CASE REPORT

**Neurological Paraneoplastic Syndromes:**
the Early Diagnosis of Lung Cancer

Andreea PAROSANU1,2, Ana-Maria POPA1,2, Cristian IACIU1,2, Mihaela OLARU1,2, Cristina ORLOV-SLAVU1,2, Horia COTAN1,2, Miruna STANCIU1,2, Radu VRABIE1,2, Cornelia NITIPIR1,2

**Abstract**

Paraneoplastic syndromes of the nervous system are rare disorders, strongly linked with lung cancer. This report aims to explore the challenges in the diagnosis and treatment of a patient with early-stage small cell lung cancer and neurological manifestations as initial clinical symptoms.

**Keywords:** neurologic paraneoplastic syndromes, small cell lung cancer, cancer management.

**Rezumat**

Sindroamele paraneoplazice sunt manifestări indirecte ale cancerelor, fiind secundare reactivității încrucișate dintre antigenele tumorale și sistemul imun.

Cazul prezentat subliniază importanța diagnosticului diferențial al sindromelor paraneoplazice și identificarea promptă a sursei de neoplazie.

**Cuvinte cheie:** sindroame paraneoplazice neurologice, cancerul pulmonar cu celule mici, tratament oncologic.

---

1Discipline of Oncology, “Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
2Clinic of Oncology, Elias University of Medicine and Pharmacy, Bucharest, Romania

**Corresponding author.**

Cristina ORLOV-SLAVU, Discipline of Oncology, „Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania. E-mail: cristina.slavu@drd.umfcd.ro

Ioana-Miruna STANCIU, Discipline of Oncology, „Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania. E-mail: ioana-miruna.stanciu@drd.umfcd.ro
BACKGROUND

In 1949, 2 French professors, Guichard and Vignon, used the first time for the term paraneoplasia. They recognized that certain symptoms were not attributable to direct tumor invasion or compression, in the case of multiple neuropathies and advanced neoplasm of the uterus.1

Currently, paraneoplastic syndromes are described as complex disorders associated with cancer, but which are not directly caused by the primary or metastatic tumors, or as a consequence of the treatment.

These conditions are induced by immune cross-reactivity between tumor antigens and normal host tissues. Therefore, these syndromes are classified by the organ affected; the most common syndromes are: endocrine, neurological, hematological, renal, cardiovascular, and gastrointestinal.2,3

Neurologic paraneoplastic syndromes are quite rare (occurring in fewer than 1% of cancer patients), and the most common type of cancer-related to paraneoplastic syndromes is lung cancer (approximately 10% of cases).4-7

The medical advances improved the understanding of the etiological mechanisms of these syndromes, their clinical implications, and possible therapeutic interventions.

The diagnosis of these diseases is particularly based on clinical suspicion, analyzing the relationship between neurological features and the presence of a specific type of tumor.

We reported a case of a 59-year-old man with the neurological paraneoplastic syndrome and early diagnosed small cell lung carcinoma.

INVESTIGATIONS

A full workup was conducted, including blood tests and imaging scans. Laboratory assays revealed normal blood counts, a high level of C-Reactive Protein, and normal renal and liver function. HIV and hepatitis were all biochemically excluded.

The patient had normal findings in studies of cerebrospinal fluid. The tests for classical paraneoplastic antibodies in serum and cerebrospinal fluid were negative and included anti-Hu, anti-Yo, anti-Ri.

The brain imaging including a CT and IRM only suggested diffuse cerebral atrophy. There were no lesions compatible with stroke, cerebellar, or trunk abnormalities.

A cardiovascular ultrasound was also performed, describing mild mitral, tricuspid, and aortic insufficiency.

Not understanding the cause of these neurological symptoms, raised the hypothesis of an autoimmune disorder. Therefore, plasmapheresis was considered medically necessary. The patient underwent one plasmapheresis procedure, with slightly clinical improvement.

To complete de imaging evaluation, the thoracic, abdominal, and pelvic CT scan showed a small 9/7 mm nodule in the right lower lobe of the lung, and a 26/30 mm lymph node in the ipsilateral pulmonary hilum, very close to the right pulmonary artery.

CASE PRESENTATION

A 59-year-old man was referred to the neurology department, in June 2020, for difficulty of coordinating movements and dysarthria. The patient reported the onset of his symptoms over the previous 4 weeks with a progressive inability to perform routine tasks.

On examination, the patient presented with a slightly left facial asymmetry, decreased proximal and abolished distal osteotendinous reflexes and tetra-ataxia.

The patient had a personal history of active smoking 35 (pack-years), diabetes mellitus type 2 complicated with peripheral neuropathy, and a previous right iliac vein thrombosis. He also reported an episode of severe acute pancreatitis in 2018 and taking oral hypoglycemic medication and oral anticoagulant.
Neurological Paraneoplastic Syndromes: the Early Diagnosis of Lung Cancer

Figure 1. CT scan at diagnosis

A bronchoscopy with a transbronchial lung biopsy was performed, and histological examination revealed small cell lung carcinoma.

According to the eighth edition, TNM stage classification for lung cancer the primary tumor was staged as cT1 cN1, stage IIB, and in August 2020, the tumor board decided to start concurrent chemoradiotherapy with Cisplatin and Etoposide. (8)

In November 2020, after 6 cycles of chemotherapy with concurrent radiotherapy, the follow-up assessment reported significant lymph node shrinkage (10/9 mm from 26/36 mm), the disappearance of the nodule from the right lower lobe of the lung, without any new lesions.

Figure 2. CT scan after therapy

After finishing the chemotherapy courses, and taking into account the patient’s request also, the tumor board decided to follow up the patient.

All neurological symptoms improved during the first weeks of oncological therapy, and resolved before the end of the treatment.

The last CT and IRM scan, in March 2021, indicated a new infracentimetric pancreatic mass and lymph node progression (from 30/25 mm from 10/9 mm). The tumor board decided to initiate a second therapy line.

DISCUSSIONS

Lung cancer is the leading cause of cancer-related death in the world, and small cell lung cancer occurs in approximately 15% of cases. Despite significant developments in oncological management, over 75% of patients have advanced disease at the time of diagnosis. The presence and early diagnosis of paraneoplastic syndromes can be helpful in this context, in diagnosing initial stage and highly treatable tumors.

When to suspect a paraneoplastic syndrome? How to diagnose it? How to treat it?

Symptoms of neurological paraneoplastic syndromes usually begin before tumor detection (4-6 months before the clinical appearance of cancer) and may prompt a search for occult malignancy. In addition, there is no association between the severity of paraneoplastic symptoms and the stage of the tumor.

In our patient, small cell lung carcinoma was diagnosed much earlier than usual and with no direct symptoms of the malignancy at presentation.

The diagnosis of paraneoplastic syndromes of the nervous system required ruling out the non-neoplastic pathologies. We took a full medical history and we performed a range of tests to see what was causing the symptoms.

Stroke, vascular injury, or lesions of the brain were the first ones to be ruled out, due to the high frequency. Therefore, an extensive diagnostic process began.

Complete brain imaging, including magnetic resonance imaging (MRI) and computed tomography (CT) did not find out images that could reveal any lesions of the brain; the electroencephalogram and nerve conduction velocity test were also normal.

The workup further excluded virus infections, dyselectrolytemia, or vitamin deficiency.
HIV is a neurotrophic virus, and at all stages of infection may cause many different conditions that affect the nervous system\textsuperscript{12}.

Hepatitis also exhibits a wide range of extrahepatic complications. For example, hepatitis C virus infection can cause in the context of mixed cryoglobulinemia, sensory and motor peripheral neuropathy, and even stroke\textsuperscript{3}.

Hepatitis virus E has also been associated with several neurological symptoms, including Guillain-Barré syndrome, and meningoencephalitis\textsuperscript{14}.

These possible differential diagnoses have all been excluded, because simple serologic tests for HIV, HVC, HVB, HVD, HVE antibodies were negative.

Intoxication with alcohol or drugs can be a major toxic cause of ataxia\textsuperscript{15}.

After detailed anamnesis, toxicologic screening, and wide laboratory investigation, we excluded toxic, or metabolic disorders.

A variety of autoimmune conditions can present with isolated nervous system involvement\textsuperscript{16}.

Autoimmune disorders and hypothyroidism were also excluded by negative biomarkers and antibodies.

When central nervous tumors and other vascular, metabolic or autoimmune causes have been excluded, the patient was considered to suffer from a paraneoplastic neurological syndrome. This group of syndromes is highly diverse, but the identification of antineuronal antibodies can confirm the paraneoplastic neurological origin of the syndrome\textsuperscript{17,18}.

Curiously the most commonly antibodies associated with several paraneoplastic neurological syndromes (anti–Hu, anti–Yo, anti–Ri) were negative in serum and cerebrospinal fluid.

Though, small cell lung cancer is the most common cancer associated with paraneoplastic syndromes. Clinical improvement and symptom resolution during therapy, also supported this diagnosis.

Therapeutic plasma exchange is an extracorporeal blood purification procedure that is designed to remove noxious molecules such as antibodies and immune complexes\textsuperscript{19}.

Therefore, our patient underwent one plasmapheresis procedure, with slightly clinical improvement.

And fortunately, in our case, the simple thoracic investigation describing a tumor mass, and the normal brain examination established the diagnosis.

The overall approach to cancer management

Due to its particularities, this case was a challenge and required to be managed by a multidisciplinary team, including neurological, radiological, surgical, neurological, and oncological evaluation.

After the radiological and histopathological assessment, the patient was classified according to AJJC 8th ed. in limited-stage IIB.

In limited-stage IIB small cell lung cancer, systemic chemotherapy with concomitant radiotherapy, has been established as standard of care. The good performance status was also an important part of cancer care that supported this indication.

Four cycles of systemic therapy with Cisplatin (60 mg/m\textsuperscript{2} on day 1) and Etoposide (120 mg/m\textsuperscript{2} in days 1, 2, 3) with concurrent radiotherapy were recommended. It should be noted that concomitant doses of chemotherapy were the same as used in the systemic treatment of metastatic disease and were sufficient to correct paraneoplastic syndrome. The patient did not experience any side effects or other allergic reactions that would compromise his quality of life.

The response assessment after completion of definitive radio-chemotherapy showed significant tumor shrinkage.

The successful results of this small cell carcinoma also favorably affected the course of neurological paraneoplastic syndrome, with the disappearance of the symptoms.

<table>
<thead>
<tr>
<th>Differential Diagnosis</th>
</tr>
</thead>
</table>
| Encephalitis            | Normal brain MRI, CT and EEG  
| Stroke                 |  
| Tumor                  |  
| **Toxic, metabolic disorders.** | Excluded by a toxicologic screening and a wide laboratory investigation  
| Virus infections (VZV, EBV, HIV, hepatitis C, B, E) | Normal serologic tests  
| **Immune-mediated disorders** | Negative biomarkers and antibodies (including anti–Hu, anti–Yo, anti–Ri)  

Table 1. Differential diagnosis
CONCLUSIONS

In conclusion, we suggest that, when a neurologic disorder of unknown etiology is present, the possibility of an occult carcinoma should be considered. The present case report suggests that cancer-associated with neurological paraneoplastic syndromes may be diagnosed at an early stage and has an indolent disease course. But, the treatment of paraneoplastic syndrome is also oncological. And the key to successful management is patient-centered therapy.

References