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Peripheral and central nervous system involvement in lung cancer

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ABSTRACT

It has been shown that 42% of lung cancer patients are diagnosed with cancer-related neurological complications either at initial presentation or at follow-up. Understanding the topic thoroughly bears prominent importance in decent clinical approach of both thoracic oncology and neurological sciences. The purpose of this review is to summarize the general knowledge obtained so far in this field while trying to inform the readers about current literature and underline the goals of multidisciplinary approach of neurological complications of lung cancer. Since the metastatic complications of lung cancer are well known, the non-metastatic complications and mostly paraneoplastic diseases will be the subject of focus in this review. [Turk J Cancer 2007;37(1):5-10]

KEY WORDS:

Lung cancer, neurological complications, paraneoplastic diseases

INTRODUCTION

It is well-known that lung cancer may cause central and peripheral nervous system involvement. Apart from metastases there may also be non-metastatic effects of cancer on the nervous system and remote effects of cancer are a major part of these. It has been shown that 42% of lung cancer patients are diagnosed with cancer-related neurological complications either at initial presentation or at follow-up and metastatic disease (intracranial and spinal lesions) and paraneoplastic syndromes are the most important of these complications (1).

METASTATIC EFFECTS OF LUNG CANCER ON NERVOUS SYSTEM

In addition to brain metastases, spinal and leptomeningeal metastases may be seen, but these are relatively rare (Figures 1, 2). Metastases of peripheral nervous system have a lower incidence than central nervous system metastases. Pancoast tumor (apical tumor of lung) metastasizing to the brachial plexus is a well-known example.

NON-METASTATIC EFFECTS OF LUNG CANCER ON THE CENTRAL AND PERIPHERAL NERVOUS SYSTEM

These may involve mainly vascular disorders such as hypocoagulability resulting in hemorrhage or hypercoagulability (infarction), side effects of therapy such as surgery, irradiation, chemotherapy and remote effects on brain and cranial nerves, spinal cord and dorsal root ganglia, peripheral nerves, neuromuscular junction and muscle (2).

Paraneoplastic syndromes (PNS)

PNS are non-metastatic syndromes, particularly remote effects that are not associated with cancer therapy, coagulopathy, infection or metabolic causes (3). Main paraneoplastic syndromes which may be the consequence of lung cancers comprise the following: Cerebellar degeneration (particularly small cell lung cancer), subacute sensory neuropathy and encephalomyelitis most of which have small cell lung cancer (SCLC) (4,5). These patients usually have anti-Hu antibodies in their serum (6).

Paraneoplastic cerebellar degeneration (PCD)

Paraneoplastic cerebellar degeneration (PCD) is the most frequently seen paraneoplastic syndrome affecting the brain. PCD is most commonly associated with cancers of the ovary, breast, and lung. The anti-Purkinje cell antibodies (anti-Yo) that specifically damage the Purkinje cells of the cerebellum are found in the patient's serum and cerebrospinal fluid. The typical presentation of PCD includes limb and truncal ataxia, often along with dysarthria. On some occasions PCD may be the presenting sign of occult malignancies (7).

Paraneoplastic limbic encephalitis (PLE)

PLE may occur in isolation or in association with encephalomyelitis or sensory neuronopathy. PLE is considered as a rare complication of SCLC (8). Cognitive decline as well as personality and mood changes can be seen in limbic encephalitis (9). PLE may be a rare neurological consequence of a variety of cancers, most commonly originating from lung, breast and testis. The etiology is believed to be immune-mediated, caused by tumor-induced autoimmunity launching an attack against one's own central nervous system (10). The patient may present with amnesia, depression, anxiety, seizures and/or personality changes. The onset of these symptoms may precede the diagnosis of malignancy by a period of up to 2 years. The malignancy may be occult and unless the syndrome is recognized, it may fail to be detected. The diagnosis of PLE is suggested by the clinical picture, Magnetic Resonance Imaging (MRI) evidence of mesial temporal lobe abnormality and cerebrospinal fluid (CSF) abnormalities such as the presence of oligoclonal bands. It may be further supported by the presence of paraneoplastic antibodies in the serum. Immunosuppression has been tried in some cases but memory impairment is often irreversible. There are several case reports in the literature of paraneoplastic limbic encephalitis but few emphasize the resulting impact that this may have on the patient's quality of life and their care-givers (10).

Paraneoplastic limbic encephalitis is a challenging and rare neurological syndrome that demands joint management by neurologists, oncologists and the palliative care team. Its prolonged and uncertain course causes distress to the patient but even more so to their care-givers. Early recognition of the syndrome is important as this will impose a thorough investigation for the responsible malignancy and consequently its early detection and management (10).

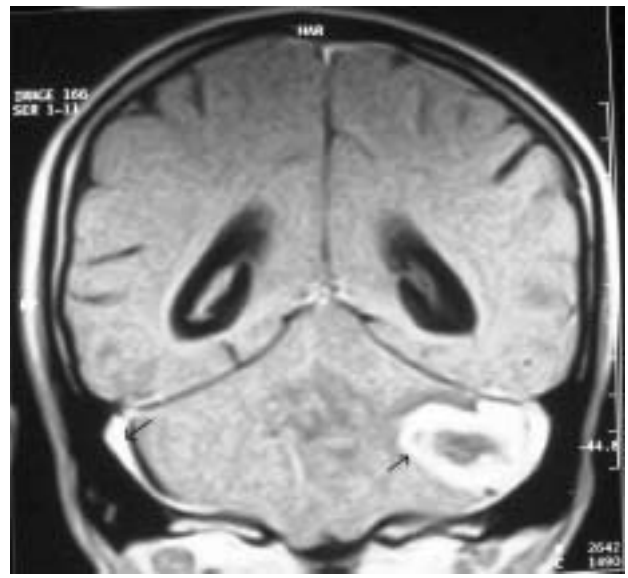

Fig 1. MRI image of contrast-enhanced infratentorial and posterior dural brain metastasis in a patient with non-small cell lung cancer (The arrows show the lesions)

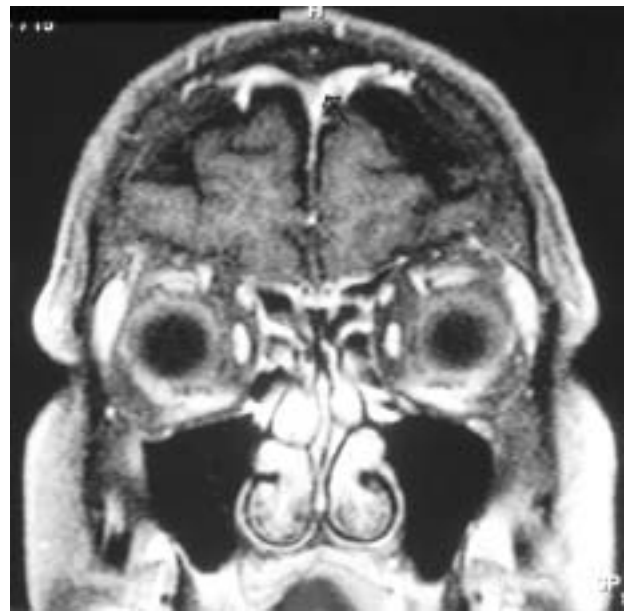

Fig 2. MRI image of leptomeningeal metastasis in non-small cell lung cancer (The arrow shows the lesion)

Subacute sensory neuronopathy

In subacute sensory neuronopathy, symptoms typically begin before the cancer is identified, with dysesthetic pain and numbness in the distal extremities or occasionally in the arms, face or trunk. The symptoms may be asymmetrical, all sensory modalities may be affected but motor function is preserved. Sensory ataxia is usually prominent. A typical sensory neuropathic pattern is seen in EMG (electromyography) (2,9).

Anti-Hu-associated paraneoplastic sensory neuropathy (PSN) is considered an autoimmune disorder involving both cell-mediated and humoral mechanisms (11). However, peripheral nerve microvasculitis in association with anti-Hu PSN is extremely rare, and only three cases have been reported in the literature (12). Generally, the presence of low titres of anti-Hu antibodies is associated with early stage, good response to chemotherapy and improved outcome (13). It is thought that anti-Hu antibodies play an important role in tumor suppression (14). Despite the favourable survival of these patients, the treatment of PSN generally remains unsatisfactory. Paraneoplastic encephalomyelitis (PEM) and paraneoplastic sensory neuronopathy (PSN) are clinically well-defined, frequently overlapping, and almost always associated with anti-Hu antibodies (i.e. type 1 anti-neuronal nuclear autoantibodies) and small-cell lung cancer (6,15). The etiology of PEM/PSN syndrome and other paraneoplastic syndromes is still unknown. The PEM/PSN syndrome is characterized by a high titer of anti-Hu IgG antibodies in the serum and CSF, the presence of inflammatory infiltrates of T cells and B cells in the nervous system, and the existence of a tumor, usually SCLC (16,17). These characteristics suggest that a mechanism mediated by the humoral or cell-mediated immunities may play a central role in the pathogenesis of this disease. PSN is sometimes manifested by cranial nerve involvement, seen as trigeminal, facial, or abducens nerve palsies (15). However, only a few cases of PSN with multiple cranial nerve involvement have been reported.

Neuromuscular junction syndromes

The neuromuscular junction syndromes due to lung cancer are Lambert-Eaton myasthenic syndrome (LEMS) and myasthenia gravis (MG). To compare the clinical features of patients with LEMS associated with carcinoma, with patients having LEMS but no cancer, reports on LEMS patients were analyzed systematically (18). Cancer was detected (CD group) in 62% of the 227 included cases. This CD group showed a male predominance (70%). No sex difference was found in patients in whom no cancer was detected (NCD group). Median age at onset of LEMS in the CD group was higher than in the NCD group (58 and 49.5 years, $p<0.01$). Median interval between onset of symptoms and diagnosis of LEMS was longest in NCD cases ($p<0.001$). CD patients had additional immunological disorders less frequently than NCD cases (6 and 27%, $p<0.001$). Symptoms distinguishing the CD group from the NCD group were weight loss ($p<0.001$) and need for prolonged artificial ventilation after anesthesia ($p<0.05$). This analysis showed significant differences between CD and NCD cases of LEMS. The male predominance and higher age at onset in patients with a tumor probably reflected the characteristics of patients with SCLC. The high frequency of additional immunological disorders in patients without malignancy, together with the younger age at onset suggested a similar etiology as other non-paraneoplastic autoimmune diseases (18).

Lambert–Eaton myasthenic syndrome (LEMS)

LEMS is an autoimmune disorder of the presynaptic neuromuscular junction caused by autoantibodies to the voltage-gated calcium channels situated at the nerve terminus (19). About 60% of patients with LEMS have small cell lung cancer while the incidence of LEMS in SCLC is 3% (2,20).

LEMS is characterized by lower extremity proximal weakness and fatigability. Bulbar musculature is not involved. MG usually affects ocular, bulbar and respiratory muscles more than extremity muscles. In contradistinction to LEMS patients, myasthenic patients grow weaker with exercise (2,21). LEMS is related with an antibody that reacts with the PQ-type voltage gated calcium channel. The same PQ-type voltage-gated calcium channels are found in small-cell lung cancers, a fact which explains the relationship between LEMS and SCLC (22).

Other neuromuscular paraneoplastic diseases

Brainstem encephalitis, paraneoplastic non-necrotizing myelitis, autonomic neuropathy, opsoclonus-myoclonus,

anti-Ri syndrome, visual loss due to encephalomyelopathy, subacute sensory-motor neuropathy and neuromuscular junction syndromes may be the result of lung cancers (2).

Polymyositis and dermatomyositis are common inflammatory muscle diseases and both of them may be paraneoplastic, although dermatomyositis patients are more prone to cancer (23,24). Muscle cramps, acquired neuromyotonia, stiff person syndrome and shoulder-hand syndrome are other paraneoplastic muscle disorders which may also be seen in lung cancer patients (2,25). Many of the diseases mentioned above mostly need electrophysiological differential diagnosis under the guidance of a neurologist, preferably an electromyographer.

Opsoclonus

Opsoclonus is a dyskinesia consisting of involuntary, arrhythmic, chaotic, multidirectional saccades, without intersaccadic intervals. In adults, the most common causes of opsoclonus include parainfectious brainstem encephalitis, paraneoplastic, and metabolic–toxic states. In many cases, the cause is never established. Such saccadic oscillations differ from nystagmus in that the phase that takes the eye off the target is always a saccade, not a smooth eye movement. In contrast to ocular flutter, which consists of horizontal back-to-back saccades, opsoclonus is multidirectional. The pathogenesis of opsoclonus is uncertain. Damage to omnipause cells in the brainstem or to the cerebellum has been implicated. Computer simulation of a saccadic system model indicated that damage of afferent projections to the oculomotor region of the fastigial nucleus could generate opsoclonus (26).

Paraneoplastic neuromyotonia

Neuromyotonia or 'syndrome of continuous muscle fiber activity' is characterized by muscle stiffness at rest and delayed muscle relaxation after a voluntary contraction resembling myotonia. Neuromyotonia is due to hyperexcitability of peripheral motor nerves. Autoimmune etiology for neuromyotonia has been described with evidence for autoantibodies directed against voltage-gated potassium channels of peripheral nerves in some patients (27,28). The autoantibodies may be associated with neoplastic lesions.

Paraneoplastic myoclonia

Myoclonia are characterized by sudden involuntary movements caused by contractions of muscle groups or groups of muscle fibers. In paraneoplastic opsoclonus-myoclonus syndrome, some patients show antibodies directed against 55 and 80-kDa antigens on neuronal nuclei called anti-Ri-antibodies. The association of neuromyotonia, sensory neuropathy, cerebellar symptoms and myoclonia with anti-Hu antibodies in a patient with SCLC was reported by Toepfer et al (29).

The shoulder-hand syndrome

The shoulder-hand syndrome is described by many authors as a sequela of myocardial infarction, hemiplegia and cancer of the lungs. The syndrome evolves in a form that resembles the post-traumatic algodystrophies. Pain, stiffness, and tenderness of the shoulder with limited movement, indistinguishable from capsulitis, are usually the first symptoms, and these sometimes progress to swelling, pain, stiffness and discoloration of the hand fingers. The mechanisms of the syndrome probably involve the central nervous system rostrally to the spinal cord as the syndrome is never seen in tetraplegic patients. Damaged afferents may activate sympathetic efferents to well-defined areas. The fact that the elbow is not involved may be only apparent. In fact, the other diseases such as tennis elbow, pain of the hand is very often accompanied by latent myofascial trigger points of the elbow (25).

ANTIBODIES SUGGESTED FOR PNS

The detection of onconeural antibodies has been very useful in helping to define the paraneoplastic etiology of a given neurological syndrome. The presence of anti-Hu antibodies strongly supports a diagnosis of paraneoplastic neurological syndrome associated with SCLC (30). Anti-Hu reacts with a 35-40 kDa neuronal nucleoprotein. Subacute sensory neuronopathy (SSN) and paraneoplastic encephalomyelitis (PEM) are known paraneoplastic complications associated with anti-Hu antibodies (31,6). Recently neoplastic gastrointestinal pseudo-obstruction and LEMS in association with anti-Hu antibodies were described (32).

Gangliosides may act as onconeural antigens in paraneoplastic neuropathies in some lung cancers (33) Myelin glycolipids may also be the target of antibodies in peripheral paraneoplastic nervous system disorders (34). Some SCLCs produce peptide hormones such as ADH (antidiuretic hormone) and thus cause syndrome of inappropriate ADH secretion (35).

Onconeural antibodies are detected in many laboratories by screening of sera on frozen sections of rat or mouse cerebellum (36). Positive immunoreactivities are usually confirmed by immunoblot of recombinant proteins or neuronal homogenates. Sera from patients with SCLC, the most common tumor associated with paraneoplastic neurological syndromes (PNS), sometimes harbor antibodies against neural antigens that have not previously been recognized as associated with PNS (37). When this happens, it is important first to establish whether the antibody is related to the presence of a specific type of cancer, and second to investigate whether the antibody is associated with a particular PNS. Even if the antibody is not directly related to the immune response that causes a PNS, it may indicate the presence of an underlying cancer undiagnosed at the time of the antibody determination. Very recently, a new antibody called anti-glial nuclear antibody (AGNA) has been described in patients with PNS and SCLC and it has been shown that the antibody is a marker for SCLC (38). AGNA has been initially identified in 24 sera by immunohistochemistry on rat cerebellum. AGNA positive sera have showed a characteristic nuclear staining of the Bergmann glia in the Purkinje cell layer. This antibody is thought to be helpful in the diagnosis of SCLC-related PNS, particularly the LEMS (38).

The authors concluded that the recognition of AGNA was helpful since this antibody was found in PNS associated with SCLC, particularly LEMS, in which other onconeural antibodies were absent (38).

THERAPEUTIC APPROACH FOR PNS

Lung cancer has the highest incidence of PNS. PNS management requires specific measures such as presence of anti-neuronal antibodies which strongly indicate that a neurological syndrome is paraneoplastic (39,40). Paraneoplastic syndromes of lung cancers should be treated by treating the lung cancer. Symptomatic medications may also be needed in many of them. Plasmapheresis is being used with considerable frequency in the management of malignant and non-malignant disorders. It has been useful in the management of hyperviscosity and occasionally of paraneoplastic syndromes (41).

A thorough neurological examination and diagnostic testing are essential for identifying lung cancer related neurological disorders, which may sometimes become diagnostic challenges. Multidisciplinary approach is highly needed both in the diagnostic and therapeutic approaches.

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