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

Introduction

Merkel cell carcinoma (MCC) is a rare, highly aggressive neuroendocrine skin cancer that typically affects the...
elderly. Until recently, the treatment of inoperable meta-
static MCC centred on radio- and/or chemotherapy, with 
poor overall response rates and early disease relapse.
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 re-

gion 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 prognos-
tic. For example, haematological malignancies are asso-
ciated with the development of MCC, evidenced by the 
increased incidence of MCC in patients with chronic 
lymphocytic leukaemia [1]. In addition, solid organ trans-
plantation is associated with an almost 24-fold in-
creased risk of the development of MCC, which may 
reflect a synergistic effect of chronic ultraviolet radiation 
posure 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 revolution-
ized by the development of immune checkpoint inhibi-
tors [5, 6]. Not only is treatment with the anti-PD-L1 
antibody avelumab or the anti-PD1 antibody pembrolizu-
mab effective, but it results in 24-month median overall 
survival rates of 36% and 68.7% after failure of upfront 
chemotherapy and in treatment-naive patients, respec-
tively [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 con-
sent 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, synapto-
ophysin 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 pri-
mary tumour and the draining lymph nodes (50 Gy). Four 
years before the diagnosis of MCC, the patient had de-
veloped polyarthritis affecting the MCP, knee, shoulder 
and elbow joints. The intermittent arthralgia was accom-
panied 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, 
ossaceous and cerebral metastases. The immunosuppres-

tive therapy was discontinued, and immunochemother-
apy with pembrolizumab 2 mg/kg and liposomal 
doxorubicin 50 mg/m² was initiated. However, the pa-
tient 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 de vel-
oped 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 condi-
tion and co-morbidities, a sentinel lymph node biopsy 
was not performed. The patient did not undergo adju-
vant 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 el-
evated serum CRP concentration.

Seven months after the diagnosis of MCC was made, 
the patient developed a s.c. swelling on the dorsal as-
pect of his left wrist, which was surgically excised. 
Histology confirmed an MCC metastasis, which ex-
tended to the surgical margins. Whilst re-excision was 
being planned, the patient developed a further 
3 cm x 4 cm nodule in the left antecubital fossa, radi-
ologically consistent with a metastasis. Further radiologi-
cal 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 tu-
mour in the surgical margins. After discussion in the in-
derdisciplinary tumour board, the patient’s 
immunosuppressive therapy was discontinued and ther-
apy with avelumab initiated (10 mg/kg, fortnightly).

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

https://academic.oup.com/rheumapt
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 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...
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 antibody (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.

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