


Immune Checkpoint Inhibitor-Associated Systemic Sclerosis in the Treatment of a Small Cell Lung Cancer Patient with Durvalumab: A Case Report

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Abstract: As one of the key cancer treatment measures, immune-checkpoint inhibitors (ICIs) have revolutionized the treatment landscape of various cancers, including malignancies previously thought to be untreatable. Immune checkpoint inhibitors work by targeting the dysfunctional immune system, to enhance cancer-cell killing by CD8-positive T cells. Despite the beneficial effects of ICIs, these treatments are also linked to a novel class of side effects, termed immune-related adverse events (irAEs). Immune-related adverse events can affect multiple organ systems, such as endocrine, neurological, gastroenteric, dermatologic, ocular, hepatic, renal, and rheumatic ones. While variable in severity, irAEs can be associated with significant morbidity, mortality, cessation of ICI treatment and can be potentially life-threatening sometimes. Among varieties of irAEs, dermatological manifestations are frequently reported, since they can be easily observed. Here, we present a case of a 74-year-old patient with widespread fibrosis of skin, eventually diagnosed as diffuse cutaneous systemic sclerosis after the treatment with durvalumab for small cell lung cancer (SCLC). Prompt recognition and treatment of immune-checkpoint inhibitors-associated systemic sclerosis may help enhance tolerance to ICIs and ensure better performance in treating tumors.

Keywords: systemic sclerosis, durvalumab, small cell lung cancer, immune checkpoint inhibitors, immune-related adverse events

Introduction

Immune-checkpoint inhibitors (ICIs) have become a crucial component of cancer treatment.¹ Starting with the approval of anti-cytotoxic T lymphocyte-associated protein 4 (anti-CTLA-4) for advanced-stage melanoma in 2011, immune checkpoint inhibitors (ICIs) have been widely applied in the treatment of a variety of malignancies.² Instead of CTLA-4 (ipilimumab), ICIs now also include antibodies against programmed cell death 1 (PD-1; nivolumab, pembrolizumab, cemiplimab, sintilimab, camrelizumab, toripalimab, tislelizumab, zimberelimab, prolgolimab, and dostarlimab) and its ligand (PD-L1; atezolizumab, avelumab, and durvalumab).³ Immune checkpoints are receptors expressed on immune cells and allow for the dynamic regulation of immunological homeostasis.¹ PD-1 and PD-L1 are expressed on T cells, tumor cells and tumor-infiltrating myeloid cells, respectively.¹ T cell exhaustion is caused by the interaction of these two proteins and is characterized by decreased or missing effector function (cytotoxicity or cytokine production), lack of reactivity to stimuli and altered transcriptional and epigenetic states.^{4,5} On the other hand, CTLA-4 is one type of negative immune regulator constitutively expressed on regulatory T (Treg) cells and upregulated on activated T cells.⁶ CTLA-4 inhibits T cell activation through various suppressive functions including competition with CD28, regulation of the inhibitory function of Treg cells, such as transendocytosis, and the control of adhesion and motility.⁶ However, more and more immune-related adverse effects (irAEs), which are unique and accompanied by a delayed onset and prolonged duration, have been reported as a result of this increased use.⁷ IrAEs can occur in any organ system and 2–16 weeks can

be the median onset after the start of therapy.⁸ Varieties of dermatological manifestations can occur associated with ICIs such as vitiligo, lichenoid dermatitis, psoriasis, bullous pemphigoid, granulomatous diseases, drug rash with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome and Sweet syndrome.^{9–11} The anti-PD-1 (34–42%) and anti-PD-L1 monotherapy (~20%) are associated with lower rates of cutaneous adverse events than anti-CTLA-4 monotherapy (44–59%), but combination therapy is linked to the highest incidence (59–72%).^{11,12} However, among these dermatological irAEs, systemic sclerosis induced by the treatment of durvalumab in small cell lung cancer (SCLC) patients has not been reported before. Here, we described a case of durvalumab-associated systemic sclerosis in a patient with SCLC after the treatment with durvalumab.

Case Presentation

A 74-year-old man was admitted to hospital with cough and chest tightness for one month. He complained of a cough with no obvious cause in the past month, which intensified into paroxysms, coughing up pus sputum, accompanied by chest tightness, shortness of breath, dyspnea, hemoptysis, and sometimes blood in the sputum. He had not had autoimmune diseases in the past, and he denied prior familial history of autoimmune diseases. After the computed tomography (CT) scan of the chest (Figure 1A), lesions biopsy by electronic bronchoscopy (Figure 2A) and positron emission tomography (PET)/CT scan (Figure 2B), he was diagnosed with limited-stage SCLC. The results of laboratory tests, including anti-Scl-70 antibody, anti-centromere antibody, anti-RNA polymerase III antibody, anti-neutrophil cytoplasmic antibody, anti-myeloperoxidase (MPO) antibody, anti-glomerular basement membrane (GBM) antibody, anti-Smith (Sm) antibody, anti-SSA antibody, anti-SSB antibody, anti-dsDNA antibody and anti-histidyl tRNA synthetase (Jo-1) antibody were all negative. Besides, the anti-nuclear antibody titer was 1:100 and the patient's eosinophils were $0.22 \times 10^9/L$. Due to the lack of surgical opportunity, he received chemotherapy plus immunotherapy. According to the treatment guidelines for SCLC, he underwent five cycles of cisplatin (130 mg/m^2) plus etoposide (100 mg/day) in combination with durvalumab (1000 mg/day). After the combination therapy of chemotherapy plus immunotherapy, he was treated with ten cycles of maintenance therapy with durvalumab from July 2021 to April 2022. However, the patient gradually felt slight swelling and tightness of the skin on his trunk and limbs accompanied by skin itching after ten cycles of durvalumab maintenance therapy (Figure 3). Besides, he had difficulty swallowing, but no Raynaud's phenomenon. Therefore, maintenance therapy with durvalumab was suspended owing to these clinical manifestations. Afterwards, he

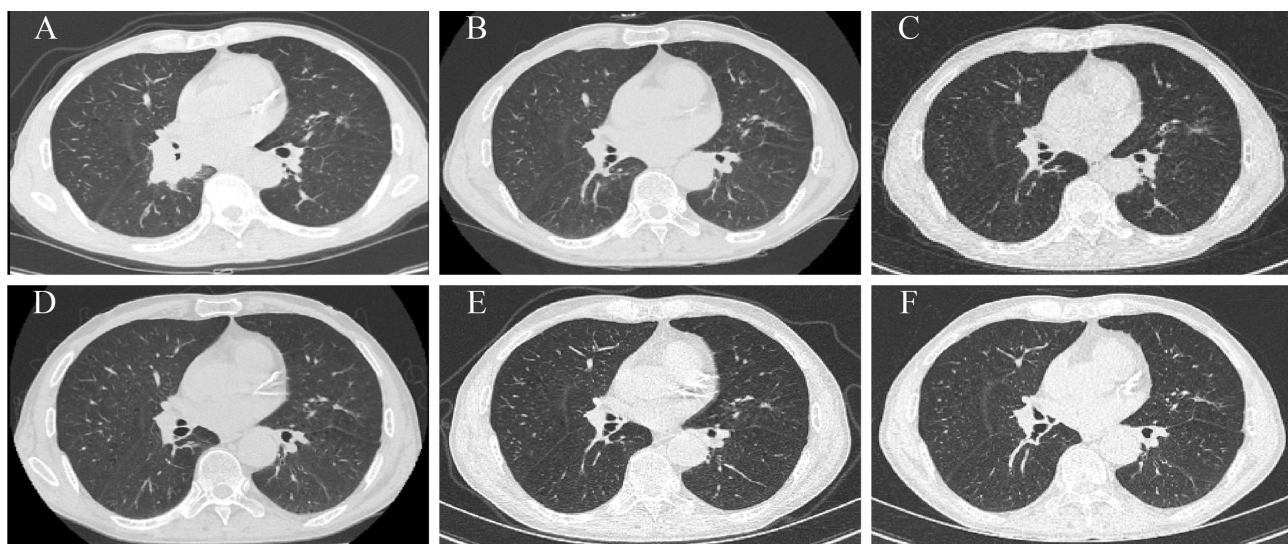


Figure 1 The images of CT scan of the patient. The patient received ten cycles of maintenance therapy with durvalumab between July 2021 and April 2022. (A) CT scan of the patient on March 10, 2021 showed massive shadow in the middle and lower lobes of the right lung near the hilar area (B) CT scan of the patient on September 25, 2021 showed significant reduction in primary tumor size (C) CT scan of the patient on February 28, 2022 showed reduction in primary tumor size (D) CT scan of the patient on August 17, 2022 showed no definite tumor recurrence or metastasis (E) CT scan of the patient on February 21, 2023 showed no definite tumor recurrence or metastasis. (F) CT scan of the patient on August 15, 2023 showed no definite tumor recurrence or metastasis.

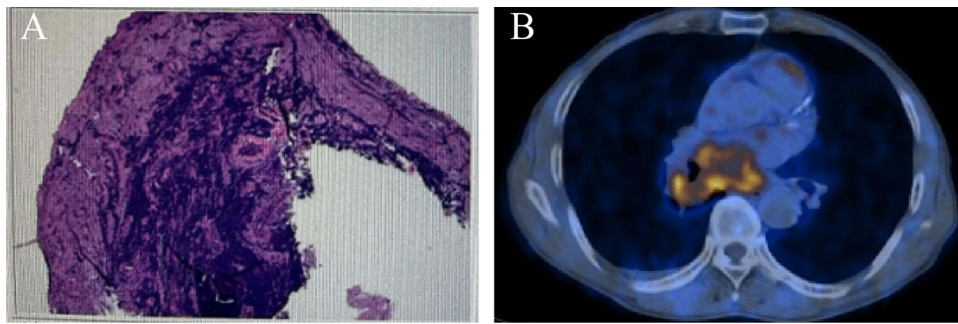


Figure 2 (A) Lesions biopsy by electronic bronchoscopy **(B)** The image of positron emission tomography (PET)/CT scan showed abnormal soft tissue density in the middle and lower lobes of the right lung near the hilar region with adjacent bronchial stenosis and occlusion, and abnormal concentration of radioactivity distribution in the corresponding area, SUVmax 6.8.

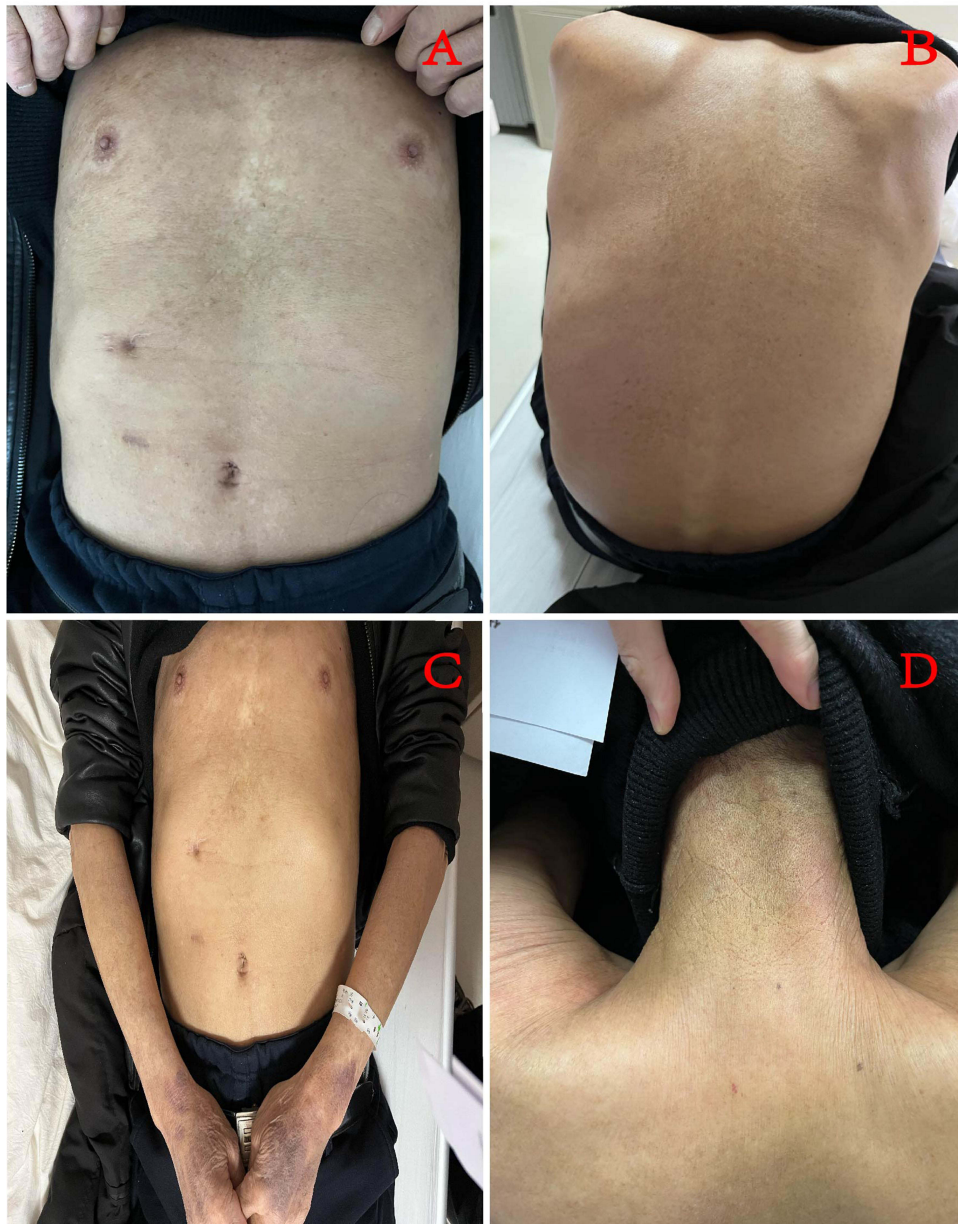


Figure 3 Widespread areas of skin sclerosis of the patient. **(A)** Chest and Abdomen **(B)** Back **(C)** Chest, Abdomen and Upper Limbs **(D)** Neck.

received routine anti-allergy treatment during his hospitalization, but there was no relief of skin symptoms after the anti-allergy treatment. During hospitalization, according to the opinion of the dermatologist, he underwent a skin biopsy. After skin biopsy of the lesion on the right abdomen, histopathologic examination was reported as systemic sclerosis (Figure 4). At the time of discharge, he was instructed to take oral prednisone acetate tablets 40 mg daily with a weekly dose reduction of 5 mg. One month later, he felt that the skin stiffness of his extremities was better than before, but the skin of neck, chest, back, and abdomen was still stiff. Therefore, he was admitted to the rheumatology department, where he received intravenous hydrocortisone (40mg/d). During hospitalization in rheumatology department, the results of laboratory tests, including erythrocyte sedimentation rate (ESR) was 28mm/h, C-reactive protein (CRP) was 11.4mg/L, decrease in complement C3 and anti-nuclear antibody titer was 1:320. In addition, anti-Scl-70 antibody, anti-centromere antibody, anti-RNA polymerase III antibody, anti-neutrophil cytoplasmic antibody, anti-MPO antibody, anti-GBM antibody, anti-Sm antibody, anti-SSA antibody, anti-SSB antibody, anti-dsDNA antibody and anti-histidyl tRNA synthetase (Jo-1) antibody were all negative. The patient's eosinophil count was $0.16 \times 10^9/L$. Esophageal manometry suggested that the patient had esophageal motor disorders. The rheumatologist considered that the patient can be diagnosed as diffuse cutaneous systemic sclerosis and the digestive tract had been affected. Therefore, he was advised to take oral mycophenolate mofetil (MMF) dispersible tablets 0.5 g twice daily plus prednisone acetate tablets 20 mg once daily, and the dose was reduced to 15 mg daily after half a month.

Fortunately, according to the CT scan (Figure 1D), there was no progression of cancer after the end of immune maintenance treatment. After regular oral prednisone treatment, the patient's systemic sclerosis is now under control, but the skin of the trunk is still hard and tight, and the patient still has dysphagia. Even though SCLC is an extremely aggressive neuroendocrine tumor, characterized by rapid growth and early metastasis.¹³ There is no recurrence or metastasis of the primary tumor after the administration of chemotherapy plus immunotherapy during regular follow-up (Figure 1E and F), though this patient had been diagnosed with SCLC for more than two years.

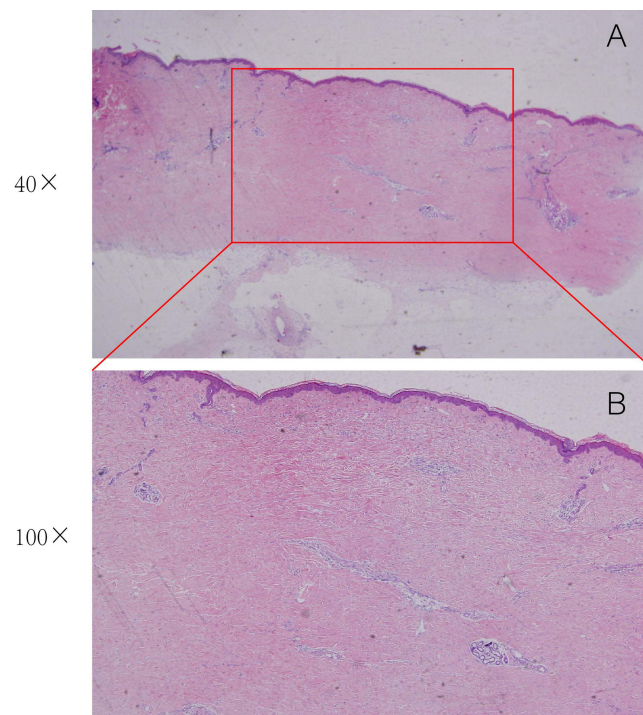


Figure 4 Hematoxylin-eosin (HE) staining of the pathology slide showing the dermis is generally normal, with coarse reddish staining of the deep dermal collagen proliferation, upward displacement of the small sweat glands and visible extrusion, and infiltration of lymphocytes, histiocytes, and a small number of plasma cells seen around the blood vessels and subcutaneous lobules (A) HE, 40X; (B) HE, 100X.

Discussion

Durvalumab is a fully human monoclonal IgG1 *k* antibody targeting PD-L1, which has been approved by the US Food and Drug Administration (FDA) to treat solid organ malignancies in 2017.^{14,15} Some cases have been reported where systemic sclerosis or morphea can be induced by atezolizumab, pembrolizumab or nivolumab.^{16–20} However, systemic sclerosis induced by durvalumab has not been reported before. Systemic sclerosis is an immune-mediated rheumatic disease characterized by fibrosis of the skin and internal organs and vasculopathy.²¹ Early vasculopathy, innate and adaptive immune system dysfunction, and aberrant connective tissue development are factors in the etiology of systemic sclerosis.²²

It is estimated that approximately 11.3% to 24.6% of patients diagnosed with cancer have pre-existing autoimmune disease (AIDs).²³ Recent studies have suggested that patients with pre-existing AIDs are more prone to developing irAEs than patients without AIDs in the past. In a systematic review conducted by Abdel-Wahab et al, they found that 75% cancer patients with pre-existing AIDs had exacerbation of pre-existing AIDs, irAEs or both after receiving ICIs treatment.²⁴ Machado et al suggested that cancer patients with gastrointestinal and rheumatologic AIDs had a higher incidence of AIDs flare-ups after ICIs treatment.²⁵ Besides, pre-existing AIDs are risk factors for irAEs.²⁶ In cancer patients, irAEs are more common with combination ICIs therapy than ICIs monotherapy.²⁷ ICIs-induced inflammatory arthritis, myositis, sicca, and vasculitis are classified as rheumatic irAEs.²⁷ New-onset systemic sclerosis induced by the treatment of ICIs accounts for approximately less than 10% of all rheumatic-irAEs (and <1% of all types of irAEs).^{28,29} There are clinical distinctions between rheumatic irAEs and pre-existing AIDs. Macklin et al suggested that ICIs-associated systemic sclerosis patients differed significantly from primary systemic sclerosis cases in that they exhibited less vascular characteristics and lower seropositivity, including antinuclear and systemic sclerosis-specific antibodies.³⁰ Although one of the three systemic sclerosis-associated antibodies (anti-Scl-70 antibody, anti-centromere antibody, or anti-RNA polymerase III antibody) is positive in 60–80% of pre-existing systemic sclerosis patients, none of the ICIs-systemic sclerosis cases showed positive systemic sclerosis-associated antibodies.^{31,32}

Barbosa et al described two cases of patients developing systemic sclerosis when pembrolizumab therapy was used for treating metastatic melanoma.¹⁷ One patient was diagnosed as diffuse systemic sclerosis after 14 cycles of pembrolizumab treatment for metastatic melanoma and the patient had normal levels of anti-nuclear antibody, anti-centromere antibody, anti-ribonucleoprotein antibody, and anti-Scl-70 antibody.¹⁷ Afterwards, the patient was advised to take prednisone 1 mg/kg daily and received intravenous immunoglobulin, 0.4 mg/kg daily for 5 days monthly, and mycophenolate mofetil, 1000 mg twice daily.¹⁷ However, the patient died of unknown causes (autopsy was declined) after subjective improvement in the skin changes.¹⁷ The other patient was diagnosed as limited systemic sclerosis with negative systemic sclerosis-related specific antibodies.¹⁷ He was advised to take hydroxychloroquine (200 mg twice daily) by a dermatologist and prednisone (1 mg/kg) by his oncologist and his skin changes improved considerably after immunosuppressant and prednisone treatment.¹⁷ Terrier et al reported two cases with underlying limited cutaneous systemic sclerosis who showed a significant increase in skin thickening after pembrolizumab treatment.²⁸ One 49-year-old woman with metastatic non-small cell lung cancer has finally been diagnosed with diffuse cutaneous systemic sclerosis after pembrolizumab treatment.²⁸ The anti-nuclear antibody was positive with a titer of 1/640, but were negative for anti-Scl-70 antibody, anti-centromere antibody, or anti-RNA polymerase III antibody, in this patient.²⁸ She received intravenous cyclophosphamide in combination with prednisone at a dose of 10 mg/day.²⁸ The other patient with pre-existing limited cutaneous systemic sclerosis finally developed diffuse extension of the skin thickening to proximal limbs and the trunk after the pembrolizumab treatment for metastatic non-small cell lung cancer.²⁸ However, the patient improved skin thickening after 6 cycles of cyclophosphamide.²⁸ In our case report, the patient developed diffuse systemic sclerosis after 10 cycles of durvalumab treatment and systemic sclerosis-related specific antibodies including anti-Scl-70 antibody, anti-centromere antibody and anti-RNA polymerase III antibody were all negative. The patient received prednisone (15–40 mg once daily) and mycophenolate mofetil 0.5 g (twice daily). Fortunately, the patient's skin symptoms got subjective improvement, and he did not experience recurrence as well as metastasis of the primary tumor despite the interruption of durvalumab therapy. Therefore, systemic corticosteroids (0.5–2 mg/kg daily, depending on the severity of symptoms) can be used to treat most irAEs.^{33,34} However, patients may require immunosuppressive or modulatory therapy, such as azathioprine, mycophenolate mofetil, cyclosporine, and tumor necrosis factor α inhibitors, if the irAEs are not responsive to corticosteroids.^{33,35} Besides, patients with systemic sclerosis secondary to ICIs treatment in our case and in the cases mentioned above usually lacked systemic sclerosis-associated specific antibodies as well as Raynaud's phenomenon.

Conclusion

In conclusion, we report a very rare case of systemic sclerosis induced by immunotherapy with durvalumab. It is consistent with recent findings in the literature that patients receiving anti-PD-1 or anti-PD-L1 antibody therapy and experiencing irAEs have better overall response rates, progression-free survival rates, and overall survival.³⁶ Given the cases, we reported on this occasion, we should keep a close eye on the irAEs during the use of ICIs. In the process of treating SCLC with ICIs, clinicians should pay attention to the patient's irAEs, especially when the patient's skin appears to be sclerotic, they should be alert to the possibility of ICIs-associated systemic sclerosis. At this time, they should actively take the appropriate treatment measures to alleviate the condition, and to prevent the aggravation of the condition, so as to avoid the negative impact on the ICIs treatment. Early identification and management of irAEs may enhance tolerance to ICIs and improve cancer survival. In addition, further studies will need to be done to develop a better understanding of the mechanisms associated with the systemic sclerosis caused by ICIs therapies.

Consent for Publication

The patient had given written informed consent for the publication of his clinical details and images. Institutional approval is not required for this case study.

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Disclosure

All authors declare that they have no conflicts of interest in this work.

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