Clinical and electrophysiological features of peripheral neuropathy in older patients with lung carcinoma

Kliničke i elektrofiziološke karakteristike periferne neuropatije kod starijih bolesnika sa karcinomom pluća

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Abstract

Background/Aim. Peripheral nervous system affection in people with lung cancer is commonly associated with paraneoplastic neuropathy. However, clinical studies evaluating the frequency, clinical, and electrophysiological characteristics of peripheral neuropathies which are not related to onconeuronal antibodies, in this, on average, older population of patients, are very rare. The aim of this study was to define the frequency, as well as clinical and electrophysiological characteristics of idiopathic neuropathies in patients suffering from lung cancer in early stages of the diseases. **Methods**. Clinical and electrophysiological data of 105 elderly subjects (age 63.4 ± 7.8 years) suffering from lung carcinoma who underwent extensive neurological and electrophysiological evaluation (nerve conduction studies) between 2013–2018 were estimated. Exclusion criteria were "classical" paraneoplastic neurological syndromes with onconeuronal antibodies present, as well as patients with typical known causes of peripheral neuropathy (e.g. diabetes, alcoholism, chronic renal insufficiency, vitamin deficiencies, etc.). **Results**. There were 19.1% patients with clinically manifest neuropathies, with additional 37.1% patients with only electrophysiological abnormalities. The most frequent pathophysiological pattern was axonal pathology (71.2%) with predominantly distal and symmetrical distribution (86.4%). **Conclusion**. Patients with lung cancer in the early stages of the disease show a high incidence of clinically minor damage of the nerves, according to the pattern of chronic sensomotor distal neuropathy, with predominance of axonal damage. These findings underline the importance of a detailed clinical and electrophysiological evaluation in this category of patients who are without the typical etiological factors for peripheral neuropathies since, during cancer therapy, patients undergo a series of treatments with additional risk for the development/aggravation of neuropathy.

Key words:
lung neoplasms; polyneuropathies; comorbidity; aged; electrophysiology.

Apstrakt

Uvod/Cilj. Zahvatanje perifernog nervnog sistema kod osoba obolelih od karcinoma pluća uobičajeno se povezuje sa paraneoplastičkim neuropatijama. Studije koje procenjuju učestalost, kliničke i elektrofiziološke karakteristike perifernih neuropatija koje nisu povezane sa onkoneuronalnim antitelima, kod ove populacije bolesnika, u proseku starije životne dobi, veoma su retke. Cilj ove studije bio je da se definišu učestalost, kao i kliničke i elektrofiziološke karakteristike idiopatskih neuropatija kod bolesnika sa karcinomom pluća u ranim stadijumima bolesti. **Methods**. Prikazani su klinički i elektrofiziološki podaci o 105 starijih bolesnika (63,4 ± 7,8 godina) obolelih od karcinoma pluća koji su bili podvrgnuti detaljnoj neurološkoj evaluaciji i ispitivanju provodljivosti nerava između 2013. i 2018. godine. Bolesnici sa "klasičnim" paraneoplastičnim neurološkim sindromima uz prisustvo onkoneuralnih antitela, kao i oni koji boluju od poznatih uzroka periferne neuropatije (npr. dijabetes, alkoholizam, hronična bubrežna insuficijencija, deficijencija vitamina D) isključeni su iz studije. **Rezultati.** U ovom istraživanju 19,1% bolesnika imalo je klinički manifestnu neuropatiju, a dodatnih 37,1% imalo je samo abnormalnosti uočene tokom ispitivanja nervne provodljivosti. Najčešći patofiziološki supstrat bila je aksonalna patologija (71,2%) sa predominantno distalnom i simetričnom distribucijom (86,4%). **Zaključak.** Bolesnici oboleli od karcinoma pluća u ranoj fazi bolesti pokazuju visoku učesta-

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lost klinički nemih oštećenja nerava, a prema obrascu hronične senzori-motorne distalne neuropatije lakog stepena ispoljavanja, uz predominaciju aksonalnih oštećenja. Ovi rezultati ukazuju na značaj detaljne kliničke i neurofiziološke evaluacije ove kategorije bolesnika bez tipičnih etioloških faktora za periferne neuropatije, budući da se to-kom lečenja bolesnici podrgavaju nizu tretmana sa dodatnim rizikom od razvoj/pogoršanja neuropatija

Introduction

Malignant lung tumors represent a leading cause of mortality in the world [1]. Therefore, early detection techniques pose an essential field of interest, especially having in mind that this tumor is often diagnosed after it has metastasized [2]. Besides the "classical" metastasis syndrome, there are other clinical presentations which can represent an effect of the tumor, and these effects are especially prevalent in the structures of the nervous system. Having in mind the general population, the paraneoplastic neurological syndromes (PNS) represent equally rare symptoms, mediated by onconeural antibodies and depends highly on the type of cancer [3].

Recent research has shown that the manifestations of the PNS on the peripheral nervous system is most common in small-cell lung cancer [4, 5], although rare even in this type of cancer [6]. Contrary to patients in the early stages of the disease, if the frequency is examined in patients in late stages, the damage of the peripheral nervous system is present in as much as 15% of patients, where this is pathophysiologically explained as metabolic and nutritive deficiencies, and/or the effects of chemotherapy as part of the primary disease treatment [7].

In cases of early PNS manifestations, or even as a first simpton of a lung tumor (as well as some other solid organ tumors), these effects are explained by the presence of typical onconeural antibodies (anti-Hu, Yo,Ri, $CV_2/CRMP_5$, Ma_2, andantiamphiphysin) in the serum of lung cancer patients. Therefore, following the recommendations of the International Panel of Neurologists, it is assumed that the two levels of evidence confirming the diagnosis of PNS as "definitive" or "possible", which is dependant on the presence of onconeural antibodies [8], mostly is based on the clinical manifestations – classical versus non-classical forms of neuropathy [3].

Nevertheless, considering that lung cancer is typically a disease of the elderly, around 70 years of age on average [9], a higher frequency of neuropathies in this population, independently of PNS, is already present, compared to a younger demographic. This frequency has been seen to arrive to up to 7% in some studies of the elderly population [10, 11]. Among the detected neuropathies, there is a notable fraction, reported going to up to 49% in elderly patients, of characteristical cryptogenic, or chronic idiopathic axonal neuropathies [12].

Having in mind the fact that older patients suffer from lung cancer more often, and equally, but not necessarily causally connected, a significant fraction of elder patients present with neuropathic symptoms, a clinical interest in defining the frequency, as well as clinical and electrophysiological characteristics of idiopathic neuropathies in patients suffering from lung cancer in early stages of the diseases, is evident.

Methods

Patients

Between December 2013 and January 2018, 105 patients with pathologically confirmed lung carcinoma were referred to our clinic regarding the screening neurological and electrophysiological evaluation aimed to diagnose peripheral neuropathy. For this study, we selected only those patients who had no other known causes of peripheral neuropathy, including classical paraneuroplastic peripheral neuropathy, but diabetes mellitus, long-term alcohol consumption, renal failure, vitamin deficiencies, thyroid gland dysfunction, paraproteins, and cachexia, as well.

The study protocol was approved by the Ethical Committee of Clinical Centre of Serbia, Belgrade, and written informed consent was obtained from each patient prior to study engagement.

Clinical neurological evaluation and electrophysiological examination were conducted immediately after the initial presentation to the medical consulting team for oncology patients prior to initiating any therapy.

Clinical neurological evaluation

Neurological examinations were performed repetitively by an experienced physician (S.T.V.) in each case. The presence of neuropathy was clinically defined through the presence of sensory or motor signs, and the reduction or absence of myotatic reflexes without pathological reflexes and symptoms (weakness, sensory disturbances, and burning paresthesia). Clinical evaluation was based on the Neurological Symptom Score and the Neurological Disability Score [13].

After a careful history and neurological examination, patients were further evaluated and the presence of neuropathy eventually confirmed by nerve conduction studies in each case.

Electrophysiological evaluation

Standard nerve conduction studies were performed bilaterally in the upper (the median and ulnar nerves) and lower limbs (the tibial and sural nerves), by standard procedures with surface electrodes for stimulation and recording using a Synergy electromyography machine (Viasys, UK).

Parameters measured included: compound motor action potentials (CMAPs) recorded from the *abductor pollicis* (APB), *abductor digiti minimi* (ADM), *extensor diggitorum brevis* (EDB) and *flexor hallucis brevis* (FHB). Distal and proximal motor latencies, (DML and PML, respectively), motor conduction velocities (MCV), and F-wave latency

were estimated (shortest at each case). The sensory nerve action potentials (SNAPs) were investigated in the median, ulnar, and sural nerves using antidromic recordings from ring electrodes at the 2nd and 5th digits for the median and ulnar nerves, respectively, and toe finger for the sural nerve.

The MCVs were calculated from the following nerve segments: wrist to elbow (median nerve), wrist to below the elbow (ulnar nerve), ankle to popliteal *fossa* (tibial nerve), and ankle to just below the fibular head (peroneal nerve), while sensory conduction velocity (SCV) was calculated for

the distal segment, using the antidromic method. The amplitudes of the CMAPs and SNAPs were measured from the baseline to the first negative peak.

Values for the lower limits of normal were defined initially as mean values reduced by 2 standard deviations of normative data for this laboratory, studied by the same method. Subsequently, we have additionally decreased the lower limit of normal of conduction velocities according to reference values [14]. Absolute values of the lower limits of normal for all electrophysiological parameters are summarized in Table 1.

Table 1
Absolute values of the lower limits of the normal and decreased values of electrophysiological parameters
(90% and 80% LLN, respectively)

Nerves	MCV* (m/s) or SCV[†] (m/s)			CMAP* (mV) or SNAP[†] (μV)		
	LLN	90% LLN	80% LLN	LLN	90% LLN	80% LLN
Motor*						
median/ ulnar	46.0	41.4	36.8	4.0	3.6	3.2
peroneal/ tibial	40.0	36.0	32.0	3.0	2.7	2.2
Sensory[†]						
median/ ulnar	46.0	41.4	36.8	8.0	7.2	6.4
sural	40.0	36.0	32.0	8.0	7.2	6.4

MCV – motor conduction velocity; CMAP – compound motor action potential; SCV – sensory conduction velocity;
SNAP – sensory nerve action potential; LLN – lower limit of normal.

For each nerve examined, we defined typical electrophysiological patterns of abnormalities: a demyelinating [15], an axonal (A), and a combined axonal/demyelinating (A/D) pattern [16]. A demyelinating (D) pattern was defined as when the MCV or SCV ≤ 80% of lower limit of the normal (LLN) and CMAP or SNAP ≥ 80% LLN or MCV or SCV ≤ 70% of LLN and CMAP or SNAP < 80% LLN; an axonal pattern as when the MCV or SCV > 90% LLN and CMAP or SNAP < LLN or MCV or SCV > 80% LLN and CMAP or SNAP < 80% LLN or complete absence of motor or sensory responses after repeated electrical stimulations; a axonal/demyelinating pattern as when the MCV or SCV 80–90% LLN and CMAP or SNAP 80–100% LLN or MCV or SCV below LLN but still above values for demyelinating pattern and CMAP or SNAP in the lower range of normal values (Table 1).

The presence of abnormalities in at least two peripheral nerves was considered as electrophysiological involvement.

Statistical analysis

Descriptive statistics were generated for all variables. The frequency of clinical and electrophysiological parameters was tested using chi-squares (χ^2), and significance was set at the $p < 0.05$ level. The SPSSfor Windows (release 10.0; SPSS, Chicago, IL, USA) was used to perform the statistical analysis.

Results

Demographics and clinical characteristics

During the study period, we have evaluated 105 patients with lung carcinoma. Of the total number of patients, small-cell lung carcinoma, adenocarcinoma, squamocelullar and large-cell carcinoma, according to confirmed histological specimens, accounted for the incidence as shown in Table 2.

Table 2
Patients' demographics and clinical characteristics

Variable	Value
Total sample, n (%)	105 (100)
Sex: male, n (%)	72 (68.6)
Age (years), mean ± SD	63.4 ± 7.8
Tumor type, n (%)	
small-cell carcinoma	32 (30.5)
non-small-cell carcinoma	73 (69.5)
adenocarcinoma	30 (28.6)
squamocelullar carcinoma	39 (37.1)
large-cell carcinoma	4 (3.8)
Neurological symptoms/signs of PNP, n (%)	20 (19.1)

SD – standard deviation; PNP – polyneuropathy.

One thousand and forty-four nerves, consisting of 584 motor, and 447 sensory nerves, on 351 extremities were studied. The mean number (± standard deviation) of studied nerves per patient was 9.85 ± 2.88, of which 5.58 ± 1.69 were motor, and 4.35 ± 1.42 sensory nerves.

Clinical peripheral neuropathy was diagnosed in 20 (19.05%) out of 105 patients, which was confirmed by electrophysiological evaluation. However, nerve conduction studies have identified electrophysiological abnormalities in additional 39 (37.14%). Patients. Overall, electrophysiological abnormalities were present in 59 out of 105 (56.2%) patients.

An axonal, a demyelinating, and a combined axonal/demyelinating patterns were diagnosed in 42/59 (71.2%), 2/59 (3.41%) and 15/59 (25.4%) patients, respectively. However, the patients with described nerve conduction abnormalities did not differ significantly regarding histopathological tumor type, small vs. non-small cell lung cancer (Mantel-Haenszel χ^2, 0.294; $p = 0.86$).

An additional analysis of the above mentioned abnormalities referred to the symmetry of peripheral nerve involvement, showed that 51 out of 59 (86.4%) patients had a symmetrical pattern of damage while only eight (13.6%) had asymmetric nerve lesions.

Considering the entire sample of patients, the distribution of the fiber types (motor vs. sensory) and the pathological mechanism of their damage is shown in Figure 1.
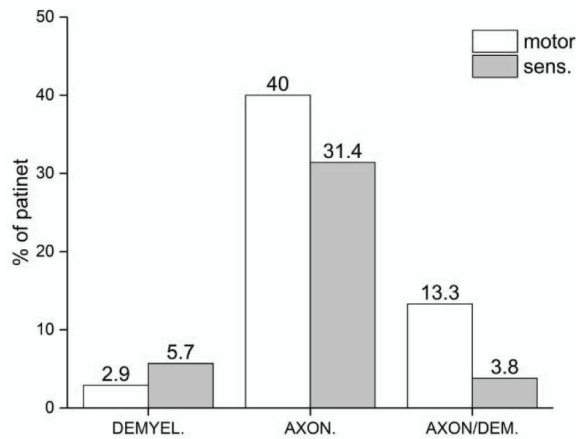

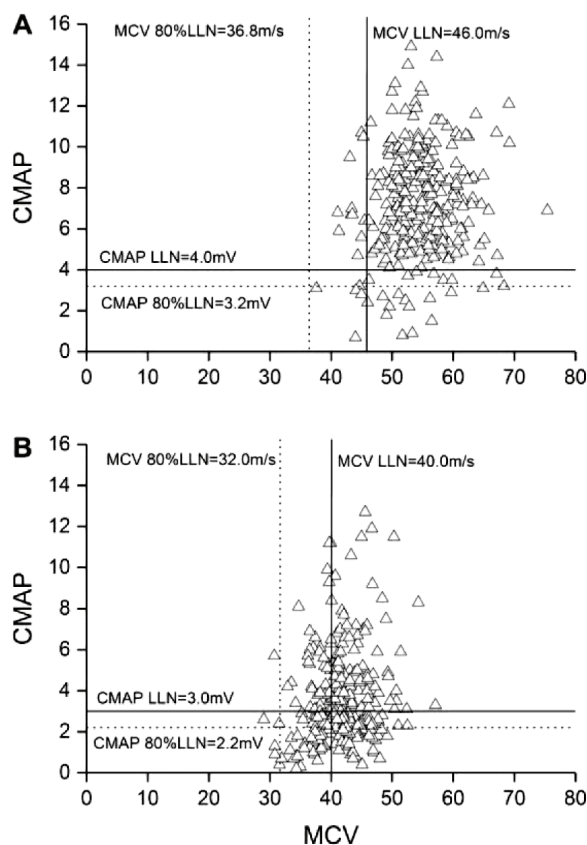**Fig. 1 – Frequency of various forms of peripheral nerve damage in patients with lung carcinoma.**

Fig. 2 – Distribution of individual data of motor conduction velocity (MCV) (x-axis) vs. compound motor action potentials (CMAP) (y-axis) in the form of bivariate scattergram for: A) a total of 307 upper limbs motor nerves (*n.medianus* + *n.ulnaris*), and B) 277 lower limbs motor nerves (*n. peroneus* + *n. tibalis*).

Regarding the type of neuropathy, we observed 19/59 (32.2%) of patients with pure motor (predominantly axonal type) neuropathy, 9/59 (15.3%) with sensory neuropathy, and 31/59 (52.5%) of patients with combined sensory-motor neuropathy.

Since the study analyzes a substantial number of peripheral motor and sensory nerves, the results of the distribution of motor and sensory nerve conductions are shown in the form of scattergram separately, as well as for the upper and lower extremities (Figures 2 and 3). These scattergrams show a notable frequency of lower CMAP amplitude (axonal pattern of damage), manifested by a significant grouping of data points in the lower part of the diagram, for motor nerves of the lower extremities, and less evident for sensory nerves of the upper extremities.
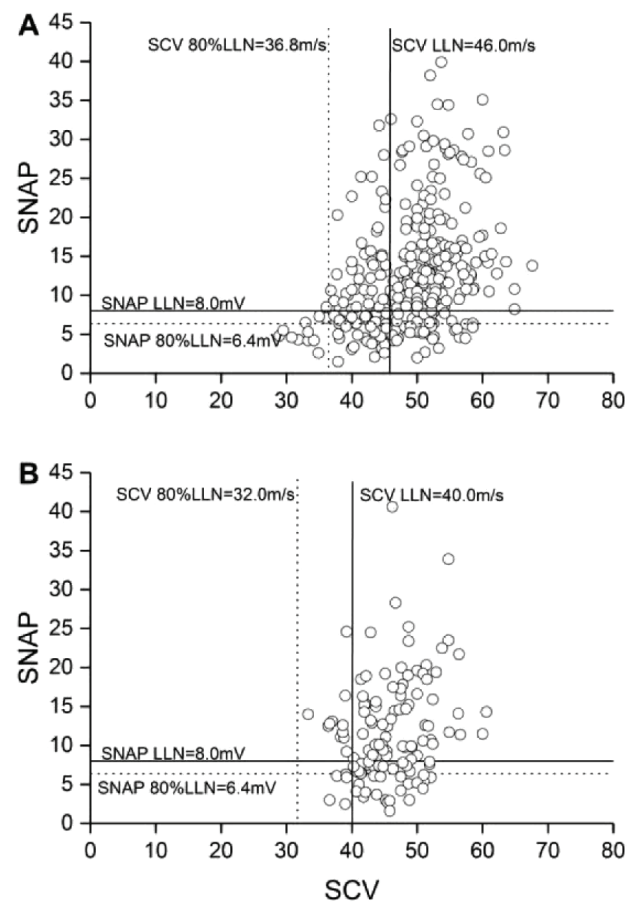

Fig. 3 – Distribution of individual data of sensory conduction velocity (SCV) (x-axis) vs. sensory nerve action potentials (SNAPs) (y-axis) in the form of bivariate scattergram for: A) a total of 324 upper limbs sensory nerves (*n. medianus* + *n. ulnaris*), and B) 123 lower limbs sensory nerves (*n. suralis*).

Discussion

The main finding of this study is the unexpectedly high incidence of clinically manifest neuropathies (19.1%) in a sample of older patients with recently diagnosed and histopathologically confirmed lung carcinoma at a very early stage, before applying any therapeutic modality. Moreover, this

frequency was seen in the category of exclusively lung carcinoma patients, where patients suffering from typical known causes of peripheral neuropathy (e.g., diabetes, alcoholism, chronic renal insufficiency, vitamin deficiencies, thyroid gland dysfunction, paraproteins, and cachexia) were excluded [15, 16]. However, the nerve conduction studies evaluation confirmed neuropathy in these patients but further revealed additional subclinical electrophysiological abnormalities in 39 (37.1%) clinically silent patients. Aggregating clinical and electrophysiological abnormalities in our sample of early-stage lung cancer patients, it was found that 59 out of 105 (56.2%) od patients showed some degree of peripheral nerves damage. The most frequent pathophysiological pattern, within the group of patients with confirmed nerve damage, was the axonal pathology for sensory (31.4%) as well as for motor (40%) nerves.

Recent studies of lung carcinoma patients point to an increasing incidence of this disease and high mortality, where the non-small-cell type of lung cancer (NSCLC) is seen in up to 85%–90% of patients, while the frequency of small-cell lung cancer (SCLC) is decreasing [17]. Alberg and Samet [18] underlined that the epidemics of lung cancer is positively correlated to cigarette smoking and that the most common histological subtypes are the squamocellular (SCC) lung cancer and SCLC. Newer studies have repeatedly shown a predominance of adenocarcinomas. Our study confirms these results. The lung adenocarcinoma was found in almost 29% of our patients. The reducing frequency of SCLC in patients who have lung cancer is explained by the reduced number of smokers and improvements of the cigarette filters [19]. Our study showed still high frequency of SCLC cancer, evident in almost 31% of our patients. A recent meta-analysis of studies exploring the influence of cigarette smoking on histological subtypes of lung cancer has shown a stronger correlation with SCLC and SCC. Considering the description of the smoking-related microcellular carcinoma, we can assume this fraction is so large in our patients because all our patients have been smoking for more than 30 years.

The distribution by gender of our patients confirmed the dominance of the male sex, with around 69% of males among the patients, although some authors report an increasing incidence of women suffering from lung carcinomas, which is leading to almost equal frequencies of male and female patients [19].

The underlying mechanisms of peripheral nerve damage in lung carcinoma patients are seen as consequences of cytotoxic chemotherapy, peripheral nerve or roots infiltration, metabolic or nutritive deficiencies. When all previously mentioned factors are excluded, and with a confirmation of the immune mechanisms activation, the neuropathy can be considered as paraneoplastic (PNN) [8]. The mechanism of damage has been connected to onconeural antibodies together with onconeural antigen-specific T-lymphocytes, although the absence of known onconeural antibodies in patients with so-called "classic" clinical presentations does not exclude the possibility of PNN [3]. These are often complicated forms of neuropathies which point to the diagnosis of the underlying disease, and sometimes cause a high level of disability regardless of cancer as the primary disease [20].

Nevertheless, the causal relationships of neuropathies, above all of sensorimotor type, in this population of patients, add controversy, considering we are discussing an elderly population (in our study 63.5 was the mean age), with many potential underlying causes of peripheral nerve damage, such as: metabolical (diabetes, chronic kidney disease), nutritive or iatrogenic (cytotoxic, e.g. paclitaxel, cisplatin, vinca alkaloids, but also non-cytotoxic pharmaceuticals, e.g. antimicrobial agents, cardiovascular medication, etc.). The etiology of these neuropathies in cancer patients can be considered multifactorial, which includes the mentioned metabolical and nutritive deficiencies, but also unrecognized factors which appear in later stages of the primary disease [21].

In our sample, the patients were meticulously selected, at the very beginning of the disease, excluding all patients with cachexy, recognizable nutritive deficits, or those with risk factors for most common metabolical, nutritive, or immunologically mediated neuropathies typical for this age group. Nevertheless, after a detailed examination and neurophysiological evaluation of each patient we have found an unexpectedly high percentage of, above all, electrophysiological, but also clinical abnormalities. Finally, the pattern of damage which appeared as the dominant one in our sample was the distal sensorimotor neuropathy, with mostly axonal damage.

In case we tried to compare our results with similar studies, we came across a relatively small number of studies exploring the etiology of peripheral neuropathies in elderly patients, but not suffering from lung cancer [22, 23]. It is important to note that, based on modern guides for diagnosis of neuropathies, with increasing accuracy over the years, more than a hundred of different causes have been identified [24]. Nevertheless, even after applying all of the proposed criteria, for a certain number of patients (around one fourth) it is impossible to identify the cause of neuropathy, and this is considered a chronic idiopathic axonal neuropathy (CIAN) [25]. In general, the pathophysiological mechanism underlying this type of neuropathy is axonal degeneration, which is, as a rule, irreversible, and consequently, a permanent loss of nerve fibers occurs. However, in addition to the increased incidence of axonal lesions on our sample of early-stage lung cancer patients and the fact that older people are more likely to determine CIAN, it is interesting to consider whether there is any relationship between the axonal type of neuropathy and lung disease in general. The possibility that a chronic obstructive pulmonary disease, based on presumed hypoxia, may lead to the axonal pathology of the peripheral nerves has been refuted so far [26]. In considering the CIAN etiology, special interest is currently focused on disturbed peripheral nerve *vasa nervorum* microcirculation, which is associated with the metabolic risk factors, but also the diseases of peripheral circulation of the atherosclerotic type [27]. As this series of patients, according to our knowledge, is the first of its kind on the patient population in our country, it is therefore not possible to link the observed neuropathic changes to lung carcinoma, as an etiological factor. In our view, future studies of similar interest should define the presence of chronic risk factors for peripheral microcirculation disorders, in particular with laboratory values (e.g. blood glucose) within the upper limits of normal.

Conclusion

Patients suffering from lung cancer at the moment of initial presentation show a high frequency of clinically apparent, as well as clinically silent neuropathies. Based on the characteristics, these neuropathies, manifesting themselves symmetrically in distal parts of the extremities, with most common electrophysiological pattern of axonal damage, suggest a common existence of a chronic axonal idiopathic neuropathy. Knowing of the possibility of a high frequency of mild subclinical neuropathies, seen mostly in the elderly population, suggests particular attention is needed when evaluating lung cancer patients in early diagnostic phase, to confirm or exclude this possibility. The most important implications of these results are on the analysis of the frequency and probability of clinically manifest neuropathies appearing during the treatment of the primary disease, e.g., using chemotherapeutic protocols.

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