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Pathophysiology of paraneoplastic rheumatologic syndromes- could be involved in the diagnosis of a pulmonary adenocarcinoma?

Corina Eugenia Budin[1,2], Dariana Elena Pătrîntașu[2], Sárközi Hédi-Katalin[3], Iuliu Gabriel Cocuz[1,4], Edith Simona Ianoși[2,3,*], Ovidiu Simion Cotoi[1,4]

[1]*Pathophysiology Department, George Emil Palade University of Medicine, Pharmacy, Science and Technology of Târgu Mures, 540139 Targu Mures, Romania*
[2] *Pneumology Department, Mures Clinical County Hospital, 540142 Targu Mures, Romania*
[3] *Pneumology Department, George Emil Palade University of Medicine, Pharmacy, Science and Technology of Târgu Mures, 540139 Targu Mures, Romania*
[4] *Pathology Department, Mures Clinical County Hospital, 540011 Targu Mures, Romania*

Abstract

English:

Paraneoplastic syndromes are diseases caused by malignancies without direct anatomical relationship with it and it is crucial to realize that paraneoplastic phenomena are not caused by metastases. A paraneoplastic phenomenon can be the first indicator of cancer in an undiagnosed individual, and in severe cases lead to fatality. Various paraneoplastic rheumatological syndromes are associated with malignant neoplasms. Although they occur within various forms of malignancy, they most often suceed lung cancer, and adenocarcinoma stands out as the most prevalent histological subtype within pulmonary cancer. This article focuses on the understanding of paraneoplastic syndromes, particularly regarding paraneoplastic rheumatic syndromes due to their challenging differentiation from idiopathic rheumatic disorders.

Keywords

paraneoplastic rheumatologic syndromes • pulmonary adenocarcinoma • occult malignancies

Fiziopatologia sindroamelor reumatologice paraneoplazice - ar putea fi implicate în diagnosticul unui adenocarcinom pulmonar?

Rezumat

Romanian:

Sindroamele paraneoplazice sunt boli cauzate de afecțiuni maligne fără relație anatomică directă cu aceasta și este crucial să cunoaștem că fenomenele paraneoplazice nu sunt cauzate de metastaze. Un fenomen paraneoplazic poate fi prima manifestare a cancerului la un individ nediagnosticat și, în cazuri grave, poate conduce la deces. Diferite sindroame reumatologice paraneoplazice sunt asociate cu neoplasme maligne. Deși apar în forme heterogene de malignitate, cel mai adesea apar relaționate cu cancerul pulmonar, iar adenocarcinomul se evidențiază ca și cel mai frecvent subtip histologic în cadrul cancerului pulmonar. Acest articol se concentrează pe înțelegerea sindroamelor paraneoplazice, în special în ceea ce privește sindroamele reumatice paraneoplazice, datorită diferențierii lor provocatoare de tulburările reumatice idiopatice.

Cuvinte-cheie

sindroame paraneoplazice reumatologice • adenocarcinom pulmonar • neoplazii ocult

**Corresponding author: Edith Simona Ianoși*
E-mail: ianosi_edith70@yahoo.com

Introduction

The notion of paraneoplastic syndrome first appeared in 1940 and is defined by signs or symptoms related to an occult tumour without direct anatomical relationship with it and cannot be explained by metastasis [1]. Therefore, clinical manifestations of paraneoplastic syndromes can often precede the onset of symptomatology of the primary tumor [2]. Paraneoplastic syndromes (PNS) are considered to be clinical and pathophysiological aberrations due to the noninvasive action of the tumor [3]. In this context, in rheumatological practice, the PNS are heterogeneous and difficult to diagnose, since they mimic common clinical conditions [4]. As a result, if a paraneoplastic condition is suspected, a screening of the original tumor should be conducted [5]. Although they occur within various forms of malignancy, they most often occur in combination with lung cancer, affecting about 10% of patients with this pathology [6].

Among the types of lung cancer, small cell lung cancer (SCLC) often causes the appearance of paraneoplastic syndromes [5, 7]. Paraneoplastic syndromes can often lead to associated pathologies on the neurologic, rheumatologic and endocrine systems, as well as renal or vascular diseases [6,8,9]. Nevertheless, a wide range of malignant neoplasms are linked with a wide range of paraneoplastic rheumatologic syndromes [1].

Pathophysiology of paraneoplastic syndromes

Paraneoplastic syndromes are pathological phenomena that occur due to the secretion of hormones, peptides or cytokines by the tumor cell [2]. It has been suggested that the release of cytokines by tumor cells causes a cross-reactivity and deposition of immune complexes in nearby and distant tissue.This triggers a breakdown in immune tolerance by creating auto-antigens and forming auto-antibodies. These antibodies subsequently contribute to the onset of paraneoplastic rheumatic syndromes (PRS) [10] Thus, this hypothesis is that of the cross-immune response between tumor cells and the body's self-cells.

Although it can affect various organs and systems, the endocrine, neurological, rheumatological, dermatological and hematological systems are most commonly affected [2, 6, 11]. The most common paraneoplastic syndromes (PNS) caused by solid tumors are neurological ones. Autoimmune hematological pathologies such as autoimmune hemolytic anemia and immune thrombocytopenia are PNS associated with lymphomas [12]. The paraneoplastic syndromes are found in patients with rheumatologic symptoms, months or years after clinical onset of the primary tumors [13]. The malignant tumors can be associated with a variety of paraneoplastic rheumatologic syndromes such as: hypertrophic osteoarthropathy, myositis/dermatomyositis, paraneoplastic vasculitis, Raynaud phenomenon, lupus - like syndrome or rheumatoid arthritis [14]. Furthermore, polymyositis (PM), which is defined as an inflammatory myositis with no rash according to Bohan and Peter's criteria, is thought to be associated with cancer [15].

The mechanisms of the musculoskeletal manifestations induced by the neoplastic disease are direct invasion of the bones and joints, synovial proliferations of the peri-joints tumors/abarticular tumors, hemarthrosis (leukemia) or the indirect approach – the paraneoplastic syndromes [13,14]. These signs and symptoms result from secretion of functional peptides or hormones from the tumor, or as a result of inappropriate immune cross-reaction between normal host cells and initially targeted tumor cells [2].

The literature showed that the tumoral pathology is diagnosed in the following twelve up to twenty four months from the onset of the rheumatologic manifestations [16]. The paraneoplastic rheumatologic syndromes are mediated by hormones and cytokines secreted by the tumor cells or are the consequence of other immunological cellular or humoral immunity mechanisms aimed against the cancer cells. In over 40% of patients diagnosed with paraneoplastic syndromes, the rheumatoid factor was positive [13, 16].

Lung adenocarcinoma and paraneoplastic syndromes

Lung cancer represents the malignancy with the highest mortality reported. It is the second most frequent cause for malignant pleural effusion in men and women as well. Thirty percent of all pleural effusions are considered to be malignant [17].

A study examining lung cancer in individuals with polymyositis (PM), revealed that small cell carcinoma, squamous cell carcinoma and adenocarcinoma were the predominant pathological subtypes and adenocarcinoma is the most prevalent as histological subtype of pulmonary cancer [15,18]. Some of the paraneoplastic syndromes associated with the adenocarcinoma are caused by the ectopic production of proinflammatory cytokines by the tumor cells or by the cross immune mediated reactions between the tumor and healthy cells. Although paraneoplastic syndromes can be found in many malignancies, they are most frequently encountered in lung cancer [19].

The histology of lung cancer influences the type of associated paraneoplastic syndrome. There is no relation between the severity of symptoms and the size of the primary tumor, and

in some cases, paraneoplastic syndromes are manifested before the diagnosis of cancer [20]. Therefore, polymyositis was reported to be associated with an increased risk of lung cancer and should be suspected in any patient who presents with progressive, varying degrees of symmetric proximal limb and truncal muscle weakness [15, 21].

A recent study conducted in Eastern Europe that included patients with lung cancer revealed a percentage of 16% of paraneoplastic syndromes. Furthermore, autoimmune conditions acting as paraneoplastic syndromes (PNPS) are not uncommon in cases of lung cancer, occurring at an approximate rate of 4.7%. Consequently, when a patient visits an outpatient clinic with suspected idiopathic inflammatory myopathies (IIM), it is advisable to routinely conduct a chest CT scan [15, 22].

The presence of paraneoplastic syndromes worsened the prognosis and decreased the survival of patients. As characteristics of the group of lung cancer patients who developed paraneoplastic syndromes, women predominated, the peripherical location of the tumor and the presence of exudative pleurisy [22, 23].

The study conducted by Khayyat in 2022 revealed that the main neoplasia correlated with the development of an inflammatory joint disease is lung cancer, especially non-small cell lung cancer (NSCLC) [4]. According to the study conducted by Kisacik et al. in 2014, pulmonary adenocarcinoma was the solid tumor most commonly associated with a paraneoplastic joint involvement [4, 24].

Although the paraneoplastic syndromes are part of the advanced pulmonary neoplastic manifestations, it can occur in early phases as well. In the last cases, the primary tumor is difficult to be diagnosed and the oncological treatment has a low or medium efficacy [25, 26].

Discussions

Paraneoplastic syndromes like paraneoplastic rheumatoid arthritis have been associated with pulmonary, breast, ovary, gastric, colon, oropharynx and blood cancers [9, 13, 27].

Furthermore, solid tumors of the oropharynx, larynx, esophagus, stomach, colon, lung, breast, ovary, and pancreas, as well as lymphoproliferative diseases, have been associated with carcinomatous polyarthritis (CP) [28,29].

The first case of paraneoplastic rheumatic disease was reported in 1916. Since then, the number of published cases in the literature has increased annually. An overall incidence of paraneoplastic rheumatic disease - 2.65%–23.1% - was consistent with these findings, and it is now a certitude regarding the fact that more or less all types of rheumatism or rheumatic symptoms are present in malignant diseases [30,31,32]. Although less frequently described as paraneoplastic syndrome, systemic sclerosis (SSC) can be associated with forms of neoplasia of the digestive tract [33]. In addition, cutaneous lesions identical to those found in SSc can arise in a variety of malignancies and are referred to as pseudoscleroderma or pseudosclerosis. Metastatic melanoma, osteoclastic myeloma, plasmacytomas, carcinoids and gastric, breast, and lung malignancies are all associated cancers [28]. Rheumatoid arthritis as paraneoplastic syndrome is a rare disorder that often precedes the diagnosis of a solid tumor [14, 25]. Cases of rheumatoid arthritis and palmar fasciitis have been described before in cases of pulmonary adenocarcinoma, but these were preceded by the diagnosis of neoplasia and were interpreted in the context of chemotherapeutic treatment [34].

Subsequently, in a retrospective cohort study carried out by Le Besnerais et al. in 2014 in France, it was discovered that 15% of individuals undergoing initial treatment for digital ischemia had an associated underlying malignancy. These malignancies encompassed adenocarcinoma, squamous cell carcinoma, and lymphoid neoplasia [35].

In a study conducted in 17 nationwide centers in France the patients presented with symmetric polyarthritis involving wrists and hands (85%) and extra-articular symptoms were frequent (84%). The researchers observed that none of them had any specific biologic or radiographic feature and that the mean delay between the rheumatic diagnosis and neoplasia diagnosis was 3.6 months, after articular symptoms occurred (88.5%).

Lung adenocarcinoma was the most encountered type of solid cancer associated with previous rheumatic paraneoplastic syndrome (60%). They also concluded that in case of tumor relapse, only 75% of these patients have had relapse of rheumatic symptoms [36]. Previous studies also evidenced the fact that malignancy was diagnosed typically within 24 months in patients with paraneoplastic rheumatic disease as presentation [37, 38].

In a Chinese study, all patients with paraneoplastic rheumatic disorders developed some type of neoplasia within 24 months of rheumatism diagnosis, with the majority (76%) developing neoplasia within 12 months from the onset of symptoms. Most frequent symptom observed was polyarthritis, which was in correspondence with literature findings [39, 40].

Usually, patients with paraneoplastic syndromes develop an asymmetric involvement of the small joints that can be misdiagnosed as seronegative rheumatoid arthritis or spondyloarthropathy [41]. The clinical onset of musculoskeletal and non-musculoskeletal (e.g. pleural effusion) manifestations of paraneoplastic syndromes is concurrent with the clinical signs and symptoms of the primary tumor [6, 13]. A variety of solid and hematological tumors have been associated

with paraneoplastic arthritis, the association with pulmonary adenocarcinoma being the most common [42]. It is different from non-neoplastic rheumatoid arthritis due to the initiation at advanced age, acute onset, asymmetrical lower extremity predominant involvement, and sparing of wrist and hand joints. Also, unlike non-neoplastic rheumatoid arthritis, the absence of erosions, deformities, rheumatoid factor, rheumatoid nodules, and family history is observed [11, 43].

The paraneoplastic symptoms do not respond to the classic DMARDs (Disease-Modifying Anti-Rheumatic Drugs) [44], and thus the regression of the paraneoplastic rheumatoid arthritis is due to the surgical and oncological treatment of the primary tumor [16, 25].

The solely presence of RF is non-specific and cannot be diagnostic for rheumatoid arthritis. The most frequent paraneoplastic syndrome associated with pulmonary cancer is paraneoplastic myositis (dermato or/ and polymyositis) [43].

The persistent pleural effusion as the only onset respiratory sign is non-specific in the context of the associated comorbidities. The paraneoplastic pleural effusion can be produced by the tumoral cells secretion of mediators that stimulate the vascular permeability, especially the vascular endothelial growth factor (VEGF), or by the growth/development of tumors on the pleura leading to the mechanical obstruction of the lymphatic drainage [17]. A mean pleural effusion can be interpreted as part of the presentation of a pulmonary thromboembolism, a plausible hypothesis due to the medical history of our patient. The evolution of the respiratory manifestations - the recurrent and hemorrhagic pleural effusion - guided the diagnosis of pleural mesothelioma or paraneoplastic pleurisy. Only one case of pleural mesothelioma is described in the literature in 2019 associated with paraneoplastic monoarthritis [45].

Because most paraneoplastic rheumatic syndromes are difficult to distinguish from idiopathic rheumatic disorders, cancer occurrence may constitute a major diagnostic challenge. That is why early detection and therapy may be of most clinical importance.

The association of rheumatoid arthritis with the diagnosis of lung cancer confers a negative prognosis and a decrease in the survival interval. Inflammatory substrate underlying the presence of rheumatoid factor in serum complicates the course of neoplastic disease [46].

Paraneoplastic rheumatic disease is common and can be easily confused with rheumatic disease without any neoplastic condition. Some studies revealed that rheumatic disorders with atypical clinical symptoms at presentation usually in older patients, nonspecific systemic features such as fever, fatigue, weight loss, adenopathy and rash, and well-recognized clinical findings compatible with the diagnosis of paraneoplastic syndromes should always be an alarm sign for clinicians regarding the possibility of an underlying malignancy. It is important to follow and monitor these patients on regular basis especially within 2 years from rheumatism diagnosis, and screen monthly for tumors within the first 6 months if vasculitis was diagnosed [47].

One should consider routine screening for malignancy, particularly for solid tumors, in patients with suspected arthritis and vasculitis, as well as screening for lymphoma in patients with suspected Sjogren's syndrome [38, 47, 48].

Conclusion

The understanding of paraneoplastic syndromes remains crucial in diagnosing occult malignancies. These syndromes often precede the primary tumor's symptomatology, posing diagnostic challenges. Paraneoplastic rheumatic syndromes (PRS) include a spectrum of heterogeneous manifestations and these manifestations primarily affect the endocrine, neurological, rheumatological, dermatological, and hematological systems.

In conclusion, paraneoplastic syndromes adversely affect prognosis and patient survival, thereby early detection of paraneoplastic syndromes remains pivotal for timely cancer diagnosis and management, warranting close surveillance and early intervention strategies in clinical practice.

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Data Availability Statement

Data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare no conflict of interest.

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