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Paraneoplastic neurological syndromes in lung cancer patients with or without onconeural antibodies

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ABSTRACT

Background: Paraneoplastic neurological syndromes (PNS) are poorly described in patients without onconeural antibodies and in patients with non-small cell lung cancer (NSCLC). We compared the clinical characteristics of PNS in lung cancer patients with and without onconeural antibodies.
Methods: Medical records from patients with lung cancer and neurological symptoms referred for onconeural antibody analysis in the period 1995–2004 were analyzed and well-established diagnostic criteria used for the retrospective diagnosis of PNS. Thirty-one patients were diagnosed with PNS and included in the study. Data from the Cancer Registry of Norway and follow-up medical data were analyzed.
Results: Small-cell lung cancer (SCLC) was the most common lung cancer in the 31 PNS patients (77%, $P < 0.01$). Onconeural antibodies were found in 18 of the PNS patients (58%). Paraneoplastic encephalomyelitis (PEM) was the most common PNS among the seropositive patients (11 of 18 patients), of which 10 had SCLC. Various types of PNS were found in the 13 seronegative patients.
Conclusion: Approximately 40% of PNS patients with lung cancer do not have onconeural antibodies. PEM was the most common PNS in the seropositive patients. Our results underline the importance of recognizing PNS in patients with NSCLC and those without onconeural antibodies.

1. Introduction

Paraneoplastic neurological syndromes (PNS) are immune-mediated disorders that occur in less than 1% of cancer patients [1]. It has been reported that 50–82% of patients with PNS have onconeural antibodies directed against neuronal proteins expressed by tumor cells [1–3]. PNS are most frequently associated with small-cell lung cancer (SCLC) [2,4], with a prevalence of 3–5% [5], but can also be seen in patients with non-small cell lung cancer (NSCLC). SCLC accounts for 15% of all lung cancers, whereas NSCLC accounts for 80% [6]. Thus, the less prevalent tumor type is more prone to be associated with PNS.

The specificity of onconeural antibodies for PNS is high and the presence of such antibodies defines the neurological disorder as paraneoplastic [7]. As there are no other markers with high specificity for PNS, the diagnosis in patients without onconeural antibodies is often debatable, and the diagnosis of a seronegative PNS is challenging if no tumor is detected initially.

The aim of this study was to describe the clinical characteristics of PNS patients with lung cancer, with special regard to the group without onconeural antibodies. Seronegative cases have not been described as thoroughly as antibody positive patients, and previous studies have usually focused on specific syndromes and not on PNS at a whole in selected cancer groups.

2. Materials and methods

2.1. Patients

The Neurological laboratory at Haukeland University Hospital, Bergen, Norway, received between 1995 and 2004 sera from 3679 patients for the analysis of onconeural antibodies. During this time period, the laboratory was the only one in Norway to perform onconeural antibody analysis. The national identification numbers of these 3679 patients were matched to lung cancer data in the Cancer Registry of Norway in the time period 1990 to 2007, to select patients that were both registered with a lung cancer diagnosis and tested for onconeural antibodies. The Cancer Registry of Norway is a national cancer database shown to have a completeness of close to 99% for the registration of solid tumors [8]. The selection of patients and PNS epidemiological data from this population regardless of cancer type has been described previously [4].

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Table 1
Clinical characteristics for 31 patients with paraneoplastic neurological syndromes and SCLC or NSCLC.

		SCLC		Sum	NSCLC		Sum
		Onconeural antibodies			Onconeural antibodies		
		+	−		+	−	
Number		15	9	24	3	4	7
Sex	Males	5	4	9	1	2	3
	Females	10	5	15	2	2	4
Age at cancer diagnosis (years)	Mean (min–max)	65 (53–74)	64 (49–80)	65	69 (61–73)	71 (60–76)	70
1-year survival (%)		33	44	38	67	50	57

SCLC: small-cell lung cancer, NSCLC: non-small cell lung cancer.

In the present work, we have studied the subgroup of patients with lung cancer in detail. Ninety-six lung cancer patients were identified and hospital records were obtained for all patients. In the following, 17 patients were excluded; three patients were excluded because of incomplete medical information and 14 patients because lung biopsy was inconclusive or not performed. Of the remaining 79 patients, 31 were diagnosed with PNS retrospectively and included in the study. Two neurologists evaluated the medical records and made the PNS diagnosis according to consensus criteria from the Paraneoplastic Neurological Syndrome Euronetwork [7]. Patients with other possible neurological explanations for the symptoms, e.g. brain metastasis and chemotherapy related polyneuropathy, were not diagnosed with PNS.

The NSCLC tumors were classified in subgroups according to pathological findings [6]. Limited disease in SCLC was defined as tumor restricted to one thoracic radiation field, whereas NSCLC was subdivided according to the TNM staging system [9].

2.2. Onconeural antibodies

The sera were analyzed for all well-characterized onconeural antibodies (anti-Hu, -Yo, -Ri, -Ma, -CRMP5 and -amphiphysin) using immunoblot (www.ravo.de), immunohistochemistry and radioimmunoassay [4]. Eleven of 13 available sera without well-characterized onconeural antibodies were used for immunohistochemical staining of rat cerebellar sections, and ten of these 13 sera were also tested for anti-Sox-1, -GAD-65 (immunoblots; www.ravo.de), -VGCC (radioimmunoassay; www.dld-diagnostika.de) -NMDAR, -Ampa1, -Ampa2, GabaRB1/B2, -CASPR2 and -Lgi1 (transfected cells; www.euroimmune.com). In the following, the term "antibody" refers to "onconeural antibody" as this is the main focus of the study.

Table 2
Clinical characteristics for 31 patients with paraneoplastic neurological syndromes and lung cancer, with and without onconeural antibodies.

		Seronegative (n = 13)	Seropositive (n = 18)	Sum
Sex	Males	6	6	12
	Females	7	12	19
Median age at cancer diagnosis in years (min–max)		66 (49–80)	67 (53–74)	
Lung cancer	SCLC	9	15	24
	NSCLC	4	3	7
PNS	PEM	3	11	14
	PCD	1	0	1
	LE	1	1	2
	SSN	2	0	2
	LEMS	1	2	3
	Neuropathy[a]	2	4	6
	Myelopathy[b]	1	0	1
	Other	2	0	2
Cause of death	Lung cancer	11	7	18
	PNS	1	2	3
	Alive	0	1	1
	Unknown	1	8	9

SCLC: small-cell lung cancer, NSCLC: non-small cell lung cancer, PNS: paraneoplastic neurological syndrome, PEM: paraneoplastic encephalomyelitis, PCD: paraneoplastic cerebellar degeneration, LE: limbic encephalitis, SSN: subacute sensory neuronopathy, LEMS: Lambert–Eaton myasthenic syndrome.

[a] Two patients had multiple mononeuropathy (both had sensory-motor affection of multiple peripheral nerves, one patient also had autonomic symptoms) and four had polyneuropathy (three patients had axonal sensory-motor polyneuropathy and one a pure motor polyneuropathy).

[b] The patient with myelopathy had spastic paraparesis and sensory deficits.

2.3. Statistics

IBM SPSS Statistics for Windows, Version 21.0 (Armonk, NY: IBM Corp.) was used for the statistical analysis. P-values < 0.05 were considered statistically significant. The association between categorical variables was explored using Pearson' square and Fischer's test. Means were compared by the use of Student's t-test. Normal distribution of data was evaluated with Normal Q–Q plots, Kolmogorov–Smirnov and Shapiro–Wilk normality tests and histograms. A binomial test was used for the analysis of binomial distributed variables. Kaplan–Meier plots and log rank test were used to analyze survival.

3. Results

3.1. Patient characteristics

Table 1 summarizes the clinical characteristics for the 31 patients with PNS, by subtype of lung cancer. SCLC was the dominating form of lung cancer among the PNS patients, occurring in 24 of the 31 patients (77%; P < 0.01). Eighteen (58%) of the PNS patients had onconeural antibodies, 15 (63%) of the SCLC and 3 (43%) of the NSCLC patients. There were no significant differences in sex, mean age at cancer diagnosis, percentage of patients with >1-year survival after cancer diagnosis, or mean survival between patients with or without onconeural antibodies in the two cancer groups. Sixty-three percent of the SCLC patients had limited disease at the time of diagnosis, of which 60% had onconeural antibodies. Among the patients with NSCLC two patients were in stage II, three in stage III and one in stage IV of the disease. Furthermore, there was no significant influence of onconeural antibody on the patients' overall survival in the SCLC group (Kaplan–Meier plot not shown). This could not be analyzed in the NSCLC group due to the small number of patients.

Twenty-three of the 31 PNS patients were diagnosed with lung cancer at or prior to the time of referral for onconeural antibodies (P = 0.011). We found the mean annual incidence rate of PNS in the lung cancer patients in the time period 1999–2004 to be approximately 13 per 10,000.

3.2. PNS in seronegative vs. seropositive lung cancer patients

Clinical characteristics for the 13 seronegative and 18 seropositive patients are listed in Table 2. There was no difference in median age at cancer diagnosis between the seronegative and seropositive groups. Fifteen of the seropositive patients had SCLC (83%; P < 0.01). The type