Abrupt progression from patch- to tumor-stage mycosis fungoides following pembrolizumab treatment

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INTRODUCTION

Mycosis fungoides (MF), the most common form of cutaneous T-cell lymphoma (CTCL), typically presenting in a chronic indolent manner, evolving through patch, plaque, and tumor stages. Pembrolizumab is an immune checkpoint inhibitor (ICI) that targets programmed cell death protein 1, enhancing the immune response against cancer cells. It has shown efficacy in treating a wide range of cancers, including melanoma and lymphoma.[1,2] However, recent reports have suggested that pembrolizumab may paradoxically contribute to the development of lymphoma.[3,4] Here, we present a case in which MF unexpectedly progressed from the patch to the tumor stage following the administration of pembrolizumab for renal cell carcinoma (RCC) treatment.

Abbreviations used:

CD:	cluster of differentiation
CTCL:	cutaneous T-cell lymphoma
ICI:	immune checkpoint inhibitor
MF:	mycosis fungoides
RCC:	renal cell carcinoma
TCR:	T-cell receptor

CASE REPORT

A 78-year-old male patient, previously treated with radical nephrectomy for RCC, presented with persistent erythematous patches on both lower limbs for 3 years (Fig 1). Initially diagnosed as tinea corporis, the lesions did not improve despite 1 year of antifungal treatment. A skin punch biopsy revealed band-like infiltration in the upper dermis, exhibiting epidermotropism consistent with patch-stage MF. The lymphocytes were predominantly cluster of differentiation (CD)4^+, expressing CD2, CD3, and CD5. The Ki-67 index was at 5%, and T-cell receptor (TCR) monoclonality was detected. Physical examination and abdominal and pelvic computed tomography imaging showed no evidence of MF involvement in the lymph nodes or visceral organs. The patient was classified as stage IA and received phototherapy (narrowband ultraviolet B therapy), with minimal progression over 2 years.

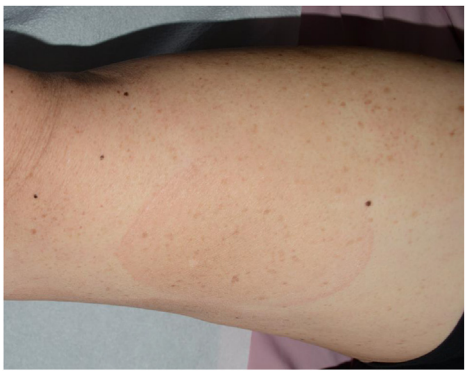

Fig 1. Erythematous patch on right thigh, initial visit.

Two years into phototherapy, the patient was diagnosed with lung metastasis of RCC. The oncology team initiated pembrolizumab, 200 mg

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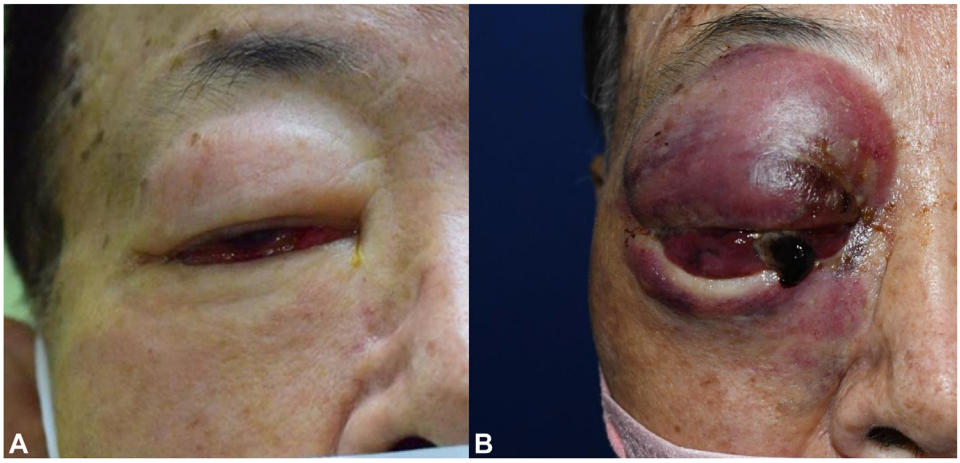

Fig 2. A, Swelling on the right eyelid 9 months after starting pembrolizumab treatment. **B,** Exophthalmos and erythema on right orbit 10 months after starting pembrolizumab treatment.

every 3 weeks. In response to pembrolizumab treatment, computed tomography imaging showed that the metastatic lesions and the primary RCC remained in a stationary state. Nine months later the patient developed swelling and proptosis in the right eye (Fig 2, *A*). Magnetic resonance imaging revealed an enlarged right medial rectus muscle with tendinous involvement, causing exophthalmos. Biopsies confirmed MF in the rectus muscle. The lymphocytes were positive for CD3, CD4, and CD8, with a predominance of $CD4^+$ cells, and negative for CD30 and CD20. TCR amplification revealed a matching clone to the original MF biopsy, indicating progression of the existing MF.

Upon revisiting the dermatology clinic, the right eye lesion rapidly progressed within a month of the first symptoms appearing and exhibited severe swelling and erythema of the eyelid and surrounding skin (Fig 2, *B*). Computed tomography imaging of the orbit revealed a mass extending to the orbital apex, involving the entire right orbit. Encasement of the right optic nerve and diffuse swelling of the right periorbital soft tissue were also observed. No other abnormalities were found outside the orbit. Quantitative Epstein-Barr virus DNA testing and HIV antigen/antibody tests showed no abnormalities.

A newly developed rapidly growing mass was found on the left thigh (Fig 3). A skin punch biopsy indicated tumor-stage MF with diffuse atypical lymphocytic infiltration throughout the entire dermis and large cell transformation. Immunohistochemical staining revealed a loss of CD4, CD5, and CD8 compared to previous biopsy. TCR gene rearrangement was evaluated, and the results indicated a matching clone to the previous 2 biopsies.

Pembrolizumab was discontinued due to concerns about its contribution to MF progression.

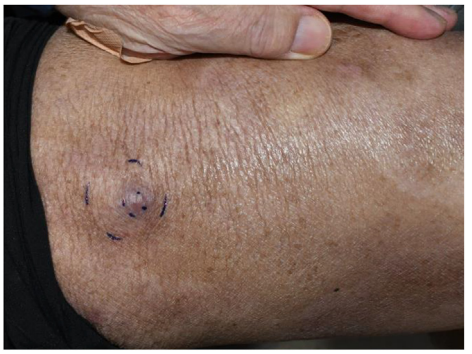

Fig 3. Tumor on the left thigh 10 months after initiation of pembrolizumab.

Radiation therapy commenced for the right eye, but the patient soon decided to halt all medical interventions. His condition deteriorated rapidly, leading to his death 3 months later.

DISCUSSION

This case details a patient with patch-stage MF experiencing a sudden progression to the tumor stage after 9 months of pembrolizumab treatment for metastatic RCC. Pembrolizumab is employed for treating various cancers, including MF. In a clinical trial investigating the response to pembrolizumab in patients with MF or Sezary syndrome stages IB to IV, 38% of patients showed response.[2] Notably, while 40% of patients with Sezary syndrome in this study experienced a skin flare reaction after pembrolizumab administration, there were no reports of sudden tumor progression as observed in our case.

Meanwhile, it has been discovered that various cancers can paradoxically undergo hyperprogression after the use of ICI.[5] Reports of progression or new onset of CTCL following ICI treatment are

relatively scarce. Previous cases include development of cutaneous $CD56^+$ T-cell lymphoma, angioimmunoblastic T-cell lymphoma or peripheral T-cell lymphoma following pembrolizumab administration.[3,4,6] In 1 reported case, pembrolizumab administered for Sezary syndrome led to the progression of preexisting CTCL and sudden tumor development.[7]

The exact mechanisms underlying cancer hyperprogression induced by ICI remain unclear. In a recent study, single-cell RNA sequencing of a patient with CTCL experiencing hyperprogression after programmed cell death protein 1 blockade revealed somatic amplification of protein kinase C theta in malignant T cells.[8] The authors hypothesized that this amplification, combined with programmed cell death protein 1 blockade, led to oncogenic activation of the TCR signaling pathway, derepressing malignant T-cell proliferation.

Notably, the sudden MF progression occurred 9 months after pembrolizumab initiation, contrasting with most ICI-induced hyperprogressive disease reports within 3 months.[9] Interestingly, a previous report of CTCL progression after ICI treatment also documented a considerably delayed progression of 6 months.[7] The delayed assessment compared to solid tumors, and potentially distinct mechanisms of ICI impact, may explain the prolonged progression in CTCL.

The causative role of pembrolizumab in the MF progression in our case remains unconfirmed. The independent progression unrelated to the treatment cannot be ruled out. Notably, the prognosis for stage IA MF is generally excellent, with a 91% to 100% overall survival and a 4% disease progression rate over 5 years.[10] The patient in the present case had maintained stable disease control with phototherapy for over 2 years. However, unusually rapid progression and rare metastasis were observed after pembrolizumab, suggesting a significant likelihood of its contribution to the progression.

This case may represent a new disease emergence, such as angioimmunoblastic T-cell lymphoma or adult T-cell leukemia/lymphoma, rather than the progression of preexisting MF, because thorough immunohistochemical studies or human T-cell lymphotrophic virus serology to definitively rule out these conditions were not performed. However, we believe pembrolizumab induced the progression of preexisting MF, as both posttreatment biopsies showed MF-consistent histopathology and a matching TCR clone to pretreatment patch-stage MF. Further case studies and extensive research are required to establish the relationship between ICI and CTCL.

Conflicts of interest

None disclosed.

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