RARE CASES OF PARANEOPLASTIC SYNDROMES ASSOCIATED WITH LUNG CANCER

LIVIA MIRELA POPA[1]

[1] *"Lucian Blaga" University of Sibiu, GinekoPro Medical, Sibiu*

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Abstract: *Endocrine paraneoplastic syndromes occur as a result of the secretion by the malignant tumor of some hormones or peptides that lead ultimately, to hormonal imbalances, which can be corrected after the primary tumor eradication. Still insufficiently studied, paraneoplastic syndromes should receive a proper diagnosis. Even though the incidence of paraneoplastic syndromes diagnosed herein is rare, their importance can not be minimized and can only be the subject of statistical studies, the quality of life of patients depending on the applied therapy.*

INTRODUCTION

Paraneoplastic syndromes are represented by all the clinical manifestations, with or without biological disturbances occurring in the development of cancer (these may occur before, upon or after diagnosis of the malignant disease) and whose expression is outside the body affected by cancer, syndromes that occur independently of any metastatic process and are not due to the direct effect (compression) of primary tumour.(1,2,3,4)

Cancers, and particularly lung cancer, may cause endocrine syndromes or syndromes associated with ectopic hormones release through synthesis of cythokines, proteins, hormones or hormone precursors released from the tumour.(4,5,6,7)

PURPOSE

The work aimed at evaluating the incidence of paraneoplastic syndromes in patients diagnosed with lung cancer in our geographical region, both at the moment of diagnosis, and during disease progression.

Another objective was to study the characteristics of these paraneoplastic syndromes according to histology and evolution of pulmonary neoplasia.

MATERIALS AND METHODS

I conducted a prospective study including patients diagnosed with lung cancer, with or without treatment, and patients who presented with symptoms of a paraneoplastic syndrome and subsequently diagnosed with this condition.

The group was selected from patients consecutively admitted within the Oncology Clinic, Internal Medicine Clinics, Neurology, Nephrology, Hematology Clinics of the County Clinical Emergency Hospital of Sibiu and patients diagnosed in Sibiu Pneumology Clinic and referred to the Oncology Clinic for specialized treatment.

Data was collected from both the observation sheets, medical history and physical examination of patients.

The following examinations were aimed at:

- The detailed objective examination focusing on certain modifications, characteristic of paraneoplastic diseases (hypocratic fingers, hypertrohphic osteoarthropathy, facies "in full moon" etc.), nutrition score assessment etc.
- Laboratory examinations:
  1. Complete blood count, differential blood count and erythrocytes morphology in case of changes in blood count, sideremia;
  2. Na, K, Ca, Mg, P;
  3. Astrup of venous blood;
  4. Serum alkaline phosphatase, creatine phosphokinase, aspartate aminotransferase, alanine aminotransferase, blood sugar;
  5. CIC, C3, IgA, IgM, IgG, cryoglobulins, rheumatoid factor, antinuclear antibodies;
  6. Inflammatory tests: erythrocyte sedimentation rate (ESR), fibrinogen, C-reactive protein (CRP);
  7. Serum urea, serum creatinine, uric acid, proteinuria, urinalysis, urine sediment calcium excretion, phosphaturia;
  8. Complete lipidogram;
  9. Determination of plasma cortisol and urinary 17-ketosteroids;
  10. Determination of parathyroid hormone (PTH);
- Bone radiographs in case of complaints or changes in the osteoarticular system;
- Abdominal ultrasound to highlight any liver metastases, tumours of the adrenal gland; ultrasound of the neck in cases diagnosed with hypercalcemia, ultrasound of other organs depending on the symptoms;
- Electroencephalogram, electromyography in patients with neurological symptoms;

The data was processed and analysed, followed by drawing conclusions.

RESULTS

Although endocrine paraneoplastic syndromes were reported in a high number of subjects (the most highlighted being hypercalcemia) in the study group, there were selected three types of paraneoplastic syndromes, which in relation to the other types of syndromes, were the rarest.

Schwartz-Bartter syndrome (Syndrome of inappropriate antidiuretic hormone secretion)

5 patients (2.06% of all lung cancers) had, at one time or another during pulmonary neoplasia evolution, values of serum Na <130 mmol/l, but not less than 115 mmol/l, which led

[1]Corresponding author: Livia Mirela Popa, Str. Distribuției, Nr. 32, Sibiu, România, E-mail: liviamirelapopa@yahoo.com, Phone: +40754 992580
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to further investigations in this regard. Plasma osmolality was assessed, which was low (<280 mOsml/l), natriuresis, and urinary osmolarity, as well which were increased (natriuresis >20mEq/l urinary osmolarity >500mmol/) in all 5 cases.

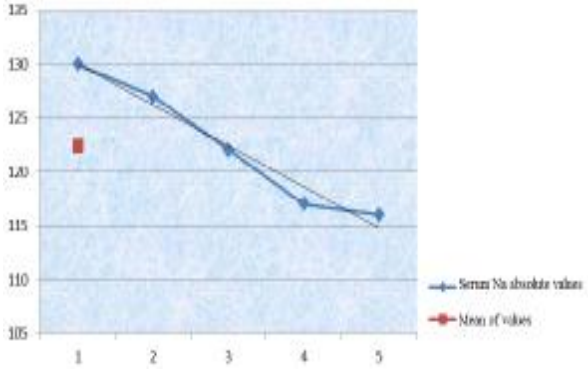
These changes, accompanied by a clinical picture characterized by anorexia, nausea, vomiting, asthenia associated with normal kidney, liver, adrenal and thyroid function have led to the conclusion that it was about the Schwartz-Bartter syndrome associated with lung neoplasia.

All cases were associated with small cell lung cancer (11.62%).

Table no. 1. Absolute values of serum Na, average values, standard deviation

No.	Absolute values of serum Na (mmol/l)	Average values	Standard deviation
1.	130 mmol/l	122.4	±6.107373
2.	127 mmol/l		
3.	122 mmol/l		
4.	117 mmol/l		
5.	116 mmol/l		

Figure no. 1. Absolute values of serum Na, mean of the values



Hyperthyroidism associated with lung cancer

This syndrome was detected in one patient (0.41% of total lung cancer cases), male, smoker for about 50 years, aged 79 years old, who presented with weight loss of about 5 kg in the last two months. Associated, he presented palpitations, marked asthenia, polydipsia.

Biological samples revealed slight anemic syndrome, normochromic, normocytic, biological inflammatory syndrome (ESR = 34mm/h, fibrinogen = 487 mg/dl, CPR = 24 mg/dl), TSH and FT4 altered in the context of hyperthyroidism. Thyroid function investigations continued with the assessment of ATPO which was normal.

ECG was performed which revealed sinus tachycardia, while neck ultrasound highlighted the thyroid gland size at the upper limit of normal and a slightly higher echogenicity.

Standard chest X-ray done routinely highlighted: left lung hilum widening with imprecise edges and without polycyclic (lymph nodes) or vascular aspect.

Further investigations were desired, performing a bronchoscopy, but the relative advanced age, altered spirogram indices (low FEV) in conjunction with the patient's clinical status contraindicated the examination. Native chest CT examination confirmed the suspected diagnosis of lung cancer.

Radiotherapy was initiated, together with specific endocrine therapy leading to a slightly favourable development of thyroid function.

This clinical picture in an older man in whom a malignant lung tumour was later on diagnosed, advocated for the diagnosis of paraneoplastic hyperthyroidism.

Skin manifestations - Acanthosis nigricans

A single patient (representing 0.41% of all lung cancer cases) was diagnosed with *Acanthosis nigricans.* Associated, in this patient hippocratic fingers were also present.

This dermatologic event was characterized by papillomatous hyperkeratosis and pigmentation of skin, localized at the level of elbows, neck, hands. The lesions were symmetrical, black, dirty and rough skin.

No correlation could be made between this condition and the histopathological type of lung cancer as the histopathological type could not be determined.

The dermatologic condition was highlighted after the diagnosis of pulmonary neoplasia.

DISCUSSIONS

Overall, endocrine paraneoplastic manifestations were found in 69 patients (28.51% of all lung cancer cases), the most important endocrine event being *hypercalcemia* in 29 patients (11.98%).

Schwartz-Bartter syndrome or hyponatremia from neoplasia has confirmed that it is the prerogative of small cell carcinoma, those 5 cases diagnosed with hyponatremia having as histopathological type, the small cell carcinoma. All cases were symptomatic, starting at a time more or less distant from lung cancer diagnosis.

No purely biological cases were diagnosed, in all cases, at least one symptom being present. Comparing the data obtained in this study regarding the incidence of these syndromes with the existing data in the literature, our values are below those in the literature.(8,9,10,11)

In one case, there has been revealed a hyperthyroidism considered paraneoplastic for several reasons: emergence in an older patient, former smoker, with a clinical picture dominated by thyrotoxicosis, without clinical or ultrasound signs of goiter, in whom lung cancer has been subsequently revealed.

The incidence of this endocrine event among the population diagnosed with lung cancer is not known.

A rare paraneoplastic manifestation, *Acanthosis nigricans*, was found in a single patient, representing 0.41% of all lung cancer cases.

The incidence of this event among cancer patients is not known, but its existence is associated to tumours in more than 50% of cases. It is more frequently associated with adenocarcinoma (gastric, colon, pancreatic), and rarely with lung cancers.(11,12,13,14)

CONCLUSIONS

1. Although endocrine paraneoplastic syndromes were diagnosed in an important number of cases, Schwartz-Bartter syndrome was diagnosed in only 5 patients (2.06% of all lung cancers).
2. Along with hematologic syndromes, endocrine paraneoplastic syndromes are highlighted in an important number of cases (69 patients), representing 28.51% of all lung cancer cases.
3. Hypercalcemia is the most important endocrine paraneoplastic syndrome being diagnosed in 11.98% of patients (n = 29).
4. There were also diagnosed rarer paraneoplastic pathologies described in the literature: hyperthyroidism, *Acanthosis nigricans*, each represented by one case (0.41% of all lung cancers).
5. The emergence of clinical and biological manifestations

suggestive of a paraneoplastic syndrome, especially in patients with risk factors for lung cancer should lead to initiation of investigations in this respect.

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