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Merkel cell carcinoma brain metastasis with radiological findings mimicking primary CNS lymphoma: illustrative case

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BACKGROUND Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine tumor with a high likelihood of distant metastasis. Approximately 30 cases of MCC brain metastasis have been reported. The authors report a case of MCC brain metastasis with imaging findings mimicking primary central nervous system lymphoma.

OBSERVATIONS A 69-year-old asymptomatic White female with a past medical history of rheumatoid arthritis and MCC of the right cheek with no known regional or distant spread presented with a right frontal lobe lesion discovered incidentally on a surveillance scan. Brain magnetic resonance imaging revealed a vividly enhancing homogeneous lesion with restricted diffusion on diffusion-weighted imaging and corresponding apparent diffusion coefficient maps. Imaging characteristics suggested a highly cellular mass consistent with primary central nervous system lymphoma; however, given the likelihood of metastasis, resection was recommended. An intraoperative frozen section suggested lymphoma. However, further examination revealed positive cytokeratin 20 staining for a tumor, and a final diagnosis of MCC brain metastasis was made.

LESSONS Imaging characteristics of MCC brain metastasis can vary widely. A high level of suspicion should be maintained in a patient with a known history of MCC. Aggressive resection is recommended, regardless of appearance on scans or pathology of frozen sections, because MCC can mimic other intracranial pathologies.

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KEYWORDS Merkel cell carcinoma; imaging findings; brain metastasis; primary CNS lymphoma

Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine tumor of the skin first described by Toker in 1972.[1] MCC spreads through the lymphatic system and has a propensity for regional and distant metastases with brain involvement in 3%–5% of the cases.[1–3] Approximately 30 cases of MCC brain metastasis had been reported as of 2019.[4] Although prognosis after brain metastasis has been reported,[5–7] the imaging characteristics of MCC brain metastasis are largely unknown.

We report a case of a patient with a past medical history of rheumatoid arthritis (RA) and MCC who presented with a single brain mass on surveillance imaging. Differential diagnosis based on imaging features included MCC metastasis, primary central nervous system lymphoma (PCNSL), and high-grade glioma. An intraoperative frozen section suggested PCNSL; however, the final histological diagnosis of MCC brain metastasis was made based on biomarkers.

Illustrative Case

The patient was a 69-year-old White female with a past medical history of RA who was receiving methotrexate and adalimumab for MCC. She presented to the emergency department after imaging detection of a brain lesion on a surveillance neck computed tomography (CT) scan. The patient had been diagnosed with MCC of the right cheek 2 years earlier. Subsequently, the patient's RA medications were changed due to concerns of immunosuppression. Extensive work-up at that time with positron emission tomography (PET), brain magnetic resonance imaging (MRI), and sentinel lymph node

ABBREVIATIONS ADC = apparent diffusion coefficient; CNS = central nervous system; CT = computed tomography; DWI = diffusion-weighted imaging; MCC = Merkel cell carcinoma; MRI = magnetic resonance imaging; PCNSL = primary central nervous system lymphoma; PET = positron emission tomography; RA = rheumatoid arthritis; SRS = stereotactic radiosurgery.

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biopsy were unrevealing, and the patient underwent Mohs surgery with negative margins. Radiation therapy with 56 Gy was delayed for 4 months due to bowel perforation secondary to diverticulitis. The patient had negative findings on a follow-up CT neck scan at 9 months and an MRI neck scan at 14 months after initial diagnosis. On a third CT neck surveillance scan 24 months after initial diagnosis, an incidental hyperdense right frontal lobe mass with surrounding vasogenic edema was detected, and the patient was admitted for further work-up. CT of the chest, abdomen, and pelvis was unrevealing. Brain MRI showed an intrinsically T1 hypointense, avidly enhancing mass after the administration of intravenous gadolinium (Fig. 1), with surrounding vasogenic edema on T2-weighted and fluid-attenuated inversion recovery imaging, as well as restricted diffusion on diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) maps (Fig. 2), which are imaging characteristics consistent with a highly cellular mass that could represent a metastasis, PCNSL, or high-grade glioma. The patient had previously been receiving methotrexate and adalimumab therapy for RA, and both drugs have been associated with development of PCNSL,[8,9] which furthered our suspicion. However, the possibility of metastasis from a primary MCC lesion was high on the differential diagnosis, and surgery was recommended.

After obtaining adequate exposure of the tumor, an intraoperative frozen section was sent for pathology, which led to an initial diagnosis of PCNSL due to the pack of small, blue, round cells seen on a hematoxylin and eosin stain (Fig. 3A). Although PCNSL is primarily managed with chemotherapy and radiation, there was a high index of suspicion for MCC brain metastasis due to similar histological appearance.[10] Thus, a gross total resection was performed without postoperative complications. Flow cytometry revealed a CD45 cell–negative population expressing CD56 biomarker. Immunohistochemical staining revealed cells staining positive for CD20, CD56, synaptophysin, and chromogranin, and a diagnosis of MCC was made (Fig. 3B).

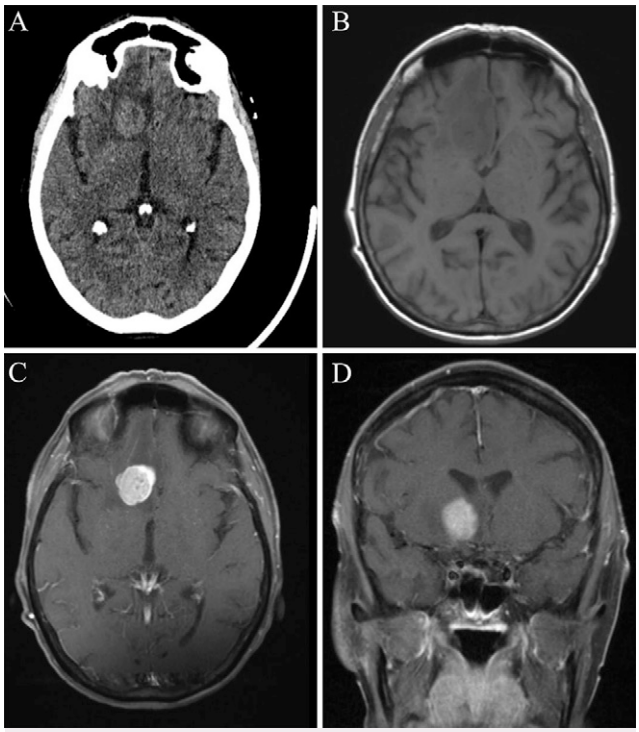

FIG. 1. A: Noncontrast CT shows a hyperdense inferior parasagittal right frontal lobe mass with surrounding hypodense edema. **B:** Axial T1-weighted MRI sequence shows a T1 isointense mass with surrounding edema. Postcontrast axial (**C**) and coronal (**D**) T1-weighted MRI sequences depict avid enhancement of the mass.

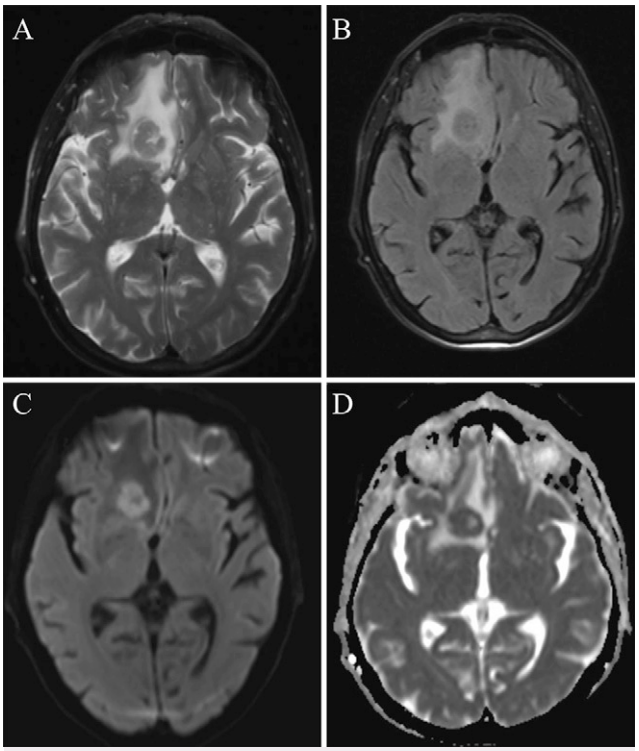

FIG. 2. Axial fat-suppressed T2-weighted (**A**) and fluid-attenuated inversion recovery (FLAIR)-weighted (**B**) MRI sequences show a T2/FLAIR isointense inferior parasagittal right frontal lobe mass with surrounding T2/FLAIR hyperintense edema and regional sulcal effacement. Axial DWI (**C**) and the associated ADC map (**D**) depict restricted diffusion within the mass, suggesting high cellularity.

The patient subsequently had a repeat PET/CT whole-body scan, which was unrevealing, and she underwent Gamma Knife stereotactic radiosurgery (SRS) with 17 Gy to the tumor bed. Although immunotherapy was discussed, the patient decided to defer treatment due to lack of definitive evidence in the treatment of MCC brain metastasis.[11,12] At her 9-month follow-up after resection, the patient had not experienced recurrence and had a Karnofsky performance scale score of 90.

Discussion

Observations

In this report, we present a case of a 69-year-old asymptomatic White female with a past medical history of RA and MCC of the right cheek with no known metastasis who presented with a right frontal lobe lesion discovered incidentally on a surveillance scan. Her history of RA treated with adalimumab, her MRI characteristics, and her intraoperative frozen section all were suggestive of primary central nervous system (CNS) lymphoma. However, a final diagnosis of MCC metastasis was made by immunohistochemistry

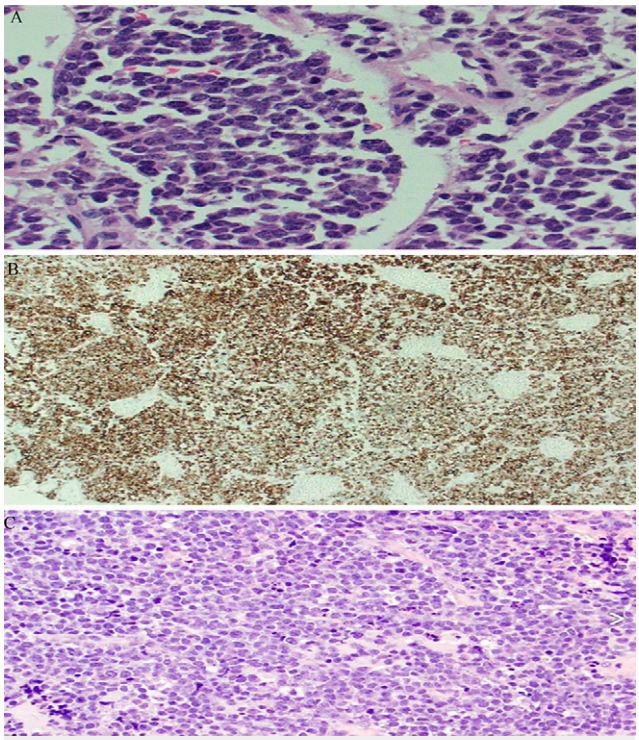

FIG. 3. A–C: Hematoxylin and eosin (H&E) and immunohistochemical staining. **A:** Intraoperative H&E-stained frozen section of MCC initially diagnosed as primary CNS lymphoma. Original magnification, 40×. **B:** Immunohistochemistry showing diffuse uptake of cytokeratin 20, a biomarker for MCC. Original magnification, 100×. **C:** Histology of primary CNS lymphoma for comparison. Original magnification, 20×. Histology shows a diffuse infiltrate of closely packed intermediate to large mononuclear cells with scant cytoplasm. Used with permission from PathologyOutlines.com and Drs. Courville and Young.

based on CD20, CD56, synaptophysin, and chromogranin staining. The patient has had durable tumor control 9 months after gross total resection and adjunct radiosurgery.

Lessons

Histology and Biomarkers for Diagnosing MCC Brain Metastasis

The incidence of MCC has steadily been increasing since 2000. Using SEER data from 2000 to 2013, the rate of MCC increased by 95% compared to that of melanoma, which increased by 57%.[13] Before the advent of more sophisticated testing, MCC was a difficult and often missed diagnosis due to the compacted number of malignant small blue cells mimicking a wide array of other malignant diseases with similar histological features.[10] Confirmatory diagnosis of MCC includes positive staining with cytokeratin 20–positive and –negative staining with thyroid transcription factor 1. Positive staining of neuroendocrine markers such as chromogranin, synaptophysin, CD56, neuron-specific enolase, and neurofilament can also be used.[10,14] As evident in this case, the intraoperative frozen section was initially misdiagnosed as primary CNS lymphoma due to the packing of small blue cells (Fig. 3). Primary CNS lymphoma is principally a nonoperative disease with first-line treatment using chemotherapy.[15,16] However, because a safe surgical trajectory had already been established and because MCC can have similar histological features, complete resection of the lesion was performed.

Immunosuppression and MCC Brain Metastasis

MCC is associated with a high rate of local recurrence, lymph node metastasis, and distant metastasis, with most occurring within 3 years after the initial diagnosis.[2,10] Risk factors for MCC include older age and light-skinned individuals with extensive sunlight exposure and immunosuppression.[10,14] Cases of patients with human immunodeficiency virus infection,[17] chronic lymphoid leukemia,[18] and RA[19] developing MCC intracranial metastasis have been reported. Grubb et al.[19] reported a case of a 71-year-old White man with a history of RA receiving hydroxychloroquine and MCC of the head and neck that was surgically excised with negative margins, negative sentinel lymph node biopsy, and radiation to the tumor bed who presented with neurological symptoms resulting from MCC brain metastasis 20 months after initial treatment. Similarly, in this case presentation, the patient developed distant metastasis 24 months after initial diagnosis even after surgical excision of the primary tumor with negative margins, negative sentinel lymph node biopsy, and radiation to the tumor bed.

Management of MCC Brain Metastasis

The median survival time after MCC brain metastasis ranges from 12 to 60 months.[7] Currently, there is no standardized guideline for the management of MCC brain metastasis. A pooled analysis of the literature comprising 40 patients with MCC brain metastasis showed that management of intracranial disease included radiotherapy (82.5%), systemic therapy (59.5%), and resection (35%). Resection was an independent predictor of overall survival, but radiotherapy and chemotherapy were not.[6] However, MCC has been shown to be a radiosensitive tumor, and due to the paucity of patients undergoing radiosurgery, Harary et al.[6] suggested that radiosurgery could potentially play a role in the management of MCC brain metastasis. Jacob et al.[20] reported a case of a patient with two separate MCC brain metastases that were both targeted with SRS and were stable at 5-month follow-up. However, the patient then developed leptomeningeal spread and underwent whole-brain irradiation. The authors suggested that management of brain metastasis with SRS can be as effective as whole-brain irradiation without increased risk of side effects. Two multicenter clinical trials using PD-L1 monoclonal antibodies, pembrolizumab[12] and avelumab,[11] have shown efficacy in the management of advanced MCC. However, in both trials, patients with brain involvement were excluded from enrollment. Few cases of MCC brain metastasis treated with immunotherapy have been reported. In 2021, Grubb et al.[19] reported the use of adjunct immunotherapy pembrolizumab and SRS after resection of a right MCC brain metastasis. At 6-months follow-up, patient is stable from his disease. In 2021, Fife et al.[21] reported four cases of MCC brain metastasis treated with avelumab. Two patients experienced immediate progression after MCC, and two patients had a partial response by Response Evaluation Criteria in Solid Tumors version 1.1 criteria.

Diagnostic Algorithm for MCC Metastasis

MCC brain metastasis have been reported to radiographically mimic sellar lesions, meningioma, CNS high grade glioma, and primary CNS lymphoma as in this case presented. PCNSL occurs in the in the frontal lobe 20%–43% of the time,[22] and there are case

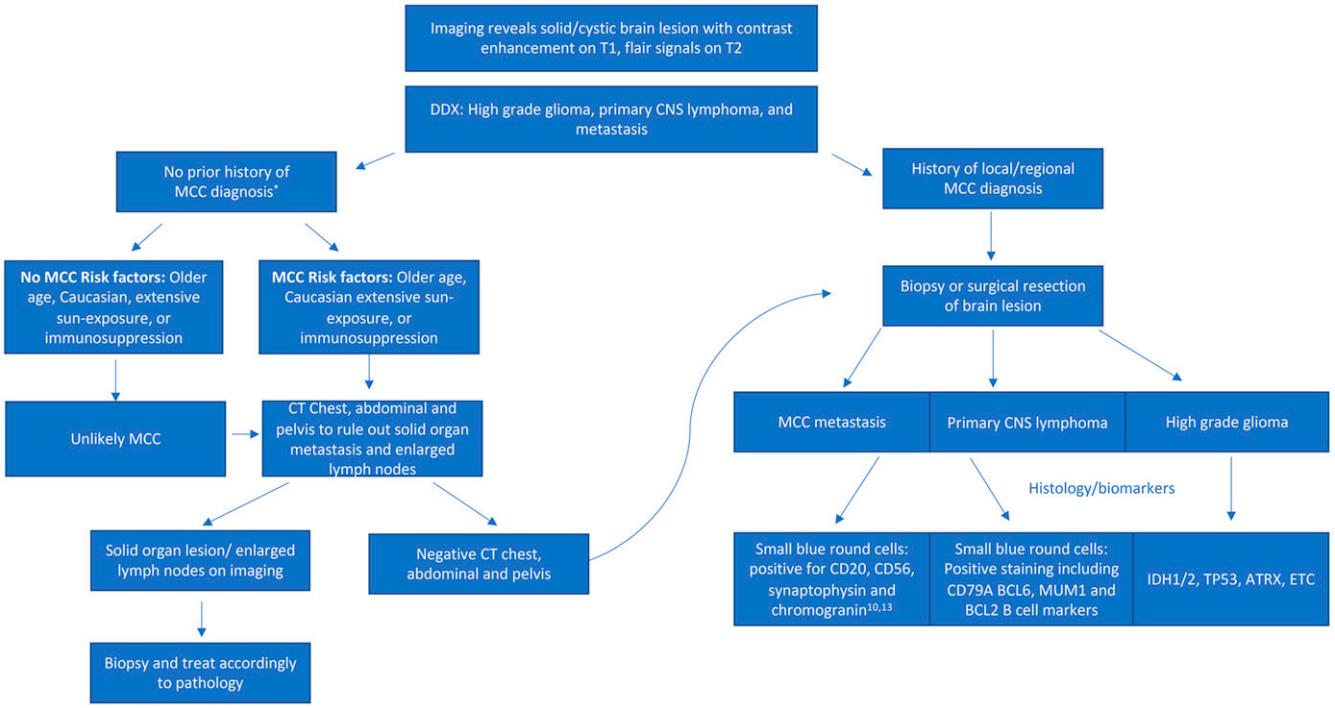

FIG. 4. MCC brain metastasis diagnostic algorithm. * Multiple cases of patients with MCC brain metastasis without a primary lesion have been reported. DDX = differential diagnosis.

reports of patients who were receiving methotrexate and adalimumab who developed PCNSL,[8,9] which made suspicion of PCNSL high on the differential diagnosis in our case because the patient had been receiving these medications before her MCC diagnosis. PCNSL characteristically enhances on postcontrast T1-weighted imaging with T2 hyperintensity secondary to high cellularity and surrounding vasogenic edema. On DWI and ADC maps, there is restricted diffusion due to the hypercellularity of PCNSL.[22,23] All of the above imaging characteristics were akin to the patient's images. An important caveat in diagnosing PCNSL is that steroids can decrease the diagnostic yield of PCNSL on biopsy and thus should be avoided.[23] In this case, the patient did not exhibit symptoms from the vasogenic edema associated with the lesion; therefore, steroids were not administered. However, if the patient were symptomatic from the edema, the decision to withhold steroids due to concern for a presumptive diagnosis of PCNSL could significantly worsen the patient's clinical condition. A diagnostic algorithm incorporating patient history, imaging findings, and histology/biomarkers is shown in Fig. 4.

MCC brain metastasis can be mistaken for meningioma[24] and high-grade gliomas.[4] Abul-Kasim et al.[24] reported a case of a patient with 3 months of gait disturbances. Further work-up showed lymph node metastasis and a meningeal metastasis that was initially thought to be a parasagittal meningioma. Advanced imaging showing high cerebral blood volume and high choline/N-acetylaspartate and choline/creatine ratios along with lymph node biopsy ultimately led to the diagnosis of MCC metastasis without a known primary lesion.[24] Caramanti et al.[4] reported a case of a patient without a primary MCC lesion presenting with 3 months of progressive headache. MRI and magnetic resonance spectroscopy showed high choline/creatine and choline/N-acetylaspartate ratios that suggested brain metastasis or glioblastoma, and ultimately tissue biopsy was needed to confirm the MCC diagnosis.

Conclusions

MCC brain metastasis is a great mimicker of many pathologies. In rare cases, distant MCC metastasis can occur without detection of a primary lesion. The patient's age, race, immunosuppression status, imaging findings, and histology/biomarkers are crucial to establishing the diagnosis. On the basis of this lesson, we recommend that patients with a history of MCC and asymptomatic brain mass lesion should be strongly considered for aggressive resection, regardless of appearance on scans or pathology on frozen sections, because MCC can mimic other intracranial pathologies.

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References

1. Toker C. Trabecular carcinoma of the skin. *Arch Dermatol.* 1972; 105(1):107–110.
2. Song Y, Azari FS, Tang R, et al. Patterns of metastasis in Merkel cell carcinoma. *Ann Surg Oncol.* 2021;28(1):519–529.
3. Lewis CW, Qazi J, Hippe DS, et al. Patterns of distant metastases in 215 Merkel cell carcinoma patients: implications for prognosis and surveillance. *Cancer Med.* 2020;9(4):1374–1382.
4. Caramanti RL, Chaddad Neto FE, Meguins LC, Rocha CE, de Moraes DF, Góes MJ. Brain metastasis of Merkel cell carcinoma – a rare case report. *Surg Neurol Int.* 2019;10:172.
5. Bailey TL, Fung MA, Gandour-Edwards R, Ellis WG, Schrot RJ. Clinical emergence of neurometastatic Merkel cell carcinoma: a surgical case series and literature review. *J Neurooncol.* 2011;102(1):147–155.
6. Harary M, Kavouridis VK, Thakuria M, Smith TR. Predictors of survival in neurometastatic Merkel cell carcinoma. *Eur J Cancer.* 2018;101:152–159.

7. Ikawa F, Kiya K, Uozumi T, et al. Brain metastasis of Merkel cell carcinoma. Case report and review of the literature. *Neurosurg Rev.* 1999;22(1):54–57.
8. Fukushima M, Katayama Y, Yokose N, et al. Primary central nervous system malignant lymphoma in a patient with rheumatoid arthritis receiving low-dose methotrexate treatment. *Br J Neurosurg.* 2013;27(6):824–826.
9. Farah RA, Alduaij A, Ugas C, Navarro R. Primary central nervous system lymphoma in a patient on adalimumab therapy for chronic plaque psoriasis. *World Neurosurg.* 2020;139:260–263.
10. Cornejo C, Miller CJ. Merkel cell carcinoma: updates on staging and management. *Dermatol Clin.* 2019;37(3):269–277.
11. 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.
12. Nghiem PT, Bhatia S, Lipson EJ, et al. PD-1 blockade with pembrolizumab in advanced Merkel-cell carcinoma. *N Engl J Med.* 2016;374(26):2542–2552.
13. Paulson KG, Park SY, Vandeven NA, et al. Merkel cell carcinoma: current US incidence and projected increases based on changing demographics. *J Am Acad Dermatol.* 2018;78(3):457–463.e2.
14. Xue Y, Thakuria M. Merkel cell carcinoma review. *Hematol Oncol Clin North Am.* 2019;33(1):39–52.
15. von Baumgarten L, Illerhaus G, Korfel A, Schlegel U, Deckert M, Dreyling M. The diagnosis and treatment of primary CNS lymphoma. *Dtsch Arztebl Int.* 2018;115(25):419–426.
16. Han CH, Batchelor TT. Diagnosis and management of primary central nervous system lymphoma. *Cancer.* 2017;123(22):4314–4324.
17. 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.
18. Folyovich A, Majoros A, Jarecsny T, et al. Epileptic seizure provoked by bone metastasis of chronic lymphoid leukemia and Merkel cell carcinoma. *Case Rep Med.* 2020;2020:4318638.
19. Grubb AF, Hankollari E. Cerebral metastasis of Merkel cell carcinoma following resection with negative margins and adjuvant external beam radiation: a case report. *J Med Case Rep.* 2021;15:118.
20. Jacob AT, Alexandru-Abrams D, Abrams EM, Lee JY. Stereotactic radiosurgery for Merkel cell carcinoma brain metastases. *J Clin Neurosci.* 2015;22(9):1499–1502.
21. Fife K, Tétu P, Prabhakaran J, Lebbé C, Grignani G. Case report: clinical experience with avelumab in patients with metastatic Merkel cell carcinoma and brain metastases treated in Europe. *Front Oncol.* 2021;11:672021.
22. Haldorsen IS, Espeland A, Larsson EM. Central nervous system lymphoma: characteristic findings on traditional and advanced imaging. *AJNR Am J Neuroradiol.* 2011;32(6):984–992.
23. Faehndrich J, Weidauer S, Pilatus U, Oszvald A, Zanella FE, Hattingen E. Neuroradiological viewpoint on the diagnostics of space-occupying brain lesions. *Clin Neuroradiol.* 2011;21(3):123–139.
24. Abul-Kasim K, Söderström K, Hallsten L. Extensive central nervous system involvement in Merkel cell carcinoma: a case report and review of the literature. *J Med Case Rep.* 2011;5:35.

Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Yu, Schreiber, Garg. Acquisition of data: Yu, Garg, Allen. Analysis and interpretation of data: Yu, Schreiber, Garg, Allen. Drafting the article: Yu, Schreiber. Critically revising the article: all authors. Reviewed submitted version of manuscript: Yu, Schreiber, Garg, Allen. Approved the final version of the manuscript on behalf of all authors: Turtz. Study supervision: Schreiber.

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