Narrative Review
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Paraneoplastic Syndromes of the Nervous System in Patients Suffering from SCLC. A Review of the Recent Literature

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Abstract

Background. Paraneoplastic Neurological Syndromes (PNS) constitute a heterogeneous cluster of disease manifestations related to various cancers. Small Cell Lung Cancer (SCLC) is strongly related to PNS. This narrative review conducted a survey in the available PubMed literature to highlight the appearance of PNSs in SCLC cases and discuss published research highlights on the subject so that general practitioners can be acquainted with the medical phenomenon present in SCLC patients. **Method.** A narrative review of the medical literature was conducted as documentary informative research in the PubMed medical database, combined with a survey of the online e-library Google Books. The key words used were: "Paraneoplastic Neurological Syndromes" and "Small Cell Lung Cancer". **Results.** Paraneoplastic syndromes are related to the presence of a malignancy and are not secondary to treatment. Paradoxally, both a malignancy and its therapeutic approach may cause a series of PNSs. Paraneoplastic cerebellar degeneration, motor neuron disorders, peripheral neuropathies, hyponatremia, and syndromes such as myasthenic Lambert-Eaton, ectopic Cushing's, Stiffman, and Opsoclonus-myoclonus syndrome may also appear in SCLC cases. Diagnosis follows specific criteria, and they are caused by tumor-directed antibodies known as onconeural antibodies. Immunosuppressants, intravenous immunoglobulins, plasma exchange, rituximab, cyclophosphamide, azathioprine, and tocilizumab could be considered as treatment agents. **Conclusions.** Most patients demonstrate poor PNS treatment results with common relapse. The time for beginning treatment of PNS is discussed. A multidisciplinary team is needed for potentially earlier diagnosis and PNS improvement, better prognosis, and increased overall survival and quality of life.

Key Words: Immune Response ▪ Neuro-Oncology ▪ Onconeural Antibodies ▪ Multidisciplinary Team.

Introduction

Paraneoplastic syndromes of the nervous system represent a group of uncommon disorders that develop in some people who have cancer. It is believed that they are a neurological response, which has been demonstrated in studies of lung malignancies in recent years (1). The pathophysiology of paraneoplastic neurological syndromes involves a complex interplay between the immune and nervous systems. While the exact mechanisms vary depending on the specific syndrome, common features have been observed, such as the immune response, which is believed to arise from the antigens expressed by both the tumor and the nervous system. These antigens are often referred to as onconeural antigens. In most cases, the immune system recognizes and eliminates cells expressing these antigens, but the acute and high volume production of tumor-directed antibodies, known as onconeural antibodies, dysregulates homeostasis. This cross-reaction results in the mistaken targeting of normal neural tissues, leading to neuronal dysfunction or damage. The cytotoxicity found in cells such as cytotoxic T cells, can infiltrate neural tissue in response to the presence of onconeural antigens.

The presence of such immune reactions may alter or disrupt normal neuronal function through various mechanisms, including blocking synaptic transmission, receptor function, induced

apoptosis, and inflammation within the nervous system, further contributing to neuronal dysfunction and tissue damage. Certain genetic factors may predispose individuals to developing PNS in response to specific tumors or immune triggers. However, the role of genetics in PNS is still not fully understood. Overall, the pathophysiology of PNS is multifactorial and involves a complex interplay between neuro- and tumor cells. Further research is needed to elucidate fully the underlying mechanisms and develop targeted treatments for these challenging disorders. Although this concept is still under survey, the fact that malignancy may cause the nervous system to produce various disorders such as torpor, stomach hyperactivity, swallowing difficulty, dementia, and motor misbalance has been mentioned in medical literature since the 18th century (2-3).

Small cell lung cancer (SCLC) is a malignant entity among the most aggressive lung tumors, known for its poor survival rates. Initially positive results of treatment are followed by a rapid development of drug resistance and fatal disease progression. Lung cancers remain the most common cause of cancer-related death in the world, while SCLC in the vast majority of cases causes relapse, with a 1-year survival rate of about 40% and a 5-year survival under 5%. SCLC, strongly related to tobacco smoking, accounts for 15-20% of all lung cancers, with an aggressive evolution, poor prognosis and limited treatment options. Paraneoplastic neurological syndromes (PNS) occur in about 0.1% of patients affected by cancer. Meanwhile, approximately 30% of SCLC patients present a serious neurological disorder during the evolution of their disease. Among them, 75% appear due to brain metastases, as these affect 24.8% of all patients with SCLC. However, a total of 25% are related to metastases in other areas than the brain, localized outside the central nervous system (1, 4). This narrative review aims to highlight the emergence of PNS in SCLC cases, and note opinions on the subject by surveying the recent medical literature, through an assessment and analysis of the already published material in a novel way.

Method

Reviews do not present new data, but do provide a summary of knowledge of what has already been published or presented on a subject. Narrative reviews constitute a type of literature synthesis partially framed as systematic, which implies a state-of-the-art, critical, and integrative review, by conducting a subjective examination and critique of the entire body of medical papers inside the database PubMed related to the subject in question (5). The search conducted for the sake of this narrative review included some informative documentary research inside the online library Google Books. The key terms used, were: "Paraneoplastic Neurological Syndromes" and "Small Cell Lung Cancer". Among the 466 articles found in the period from 1997 to 2024, 33 papers in English were included in this review. The title of the paper was examined, as well as full text availability. Furthermore, by reviewing the abstract, papers discussing exclusively SCLC and PNSs were included. We chose to use only the board term Paraneoplastic Nervous Syndromes due to its clinical significance.

Results

Although PNSs appear rarely and are manifested through complex clinical symptoms occurring in association with a tumor, SCLC association with them is more frequent. Some researchers have reported that the use of immunotherapy in SCLC cases is strongly related to a concomitant increase in autoimmune neurological syndromes (1). The main criterion for diagnosis of PNS is the absence of a direct trigger or compression. PNSs arise from tumor secretions of hormones, peptides or cytokines, or from immune cross-reactivity between malignant and healthy tissue (6). Paraneoplastic cerebellar degeneration is one of the most prevalent PNSs associated with SCLC (6, 7). Motor neuron disorders, peripheral neuropathies, hyponatremia and syndromes, such as myasthenic Lambert-Eaton, ectopic Cushing's and Stiffman were among the first to be recognized as PNS (5, 8).

Opsoclonus-myoclonus syndrome (Kinsbourne or Dancing Eyes Syndrome) may also appear in extremely rare cases (9). Opsoclonus-Myoclonus Syndrome, followed by the rapid progression of cerebellar ataxia, is the most common form of PNS in children, and is usually associated with neuroblastoma (10).

SCLC is equally prevalent among males and females, while the percentage of the elderly who suffer from it is increasing. Its main characteristic is its rapid response to chemotherapy and sensitivity to radiotherapy. However, due to its early treatment resistance the 5-year overall survival is <10% (11). Various poor prognostic factors in SCLC include impaired performance status, weight loss, older age, male sex, elevated lactate dehydrogenase, and low sodium. Due to its rapid progression and the early treatment resistance, combined with the long term toxicity of chemotherapeutic and radiotherapy methods, neurocognitive decline and PNS soon emerge to further complicate disease progression (12, 13). PNS have an immune-mediated pathogenesis that is supported by the frequent presence of specific neuronal antibodies. This involvement of the nervous system may provoke reactions which mimic infections, autoimmune non-paraneoplastic diseases, other tumors, neurodegenerative disorders, general toxicity, or metabolic alternations. Specific antibodies may be detected and provide for the possible identification of PNS, but the majority of SCLC PNS cases are difficult to diagnose (14-16). To aid diagnosis of PNS, a cluster of criteria was formed in 2004, and updated with a clinical scoring system in 2021 (Table 1) to increase diagnostic accuracy in complicated clinical cases. In the 2021 update, diagnostic certainty was divided into 3 levels (possible, probable, and definite PNS), taking into consideration the coherence between the clinical phenotype, antibodies, and the cancer (17-18). Even in cases demonstrating detectable onconeural antibodies, the suggestion is that a diagnosis of PNS is definite only after other possible causes of a particular neurological syndrome have been excluded (19). Radiology and nuclear medicine neuroimaging (CT, MRI, 18FDG-PET) and electroencephalography are only used for PNS that affect the central nervous system to differentially diagnose and exclude metastasis or meningeal malignancy, and other diseases, such as encephalitis (14). Meanwhile, the broad differential diagnosis for PNS renders their recognition a challenge at

Table 1. 2004 Criteria for PNS and 2021 Criteria Scoring Update

N/A	2004 Criteria		2021 Scoring Update
	Definite PNS	Possible PNS	Definite, Probable, Possible, Non-PNS
1	A classical post cancer syndrome which develops within five years of the neurological onset diagnosis	A classical syndrome with no onconeural antibodies, no cancer but with a high risk of an underlying malignancy	-
2	A non-classical post cancer treatment syndrome which later resolves or significantly improves, provided that the syndrome is not susceptible to spontaneous remission	A classical or non-classical neurological syndrome with partially characterized onconeural antibodies detected and no cancer manifestation	High-risk antibodies, Intermediate risk antibodies, Lower risk antibody Negative for antibodies
3	A non-classical syndrome with onconeural antibodies (well characterized or not) detected, while cancer develops within a five-year period of the onset and diagnosis of the neurological disorder	A non-classical syndrome with no onconeural antibodies detected and cancer appearance within a two-year period of the onset of diagnosis of the neurological disorder	Cancer presence plus +/- antibodies Non-cancer, a two-year period of follow-up No cancer found within a two-year period of follow-up
4	A classical or non-classical neurological syndrome with well characterized onconeural antibodies detected (anti-Hu, Yo, CV2, Ri, Ma2, amphiphysin) and no cancer manifestation	-	-

N/A=Number of Answer; PNS= Paraneoplastic Neurological Syndromes.

the very least. Infections, toxic and metabolic etiologies, brain metastases, leptomeningeal disease, spinal cord and nerve root compression, and the adverse effects of treatments (radiation therapy, platinums, taxanes, vinca alkaloids) may all mimic PNS (20).

Cancer treatment itself and/or cortico-therapy are used to combat PNS. Most PNS patients with classical onconeural antibodies do not improve, with the exception of some cases which demonstrate some improvement due to the immediate initiation of treatment after the onset of symptoms. Even though in the majority of the PNS cases with onconeural antibodies immunosuppressants, intravenous immunoglobulins and plasma exchange/cyclophosphamide are used, they have showed no statistically significant therapeutic results, while about 30% to 50% remain severely disabled. On the other hand, PNS patients with onconeural surface-binding antibodies have responded to immunosuppressive treatment. If first-line immunosuppressive agents do not show results, then rituximab, cyclophosphamide, azathioprine, tocilizumab (anti-interleukin-6 antibody) should be considered as options for escalation of treatment. Although some responses do actually occur, in 15% to 39% of the cases where a response occurred, there was a subsequent relapse (21-23).

Discussion

An estimated 1% to 7.4% of patients with cancer will develop PNS, while up to 30% of those with SCLC will manifest it (24). Among the cluster of PNS disorders related to SCLC, Lambert-Eaton syndrome may signify this type of cancer (25). Paraneoplastic motor neuron disease may rarely appear in SCLC, but when it does, it is usually related to the SCLC. Sensory neuronopathy, cerebellar ataxia and/or limbic encephalitis, signify SCLC. Among them, encephalitis is the most common manifestation of a PNS (26). Although sex is referred to as a non-indicating factor, various reviews note that male sex is prevalent (18). PNS in patients with lung cancers mainly progress with malfunctions in endocrine, neurological, dermatological and rheumatological regulation. Meanwhile, the less common PNSs manifest in hematological and ophthalmological syndromes. PNSs are detected before a cancer is diagnosed in 80% of cases (24, 27). Rapid PNS diagnosis may indicate an association with a cancer type, resulting in an opportunity for early stage cancer diagnosis and intervention (24).

There is a debate about whether to allow a PNS to progress until the diagnosis of the basic disease is made, or to treat it immediately. Moreover, there is an ongoing discussion as to whether more aggressive early immunosuppression is needed to reduce PNS relapse rates. There are still no definitive study results in the literature (21). There are reports about patients experiencing a worsening of the symptoms after the initiation of PNS immunotherapy (28). Various pathologies may appear as PNS, such as amyotrophic lateral sclerosis, or a PNS may appear soon after the therapeutic intervention (27). Moreover, a report exists of a durvalumab-related PNS, with the development of paraneoplastic myelitis after immune activation by durvalumab (28). As neurology is implicated, pregabalin and antidepressant agents are used to improve the patient's numbness in some cases (29). The heterogeneous group of PNS manifestations signals the need for interdisciplinary/multidisciplinary interaction between oncology, pathology, neurology, radiology, nuclear medicine, surgery, endocrinology, nursery, physiotherapy and palliative care, for prognosis and symptom stabilization. This approach has been highlighted in recent decades (30, 31). A study conducted by Graus et al. in 1997 stated that cases of SCLC presenting with anti-Hu antibodies are more likely to achieve a complete response after treatment than those without. This observation, that anti-Hu antibodies recognize the antigens expressed by neurons and SCLC, raises the possibility that treatment of PNS with immune modulation may surprisingly result in further cancer progression.

This hypothesis, however, has not yet been clinically demonstrated (19, 32). Various PNSs are allied with a series of antibodies against both central nervous (CVS), or peripheral nervous system

(PNS) targets. These sets of antibodies may be broadly divided into those which set their targets intracellularly finding neuronal antigens and those targeting neuroglial cell surface antigens. In the cases when more than one set of CNS autoantibodies are detected, the likelihood of a malignancy is increased. The presence of anti-Hu antibodies increases the possibility of a SCLC up to 83%. Meanwhile, reports noted that when anti-Hu antibodies co-exist with either Collapsin response-mediator protein-5 antibody, or P/Q type voltage gated calcium channel antibodies, the likelihood of SCLC rises up to 100% (33).

In another aspect of PNSs in SCLCs, a PNS may perform as a surrogate marker for clinically significant patient defense against the tumor. This intriguing theory may represent a potential rationale for immunotherapy, while at the same time immunotherapy may also provoke a PNS as a side defect. This dilemma should always be in physicians' minds, even though most studies report no neurological toxicity, recording patients' deaths due to pneumonitis and disease progression. Some anecdotal reports on spontaneous regression of SCLC cases without treatment, in patients with onconeural antibodies, may only signify that an effective host immune response was directed against both the cancer and the nervous system, altering the course of the malignancy, without however saving the patients from a fatal outcome (34).

It is nowadays clear that PNSs occasionally appear with multifocal involvement and plural antineuronal antibodies which can be found in a single patient with SCLC, testifying of a heterogeneous autoimmune mechanism, resulting in strong neurological involvement (35). Still, it seems that PNSs are still a medical mystery among physicians, requiring better knowledge and more research (30, 31).

Strengths and Limitations

Those syndromes may be well known among neurologists and oncologists, however, they constitute a riddle for the general practitioner, who should be aware of PNSs and bear in mind that PNSs and SCLC are closely related in some cases. Although this review presents the not fully understood neurological entities in SCLC, it does not include all the medical literature as in the case of a systematic review, remaining simple in the terms researched and avoiding fully presenting phenotypes and categorization as indicated in various other studies (22).

Conclusions

Advances in recent studies have directed health professionals towards a greater understanding of PNS development, and improved diagnostic tools and therapeutic options. PNS awareness in SCLC may promote earlier diagnosis, to potentially improve patients' overall survival and prognosis. Their heterogeneous pathophysiology, the continuous discovery of antibodies, patients' recovery failure, and the mysterious triggers of the immune system require further PNS-related research.

What Is Already Known on This Topic:
Paraneoplastic syndromes are related to the presence of a malignancy and are not secondary to treatment.

What This Study Adds:
This study gives a review of the recent developments in the study of paraneoplastic syndrome in patients suffering from SCLC.

Authors' Contributions: Concept and design: EG and TZ; Acquisition, analysis and interpretation of data: EG and TZ; Drafting the article: EG, TZ and EM; Revising it critically for important intellectual content: EG, TZ and EM. Approved final version of the manuscript EG, TZ and EM.

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