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A case of Merkel cell carcinoma mimicking cellulitis during Janus kinase inhibitor therapy

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Dear Editors,

Merkel cell carcinoma (MCC) is a highly aggressive, rare cutaneous neuroendocrine carcinoma prone to for local recurrence and distant metastasis. Although Merkel cell polyomavirus (MCPyV) asymptomatically infects mostof the general population, its clonal integration acts as the primary oncogenic driver in approximately 80% of MCC cases, with the remainder linked to ultraviolet radiation exposure. Immunosuppression is a well-established risk factor for MCPyV-positive MCC, highlighting the critical role of host immunosurveillance in suppressing this viral oncogenesis. Janus kinase (JAK) inhibitors are increasingly used for various inflammatory and autoimmune conditions, including rheumatoid arthritis (RA). While large-scale clinical trials have demonstrated that JAK inhibitors do not significantly increase the overall risk of common non-melanoma skin cancers [1], sporadic MCC cases during JAK inhibitor therapy have been recently reported [2–5]. Herein, we report a rapidly progressing, stage IV MCC with an atypical cellulitis-like presentation that developed during combined treatment with a JAK inhibitor and methotrexate (MTX).

A 74-year-old female with a history of RA had received long-term MTX (8 mg/week), with tofacitinib (10 mg/day) added 4 years prior. Two months before presentation, localized erythema and swelling developed on her right lower leg. Initially diagnosed as cellulitis and treated with oral antibiotics at a local clinic, the lesion failed to respond, rapidly expanding with multiple erythematous papules emerging within and around the plaque.

Physical examination revealed circumferential, indurated, edematous erythema mimicking cellulitis on the right lower leg, bordered by multiple well-demarcated, firm red papules. Scattered erythematous papules were also noted on the right knee and right dorsal hand (Figures 1A,B). Initial laboratory investigations revealed a normal white blood cell count of 5.79 × 10^3/mL (neutrophils, 74.6%) and a remarkably low C-reactive protein level of 0.82 mg/dL, inconsistent with typical infectious cellulitis. Conversely, serum neuron-specific enolase (NSE) was elevated at 48.1 ng/mL.

Biopsy of the leg papule revealed a dense dermal-to-subcutaneous proliferation of small, round-to-short spindle-shaped tumor cells in large solid sheets, with hyperchromatic nuclei and frequent mitoses (Figures 1C,D). Immunohistochemically, the neoplastic cells were diffusely positive for chromogranin A, showed characteristic perinuclear dot-like cytokeratin 20 positivity, and were positive for MCPyV large T antigen (clone CM2B4), confirming MCC (Figures 1E,F). Subsequent whole-body PET-CT demonstrated increased uptake in the right lower leg, right inguinal/external iliac lymph nodes, right upper arm, and right dorsal hand (also pathologically confirmed as MCC), establishing Stage IV disease.

Tofacitinib was discontinued, and avelumab (10 mg/kg) was initiated. Within 1 month, the leg lesions completely cleared, the inguinal lymph nodes significantly regressed

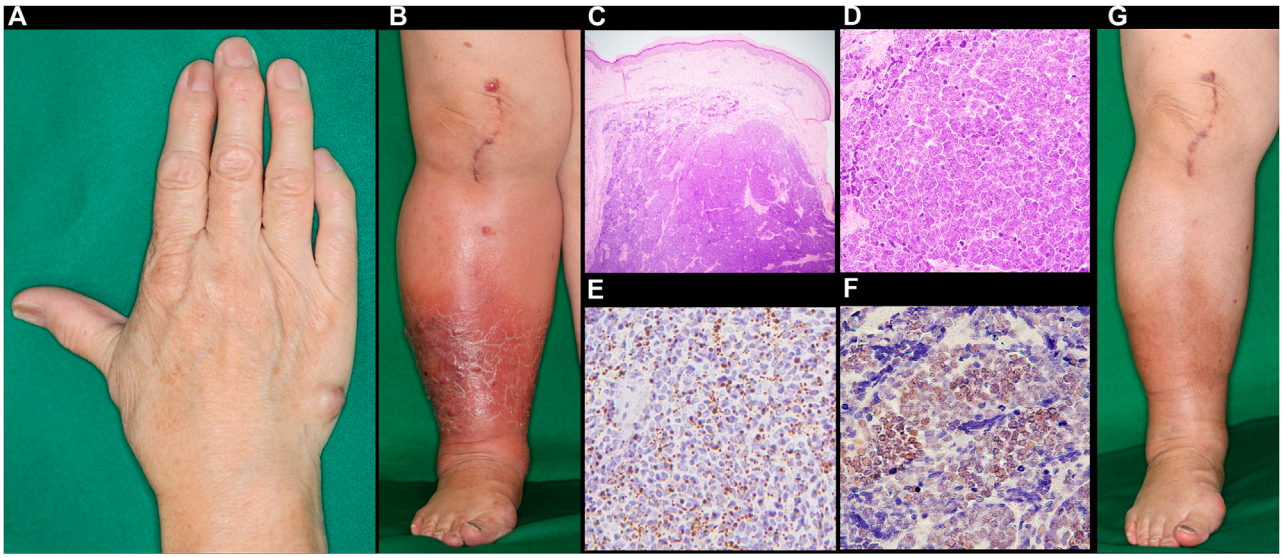

FIGURE 1
Clinical findings of the patient. **(A)** A well-demarcated erythematous papule on the dorsal aspect of the right hand at initial presentation. **(B)** Circumferential indurated erythema on the right lower leg mimicking cellulitis, accompanied by a solitary erythematous papule on the right knee. **(C,D)** Histopathologic examination reveals **(C)** a dense dermal-to-subcutaneous proliferation of tumor cells in solid sheets and **(D)** small, round-to-short spindle-shaped cells with hyperchromatic nuclei and frequent mitoses (hematoxylin-eosin; original magnifications: c, ×40; d, ×400). **(E,F)** Immunohistochemically, the neoplastic cells exhibit **(E)** typical perinuclear dot-like positivity for cytokeratin 20 and **(F)** positivity for MCPyV large T antigen (clone CM2B4) (original magnification: e, f, ×400). **(G)** Clinical appearance 1 month after initiating avelumab treatment, showing marked improvement in erythema, papules, and edema.

(Figure 1G), and the NSE level normalized to 11.1 ng/mL. She subsequently developed Grade 3 immune-related interstitial pneumonia (CTCAE v5.0), leading to permanent avelumab discontinuation after five doses. Two courses of systemic corticosteroid pulse therapy (methylprednisolone 1,000 mg/day for 3 days), and a gradual tapering regimen, successfully resolved the pneumonia. Notably, the patient remains completely recurrence-free 36 months after avelumab discontinuation, without resuming JAK inhibitor therapy.

This case highlights the atypical cellulitis-like manifestation and specific patient characteristics associated with JAK inhibitor therapy. Typical MCC predominantly affects patients > 75 years) on sun-exposed areas like the head and neck. In contrast, JAK inhibitor-associated cases [2–5], frequently occur in younger individuals (<75 years) and often emerge at sun-protected sites such as the trunk or lower extremities. Furthermore, our patient presented with circumferential erythema and induration of the lower leg, which we attributed primarily to severe lymphedema secondary to right inguinal lymph node metastasis which likely facilitated extensive dermal lymphatic invasion by tumor cells, resulting in a "carcinoma erysipelatoides"-like presentation. The absence of elevated inflammatory markers, combined with the lack of response to initial antibiotic therapy, was a crucial clue prompting a diagnostic skin biopsy.

Regarding etiology, large-scale clinical trials indicate that tofacitinib does not significantly increase the overall incidence of non-melanoma skin cancers in RA [1]. However, subsequent long-term data revealed that higher doses of JAK inhibitors are associated with an increased risk of these malignancies, suggesting a dose-dependent relationship reflecting the degree of pharmacological JAK suppression. This implies that while the general risk remains low at standard doses, a more profound pharmacological JAK suppression may specifically disrupt antiviral immunosurveillance in susceptible individuals. Indeed, as observed in our case and others [2–5], individual instances of MCC during JAK inhibitor therapy exhibit a distinct pattern of younger age and atypical distribution. Among the four previously reported cases, the administered agents were ruxolitinib (two cases) and tofacitinib (two cases). Notably, similar to our patient, both tofacitinib-treated cases were MCPyV-positive. Although our patient was receiving concomitant MTX, making it difficult to completely exclude its contribution, it is highly notable that previously reported cases of tofacitinib-associated MCC developed during tofacitinib monotherapy after MTX discontinuation. These observations suggest that pharmacological JAK inhibition may play a more prominent role than MTX in disrupting antiviral immunosurveillance. Tofacitinib inhibits JAK1 and JAK3, thereby suppressing interferon signaling and natural killer cell functions, which are pivotal in the host defense against MCPyV. In our case, the synergistic effect of baseline MTX and the specific anti-viral impairment by tofacitinib likely permitted the uncontrolled oncogenic proliferation of MCPyV.

Additionally, the marked clinical response to avelumab and the subsequent severe pneumonitis likely relate to the patient's prior immunosuppression. The abrupt cessation of the JAK inhibitor likely initiated an immune reconstitution phase. The introduction of PD-L1 blockade during this critical window may have synergistically reversed T-cell exhaustion, which had been induced by the prior immunosuppressive state. This reversal likely triggered a robust, hyper-reactive anti-tumor response,

simultaneously resulting in rapid tumor regression and the development of severe immune-related pneumonitis.

In conclusion, clinicians must remain vigilant for MCC in patients receiving JAK inhibitors, even if large-scale data do not flag a general risk. Because these cases can manifest with rapid progression at atypical sites in younger patients, a low threshold for skin biopsy is essential for early diagnosis and intervention.

This study was conducted under the opt-out policy in accordance with the requirements of the Institutional Review Board (approval No. E-2020-2082).

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

This study was conducted under the opt-out policy in accordance with the requirements of the Institutional Review Board (approval No. E-2020-2082).

Author contributions

All authors participated in the design, interpretation of the studies and analysis of the data and review of the manuscript; TS conducted the clinical data collection and drafted the manuscript, TK provided critical clinical insights and supervised the diagnostic process, and all authors contributed to the final revision and approval of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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