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Concise report

The treatment of Merkel cell carcinoma with immune checkpoint inhibitors: implications for patients with rheumatoid arthritis

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Abstract

Objectives. Merkel cell carcinoma (MCC) is a rare, highly aggressive neuroendocrine skin cancer, which typically affects elderly and immunocompromised and/or immunosuppressed patients. The checkpoint inhibitor avelumab, a mAb targeting the anti-programmed cell death ligand 1 (anti-PD-L1), has revolutionized the treatment of metastatic MCC, achieving dramatic improvements in disease control and overall survival. However, checkpoint inhibitors are associated with the development of immune-related adverse events, such as exacerbation of pre-existing RA. Although most immune-related adverse events can be managed successfully with CSs, their frequent and/or long-term use runs the risk of undermining the efficacy of immune checkpoint inhibition.

Methods. We report two cases of MCC, in which immunosuppressive therapy for the management of RA was administered.

Results. Immunosuppression for (i) pre-existing and (ii) immune checkpoint inhibitor-exacerbated RA was associated with progression of metastatic MCC.

Conclusion. Any decision to initiate immunosuppressive treatment for RA in patients receiving immune checkpoint inhibitor therapy should include careful consideration of the risk of potentially fatal cancer progression and be taken after consultation with the patient's oncologist and rheumatologist. When the immunosuppressive treatment is required, it should be administered for as short a time as possible and under strict clinical and radiological surveillance.

Key words: Merkel cell carcinoma, immune checkpoint inhibition, PD-L1, PD-1, immunosuppression

CLINICAL SCIENCE

Key messages

- Immune checkpoint inhibition (ICI) may exacerbate RA.
- Reducing systemic inflammation should be balanced against the risk of promoting tumour progression in patients with RA flares during ICI.
- Patients with RA receiving concomitant ICI and immunosuppression must be monitored closely for cancer progression.

Introduction

Merkel cell carcinoma (MCC) is a rare, highly aggressive neuroendocrine skin cancer that typically affects the

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elderly. Until recently, the treatment of inoperable metastatic MCC centred on radio- and/or chemotherapy, with poor overall response rates and early disease relapses. Metacarpophalangeal joints virus (MCPyV) infection and chronic ultraviolet radiation exposure are key risk factors that help to explain the predilection of MCC for photo-exposed areas, specifically the head and neck region and the extremities. Not only is the incidence of MCC increased in immunocompromised patients, but immunosuppression itself is also associated with a more aggressive clinical course and a poorer overall prognosis. For example, haematological malignancies are associated with the development of MCC, evidenced by the increased incidence of MCC in patients with chronic lymphocytic leukaemia [1]. In addition, solid organ transplantation is associated with an almost 24-fold increased risk of the development of MCC, which may reflect a synergistic effect of chronic ultraviolet radiation exposure and immunosuppression [2]. Perhaps less well appreciated is the increased risk of MCC in patients with chronic inflammatory diseases, including RA [3, 4].

The treatment of metastatic MCC has been revolutionized by the development of immune checkpoint inhibitors [5, 6]. Not only is treatment with the anti-PD-L1 antibody avelumab or the anti-PD1 antibody pembrolizumab effective, but it results in 24 month median overall survival rates of 36% and 68.7% after failure of upfront chemotherapy and in treatment-naïve patients, respectively [7, 8]. However, the clinical trials of immune checkpoint inhibition for the treatment of metastatic MCC routinely exclude both patients with RA and patients undergoing immunosuppressive therapy. Therefore, the efficacy of immune checkpoint inhibition in these patient populations is unclear. Thus, we report two cases of MCC in elderly male patients with pre-existing RA. Both had received immunosuppressive treatment before and/or during treatment with immune checkpoint inhibitors.

Ethical approval was received from the University of Luebeck's Ethics Committee (ref. 21-055). Given that the clinical data were anonymized, written informed consent from the patients was not required. Nevertheless, Patient 2 provided written consent to publish the clinical images.

Case 1

An 80-year-old male presented with a retro-auricular erythematous nodule. MCC was confirmed histologically; positive for the typical markers cytokeratin 20, synaptophysin and chromogranin A. After wide local excision with 2 cm surgical safety margins, the patient was treated with adjuvant radiotherapy to the site of the primary tumour and the draining lymph nodes (50 Gy). Four years before the diagnosis of MCC, the patient had developed polyarthralgia affecting the MCP, knee, shoulder and elbow joints. The intermittent arthralgia was accompanied by joint swelling and erythema, which resulted in functional impairment and reduced range of movement of the affected joints. In addition, the patient complained of fatigue and malaise. Laboratory investigations revealed an elevated CRP (126 U/l) and a positive RF. The patient underwent multiple RA therapies, including LEF and prednisolone. The patient was undergoing treatment with MTX (15 mg s.c., weekly) and anakinra 100 mg s.c., daily at the time of diagnosis of MCC, with moderate RA disease activity. Given the severity of his RA, this treatment was continued. Nine months after the initial diagnosis of MCC, the patient developed a swollen ipsilateral cervical lymph node, and radiological staging examinations demonstrated disseminated hepatic, renal, osseous and cerebral metastases. The immunosuppressive therapy was discontinued, and immunochemotherapy with pembrolizumab 2 mg/kg and liposomal doxorubicin 50 mg/m^2 was initiated. However, the patient died due to his advanced metastatic disease only 2 weeks after the first treatment cycle.

Case 2

The second patient was an 84-year-old male who developed an erythematous nodule on the proximal phalanx of the left ring finger, which had suddenly increased in size. A biopsy confirmed MCC, which was positive for MCPyV (Fig. 1). Given that the surgical margins were not clear after local excision, the decision was made to amputate the digit. In light of the patient's overall condition and co-morbidities, a sentinel lymph node biopsy was not performed. The patient did not undergo adjuvant radiotherapy.

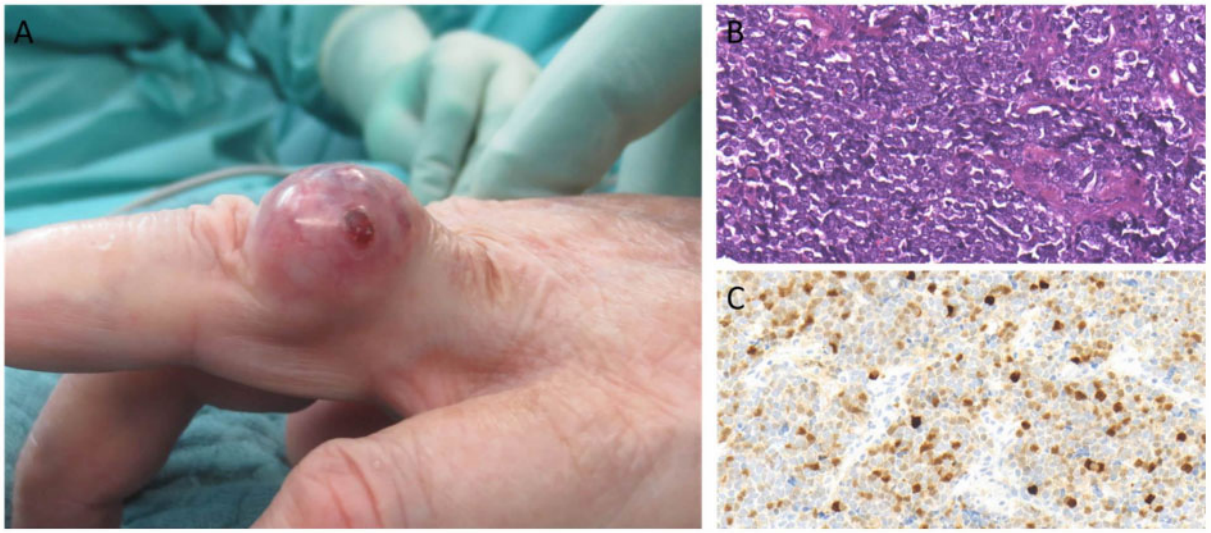
The patient had been diagnosed with seropositive RA by a rheumatologist some 5 years previously. The RA had initially been treated with intermittent courses of systemic CSs. His symptoms included pain and swelling in the fingers, particularly affecting the MCP joints. MTX (10 mg s.c., weekly) had been initiated 5 months before the diagnosis of MCC by his rheumatologist owing to persistent and significant disease activity, reflected in elevated serum CRP concentration.

Seven months after the diagnosis of MCC was made, the patient developed a s.c. swelling on the dorsal aspect of his left wrist, which was surgically excised. Histology confirmed an MCC metastasis, which extended to the surgical margins. Whilst re-excision was being planned, the patient developed a further 3 cm $\times$ 4 cm nodule in the left antecubital fossa, radiologically consistent with a metastasis. Further radiological staging showed no evidence of visceral or bony metastases.

The patient was referred to our department to assess suitability for systemic anti-tumour therapy, given both the rapid disease progression and the persistence of tumour in the surgical margins. After discussion in the interdisciplinary tumour board, the patient's immunosuppressive therapy was discontinued and therapy with avelumab initiated (10 mg/kg, fortnightly).

Initial staging after 3 months of treatment revealed complete remission of the MCC metastasis over the

Fig. 1 Clinical findings of primary tumor



(**A**) Approximately 2-cm-large, skin-coloured to livid, shiny, shimmering nodule with telangiectases and an ulceration on the left ring finger. (**B**) Histology of Merkel cell carcinoma in Haematoxylin and Eosin staining. (**C**) Immunohistochemical detection of Merkel cell polyoma virus (MCPyV) (antibody CM2B4, Santa Cruz Biotechnology, 1:100). Objective magnification ×40 (in B and C).

dorsal aspect of the left wrist and a significant reduction in the size of the metastasis in the antecubital fossa. The decision was made to continue the treatment. One month later, the patient experienced a significant relapse of his RA, with erythema, swelling and pain affecting the MCP joints, in the context of an anti-PD-L1 immune-related adverse event. Prednisolone (10 mg) daily was commenced. Routine staging investigations 3 months later revealed a recurrent metastasis over the left humeral epicondyle, compressing the basilic vein. In the absence of further metastases, radiotherapy was initiated (50 Gy). Treatment with avelumab was recommenced because the patient's RA was no longer symptomatic despite tapering and withdrawal of prednisolone therapy.

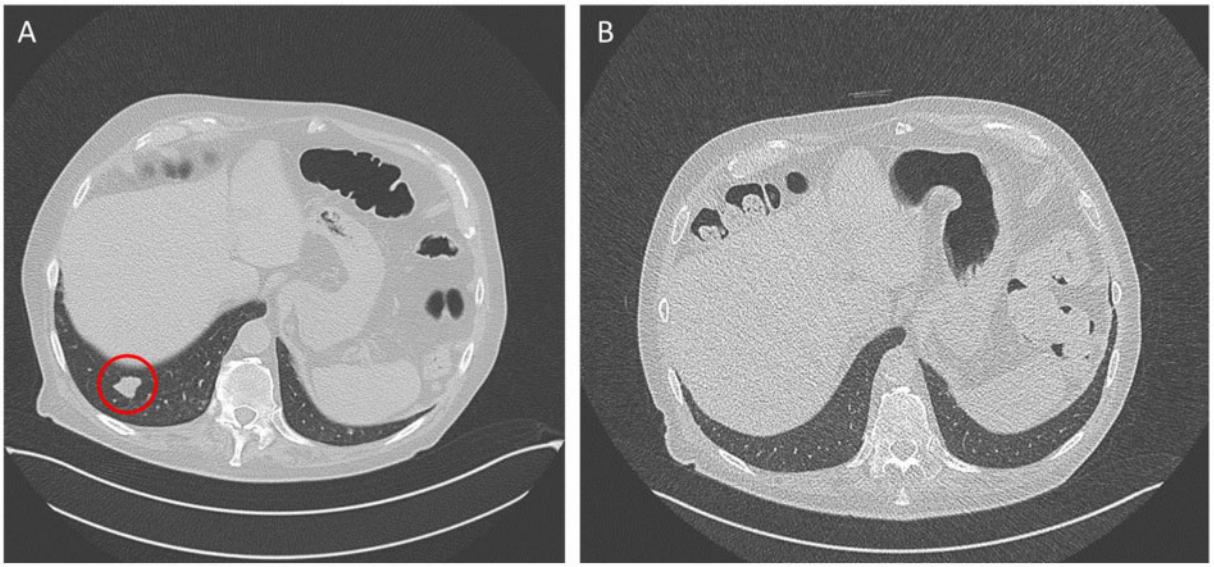
However, shortly after recommencing avelumab the patient again experienced a flare of his RA, with the same rheumatological symptoms. After consulting his rheumatologist, the patient began treatment with MTX (10 mg. s.c, once per week) and avelumab treatment was temporarily interrupted. Unfortunately, the metastasis over the left humeral epicondyle increased in size, prompting surgical removal. Despite having experienced two flares of his RA during avelumab therapy, the patient was keen for avelumab to be re-introduced under ongoing MTX therapy. Routine staging investigations 3 months later revealed multiple pulmonary (Fig. 2A) and lymph node (mediastinal and left axillary) metastases. MTX treatment as withdrawn in view of the development of widespread metastases. Continued administration of avelumab resulted in a complete remission of the MCC, with no evidence of distant (Fig. 2B) or local disease recurrence for >8 months. To date, there have been no other immune-related adverse events and no further exacerbations of the patient's RA.

Discussion

Immunosuppression not only plays an important role in the aetiology of MCC, but is also associated with disease progression and mortality. It is therefore unsurprising that immunosuppressed patients have lower MCC-specific survival rates when compared with immunocompetent patients with MCC [9]. Indeed, overall response rates to avelumab from as little as 18.8% have been reported in patients with metastatic MCC and co-existing haemato-oncological diseases [10]. Perhaps less well recognized is that in addition to the immunosuppression associated with co-existent haematological malignancies, such as chronic lymphatic leukaemia, immunosuppression attributable to autoimmune disorders and their treatment can also contribute to disease progression and increased mortality from MCC. Immunocompromised patients with metastatic MCC also have lower rates of response to immune checkpoint inhibition with avelumab when compared with the overall patient population at 37.5% and 46.7%, respectively [11].

We report two cases of MCC where immunosuppressive therapy for the management of RA was administered. Although the cases of RA were relatively atypical, both being of late onset and affecting elderly males, the patients re-presented with typical symptoms and laboratory findings of RA, and the diagnosis was made by rheumatologists. Indeed, the first case demonstrates that immunosuppressive treatment of RA, in this case

Fig. 2 CT morphological pulmonary metastasis



(**A**) During immunotherapy with avelumab and simultaneous immunosuppressive therapy with MTX. (**B**) After discontinuation of MTX, 7 months later.

MTX and IL-1 receptor antagonists, can be associated with rapid and fatal disease progression. Moreover, even intermittent immunosuppression to treat flares of RA, as in Patient 2, can promote tumour progression. From the temporal association between avelumab administration and the development of rheumatological symptoms, it seems likely that the exacerbations of RA were immune-related adverse events. Immune checkpoint inhibition is reportedly associated with flares of pre-existing RA in 55% of cases [12]. In contrast, immune checkpoint inhibitor-mediated arthritis, in the absence of pre-existing rheumatological disease, is a relatively rare immune-related adverse event, with a prevalence of 3.5–3.8% [13, 14].

Ultimately, bearing in mind that patients with active RA and metastatic MCC may already have a poorer overall prognosis, which might be worsened by the use of potent immunosuppressive agents, the decision to initiate immunosuppression to treat disease flares should be made carefully, after consultation between the patient's dermato-oncologist and rheumatologist [15]. Temporary interruption of immune checkpoint inhibition, when feasible, may facilitate resolution of rheumatological symptoms, as in Patient 2, without necessarily resulting in a loss of cancer treatment response. Moreover, re-introduction of anti-PD-L1 treatment does not always result in a disease flare. In mild active arthritis, NSAIDs may be sufficient to control symptoms. HCQ and low-dose CSs (<10 mg/day prednisolone) are useful treatment options in mild to moderate arthritis owing to immune checkpoint inhibition. Intra-articular glucocorticoid injections may be preferable in mono- or oligoarthritis to avoid systemic immunosuppression, especially in patients with active tumour disease and a high risk of progression.

Additional treatment options include conventional systemic DMARDs (csDMARDs), for example MTX or SSZ, where the risk of disease of progression is low. The European Society for Medical Oncology (ESMO) guidelines 2018 recommend reserving anti-TNF-α therapy for patients with severe rheumatological disease [16]. Of course, the use of biologic DMARDs must be weighed against the risk of tumour progression. Reassuringly, a recent meta-analysis failed to show an increased risk of malignancy during anti-TNF-α, rituximab, anakinra or csDMARD therapy in 13 598 patients with RA. However, it should be pointed out that data from these register studies did not specifically include patients receiving immune checkpoint inhibition [15]. European League Against Rheumatism (EULAR) recommends IL-6 inhibitors as an alternative biological DMARD after csDMARD failure [17]. In severe or systemic life-threatening disease, such as Anti-neutrophil cytoplasmic antibodie (ANCA) vasculitis or connective tissue diseases, rituximab is a useful option owing to the low risk of tumour progression. Targeted synthetic DMARDs should be avoided in tumour patients. In a recent post-marketing safety study, tofacitinib was associated with 1.5-fold increased cancer risk compared with TNF inhibitors.

The management of rheumatological immune-related adverse events in the context of immune checkpoint inhibition treatment for cancer poses a significant clinical challenge. Decisions to interrupt anti-cancer therapy and/or initiate of immunosuppression should be based on the risk of disease progression and the severity of the rheumatological symptoms [17, 18]. When potent immunosuppression is required, it should be administered for as short a time as possible and under strict clinical and radiological surveillance.

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Data availability statement

The data underlying this article are available in the article.

References

1 Koljonen V, Kukko H, Pukkala E *et al.* Chronic lymphocytic leukaemia patients have a high risk of Merkel-cell polyomavirus DNA-positive Merkel-cell carcinoma. Br J Cancer 2009;101:1444–7.

2 Clarke CA, Robbins HA, Tatalovich Z *et al.* Risk of merkel cell carcinoma after solid organ transplantation. J Natl Cancer Inst 2015;107:dju382.

3 Sahi H, Sihto H, Artama M *et al.* History of chronic inflammatory disorders increases the risk of Merkel cell carcinoma, but does not correlate with Merkel cell polyomavirus infection. Br J Cancer 2017;116:260–4.

4 Lanoy E, Engels EA. Skin cancers associated with autoimmune conditions among elderly adults. Br J Cancer 2010;103:112–4.

5 Terheyden P, Mohr A, Langan EA. Immuncheckpointinhibition beim Merkel-Zell-Karzinom [Immune checkpoint inhibition in Merkel cell carcinoma]. Hautarzt 2019;70:684–90.

6 Terheyden P, Becker JC. New developments in the biology and the treatment of metastatic Merkel cell carcinoma. Curr Opin Oncol 2017;29:221–6.

7 Kaufman HL, Russell J, Hamid O *et al.* Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. Lancet Oncol 2016;17:1374–85.

8 Nghiem P, Bhatia S, Lipson EJ *et al.* Durable tumor regression and overall survival in patients with advanced Merkel cell carcinoma receiving pembrolizumab as first-line therapy. J Clin Oncol 2019;37:693–702.

9 Schadendorf D, Lebbé C, Zur Hausen A *et al.* Merkel cell carcinoma: epidemiology, prognosis, therapy and unmet medical needs. Eur J Cancer 2017;71:53–69.

10 Leiter U, Loquai C, Reinhardt L *et al.* Immune checkpoint inhibition therapy for advanced skin cancer in patients with concomitant hematological malignancy: a retrospective multicenter DeCOG study of 84 patients. J Immunother Cancer 2020;8:e000897.

11 Walker JW, Lebbé C, Grignani G *et al.* Efficacy and safety of avelumab treatment in patients with metastatic Merkel cell carcinoma: experience from a global expanded access program. J Immunother Cancer 2020;8:e000313.

12 Efuni E, Cytryn S, Boland P *et al.* Risk of toxicity after initiating immune checkpoint inhibitor treatment in patients with rheumatoid arthritis. J Clin Rheumatol 2020; 10.1097/RHU.0000000000001314.

13 Lidar M, Giat E, Garelick D *et al.* Rheumatic manifestations among cancer patients treated with immune checkpoint inhibitors. Autoimmun Rev 2018;17:284–9.

14 Kostine M, Rouxel L, Barnetche T *et al.* Rheumatic disorders associated with immune checkpoint inhibitors in patients with cancer—clinical aspects and relationship with tumour response: a single-centre prospective cohort study. Ann Rheum Dis 2018;77:393–8.

15 Xie W, Xiao S, Huang Y *et al.* A meta-analysis of biologic therapies on risk of new or recurrent cancer in patients with rheumatoid arthritis and a prior malignancy. Rheumatology (Oxford) 2020;59:930–9.

16 Haanen JBAG, Carbonnel F, Robert C *et al.*; ESMO Guidelines Committee. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018;29:iv264–iv266.

17 Kostine M, Finckh A, Bingham CO *et al.* EULAR points to consider for the diagnosis and management of rheumatic immune-related adverse events due to cancer immunotherapy with checkpoint inhibitors. Ann Rheum Dis 2021;80:36–48.

18 Terheyden P. Therapie eines 85-jährigen MCC-Patienten mit rheumatoider Arthritis Thieme Case Report. PD-L1-Inhibitor Avelumab 2021;1–20.