CLINICAL VIGNETTE

Lambert-Eaton Myasthenic Syndrome and Small Cell Lung Cancer Associated with Voltage-Gated Calcium Channel Antibody – Case Report and Review of Literature

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Introduction

Lambert-Eaton myasthenic syndrome (LEMS) is originally described as a neuromuscular disorder associated with lung cancer.[1] The mechanism was further elucidated by passive transfer of IgG from LEMS patients to mice suggesting its autoimmune nature.[2] Voltage-gated calcium channels (VGCC) are present in neuromuscular junctions and in small cell lung cancer. The release of acetylcholine in the neuromuscular junctions is regulated by influx of calcium through the voltage-gated calcium channels. The calcium channel blocker, nifedipine, and IgG from LEMS patients both inhibit voltage-gated calcium influx in a human small cell cancer line.[3] Apparently VGCC in small cell lung cancer evokes the production of autoimmune IgG that affects presynaptic VGCC at the neuromuscular junction leading to decrease release of acetylcholine and reduction in amplitude of the resting compound muscle action potential in the LEMS patients.[4,5]

We report a case of Lambert-Eaton myasthenic syndrome that predated the diagnosis of small cell lung cancer by two years which was associated with positive VGCC antibody which correlated with clinical course of the illness.

Case History

A 78-year-old African-American female with history of DCIS and left lumpectomy, hypertension and chronic bronchitis who initially presented with progressive lower limb weakness for four months to an outside institution. She was barely able to ambulate and subsequently diagnosed with Lambert-Eaton myasthenic syndrome (LEMS) with positive VGCC antibody. MRI of the lumbar spine showed mild spinal canal stenosis at L3-4 and L4-5 region, multilevel neuroforaminal stenosis and degenerative changes. CT scan of the chest, abdomen and pelvis revealed a 1.7 cm right apical stellate lesion associated with right hilar adenopathy. Subsequent PET scan showed mildly hypermetabolic activity in the right apical lesion. Bronchoscopy and bronchial washing/brushing cytology was negative for malignancy and CT guided needle biopsy of the right upper lung mass showed atypical glandular cells associated with fibrosis. Three months later repeat bronchoscopy with endobronchial ultrasound determined that right upper lobe nodule was either scar tissue or mucus impaction of the airway and no lymphadenopathy was noted. Since then she has been wheelchair-bound. Eighteen months later she developed progressive shortness of breath and hemoptysis. CT scan of the chest showed complete collapse of the right lung associated with a 3.9 cm right hilar mass. Repeat bronchoscopy revealed complete obstruction of right main stem bronchus and biopsy of the endobronchial mass confirmed small cell lung cancer. She was then referred to UCLA. She was wheelchair bound and dependent on oxygen. Bone scan showed no evidence of bony metastasis. MRI brain showed no evidence of metastasis. With limited stage of small cell lung cancer, she was started on systemic chemotherapy consisting of cisplatin and etoposide concurrent with radiation. The VGCC antibody was 392.7 pmol/L as measured by quantitative radioimmunoassay (negative, 0-24.5; indeterminate, 24.6-45.6; positive, 45.7 or above, ARUP Laboratories) before chemotherapy. It decreased to 88.7 pmol/L after 3 cycles and was undetectable after 6 cycles of chemotherapy. Six month follow up CT scan chest abdomen and pelvis showed focal right upper lung scarring and no lymphadenopathy. During the chemotherapy the neurological deficit improved slowly to a point that the patient was able to stand on her feet with minimal support. Another three months later, the patient complained of progressive weakness again and was mentally confused sporadically. Three month follow up CT scan of the chest abdomen and pelvis showed residual or recurrent right lung lesion, multiple right gluteal masses and enlarged right inguinal and iliac lymph nodes suggestive of metastasis. MRI brain showed multifocal metastatic disease in the bilateral cerebrum and cerebellum. Repeat VGCC antibody was found to be positive. The patient decided not to take any chemotherapy or brain radiation. She was referred to hospice.

Discussion

Since LEMS is frequently associated with malignancy, initial workup and, if negative, periodic screening for malignancy is imperative and essential.[6,7] In our patient, the diagnosis of LEMS predated the diagnosis of small cell lung cancer by almost two years. She presented with lower limb weakness and right apical lung lesion. However, CT guided needle biopsy, bronchoscopy and endoscopic ultrasound failed to diagnose the cancer at that time. Her lung cancer was finally diagnosed when she developed hemoptysis, dyspnea and right lung collapse with obstruction of the right main stem bronchus. Her cancer may have been diagnosed earlier if she had undergone surgical resection of the right upper lobe lesion after three negative biopsies in 2015.

In addition to small cell lung cancer, LEMS has been reported in other histologic types of lung cancer and other primary cancers.[8-13] While VGCC antibodies are usually believed to be specific to LEMS, Graus et al reported that VGCC antibodies were detected in 23% patients with paraneoplastic cerebellar degeneration and small cell lung cancer without LEMS.[14] In our patient, the neurological deficit improved significantly after treatment with effective chemotherapy. The VGCC antibody titer by radioimmunoassay appeared to correlate with the disease activity. More prospective study is required to confirm this observation.

It is speculative if autoimmune antibodies may be able to reduce tumor growth. Maddison et al conducted a prospective study of 100 consecutive patients with small cell lung cancer, VGCC was detected in 10 (10%) patients of whom 4 patients had LEMS, 1 had limbic encephalitis and 5 had no neurological signs. The median survival of the 4 VGCC antibody positive LEMS patients was considerably longer than those being antibody negative, 19.6 versus 8.9 months.[15,16] Monstad et al studied 200 patients with small cell lung cancer receiving chemotherapy for the presence of Hu and VGCC antibodies. Hu antibodies were detected in 51 patients (25%) and VGCC antibodies in 10 (5%). There was no association between the presence of antibodies and extent of disease and survival.[17] Payne et al studied 63 patients with small cell lung cancer. Seven patients (11%) were diagnosed with LEMS with five patients (8%) positive for VGCC antibodies. There was no association between VGCC antibody titer and survival.[18] It is possible that the apparent survival benefit may result from lead-time bias due to earlier diagnosis of small cell lung cancer in patients who presented with neurological symptoms, though this conclusion's not without controversy.[19]

Given that small cell lung cancer is often associated with autoimmune antibodies, VGCC and Hu antibodies, the use of immunotherapy of small cell lung cancer is an intriguing topic. Immune checkpoint pathway through PD-1/PD-L1 interaction is a physiological mechanism to down-regulate T-cell activation to prevent excessive immune attack. However, the cancer cells can evade elimination by host immunity by exploiting the similar mechanism. PD-1/PD-L1 inhibitors like nivolumab and pembrolizumab, by restoring this anti-cancer immunity, has been shown to be an effective therapy for various types of cancer. So far there is limited data on the use of PD-1/PD-L1 inhibitors in small cell lung cancer.

Antonia et al reported the Phase I/II CheckMate-032 trial of nivolumab alone and nivolumab plus ipilimumab in 216 patients with recurrent small cell lung cancer. This trial showed overall objective response rate of 16%.[20] Ott et al published the Phase Ib Keynote-028 trial of pembrolizumab 10 mg/kg every 2 weeks in 24 patients with extensive stage small cell lung cancer and PD-L1 expression >1% who failed standard chemotherapy. The overall response rate was 33.3%, with median duration of response of 19.4 months.[21] VGCC or Hu antibodies, which are expected to be positive in 10-30% cases of small cell lung cancer, were not mentioned in either study.

As the mechanism of the PD-1/PD-L1 inhibitors is to activate T-cell function, the obvious side effects of PD-1/PD-L1 inhibitors is the occurrence of various autoimmune diseases, such as dermatitis, endocrinopathies, colitis, pneumonitis etc. Indeed the incidence of immunotherapy-associated myasthenia gravis has increased in recent years.[22] Immunotherapy employing PD-1/PD-L1 inhibitors may theoretically aggravate LEMS. In the CheckMate-032 trial Antonia et al reported two patients who developed limbic encephalitis and one patient myasthenia gravis as adverse effect of the immunotherapy.[20] Further study is required to determine the relative merits of immunotherapy in patients with small cell lung cancer associated with VGCC or Hu antibodies.

REFERENCES

1. **Eaton LM, Lambert EH**. Electromyography and electric stimulation of nerves in diseases of motor unit; observations on myasthenic syndrome associated with malignant tumors. *J Am Med Assoc*. 1957 Mar 30;163(13):1117-24. PubMed PMID:13405774.
2. **Fukunaga H, Engel AG, Lang B, Newsom-Davis J, Vincent A**. Passive transfer of Lambert-Eaton myasthenic syndrome with IgG from man to mouse depletes the presynaptic membrane active zones. *Proc Natl Acad Sci U S A*. 1983 Dec;80(24):7636-40. PubMed PMID: 6584877; PubMed Central PMCID: PMC534395.
3. **Roberts A, Perera S, Lang B, Vincent A, Newsom-Davis J.** Paraneoplastic myasthenic syndrome IgG inhibits 45Ca2+ flux in a human small cell carcinoma line. *Nature*. 1985 Oct 24-30;317(6039):737-9. PubMed PMID: 2414666.
4. **Lang B, Vincent A, Murray NM, Newsom-Davis J.** Lambert-Eaton myasthenic syndrome: immunoglobulin G inhibition of Ca2+ flux in tumor cells correlates with disease severity. *Ann Neurol*. 1989 Mar;25(3):265-71. Pub Med PMID: 2543262.
5. **Lennon VA, Lambert EH**. Autoantibodies bind solubilized calcium channel-omega-conotoxin complexes from small cell lung carcinoma: a diagnostic aid for Lambert-Eaton myasthenic syndrome. *Mayo Clin Proc*. 1989 Dec; 64(12):1498-504. PubMed PMID: 2557495.
6. **McEvoy KM**. Diagnosis and treatment of Lambert-Eaton myasthenic syndrome. *Neurol Clin*. 1994 May;12(2):387-99. Review. PubMed PMID: 8041348.
7. **Mareska M, Gutmann L**. Lambert-Eaton myasthenic syndrome. *Semin Neurol*. 2004 Jun;24(2):149-53. Review. PubMed PMID: 15257511.
8. **Grommes C, Preston DC, Al-Kadhimi Z, Alshekhlee A**. Lambert-Eaton syndrome with large-cell neuroendocrine carcinoma of the lung. *Muscle Nerve*. 2008 Jun;37(6):786-9. doi: 10.1002/mus.21032. PubMed PMID: 18506722.
9. **Taketa T, Ohigashi S, Suzuki K, Sudo K, Shiozaki H, Suzuki A, Blum MA, Ajani JA, Onodera H**. Paraneoplastic neurological syndromes associated with gastric cancer: a case report and review of the literature. *Clin J Gastroenterol*. 2012 Oct;5(5):355-60. doi: 10.1007/

s12328-012-0328-z. Epub 2012 Aug 28. PubMed PMID: 26181075.

10. **Arai H, Inui K, Hashimoto K, Kan-O K, Nishii T, Kishida H, Okudela K, Tsuboi M, Nozawa A, Kaneko T, Masuda M**. Lung adenocarcinoma with Lambert-Eaton myasthenic syndrome indicated by voltage-gated calcium channel: a case report. *J Med Case Rep*. 2012 Sep 5;6:281. doi: 10.1186/1752-1947-6-281. PubMed PMID:22950670; PubMed Central PMCID: PMC3537700.
11. **Pavolucci L, Giannini G, Giannoccaro MP, Foschini MP, Lang B, Avoni P, Tinuper P, Vincent A, Liguori R**. Paraneoplastic cerebellar degeneration and lambert-eaton myasthenia in a patient with merkel cell carcinoma and voltage-gated calcium channel antibodies. *Muscle Nerve*. 2017 Nov;56(5):998-1000. doi: 10.1002/mus.25530. Epub 2017 Mar 23. PubMed PMID: 28006860.
12. **Takasugi J, Shimamura M, Koda T, Kishikawa T, Hanamoto A, Inohara H, Sato K, Morii E, Motomura M, Sakaguchi M, Nakatsuji Y, Mochizuki H**. Paraneoplastic Cerebellar Degeneration and Lambert-Eaton Myasthenic Syndrome Associated with Neuroendocrine Carcinoma of the Oropharynx. *Intern Med*. 2018 Feb 15;57(4):587-590. doi: 10.2169/internalmedicine.9333-17. Epub 2017 Nov 1. PubMed PMID: 29093415.
13. **Maddison P, Lang B, Mills K, Newsom-Davis J**. Long term outcome in Lambert-Eaton myasthenic syndrome without lung cancer. *J Neurol Neurosurg Psychiatry*. 2001 Feb;70(2):212-7. PubMed PMID: 11160470; PubMed Central PMCID:PMC1737207.
14. **Graus F, Lang B, Pozo-Rosich P, Saiz A, Casamitjana R, Vincent A**. P/Q type calcium-channel antibodies in paraneoplastic cerebellar degeneration with lung cancer. *Neurology*. 2002 Sep 10;59(5):764-6. PubMed PMID: 12221175.
15. **Maddison P, Newsom-Davis J, Mills KR, Souhami RL**. Favourable prognosis in Lambert-Eaton myasthenic syndrome and small-cell lung carcinoma. *Lancet*. 1999 Jan 9;353(9147):117-8. PubMed PMID: 10023900.
16. **Maddison P, Lang B**. Paraneoplastic neurological autoimmunity and survival in small-cell lung cancer. *J Neuroimmunol*. 2008 Sep 15;201-202:159-62. doi: 10.1016/j.jneuroim.2008.05.024. Epub 2008 Jul 29. PubMed PMID: 18667241.
17. **Monstad SE, Drivsholm L, Storstein A, Aarseth JH, Haugen M, Lang B, Vincent A, Vedeler CA**. Hu and voltage-gated calcium channel (VGCC) antibodies related to the prognosis of small-cell lung cancer. *J Clin Oncol*. 2004 Mar 1;22(5):795-800. PubMed PMID: 14990634.
18. **Payne M, Bradbury P, Lang B, Vincent A, Han C, Newsom-Davis J, Talbot D**. Prospective study into the incidence of Lambert Eaton myasthenic syndrome in small cell lung cancer. *J Thorac Oncol*. 2010 Jan;5(1):34-8. doi:10.1097/JTO.0b013e3181c3f4f1. PubMed PMID: 19934775.
19. **Maddison P, Gozzard P, Grainge MJ, Lang B**. Long-term survival in paraneoplastic Lambert-Eaton myasthenic syndrome. *Neurology*. 2017 Apr 4;88(14):1334-1339. doi: 10.1212/WNL.0000000000003794. Epub 2017 Mar 1. PubMed PMID: 28251917.
20. **Antonia SJ, López-Martin JA, Bendell J, Ott PA, Taylor M, Eder JP, Jäger D, Pietanza MC, Le DT, de Braud F, Morse MA, Ascierto PA, Horn L, Amin A, Pillai RN, Evans J, Chau I, Bono P, Atmaca A, Sharma P, Harbison CT, Lin CS, Christensen O, Calvo E**. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. *Lancet Oncol*. 2016 Jul;17(7):883-895. doi: 10.1016/S1470-2045(16)30098-5. Epub 2016 Jun 4. Erratum in: *Lancet Oncol*. 2016 Jul;17 (7):e270. PubMed PMID: 27269741.
21. **Ott PA, Elez E, Hiret S, Kim DW, Morosky A, Saraf S, Piperdi B, Mehnert JM**. Pembrolizumab in Patients With Extensive-Stage Small-Cell Lung Cancer: Results From the Phase Ib KEYNOTE-028 Study. *J Clin Oncol*. 2017 Dec 1;35(34):3823-3829. doi: 10.1200/JCO.2017.72.5069. Epub 2017 Aug 16. PubMed PMID: 28813164.
22. **Makarious D, Horwood K, Coward JIG**. Myasthenia gravis: An emerging toxicity of immune checkpoint inhibitors. *Eur J Cancer*. 2017 Sep;82:128-136. doi: 10.1016/j.ejca.2017.05.041. Epub 2017 Jun 27. Review. PubMed PMID: 28666240.

Submitted March 12, 2018