

Merkel cell carcinoma metastatic to cervical lymph node in a patient with rheumatoid arthritis: a case report

This article was published in the following Dove Medical Press journal:
OncoTargets and Therapy

Na Li¹
Guodong Wang²
Xiaohong Jiang¹
Minguan Huang²
Huanyong Tian²
Feng Xuan²
Yufeng Zhang²
Yanting Lv³
Mengjun Hu³
Zhen Wang²
Peng Ren¹
Maoyi Xu²

¹Department of Pathology, Jiaying University Affiliated Women and Children Hospital, Jiaying Maternity and Child Health Care Hospital, Jiaying University, Jiaying, Zhejiang 314051, China; ²Department of Radiotherapy Oncology, Zhuji People's Hospital of Zhejiang Province, The Zhuji Affiliated Hospital of Wenzhou Medical University, Zhuji, Zhejiang 311800, China; ³Department of Pathology, Zhuji People's Hospital of Zhejiang Province, The Zhuji Affiliated Hospital of Wenzhou Medical University, Zhuji, Zhejiang 311800, China

Correspondence: Maoyi Xu
Department of Radiotherapy Oncology, Zhuji People's Hospital of Zhejiang Province, The Zhuji Affiliated Hospital of Wenzhou Medical University, No. 9, Jianmin Road, Taozhu Street, Zhuji, Zhejiang 311800, China
Tel +86 575 8718 2622
Fax +86 575 8718 7700
Email maoyixu1991@163.com

Abstract: Merkel cell carcinoma (MCC) is a rare, aggressive skin malignancy that has a propensity for local recurrence and metastasis to the lymph nodes. In this case report, we discuss a 54-year-old female with rheumatoid arthritis (RA) who had received treatment with prednisone (15 mg/day) for symptom relief and management. The patient visited our hospital with complaints of a nodule in right preauricular area. Computed tomography (CT) scans revealed no distant metastasis. The patient underwent surgical resection and histopathological evaluation of the nodule led to the diagnosis of MCC. The patients received post-surgical treatment with 6 MeV electronic wire radiotherapy. Six months later, CT of the head, neck, abdomen and chest demonstrated a right cervical lymph node mass at the C2 level. The patient then underwent cervical lymph node biopsy and pathological diagnosis confirmed metastatic MCC. One month after the lymph node biopsy, the patients received postoperative intensity modulated radiation therapy in the biopsied area. The patient did not experience any adverse effects to the therapy. In conclusion, the MCC patients with RA can tolerate radiation therapy. As MCC is a highly malignant neoplasia, considering the immune checkpoint inhibitors can lead to immune-related adverse events, detection of MCC at earlier stages is associated with better survival. The treatment decisions of MCC patients with RA continues is still challenging.

Keywords: Merkel cell carcinoma, metastasis, cervical lymph node, rheumatoid arthritis

Introduction

Merkel cell carcinoma (MCC), also termed trabecular carcinoma, was initially described in 1972 by Toker.¹ The clinical features of symptomatic and asymptomatic MCC include; rapid expansion (<3 months), immune suppression, patient >50 years and UV-exposed site on fair skin.² MCC cells express neuroendocrine markers such as Synaptophysin (Syn) and Cytokeratin 20 (CK20).³ CK20 is a fairly specific and sensitive marker of MCC, with a characteristic paranuclear dot-like positivity.

MCC has a propensity for widespread metastases and commonly occurs on sun exposed areas of the head and neck. Biologically, MCC is characterized by local recurrence (30%), regional lymph node metastases (65%) and distant metastases (40%). Surgery is the primary treatment strategy for patients with MCC. Wide surgical excision of the primary lesion is the treatment of choice, while the role of prophylactic regional lymphadenectomy is controversial.⁴ Adjuvant radiotherapy and chemotherapy is frequently associated.

Case report

A 54-year-old female patient was admitted for cutaneous and subcutaneous nodule of right preauricular area. She had no history of smoking, alcohol use, blood transfusion, travel abroad or raw meat intake. Twenty-seven years earlier, she had suffered polyarthralgia, morning stiffness in multiple joints and joint swelling of the wrists, knees and feet. Immunology tests revealed that the patient was positive for antinuclear antibodies, rheumatoid factor and cyclic citrullinated peptide at the time of diagnosis. The patient was diagnosed with rheumatoid arthritis (RA) (Steinbrocker classification: stage I, class II), with an unknown Disease Activity Score-28 (DAS28) and received symptomatic treatment (the specific treatment was unknown). Subsequently, she achieved remission of the symptoms, but the symptoms of joint pain and swelling reoccurred, and the patient received treatment with 15 mg/day prednisone. The symptoms and activity of RA were reduced and stable for ten years. A slow-growing cutaneous and subcutaneous nodule was first noted in March 2017, but the patient declined treatment until August 2017. Computed tomography (CT) scans (completed on August 26, 2017) of the head, neck, abdomen

and chest were performed. No distant metastases were detected. The patient underwent surgical treatment on the 26 August 2017 (Figure 1). The mass, with a diameter of 1 cm, was excised from the right preauricular area. Pathological examination revealed a diagnosis of MCC (stage I) with negative margins (Figure 1). Immunohistochemical staining showed that tumor cells were positive for CK20, CD56, chromogranin A (CgA) and Syn (Figure 1). The proliferative activity (Ki-67) reached ~ 80% (Figure 1). At the 2-week post operation follow-up, whole body examination with 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT was performed (Figure 2). The 18F-FDG PET/CT scan (September 14, 2017) demonstrated a nodule (0.3×0.8 cm) in the post-operative site and the maximum standardized uptake value was 1.7. Postoperative change was considered. No distant metastases were detected. One-month post-operation (October 09, 2017), the area was treated with 6 MeV electronic wire radiation therapy (50 Gy/25 fractions). The patient did not report any adverse effects.

Six months post-surgery, the patient was admitted to hospital for review. The general condition of the patient according to Eastern Cooperative Oncology Group

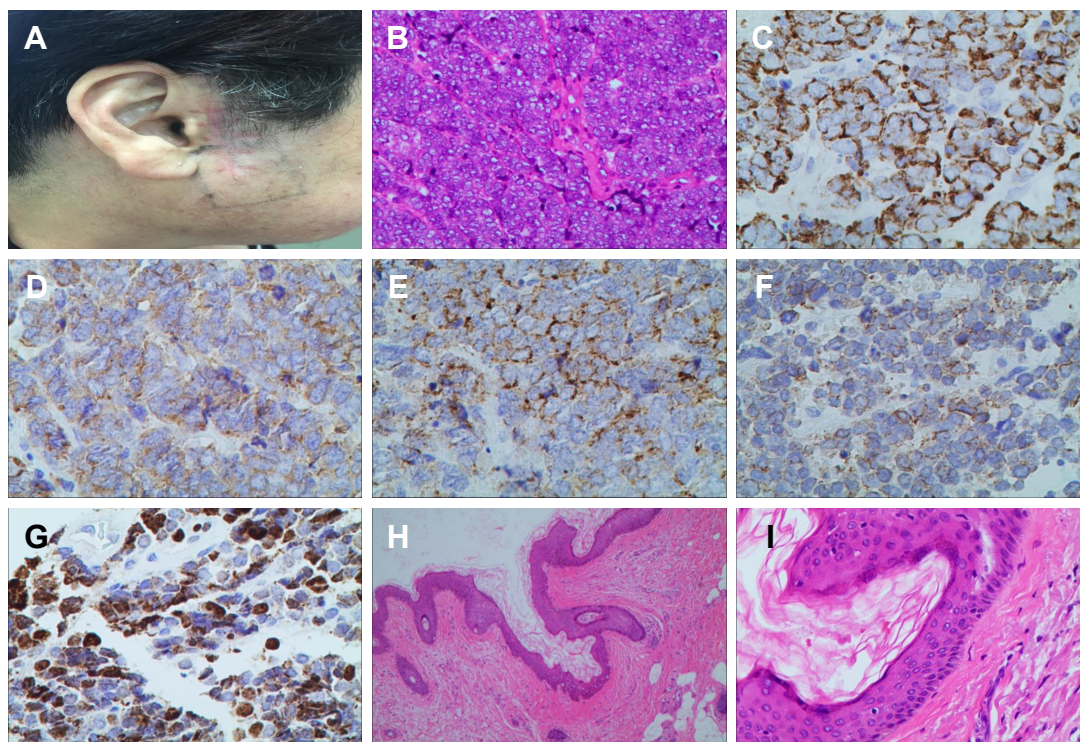


Figure 1 Location of facial malignant tumor and histopathological findings of Merkel cell carcinoma.

Notes: (A) Merkel cell carcinoma was excised from the right preauricular area. (B) H&E staining revealed diffuse proliferation of atypical and pleomorphic tumor cells; small, round basophilic cells are arranged in cordlike structures (original magnification ×200). Histology of the tumor. (C–G) Immunohistochemical analysis found that the tumor cells were positive for (C) CK20, (D) Syn, (E) CgA, (F) CD56 and (G) Ki67 (original magnification ×400). (H, I) Excisional biopsy revealed Merkel cell carcinoma with negative margins (original magnification: H ×40; I ×200).

Abbreviations: CT, Computed tomography; PET, positron emission tomography.

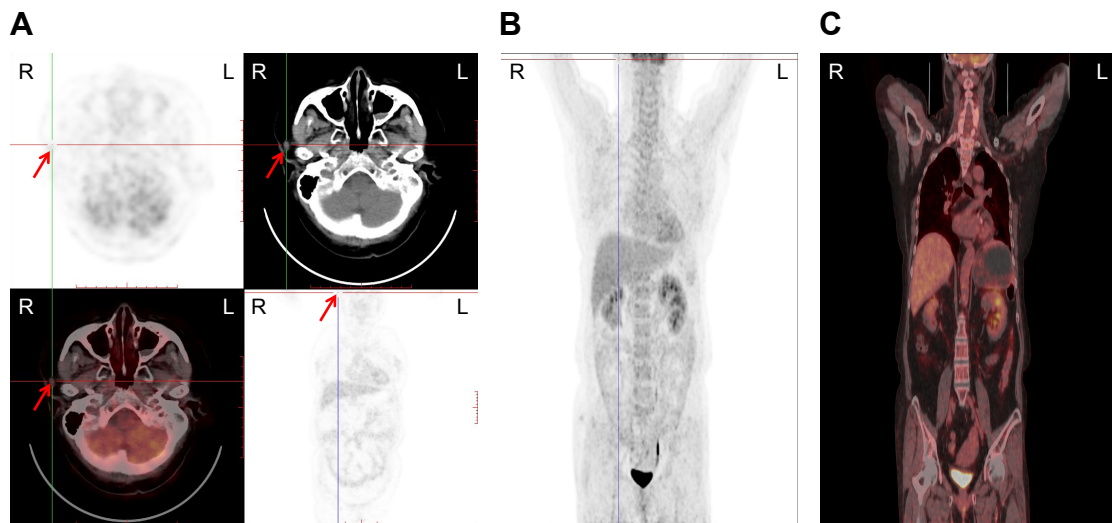


Figure 2 Images of the whole-body PET/CT scan 2 weeks post-surgical excision showing a nodule (red arrow) (0.3*0.8 cm) in the post-operative site with maxSUV values of 1.7 (A). No distant metastases were detected (B, C).

Abbreviations: CT, computed tomography; PET, positron emission tomography.

performance status was 1, and a Disease Activity Score-28 (DAS28-CRP) of 2.58. CT scans (March 01, 2018) of the head, neck, abdomen and chest were performed. The scan demonstrated a right cervical lymph node mass at the C2 level (Figure 3). There was no evidence of metastatic disease elsewhere. Then, the patient underwent cervical lymph node biopsy (March 05, 2018) and pathological diagnosis confirmed metastatic MCC (Figure 4). One month after the lymph node biopsy (April 16, 2018), the lymph node biopsy area received intensity modulated radiation therapy (64 Gy/32 fractions). At follow-up, 1 year after the first operation, the patient was in good general health. The patient did not experience any adverse effects of the therapy. The treatment timeline is presented in Figure 5.

Discussion

MCC is an uncommon neuroendocrine carcinoma of the skin. MCC has a highly prevalent local recurrence and metastases (including liver, lung, cardiac, bone, pancreatic and other organs).⁵⁻⁹ MCC is more frequent in immunosuppressed patients. Immune surveillance plays a critical role in the control of tumour growth and progression.¹⁰ Moreover, immunosuppressive conditions (including HIV infection,¹¹ solid organ transplantation,¹² lymphoma,¹³ and autoimmune disease)¹⁴ are associated with an increased risk of MCC development. Chronic inflammatory disorders increase the risk of MCC significantly, and patients with chronic inflammatory disorders are at higher risk for aggressive MCC.¹⁴ Indeed, connective tissue diseases are also associated with higher incidence of MCC and show poorer MCC-specific survival.^{14,15}

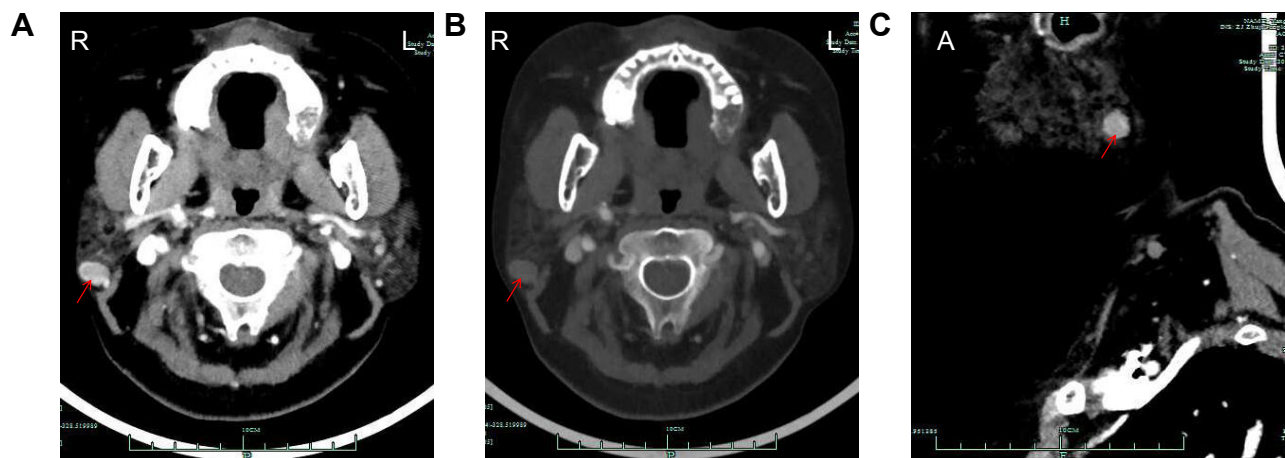


Figure 3 Computed tomography scan (A, B) neck demonstrating a mass (red arrow) in relation to the (C) cervical lymph node mass (red arrow).

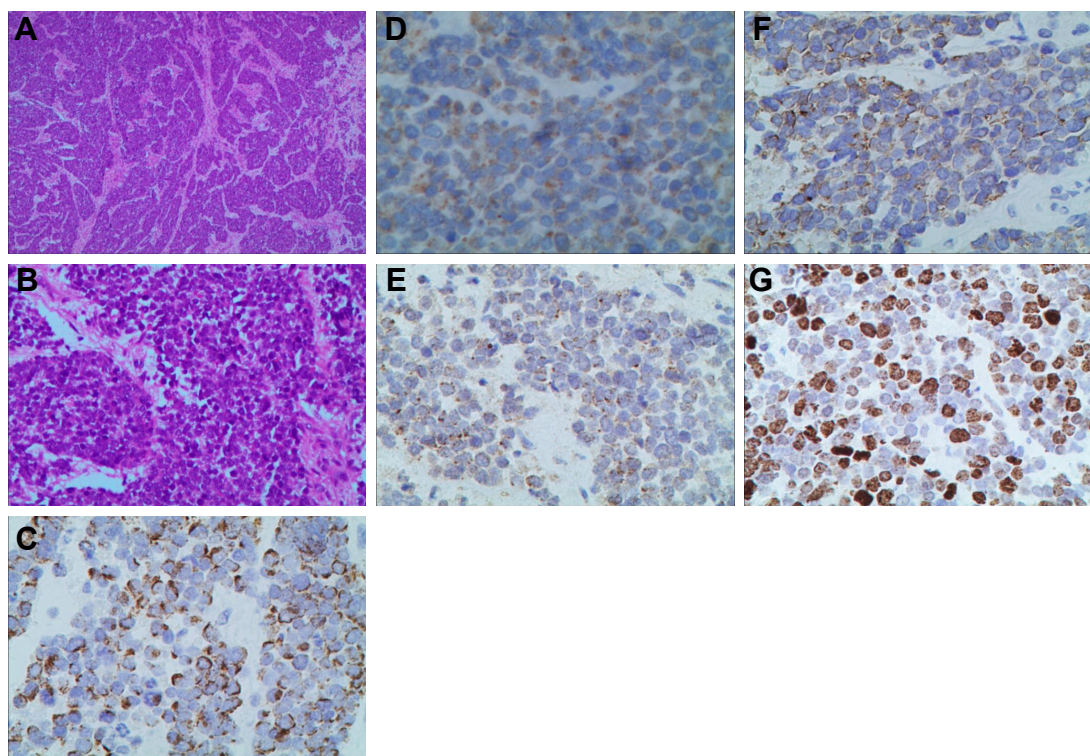


Figure 4 Histology of the resected cervical lymph node biopsy mass.

Notes: (A, B) H&E staining found diffuse proliferation of atypical and pleomorphic cells (original magnification: A $\times 40$; B $\times 200$). (C–G) Immunohistochemical analysis found that the resected mass was positive for (C) CK20, (D) Syn, (E) CgA, (F) CD56 and (G) Ki67 (original magnification $\times 400$).

Connective tissue diseases include RA systemic lupus erythematosus (SLE), systemic sclerosis (SSc), scleroderma, polymyositis-dermatomyositis and vasculitis. MCC in a patient with rheumatoid arthritis is very rarely reported in literature. Furthermore, there is debate about whether patients with connective tissue diseases can tolerate radiation. Many treatment strategies have been considered for patients with connective tissue diseases such as reducing dose prescription, avoiding concomitant treatment and improvement of radiotherapy technology.¹⁶

As mentioned previously, MCC has a highly prevalent local recurrence and distant metastasis. The anti-programmed death-1 (anti-PD-1) antibody, pembrolizumab, is a systemic

therapy option for patients with advanced stage MCC.⁴ Furthermore, Avelumab, an anti-programmed death ligand-1 (anti-PD-L1) monoclonal antibody, is a second line therapy for patients with stage IV MCC that progressed following cytotoxic chemotherapy.¹⁷ Previous studies have demonstrated that anti-PD-1/PD-L1 can lead to immune-related adverse events, which could be lethal.^{18–21}

T cells are major players involved in the pathogenesis of RA and increasing serum soluble PD-1, which has been reported in RA patient.^{22,23} Furthermore, soluble PD-1 can enhance T cell responses by interfering with PD-1/PD-L1 pathway in autoimmune and tumor.^{24–26} Glucocorticoids (eg, prednisone) are anti-inflammatory

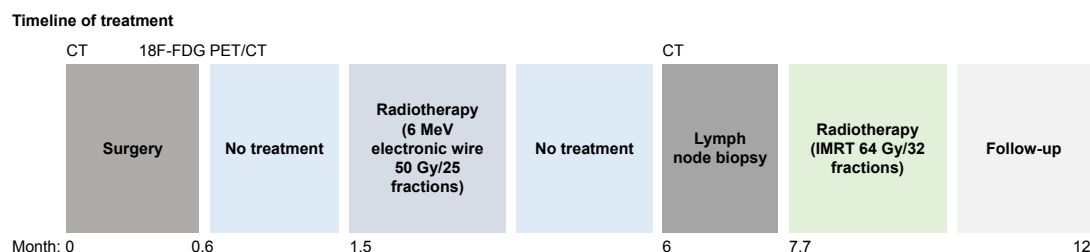


Figure 5 The various treatments the patient received and the duration of each treatment.

Abbreviations: FDG, 18F-fluorodeoxyglucose; IMRT, intensity modulated radiation therapy; PET-CT, positron emission tomography-computed tomography.

and immunosuppressive agents that are able to reduce the inflammation and the progression of RA. However, it was reported that a baseline corticosteroid use of ≥ 10 mg of prednisone or equivalent was associated with poorer outcome in non-small-cell lung cancer patients treated with immunotherapy.²⁷ And prudent use of corticosteroids at the time of initiating immunotherapy is recommended.²⁷ Considering the involvement of activated T cells and the development of immune-related adverse events in anti-PD-1 antibody therapeutics. In this case, clinicians should be aware of the possibility of anti-PD-1/PD-L1-related adverse effects, such as inflammatory arthritis,²⁸ especially in patients with RA. In this case report, the patient with RA tolerated radiation therapy without any adverse side effects. As with MCC of other areas, metastasis or local recurrence can occur after a certain period. Chemotherapy might be a therapeutic option in chemo-sensitive metastatic MCC, and further evaluation is warranted.

Therefore, clinicians should be aware of the use of immune checkpoint inhibitors in MCC patients with RA. We presented a unique case of MCC metastatic to cervical lymph node in a patient with RA. We aim to highlight that the treatment decisions to patients with RA continues to be challenging.

Ethics statement

Written informed consent was obtained from the patient for the publication of this case report and accompanying images. This study was approved by the Institutional Review Board of Zhuji People's Hospital.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Toker C. Trabecular carcinoma of the skin. *Arch Dermatol*. 1972;105(1):107–110.
2. Heath M, Jaimes N, Lemos B, et al. Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: the AEIOU features. *J Am Acad Dermatol*. 2008;58(3):375–381.
3. Maricich SM, Wellnitz SA, Nelson AM, et al. Merkel cells are essential for light-touch responses. *Science*. 2009;324(5934):1580–1582.
4. Bichakjian CK, Olencki T, Aasi SZ, et al. Basal cell skin cancer, version 1.2016, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2016;14(5):574–597.
5. Shoda K, Ikoma H, Yamamoto Y, et al. A case of long-term survival following hepatectomy for liver metastasis of Merkel cell carcinoma. *Surg Case Rep*. 2015;1(1):30.
6. Suttie CF, Hruby G, Horvath L, Thompson J. Cardiac metastasis in Merkel cell carcinoma. *J Clin Oncol*. 2014;32(13):e52–e53.
7. Fong LS, Mathur M, Bhindi R, Figtree GA. Right atrial Merkel cell tumour metastasis characterization using a multimodality approach. *Eur Heart J*. 2012;33(17):2205.
8. Peloschek P, Novotny C, Mueller-Mang C, et al. Diagnostic imaging in Merkel cell carcinoma: lessons to learn from 16 cases with correlation of sonography, CT, MRI and PET. *Eur J Radiol*. 2010;73(2):317–323.
9. Maimone A, Bianchi ML, Lorenzini P, de Leone A, De Luca L. Endoscopic ultrasound-guided fine needle biopsy of pancreatic metastasis from Merkel cell carcinoma. *Endoscopy*. 2016;48(S 01):E199–E200.
10. Becker JC, Stang A, DeCaprio JA, et al. Merkel cell carcinoma. *Nat Rev Dis Primers*. 2017;3:17077.
11. Engels EA, Frisch M, Goedert JJ, Biggar RJ, Miller RW. Merkel cell carcinoma and HIV infection. *Lancet*. 2002;359(9305):497–498.
12. Clarke CA, Robbins HA, Tatalovich Z, et al. Risk of Merkel cell carcinoma after solid organ transplantation. *J Natl Cancer Inst*. 2015;107(2):dju382.
13. Ziprin P, Smith S, Salerno G, Rosin RD. Two cases of Merkel cell tumour arising in patients with chronic lymphocytic leukaemia. *Br J Dermatol*. 2000;142(3):525–528.
14. Sahi H, Sihto H, Artama M, Koljonen V, Böhring T, Pukkala E. 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(2):260–264.
15. Paulson KG, Iyer JG, Blom A, et al. Systemic immune suppression predicts diminished Merkel cell carcinoma-specific survival independent of stage. *J Invest Dermatol*. 2013;133(3):642–646.
16. Gajj-Levra N, Sciascia S, Fiorentino A, et al. Radiotherapy in patients with connective tissue diseases. *Lancet Oncol*. 2016;17(3):e109–e117.
17. 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(10):1374–1385.
18. Wang PF, Chen Y, Song SY, et al. Immune-related adverse events associated with anti-PD-1/PD-L1 treatment for malignancies: a meta-analysis. *Front Pharmacol*. 2017;8:730.
19. Nishino M, Ramaiya NH, Awad MM, et al. PD-1 inhibitor-related pneumonitis in advanced cancer patients: radiographic patterns and clinical course. *Clin Cancer Res*. 2016;22(24):6051–6060.
20. Cappelli LC, Gutierrez AK, Baer AN, et al. Inflammatory arthritis and sicca syndrome induced by nivolumab and ipilimumab. *Ann Rheum Dis*. 2017;76(1):43–50.
21. Spallarossa P, Meliotta G, Brunelli C, et al. Potential cardiac risk of immune-checkpoint blockade as anticancer treatment: what we know, what we do not know, and what we can do to prevent adverse effects. *Med Res Rev*. 2018;38(5):1447–1468.
22. Isaacs JD. Therapeutic T-cell manipulation in rheumatoid arthritis: past, present and future. *Rheumatology (Oxford)*. 2008;47(10):1461–1468.
23. Guo Y, Walsh AM, Canavan M, et al. Immune checkpoint inhibitor PD-1 pathway is down-regulated in synovium at various stages of rheumatoid arthritis disease progression. *PLoS One*. 2018;13(2):e0192704.
24. Shin SP, Seo HH, Shin JH, et al. Adenovirus expressing both thymidine kinase and soluble PD1 enhances antitumor immunity by strengthening CD8 T-cell response. *Mol Ther*. 2013;21(3):688–695.
25. Dai S, Jia R, Zhang X, Fang Q, Huang L. The PD-1/PD-Ls pathway and autoimmune diseases. *Cell Immunol*. 2014;290(1):72–79.
26. Zhu X, Lang J. Soluble PD-1 and PD-L1: predictive and prognostic significance in cancer. *Oncotarget*. 2017;8(57):97671–97682.
27. Arbour KC, Mezquita L, Long N, et al. Impact of baseline steroids on efficacy of programmed cell death-1 and programmed death-ligand 1 blockade in patients with non-small-cell lung cancer. *J Clin Oncol*. 2018;36(28):2872–2878.
28. Cappelli LC, Gutierrez AK, Baer AN, et al. Inflammatory arthritis and sicca syndrome induced by nivolumab and ipilimumab. *Ann Rheum Dis*. 2017;76(1):43–50.

OncoTargets and Therapy

Dovepress

Publish your work in this journal

OncoTargets and Therapy is an international, peer-reviewed, open access journal focusing on the pathological basis of all cancers, potential targets for therapy and treatment protocols employed to improve the management of cancer patients. The journal also focuses on the impact of management programs and new therapeutic agents and protocols on

patient perspectives such as quality of life, adherence and satisfaction. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <http://www.dovepress.com/oncotargets-and-therapy-journal>