Pembrolizumab-associated tumor development in a patient with Sézary syndrome

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Key words: cutaneous T-cell lymphoma; immunotherapy; pembrolizumab; Sézary syndrome.

INTRODUCTION

Cutaneous T-cell lymphoma (CTCL) is a heterogenous lymphoproliferative disorder. Mycosis fungoides is the most common variant; Sézary syndrome (SS) is the leukemic counterpart of mycosis fungoides.[1] Treatment ranges from skin-directed therapies to systemic modalities including interferons, extracorporeal photopheresis (ECP), biological agents, and chemotherapy[2]; the latter are indicated for patients with SS. Transformed SS, characterized by the development of skin tumors consisting of large atypical T cells, represents late-stage disease with a poor prognosis.[3] Here we report a case of transformed SS subsequent to pembrolizumab therapy.

Abbreviations used:

BSA:	body surface area
CTCL:	cutaneous T-cell lymphoma
ECP:	extracorporeal photopheresis
PD-1:	programmed cell death-1
SS:	Sézary syndrome

REPORT OF A CASE

An 80-year-old man with SS (stage IVA, T4,N0,M0,B2), diagnosed 8 years ago, presented during pembrolizumab therapy with worsening disease that included new-onset skin tumors and 25-pound weight loss. He previously did not respond to systemic bexarotene, interferon-α, vorinostat, and ECP. Before pembrolizumab therapy, he was erythrodermic without lymph node involvement, and his Sézary cell count was 1251 $CD3^+CD4^+CD26^-$ cells/μL. Current treatment was monthly ECP, twice-weekly narrow-band ultraviolet B therapy, and monthly pembrolizumab (6 cycles). Physical examination found lymphadenopathy; erythematous, lichenified patches involving 72.5% body surface area (BSA) (Fig 1); and new, scattered, 0.5- to 2.0-cm, firm, erythematous nodules involving 4.8% BSA (Fig 2).

Positron emission tomography/computed tomography scan after 6 cycles of pembrolizumab found new, hypermetabolic subcutaneous nodules and lymphadenopathy. The patient declined lymph node biopsy. His Sézary cell count had increased to 1779 cells/μL from 1251 cells/μL. Biopsies of 2 patches from the back found psoriasiform hyperplasia and a nonepidermotropic, superficial perivascular infiltrate of small, cerebriform hyperchromatic lymphocytes with a CD2/CD3/CD4/$CD5^+$, $CD7/CD30^-$ phenotype; 10% had circumferential programmed cell death-1 (PD-1) positivity. The CD4/CD8 ratio was 4. These findings were consistent with erythroderma and a leukemic infiltrate of Sézary lymphocytes. Biopsy of a scalp nodule found a diffuse, deep dermal infiltrate of immunophenotypically identical epidermotropic small cerebriform lymphocytes with admixed eosinophils. A CD4/CD8 ratio of greater than 5 supported a diagnosis of SS with tumors (Fig 3).

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Funding sources: None.
Conflicts of interest: None disclosed.

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JAAD Case Reports 2020;6:16-8.
2352-5126

https://doi.org/10.1016/j.jdcr.2019.11.005

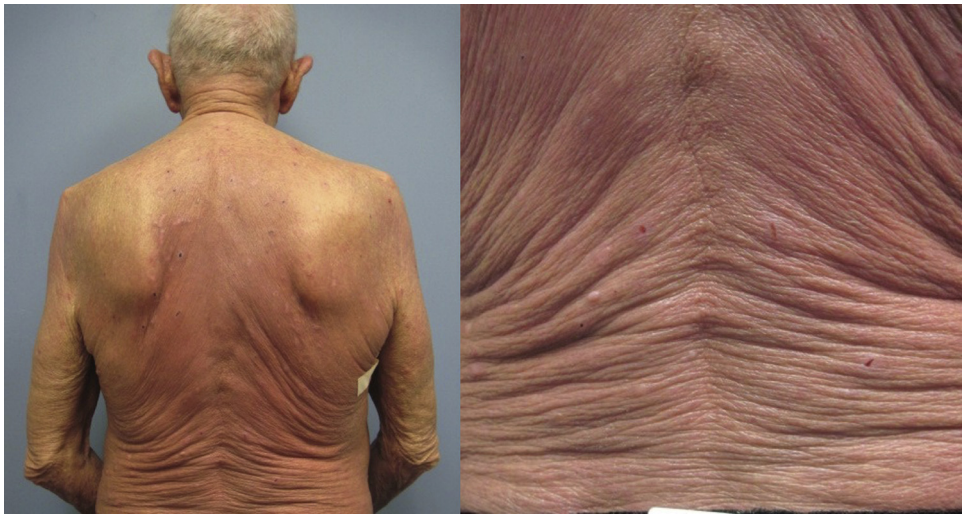

Fig 1. Diffuse erythema involving 72.5% BSA.

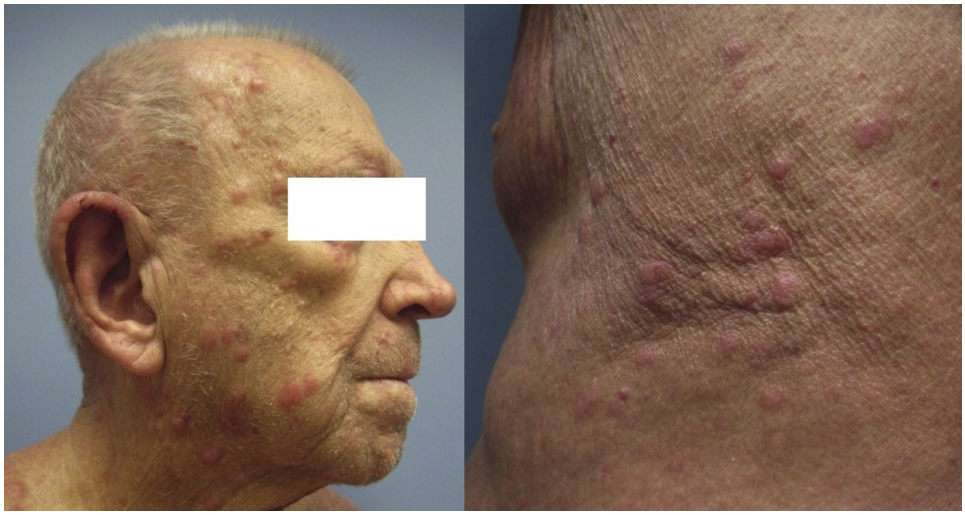

Fig 2. Scattered, 0.5-2.0 cm, firm, pink-purple nodules and tumors.

Large cell transformation and clonal T-cell receptor rearrangement in the skin were not detected.

Considering the clinical, laboratory, and histologic evidence of tumor progression, pembrolizumab was discontinued. The patient's health continued to deteriorate, and he died 1 year after the initiation of pembrolizumab.

DISCUSSION

Pembrolizumab is a monoclonal antibody that targets the PD-1 receptor on lymphocytes, crippling their ability to activate cytotoxic T cells via the PD-1 ligand.[4] Malignant cells may upregulate expression of PD-1 ligand to evade the host immune response; this phenomenon has been noted in circulating T cells from patients with SS.[4-6] Pembrolizumab, which is approved by the US Food and Drug Administration for multiple malignancies, binds and blocks the PD-1 receptor on lymphocytes, allowing the host immune response to destroy cancerous cells that would otherwise escape host defenses via inappropriately upregulated PD-1 ligand.[5,7] Although clinical evidence for its efficacy in CTCL is limited, pembrolizumab was found to provide benefit in other lymphomas; a recent study by Khodadoust et al[8] suggests utility in CTCL.[5,8] There are currently 8 active clinical trials investigating its use in CTCL; 4 of these include SS.[9]

The most common adverse events with pembrolizumab are cutaneous, including nonspecific rashes and hypopigmentation.[10] These manifestations are thought to be mediated by activation of $CD4^+$ and $CD8^+$ T cells, although the exact mechanism is poorly understood. There is one

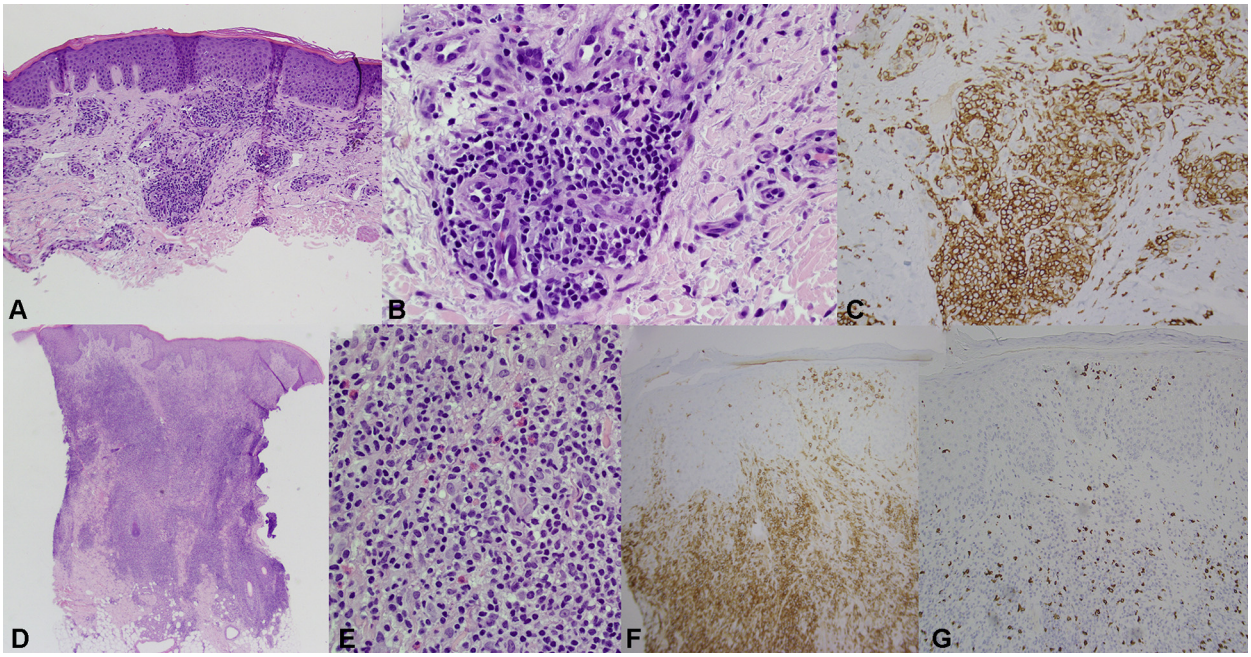

Fig 3. **A-C**, Histopathologic findings before pembrolizumab show psoriasiform hyperplasia with mild spongiosis (**A**), superficial perivascular infiltrate of atypical, cerebriform lymphocytes (**B**), strongly positive for CD4 (**C**), consistent with cutaneous infiltrate of Sézary cells in a background of erythroderma. **D-G**, Histopathologic findings after pembrolizumab of a tumor show nodular and diffuse infiltrate of cerebriform lymphocytes admixed with eosinophils (**D** and **E**), with CD4/CD8 ratio of 5:1 in the dermis and 4-5:1 in the epidermis (**F,G**).

case report of a patient who had a form of CTCL during pembrolizumab therapy for metastatic melanoma.[11] Given that pembrolizumab induces proliferation of T cells, it is plausible that some patients with CTCL may suffer progression via this mechanism.[4] Alternatively, pembrolizumab-induced proliferation may magnify the risk of mutations in a population of genetically defective T cells. Although one must consider that this patient's progression was merely a manifestation of refractory/progressive disease, continued vigilance for the potential of pembrolizumab to exacerbate T-cell lymphoproliferative disorders seems prudent.

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