Paraneoplastic Neurologic Syndromes

Genjiro Hirose

Paraneoplastic neurologic syndromes are degenerative diseases of the central or peripheral nervous system that develop in association with a systemic neoplasm without a direct invasion by tumor. The pathogenesis of this disorder has been hypothesized in the past, and now there is increasing evidence that autoimmune processes triggered by the underlying neoplasm play a major role in the pathophysiology, as documented by many reports of identification of autoantibodies that react with both the target neural tissue and the underlying neoplasm, as evidenced by the extensive application of molecular biology techniques. The presence of antibodies in serum or CSF of some patients with this disorder now accurately identifies the subgroup of the disorders related to specific neoplasms. The trend of recent studies on the pathogenesis of this disease may in the future lead to a new era to clarify the pathogenesis.

(Key words: autoantibodies, onconeural antigen, subacute cerebellar degeneration, encephalomyelitis/sensory neuronopathy)

Introduction

An association between malignant disease such as carcinoma and specific neuro-muscular diseases independent of metastasis has been well recognized by a number of papers (1, 2). The term paraneoplastic syndrome was first introduced by Shnider et al (3) in 1979 for a group of disorders that are associated with cancer without a direct invasion by the primary tumor mass or metastasis to the involved organ. Therefore paraneoplastic syndromes can affect many organs. Among paraneoplastic syndromes, paraneoplastic neurologic syndromes include the disorders of all nervous systems in patients with systemic cancer not caused by tumor mass, metastasis or radiation effect (Table 1). These disorders once were named as remote effects of cancer on the nervous system (4), but there is increasing evidence that autoimmune mechanisms caused by the underlying malignancy play a major role in the pathogenesis. This autoimmune theory has been supported by the identification of antibodies that react with both the target neurologic organ and the underlying cancer (onconeural antigen) in the serum of patients with this disorder. The presence of serum antibodies in some paraneoplastic neurologic syndromes now identifies subgroups of patients with particular paraneoplastic syndromes related to specific cancers. Now we have more information regarding the pathogenesis of this disorder via the extensive use of molecular biology techniques. However, the true pathogenesis is yet to be defined.

Incidence

The incidence of paraneoplastic neurologic disorders is relatively high if we include disorders of the peripheral nerve. Cavaletti et al (5) reported that over 50 percent of patients with ovarian epithelial cancer had some evidence of peripheral neuropathy. In patients with small-cell carcinoma of lung, peripheral nerve disorders have been clinically seen in 45 percent, with autopsy-proven pathological changes in dorsal root ganglia in 70 percent (6). However these peripheral neuropathies are often attributable to other etiological causes, such as mechanical, toxic and metabolic etiologies. According to Croft and Wilkinson, the incidence of paraneoplastic neuromyopathy was 7 percent in a series of 1,476 patients with cancer (7). Anderson et al (8) reported less than 1 percent incidence of paraneoplastic neurologic syndromes affecting the central nervous system (CNS).

Pathogenesis

Several etiological considerations have been proposed for the paraneoplastic neurological syndromes, including toxins, viruses, nutritional deficiencies and autoimmune disorder.

An autoimmune dysfunction, in which antibodies react with coexisting antigens (onconeural antigen) in tumor and CNS or the peripheral nervous system, seems to be the most attractive explanation for the pathogenesis. However, some patients that
Table 1. Paraneoplastic Neurologic Syndromes

<table>
<thead>
<tr>
<th>Disorders</th>
<th>Associated neoplasm</th>
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<tbody>
<tr>
<td>Central nervous system</td>
<td></td>
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<tr>
<td>Encephalomyelitis:</td>
<td></td>
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<tr>
<td>limbic encephalitis</td>
<td>small cell lung cancer (SCLC)</td>
</tr>
<tr>
<td>bulbar encephalitis</td>
<td>SCLC</td>
</tr>
<tr>
<td>necrotizing myelitis</td>
<td>SCLC, lymphoma</td>
</tr>
<tr>
<td>Subacute cerebellar degeneration</td>
<td>ovarian-uterine cancer (CA), breast CA, Hodgkin’s disease, SCLC</td>
</tr>
<tr>
<td>Opsoclonus-myoclonus syndrome</td>
<td>SCLC, breast CA, neuroblastoma</td>
</tr>
<tr>
<td>Acute pandysautonomia</td>
<td>SCLC</td>
</tr>
<tr>
<td>Cancer associated retinopathy</td>
<td>SCLC</td>
</tr>
<tr>
<td>Peripheral nervous system</td>
<td></td>
</tr>
<tr>
<td>Subacute sensory neuronopathy</td>
<td>SCLC</td>
</tr>
<tr>
<td>Sensory-motor neuropathy</td>
<td>SCLC</td>
</tr>
<tr>
<td>Muscular system</td>
<td></td>
</tr>
<tr>
<td>Lambert-Eaton syndrome</td>
<td>SCLC</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>thymoma</td>
</tr>
<tr>
<td>Polymyositis-Dermatomyositis</td>
<td>various cancers</td>
</tr>
</tbody>
</table>

clinically meet the criteria for paraneoplastic syndromes do not have autoantibodies. This evidence has raised questions about this pathogenesis. But we now have enough evidence to support this autoimmune theory. Some patients have antineuronal antibodies in serum and cerebrospinal fluid, which cross-react with autologous tumor antigens. These autoantibodies localize within the CNS as documented by histochemical studies. The titers of these antibodies are reduced after tumor removal or chemotherapy.

The background of autoimmune pathogenesis is based on the hypothesis that quiescent memory T-cells, exposed to the antigen in fetal life might escape from thymic deletion and stay in the periphery until the antigen is abnormally expressed by the presence of a tumor and processed by antigen presenting cells. T-cell mediated B-cell proliferation in response to tumor antigen would result in production of autoantibody, which would erroneously be targeted at a similar neuronal antigenic epitope. Finally complement-mediated antibody-dependent cytotoxicity or antigen-dependent T-cell and cytokine-mediated neuronal damage or lysis would occur (9).

Several autoantibodies and their associated antigens have now been characterized by the molecular biology techniques in paraneoplastic neurologic syndromes (Table 2). The presence of these antibodies in some patients with paraneoplastic neurologic syndrome can be used as a diagnostic marker that the patient with a neurologic disorder has underlying cancer.

In regard to the antibody-negative patients, there are two possibilities that the disorder is not autoimmune or is autoimmune, and antibody is present in serum, but this has not been identified by our current methodologies.

Specific Clinical Syndromes

Encephalomyelitis-sensory neuronopathy
The term “encephalomyelitis associated with carcinoma” was introduced by Henson et al (19) to describe patients with cancer who develop clinical signs of dysfunction of various parts of the neuraxis and signs of inflammation within the brain, brain stem, spinal cord, dorsal root ganglia and nerve roots as found by postmortem examination. Henson and Urich (20) found that encephalomyelitis and paraneoplastic sensory neuronopathy frequently develop together and that most frequently associated tumor is small-cell lung cancer (SCLC).

The neurologic signs and symptoms often precede diagnosis of the tumor by up to 2 years. Symptoms usually progress over several weeks insidiously. In this disease, subacute sensory neuronopathy in association with variable degrees of dorsal column and motor neuron disorders, may be the most common clinical syndrome. The next common syndrome includes limbic encephalitis, cerebellar degeneration, myelitis and sensory neuronopathy. Anxiety and depression are common neurologic symptoms, followed by severe impairment of recent memory in limbic encephalitis. Common manifestations of brain stem encephalitis include vertigo, nystagmus, ataxia, bulbar palsy, oculomotor disturbance and pyramidal dysfunction. In patients with myelitis, progressive weakness with atrophy and
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Table 2. Autoantibodies in Paraneoplastic Neurologic Syndromes

<table>
<thead>
<tr>
<th>Clinical Syndrome</th>
<th>Antibody</th>
<th>Western Blot Antigen</th>
<th>Recombinant Antigen</th>
<th>Genes</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalomyelitis</td>
<td>Anti-Hu</td>
<td>35-40</td>
<td>HuD</td>
<td>HuD</td>
<td>Szabo et al 1991 (10)</td>
</tr>
<tr>
<td>(Type IIa) (ANNA-1)</td>
<td></td>
<td>35-40</td>
<td>HuC</td>
<td>HuC</td>
<td>Manley et al 1994 (11)</td>
</tr>
<tr>
<td>Anti-Hel-N1</td>
<td></td>
<td>35-40</td>
<td>ple21</td>
<td>ple21</td>
<td>Sakai et al 1994 (12)</td>
</tr>
<tr>
<td>Cerebellar degeneration</td>
<td>Anti-Yo</td>
<td>62</td>
<td>Yo</td>
<td>CDR62</td>
<td>Fathallah-Shaykh et al 1991 (14)</td>
</tr>
<tr>
<td>(Type I) (PCA-1)</td>
<td></td>
<td>34</td>
<td>pCDR13</td>
<td>CDR34</td>
<td>Dropcho et al 1987 (15)</td>
</tr>
<tr>
<td>Opsoclonus-myoclonus</td>
<td>Anti-Ri</td>
<td>55</td>
<td>Ri</td>
<td>NOVA</td>
<td>Buckanovich et al 1993 (17)</td>
</tr>
<tr>
<td>(Type IIb) (ANNA-2)</td>
<td></td>
<td>23-26</td>
<td>CAR</td>
<td></td>
<td>Thirkill et al 1992 (18)</td>
</tr>
<tr>
<td>Cancer-associated retinopathy (CAR)</td>
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fascillation is often seen in association with corticospinal and posterior column signs. In patients with sensory neuronopathy, the onset is subacute, often accompanied by dysesthetic pain in distal limbs. The symptoms spread to proximal limbs and the trunk. Finally sensory ataxia ensues. Nerve conduction studies reveal delayed sensory nerve latencies with preservation of motor nerve conduction.

Most of the patients with this type encephalomyelitis have mild mononuclear cell pleocytosis, elevated IgG content and oligoclonal IgG bands in CSF. Common pathological findings in these disorders include neuronal loss, gliosis, mononuclear cell infiltration, microglia proliferation, and secondary tract degeneration.

Anti-neuronal nuclear antibody (21), type 1, also called "anti-Hu" (22) was present in serum and CSF of patients with this disease. This antibody is synthesized in the CNS as well as systemically and is localized in the tumor and in areas of the lesions of the nervous system. This antibody binds to a 35–40kD neuronal protein antigen. The targets of this antibody defined by molecular biological techniques belong to a family of RNA-binding proteins, that includes HuD (10), HuC (11)/ple21 (12) and Hel-N1 (13).

We recently identified a new hippocampal autoantigen which was recognized by the antibody present in the serum of a patient with paraneoplastic limbic encephalitis and small cell lung cancer (12). The isolated cDNA clone ple21 comprises an ORF of 1,053 nucleotides encoding a 350 aminoacid protein with deduced molecular weight of 38kD (Fig. 1). The antigen was not only recognized by the antibody from a patient with paraneoplastic limbic encephalitis, but also was recognized by the sera from the patients with SCLC-associated paraneoplastic sensory neuronopathy (Fig. 2). This autoantigen is highly homologous to HuC antigen in its aminoacid sequence.

No beneficial treatment has been reported except for very rare spontaneous remission and improvement after treatments of the underlying tumor.

Paraneoplastic cerebellar degeneration (PCD)

This disorder accounts for about 9 percent of paraneoplastic neurology syndromes. This disease occurs almost exclusively in women with gynecological tumors such as adenocarcinoma of the ovary, uterus and breast. Men with adenocarcinoma of prostate or gastrointestinal tract rarely develop this cerebellar degeneration.

Patients usually develop neurologic signs prior to the time of tumor discovery. Symptoms start with dizziness, vertigo, nausea and imbalance of equilibrium. In weeks or months, dysmetria, tremor, truncal ataxia and dysarthria develop. Occasionally signs of dysfunction of other areas of the nervous system may occur, including corticospinal tract signs and bulbar symptoms. These patients are known to have anti-Purkinje cell antibodies, designated anti-Yo (14), type 1, PCA-1 (16), reactive with 62- or 34-, and 52kD neuronal cytoplasmic protein antigens, respectively. The anti-Yo (PCA-1) antibody is reactive with cloned antigens appear to be DNA-binding proteins.

The pathological findings in this disease are total loss of Purkinje cells in the cerebellum, a drop-out of granular cells, perivascular mononuclear cell infiltration and brain stem tract degeneration.

Treatment has so far been ineffective and conservative treatments are indicated.

Opsoclonus-myoclonus syndrome

Opsoclonus-myoclonus syndrome (OMS) is occasionally seen in children with neuroblastoma but this syndrome is rarely seen in adults in association with underlying neoplasms and the
Figure 1. Nucleotide and deduced amino acid sequences of the ple21 cDNA clone. The nucleotide and amino acid sequences are numbered from the initiation codon, and the termination codon is indicated by an asterisk.

presence of antibody. Approximately 19 percent of patients with OMS have underlying neoplasms. In a subset of adult OMS usually associated with breast cancer, an antineuronal autoantibody designated “anti-Ri” (type IIb, ANNA-2) has been found in the serum and the CSF (23). This antibody reacts with the nuclei of neurons throughout the nervous system and with the nuclei or cytoplasm of breast cancer cells. The Ri antigen is a 55-kD neural protein antigen identified on Western immunoblots. Recently, cDNA encoding an antigen (NOVA) was cloned, which is recognized by anti-Ri sera (17). The role of this antibody in the pathogenesis of this disorder is unknown, but a recent report suggests that anti-Ri antibody inhibits onconeural antigen Nova 1-RNA interactions and this inhibition may cause the disease (24).

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Figure 2. Immunoblot of the PLE21 fusion protein probed with the sera (1:250 dilution) of a patient with small cell lung cancer and PLE, 2 patients with small cell lung cancer and PSN, a patient with uterine cancer and PCD, one patient with SCLC without any neurological deficits and a healthy volunteer (control).

References

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