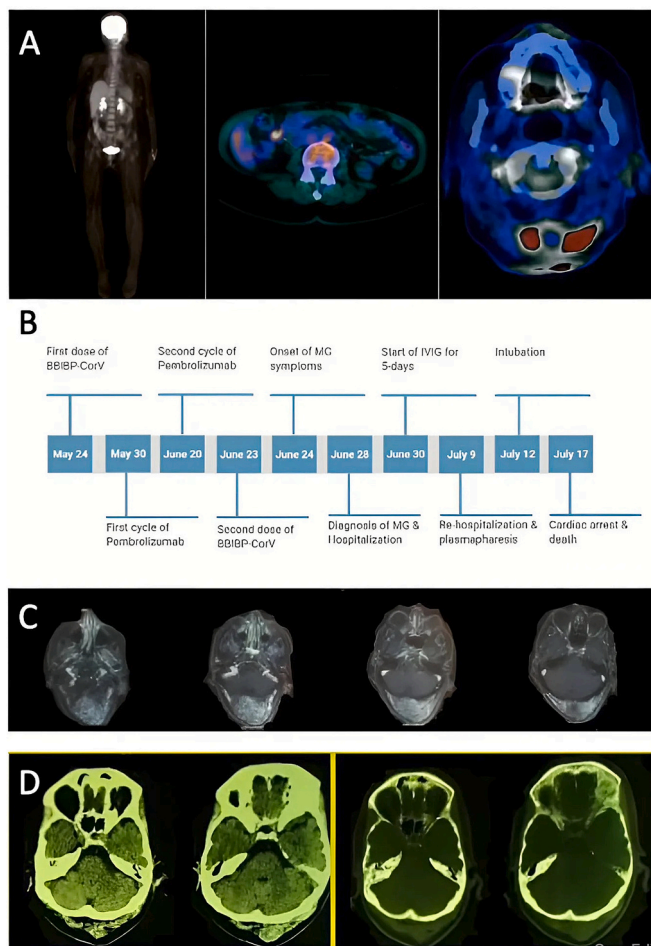


Fig. 1. (A) Patient's initial PET/CT-scan showed FDG avid soft tissue mass adjacent to the surgical bed indicative of residual malignancy and an FDG avid subhepatic peritoneal soft tissue nodule in favor of metastasis; (B) Clinical timeline from diagnosis of tumor resection to MG diagnosis and hospitalization; (C) Patient's neck and brain MRI before starting immunotherapy showing a large soft tissue mass; (D) Significant tumor regression after two cycles of pembrolizumab.

raises concerns about heightened immunity and irAEs in those receiving ICIs and anti-SARS-CoV-2 vaccines [17]. Several small-scale retrospective studies have assessed vaccine safety in these patients (Table 1).

Weissengrin et al. studied the short-term safety of the Pfizer-BioNTech mRNA SARS-CoV-2 vaccine (BNT162b2) in 134 cancer patients on ICIs. They found higher muscle soreness and fatigue after the second dose in the vaccinated group but no new or worsening irAEs [3]. Chen and Lasagna et al. retrospectively analyzed ICI-treated cancer patients vaccinated with BNT162b2; Chen et al. reported 6 of 81 (7 %) patients with irAEs, while Lasagna found 1 of 88 (1 %) patients with irAEs [4,5]. Lasagna et al. also noted a case of hepatitis and colitis after the first vaccine dose [5]. Widman et al. reported a 7 % irAE rate among 408 cancer patients on immunotherapy, with one and three patients experiencing grade 3 colitis and diarrhea, respectively [8]. Guo et al. concluded that COVID-19 vaccination does not increase irAE risk, identifying ipilimumab plus nivolumab as the only significant factor for irAE in their multivariate analysis [9].

Studies on the safety of anti-SARS-CoV-2 vaccines in ICI-treated patients have mainly focused on BNT162b2 or Moderna's mRNA vaccines, excluding others. Therefore, their findings may not apply to those vaccinated with inactivated vaccines like BBIBP-CorV, CoronaVac, and Covaxin, which account for 3.5 billion doses globally [18]. These

vaccines use the inactivated SARS-CoV-2 Spike (S) protein with an adjuvant to generate neutralizing antibodies [19]. However, studies suggest potential cross-reactivity between antibodies targeting the S-protein and healthy tissue antigens, possibly triggering systemic autoimmunity through molecular mimicry [20].

Comparative studies show significant differences in immune responses between BBIBP-CorV and mRNA vaccines against SARS-CoV-2. mRNA vaccines generate stronger immunity, mainly targeting the S-protein [21]. BBIBP-CorV elicits a broader but less specific immune response targeting spike, nucleocapsid, and membrane protein epitopes [22]. This results in T-cell proliferation with increased PD-1 expression [23]. Subsequent PD-1 blockade may lead to a synergistic immunomodulatory response, enhancing T-cell effector functions and releasing inflammatory cytokines, potentially resulting in irAEs, such as refractory myasthenia gravis. Previous studies indicate that vaccines, including the influenza vaccine, can amplify the anti-neoplastic effects of PD-1 inhibitors. For example, Läubli et al. found that vaccinating cancer patients undergoing PD-1 inhibitor therapy with the trivalent inactivated influenza vaccine increased irAE risks [24]. Similar effects might occur with inactivated SARS-CoV-2 vaccines. This immunological response correlates with the tumor regression seen in our patient after two cycles of pembrolizumab (Fig. 2).

Table 1

Summary of studies evaluating immune-related adverse events after COVID-19 vaccination in patients with cancer receiving immune-checkpoint inhibitors.

Study	Study type	Cancer type	COVID-19 vaccine	ICIs	irAE incidence	irAE type	Median onset time after vaccination
Waissengrin et al. [3]	Retrospective cohort	Lung (49 %) Melanoma (11 %) GU (11 %) GI (8 %) Other (19 %)	BNT162b2	Pembrolizumab (55 %) Nivolumab (18 %) Nivolumab + ipilimumab (5 %) Durvalumab (11 %) Other (9 %)	None of 134	NR	NR
Chen et al. [4]	Retrospective cohort	Lung (27 %) Melanoma (23 %) Kidney (14 %) GI (11 %) Head & Neck (9 %) Other (16 %)	BNT 162b2 (83 %) mRNA-1273 (17 %)	Pembrolizumab (56 %) Nivolumab (27 %) Durvalumab (7 %) Other (10 %)	6 of 81 (7.4 %)	Pancreatitis (1.2 %) Shock (2.4 %) Myositis (1.2 %) Hemolytic anemia (1.2 %) Respiratory distress (1.2 %)	2.5 days
Lasagna et al. [5]	Longitudinal cohort	Lung (76 %) Melanoma (9 %) Kidney (8 %) Other (7 %)	BNT162b2	Pembrolizumab (61 %) Nivolumab (19 %) Durvalumab (11 %) Other (4 %)	1 of 88 (1.1 %)	Colitis and hepatitis (1.1 %)	10 days
Strobel et al. [10]	Retrospective cohort	Melanoma (89 %) Skin SCC (7 %) MCC (4 %)	Pfizer-BioNTech (86 %) AstraZeneca (9 %) Moderna (2 %) Combination (2 %)	PD-1 Ab (71 %) PD-1 Ab + CTLA4 Ab (22 %) PD-L1 (7 %)	15 of 89 (17 %)	Colitis (3 %) Hepatitis (1 %) Myositis (2 %) Myocarditis (1 %) Thyroiditis + colitis (1 %) Arthralgia (0.7 %) Arthritis with rash (0.5 %) Colitis (0.2 %) Dermatitis (2.4 %) Diarrhea (1.2 %) Pneumonitis (0.7 %) Thyroiditis (0.2 %) Transaminitis (0.5 %)	11 weeks
Widman et al. [8]	Retrospective cohort	Thoracic (30 %) GU (21 %) Melanoma (12 %) Upper GI (12 %) Gyn (10 %) Sarcoma (5 %) Head & neck (5 %) Other (6 %)	Pfizer-BioNTech (95 %)	Pembrolizumab (65 %) Nivolumab (24 %) Nivolumab + ipilimumab (10 %) Other (1 %)	27 of 408 (7 %)	Colitis (0.2 %) Dermatitis (2.4 %) Diarrhea (1.2 %) Pneumonitis (0.7 %) Thyroiditis (0.2 %) Transaminitis (0.5 %)	Not mentioned
Gilbert et al. [11]	Retrospective cohort	Melanoma (41 %) Kidney (20 %) Bladder (14 %) Other (25 %)	Pfizer-BioNTech (56 %) Moderna (42 %) Johnson & Johnson (2 %)	ICI alone (71 %) ICI + ICI (19 %) ICI + other (10 %)	29 of 284 (10.2 %)	NR	15 days
Guo et al. [9]	Retrospective cohort	Not mentioned	BNT162b2 mRNA-1273	Not mentioned	48 of 251 (19.1 %)	Not mentioned	161 days
Au et al. [7]	Case report	Colorectal	BNT162b2	Anti-PD-1	1 of 1	Ataxia	Two months

Abbreviations: AB, antibody; ICI, immune checkpoint inhibitor; MCC, Merkle cell carcinoma; NR, not reported; SCC, squamous cell carcinoma.

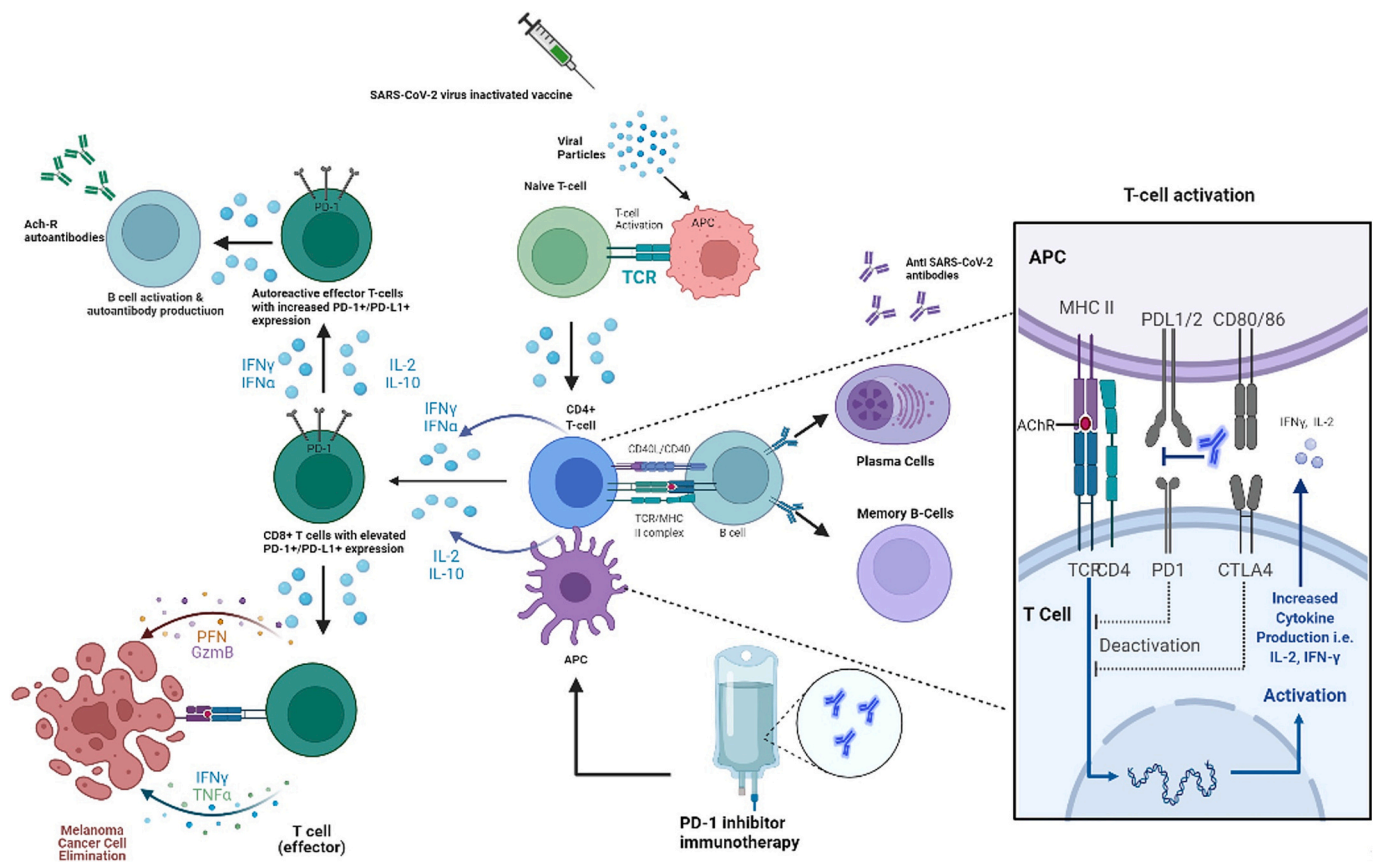


Fig. 2. Schematic illustration of the potential mechanism of myasthenia gravis caused by the synergistic immune response from concurrent administration of immune checkpoint inhibitors and inactivated SARS-CoV-2 vaccine. The patient had increased expression of PD-1/PD-L1 on the malignant cells, which made her an optimal candidate for ICI therapy. The SARS-CoV-2 vaccine may have led to increased PD-1⁺/PD-L1⁺ T-cell production, which would, in turn, become hyperactivated with the administration of PD-1 inhibitor. This leads to exaggerated T-cell activity against both tumoral and healthy tissue antigens, with the eventual formation of autoreactive effector T-cells leading to her development of severe myasthenia gravis.

This case exemplifies the potential for heightened immune responses in cancer patients undergoing immune checkpoint inhibitor therapy, particularly following concurrent SARS-CoV-2 vaccination. The patient's presentation of de novo MG after receiving both pembrolizumab and a SARS-CoV-2 vaccine highlights the complex immunological interplay that can arise in such scenarios. The immune activation from both the ICI and the vaccine may have contributed to a synergistic immunomodulatory response, as observed in previous studies where vaccines amplified the anti-tumor effects of ICIs and increased the risk of irAEs [24]. In our patient, this response not only induced tumor regression after two pembrolizumab cycles but may also have triggered an autoimmune process, leading to MG. Furthermore, the patient's elevated CK levels, while unusual for isolated MG, could reflect additional immune-mediated muscle involvement, as seen in cases of myositis linked to ICI therapy. This case underscores the need for careful monitoring of cancer patients receiving ICIs and vaccines, especially given the limited data on the safety and immunological effects of concurrent SARS-CoV-2 vaccination in this population. Clinicians should remain vigilant for atypical presentations of irAEs, as early detection and management are critical for improving patient outcomes.

4. Conclusions

The close temporal relationship between our patient's vaccination and the start of pembrolizumab treatment, along with her clinical symptoms, strongly suggest that the simultaneous use of the vaccine and ICI likely triggered her MG. While the advantages of COVID-19 vaccination far surpass the drawbacks for both the general population and

cancer patients, comprehensive studies are essential to assess the potential interactions between inactivated viral vaccines and ICI therapy. Until such studies are conducted, healthcare providers should exercise considerable pharmacovigilance and clinical discretion when administering these vaccines concurrently with initiating ICIs.

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Informed consent

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CRediT authorship contribution statement

Mohadese Shahin: Writing – original draft, Conceptualization. **Pedram Fadavi:** Visualization, Investigation. **Mohammad Mostafa Ansari Ramandi:** Writing – original draft. **Soroush Shahrokh:** Writing – original draft. **Farzad Taghizadeh-Hesary:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare no conflict of interest.

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