OSTEOARTICULAR PARANEOPLASTIC SYNDROMES ASSOCIATED TO LUNG CANCER

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Abstract: *Paraneoplastic syndromes are a group of disorders associated with malignancies, independent of the location or size of the tumor. They are mediated by soluble mediators such as hormones and cytokines released by tumor tissue. In the case of paraneoplastic rheumatologic syndromes, symptoms occur in joints, muscles, boness, fascia, generally not more than 2 years before the diagnosis of cancer, and therefore, can be of great clinical importance through early detection and initiation of appropriate therapy.*

INTRODUCTION

Paraneoplastic syndromes are described as non-specific clinical and biological manifestations occurring in patients with malignancies, and those that accompany lung cancer are numerous and extremely varied. These manifestations can precede the symptoms of tumour, occur simultaneously or afterwards.(1,2,3)

PURPOSE

The work aimed at evaluating the incidence of osteoarticular paraneoplastic syndromes in patients diagnosed with lung cancer in our geographical region, both at the time 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 (hyppocratic 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

Regarding the study group, I have selected two types of osteoarticular paraneoplastic syndromes.

Digital hypocratism

Digital clubbing had a higher incidence among the study patients; in 68 (28.09% of all lung cancer cases) this sign has been highlighted. 3 (1.23%) patients had this sign at time of diagnosis of lung cancer, while in the remaining patients (26.85%), it occurred during disease progression. This type of paraneoplastic syndrome appeared simultaneously with other paraneoplastic syndromes, its single presence being rare.

These patients' nails were curved longitudinally, others were transversely and others presented a mixed curvature being associated with hypertrophy of fingers pulp, elastic, with pink burelet. In some patients, similar changes, but at a smaller scale were present in toes, as well.

Association with the histopathological type was made as follows: 44 digital clubbings were found in patients

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diagnosed with epidermoid carcinoma simultaneously, 7 patients with adenocarcinoma, 5 patients with small cell carcinoma, the remaining 12 patients having no histological confirmation.

Table no. 1. Distribution of patients with digital clubbing depending on the histopathological type of lung cancer

Histopathological type	No. of patients with digital clubbing
Epidermoid carcinoma	44
Adenocarcinoma	7
Small cell carcinoma	5
Undetermined histopathologic type	12

Figure no. 1. Distribution of patients with digital clubbing depending on the histopathological type of lung cancer

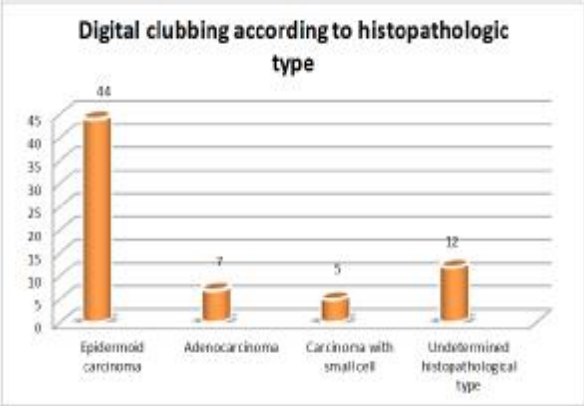
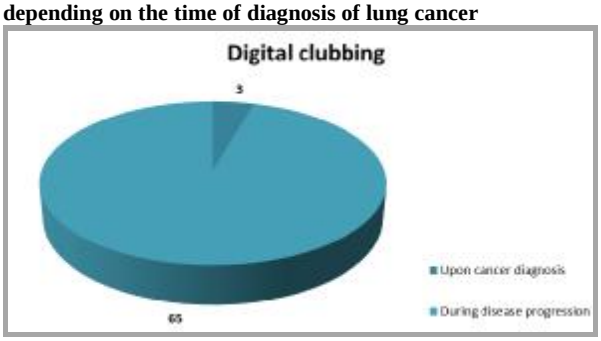


Table no. 2. Distribution of patients with digital clubbing depending on the time of diagnosis of lung cancer

The time when digital clubbing signs occurred	No. of patients
Upon diagnosis of lung cancer	3
During disease progression	65

Figure no. 2. Distribution of patients with digital clubbing depending on the time of diagnosis of lung cancer



Hypertrophic pulmonary osteoarthropathy

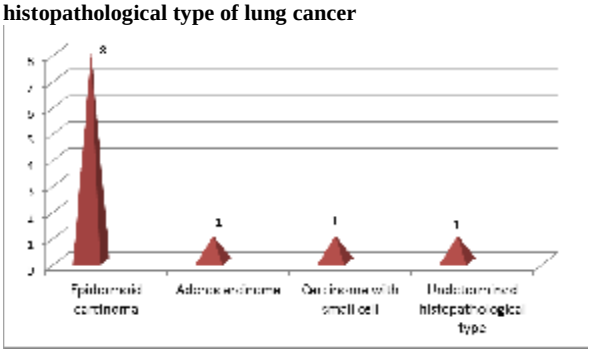
Hypertrophic pulmonary osteoarthropathy, in its complete form, was present in 11 patients (4.54% of all lung cancer cases). Two of the patients went to the doctor for rheumatoid syndrome manifested by pain and swelling joints, symmetrical at the level of radiocarpal joints, knees or ankles. Associated, they presented digital clubbing, excessive growth of the soft tissues of the extremities accompanied by vasomotor disturbances at this level. Subsequently, chest radiograph examination revealed lung cancer, confirmed by chest CT scan and bronchoscopy with histopathological type determination. In 9 patients, this kind of events has occurred subsequently to the diagnosis of lung cancer, in different stages of the disease.

Association with the histopathological type was made as follows: 8 patients were diagnosed with epidermoid carcinoma, 1 with adenocarcinoma, 1 with small cell carcinoma, and in 1 patient, no histopathological type was revealed.

Table no. 3. Distribution of patients diagnosed with hypertrophic pulmonary osteoarthropathy according to histopathological type of lung cancer

Histopathological type	No. of patients with hypertrophic pulmonary osteoarthropathy
Epidermoid carcinoma	8
Adenocarcinoma	1
Small cell carcinoma	1
Undetermined histopathologic type	1

Figure no. 3. Distribution of patients diagnosed with hypertrophic pulmonary osteoarthropathy according to histopathological type of lung cancer



DISCUSSIONS

Although lung cancer is a cause of severe illness and its incidence is continuously increasing, paraneoplastic syndromes associated to this (numerous and extremely varied) are insufficiently studied. These paraneoplastic syndromes may precede the occurrence of clinical manifestations of cancer. Their knowledge is very important in setting an early diagnosis. Symptoms may occur once the clinical externalization of the tumour or at any other time of its progression. Within these conditions, paraneoplastic syndrome can dominate the clinical stage and the neoplasm can be ignored, hence the mistakes of diagnosis and treatment. When the syndrome occurs during the progression of an already known cancer, it can be erroneously misinterpreted as in connection with a metastasis, which can lead to serious errors. It can regress after tumour resection and reoccur in case of metastasis or relapses.

Their incidence is not exactly known. Today, it is accepted that they are present in up to 15% of patients with cancer diagnosis and up to 70% of patients with lung cancer may have one of these syndromes during the course of the disease.(4,5,6)

Some of the few cohort studies were those of Croft and Wilkinson on paraneoplastic neurologic syndromes, in which more than 1400 study patients had an incidence ranging between 0.5 and 16.4%, with the average of 6.6 %. In a control group, these authors have found neurological changes between 1 and 2%. It their etiology, the first place was held by lung cancer. In another study, these syndromes were detected in 7% of almost 1500 patients with tumours. Tumours that are most frequently associated with paraneoplastic neurologic syndromes are lung cancer (47%), gastric (12%), breast (12%), ovarian (9%), and colon cancer (6%).(6,7,8)

Another published study show that isolated monoarthritis of the knee is a paraneoplastic syndrome previously described that evokes lung cancer without small cells in an early stage.(9)

While paraneoplastic syndromes are found in approximately 10-20% of cases of small cell lung cancer, monoarthritis of the knee are more common in lung cancer without small cells.(10,11)

Osteoarticular manifestations were the most frequently encountered among the study population, digital clubbing occupying the first place, both regarding the osteoarticular manifestations and in paraneoplasia.

The data is compared with that existing in the literature.(12) Digital clubbing was manifested clinically in 68 patients (28.09% of all lung cancer cases), in 3 of them it was an inaugural sign and in the rest of the patients it occurred during disease progression. It was found in all histopathological types of lung cancer without any of them to prevail.

Hypertrophic pulmonary osteoarthropathy was diagnosed in its complete form in 11 patients (4.54%).

The predominant histopathological type of lung cancer was the epidermoid carcinoma, data confirmed by that in the literature.

In 2 patients, the syndrome preceded the diagnosis of pulmonary neoplasia, in the remaining 9 patients this event occurring during the course of the disease.

Rheumatic paraneoplastic syndromes were diagnosed in 22 patients (9.09%).

In 9 patients, symptoms were visible before the diagnosis of cancer, joint pain being the reason for which the patients went seeing a doctor. 13 patients evidenced a form more or less severe of rheumatoid syndrome during the course of the disease. 18 of them had bilateral pain, largely symmetrical, localized especially in the large joints of the limbs, only 4 were diagnosed with knee monoarthritis (1.65%). The percentages are comparable to those found in the literature.

CONCLUSIONS

1. 2.06% of patients (n = 5) were diagnosed with dysacromelia-gynecomastia syndrome consisting of a combination of digital clubbing and gynecomastia.
2. The most common paraneoplastic manifestation is represented by digital clubbing, being encountered in 68 patients (28.09%).
3. The predominant histopathological type in hypertrophic pulmonary osteoarthropathy and rheumatoid syndromes is represented by the epidermoid carcinoma, 8 patients, respectively 14 patients being diagnosed with this histopathological type.
4. Paraneoplastic syndromes are numerically important since the diagnosis of lung cancer.
5. It is noted an association of one or more paraneoplastic syndromes in the same patient.

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