Paraneoplastic Diseases of the Peripheral Nervous System

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Bruno Giometto, Anna Grisold, Marco Zoccarato, and Wolfgang Grisold

17.1 Introduction

Peripheral nervous system involvement is a frequent condition in patients with paraneoplastic neurological syndromes (PNS), yet its clinical manifestations are highly heterogeneous. The peripheral nervous system can be variously involved, but the most frequently affected sites are the dorsal root ganglia and presynaptic nerve endings of the neuromuscular junction, whereas the extent of axonal and myelin damage of peripheral nerves is still unresolved. Several of the autoimmune neuropathies have a subacute and rapid development. The discussion of the therapeutic window of possible interventions is ongoing [1, 2].

While peripheral nervous system damage can be induced by various mechanisms in patients with systemic malignancy, in patients with neuropathy, it is usually of autoimmune origin and only rarely associated with direct tumour infiltration or at a later stage caused by chemotherapy. Chemotherapy-induced neuropathy, although frequent, has a different time profile and appears as conventional neurotoxic neuropathies [3].

Metabolic-related causes are uncommon. PNS arise in less than 1% of patients with malignancy, preceding the diagnosis of cancer by months or even years in the majority of cases. Specific serological markers can be used to screen for classical paraneoplastic syndromes, as defined by Graus et al. [4, 5].

B. Giometto
Department of Neurology, Ospedale Santa Chiara, Trento, Italy

A. Grisold
Department Neurology, Medical University, Vienna, Austria

M. Zoccarato
Department of Neurology, O.S.A—Azienda Ospedaliera di Padova, Padua, Italy

W. Grisold (✉)
Ludwig Boltzmann Institute for Experimental und Clinical Traumatology, Vienna, Austria

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In this chapter, the issue of neuropathies and disorders of the neuromuscular junction will be discussed. Specific cancer-associated muscular syndromes will be discussed in Chaps. 6 and 7.

Subacute sensory neuronopathy (SSN) and Lambert-Eaton myasthenic syndrome (LEMS) are classified as classical paraneoplastic syndromes. Other diseases like neuromyotonia or inflammatory neuropathies like Guillain–Barré syndrome (GBS) or chronic inflammatory demyelinating polyneuropathy (CIDP) associate with tumours in a minority of cases.

Onconeural antibodies directed against neural antigens expressed by the tumour may occur in most affected patients, suggesting an underlying autoimmune process [6]. Conversely endplate disorders as LEMS and neuromyotonia are caused by surface antibodies. The emerging spectrum of surface antibody-associated neuromuscular disorders has shown, that, contrary to onconeuronal antibodies, there is a large overlapping field with other autoimmune diseases.

The disorders are presented here below according to peripheral nervous system site (Table 17.1).

The clinical referral to neurological consultation is often neuropathy of unknown cause. Apart from the fact that in the age group of 50 years and more, 30–40% of neuropathies remain idiopathic, usually a screen for cancer is not warranted in sensory motor neuropathy. However if sensory ataxia, pain, and rapid onset appear, a sensory neuronopathy seems likely and can be associated with a PNS. However, also this is not specific as paraneoplastic neuropathy can be found in a range of other conditions (e.g., idiopathic Sjögren syndrome).

Table 17.1 Paraneoplastic diseases of the peripheral nervous system: a summary

Neuropathies
Subacute sensory neuronopathy
Monoclonal gammopathy and neuropathy
Paraneoplastic vasculitic neuropathy
Paraneoplastic dysautonomic neuropathy
Disputed and uncharacteristic:
Sensory neuropathy
Sensorimotor neuropathy
Inflammatory neuropathies:
Guillain-Barré syndrome (sporadic cases)
Chronic inflammatory demyelinating polyneuropathy associated with lymphoma
Motor neuron disease
Neuromuscular junction
Lambert-Eaton myasthenic syndrome
Myasthenia gravis
Neuromyotonia
Myopathies: see Chaps. 6 and 7
Cachexia: see Chap. 10

17.1.1 Subacute Sensory Neuronopathy

SSN, firstly described by Denny-Brown in 1948 [7], results from lymphocytic-inflammation with destruction of sensory neurons in the dorsal root ganglia. It is characterised by subacute, rapidly progressive onset, with chiefly multifocal or asymmetrical sensory loss, symptoms of paraesthesia and pain and, typically, asymmetric upper limb involvement, extending in some cases to the face, chest, or abdomen. Sensory loss, most markedly affecting deep sensation, leads in many cases to severe sensory ataxia of the four limbs. Sensory perception is markedly reduced and often slight touch is associated with allodynic pain. Fine motor tasks as buttoning, writing even holding a cup for drinking may be impossible.

Although very disabling, subacute sensory neuronopathy has been reported to have an indolent clinical course [8] often described as plateau phase. The prognostic aspects in regard to recovery and rehabilitation are poor.

SSN is the hallmark characteristic in over 50% of patients with paraneoplastic encephalomyelitis (PEM). Many patients with SSN also present signs and symptoms suggestive of multifocal limbic, cerebellar, brainstem, or spinal cord involvement, determining the picture of paraneoplastic encephalomyelitis [8–10].

Paraneoplastic SSN is characterised by a marked loss of primary, most notably large-diameter sensory neurons in the dorsal root ganglia, following a diffuse but patchy, asymmetric pattern. Signs of non-specific degenerative changes are present in the remaining neurons. Infiltration by T and B lymphocytes, plasma cells, and macrophages varies considerably and often shows perivascular distribution. Myelinated fibres are severely depleted in the dorsal columns, posterior nerve roots, and peripheral sensory nerves, believed to be secondary to the loss of dorsal root [11]. Sural nerve biopsy reveals non-specific axonal degeneration and a decrease in myelinated fibres [12, 13] and is rarely necessary.

Cerebrospinal fluid is usually altered (with non-specifically raised protein, mild mononuclear pleocytosis, elevated IgG index, and/or oligoclonal bands) but is reported to be normal in at least 10% of patients.

At electrophysiology exam, sensory nerve potentials are characteristically absent or severely diminished in amplitude, with normal or only slightly reduced sensory nerve conduction velocities, when a response can be elicited. Some uncharacteristic electrophysiological abnormalities can be seen in motor nerve conduction and are observed in the majority of patients, with or without symptoms of mixed sensorimotor polyneuropathy, but motor nerve is almost always less impaired than sensory nerve conduction. In patients with a motor, an additional motor neuropathy speculatively additional anterior horn cell involvement has been suspected.

The differential diagnosis of paraneoplastic sensory neuronopathy [14] includes dorsal root ganglionitis associated with Sjogren's syndrome [15], sensory neuropathy associated with anti-disialosyl ganglioside antibodies and idiopathic forms.

In the presence of a known cancer diagnosis, the differential diagnosis includes cisplatin- or paclitaxel-induced sensory neuropathy but is only relevant after sufficient treatment exposure. In addition, SSN usually develops at the time of cancer presentation and not during its course.

Table 17.2 Onconeural antibodies in paraneoplastic neuropathies (SSN)

Onconeuronal antibody-associated tumour(s) antibody	
Antibody	Associated to cancer
Anti-Hu (ANNA-1)	Small-cell lung cancer
Anti-CV2 (CRMP-5)	Small-cell lung cancer, other carcinomas
Anti-Ma2	Lung, testis, and other carcinomas

Although SSN can be associated with various tumours, small-cell lung cancer accounts for 70–80% of cases [8]. Most patients harbour anti-Hu antibodies, which show 99% specificity and 82% sensitivity for the diagnosis of cancer in patients with suspected SSN [6]. Anti-Hu antibodies stain the nuclei and, to a lesser degree, the cytoplasm of all neurons in the dorsal root ganglia, autonomic ganglia, and central nervous system. They react with a group of closely related 35–40 kD RNA-binding proteins, several of which have been cloned.

Expression Hu auto-antigens is frequent but not universal among small-cell lung carcinomas, including tumours of patients with SSN/PEM and anti-Hu antibodies and tumours of patients with no neurological symptoms. A small number of patients with SSN/PEM associated with small-cell lung carcinoma or with another malignancy either have no detectable anti-neuronal autoantibodies or harbour antibodies with patterns of immunoreactivity that differ from anti-Hu antibodies (Table 17.2). These include anti-CV2 (CRMP-5) antibodies targeted against a group of proteins expressed by neurons and oligodendrocytes, anti-amphiphysin antibodies and anti-Ma antibodies.

Anti-Hu-antibody-negative patients do not reliably differ from the spectrum of signs and symptoms seen in patients with anti-Hu antibodies. Anti-Hu or other anti-neuronal antibodies in patients with sensory neuronopathy are a robust (but not absolute) marker of an underlying tumour. Nevertheless, a paraneoplastic condition and an occult neoplasm may be present even in the absence of anti-neuronal antibodies.

17.1.2 Monoclonal Gammopathy and Neuropathy

Neuropathies associated with monoclonal gammopathy in some cases may be of paraneoplastic origin. Indeed, monoclonal gammopathy may underscore or transform into a haematological malignancy on whose treatment neurological improvement often depends [16].

In particular, the neuropathy associated with monoclonal gammopathy requires further investigation in the presence of IgM gammopathy to exclude Waldenström's macroglobulinaemia or other lymphomas [17].

Peripheral neuropathy causes complications in as many as 20% of patients with Waldenström's macroglobulinaemia [18], and the IgM antibodies may be directed at the myelin sheath [19]. Solitary plasmacytoma, multiple myeloma, or polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes

(POEMS) should be considered in patients with IgG or IgA monoclonal gammopathy. Peripheral neuropathy at the time of diagnosis is uncommon in patients with multiple myeloma, and neuropathies are often secondary to the use of neurotoxic drugs (e.g., thalidomide and bortezomib).

POEMS (or Crow-Fukase syndrome) is a rare plasma cell condition with multiorgan involvement. Its aetiology is not yet known, but there is an increasing body of evidence that vascular endothelial growth factor (VEGF) may play a role. Diagnosis continues to be based on clinical findings [20] since there are no specific tests or pathognomonic signs. POEMS syndrome targets in particular peripheral nerves, and neuropathic symptoms dominate the clinical picture [21]. It is frequently misdiagnosed as CIDP due to its prominent features of demyelination and axonal degeneration.

The associated monoclonal gammopathy is generally IgG or IgA, often carrying a lambda light chain. Correct diagnosis is critically dependent on the concurrent presence of systemic symptoms/signs (including organomegaly, endocrinopathy, pleural effusions, ascites, peripheral oedema, Castleman's disease, sclerotic bone lesions, thrombocytosis, skin changes, papilloedema) and increased levels of serum VEGF. Early treatment is crucial [22]. First-line therapy in patients with dominant sclerotic plasmacytoma includes radiation of the lesion. Systemic therapy is indicated for patients with diffuse disease [23–25] and also other haematological therapies as bone marrow transplant are used. Clinical response to treatment is associated with VEGF levels [21].

Immunoglobulin Light Chain (AL) Amyloidosis is a plasma cell disorder determined by deposition of monoclonal light chains in several tissues. Peripheral nerves are often involved, together with kidney, heart, lung, and liver. Fatigue and weight loss are frequent onset symptoms. Peripheral nervous system involvement consists in an axonal symmetric length-dependent neuropathy with loss of temperature sensation, neuropathic pain, and dysautonomia. Diagnosis is performed with bone marrow biopsy combined with abdominal subcutaneous fat aspiration [20].

17.1.3 Paraneoplastic Vasculitic Neuropathy

Peripheral nerve microvasculitis may be rarely associated with lymphomas or carcinoma of the lung, prostate, uterus, kidney, or stomach [26, 27].

Neurological symptoms usually precede diagnosis of the tumour. The disorder usually presents as mononeuritis multiplex or asymmetric distal sensorimotor neuropathy. Pain is frequently reported. Patients' sedimentation rate is usually high, but cutaneous vasculitis or other systemic symptoms are rarely present. Clinical involvement is asymmetric as shown in nerve conduction studies by varying levels of motor and sensory axonal degeneration. Sural nerve biopsy or autopsy demonstrates focal mononuclear cell infiltration of epineurial vessel walls and active nerve fibre degeneration. Additionally, arteriolar fibrinoid necrosis may be present with obliteration of lumina. Patients with peripheral nerve vasculitis and small-cell lung cancer may also present clinical and pathological features of SSN/PEM. Patients with small-cell

lung cancer can harbour anti-Hu antibodies, with or without overt central nervous system involvement [28].

Vasculitic neuropathies can also occur as a rare complication of immune check point inhibitor therapy [29].

17.1.4 Paraneoplastic Dysautonomic Neuropathy

Dysautonomia may be considered to be an isolated paraneoplastic peripheral neuropathy in a minority of patients. Chronic pseudo-obstruction is the most common syndrome. Symptoms may include severe, progressive gastrointestinal dysmotility, as gastroparesis, chronic intestinal pseudo-obstruction, and severe constipation/obstipation, preceding detection of the small-cell lung carcinoma by several months [8, 9].

The majority of patients do, however, develop dysautonomia alongside another paraneoplastic syndrome (mostly sensory neuronopathy), and the association with lung tumours, especially small-cell lung carcinoma, and Hu antibodies is robust [30, 31]. The syndrome responds rarely to tumour treatment, and no case studies have been conducted with immunotherapy. A recent review suggest that autonomic syndromes may be more frequent in cancer patients as currently assumed [32].

17.1.5 Other Paraneoplastic Neuropathies

Cases of sensory and sensorimotor neuropathies associated to malignancy, in the absence of onconeural antibodies, have been reported. Graus et al. [5] classifies these as possible PNS, if a tumour is detected within 3 years. To classify these cases as paraneoplastic, further investigation is needed: firstly, to rule out any pre-existing neuropathies or carcinomatous neuropathy associated with severe illness and/or weight loss and, secondly, bearing in mind that some tumours, as multiple myeloma, may give rise to several types of peripheral neuropathy (see above).

In addition, several novel observations and antibodies are described [33, 34]. The robustness and reliability of new observations will decide on the future use and application.

Some controversy surrounds the possible relationship between inflammatory neuropathy-like GBS and cancer, and the existence of a paraneoplastic form of GBS has not been confirmed. The cases with malignancies are usually clinically similar to the other cases of GBS [35], and 18 patients in the PNS Euronetwork database (unpublished reports) have been diagnosed with GBS or CIDP and a tumour. Several patients had both Hu antibodies and signs of demyelination on electromyography. These cases are most likely rare variants of Hu antibody-associated neuropathies.

Lymphoproliferative malignancies can favour the occurrence of inflammatory neuropathies, like GBS (more associated with Hodgkin's disease) or CIDP (more common in Non-Hodgkin Lymphoma) [36].

17.1.6 Motor Neuron Disease

Amyotrophic lateral sclerosis is not considered a paraneoplastic disease although association with onconeural antibodies and cancer in motor neuron disease (MND) has been reported [37]. A rapidly progressive form of MND could be raised the suspicion of an associated cancer [38]. Motor neuron involvement is recognised also in the context of anti-Ma2 paraneoplastic syndrome [39].

17.2 Syndromes of the Neuromuscular Junction

17.2.1 Presynaptic Disorders

17.2.1.1 Acquired Neuromyotonia

Neuromyotonia (NMT) is a generalised peripheral nerve hyperexcitability disorder. The characteristic clinical picture is of muscle stiffness, twitching (fasciculations) and/or rippling (myokymia), painful cramps, impaired muscle contraction or pseudomyotonia, and muscle weakness. Muscle hypertrophy can develop. The limb or limb and trunk muscles are most frequently affected [40]. One-third of patients also have sensory symptoms and approximately 50% develop hyperhidrosis. Central nervous system features (as hallucinosis, insomnia, chorea) could be present and, in its florid form, may be referred to as Morvan's syndrome. EMG reveals neuromyotonic and or myokymic discharges.

Neuromyotonia is paraneoplastic in around 25% of cases (5–10% in the PNS Euronetwork database) and can precede the discovery of a tumour by up to 4 years. The most frequently associated tumours are thymoma with or without myasthenia gravis, small-cell lung cancer, and haematological malignancies. Anti-voltage-gated potassium channel (anti-VGKC) antibodies are usually associated with these syndromes and are found in about 35% of all patients with peripheral nerve hyperexcitability and in as many as 80% in the presence of thymoma. They do not, however, differentiate the paraneoplastic from the non-paraneoplastic form. In 2010, true targets of anti-VGKC's antibodies were identified in channel-associated proteins, namely leucine-rich glioma inactivated 1 (LGI1) and contactin-associated protein-like 2 (CASPR2). These antibodies act by modulating degradation or expression of VGKCs in the presynaptic surface [41].

Anti-LGI1 antibodies are usually found in patients with limbic encephalitis. Differently, anti-CASPR2 antibodies are described in a clinical spectrum ranging from pure peripheral involvement, for example, neuromyotonia, to central nervous system manifestations, for example, limbic encephalitis. Morvan's syndrome, in which peripheral hyperexcitability coexist with dysautonomia, psychiatric disturbances, and sleep disfunction, is strongly associated with anti-CASPR2 antibodies although seronegative cases are reported [42]. In 20% of patients with anti-CASPR antibodies, a tumour, mostly thymoma, can be detected [43].

Notably, neuromyotonia and Morvan's syndrome have also been reported in children "double positive" for anti-LGI1 and anti-CASPR2 antibodies [44, 45].

17.2.1.2 Lambert-Eaton Myasthenic Syndrome

LEMS is a presynaptic disorder of the cholinergic neuromuscular and autonomic synapses. It is paraneoplastic in 60% of cases and usually associated with small-cell lung cancer [46]. Muscle weakness is the predominant feature in the proximal lower limbs and can extend to other skeletal muscles, rarely including the eye muscles. Respiratory failure is uncommon and tendon reflexes are depressed or abolished. Autonomic dysfunction is characterised by mouth or eye dryness, blurred vision, impotence, constipation, impaired sweating, or orthostatic hypotension [47]. Paraneoplastic forms usually have a more rapid progression of symptoms [48]. Repetitive nerve stimulation usually shows low compound muscle action potentials after nerve stimulation, with decrement at low-frequency stimulation and increment of over 100% after high-frequency stimulation or brief maximal effort. In a minority of patients, LEMS is associated with paraneoplastic cerebellar degeneration [49].

This syndrome depends on antibodies directed to P/Q-type voltage-gated calcium channels (VGCC). 10–15% of patients are negative for anti-VGCC antibodies; these are patients with similar clinical phenotype but with a lower incidence of associated small-cell lung cancer.

A recently described antibody marker, anti-SOX1, has been shown to be associated with paraneoplastic LEMS (65% of patients), rather than non-tumoural LEMS in which usually it is not detected [50].

17.2.2 Post-synaptic Disorders

17.2.2.1 Myasthenia Gravis

Myasthenia gravis (MG) is the most common autoimmune neuromuscular disease, characterised by muscle weakness especially after exercise. It is determined by autoantibodies against antigens placed in the postsynaptic membrane of the neuromuscular junction (sarcolemma).

In 85% of MG patients, antibodies against acetylcholine receptors (AchRs) are found, especially of the subclass IgG1 and IgG3. Another portion of patients has antibodies against MuSK and LRP4, which is protein involved in the clustering of AchRs. MuSK antibodies are mainly against the IgG4 subclass and determine a reduction of AchR density.

MG is considered a paraneoplastic disease in 10–15% of cases, in which a thymoma is found. Usually, paraneoplastic MG is found in AchRs-positive patients with higher anti-AchR antibody titre and severe disease [41]. Up to 40% of patients affected with thymoma can develop MG [51].

Usually, MG is not considered to be paraneoplastic in other tumours.

17.3 Differential Diagnosis

In investigating neuropathies of unknown origin, often a paraneoplastic cause is suspected.

Several other types of neuropathies are often considered to be paraneoplastic in the search of a possible cause. It is important to emphasise that 30–40% of

neuropathies in persons aged over 50 years are cryptogenic [52]. Extensive workup rarely reveals additional information regarding the diagnosis. From the clinical point SSN, LEMS, NMT need to be carefully checked for paraneoplastic neurological causes.

17.3.1 Neoplastic Neuropathies

Depending on the cancer type, several different types of peripheral nerve involvement exist, all of which are rare and are often focal and rarely resemble a symmetric neuropathy.

1. In rare cases, meningeal spread can mimic peripheral neuropathy. Severe meningeal carcinomatosis can affect multiple roots and resemble neuropathy. Rarely, isolated infiltration of the cauda equina can produce flaccid paraparesis, which is usually associated with pain, some asymmetry, and additional cranial nerve and central nervous system involvement. Neuropathies caused by immune therapies may mimic meningeal carcinomatosis [53].
2. Infiltration of peripheral nerves by cancer can be widespread and occur in a neuropathy-like lesion, can affect individual parts of peripheral nerves and the plexus, and can also spread along peripheral nerves. Anastomosis between cranial nerves can also be the target of cancer infiltration [54].
3. Symmetric involvement of peripheral nerves mimicking polyneuropathy is almost exclusively observed in lymphoma and leukaemia. In lymphoma in particular, the term neurolymphomatosis is used, in addition to the intravascular type. Several reports have suggested that neurolymphomatosis can mimic CIDP [55].

17.3.2 Chemotherapy-Induced Peripheral Neuropathy (CIPN)

In patients being treated for cancer, neuropathies are usually caused by therapy. In addition to the cumulative toxicities observed with vinca alkaloids, taxanes, platinum drugs, bortezomib, and thalidomide [56], several other paradigms need to be considered.

17.3.2.1 Acute Effects of Chemotherapy

Effects are observed with oxaliplatin [57], and taxanes can in some cases produce acute effects. In addition to acute effects, oxaliplatin also develops cumulative toxicity. A new class of drugs, delivering neurotoxic agents by targeted antibodies, as brentuximab or ado trastuzumab emtansine, are under evaluation.

17.3.2.2 Late Effects

There are increasing reports of the late effects of chemotherapy [58]. These manifest in persisting neuropathic symptoms as pain and Raynaud's syndrome.

17.3.2.3 Autoimmune Effects

Autoimmune diseases and inflammatory neuropathies have appeared in therapies with immune checkpoint inhibitors [59, 60].

17.3.2.4 Mimics

In addition to the differential diagnosis, the clinician must also be aware of local cauda compression, acute myopathies, and electrolyte disorders.

17.4 Conclusions

Peripheral nerves are a target for paraneoplastic diseases. In neuropathies, there is a clear predominance of SSN with well-established clinical features and oncological and immunological associations.

However, the association between onconeural antibodies and a specific clinical picture and outcome remains to be demonstrated. In addition, no randomised clinical trials have been conducted on the treatment of SSN, and it is general (but not evidence based) opinion that the best treatment opportunity for these cases is through early tumour detection [61].

Paraneoplastic vasculitic and dysautonomia are rare and documented. They may fail to respond to immunotherapy and rarely improve with cancer treatment.

The occurrence of other neuropathies as sensory, sensorimotor, and also inflammatory neuropathies still not resolved, except some small series in lymphoma.

In the presence of a neuropathy associated with a monoclonal gammopathy, a combined neurological and haematological approach is recommended to exclude any underlying malignancies. IgM monoclonal gammopathy of undetermined significance (MGUS) neuropathies are mainly demyelinating, more sensory than motor in character, slowly progressive, and sometimes associated with anti-MAG antibodies. The underlying tumour may be Waldenström's macroglobulinaemia. The neuropathies associated with IgG or IgA MGUS present with a CIDP- like course, but multiple myeloma, solitary plasmacytoma, and POEMS should be ruled out. Treatment depends on both the severity of the neuropathy and the haematological condition.

Acquired NMT is a generalised peripheral nerve hyperexcitability disorder. The characteristic clinical picture is of muscle stiffness, twitching (fasciculations) and/or rippling (clinical myokymia), painful cramps, impaired muscle contraction and muscle weakness. The limb or limb and trunk muscles are most frequently affected, a specific form "limb myotonia" has been described. Association with anti-CASPR2 antibodies has been described. Not all cases of myotonia are paraneoplastic.

LEMS is an autoimmune disorder of paraneoplastic and non-paraneoplastic origin. LEMS patients should thus be screened not only for VGCC antibodies but also for onconeural and SOX1 gene (protein coding) to search for a paraneoplastic origin.

MG is a paraneoplastic disease in 10–15% of cases in thymoma. Usually, AchRs-positive patients with severe disease are detected.

The relation of cancer and the muscular system (muscle) is discussed in Chaps. 6 and 7.

The relation of cancer and the neuromuscular system is important in clinical practice, and is within the primary responsibility of a neurologist to identify neuromuscular disorders of paraneoplastic origin, not only to detect cancer, but also being able to treat the often debilitating neurological diseases.

The meta level is the relation of the tumours and the neuromuscular system, which seems to be diversified into several mechanisms as onconeuronal antibodies, surface antibodies, antibodies within the paraproteinaemias, antibodies against muscle tissue and no detectable antibodies, as in cachexia, and in the often indolent late-stage neuropathies of cancer patients.

The primary clinical tool is the complex neurological investigation, aided by electrophysiology and increasingly imaging.

Further studies are warranted (a) to better characterise the relationship between sensorimotor neuropathies and malignancies after ruling out all potential confounding conditions related to treatment toxicity and (b) to better characterise the oncological profile of patients with paraneoplastic neuropathies in addition to the consolidated relationship with small-cell lung cancer.

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