1. Introduction
Paraneoplastic neurologic syndromes (PNS) are manifestations of cancers located outside the central nervous system. They appear before the diagnosis of cancer in most of the patients. Frequency among all cancer patients is 0.01%. They show close association with some kinds of cancer. These disorders occur due to stimulation of immune response by some proteins which are formed by a tumor, against both tumor and the nervous system. For diagnosis, cancer associated with paraneoplastic syndrome should be detected and antibody should be demonstrated. Neurologists should be aware of these syndromes so that appropriate diagnostic and treatment options can be applied sooner. Because the tumor examination and treatment plan should be made following the diagnosis.

Epidemiology
PNS are rare disorders in cancer patients. Frequency in all cancer patients is 0.01% (Darnell and Posner, 2003). Women/men ratio is approximately 3:1. It is usually observed beyond mid-life. They show a closer association with some kinds of cancer. They have a more frequent association especially with hematologic diseases such as small cell lung cancer (SCLC), thymoma, and monoclonal gammopathy. Other cancer types associated with PNS include breast, gynecological cancers such as ovarian and Hodgkin’s, non-Hodgkin’s lymphoma, testicular cancer and neuroblastoma (Toothaker and Rubin, 2009). Furthermore, development of PNS is possible in almost all neoplasms (Bataller and Dalmau, 2003).

Pathogenesis
A widely accepted opinion is that these disorders occur due to stimulation of immune response by some proteins which are formed by a tumor, against both the tumor and the nervous system (Tüzün, 2010). Cytotoxic T-cell responses have a very important role in pathogenesis of PNS (Bradley, 2008). T-cells are responsible for both of the antibody-mediated processes (Albert et al., 1998). Lymphocytic pleocytosis and oligoclonal band positivity may be observed in BOS analysis (Armstrong et al., 2005).

PNS are formed by antibodies developed against the intracellular antigen or neuronal surface antigen. In limbic encephalitis, there are antibodies for both regions. Anti Hu, anti Yo, anti Ri, anti Ma2, Cv2/CRMP5 are antibodies associated with intracellular antigen, whereas the VGKC complex...
Table 1. Paraneoplastic neurologic disorders

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<td>Retinopathy</td>
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<th>Peripheral nervous system</th>
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<td>Vasculitic neuropathy</td>
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<td>Brachial neuritis</td>
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<td>Polymyositis</td>
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<td>Inflammatory myopathy</td>
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Possible PNS criteria

Undetectable underlying cancer and antibody but high risk of underlying tumor in a patient with classical neurologic syndrome. Detection of anti-neuronal antibody despite the absence of neurologic syndrome or cancer. Presence of classical neurologic syndrome and cancer (within two years of diagnosis of syndrome) in a patient without anti-neuronal antibodies.

Paraneoplastic Syndromes

Limbic encephalitis

Characteristic features of limbic encephalitis are subacute confusion and impairment of short-term memory (Tüzün and Dalmau, 2007). Manifestation is usually accompanied by epileptic seizures. Depression, psychosis and sleep disturbances are also observed. Most commonly detected cancer type is SCLC with the rate of approximately 50%. Furthermore, testicular cancer and breast cancers are observed with the rates of 20% and 8%, respectively (Gultekin et al., 2000). Although rarely, ovarian teratoma, thymoma and Hodgkin’s disease may be observed. Prognosis is usually poor if limbic encephalitis is developed due to an underlying cancer (Tüzün and Dalmau, 2007). In patients with limbic encephalitis developed due to intracellular antigens such as Hu, Ma2, CV2 and amphiphysin, usually an underlying cancer exists and prognosis is poor (Tüzün, 2010; Dalmau et al., 2004). In cases with limbic encephalitis due to the cell membrane antigens such as N-Methyl-D-aspartate-type glutamate receptor (NMDAR) and voltage-gated potassium channels (VGPC), usually no underlying cancer is observed and treatment responses are good (Tüzün and Dalmau, 2007). Anti Hu is the most commonly detected antibody (in 60% of the cases). Type of underlying cancer is SCLC in 94% of these patients (Toothaker and Rubin, 2009). T2 and flair hyperintense lesions are observed in one or both of the medial temporal lobe structures in 80% of patients with limbic encephalitis. Even if magnetic resonance imaging (MRI) is normal, positron emission tomography (PET) may show involvement in these regions (Ances et al., 2005; Bataller et al., 2007). Lymphocytic pleocytosis, increased protein, and oligoclonal band positivity may be observed in BOS analysis. Epileptic discharges may be observed in temporal regions in electroencephalography (EEG) (Toothaker and Rubin, 2009).

Diagnosis

For diagnosis, the cancer associated with syndrome should be detected and antibody should be demonstrated. Neurological symptoms appear before the diagnosis of underlying tumor in approximately 60% of the patients with PNS (Bradley, 2008). A number of diagnostic criteria have been established for diagnosis of PNS (Honnorat and Antoine, 2007; Graus and Dalmau, 2007; Tüzün and Dalmau, 2007; Toothaker and Rubin, 2009; Sadeghian and Vernigo, 2010; Tüzün, 2010). Anti-neuronal antibodies and associated cancer types are provided in Table 2.

Table 2. Anti-neuronal antibody

<table>
<thead>
<tr>
<th>Anti-neuronal antibody</th>
<th>Cancer type</th>
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<tr>
<td>Anti-Hu</td>
<td>Lung (most common SCLC), prostate, GIS</td>
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<tr>
<td>Anti-Yo</td>
<td>Ovary, breast</td>
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<tr>
<td>Anti-Ri</td>
<td>Ovary, breast</td>
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<tr>
<td>Anti-Ma2</td>
<td>Testicle, lung</td>
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<tr>
<td>Anti-amphiphysin</td>
<td>SCLC, breast</td>
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<td>Anti-Tr</td>
<td>Hodgkin’s lymphoma</td>
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<tr>
<td>Anti-NMDAR</td>
<td>Ovary (teratoma)</td>
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<tr>
<td>Anti-mGlur1</td>
<td>Hodgkin’s lymphoma</td>
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<td>VC2/CRMP5</td>
<td>Thymoma, SCLC</td>
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Absolute PNS criteria

1. Detection of classical neurologic syndrome (encephalomyelitis, limbic encephalitis, subacute cerebellar degeneration, sensory neuropathy, opsoclonus myoclonus, Lambert-Eaton myasthenic syndrome and dermatomyositis) and associated cancer (within 5 years of diagnosis of syndrome).
2. Healing or pronounced recovery in a non-classical syndrome following the cancer treatment.
3. Detection of anti-neuronal antibody together with the non-classical syndrome and cancer.
4. Detection of a well-characterized anti-neuronal antibody (anti Ri, anti Hu, anti Yo, anti Ma2, anti CV2 and anti-amphiphysin) together with the neurologic syndrome in the absence of accompanied cancer.
Subacute cerebellar degeneration

Subacute cerebellar degeneration is a paracerebellar syndrome resulting from the common and severe lost of the cerebellar purkinje cells. It is associated with gynecologic, breast cancers, SCLC and Hodgkin’s lymphoma (Graus and Dalmau, 2007). Cerebellar symptoms such as ataxia, dysarthria and nystagmus are followed by gait and posture disorders, and the patients become non-functional in daily activities within weeks (Hammack et al., 1992; Peterson et al., 1992). Initial MRI findings of the patients may be normal. In late stage, cerebellar atrophy and inflammation findings in BOS are developed (Graus and Dalmau, 2007). These are most commonly occurred associated with anti-Yo. Furthermore, antibodies such as Tr, Hu, Ma2, and Ri may be detected. Treatment response is usually poor; however, a response may be obtained with early interventions of aggressive immunotherapy and cancer therapy. There are also publications indicating that intravenous immunoglobulin (IVIG) is beneficial (Widness-Walsh et al., 2003; Phuphanich and Brock, 2007).

Opsoclonus-myoclonus

There are involuntarily, arrhythmic, high-amplitude, versatil saccadic movements and myoclonic jerks. Furthermore, cerebellar ataxia may be observed. It is observed in association with SCLC, breast and gynecologic cancers in adults and in cases with neuroblastoma in children. Its association with neuroblastoma is 2-3%. Neuroblastoma is accompanied by 40% in case of pediatric opsoclonus-myoclonus. In this case, findings such as hypotonia, mental retardation may be observed (Rudnick et al., 2001; Tate et al., 2005). The brain MRI is usually normal. Mild pleocytosis may be observed in BOS. Anti-Ri antibody accompanied with breast and gynecologic cancers was detected in adult cases, while no antibody was detected in pediatric group (Wong, 2007).

It is one of the PNS showing the best response to treatment. IVIG, corticosteroids and plasmapheresis may be usefull in the treatment. Treatment possibility is less in children when compared to adults (Bataller et al., 2001). Rituximab therapy may be tried in suitable patients (Pranzatelli et al., 2006).

Encephalomyelitis

Paraneoplastic encephalomyelitis is characterized by neuronal loss and inflammation in multiple regions of nervous system (Graus et al., 2001). Involved regions include hippocampus, cerebellum, brain stem and medulla spinalis. Dorsal root ganglion may be involved in sympathetic and parasympathetic ganglia. Symptoms are occurred in patients as per the situations of affected neurons in these involved regions. Myelitis, brainstem encephalitis, cerebellar degeneration, sensory neuropathy, orthostatic hypotension, and arrhythmia may develop (Antonie et al., 1993; Graus et al., 2001). The most commonly detected conditions are SCLC and anti-Hu. Furthermore, antibodies of CV2, amphiphysin and Ri may be detected (Graus and Dalmau, 2007). Lymphocytic pleocytosis, increased protein, and oligoclonal band positivity are likely to be observed in BOS analysis of patients.

Peripheral neuropathy

This is a mixed axonal/demyelinating disorder (Camdessanche et al., 2002) and it occurs in result of the damage in all peripheral nerves of axonal, motor, sensory and autonomous by effect of cancer. Damage generally occurs due to direct spread effect of cancer, radiotherapy, chemotherapy, nutritional deficiency and leptomeningeal metastases (Antoine and Camdessanche, 2007). The most commonly seen form of paraneoplastic peripheral neuropathy is subacute sensory neuropathy. It is observed in patients with anti-Hu positive SCLC (Molinuevo et al., 1998). As with other paraneoplastic disorders, pleocytosis, increased protein, and oligoclonal band positivity may be observed in BOS also in sensory neuropathy (Antoine and Camdessanche, 2007). Cases with anti CV2 positive SCLC and thymoma are usually accompanied by monoclonal gammopathy, multiple myeloma, and sensory neuropathy in Waldenstöm megaglobulinemia (Antoine et al., 2001; Levine et al., 2006).

Paraneoplastic autonomous neuropathy is usually observed in patients with anti-Hu positive SCLC. Manifestations usually accompanied by limbic encephalitis and sensory neuropathy. Furthermore, findings such as pseudo-obstruction, orthostatic hypotension, bladder dysfunction, and arrhythmia may also be observed (Dalmau et al., 1992).

Retinopathy

There are three types of retinopathy associated with cancer. Cancer associated retinopathy (CAR), melanoma associated retinopathy (MAR) and paraneoplastic optic neuropathy (Damek, 2005). Vision loss without pain, photosensitivity and scotoma are observed in patients with CAR. The most commonly detected antibody that shows SCLC is recoverin in patients with CAR (Bataller and Dalmau, 2004).

No defects in visual acuity are observed in patients with MAR, however, sudden night blindness is observed (Damek, 2005). Several MAR-like syndromes are associated with colon cancer. Otherwise, it is almost always associated with melanoma (Jacobson and Adamus, 2001). Paraneoplastic optic neuropathy is rarely seen alone. It is usually observed with encephalomyelitis and SCLC (Toothaker and Rubin, 2009).

Lambert-Eaton myasthenic syndrome (LEMS)

An autoimmune disease of neuromuscular junction characterized by muscle weakness and autonomous dysfunction. LEMS is paraneoplastic in 60% and highly associated with SCLC. Less often, it is associated with lymphoma. 3 percent of the SCLC patients LEMS develops (O’Neill et al., 1988; Newsom-Davis, 2004). P/Q-type voltage-gated calcium channels (VGCC) channel antibodies are responsible for the development of disease. Compound muscle action potentials (CMAP) of low amplitude and normal latency at low frequencies such as 1-5 Hz are obtained with the consecutive nerve stimulations performed electrophysiologically to the patient. CMAP with amplitude increased by 100% or more is obtained with the consecutive nerve stimulation following exercise. This is due to increase in release of acetylcholine by the calcium accumulated in the nerve terminal during exercise (Mareska and Gutmann, 2004). Treatment of paraneoplastic cases is targeted the underlying tumor, whereas in antibody-mediated cases without underlying malignancy, IVIG and plasma exchange may be used. There are publications indicating that 3,4-diaminopyridine may be beneficial (Chalk et al., 1990; Sanders et al., 2000).
Dermatomyositis, polymyositis

Dermatomyositis is a manifestation where characteristic skin lesions composed of periungual telangiectasia, photosensitivity, heliotrope rash and erythematous scaly plaques are accompanied by idiopathic inflammatory myopathy. Predominant proximal symmetric myopathy is observed and it has a slow progression. Disease is considered as paraneoplastic with a possibility of 30%. In this case, gynecologic, lung, pancreas, colon, stomach cancers and Non-Hodgkin lymphoma may underlie (Sigureirsson et al., 1992; Hill et al., 2001). Antibodies are usually undetectable in cases with underlying tumor. Priority in paraneoplastic cases is the treatment of tumor. Otherwise, corticosteroids, azathioprine, IVIG and immunosuppressives may be used in autoimmune and paraneoplastic patients (Honnorat and Antoine, 2007).

The form of muscle weakness is as dermatomyositis in polymyositis as well. No skin findings are observed. Malignancy rate is lower by about 15-18%. Lung, bladder and Non-Hodgkin lymphoma may exist (Amoura et al., 2005; Targoff et al., 2006).

Stiff-Person syndrome

Stiff-Person syndrome is characterized by muscle stiffness developed in months, which is particularly prominent in back and leg muscles. Widespread muscle pains and painful muscle spasms are observed (Rosenfeld and Dalmau, 2010). Continuous motor activity is observed in EMG. It occurs with autoimmune mechanisms in 70% of the patients and contains anti-GAD antibody (Honnorat and Antoine, 2007). Patients developed it as paraneoplastic are usually women with anti-amphiphysin positive breast cancer (Folli et al., 1993; Petzold et al., 2004). Treatment primarily targets the underlying disease, however corticosteroids, IVIG, diazepam and GABAergic agents may also be used (Rosenfeld and Dalmau, 2010).

Motor neuron disease

A progressive, degenerative disease which involves upper or lower neurons or both. Patients show the lower motor neuron damage findings such as weakness, atrophy, fasciculation and upper motor neuron findings such as extensor plantar response and increased deep tendon reflexes. 3-5 years survival in amyotrophic lateral sclerosis (ALS) is 50% (Rowland and Shneider, 2001). Motor neuron disease is usually idiopathic. There are no significant evidences on its association with cancer (Kurtzke and Beebe, 1980; Chio et al., 1988). Only a small number of anti-neuronal antibodies have been detected in motor neuron disease (Stich et al., 2007). However, there are patients with motor neuron disease that have been reported associated with anti-Hu in SCLC and anti-Yo in ovarian cancer (Verma et al., 1996; Khwaja et al., 1998).

Treatment

Treatment protocol for patients with paraneoplastic neurologic disorder is unclear. Small case series and anecdotal approaches are used for treatment. Best treatment approach, which is applicable for all diseases, is to treat the underlying tumor. Prospective studies conducted with a great number of patients are needed to determine the treatment protocols (Bataller and Dalmau, 2003; Graus and Dalmau, 2012).

2. Conclusion

As paraneoplastic syndromes are seen rarely, it is hard to diagnose them and frequently diagnosis may be missed. Neurological signs are observed before diagnosis of tumor. Anti-neuronal antibodies are very important in detecting these syndromes. Neurologists should well-recognize and determine these diseases because the tumor examination and treatment plan should be made following the diagnosis.

REFERENCES


Antoine, J.C., Honnorat, J., Camdessanche, J.P., Magistris, M., Absi, L., Mosnier, J.F., Petitot, P., Kopp, N., Michel, D., 2001. Paraneoplastic anti-neuronal antibodies are very important in detecting these syndromes. Neurologists should well-recognize and determine these diseases because the tumor examination and treatment plan should be made following the diagnosis.


