A rare case of Merkel cell carcinoma presenting as a giant intra-thoracic mass
A case report and review of the literature

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Abstract
Rationale: Merkel cell carcinoma (MCC) is an aggressive neuroendocrine-derived cutaneous cancer. Ectopic or single metastatic MCC located in thorax is extremely rare; meanwhile, its definite management has not been elucidated yet.

Patient concerns: A 64-year-old female patient with a giant mass located in her left thorax was presented for stuffy pain of left chest for 6 months and fever for half a month. She underwent radical resection of vulvar MCC 10 years ago.

Diagnoses: Computed tomography (CT)-guided biopsy of the intrathoracic mass revealed a diagnosis of MCC, without synchronous urogenital lesions on pelvic CT images.

Interventions: This bulky tumor was completely resected via thoracotomy, along with the adjacent pulmonary lobe, pericardium, pleura, and diaphragm.

Outcomes: The patient survived without local-regional recurrence or distant metastasis during the follow-up of 1 year up to now.

Lessons: Ectopic or single metastatic MCC should be considered in the differential diagnosis of intrathoracic tumors, especially in patients with a history of MCC. Besides, a timely surgery combined with chemotherapy is effective for this disease.

Abbreviations: AUC = area under the curve, CT = computed tomography, MCC = Merkel cell carcinoma, MRI = magnetic resonance image.

Keywords: ectopic, extensive radical resection, Merkel cell carcinoma (MCC), neuroendocrine tumor, oligometastasis

1. Introduction
Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine tumor that occurs predominantly in the head and neck region, which is preferentially occurs in elderly and immunosuppressed patients with a high mortality. Accurate differential diagnosis and staging of MCC depend on biopsy using immunohistochemical staining. Its aggressive nature results in the necessity of multidisciplinary treatment. Surgery combined with adjuvant radiotherapy is effective for resectable cases, while definitive radiotherapy could be considered for unresectable lesions, because MCC is highly sensitive to radiotherapy. However, there are still no approved treatments for patients with metastatic MCC. Herein, an extremely rare case with ectopic (or single metastatic) MCC merely located in thorax was presented for discussion, followed by critical review of related literature, with the aim of promoting the identification and management of MCC.

2. Case presentation
A 64-year-old female patient was admitted for moderate stuffy pain of the left chest for 6 months, and productive cough with fever in the recent half a month, without significant loss of weight. Her highest temperature during this period was 38.5°C. She was initially diagnosed as pneumonia in a community hospital, but the therapy using antibiotics of piperacillin-tazobactam for 1 week did not work. She had been working near a coal mine for more than 10 years, without history of hypertension or coronary heart disease. Her family and social histories were unremarkable. The patient underwent extensive radical resection of vulvar cutaneous MCC 10 years ago, and the surgical margin as well as inguinal lymph nodes were tumor-negative. She took cranial magnetic resonance, chest and abdomen computed tomography...
administered for 7 days before the surgery, and her temperature was reduced to 37°C. Then thoracotomy was performed through the 5th intercostal space, under general anesthesia and double-lumen endotracheal intubation. After the collapse of the left pulmonary lobes, fortunately, the significant distance between the tumor and thoracic aorta emerged. Meanwhile, adhesion of the mass with adjacent pericardium and pleura was observed during the surgery. Then a single-stage operation including left lower lobectomy, extensive resection of the mass, and mediastinal lymph node dissection was performed successfully, which took 290 minutes. Postoperative pathological staining of the mass revealed neuroendocrine carcinoma (Fig. 1D), which involved the left lower pulmonary lobe, adjacent pericardium, diaphragm, and pleura. The surgical margins and dissected lymph nodes were tumor-negative. In addition, the feeding vessels of the tumor were verified to be branches of internal thoracic vessels. Further immunohistochemical staining suggested positive expression of CD56 and Ki67 (25%), and negative chromogranin A, synaptophysin, CD10, P63, CK5/6, human leukocyte common antigen, vimentin and desmin, which revealed MCC.

Based on these findings, a diagnosis of intrathoracic ectopic, or single metastatic MCC (oligometastasis) was established, because her physical examination and pelvic CT did not indicate synchronous vulvar lesions. The patient was staged as IIIB tentatively according to the 8th AJCC consensus guidelines for MCC (primary tumor invaded fascia, muscle, cartilage or bone, without regional lymph node metastases).[4] However, it was not a definite diagnosis for insufficient histological evidence.

The postoperative recovery of the patient was mainly uneventful. Her body temperature returned to normal after the administration of piperacillin-tazobactam for another 7 days, and her chest pain was alleviated gradually. She was discharged 14 days after the surgery. Subsequently, she received 4 cycles of adjuvant chemotherapy with a mean interval of 21 days, using carboplatin (area under the curve [AUC]=5) on day 1, and etoposide 100mg daily on day 1 to 4. This patient survived without loco-regional recurrence or distant metastasis during the follow-up of 1 year.

3. Discussion
The clinical thinking process of this case in terms of safety and etiological analysis should be criticized. First, the symptoms of chest pain and fever might be correlated with many diseases, such as acute bronchitis, pneumonia, tuberculosis, pericarditis, myocarditis, coronary artery disease, lung cancer, heart attack, angina, acid reflux (gastro-esophageal reflux disease), esophagitis, asthma, fever, pericarditis, myocarditis, angina, acid reflux (gastro-esophageal reflux disease), esophaeitis, or necrosis within the intrathoracic MCC and atelectasis.
of the adjacent lobe may lead to atypical fever and chest pain, which were alleviated lastly after the surgery and the administration of perioperative antibiotics. However, there is no clear evidence available that atelectasis is associated with fever.[15]

Based on the complaints of this patient on admission, the initially suspected diseases need to be distinguished step by step, including acute coronary syndrome, coronary heart disease, aortic dissection, pulmonary embolism, silicosis, atelectasis, and pneumonia with specific infection by tuberculosis, fungus or parasites, rheumatic disease, recurrence of the MCC, and newly emerged malignancy. Related work-up and examinations of neurogenic mediatinal and chest malignancies including the tumor markers, serum cardiac enzymes such as lactate dehydrogenase, creatine phosphokinase, creatine kinase-MB, and alpha-hydroxybutyric dehydrogenase should be taken, which is helpful for differential diagnosis.

Second, anterior, middle, and posterior mediastinal tumors should be taken into account before surgery, which could invade into the thorax and mimic intrathoracic tumor. MRI and biopsy are useful for the diagnosis of mediatinal masses. Because of the proximity of thoracic aorta to MCC and potential adhesion between each other, the preoperative assessment of aorta with surgical plan is necessary. In detail, an aortic specialist surgeon with preparation for thoracic endovascular aortic repair ought to participate in this operation according to the basic standards of clinical care, because the patient would take the risk of accidental aortic rupture during the surgery.

The incidence of MCC is increasing for unknown reasons, which is estimated to be 0.32/100,000 in the United States.[6] MCC has a high rate of sentinel lymph node involvement, local-regional recurrence, and mortality.[7] It is reported that 65% of MCC patients are admitted with local disease, whereas 26% and 8% are presented with nodal and distant disease, respectively.[3] Risk factors for the onset of MCC include Merkel cell polyomavirus (MCPyV) infection, ultraviolet light exposure, history of chronic inflammatory disorders, immunosuppression, and advanced age.[8,10] MCPyV infection is highly prevalent in the skin of the general population, which has been identified to be in up to 80% of MCC cases, especially in elderly and immunosuppressed patients.[9,10] Approximately 20% of MCCs are not driven by MCPyV (virus-negative), which can be identified by immunochemistry using the CM2B4 antibody, and then represent a more aggressive subtype.[11] The tumorigenesis of virus-negative MCC is linked to UV-induced DNA damage.[12]

Neuroendocrine MCC with highly aggressive behavior rarely arise in the vulva,[13] which originates from mechanoceptor Merkel cells of the stratum basale of epidermis.[14] However, the evidence regarding the actual origin and etiology of MCC is insufficient due to its rarity.[13] The presented patient with ectopic or second MCC in our report has performed radical surgical resection of vulvar MCC 10 years ago, which indicates that long-term follow-up is mandatory. Although MCC is chemosensitive and radiosensitive, responses in advanced stages are mostly of short duration.

There are still no approved treatments for patients with metastatic MCC.[2] The treatment choice depends on stage at presentation, regional lymph node status, and comorbidities of the patient. Surgical resection with clear margins and lymph nodes dissection, followed by adjuvant radiotherapy, is recommended for MCC patients with local-regional nodal involvement.[2,15] Reconstructed models of sophisticated anatomical structures by means of 3D rapid prototyping, which provide better visualization, can be used to facilitate surgical planning and to assess the invasion of vital structures such as thoracic aorta by adjacent tumors.[16]

As for the patient in this study, preoperative simulation using 3D printing of this complicated tumor might be more helpful than CT images to understand its location, and relationship with adjacent thoracic aorta. Meanwhile, a timely extensive radical resection of MCC could also deliver satisfactory disease control. Definitive radiotherapy for localized MCC may confer regional control.[17] Radiotherapy alone, or in combination with chemotherapy, can be considered for unresectable MCC; meanwhile, chemotherapy remains the most commonly used regimen for distant metastatic MCC.[5] The tumor should be excised with 1–2 cm margins, and radical lymphadenectomy should be performed simultaneously if the regional lymph node is involved.[13] Wide local excision, selective lymphadenectomy, and loco-regional radiotherapy are now served as the mainstay of treatment for aggressive primary MCC, with acceptable loco-regional disease control. Chemotherapy is reserved for advanced-stage MCC and palliative therapy.[18] The discovery of molecular alterations and MCPyV of MCC lead to novel targeted therapy and immunotherapy trials.[12,19] Checkpoint inhibitors are emerging therapeutic options.[20] Immunotherapy targeting the programmed cell death receptor 1/programmed cell death ligand 1 (PD-1/PD-L1) checkpoint may provide durable responses for advanced MCC.[18] Avelumab is a promising new therapeutic agent for patients with metastatic Merkel cell carcinoma.[21]

Furthermore, the metastatic lesions of MCC demonstrated avidity to both somatostatin receptors and (18)F-FDG, and an excellent partial response to a single cycle of peptide receptor radionuclide therapy with ([177]Lu-DOTATATE is demonstrated, which may be reasonable as the first-line therapy for metastatic MCC.[22] The specific biomarkers of MCC include platelet-derived growth factor receptor, CD117, phosphoinositiode 3-kinase, PD-L1, p63, vascular endothelial growth factor receptor, Ki-67, CD34, epithelial cellular adhesion molecule (EpCAM), nuclear factor kappa B, sonic hedgehog pathway proteins, and matrix metalloproteinase, which have been suggested to predict the prognosis of these patients.[5] Up to date, no effective systemic treatment for end stage MCC is available.[23] Therefore, more high-quality studies are needed for the establishment of the optimal therapeutic regimens, and detailed indications of aggressive surgery for these patients.

4. Conclusion

In summary, ectopic or single metastatic MCC should be kept in mind during the differential diagnosis of newly emerged intrathoracic masses, especially for patients with an MCC history. Moreover, single-stage extensive radical resection of MCC combined with chemotherapy is effective for selected patients.

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