

# Paraneoplastic cerebellar degeneration and Lambert-Eaton syndrome in patient with Merkel cell carcinoma and voltage-gated calcium channel antibodies

L Pavolucci\*, G Giannini\*, P Avoni°, MP Foschini\*, P Tinuper° and R Liguori°

\* DIBINEM Department of Biomedical and Neuromotor Sciences – University of Bologna

° DIBINEM Department of Biomedical and Neuromotor Sciences, ISNB Institute of Neurological Sciences of Bologna – University of Bologna

## INTRODUCTION:

Paraneoplastic cerebellar degeneration (PCD) and Lambert-Eaton myasthenic syndrome (LEMS) are rare conditions associated with neuroendocrine tumors, such as small cell lung carcinoma or other malignancy such as breast cancer, lymphoma, thymoma and gynecologic tumors. Detection of onconeural and/or neuronal surface antibodies could strengthen the clinical suspicion of paraneoplastic syndrome. We describe a combination of PCD and LEMS in a male patient with extracutaneous Merkel cell carcinoma (MCC) and the detection of voltage-gated calcium channel (VGCC) antibodies.

## MATERIALS AND METHODS:

A healthy 67-year-old man developed acute ataxia, vertigo and nausea. Subsequently he also presented with dysarthria, occasional diplopia, xerostomia, fatigability and progressive anorexia. After 10 days he was no longer able to walk independently. Neurologic examination revealed cerebellar ataxia with dysarthria and nystagmo, while the sensory and strength assessment was normal. Dermatological examination did not detect malignant skin lesions. The patient underwent a full diagnostic workup including serological and cerebrospinal fluid (CSF) analysis, nerve conduction studies (NCSs) with repetitive nerve stimulation (RNS), neuroradiological studies, thoracic and abdominal CT scan, total body PET study and finally an axillary biopsy. The tissues were formalin fixed and routinely paraffin embedded. Immunohistochemistry was performed with the automated Benchmark system (Ventana, Tucson, Arizona). All the antibodies were purchased by Ventana.

## RESULTS:

Serological testing highlighted a mild increase in neuronal specific enolase (NSE), a positive titer of VGCC antibodies (240.74 pmol/L; reference range < 80 pmol/L) and a negative titer of acetylcholine receptor antibodies. CSF analysis, including cytological, virological and bacteriological testing, was unremarkable. NCSs demonstrated low compound muscle action potential amplitude with normal sensory responses, whereas 3Hz RNS revealed decrease in compound muscle action potential amplitude and post-exercise facilitation.

Brain CT and MRI were normal and MRA excluded cerebrovascular abnormalities. Thoracic and abdominal CT did not show any pathological findings, while a total body PET study highlighted hypermetabolic lesions in the left axillary and ipsilateral retro-pectoral region.

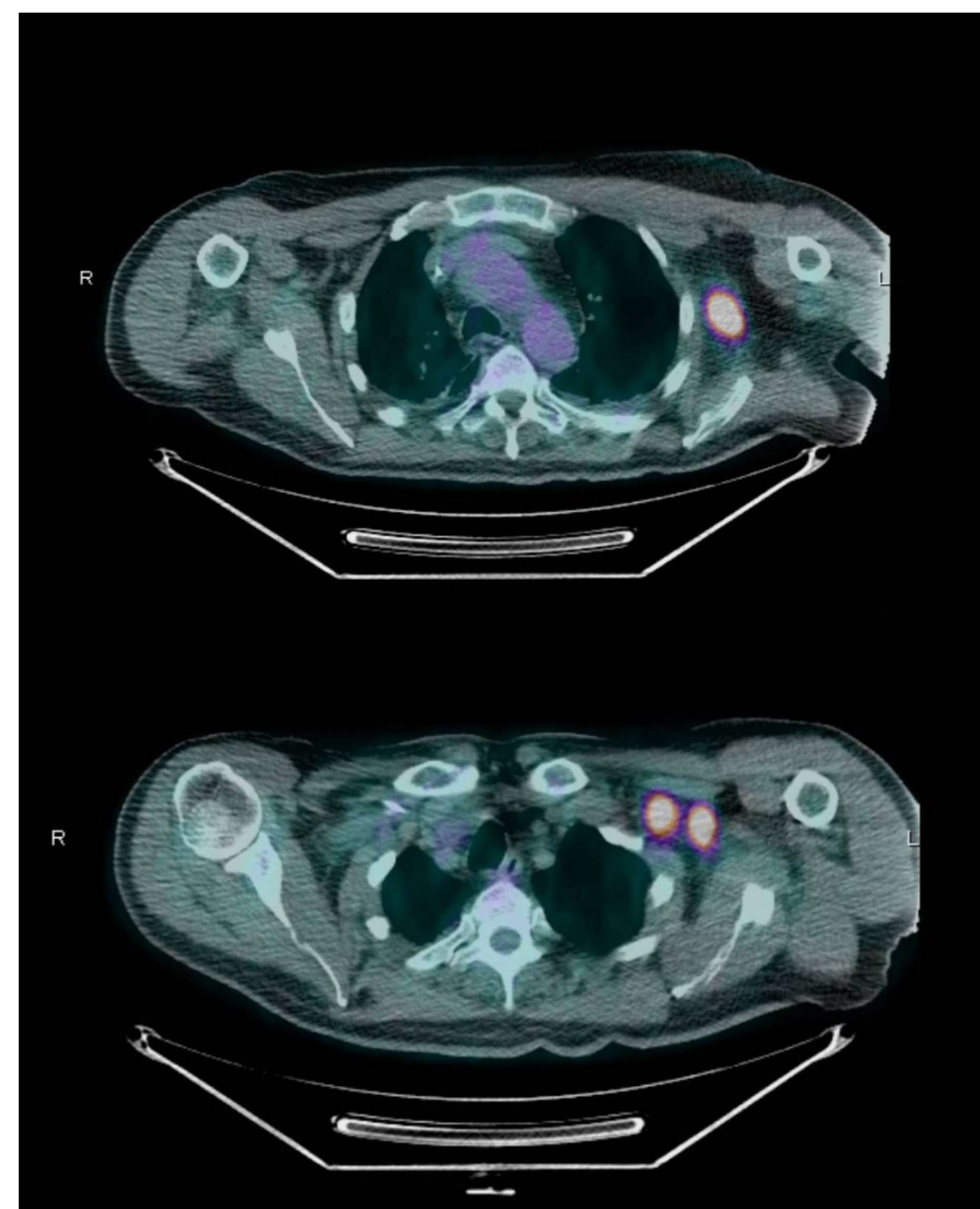
Subsequently the patient underwent a diagnostic biopsy, which detected a high-grade neuroendocrine carcinoma expressing low-molecular-weight cytokeratin (CAM 5.2), cytokeratin 20 (dotlike pattern), chromogranin (dotlike pattern), CD56, and synaptophysin. This immunoprofile was consistent with MCC. During the diagnostic workup the patient was treated with a high dose of steroids (methylprednisolone 1 gr for 5 days) followed by intravenous immunoglobulin treatment with improvement of walking ataxia and dysarthria. After post-operative decors, the patient was transferred to a rehabilitation department and referred to an oncology team and subsequently chemotherapy was performed with cisplatin and etoposide. Five months after initial presentation we observed improvement of ataxia to upper extremities, partial resolution of dysarthria and fatigue, but persistence of walking imbalance so he had wheelchair-dependent.

## DISCUSSION:

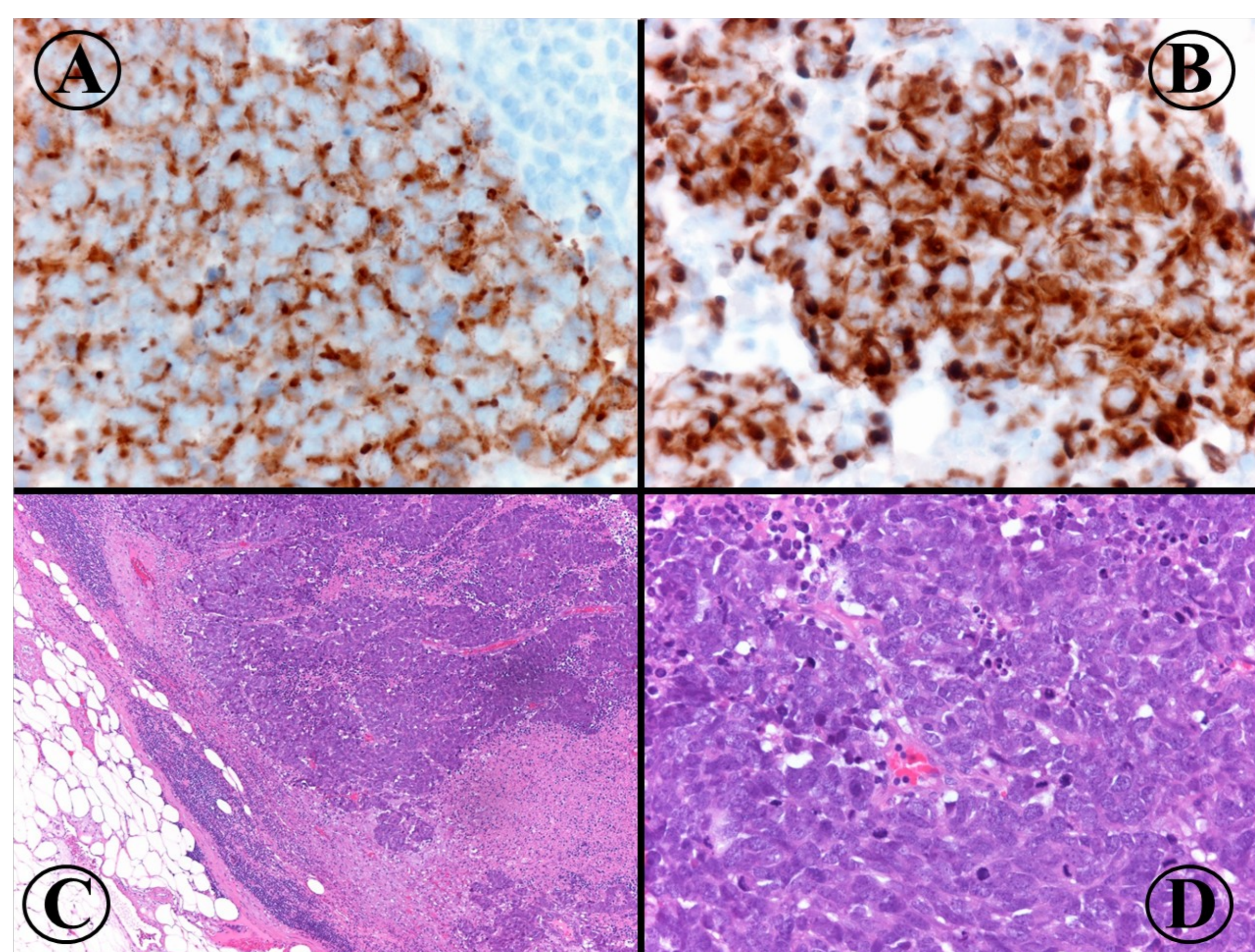
To date, very few cases of Merkel cell carcinoma associated with PCD or LEMS have been reported. We describe the first case of paraneoplastic syndrome in extracutaneous MCC with both conditions. An autoimmune reaction to MCC is most probably responsible for the production of VGCC antibodies attacking voltage-gated calcium channels expressed in cerebellar neurons and motor nerve terminals.

## BIBLIOGRAPHY:

1. Zhang C, Emery L, Lancaster E. Paraneoplastic cerebellar degeneration associated with noncutaneous Merkel cell carcinoma. *Neurology Neuroimmunology Neuroinflammation* 2014, 1: e17; doi: 10.1212/NXI.0000000000000017
2. Eggers SD, Salomao DR, Dinapoli RP, Vernino S. Paraneoplastic and Metastatic Neurologic Complications of Merkel Cell Carcinoma. *Mayo Clinic Proceedings* 2001; 76: 327-330.
3. Clouston PD, Saper CB, Arbizu T, et al. Paraneoplastic cerebellar degeneration. III. Cerebellar degeneration, cancer, and Lambert-Eaton myasthenic syndrome. *Neurology* 1992; 42: 1944-1950.



PET/CT total body documents the presence of hypermetabolic lesions in the left axillary (scan top) and ipsilateral retro-pectoral region (scan down).



A) The neoplastic cells were positive for chromogranin, with dot-like features; B) On immunohistochemistry the neoplastic cells were positive for cytokeratin 20, with dot-like features; C) At low power view a thin peripheral rim of lymph-node tissue was present. The lymph-node was almost completely substituted by a neoplastic growth with necrotic areas; D) The neoplastic cells had scanty cytoplasm, central nucleus with fine chromatin. Atypical mitotic figures were numerous.