Paraneoplastic neuropathies

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Purpose of review
This review describes relevant advances in paraneoplastic neuropathies with emphasis on particular syndromes and the impact of new therapies.

Recent findings
Sensory neuronopathy may present with symptoms that do not raise the suspicion of a paraneoplastic origin. A recent study on sensory neuronopathies of different causes identified paraneoplastic cases in a group of older (>60 years) male patients with subacute onset early pain, and frequent involvement of the arms. Paraneoplastic sensorimotor polyneuropathies may be confused with chronic inflammatory demyelinating polyneuropathy (CIDP) and in lymphomas with direct infiltration of nerves (neurolymphomatosis). Recent neurophysiological studies indicate that the polyneuropathy of POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M component, and skin changes) can be differentiated from CIDP by the presence of diffuse demyelination and more severe axonal loss. Neuropathy in Waldenström macroglobulinemia is heterogeneous. Up to 38% have demyelinating features and the rest show axonal degeneration due to different causes (dysimmune, amyloidosis, or tumoral infiltration). Isolated case reports suggest that the combination of cyclophosphamide and rituximab may be effective in paraneoplastic neuronopathies. Lenalidomide and dexamethasone are effective to control the neuropathy of POEMS patients who are not suitable for or progress after autologous stem cell transplantation.

Summary
Clinical and neurophysiological studies are helpful to correctly identify particular paraneoplastic neuropathies.

Keywords
antibodies, autonomic ganglionopathy, paraneoplastic, polyneuropathy, sensory neuronopathy

INTRODUCTION

The recognition by neurologists of the different causes of peripheral neuropathy in patients with cancer is important for several reasons. First, the neuropathy may antedate the initial diagnosis or relapse of systemic cancer. Second, the diagnosis has to be done before the neuropathy has inflicted an important disability that may not be reversible when treatment is started. Third, different causes such as paraneoplastic, treatment-induced, tumor infiltration, may present with a similar neuropathic syndrome. The correct identification of the cause is crucial to offer the appropriate therapy [1,2].

The present review focuses on the most relevant advances in the field of paraneoplastic neuropathies. The current hypothesis that most paraneoplastic neurological syndromes are immune-mediated is based on the detection in the serum of these patients of antibodies with a high diagnostic specificity [3]. However, it is important to know that these antibodies are not present in many types of paraneoplastic neuropathies and the correct diagnosis remains on a high degree of clinical suspicion [4]. Paraneoplastic neuropathies have been discussed in two previous issues of *Current Opinion in Neurology* [5,6] and recently addressed in other journals [7▪▪,8▪▪]. In the present study, articles published in English on paraneoplastic neuropathies from March 2012 until March 2013 were identified by search of PubMed and from relevant articles and personal files of the authors.

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KEY POINTS

- A set of clinical criteria is useful to identify paraneoplastic sensory neuronopathies from those of other causes.
- Neurographic studies may help to differentiate the neuropathy of POEMS from CIDP.
- The causes of neuropathy in Waldenström macroglobulinemia are heterogeneous.
- Lenalidomide and dexamethasone may be an effective alternative to the treatment of the neuropathy of POEMS syndrome.

A practical way to classify the paraneoplastic neuropathies is according to the clinical features (Table 1). With the exception of subacute sensory neuronopathy and chronic pseudoobstruction, which are considered classical paraneoplastic syndromes, the incidence of cancer in other types of neuropathy is relatively low and the aggressive search for an occult neoplasm is probably not indicated [9,10].

PARANEOPLASTIC NEURONOPATHIES

The neuronal cell body may be the primary target of an immune attack induced by a tumor [11]. The attack may selectively target a specific type of neuron and cause pure motor, sensory, or autonomic neuronopathies or damage more than one cell type. The latter setting is more frequent in patients with small-cell lung carcinoma (SCLC) and Hu antibodies. The most common combinations are sensory and autonomic neuronopathies, whereas the combined damage of motor and sensory neurons is less frequent [12].

Motor neuronopathy

In a given patient who presents with a clinical syndrome compatible with a lower motor neuron disease, the subacute development of the symptoms and preservation of the bulbar muscles may indicate a possible paraneoplastic origin. In patients with lymphoma, weakness usually appears after the diagnosis of the tumor, tends to be asymmetric, and greater in the legs. Muscle weakness is rarely severe and sometimes stabilizes or improves without any specific treatment. This syndrome, defined as subacute motor neuropathy, has been rarely reported after its initial description in 1979 [13,14]. In contrast, isolated lower motor neuron syndromes associated with Hu antibodies and SCLC almost never improve.

A study of the Paraneoplastic Neurological Syndromes Euronetwork consortium, which includes 20 European centers, identified eight patients who developed two different paraneoplastic neurological syndromes during a median interval period of 15 months. Six of the patients had SCLC and Hu or CV2 (CRMP5) antibodies. The development of the second paraneoplastic syndrome indicated cancer relapse in four patients and a second cancer in one. The three patients without cancer relapse had Hu antibodies and an isolated lower motor neuron syndrome [15].

Patients with breast cancer may present with a paraneoplastic motor neuron syndrome mostly involving upper motor neurons [16]. However, a predominant lower motor neuron syndrome has been described in a patient with Yo (PCA1) antibodies who also developed cerebellar ataxia

Table 1. Paraneoplastic neuropathies

Syndrome	Tumors (antibodies)	Comments
Neuronopathy		
Motor	SCLC (Hu), lymphoma	Isolated paraneoplastic lower motor neuron syndromes are rare
Sensory	SCLC (Hu), lymphoma, adenocarcinomas	Up to 16% of patients are seronegative
Autonomic	SCLC (Hu), lymphoma, adenocarcinomas, thymoma	Ganglionic AChR antibodies present in 10–20% of patients
Polyneuropathy		
Axonal	Adenocarcinomas (usually seronegative), SCLC (CV2, Hu)	Axonal neuropathy more typical of SCLC and adenocarcinomas
Demyelinating	Lymphomas, adenocarcinomas, SCLC (CV2)	Neurolymphomatosis may mimic paraneoplastic neuropathy
Paraprotein	Waldenström (MAG antibodies in <50%), myeloma, POEMS	VEGF excellent marker of POEMS activity
Vasculitis	Lung, genitourinary, lymphoma	Clinical presentation as mononeuritis multiplex is uncommon

AChR, acetylcholine receptor; MAG, myelin-associated glycoprotein; POEMS, polyneuropathy, organomegaly, endocrinopathy, M component, and skin changes; SCLC, small-cell lung carcinoma; VEGF, vascular endothelial growth factor.

[17] and another patient with an antibody against β4 spectrin [18]. Lastly, a recent report described a rapidly progressive motor neuronopathy that antedated the diagnosis of Hodgkin lymphoma [19▪].

Sensory neuronopathy

Sensory neuronopathy is a classical paraneoplastic neurologic syndrome caused by loss of the sensory neurons in the dorsal root ganglia [3]. The neuropathy may present isolated or more often with involvement of other areas of the nervous system as part of the syndrome termed paraneoplastic encephalomyelitis [12]. SCLC accounts for more than 80% of the tumor types associated with sensory neuropathy. However, it has also been reported in patients with different types of adenocarcinomas, lymphoma, and thymoma [12,20▪]. The clinical course is subacute and rapidly progressive in weeks. However, up to 10% of patients may have a more chronic and less severe course [21]. At symptom onset, the main complaints are numbness in the upper or lower limbs that may be very asymmetric. Neurological examination reveals involvement of all modalities of sensation with severe impairment of joint position and vibratory sensation. Deep tendon reflexes are abolished. Some patients may present with severe pain, paresthesias, allodynia, and less evidence of sensory ataxia [22]. Cranial nerves may be involved with sensorineural hypoacusia, loss of taste, and numbness of the face.

Laboratory studies, other than the presence of onconeural antibodies (particularly Hu), do not differentiate paraneoplastic sensory neuronopathy from sensory neuronopathies of other causes. A recent study on sensory neuronopathies of different causes identified paraneoplastic cases in a group of older (>60 years) male patients with subacute onset, early pain, and frequent involvement of the arms [23▪▪]. The most helpful laboratory test to establish the diagnosis of sensory neuronopathy is the determination of serum anti-Hu antibodies [24]. Some patients harbor anti-CV2 (CRMP-5) [25,26] or amphyphisin [27] antibodies. Patients with anti-CV2 antibodies are more likely to have motor involvement and demyelinating features in the neurophysiological studies than those with anti-Hu antibodies [26]. Up to 16% of paraneoplastic sensory neuropathies are seronegative [28]. The presence of inflammatory infiltrates with a predominant population of $CD8^+$ T cells strongly suggests that this neuronopathy may be T-cell mediated [29].

Autonomic neuronopathy

Patients with paraneoplastic autonomic neuronopathy may present with diverse clinical syndromes. The most common is an isolated, severe gastrointestinal dysmotility syndrome due to loss of neurons of the enteric plexuses. The syndrome, also defined as chronic intestinal pseudo-obstruction, is usually associated with SCLC [30]. Patients present with nausea, early satiety, persistent constipation, weight loss, and abdominal distention. Imaging studies demonstrate dilated intestinal loops without evidence of obstruction. Some patients develop during their clinical course signs of sensory neuronopathy or a more widespread autonomic dysfunction [12].

A less common paraneoplastic autonomic neuronopathy is characterized by subacute pandysautonomia with impairment of the sympathetic (orthostatic hypotension, anhydrosis) and parasympathetic function (impaired pupillary responses, dry mouth, gastrointestinal dysmotility, urinary retention, erectile dysfunction, and fixed heart rate). The syndrome, also known as autoimmune autonomic ganglionopathy, usually is not paraneoplastic. However, the presence of neurological symptoms beyond the autonomic nervous system is highly suspicious of a paraneoplastic cause [31,32▪▪].

Diagnosis is confirmed by the detection of Hu antibodies that are usually found in patients with an underlying SCLC [9]. Up to 20% of patients with paraneoplastic autonomic neuronopathy harbor ganglionic acetylcholine receptor (AChR) antibodies [33,34]. However, ganglionic AChR antibodies are not markers of paraneoplasia and they are usually identified in patients with autoimmune autonomic neuronopathies [31].

PARANEOPLASTIC SENSORIMOTOR NEUROPATHIES

Paraneoplastic sensorimotor neuropathies antedating the diagnosis of cancer are uncommon. In patients with peripheral neuropathies of undetermined causes, including sensory neuronopathies, an underlying neoplasm was found in 14 of 187 (7.5%) consecutive patients [35]. In a similar study, 26 of 422 (6.1%) patients with peripheral neuropathies developed cancer shortly after the neurological symptoms. The frequency of cancer varied with the type of neuropathy: from 47% in sensory neuronopathy to 1.7% in Guillain–Barré syndrome (GBS) [36].

Paraneoplastic sensorimotor neuropathies do not have distinctive clinical features, they usually run a subacute course, and depending on the clinical and electrophysiological data the differential diagnosis with chronic inflammatory demyelinating polyneuropathy (CIDP) may be difficult (see below). Paraneoplastic sensorimotor neuropathies

are usually associated with SCLC, but they have been reported with different types of adenocarcinomas, melanoma, seminoma, and lymphomas [3]. Onconeural antibodies are usually negative with the exception of those associated with SCLC, which may associate with CV2 (CRMP5) and less frequently Hu antibodies [37].

Paraneoplastic demyelinating neuropathies

Paraneoplastic sensorimotor neuropathies may fulfill the diagnostic criteria of GBS, CIDP, Miller–Fisher syndrome [38▪], or multifocal motor neuropathy with conduction blocks [39▪]. The incidence of cancer in patients with GBS is difficult to establish due to design limitations of most studies. In a population-based study, the risk of cancer in patients with GBS was slightly increased (odds ratio 2.43; 95% confidence interval 1.09–4.50) with a cancer distribution similar to that expected in the general population [40]. However, the analysis of case reports indicates that GBS is more frequently associated with Hodgkin disease and SCLC [41,42]. Paraneoplastic demyelinating polyneuropathies may mimic CIDP. In 33 consecutive patients with probable or definite CIDP, three cases of gastrointestinal cancer were diagnosed shortly in the follow-up [43]. However, review of reported cases does not suggest an association with a particular type of cancer [3]. Paraneoplastic demyelinating polyneuropathies are also associated with lymphomas [44,45]. Paraneoplastic neuropathies are more common in Hodgkin and non-Hodgkin lymphoma (NHL) with monoclonal bands. In contrast, neuropathies in large cell lymphomas are more frequently caused by direct infiltration of the peripheral nerves (neurolymphomatosis) [46▪▪]. Patients with a CIDP variant characterized by predominant sensory symptoms, absence of anti-myelin-associated glycoprotein (MAG) antibodies, and disproportionately prolonged distal motor latencies are sometimes associated with chronic lymphocytic leukemia and NHL [47].

Sensorimotor polyneuropathies and malignant monoclonal gammopathies

Sensorimotor polyneuropathies may antedate the diagnosis of multiple myeloma and sclerotic myeloma, which are typically associated with IgG or IgA paraproteins, and Waldenström macroglobulinemia, NHL, and chronic lymphocytic leukemia, which are associated with IgM paraproteins. About 30% of patients with peripheral neuropathies and IgM paraprotein have an underlying lymphoma or Waldenström macroglobulinemia; in these patients the IgM paraprotein contains anti-MAG antibodies less frequently than in those without cancer [48,49]. The neuropathies associated with Waldenström macroglobulinemia are heterogeneous: in a recent retrospective study of 40 patients with neuropathy [50▪▪], 15 (37.5%) had demyelinating neuropathy and 25 patients (62.5%) had axonal neuropathy of a possible dysimmune cause (six patients), amyloidosis (5), cryogrobulinemia (5), tumoral infiltration (2), or vasculitis (2). The mechanism of the axonal neuropathy was unclear in five patients.

Osteosclerotic myeloma represents less than 5% of all myeloma cases, but more than 50% of these patients develop peripheral neuropathy usually before the diagnosis of the tumor. The IgG or IgA paraprotein almost always have a lambda light chain. The neuropathy of patients with sclerotic myeloma evolves as a chronic, distal, and large-fiber sensorimotor neuropathy. The disorder resembles a CIDP with motor predominance and high cerebrospinal fluid (CSF) protein content. All or some features of the POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M component, and skin changes) can be present. Correct and early diagnosis of POEMS syndrome is important because the treatment of the neuropathy is different than that associated with a solitary osteosclerotic myeloma or CIDP [51▪▪]. Recent studies suggest that comprehensive neurophysiological testing may suggest POEMS syndrome during the evaluation of a neuropathy with the clinical diagnosis of CIDP. The neuropathy in POEMS syndrome compared with that of CIDP shows a more uniform demyelination and a more severe axonal loss [52▪,53▪,54▪▪].

Vasculitic neuropathy

Paraneoplastic vasculitis involving nerves, and sometimes also muscle, without clinical evidence of systemic vasculitis has been reported in a few patients with solid tumors, particularly prostate, kidney, gastrointestinal and lung cancers, and lymphomas [55,56▪,57] The clinical course is characterized by a progressive, initially asymmetric, painful sensorimotor neuropathy. The clinical syndrome of mononeuritis multiplex is less common. The proximal muscle weakness observed in some patients probably reflects the coincident muscle vasculitis. Typically, the erythrocyte sedimentation rate is elevated and the CSF shows a high protein content. Electrophysiological studies are consistent with a multifocal mononeuropathy, or a diffuse axonal polyneuropathy with asymmetric involvement [58]. Nerve biopsy shows inflammatory infiltrates in vessel walls and perivascular regions, usually without necrotizing vasculitis. Analysis of the inflammatory infiltrates suggests that the disorder

is mediated by $CD8^+$ T cells [59]. Combined biopsy of the nerve and muscle increases the probability of demonstrating the vasculitis.

TREATMENT

The goal in the management of a patient with a paraneoplastic neurological syndrome is to cure the underlying cancer and to improve or stabilize (in those syndromes associated with neuronal death) the neurological dysfunction. Early tumor diagnosis is the best guarantee to improve or stabilize the paraneoplastic neurological syndrome. A compelling example is the paraneoplastic neuropathy associated with osteosclerotic myeloma or POEMS syndrome. In POEMS, the neuropathy rarely improves with immunotherapy unless the underlying myeloma is controlled. The most effective therapy is high-dose melphalan followed by autologous stem cell transplantation. This treatment improves or at least arrests the progression of the neuropathy in the majority of the patients [60,61]. For patients who are not candidates for autologous stem cell transplantation, or progress after it, treatment with lenalidomide and dexamethasone induces a durable response with a stabilization or improvement of the neuropathy in more than 80% of the patients [62▪▪,63]

Several immunosuppressants including corticosteroids, plasma exchange, rituximab, and intravenous immunoglobulins have been used in the treatment of paraneoplastic neuropathies. The impact of these therapies is unclear because the number of patients treated are low, patients also receive antineoplastic treatment, and randomized prospective studies are lacking [64▪,65▪▪]. Although theoretically immunosuppression could exacerbate tumor growth, we did not find that these treatments were an adverse prognostic factor for survival [66]. The possible benefit of immunotherapy should be assessed according to the type of paraneoplastic neuropathy. In patients with demyelinating neuropathies who have the potential for myelin regeneration, immunotherapy with steroids or intravenous immunoglobulins can be effective. In neuronopathies and neuropathies with axonal degeneration, there is a variable degree of irreversible neuronal damage so a reasonable aim of any immunotherapy can be the stabilization of neurological symptoms. Sensory neuronopathy, sensorimotor neuropathies, and gastrointestinal pseudo-obstruction, which often associate with anti-Hu antibodies, may have a very aggressive course and immunotherapy is often ineffective or leaves the patient with stable but severe deficits. In patients with a less aggressive clinical course, we favor a trial of immunotherapy, based on the strong evidence that most of these neuropathies are immune mediated, and the benefit observed in a few case reports [64▪,67]. If there is no response to these treatments, a trial with pulses of cyclophosphamide and rituximab should be considered, based on the improvement noted in isolated case reports [68▪]. Paraneoplastic autonomic neuronopathy (ganglionopathy) is probably mediated by ganglionic AChR antibodies that cause a functional rather than structural neuronal damage, and for these patients the chance to respond to immunotherapy is higher [69].

CONCLUSION

Paraneoplastic neuropathies may present with clinical and electrophysiological features that do not raise the suspicion of a paraneoplastic origin. However, recent studies indicate that a careful clinical evaluation helps to correctly identify paraneoplastic sensory neuronopathies from other causes. Similarly, electrophysiological studies can assist to differentiate the polyneuropathy of POEMS syndrome from CIDP. Lenalidomide and dexamethasone are often effective in patients with POEMS syndrome, who are not candidates for autologous hematopoietic stem cell transplantation or fail after it.

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Conflicts of interest

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