

Lambert-Eaton Myasthenic Syndrome and Merkel Cell Carcinoma

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PRACTICE POINTS

- Approximately 50% to 60% of patients with Lambert-Eaton myasthenic syndrome (LEMS) have an underlying tumor, most commonly small cell lung carcinoma.
- A thorough search for an underlying malignancy is highly recommended in patients with diagnosed LEMS without clear cause; to this end, a screening protocol comprising computed tomography and total-body fludeoxyglucose positron emission tomography has been established.
- Because Merkel cell carcinoma (MCC) can present as occult lymph node involvement with primary cutaneous findings absent, it is recommended that MCC be considered in the differential diagnosis of an underlying malignancy in a LEMS patient.
- Early identification and treatment of the primary tumor can lead to improvement of neurologic symptoms.

Lambert-Eaton myasthenic syndrome (LEMS) is an antibody-mediated disorder of the neuromuscular junction that is most commonly diagnosed in association with small cell lung carcinoma (SCLC). Small cell lung carcinoma is histologically similar to the aggressive cutaneous neuroendocrine malignancy Merkel cell carcinoma (MCC). We provide a full report and longitudinal clinical follow-up of a case of LEMS occurring with MCC. We also review the literature on paraneoplastic syndromes associated with MCC and other nonpulmonary small cell carcinomas.

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Merkel cell carcinoma (MCC) is an aggressive neuroendocrine malignancy of the skin that is thought to arise from neural crest cells. It has an estimated annual incidence of 0.6 per 100,000 individuals, typically occurs in the elderly population, and is most common in white males.¹ The tumor presents as a rapidly growing, violaceous nodule in sun-exposed areas of the skin; early in the course, it can be mistaken for a benign entity such as an epidermal cyst.² Merkel cell carcinoma has a propensity to spread to regional lymph nodes, and in some cases, it occurs in the absence of skin findings.³ Histologically, MCC is nearly indistinguishable from small cell lung carcinoma (SCLC).⁴ The overall prognosis for patients with MCC is poor and largely dependent on the stage at diagnosis. Patients with regional and distant metastases have a 5-year survival rate of 26% to 42% and 18%, respectively.³

Lambert-Eaton myasthenic syndrome (LEMS) is a paraneoplastic or autoimmune disorder of the neuromuscular junction that is found in 3% of cases of SCLC.⁴ Reported cases of LEMS in patients with MCC are exceedingly rare.⁵⁻⁸ We provide a full report and longitudinal clinical follow-up of a case that was briefly discussed by Simmons et al,⁸ and we review the literature regarding paraneoplastic syndromes associated with MCC and other extrapulmonary small cell carcinomas (EPSCCs).

Case Report

A 63-year-old man was evaluated in the neurology clinic due to difficulty walking, climbing stairs, and performing push-ups over the last month. Prior to the onset of symptoms, he was otherwise healthy, walking 3 miles daily;

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however, at presentation he required use of a cane. Leg weakness worsened as the day progressed. In addition, he reported constipation, urinary urgency, dry mouth, mild dysphagia, reduced sensation below the knees, and a nasal quality in his speech. He had no ptosis, diplopia, dysarthria, muscle cramps, myalgia, or facial weakness. He denied fevers, chills, and night sweats but did admit to an unintentional 10- to 15-lb weight loss over the preceding few months.

The neurologic examination revealed mild proximal upper extremity weakness in the bilateral shoulder abductors, infraspinatus, hip extensors, and hip flexors (Medical Research Council muscle scale grade 4). All deep tendon reflexes, except the Achilles reflex, were present. Despite subjective sensory concerns, objective examination of all sensory modalities was normal. Cranial nerve examination was normal, except for a slight nasal quality to his voice.

A qualitative assay was positive for the presence of P/Q-type voltage-gated calcium channel (VGCC) antibodies. Other laboratory studies were within reference range, including acetylcholine-receptor antibodies (blocking, binding, and modulating) and muscle-specific kinase antibodies.

Lumbar and cervical spine magnetic resonance imaging revealed multilevel neuroforaminal stenosis without spinal canal stenosis or myelopathy. Computed tomography (CT) of the chest was notable for 2 pathologically enlarged lymph nodes in the left axilla and no evidence of primary pulmonary malignancy. Nerve-conduction studies (NCSs) in conjunction with other clinical findings were consistent with the diagnosis of LEMS.

Ultrasound-guided biopsy of the enlarged axillary lymph nodes demonstrated sheets and nests of small round blue tumor cells with minimal cytoplasm, high mitotic rate, and foci of necrosis (Figure 1). The tumor cells were positive for pancytokeratin (Lu-5) and cytokeratin (CK 20

in a perinuclear dotlike pattern (Figure 2), as well as for the neuroendocrine markers synaptophysin (Figure 3), chromogranin A, and CD56. The tumor cells showed no immunoreactivity for CK7, thyroid transcription factor 1, CD3, CD5, or CD20. Flow cytometry demonstrated low cellularity, low specimen viability, and no evidence of an abnormal B-cell population. These findings were consistent with the diagnosis of MCC.

The patient underwent surgical excision of the involved lymph nodes. Four weeks after surgery, he reported dramatic improvement in strength, with complete resolution of the nasal speech, dysphagia, dry mouth, urinary retention, and constipation. Two months after surgery, his strength had normalized, except for slight persistent weakness in the bilateral shoulder abductors, trace weakness in the hip flexors, and a slight Trendelenburg gait. He was able to rise from a chair without using his arms and no longer required a cane for ambulation.

The patient underwent adjuvant radiation therapy after 2-month surgical follow-up with 5000-cGy radiation treatment to the left axillary region. Six months following primary definitive surgery and 4 months following adjuvant radiation therapy, he reported a 95% subjective return of physical strength. The patient was able to return to near-baseline physical activity. He continued to deny symptoms of dry mouth, incontinence, or constipation. Objectively, he had no focal neurologic deficits or weakness; no evidence of new skin lesions or lymphadenopathy was noted.

Comment

MCC vs SCLC—Merkel cell carcinoma is classified as a type of EPSCC. The histologic appearance of MCC is indistinguishable from SCLC. Both tumors are composed of uniform sheets of small round cells with a high nucleus to cytoplasm ratio, and both can

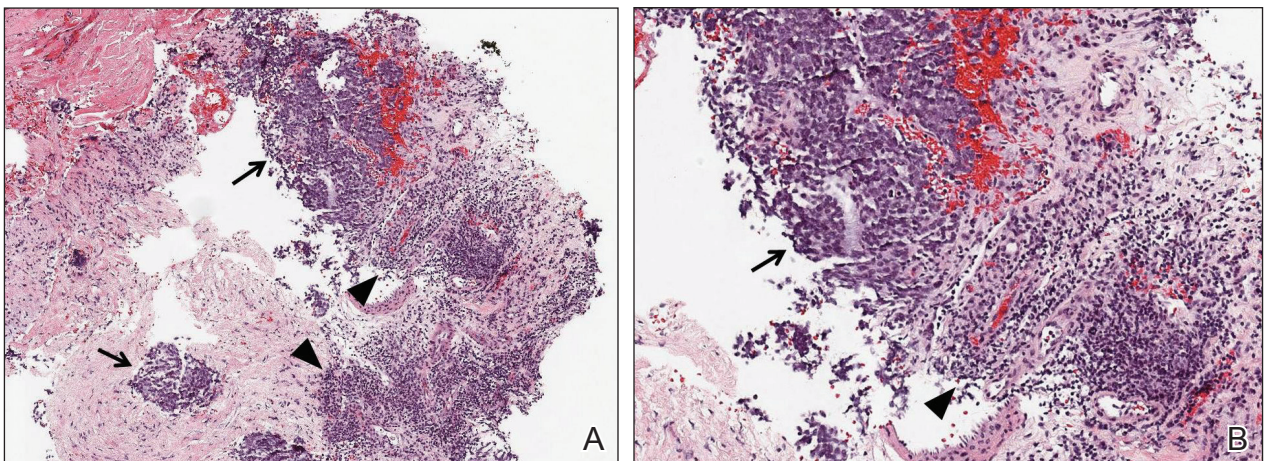


FIGURE 1. A, Biopsy of axillary lymph nodes demonstrated small round blue tumor cells (arrows), associated lymphoid tissue (arrowheads), and fibrous stroma (H&E, original magnification $\times 40$). B, Higher magnification further contrasted the small round blue tumor cells (arrow) and associated lymphocytes (arrowhead) (H&E, original magnification $\times 200$).

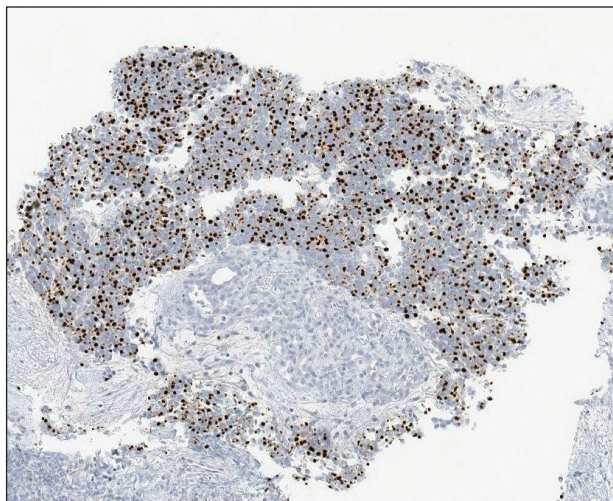


FIGURE 2. Perinuclear dotlike positivity for cytokeratin (CK) 20 in tumor cells, with adjacent lymphoid tissue and stroma negative for CK20 (original magnification $\times 200$).

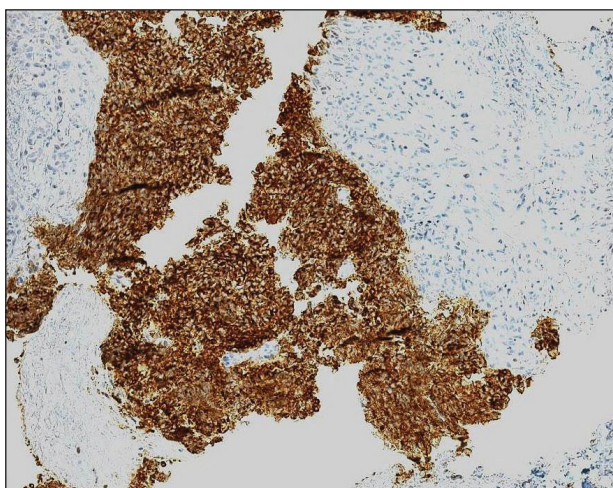


FIGURE 3. Tumor cells exhibited diffuse cytoplasmic reactivity to synaptophysin staining (original magnification $\times 200$).

express neuroendocrine markers, such as neuron-specific enolase, chromogranin A, and synaptophysin.⁹ Immunohistochemical positivity for CK20 and neurofilaments in combination with negative staining for thyroid transcription factor 1 and CK7 effectively differentiate MCC from SCLC.⁹ In addition, MCC often displays CK20 positivity in a perinuclear dotlike or punctate pattern, which is characteristic of this tumor.^{3,9,10} Negative immunohistochemical markers for B cells (CD20) and T cells (CD3) are important in excluding lymphoma.

LEMS Diagnosis—Lambert-Eaton myasthenic syndrome is a paraneoplastic or autoimmune disorder involving the neuromuscular junction. Autoantibodies to VGCC impair calcium influx into the presynaptic terminal, resulting in marked reduction of acetylcholine release into the synaptic cleft. The reduction in acetylcholine

activity impairs production of muscle fiber action potentials, resulting in clinical weakness. The diagnosis of LEMS rests on clinical presentation, positive serology, and confirmatory neurophysiologic testing by NCS. Clinically, patients present with proximal weakness, hyporeflexia or areflexia, and autonomic dysfunction. Antibodies to P/Q-type VGCCs are found in 85% to 90% of cases of LEMS and are thought to play a direct causative role in the development of weakness.¹¹ The finding of postexercise facilitation on motor NCS is the neurophysiologic hallmark and is highly specific for the diagnosis.

Approximately 50% to 60% of patients who present with LEMS have an underlying tumor, the vast majority of which are SCLC.¹¹ There are a few reports of LEMS associated with other malignancies, including lymphoma; thymoma; neuroblastoma; and carcinoma of the breast, stomach, prostate, bladder, kidney, and gallbladder.¹² Patients with nontumor or autoimmune LEMS tend to be younger, and there is no male predominance, as there is in paraneoplastic LEMS.¹³ Given the risk of underlying malignancy in LEMS, Titulaer et al¹⁴ proposed a screening protocol for patients presenting with LEMS, recommending initial primary screening using CT of the chest. If the CT scan is negative, total-body fludeoxyglucose positron emission tomography should be performed to assess for fludeoxyglucose avid lesions. If both initial studies are negative, routine follow-up with CT of the chest at 6-month intervals for a minimum of 2 to 4 years after the initial diagnosis of LEMS was recommended. An exception to this protocol was suggested to allow consideration to stop screening after the first 6-month follow-up chest CT for patients younger than 45 years who have never smoked and who have an HLA 8.1 haplotype for which nontumor LEMS would be a more probable diagnosis.¹⁴

In addition to a screening protocol, a validated prediction tool, the Dutch-English LEMS Tumor Association prediction score, was developed. It uses common signs and symptoms of LEMS and risk factors for SCLC to help guide the need for further screening.¹⁵

Paraneoplastic Syndromes Associated With MCC—Other paraneoplastic syndromes have been reported in association with MCC. A patient with brainstem encephalitis associated with MCC was reported in a trial of a novel immunotherapy for paraneoplastic neurologic syndromes.^{16,17} A syndrome of inappropriate antidiuretic hormone (SIADH) secretion was reported in a patient with N-type calcium channel antibodies.¹⁸ Two cases of paraneoplastic cerebellar degeneration have been reported; the first was associated with a novel 70-kD antibody,¹⁹ and the second was associated with the P/Q-type VGCC antibody.²⁰ Anti-Hu antibodies have been found in a handful of reports of neurologic deterioration in patients with MCC. Hocar et al²¹ reported a severe necrotizing myopathy; Greenlee et al²² described a syndrome of progressive sensorimotor and autonomic neuropathy with encephalopathy; and Lopez et al²³ described a constellation of

vision changes, gait imbalance, and proximal weakness. Support for a pathophysiologic connection among these 3 cases is suggested by the finding of Hu antigen expression by MCC in 2 studies.^{24,25} Because MCC can present with occult lymph node involvement in the absence of primary cutaneous findings,³ there are more cases of paraneoplastic neurologic syndromes that were not recognized.

Extrapulmonary small cell carcinomas such as MCC are morphologically indistinguishable from their pulmonary counterparts and have been reported in most anatomic regions of the body, including gynecologic organs (eg, ovaries, cervix), genitourinary organs (eg, bladder, prostate), the gastrointestinal tract (eg, esophagus), skin (eg, MCC), and the head and neck region. Extrapulmonary small cell carcinoma is a rare entity, with the most common form found in the gynecologic tract, representing only 2% of gynecologic malignancies.²⁶

Paraneoplastic syndromes of EPSCC are rare given the paucity of the malignancy. Several case reports discuss findings of SIADH in EPSCC of the cervix, as well as hypercalcemia, polyneuropathy, Cushing syndrome, limbic encephalitis, and peripheral neuropathy in EPSCC of the prostate.^{27,28} In contrast, SCLC has long been associated with paraneoplastic syndromes. Numerous case reports have been published describing SCLC-associated paraneoplastic syndromes to include hypercalcemia, Cushing syndrome, SIADH, vasoactive peptide production, cerebellar degeneration, limbic encephalitis, visceral plexopathy, autonomic dysfunction, and LEMS.²⁹ As more cases of EPSCC with paraneoplastic syndromes are identified and reported, we might gain a better understanding of this interesting phenomenon.

Conclusion

Merkel cell carcinoma is an aggressive neuroendocrine malignancy associated with paraneoplastic neurologic syndromes, including LEMS. A thorough search for an underlying malignancy is highly recommended in patients with diagnosed LEMS without clear cause. Early identification and treatment of the primary tumor can lead to improvement of neurologic symptoms.

We present a case of LEMS with no clearly identifiable cause on presentation with later diagnosis of metastatic MCC of unknown primary origin. After surgical excision of affected lymph nodes and adjuvant radiation therapy, the patient had near-complete resolution of LEMS symptoms at 6-month follow-up, without additional findings of lymphadenopathy or skin lesions. Although this patient is not undergoing routine surveillance imaging to monitor for recurrence of MCC, a chest CT or positron emission tomography–CT for secondary screening would be considered if the patient experienced clinical symptoms consistent with LEMS.

In cases of LEMS without pulmonary malignancy, we recommend considering MCC in the differential diagnosis during the workup of an underlying malignancy.

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