Merkel cell carcinoma (MCC) is a rare, highly aggressive neuroendocrine carcinoma of the skin, first described in 1972. Presenting as a painless, rapidly growing nodule predominantly in the head and neck, MCC tends toward ganglionic or vascular invasion, and can occur synchronously or metachronously with squamous cell carcinomas or basal cell carcinomas. MCC incidence has increased in Western countries with the increase of known risk factors: senescence, immunosuppression, Caucasian race, and UV-light exposure. Recent studies have demonstrated an association between MCC oncogenesis and the Merkel cell polyomavirus (MCPyV). Increased detection of MCC can be attributed to immunohistochemical staining for neuroendocrine markers, MCPyV, and special AT-rich sequence-binding protein 2 (SATB2), a protein involved in transcriptional regulation and chromatin remodeling.

1 | INTRODUCTION

Merkel cell carcinoma (MCC) is an uncommon, highly aggressive neuroendocrine carcinoma of the skin, first described in 1972. Presenting as a painless, rapidly growing nodule predominantly in the head and neck, MCC tends toward ganglionic or vascular invasion, and can occur synchronously or metachronously with squamous cell carcinomas or basal cell carcinomas. MCC incidence has increased in Western countries with the increase of known risk factors: senescence, immunosuppression, Caucasian race, and UV-light exposure. Recent studies have demonstrated an association between MCC oncogenesis and the Merkel cell polyomavirus (MCPyV). Increased detection of MCC can be attributed to immunohistochemical staining for neuroendocrine markers, MCPyV, and special AT-rich sequence-binding protein 2 (SATB2), a protein involved in transcriptional regulation and chromatin remodeling.
MCC is characterized by frequent recurrence, regional lymph node involvement, and distant metastases to sites like liver, lung, bone, and brain. Localized MCC disease has a 5-year survival rate of approximately 51%, which decreases to 26.8% for patients with clinically detected nodal disease, and only 13.5% for patients with distant metastatic disease. Despite its increasing incidence, distant metastatic MCC involving body cavity effusions is very rare. We have identified less than 10 cases of metastatic pleural effusion MCCs in the literature, and one case of metastatic MCC in ascitic fluid.

Here, we report on a case of a 65-year-old male presenting with a right pleural effusion with a remote history of MCC, unknown to us at the time of cytologic evaluation of the effusion. To the best of our knowledge, this is the sixth case of metastatic MCC diagnosed by body fluid cytology reported in English literature, and the first one reported in a patient previously admitted for the SARS-CoV-2 virus (COVID-19).

### Table 1

Previously reported Merkel Cell Carcinoma (MCC) cases involving body cavities

| Case | Age, gender | Past medical history | Presentation | Primary tumor site | Involved body cavity | Cytologic findings | Immunohistochemistry | Reference |
|------|-------------|----------------------|--------------|-------------------|---------------------|-------------------|----------------------|-----------|
| 1    | 70 F        | MCC and CLL          | Dyspnea due to pleural effusion | Right anterior tibia | Pleura | Small lymphocytes with hypercondensed nuclear chromatin and large atypical cells with mitoses | (+) CK20, EMA, EpCAM, NSE, synaptophysin, chromogranin, CD56; (-) CK7, CD45, TTF1 | 12        |
| 2    | 68 F        | MCC                   | Bilateral pleural effusion | Left buttock | Pleura | Small round blue cells with hyperchromatic nuclei, salt, and pepper chromatin, occasional mitoses and nuclear molding | (+) CK20, CD56, chromogranin, synaptophysin | 13        |
| 3    | 46 F        | No known history of MCC | Abdominal pain and new onset ascites | Unknown | Peritoneum | Cells with round to oval nuclei, irregular nuclear borders, stippled chromatin, inconspicuous nucleoli, and scant cytoplasm showing occasional mitoses and nuclear molding | (+) AE1/AE3, CK20, chromogranin, synaptophysin, MCPyV, monoclonal antibody (CM2B4); (-) CK7, CEA, B72.3, CD45, CD138, CD56, TTF-1, BerEp4, S-100, Hep Par1, CK5/6, calretinin | 16        |
| 4    | 77 F        | MCC and colon adenocarcinoma | Dyspnea due to pleural effusion | Right buttock | Pleura | Small round single cells with granular salt and pepper chromatin with multiple mitoses | (+) CK20 | 14        |
| 5    | 57 M        | MCC                   | Skin lesions, pleural effusion, hemoptysis, recurrent right upper quadrant abdominal mass, renal failure, anemia, and sepsis | Left hip | Pleura | Small, round/oval cells with large nuclei, fine granular chromatin, inconspicuous nucleoli and scant, pale cytoplasm | Not performed. Confirmed by electron microscopy. | 15        |

Abbreviations: CLL, chronic lymphocytic leukemia; F, female; M, male; MCC, Merkel cell carcinoma; MCPyV, Merkel cell polyomavirus; (+) Positive; (-) Negative.
collected and sent for cytology. The patient’s respiratory status improved to his baseline, and he was discharged after 4 days.

A Papanicolaou stained ThinPrep slide and a cell block were prepared. Both displayed clusters of predominantly small to medium sized blue round cells with hyperchromatic nuclei, scant cytoplasm, and fine chromatin, in a background of rare mesothelial cells, macrophages and numerous lymphocytes. Based on morphology and location, lymphoma versus neuroendocrine carcinoma were initially considered the differential diagnosis. Therefore, a broad initial immunohistochemical (IHC) panel was ordered upfront, in order to avoid exhausting the limited available tissue: CD45, CD20, CD3, CK7, CK20, Ber-EP4, CD68, CK5/6, TTF-1, Napsin-A, AE1/AE3, CAM 5.2, CD56, chromogranin, synaptophysin, and Ki67. IHC studies showed positive perinuclear dot-like staining pattern for CK20, AE1/AE3, and CAM 5.2 markers [Figure 1], as well as immunoreactivity for the neuroendocrine markers: CD56, chromogranin, and synaptophysin. Ki-67 proliferative index was approximately 40% [Figure 2], while CD45 highlighted the background lymphocytes. All other IHC stains, including TTF-1, were negative in the neoplastic cells.

Due to positivity for CK20 and neuroendocrine markers, SATB2 and MCPyV (MCPyV, Mayo Laboratories) immunostains were performed. Both demonstrated strong nuclear reactivity [Figure 3], confirming the MCC diagnosis.

The primary care physician was contacted to report the unexpected findings. This revealed the patient’s past medical history was significant for MCC post wide local excision and lymph node
dissection at an outside institution 4 years prior to the current presentation. A copy of the surgical pathology report was obtained. The primary tumor measured 6.5 cm, was located on the right ulnar forearm, and extended to the skeletal muscle. IHC staining was positive for anti-MCPyV large T-antigen (CM2B4). Micrometastases in axillary sentinel lymph nodes were identified by IHC staining for CK20 and AE1/AE3 at the time of the original diagnosis.

3 | DISCUSSION

This is to the best of our knowledge the third case of metastatic MCC diagnosed in pleural effusion reported in the United States, and the sixth case of MCC diagnosed in body fluid cytology reported in English literature. There was only one male patient in the previously reported cases (1/5). Most of the recurrences in body fluids involved the pleura (including our case). One case was previously reported in ascites. The first case report confirmed MCC diagnosis based on electron microscopy, and was the only other case reported in a man.15

The latter cases used IHC positivity for CK20, epithelial markers (CAM 5.2, EMA), and neuroendocrine markers (synaptophysin, chromogranin, and CD56) to confirm their diagnoses.12-14,16 MCPyV positivity was detected in the case of metastatic MCC in ascites.16

Our case is unique in that we also used one of the newer neuroendocrine markers, SATB2, to confirm the diagnosis.

Metastatic MCC represents a diagnostic challenge, in part to its extreme rarity in body fluid cytology. Lack of provided medical history can also contribute to MCC not being considered in the differential diagnosis. Other entities (i.e., chronic lymphocytic lymphoma, small cell lung carcinoma, carcinoid tumor) are more commonly encountered in pleural effusions. MCC can be confused with other small blue round cell tumors that share similar cytologic features such as monomorphic, small to medium-sized cells with hyperbasophilic cytoplasm.17

MCC, small cell lung carcinomas and carcinoid tumors express both epithelial and neuroendocrine markers. However, small cell lung carcinomas and carcinoid tumors are usually diffusely positive for TTF-1 immunostain. While MCC is usually TTF-1 negative, there have been cases of mixed squamous cell and MCC that express aberrant TTF-1 antibody clones.18-22 Additional markers available to differentiate these tumors include CK20, which is highly sensitive and specific for MCC, as well as MCPyV and SATB2, which has recently shown to be reactive in MCC.9,10,23 Therefore, it is essential to maintain a high index of suspicion to apply the necessary IHC panel for a diagnosis of MCC.

A novel aspect to our case is the immunosuppressive treatment the patient received due to his COVID-19 hospitalizations, including tocilizumab, an interleukin-6 inhibitor, and corticosteroids. The mechanism by which immunosuppression interacts with MCPyV and/or UV radiation in MCC pathogenesis and recurrence is currently unknown.11 MCC has been incidentally reported in patients receiving immunosuppressive treatment for rheumatoid arthritis, but clinical trials did not find a significant increased cancer risk in patients receiving tocilizumab treatment.24-28

Current guidelines for COVID-19 treatment in cancer patients are the same as the general population, which recommends steroids and tocilizumab for critically acute patients.29 To the best of our knowledge, there have been no other reported cases of de novo or recurrent malignancies in patients treated with tocilizumab for COVID-19. Further studies are warranted to delineate a possible increase in the incidence of malignant neoplasms associated with immunosuppression due to tocilizumab treatment during the pandemic.

In conclusion, MCC is a highly aggressive malignancy rarely reported in body fluids. Because of its metastatic nature and rising incidence of risk factors, MCC should be included in the differential diagnosis of malignant pleural effusions, especially in cases of small blue round cell entities. The use of adequate IHC studies, like CK20 and neuroendocrine markers, including the newer SATB2 marker, can lead to an accurate diagnosis. Additional reporting of such cases may increase awareness, especially where prior history is not readily available, such as in this present instance.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.
AUTHOR CONTRIBUTIONS

All authors contributed to all aspects of writing and proofreading the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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