Antineuronal antibodies in small cell lung carcinoma — a significance for paraneoplastic syndromes?

W. Grisold¹, M. Drlicek², W. Popp³, and K. Jellinger¹

¹ L. Boltzmann Institut für klinische Neurobiologie, Wolkersbergenstrasse 1, A-1130 Vienna, Austria
² Pathologisch-Anatomisches Institut des Psychiatrischen Krankenhauses der Stadt Wien, Baumgartnerhöhe 1, A-1140 Vienna, Austria
³ Pulmologische Abteilung des Krankenhauses Lainz, Wolkersbergenstrasse 1, A-1130 Vienna, Austria

Summary. In recent years a cause-effect relationship between the existence of circulating antineuronal antibodies (CANA) and neurological paraneoplastic syndromes has been described by several authors suggesting specificity of such antibodies for paraneoplastic syndromes. The present study is a systematic approach to elucidate the significance of CANA in tumor patients. Forty patients with biopsy-proven small cell cancer of the lung (SCLC) were compared to 70 non-SCLC patients and 20 controls in respect to clinical and neurophysiological findings. CANA were found in 17 patients with SCLC. However, only one of these patients with SCLC and positive CANA displayed a sensory neuropathy of the Denny-Brown type, which appeared to be unrelated to CANA titers and oncological course. Contrary to recent reports, we were not able to confirm an association between the existence of CANA and an increased incidence of paraneoplastic neurological syndromes. These data suggest that the antineuronal antibodies appear to be specific for SCLC, but are not necessarily related to paraneoplastic neurological syndromes.

Key words: Antineuronal antibodies — Paraneoplastic syndromes — Sensory neuropathy — Small cell lung carcinoma

In this study the sensitivity and specificity of circulating antineuronal antibodies (CANA) related to the clinical course, and in particular to the occurrence of paraneoplastic syndromes, is explored. One patient with paraneoplastic subacute sensory neuropathy is described and his CANA-titer values are demonstrated in relation to the course of the malignancy.

Material and methods

Sera for indirect immunofluorescence test (IIFT) were collected from 40 patients with biopsy-proven SCLC, 70 patients with non-SCLC, 10 patients with various other diseases and 10 healthy controls and kept frozen at minus 70°C. CSF was not available for the study.

IIFT was performed on 5-µm-thick cryostat sections of cerebellum and dorsal root ganglia obtained from patients who died of trauma or pulmonary embolism. The cryostat sections were incubated in serum dilutions with phosphate-buffered saline (PBS, pH 7.2) 1:50 up to 1:1600 for 30 min at room temperature. After rinsing three times in PBS sections were incubated in monoclonal goat anti-human IgG, IgM, IgA, IgD, IgE and C 3 antibodies conjugated with fluorescein isothiocyanate (FITC) for 30 min (Atlantic antibodies, Scarborough/USA). The dilution for the second antibody was 1:100 for IgG and IgM and 1:50 for the others. Sections were rinsed three times in PBS and evaluated in a Leitz fluorescence microscope with a FITC outfit.

In one patient (Case report) direct immunofluorescence test (DIFT) was performed on cryostat sections of his own dorsal root ganglia obtained at autopsy. The sections were incubated with monoclonal FITC-conjugated IgG, M, A, D, E and C 3 antibodies for 30 min. After rinsing three times in PBS the sections were evaluated as described in IIFT [18].

In neurological examination of patients was performed clinically and with nerve conduction (NCV) studies. NCV studies comprised median motor and sensory (antidromic) and motor peroneal nerve conduction studies. The studies were performed with a Medelec MS 92 apparatus according to standard techniques [13]. Results were compared to normal laboratory values.

Classification of neuropathy was performed according to clinical and NCV data. Subclinical neuropathy, sensorimotor neuropathy and sensory neuronopathy were distinguished.

Antibodies directed against cerebellar neurons have been reported to occur in association with paraneoplastic neurological syndromes, e.g., subacute cerebellar degeneration [5] and subacute sensory neuronopathy [3]. Patients with lung cancer of the small cell type (SCLC), ovarian carcinoma, Hodgkin's disease and breast carcinoma have been reported to harbor this type of antibody sporadically [4, 16, 19].

Offprint requests to: W. Grisold (address see above)
Fig. 1. Clinical and serological data of case report: circulating antineuronal antibodies (CANA) values are demonstrated in relation to therapy, body weight, neuron-specific enolase (NSE) values and duration of the oncologic disease. ——: Body weight (kg); ———: CANA titers; ----: NSE (ng/ml); CT: chemotherapy (doxorubicin, cyclophosphamide); IT: immunotherapy (immunoglobulin).

Case report

A 72-year-old white Austrian male presented with tingling sensations in arms and legs, which were soon followed by painful dysaesthesias. Concomitantly also sensory ataxia occurred. CCT scan was normal, CSF had elevated protein content (71 mg%, Normal 50 mg%). CSF cytology was normal. Sensory neuronopathy was diagnosed and a small cell carcinoma of the lung was discovered by X-ray studies and biopsy.

Neurological examination

The patient was alert, fully orientated and cooperative. Cranial nerves were normal except dysaesthesias in mental branch of trigeminal nerve bilaterally. No nystagmus or diplopia was noted. Reflexes were absent on upper and lower extremities, plantar reflexes were flexor. Coordination was severely impaired and movements were ataxic. Truncal ataxia appeared in sitting position. Sensory symptoms were pronounced distally and discrimination of sensory qualities was poor. Painful stimuli were perceived with temporal dispersion. Slight touch (for instance pressing the bell button to call the nurse) caused painful persisting sensations. Sphincter functions were normal. The patient was confined to bedrest due to the sensory impairment and sensory ataxia. The neurological symptoms remained unchanged from the onset and lasted 5 months to the patients death.

CANA titer values are listed in Fig. 1. Despite changes of CANA titer the neurological symptoms did not change. Electrophysiological examination showed absent sensory NCV on upper and lower extremities, and prolonged distal latencies and amplitude reduced compound action potentials in lower extremity nerves, giving indication of some motor involvement possibly due to weight loss.

Single fiber EMG examination of extensor digitorum communis muscle, evaluating fiber density and jitter were normal. Somatosensory-evoked potential (SEP) latencies were pathologically prolonged on upper extremities and absent on lower extremities. The clinical findings suggested a case of sensory neuronopathy with truncal ataxia as previously described to occur in association with bronchus carcinoma [1].

Fig. 2. Indirect immunofluorescence test (IIFT) on frozen section of normal human cerebellum incubated with the serum of the patient (see Case report) at a dilution of 1:400. There is prominent staining of the nucleus of the Purkinje cells with sparing of the nucleoli and weaker fluorescence of the cytoplasm. Glial and endothelial cells are negative. × 250

Fig. 3. a IIFT on frozen section of normal dorsal root ganglion incubated with the serum of the patient (see Case report) at a dilution of 1:200. Similar to Purkinje cells there is prominent staining of the nucleus with sparing of nucleoli and weaker fluorescence of the cytoplasm. Glial and endothelial cells are negative. × 400. b Direct immunofluorescence test (DIFT) of dorsal root ganglion of patient (see Case report) with anti-human IgG. There is staining of the cell membrane with sparing of nuclei and intracytoplasmatic structures. × 400

Results

CANA were demonstrated in the sera of patients with SCLC by IIFT. CANA were directed against various morphological structures; i.e., nuclei and cytoplasm of neurons, or cytoplasm only. IIFT displayed the brightest staining in Purkinje cells of the cerebellum and to a minor degree in stratum granulare and dorsal root ganglia cells.