INTRODUCTION

PNS are a rare group of conditions affecting less than 1 out of every 10,000 patients diagnosed with cancer. SCLC is the most common malignancy associated with PNS. PNS occur as a result of neoplastic mechanisms that are not related to the tumour, metastatic disease, infections, ischemia or metabolites. These syndromes are thought to occur due to immunologic mechanisms. A number of studies have confirmed the presence of onconeural antibodies in patients with PNS and suggest that the neurologic manifestations stem from an antibody-induced inflammatory reaction. The neurologic presentation varies depending on the site of the lesion. PNS can affect one or multiple regions of the nervous system, resulting in a variety of clinical manifestations. A number of classical PNS found in SCLC have known associations with particular antibodies (Table 1). These associations may have prognostic importance. For example, the presence of anti-Hu antibodies in SCLC has been shown to be a predictor of treatment response; patients who are positive for the antibodies show longer survival.

PRESENTATION AND DIAGNOSIS

The majority of patients diagnosed with PNS initially present with a neurologic complaint; subsequent evaluation leading to a diagnosis of malignant disease. Due to the rarity of PNS, a delay in diagnosis of the primary malignancy is not uncommon and may lead to poor outcomes. Any patient presenting with a neurologic complaint should undergo investigation, starting with a thorough history and physical examination to determine the etiology of the deficit, first ruling out nonmalignant etiologies. In the event of an unexplained neurologic abnormality and the presence of risk factors for malignancy, the diagnosis of PNS should be further investigated.

A definite diagnosis of PNS requires one of the following criteria:

1. A classical syndrome and a documented malignancy within 5 years of the onset of the syndrome
2. A nonclassical syndrome that (a) shows some resolution after treatment for a known malignancy, or (b) is present within 5 years of a cancer diagnosis and a presence of onconeural antibodies
3. Any neurologic syndrome in the presence of well-characterized onconeural antibodies, regardless of a cancer diagnosis

When a clinical abnormality leads to the suspicion of PNS, an initial screen should be performed to identify the presence of onconeural antibodies. Early screening used immunohistochemistry techniques to identify known patterns. This also required immunoblotting with recombinant proteins to confirm their specificities. In recent years, serum testing has been developed as an effective tool to
identify onconeural antibodies in the blood. Because many PNS are related to a number of antibodies, it is recommended to screen the serum using a panel of common onconeural antigens. Well-characterized antibodies may provide the most reliable, evidence-based, diagnostic information since they have:

1. Recognizable patterns on routine immunohistochemistry (using earlier detection methods);
2. Well-characterized neurologic syndromes associated with the antibodies;
3. Reproducibility validation within the literature;
4. A lower frequency of these antibodies in patients without cancer.

Currently, well-characterized antibodies include anti-Hu, Yo, CRMP5/CV2, Ri, Ma2 and amphiphysin. Commercial immunoblots containing panels of the corresponding onconeural antigens are now readily available.

### Table 1: Major paraneoplastic neurologic syndromes and antibodies associated with small cell lung cancer

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Clinical presentation</th>
<th>Associated antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paraneoplastic encephalomyelitis</td>
<td>Epileptic seizures or epilepsy partialis continua, extrapyramidal symptoms, sensory neuropathy and autonomic dysfunction, often presenting as gastrointestinal dysmotility</td>
<td>Hu, CRMP5 &quot;; PCA2; Amphiphysin &quot;;</td>
</tr>
<tr>
<td>Limbic encephalitis</td>
<td>Epileptic seizures, depression, personality changes and cognitive dysfunction</td>
<td>Hu, CRMP5 &quot;; ANNA-3 &quot;; VGKC &quot;;</td>
</tr>
<tr>
<td>Brainstem encephalitis</td>
<td>Gaze palsy, diplopia, reduced consciousness and central sleep apnea</td>
<td>Hu, Mo2 &quot;;</td>
</tr>
<tr>
<td>Extrapyramidal syndromes</td>
<td>Extrapyramidal features such as chorea, ballistic movements and dystonia</td>
<td>Hu, CRMP5 &quot;;</td>
</tr>
<tr>
<td>Paraneoplastic cerebellar degeneration</td>
<td>Severe pancerebellar involvement, with ataxia of the limbs and trunk, dysarthria, dysphagia and nystagmus</td>
<td>CRMP5 &quot;; Hu, Zic4 ANNA-3 &quot;; CRMP5 &quot;;</td>
</tr>
<tr>
<td>Paraneoplastic opsoclonus-myoclonus</td>
<td>Multidirectional saccades</td>
<td>Hu</td>
</tr>
<tr>
<td>Visual syndromes</td>
<td>Progressive retinopathy, usually bilateral</td>
<td>Recoverin CRMP5</td>
</tr>
<tr>
<td>Sensorimotor peripheral neuropathy</td>
<td>Mixed axonal and demyelinating sensorimotor neuropathy, optic neuritis, cerebellar dysfunction and extrapyramidal symptoms</td>
<td>Hu Amphiphysin CRMP5 &quot;;</td>
</tr>
<tr>
<td>Subacute sensory neuropathy</td>
<td>Paresthesia, hypoesthesia, proprioceptive loss and sensory ataxia; usually asymmetrical upper limb involvement</td>
<td>Hu Amphiphysin ANNA-3 &quot;; CRMP5 &quot;;</td>
</tr>
<tr>
<td>Paraneoplastic peripheral nerve hyperexcitability</td>
<td>Spontaneous and continuous twitching and painful cramps; often accompanied by various combinations of stiffness, pseudomyotonia, pseudotetany and weakness</td>
<td>VGKC &quot;;</td>
</tr>
<tr>
<td>Lambert-Eaton myasthenic syndrome</td>
<td>Proximal muscle weakness and generalized fatigue, with a sparing of the ocular and bulbar muscles; autonomic dysfunction, often presenting as dry mouth</td>
<td>VGCC</td>
</tr>
</tbody>
</table>

ANNA-3=antineuronal nuclear autoantibody type 3; CRMP5=collapsin response mediator protein 5; PCA-2=Purkinje cell antibody; VGCC=voltage-gated calcium channel; VGKC=voltage-gated potassium channel

*Antibodies may be associated with other malignancies in addition to SCLC.*
available, which allows for easy serum analysis. As the immune response is made in proximity to the tumour, antibodies are at highest concentration in the serum, rather than the central nervous system. The presence of onconeural antibodies can then guide further diagnostic evaluation aimed at locating the primary malignancy. Computed tomography (CT) and positron-emission tomography (PET) can be recommended to aid in the detection of the primary tumour as well as providing information on extent of disease. Sensitivity of CT-thorax has been estimated in the range of 80–85% for the detection of SCLC in PNS. In the event that a tumour is identified but is of a different type than what would be expected, it is recommended to continue investigations in the case of a second malignancy. It should be noted that onconeural antibodies are not always present in PNS, while conversely, they have been detected in patients with neurologic complaints in the absence of malignancies. Because of this, the presence or absence of antibodies in a patient with a classical PNS should not dissuade the clinician from investigating for malignancy.

MULTIDISCIPLINARY MANAGEMENT

Once a diagnosis of PNS is made, strong interdisciplinary communication is required to ensure adequate care of patients. A multidisciplinary care plan should be created with cooperation between the medical oncologist, radiation oncologist, thoracic surgeon (if required) and neurologist. Early detection offers the greatest advantage to the patient, as the primary malignancy may have a more favourable prognosis. The associated neurologic deficits may also be more manageable with earlier intervention.

The management of PNS has 3 main components: treatment of the underlying malignancy, treatment of the PNS and long-term followup. Treatment of the underlying malignancy comprises the mainstay of management in PNS. This may remove autoantibody activity and improve PNS symptoms. For example, 30% of patients with paraneoplastic limbic encephalitis showed some symptom resolution with treatment of the SCLC. Treatment of the PNS may also include immune therapy and symptomatic treatment. Immune therapy consists of steroids, plasma exchange or intravenous immunoglobulin. These therapies may be of benefit to certain subgroups of patients with PNS, including those with Lambert-Eaton myasthenic syndrome and paraneoplastic peripheral nerve hyperexcitability and pediatric patients with paraneoplastic opsoclonus-myoclonus. In patients with other PNS, a clear benefit of immune therapy has not yet been shown. All patients should also be considered for other symptomatic treatment to improve quality of life, including cognitive and/or physical rehabilitation.

A delay in the diagnosis of PNS is a common occurrence due to the vague nature of the presenting symptoms and the often unusual constellation of neurologic findings. Early identification and the use of diagnostic and management algorithms may lead to an improved prognosis in this patient population. Multimodality therapy is required to promote continuous symptomatic improvement throughout the treatment of the primary tumour/metastases and PNS.

REFERENCES


Disclosure

Drs. Lalani and Brade have no disclosures/conflicts of interest to declare pertaining to this article.