

# World Journal of *Clinical Cases*

*World J Clin Cases* 2021 June 26; 9(18): 4460-4880



### OPINION REVIEW

- 4460** Surgery for pancreatic tumors in the midst of COVID-19 pandemic

*Kato H, Asano Y, Arakawa S, Ito M, Kawabe N, Shimura M, Hayashi C, Ochi T, Yasuoka H, Higashiguchi T, Kondo Y, Nagata H, Horiguchi A*

### REVIEW

- 4467** Roles of exosomes in diagnosis and treatment of colorectal cancer

*Umwali Y, Yue CB, Gabriel ANA, Zhang Y, Zhang X*

### MINIREVIEWS

- 4480** Dynamics of host immune responses to SARS-CoV-2

*Taherkhani R, Taherkhani S, Farshadpour F*

- 4491** Current treatment for hepatitis C virus/human immunodeficiency virus coinfection in adults

*Laiwatthanapaisan R, Sirinawasatien A*

- 4500** Anti-tumor effect of statin on pancreatic adenocarcinoma: From concept to precision medicine

*Huang CT, Liang YJ*

- 4506** Roles of vitamin A in the regulation of fatty acid synthesis

*Yang FC, Xu F, Wang TN, Chen GX*

### ORIGINAL ARTICLE

#### Basic Study

- 4520** Identification of the circRNA-miRNA-mRNA regulatory network and its prognostic effect in colorectal cancer

*Yin TF, Zhao DY, Zhou YC, Wang QQ, Yao SK*

- 4542** Tetramethylpyrazine inhibits proliferation of colon cancer cells *in vitro*

*Li H, Hou YX, Yang Y, He QQ, Gao TH, Zhao XF, Huo ZB, Chen SB, Liu DX*

#### Case Control Study

- 4553** Significance of highly phosphorylated insulin-like growth factor binding protein-1 and cervical length for prediction of preterm delivery in twin pregnancies

*Lan RH, Song J, Gong HM, Yang Y, Yang H, Zheng LM*

**Retrospective Cohort Study**

- 4559** Expected outcomes and patients' selection before chemoembolization—"Six-and-Twelve or Pre-TACE-Predict" scores may help clinicians: Real-life French cohorts results

*Adhoute X, Larrey E, Anty R, Chevallier P, Penaranda G, Tran A, Bronowicki JP, Raoul JL, Castellani P, Perrier H, Bayle O, Monnet O, Pol B, Bourliere M*

**Retrospective Study**

- 4573** Application of intelligent algorithms in Down syndrome screening during second trimester pregnancy  
*Zhang HG, Jiang YT, Dai SD, Li L, Hu XN, Liu RZ*
- 4585** Evaluation of a five-gene signature associated with stromal infiltration for diffuse large B-cell lymphoma  
*Nan YY, Zhang WJ, Huang DH, Li QY, Shi Y, Yang T, Liang XP, Xiao CY, Guo BL, Xiang Y*
- 4599** Efficacy of combination of localized closure, ethacridine lactate dressing, and phototherapy in treatment of severe extravasation injuries: A case series  
*Lu YX, Wu Y, Liang PF, Wu RC, Tian LY, Mo HY*
- 4607** Observation and measurement of applied anatomical features for thoracic intervertebral foramen puncture on computed tomography images  
*Wang R, Sun WW, Han Y, Fan XX, Pan XQ, Wang SC, Lu LJ*
- 4617** Histological transformation of non-small cell lung cancer: Clinical analysis of nine cases  
*Jin CB, Yang L*
- 4627** Diagnostic value of amygdala volume on structural magnetic resonance imaging in Alzheimer's disease  
*Wang DW, Ding SL, Bian XL, Zhou SY, Yang H, Wang P*
- 4637** Comparison of ocular axis and corneal diameter between entropion and non-entropion eyes in children with congenital glaucoma  
*Wang Y, Hou ZJ, Wang HZ, Hu M, Li YX, Zhang Z*

**Observational Study**

- 4644** Risk factors for postoperative delayed gastric emptying in ovarian cancer treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy  
*Cui GX, Wang ZJ, Zhao J, Gong P, Zhao SH, Wang XX, Bai WP, Li Y*
- 4654** Clinical characteristics, gastrointestinal manifestations and outcomes of COVID-19 patients in Iran; does the location matters?  
*Mokarram P, Dalivand MM, Pizuorno A, Aligolighasemabadi F, Sadeghdoust M, Sadeghdoust E, Aduli F, Oskrochi G, Brim H, Ashktorab H*
- 4668** AWGS2019 vs EWGSOP2 for diagnosing sarcopenia to predict long-term prognosis in Chinese patients with gastric cancer after radical gastrectomy  
*Wu WY, Dong JJ, Huang XC, Chen ZJ, Chen XL, Dong QT, Bai YY*

**Prospective Study**

- 4681** Clinical outcomes and 5-year follow-up results of keratosis pilaris treated by a high concentration of glycolic acid

*Tian Y, Li XX, Zhang JJ, Yun Q, Zhang S, Yu JY, Feng XJ, Xia AT, Kang Y, Huang F, Wan F*

**Randomized Controlled Trial**

- 4690** Tenofovir disoproxil fumarate in Chinese chronic hepatitis B patients: Results of a multicenter, double-blind, double-dummy, clinical trial at 96 weeks

*Chen XF, Fan YN, Si CW, Yu YY, Shang J, Yu ZJ, Mao Q, Xie Q, Zhao W, Li J, Gao ZL, Wu SM, Tang H, Cheng J, Chen XY, Zhang WH, Wang H, Xu ZN, Wang L, Dai J, Xu JH*

**SYSTEMATIC REVIEWS**

- 4700** Mesenteric ischemia in COVID-19 patients: A review of current literature

*Kerawala AA, Das B, Solangi A*

- 4709** Role of theories in school-based diabetes care interventions: A critical review

*An RP, Li DY, Xiang XL*

**CASE REPORT**

- 4721** Alport syndrome combined with lupus nephritis in a Chinese family: A case report

*Liu HF, Li Q, Peng YQ*

- 4728** Botulinum toxin injection for Cockayne syndrome with muscle spasticity over bilateral lower limbs: A case report

*Hsu LC, Chiang PY, Lin WP, Guo YH, Hsieh PC, Kuan TS, Lien WC, Lin YC*

- 4734** Meigs' syndrome caused by granulosa cell tumor accompanied with intrathoracic lesions: A case report

*Wu XJ, Xia HB, Jia BL, Yan GW, Luo W, Zhao Y, Luo XB*

- 4741** Primary mesonephric adenocarcinoma of the fallopian tube: A case report

*Xie C, Shen YM, Chen QH, Bian C*

- 4748** Pancreas-preserving duodenectomy for treatment of a duodenal papillary tumor: A case report

*Wu B, Chen SY, Li Y, He Y, Wang XX, Yang XJ*

- 4754** Pheochromocytoma with abdominal aortic aneurysm presenting as recurrent dyspnea, hemoptysis, and hypotension: A case report

*Zhao HY, Zhao YZ, Jia YM, Mei X, Guo SB*

- 4760** Minimally invasive removal of a deep-positioned cannulated screw from the femoral neck: A case report

*Yang ZH, Hou FS, Yin YS, Zhao L, Liang X*

- 4765** Splenic Kaposi's sarcoma in a human immunodeficiency virus-negative patient: A case report

*Zhao CJ, Ma GZ, Wang YJ, Wang JH*

- 4772** Neonatal syringocystadenoma papilliferum: A case report  
*Jiang HJ, Zhang Z, Zhang L, Pu YJ, Zhou N, Shu H*
- 4778** Disappeared intralenticular foreign body: A case report  
*Xue C, Chen Y, Gao YL, Zhang N, Wang Y*
- 4783** Femoral neck stress fractures after trampoline exercise: A case report  
*Nam DC, Hwang SC, Lee EC, Song MG, Yoo JI*
- 4789** Collision carcinoma of the rectum involving neuroendocrine carcinoma and adenocarcinoma: A case report  
*Zhao X, Zhang G, Li CH*
- 4797** Therapeutic effect of autologous concentrated growth factor on lower-extremity chronic refractory wounds: A case report  
*Liu P, Liu Y, Ke CN, Li WS, Liu YM, Xu S*
- 4803** Cutaneous myiasis with eosinophilic pleural effusion: A case report  
*Fan T, Zhang Y, Lv Y, Chang J, Bauer BA, Yang J, Wang CW*
- 4810** Severe hematuria due to vesical varices in a patient with portal hypertension: A case report  
*Wei ZJ, Zhu X, Yu HT, Liang ZJ, Gou X, Chen Y*
- 4817** Rare coexistence of multiple manifestations secondary to thalamic hemorrhage: A case report  
*Yu QW, Ye TF, Qian WJ*
- 4823** Anderson-Fabry disease presenting with atrial fibrillation as earlier sign in a young patient: A case report  
*Kim H, Kang MG, Park HW, Park JR, Hwang JY, Kim K*
- 4829** Long-term response to avelumab and management of oligoprogression in Merkel cell carcinoma: A case report  
*Leão I, Marinho J, Costa T*
- 4837** Central pontine myelinolysis mimicking glioma in diabetes: A case report  
*Shi XY, Cai MT, Shen H, Zhang JX*
- 4844** Microscopic transduodenal excision of an ampullary adenoma: A case report and review of the literature  
*Zheng X, Sun QJ, Zhou B, Jin M, Yan S*
- 4852** Growth hormone cocktail improves hepatopulmonary syndrome secondary to hypopituitarism: A case report  
*Ji W, Nie M, Mao JF, Zhang HB, Wang X, Wu XY*
- 4859** Low symptomatic COVID-19 in an elderly patient with follicular lymphoma treated with rituximab-based immunotherapy: A case report  
*Łęcki S, Wyżgolik K, Nicze M, Georgiew-Nadziakiewicz S, Chudek J, Wdowiak K*

- 4866** Adult rhabdomyosarcoma originating in the temporal muscle, invading the skull and meninges: A case report

*Wang GH, Shen HP, Chu ZM, Shen J*

- 4873** *Listeria monocytogenes* bacteremia in a centenarian and pathogen traceability: A case report

*Zhang ZY, Zhang XA, Chen Q, Wang JY, Li Y, Wei ZY, Wang ZC*

**ABOUT COVER**

Editorial Board Member of *World Journal of Clinical Cases*, Shingo Tsujinaka, MD, PhD, Assistant Professor, Senior Lecturer, Surgeon, Department of Surgery, Saitama Medical Center, Jichi Medical University, Saitama 330-8503, Japan. tsujinakas@omiya.jichi.ac.jp

**AIMS AND SCOPE**

The primary aim of *World Journal of Clinical Cases* (WJCC, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

**INDEXING/ABSTRACTING**

The WJCC is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, PubMed, and PubMed Central. The 2021 Edition of Journal Citation Reports® cites the 2020 impact factor (IF) for WJCC as 1.337; IF without journal self cites: 1.301; 5-year IF: 1.742; Journal Citation Indicator: 0.33; Ranking: 119 among 169 journals in medicine, general and internal; and Quartile category: Q3. The WJCC's CiteScore for 2020 is 0.8 and Scopus CiteScore rank 2020: General Medicine is 493/793.

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: Ji-Hong Lin; Production Department Director: Xiang Li; Editorial Office Director: Jin-Lai Wang.

**NAME OF JOURNAL**

*World Journal of Clinical Cases*

**ISSN**

ISSN 2307-8960 (online)

**LAUNCH DATE**

April 16, 2013

**FREQUENCY**

Thrice Monthly

**EDITORS-IN-CHIEF**

Dennis A Bloomfield, Sandro Vento, Bao-Gan Peng

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

**PUBLICATION DATE**

June 26, 2021

**COPYRIGHT**

© 2021 Baishideng Publishing Group Inc

**INSTRUCTIONS TO AUTHORS**

<https://www.wjgnet.com/bpg/gerinfo/204>

**GUIDELINES FOR ETHICS DOCUMENTS**

<https://www.wjgnet.com/bpg/GerInfo/287>

**GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH**

<https://www.wjgnet.com/bpg/gerinfo/240>

**PUBLICATION ETHICS**

<https://www.wjgnet.com/bpg/GerInfo/288>

**PUBLICATION MISCONDUCT**

<https://www.wjgnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>

## Long-term response to avelumab and management of oligoprogression in Merkel cell carcinoma: A case report

Inês Leão, Joana Marinho, Telma Costa

**ORCID number:** Inês Leão 0000-0002-6586-4980; Joana Marinho 0000-0003-3665-4666; Telma Costa 0000-0002-9625-1124.

**Author contributions:** All authors reviewed the literature and were involved in data collection, analysis and interpretation, manuscript writing, and approval of final article.

**Informed consent statement:** All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

**Conflict-of-interest statement:** Dr. Marinho reports grants from Merck KGaA, during the conduct of the study; personal fees from Merck KGaA, non-financial support from Servier, non-financial support from Astellas, non-financial support from Roche, non-financial support from Lilly, non-financial support from Merck, outside the submitted work. "The patient was treated in the expanded access program and avelumab was provided by Merck KGaA, as part of an Alliance between Merck KGaA and Pfizer". The development of this publication was financially supported by Merck KGaA, Darmstadt, Germany through an independent medical writing

**Inês Leão, Joana Marinho, Telma Costa,** Department of Oncology, Centro Hospitalar Vila Nova de Gaia/Espinho, Vila Nova de Gaia 4434-502, Portugal

**Corresponding author:** Telma Costa, MD, Doctor, Department of Oncology, Centro Hospitalar Vila Nova de Gaia/Espinho, Rua Conceição Fernandes, Vila Nova de Gaia 4434-502, Portugal. [telma.r.c.costa@gmail.com](mailto:telma.r.c.costa@gmail.com)

### Abstract

#### BACKGROUND

Merkel cell carcinoma (MCC) is a rare and aggressive cutaneous neuroendocrine neoplasia, with high risk of recurrence and metastasis and poor survival. Immune checkpoint inhibitors, like the anti-programmed death-ligand 1 agent avelumab, were recently approved for the treatment of advanced MCC. We, herein, report the first case of advanced MCC with oligoprogression managed with avelumab and local radical treatment.

#### CASE SUMMARY

A 61-year-old man was presented to the hospital with sporadic fever and an exudative malodorous mass (10 cm of diameter), located on the right gluteal region. The final diagnosis was MCC, cT4N3M1c (AJCC, TNM staging 8<sup>th</sup> edition, 2017), with invasion of adjacent muscle, in-transit metastasis, and bone lesions. Patient started chemotherapy (cisplatin and etoposide), and after six cycles, the main tumor increased, evidencing disease progression. Two months later, the patient started second line treatment with avelumab (under an early access program). After two cycles of treatment, the lesion started to decrease, achieving a major response. Local progression was documented after 16 cycles. However, as the tumor became resectable, salvage surgery was performed, while keeping the systemic treatment with avelumab. Since the patient developed bilateral pneumonia, immunotherapy was suspended. More than 2.5 years after surgery (last 19 mo without systemic therapy), the patient maintains complete local response and stable bone lesions.

#### CONCLUSION

This report highlights the efficacy and long-term response of avelumab on the management of a chemotherapy resistant advanced MCC, with evidence of oligoprogression, in combination with local radical treatment.

**Key Words:** Merkel cell carcinoma; Unresectable tumor; Avelumab; Oligoprogression;



grant, as part of an Alliance between Merck KGaA and Pfizer. The views and opinions described in this publication do not necessarily reflect those of the grantor.

#### CARE Checklist (2016) statement:

The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Unsolicited manuscript

**Specialty type:** Medicine, research and experimental

**Country/Territory of origin:** Portugal

#### Peer-review report's scientific quality classification

Grade A (Excellent): 0  
Grade B (Very good): 0  
Grade C (Good): 0  
Grade D (Fair): 0  
Grade E (Poor): 0

**Received:** February 8, 2021

**Peer-review started:** February 8, 2021

**First decision:** April 25, 2021

**Revised:** May 4, 2021

**Accepted:** May 8, 2021

**Article in press:** May 8, 2021

**Published online:** June 26, 2021

**P-Reviewer:** Lee HJ

**S-Editor:** Fan JR

**L-Editor:** Filipodia

**P-Editor:** Xing YX

Surgery; Chemotherapy; Case report

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core Tip:** This report highlights the efficacy and long-term response of avelumab on the management of a chemotherapy resistant advanced Merkel cell carcinoma. It shows also a successful approach to oligoprogression with local radical treatment, surgery, and radiotherapy, while maintaining systemic therapy with avelumab. The results support the effectiveness of this strategy for the management of unresectable Merkel cell carcinoma.

**Citation:** Leão I, Marinho J, Costa T. Long-term response to avelumab and management of oligoprogression in Merkel cell carcinoma: A case report. *World J Clin Cases* 2021; 9(18): 4829-4836

**URL:** <https://www.wjgnet.com/2307-8960/full/v9/i18/4829.htm>

**DOI:** <https://dx.doi.org/10.12998/wjcc.v9.i18.4829>

## INTRODUCTION

Merkel cell carcinoma (MCC) is a rare and aggressive cutaneous neuroendocrine neoplasia, with early metastatization and low survival rates[1]. The majority of patients can be included in one of the following risk groups: Elderly, immunocompromised patients, patients with history of high ultraviolet radiation exposure, and patients with hematological malignancies or other skin tumors[1-3]. MCC can also be associated with the presence of Merkel cell polyomavirus, an ubiquitous virus present in the skin of the majority of healthy people, which can be detected in about 80% of MCC tumors [3-5].

Treatment of MCC depends on both tumor characteristics and patient performance status[6]. For the management of localized resectable tumors, international guidelines recommend wide local excision. This strategy is often a challenge since most of these tumors occur across the head and neck region. Until 2016, chemotherapy was the standard of care for unresectable MCCs, with immediate response, but with early recurrence and low survival rates[7-10]. The emergence of immune checkpoint inhibitors revolutionized the therapeutic strategies adopted for several tumor types. MCC is not an exception[11], due to the frequent expression of programmed death-ligand 1 on MCC tumor cells and of programmed death 1 on Merkel cell polyomavirus-specific T cells. Characteristics like specificity, reduced toxicity, and ability to activate the immune system are the most important features of this approach, which is now becoming the standard of care for different tumors[12].

We can only find a few reports on the use of avelumab in MCC treatment[13-15]. We, herein, report the first case of advanced MCC, with oligoprogression, managed with avelumab and local radical treatment, presenting long-term disease control after immunotherapy suspension.

## CASE PRESENTATION

### Chief complaints

A 61-year-old man was presented to the hospital with sporadic fever and an exudative mass, located on the right gluteal region.

### History of present illness

One year before the medical oncology consultation, the patient noticed a small nodule located on the right gluteal region, which kept growing and became exudative and bloody. For several weeks the patient refused to leave his house, as he was uncomfortable due to physical constraints. When he decided to attend the emergency department, the lesion was about 9 cm in diameter and was bloody and exudative. The patient also reported episodic fever, predominantly in the morning, in the week before



the consultation. A biopsy was performed on that same day, and the patient was reassessed a few weeks later on a medical oncology consultation.

### **History of past illness**

The patient had a history of arterial hypertension, type 2 diabetes, and chronic obstructive pulmonary disease (COPD).

### **Personal and family history**

The patient had a history of arterial hypertension, type 2 diabetes, and COPD.

### **Physical examination**

On the first medical oncology consultation, the patient presented a 10 cm (diameter) malodorous painless mass, located on the right gluteal region, with hard consistency and bloody seropurulent discharge. Upon physical examination, two painless inguinal lymph nodes were also found, both fixed, with hard consistency and diameter of 2 cm on the left side and 3.5 cm on the right side.

### **Laboratory examinations**

**Anatomopathological analysis:** The anatomopathological examination of the right gluteal mass confirmed the diagnosis of MCC positive for cytokeratin AE1/AE3 and chromogranin.

### **Imaging examinations**

Imaging studies were obtained. An abdomen and pelvic computed tomography highlighted a large mass in the right gluteal region measuring 9.6 cm × 3.2 cm × 9.0 cm (in transverse, anteroposterior and longitudinal diameters, respectively), and a similar nodular soft tissue lesion with 2.4 cm × 1.5 cm × 2.4 cm in the vicinity of the mass. Large inguinal heterogeneous lymph nodes were also identified, with the largest one located on the right side (2.6 cm × 1.8 cm × 5.0 cm).

Pelvic magnetic resonance imaging (MRI) confirmed the existence of an expansive, heterogeneous lesion with lobulated contour and exophytic component located in the right gluteal region, involving the skin, subcutaneous tissue, and extending to the right gluteus maximus muscle in its inner portion (7.5 cm × 4.8 cm × 7.7 cm; [Figure 1A](#)). The images confirmed other subcutaneous lesion, with similar characteristics, measuring 2.4 cm × 1.2 cm, and three other small nodules, permeating the muscles between the gluteus maximus and maxillary muscles near the right hip. Bilateral inguinal lymph nodes, with 3.8 cm × 1.9 cm and 3.3 cm × 2.0 cm, were also evident and highly suspicious. The exam also revealed two bone lesions, one in the sacrum (2.8 cm) and another in the left iliac wing (2.4 cm), both compatible with bone metastasis. However, these lesions were not visible in the bone scintigraphy that was also performed, which in turn revealed two other bone lesions on the body of D11 and in the ninth right costal arch, with uncertain etiology and suspected of metastasis, in the additional MRI.

## **MULTIDISCIPLINARY EXPERT CONSULTATION**

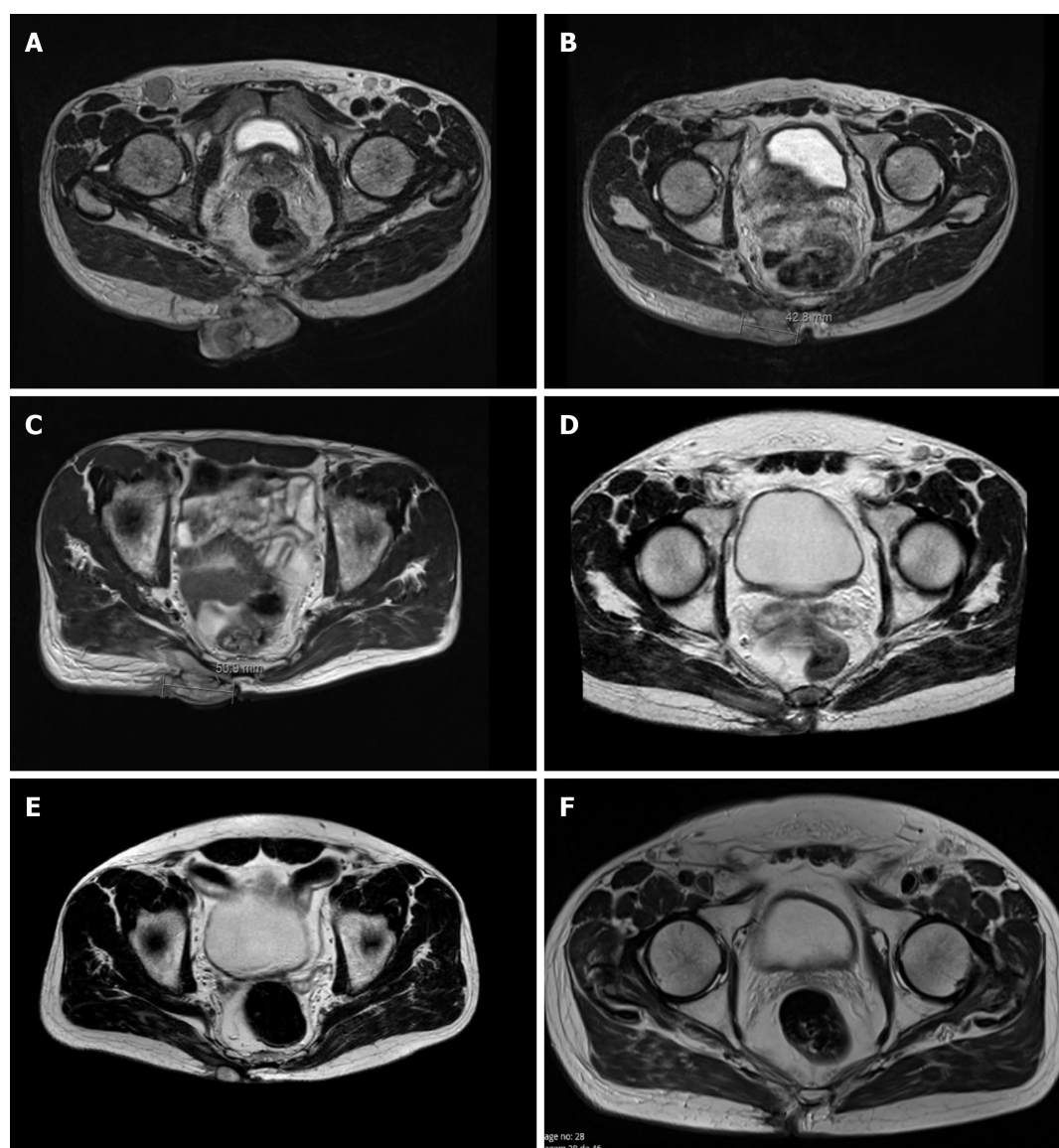
The case was discussed in the Multidisciplinary Tumor Board, with the presence of Medical Oncology, Radio-Oncology, Dermatology, and Plastic Surgery specialists. Considering the diagnosis of unresectable tumor, the Multidisciplinary Tumor Board decided for palliative chemotherapy.

## **FINAL DIAGNOSIS**

The final diagnosis was MCC of the right gluteal region, cT4N3M1c (AJCC, TNM staging 8<sup>th</sup> edition, 2017), with invasion of adjacent muscle, in-transit metastasis (with regional lymph nodes), and bone metastasis.

## **TREATMENT**

Patient started chemotherapy, with cisplatin 75 mg/m<sup>2</sup> D<sub>1</sub> and etoposide 100 mg/m<sup>2</sup> D<sub>1</sub>-D<sub>3</sub> every 3 wk. After cycle 1, we observed a reduction of the primary tumor,



**Figure 1** Magnetic resonance imaging images of the primary Merkel cell carcinoma lesion. A: Baseline; B: After two cycles of chemotherapy (partial response); C: After six cycles of chemotherapy (progression of the disease); D: After seven cycles of avelumab (partial response); E: After 14 cycles of avelumab (partial response); F: After 28 cycles of avelumab.

evidencing clinical response, and the quality of life of the patient improved. Following cycle 2, radiological evaluation confirmed a partial response (Figure 1B). Treatment proceeded with good tolerance, apart from grade 4 neutropenia (Common Terminology Criteria for Adverse Events v.5), after cycle 2, managed with granulocyte-colony stimulating factor support, in the subsequent treatments. However, after six cycles of chemotherapy, the main tumor increased in size, evidencing disease progression (Figure 1C). The case was discussed, and the Board proposed second-line treatment with avelumab 10 mg/kg, every 2 wk. At this time, avelumab had not been approved in Portugal, so the patient was included in an early access program. The treatment started on August 2017, 2 mo after disease progression was documented (Figure 2A).

## OUTCOME AND FOLLOW-UP

The patient started avelumab with good tolerance and no adverse events. Clinical response was reported after two cycles as the gluteal lesion started to decrease in size (6 cm × 7 cm), presenting signs of necrosis (Figure 2B), but with improvement in patient's quality of life. By cycle 5, the lesion was significantly reduced, closed completely, and became flat and dry. Maximum clinical response was achieved after





**Figure 2** Photographic registries of the evolution of the primary Merkel cell carcinoma lesion. A: Baseline avelumab; B: After two cycles of avelumab; C: After seven cycles of avelumab; D: After 16 cycles of avelumab; E: After surgery, radiotherapy, and 28 cycles of avelumab; F: Follow-up, more than 2.5 years after surgery.

seven treatments (Figure 2C). Lymph nodes became infracentimetric, and the patient recovered appetite and reported feeling generally well. This clinical response was confirmed by MRI, which showed a reduction of the lesion located in the gluteal region (5.7 cm × 6.0 cm × 1.9 cm; Figure 1D) and evidenced a shrinkage of the infiltrative lesions involving the right wing of the sacrum (maximum diameter: 2.6 cm) and the iliac bone (maximum diameter: 2.1 cm). An MRI performed at cycle 14 confirmed further reduction of the tumoral wound (3.8 cm × 3.5 cm × 1.2 cm; Figure 1E).

However, after 16 cycles of treatment, the tumoral wound showed an increase (about 3 cm), compatible with primary tumor progression (Figure 2D). Bone and lymph node metastases were stable. Nevertheless, as the primary tumor was considered resectable at this point, the patient was proposed for surgery followed by radiotherapy.

The lesion was excised with tumor free margins (R0) and, 3 wk after surgery, the patient started radiotherapy, with a total dose of 56 Gy in 28 fractions, 2 Gy/fr, five times a week. At this time, he also resumed the systemic treatment with avelumab, at the same dose and schedule. Three months later (cycle 28), a pelvic MRI showed no evidenced of local disease (Figures 1F and 2E).

After 41 cycles of avelumab, treatment was interrupted due to a bilateral pneumococcal pneumonia, with bacteremia and respiratory failure (lung infection grade 4, Common Terminology Criteria for Adverse Events v.5.0). As the patient had a history of pulmonary chronic disease, it was not possible to assume a treatment-related

adverse event. However, after discussing with the patient possible alternatives and outcomes, the medical team decided to suspend immunotherapy and maintain follow-up.

More than 40 mo after starting avelumab, the patient is alive and well. Since surgery, with more than 2.5 years of follow-up, the patient maintains complete local response (Figure 2F) and stable bone lesions, even after stopping systemic immunotherapy more than 1.5 years ago.

## DISCUSSION

MCC is a rare cutaneous aggressive disease, with high risk for metastasis and increased case-fatality rate when compared to other skin cancers[1,16]. Immune checkpoint inhibitors were recently approved for the treatment of advanced MCC[17]. Avelumab is an anti-programmed death-ligand 1 monoclonal antibody, approved by the United States Food and Drug Administration (2017) and the European Medicine Agency (2018) as the first line treatment for metastatic MCC, based on the results of a phase II clinical trial[18-20]. The trial included patients unresponsive to chemotherapy and reported an objective response rate of 33.0% as well as a median overall survival of 12.9 mo (95%CI: 7.5-not estimable), with a good safety profile. Since then, several studies and trials highlighted immunotherapy as a turning point in MCC patients care [21].

To the best of our knowledge, the presented case is the first report describing the evolution of an unresectable MCC with bone metastasis and its management after oligoprogression. Our patient was presented to the first oncology appointment highly debilitated and symptomatic, with an advanced stage disease, a massive irresectable primary tumor, and bone metastization. Despite undetected by bone scintigraphy, two bone lesions in the sacrum and left iliac wing were highly suspicious in MRI imaging. Since MCC bone metastasis can be osteolytic or osteoblastic, bone scintigraphy may not be the best exam to diagnose or exclude bone metastasis. Nevertheless, two other bone lesions on D11 and in the ninth right costal arch were seen in both exams.

Considering the diagnosis, we decided for a palliative care based on chemotherapy with etoposide and cisplatin. The treatment provided a good initial response but without long lasting effects, as previously described by other authors[7]. For second line treatment, the patient integrated an early access program, with avelumab. Immunotherapy had a dramatic effect on primary tumor, with downsizing of the lesion and promotion of the cicatricial process, with positive impact on patient's symptoms and improved autonomy, allowing the patient to return to work. With these effects, the lesion became resectable and surgery became possible upon a local progression scenario. The use of avelumab, as an induction treatment strategy, followed by surgery and radiotherapy, showed to be an effective strategy to manage oligoprogressive disease.

The concept of oligoprogressive disease has been mainly discussed in lung cancer. The proposed treatment approach is based on keeping the strategy that proved to control the greater proportion of the disease, while using other strategies to treat the area of disease in progression[22,23]. In fact, this concept totally resembles our case: After 14 cycles of treatment, even though the disease was overall controlled (bone metastasis were stable and no de-novo lesions were detected), there were signs of primary tumor progression (oligoprogression). The adopted approach allowed to maintain the control of the metastatic disease, while providing conditions to manage the primary lesion with radical local therapy.

The rapid and durable response observed in this clinical case (a chemotherapy-refractory patient), along with the idea suggested by Kaufman *et al*[18] that the immune system may be more functional in patients who received fewer lines of therapy[18], advocates that a brief period of neoadjuvant therapy might suffice to mediate substantial tumor regression, potentially enabling surgery in patients with localized unresectable MCC, as reported in a recent clinical case report[13]. Similarly, in the CheckMate 358 Trial, Topalian *et al*[24] evaluated the safety and efficacy of neoadjuvant nivolumab in resectable MCC and reported that, among the 36 patients who underwent surgery, the polymerase chain reaction rate was 47.2%. However, 3 patients did not undergo surgery because of disease progression or adverse events[24].

It is estimated that about 1% of the patients treated with avelumab develop immune-related pneumonitis[18], usually in the first few months of treatment, and that COPD is a risk factor for drug-induced pulmonary toxicity[25]. Therefore, even though it is not reasonable to establish a direct causal association between immuno-

therapy and pulmonary disease, avelumab may have played a role in the predisposition of this patient with COPD to develop severe bacterial pneumonia. In this context, before starting immunotherapy, it might be advisable to characterize fully these types of comorbidities and perform a specialized evaluation by a pneumologist in order to optimize patients' comorbidities, in advance.

In case of progression, it is of major importance to have a risk/benefits discussion with the patient. Due to the rarity of this disease and to the lack of solid evidence, inclusion in a clinical trial is advisable. If not available, the multidisciplinary group shall consider the possibility to resume immunotherapy with caution (because of the pulmonary adverse event reported), as avelumab was suspended more than 12 mo and the response rate and duration of response to chemotherapy are very limited[9]. Local radical treatment options may also be considered in case of oligoprogression. Furthermore, recent case reports showed optimistic results on the use of nivolumab and ipilimumab in MCC refractory to avelumab[26,27]. However, a substantial increased risk for immune-related adverse events is a major concern.

## CONCLUSION

To the authors' knowledge, the use of avelumab beyond progression in MCC or as part of oligoprogression management strategies has not been reported previously. Considering the heterogeneity of these tumors, with different location and distinct degrees of disease progression, the real potential of avelumab is yet to be known. In this context, clinicians and researchers shall share the outcomes of their clinical practice, mainly in a rare disease like MCC. This report highlights the long-term efficacy of avelumab on the management of a chemotherapy resistant advanced MCC. It also shows a successful approach to oligoprogression with local radical treatment, surgery, and radiotherapy, while maintaining systemic therapy with avelumab.

## ACKNOWLEDGEMENTS

The authors thank Paula Pinto, PharmD, PhD (PMA-Pharmaceutical Medicine Academy) for providing medical writing and editorial assistance.

## REFERENCES

- 1 **Becker JC**, Stang A, DeCaprio JA, Cerroni L, Lebbé C, Veness M, Nghiem P. Merkel cell carcinoma. *Nat Rev Dis Primers* 2017; **3**: 17077 [PMID: [29072302](#) DOI: [10.1038/nrdp.2017.77](#)]
- 2 **Tetzlaff MT**, Nagarajan P. Update on Merkel Cell Carcinoma. *Head Neck Pathol* 2018; **12**: 31-43 [PMID: [29556962](#) DOI: [10.1007/s12105-018-0898-2](#)]
- 3 **Kervarrec T**, Samimi M, Guyétant S, Sarma B, Chéret J, Blanchard E, Berthon P, Schrama D, Houben R, Touzé A. Histogenesis of Merkel Cell Carcinoma: A Comprehensive Review. *Front Oncol* 2019; **9**: 451 [PMID: [31245285](#) DOI: [10.3389/fonc.2019.00451](#)]
- 4 **Feng H**, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human Merkel cell carcinoma. *Science* 2008; **319**: 1096-1100 [PMID: [18202256](#) DOI: [10.1126/science.1152586](#)]
- 5 **DeCaprio JA**. Merkel cell polyomavirus and Merkel cell carcinoma. *Philos Trans R Soc Lond B Biol Sci* 2017; **372** [PMID: [28893943](#) DOI: [10.1098/rstb.2016.0276](#)]
- 6 **Cassler NM**, Merrill D, Bichakjian CK, Brownell I. Merkel Cell Carcinoma Therapeutic Update. *Curr Treat Options Oncol* 2016; **17**: 36 [PMID: [27262710](#) DOI: [10.1007/s11864-016-0409-1](#)]
- 7 **Steven N**, Lawton P, Poulsen M. Merkel Cell Carcinoma - Current Controversies and Future Directions. *Clin Oncol (R Coll Radiol)* 2019; **31**: 789-796 [PMID: [31594644](#) DOI: [10.1016/j.clon.2019.08.012](#)]
- 8 **Tai PT**, Yu E, Winkquist E, Hammond A, Stitt L, Tonita J, Gilchrist J. Chemotherapy in neuroendocrine/Merkel cell carcinoma of the skin: case series and review of 204 cases. *J Clin Oncol* 2000; **18**: 2493-2499 [PMID: [10856110](#) DOI: [10.1200/JCO.2000.18.12.2493](#)]
- 9 **Nghiem P**, Kaufman HL, Bharmal M, Mahnke L, Phatak H, Becker JC. Systematic literature review of efficacy, safety and tolerability outcomes of chemotherapy regimens in patients with metastatic Merkel cell carcinoma. *Future Oncol* 2017; **13**: 1263-1279 [PMID: [28350180](#) DOI: [10.2217/fon-2017-0072](#)]
- 10 **Villani A**, Fabbrocini G, Costa C, Carmela Annunziata M, Scalvenzi M. Merkel Cell Carcinoma: Therapeutic Update and Emerging Therapies. *Dermatol Ther (Heidelb)* 2019; **9**: 209-222 [PMID: [30820877](#) DOI: [10.1007/s13555-019-0288-z](#)]
- 11 **Seebacher NA**, Stacy AE, Porter GM, Merlot AM. Clinical development of targeted and immune



- based anti-cancer therapies. *J Exp Clin Cancer Res* 2019; **38**: 156 [PMID: 30975211 DOI: 10.1186/s13046-019-1094-2]
- 12 **Specenier P**, Vermorken JB. Optimizing treatments for recurrent or metastatic head and neck squamous cell carcinoma. *Expert Rev Anticancer Ther* 2018; **18**: 901-915 [PMID: 29999437 DOI: 10.1080/14737140.2018.1493925]
- 13 **Abdallah N**, Nagasaka M, Chowdhury T, Raval K, Hotaling J, Sukari A. Complete response with neoadjuvant avelumab in Merkel cell carcinoma - A case report. *Oral Oncol* 2019; **99**: 104350 [PMID: 31277904 DOI: 10.1016/j.oraloncology.2019.06.031]
- 14 **Ramachandran P**, Erdinc B, Gotlieb V. An Unusual Presentation of Merkel Cell Carcinoma in a HIV Patient: A Case Report and Literature Review. *J Investig Med High Impact Case Rep* 2019; **7**: 2324709619836695 [PMID: 30938171 DOI: 10.1177/2324709619836695]
- 15 **Cardis MA**, Jiang H, Strauss J, Gulley JL, Brownell I. Diffuse lichen planus-like keratoses and clinical pseudo-progression associated with avelumab treatment for Merkel cell carcinoma, a case report. *BMC Cancer* 2019; **19**: 539 [PMID: 31164102 DOI: 10.1186/s12885-019-5759-1]
- 16 **Emge DA**, Cardones AR. Updates on Merkel Cell Carcinoma. *Dermatol Clin* 2019; **37**: 489-503 [PMID: 31466589 DOI: 10.1016/j.det.2019.06.002]
- 17 **Gaiser MR**, Bongiorno M, Brownell I. PD-L1 inhibition with avelumab for metastatic Merkel cell carcinoma. *Expert Rev Clin Pharmacol* 2018; **11**: 345-359 [PMID: 29478343 DOI: 10.1080/17512433.2018.1445966]
- 18 **Kaufman HL**, Russell J, Hamid O, Bhatia S, Terheyden P, D'Angelo SP, Shih KC, Lebbé C, Linette GP, Milella M, Brownell I, Lewis KD, Lorch JH, Chin K, Mahnke L, von Heydebreck A, Cuillerot JM, Nghiem P. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. *Lancet Oncol* 2016; **17**: 1374-1385 [PMID: 27592805 DOI: 10.1016/S1470-2045(16)30364-3]
- 19 **Kaufman HL**, Russell JS, Hamid O, Bhatia S, Terheyden P, D'Angelo SP, Shih KC, Lebbé C, Milella M, Brownell I, Lewis KD, Lorch JH, von Heydebreck A, Hennessy M, Nghiem P. Updated efficacy of avelumab in patients with previously treated metastatic Merkel cell carcinoma after ≥1 year of follow-up: JAVELIN Merkel 200, a phase 2 clinical trial. *J Immunother Cancer* 2018; **6**: 7 [PMID: 29347993 DOI: 10.1186/s40425-017-0310-x]
- 20 **De Sousa Linhares A**, Battin C, Jutz S, Leitner J, Hafner C, Tobias J, Wiedermann U, Kundi M, Zlabinger GJ, Grabmeier-Pfistershammer K, Steinberger P. Therapeutic PD-L1 antibodies are more effective than PD-1 antibodies in blocking PD-1/PD-L1 signaling. *Sci Rep* 2019; **9**: 11472 [PMID: 31391510 DOI: 10.1038/s41598-019-47910-1]
- 21 **Chan IS**, Bhatia S, Kaufman HL, Lipson EJ. Immunotherapy for Merkel cell carcinoma: a turning point in patient care. *J Immunother Cancer* 2018; **6**: 23 [PMID: 29566749 DOI: 10.1186/s40425-018-0335-9]
- 22 **Laurie SA**, Banerji S, Blais N, Brule S, Cheema PK, Cheung P, Daaboul N, Hao D, Hirsh V, Juergens R, Laskin J, Leigh N, MacRae R, Nicholas G, Roberge D, Rothenstein J, Stewart DJ, Tsao MS. Canadian consensus: oligoprogressive, pseudoprogressive, and oligometastatic non-small-cell lung cancer. *Curr Oncol* 2019; **26**: e81-e93 [PMID: 30853813 DOI: 10.3747/co.26.4116]
- 23 **Rowe SP**, Tran PT, Fishman EK, Johnson PT. Oligoprogression: What Radiologists Need to Know About This Emerging Concept in Cancer Therapeutic Decision-making. *Acad Radiol* 2017; **24**: 898-900 [PMID: 28341411 DOI: 10.1016/j.acra.2016.12.018]
- 24 **Topalian SL**, Bhatia S, Amin A, Kudchadkar RR, Sharfman WH, Lebbé C, Delord JP, Dunn LA, Shinohara MM, Kulikauskas R, Chung CH, Martens UM, Ferris RL, Stein JE, Engle EL, Devries LA, Lao CD, Gu J, Li B, Chen T, Barrows A, Horvath A, Taube JM, Nghiem P. Neoadjuvant Nivolumab for Patients With Resectable Merkel Cell Carcinoma in the CheckMate 358 Trial. *J Clin Oncol* 2020; **38**: 2476-2487 [PMID: 32324435 DOI: 10.1200/JCO.20.00201]
- 25 **Chuzi S**, Tavora F, Cruz M, Costa R, Chae YK, Carneiro BA, Giles FJ. Clinical features, diagnostic challenges, and management strategies in checkpoint inhibitor-related pneumonitis. *Cancer Manag Res* 2017; **9**: 207-213 [PMID: 28652812 DOI: 10.2147/CMAR.S136818]
- 26 **Glutsch V**, Kneitz H, Goebeler M, Gesierich A, Schilling B. Breaking avelumab resistance with combined ipilimumab and nivolumab in metastatic Merkel cell carcinoma? *Ann Oncol* 2019; **30**: 1667-1668 [PMID: 31350554 DOI: 10.1093/annonc/mdz230]
- 27 **Khaddour K**, Rosman IS, Dehdashti F, Anstas G. Durable remission after rechallenge with ipilimumab and nivolumab in metastatic Merkel cell carcinoma refractory to avelumab: Any role for sequential immunotherapy? *J Dermatol* 2021; **48**: e80-e81 [PMID: 33161593 DOI: 10.1111/1346-8138.15621]



Published by **Baishideng Publishing Group Inc**  
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)

**Help Desk:** <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

