Paraneoplastic autoimmunity and small-cell lung cancer: Neurological and serological accompaniments

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Introduction
Paraneoplastic neurological autoimmunity is associated with small-cell lung cancer (SCLC), a highly malignant neuroendocrine tumor. The neurological presentations are more diverse than traditionally recognized and can be misdiagnosed as neurodegenerative disorders or cancer progression. The profile of neural autoantibodies in a patient’s serum reflects the onconeural antigens expressed by the tumor.1 It is not unusual for multiple autoantibodies and paraneoplastic disorders to co-exist in one patient.2

More than 90% of patients with newly diagnosed SCLC and neurological impairment are seropositive for one or more SCLC-predictive autoantibodies; seropositivity for any neural autoantibody has been reported in 40% of SCLC patients without a clinically evident paraneoplastic neurological disorder.2 Paraneoplastic autoimmunity indicates an inefficient antitumor immune response. Patients with SCLC and Lambert–Eaton myasthenic syndrome (LEMS) have longer survival than patients without.3 Certain autoantibodies are associated with longer survival in SCLC patients without neurological symptoms.4

The introduction of immune checkpoint inhibitor therapy to oncology practice has been accompanied by an increasing incidence of paraneoplastic autoimmune disorders, both organ and non-organ specific.5 Ascertainment of...
a patient’s baseline serological profile before initiating this therapy may aid in predicting the risk of autoimmune neurological complications.6

The aim of this study was to describe the neurological manifestations and onconeural autoantibody profiles of patients with SCLC with or without neurological autoimmunity and assess their impact on survival.

Methods

The institutional review board at Mayo Clinic approved this study. Patients with histopathologically confirmed SCLC were identified in the Neuroimmunology Laboratory database. Sera from 71 patients with neurological symptoms were submitted for clinical service evaluation of neural autoantibodies, and sera were collected from 45 patients without neurological symptoms. Sera were collected from patients evaluated clinically at Mayo Clinic from 1980 to 2004 and medical records were reviewed. For patients with multiple specimens, we tested the earliest available specimen. Patients surviving at least seven years after diagnosis of limited disease or three years after diagnosis of extensive disease were considered exceptional survivors, while typical survivors were identified as surviving less than three years with limited and no more than one year with extensive SCLC.

Autoantibody assays

Sera were stored at −30°C and tested in the Mayo Clinic Neuroimmunology Laboratory using clinically validated methods. Radioimmunoprecipitation assays for muscle and ganglionic acetylcholine receptor (AChR), voltage-gated (Kv1) potassium channel (VGKC)-complex, glutamic acid decarboxylase 65 (GAD65), and P/Q-type and N-type voltage-gated calcium channel (VGCC) autoantibodies were conducted as previously described.7,8 Striational antibodies were detected by enzyme-linked immunosorbert assay. Neuronal nuclear and cytoplasmic immunoglobulin Gs (IgGs, screened by both mouse tissue-based indirect immunofluorescence and Euroline protein blots, Euroimmun AG, Lübeck, Germany) included anti-neuronal nuclear antibody (ANNA)-1, ANNA-2, ANNA-3, Purkinje cell antibody (PCA)-1, PCA-2, PCA-Tr, amphiphysin, CRMP5, and SOX1. Autoantibodies specific for N-methyl-D-aspartate (NMDAR), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), γ-aminobutyric acid-B (GABAγR), glycine (GlyR) receptors, and AQP4 were tested by cell-binding immunofluorescence assays on human embryonic kidney (HEK293) cells transfected with plasmids encoding the respective antigens (Euroimmun AG or in-house).

Statistical analysis

Data were summarized as frequencies and percentages or medians and ranges, as appropriate. Continuous measures were compared between patients using Wilcoxon rank-sum tests. Dichotomous variables were compared with Fisher’s exact tests. Survival time was analyzed using Kaplan–Meier curves. P values < 0.05 were considered statistically significant. Analyses were performed using SPSS 2.0 (IBM Corp., Armonk, NY, USA).

Results

Demographics of the 116 patients are summarized in Table 1. SCLC at cancer diagnosis was limited stage in 41% of patients and extensive in 46%, and information was lacking for 13%. The frequency of neural autoantibodies and autoimmune neurological manifestations did not differ significantly with limited or extensive stage SCLC. Seventy-five percent of patients received cancer treatment (chemotherapy, radiation, and/or resection), 3% did not, and information was lacking for 22%.

Serological findings and neurological manifestations

The detection frequencies of neural autoantibodies are summarized in Table 2; serum was available before cytotoxic therapy in 73 patients. ANNA-1 was the most frequently detected autoantibody among patients with neurological manifestations, followed by VGCC (N-type and P/Q-type), GAD65, SOX1, muscle-AChR, CRMP5, VGKC, ganglionic-AChR, GABAγR, and striational autoantibodies.

ANNA-1 and VGCC-N-type autoantibodies were detected more frequently in patients with neurological manifestations than in those without. The VGCC-P/Q-type autoantibody was more frequent in patients with LEMS.
(P = 0.002), muscle-AChR-IgG in patients with myasthenia gravis (P = 0.01), and ANNA-1 in patients with peripheral somatic or autonomic neuropathy (P < 0.001 for both).

Seventy-one patients had autoimmune neurological manifestations attributable to SCLC (Fig 1). In 86% of cases, neurological symptoms and signs preceded cancer diagnosis. Neurological manifestations often involved multiple levels of the neuraxis and the detected autoantibodies tended to be consistent with the spectrum of manifestations recognized to associate with the neurological phenotype. Peripheral neuropathy was most common (31%, excluding patients whose neuropathy developed after chemotherapy). Dysautonomia was documented in 20 patients, and gastrointestinal dysmotility was a frequent manifestation of ANNA-1 autoimmunity. Encephalopathy was also common (24%). Autoantibody specificities detected with cerebellar ataxia included ANNA-1 (5 patients), VGCC-P/Q-type (5 patients), and CRMP5 (1 patient); none had amphiphysin-IgG. Ten of the 13 patients with a neuromuscular junction disorder had Lambert–Eaton myasthenic syndrome, two had myasthenia gravis, and one was not specified. All patients diagnosed with Lambert–Eaton myasthenic syndrome were VGCC-P/Q-IgG positive (only 2 had co-existing SOX1-IgG) and both patients with myasthenia gravis were muscle-AChR-IgG-positive. Two of the three patients with cranial neuropathy were CRMP5-IgG-positive and one was ANNA1-positive. CRMP5-IgG and ANNA1-IgG also were detected in two patients with myelopathy.

Survival

The overall average survival or follow-up period was 39 (range: 0–368) months. Twenty-two patients were exceptional survivors, 66 were typical survivors, and the remainder had an intermediate survival rate. The only independent predictor for longer survival was limited stage disease (tested both as a continuous variable or dichotomous in exceptional versus typical survivors). The presence of neurological signs or detection of a neural autoantibody did not correlate significantly with survival, except for shorter survival in the two patients who had myelopathy.

Discussion

The results of our study confirm that neural autoantibodies are frequently found in patients with SCLC, even in neurologically asymptomatic patients, as we previously
reported for patients with thymoma.9 Interestingly, IgGs targeting extracellular domains of plasma membrane antigens (e.g. GABAB, muscle-AChR) and thus having pathogenic potential, were also found in neurologically unaffected patients. The individual patient’s autoantibody profile reflects antigens expressed by the tumor and is consistent with the neuroendocrine nature of SCLC.1

Among patients with neurological autoimmunity, the most common clinical manifestations were neuropathy and dysautonomia, the latter frequently manifesting as gastrointestinal dysmotility (an often under-recognized paraneoplastic disorder). Classic neurological paraneoplastic syndromes included LEMS, encephalitis with seizures, and cerebellar ataxia. The frequency of the neurological presentations we have reported are not representative of their incidence in the SCLC population, but rather reflect the referral bias of patients whose specimens are submitted to our laboratory.

Prospective studies of SCLC patients have reported longer survival in patients with ANNA1-IgG or other neuronal nuclear autoantibodies or clinical manifestations of Lambert-Eaton myasthenic syndrome.3,4 Although 22 of the 116 patients in our study had exceptional survival time, we found no correlation between extended survival and any neural autoantibody (more extensive screening than prior studies) or autoimmune neurological disorder. This finding can perhaps be explained by the dampening of the anti-cancer immune response and its presumed host survival advantage as a result of the cytotoxic chemotherapy ultimately administered to most of the study patients. Other factors potentially limiting interpretation of the study’s findings include its retrospective design and the relatively small patient sample. In addition, 37% of the patient samples were collected after chemotherapy, which might have affected IgG-seropositivity.

We anticipate the frequency of paraneoplastic neurological autoimmunity to increase with the use of checkpoint inhibitor therapy for SCLC. This behooves oncologists to be aware of the spectrum of potential autoimmune neurological sequelae as early recognition and judicious management will optimize oncological and neurological outcomes. Perhaps prospective monitoring of patients’ serum autoantibody profiles before, during, and after such therapy will reveal whether and which neural autoantibodies correlate with long term cancer survival and also might predict a high risk for autoimmune neurological complications.5

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Disclosure

No authors report any conflict of interest.

References

1 Zekeridou A, Griesmann GE, Lennon VA. Mutated cancer autoantigen implicated cause of paraneoplastic myasthenia gravis. Muscle Nerve 2018; 58: 600–4.
2 Gozzard P, Woodhall M, Chapman C et al. Paraneoplastic neurologic disorders in small cell lung carcinoma: A prospective study. Neurology 2015; 85: 235–9.
3 Maddison P, Gozzard P, Grainge MJ, Lang B. Long-term survival in paraneoplastic Lambert-Eaton myasthenic syndrome. Neurology 2017; 88: 1334–9.
4 Gozzard P, Chapman C, Vincent A, Lang B, Maddison P. Novel humoral prognostic markers in small-cell lung carcinoma: A prospective study. PLoS One 2015; 10: e0143558.
5 Chen DS, Mellman I. Oncology meets immunology: The cancer-immunity cycle. Immunity 2013; 39: 1–10.
6 Mammen AL, Rajan A, Pak K et al. Pre-existing antiacetylcholine receptor autoantibodies and B cell lymphopaenia are associated with the development of myositis in patients with thymoma treated with avelumab, an immune checkpoint inhibitor targeting programmed death-ligand 1. Ann Rheum Dis 2019; 78: 150–2.
7 Meeser JW, Klein CJ, Pirko I et al. Potassium channel complex autoimmunity induced by inhaled brain tissue aerosol. Ann Neurol 2012; 71: 417–26.
8 Lennon VA, Kryzer TJ, Griesmann GE et al. Calcium-channel antibodies in the Lambert-Eaton syndrome and other paraneoplastic syndromes. N Engl J Med 1995; 332: 1467–74.
9 Zekeridou A, McKeon A, Lennon VA. Frequency of synaptic autoantibody accompaniments and neurological manifestations of thymoma. JAMA Neurol 2016; 73: 853–9.