Paraneoplastic disorders of the peripheral nervous system

Jean-Christophe Antoine¹,²,³, Jean-Philippe Camdessanche¹,²,³

1. University Hospital of Saint-Étienne, Department of Neurology, Saint-Étienne, France
2. Reference Center for Paraneoplastic Neurological Syndrome, Lyon, Paris and Saint-Étienne, France
3. Rhône-Alpes Reference Center for Rare Neuromuscular Diseases, Saint-Étienne, France

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Correspondence:
Jean-Christophe Antoine, CHU de Saint-Étienne, Service de Neurologie, 42055 Saint-Étienne cedex 02, France.
j.christophe.antoine@chu-st-etienne.fr

Summary

Paraneoplastic neurological syndromes are rare but can affect any part of the peripheral nervous system (PNS) including motor neurons, sensory ganglia, nerve roots, plexuses, cranial and peripheral nerves, and neuromuscular junctions. The type of cancer, lymphoma or solid tumour, is a determinant factor of the underlying mechanism. With solid tumour, antibodies directed to intracellular (anti-Hu or anti-CV2/CRMP5 antibodies) or surface antigens (anti-VGCC, or LGI1 and Caspr2 antibodies) have been identified while with lymphoma, the neuropathy is usually linked to a monoclonal gammopathy. This review discusses the different etiologies and mechanisms of paraneoplastic disorders of the PNS in patients emphasising their evaluation, diagnosis and treatment.
roots, plexuses, cranial and peripheral nerves, and the neuromuscular junction. The third level corresponds to the cellular structures that are targeted, neuron cell body, axon membrane or myelin sheath. The nature of cancer is responsible for the fourth and last level of complexity since lymphoma and carcinoma have a different ability to induce paraneoplastic disorders. All of these points have practical consequences for the diagnosis and management of patients.

**Classification of paraneoplastic disorders of the PNS**

The known mechanisms by which paraneoplastic disorders may develop are mostly autoimmune. With carcinoma, the expression by the tumour of a self-antigen present on different components of the nervous system may lead to a breakdown of immune tolerance, activation of auto-aggressive B and T cells resulting in the production of autoantibodies and cytotoxic T-lymphocytes [3,4]. Two categories of antigens are now distinguished, namely intracellular and cell surface antigens [5,6]. This distinction has important consequences since although antibodies are produced with both types of antigens, it is probable that they do not have access to their target when the antigen is intracellular and that T cells are then the main effectors of the immune process. The situation is different when the antigen is incorporated in the cell membrane, such as receptor or ion channel proteins or proteins associated to them since a number of evidences clearly shows that in this case antibodies have access to their target and may modulate the cell surface expression of the protein or by complement activation damage the cell membrane [5,7]. The practical consequence is that antibody-mediated disorders are likely to be better responders to immune treatments than the cell-mediated ones. Another important difference between intracellular and cell surface antigens is that with the former, the immune response is almost universally associated with an underlying tumour, while with the later a cancer may or may not be present [7]. Two intracellular antigens are specifically associated with paraneoplastic PNS disorders, namely the HuD and CV2/CRMP5 proteins. HuD is a nuclear and cytoplasmic protein associated to mRNAs which is widely expressed in neurons of the central and peripheral nervous system including autonomic neurons [8]. The CV2/CRMP5 protein is a developmentally regulated protein which in the adult persists in sensory neurons and in axons and Schwann cell of the peripheral nerves [9]. Concerning cell surface antigens, two motor axon membrane proteins of the peripheral nerve are in this category: the voltage-gated calcium channels (VGCC) of motor nerve terminals which are involved in acetylcholine release through calcium entry at the presynaptic level [10] and CASPR2, a protein associated with potassium voltage-gated channels (VGKC) [11,12].

With lymphoma, the known mechanisms are somewhat different. As a rule, the tumour is responsible for the secretion of factors that induce the disorders. Usually, this factor is a monoclonal immunoglobulin produced by malignant plasmocytes (IgG or IgA) or lymphoplasmocytes (IgM). Monoclonal IgM can behave as autoantibodies reacting in all the identified cases with a membrane antigen present on the axon or the myelin sheath. The myelin-associated glycoprotein (MAG) or gangliosides of the axon or neuron cell surface are the main targets of these antibodies. As with carcinoma, antibodies are likely to be responsible for the disorder and may occur without malignant condition that is to say with monoclonal gammopathy of unknown significance. In other circumstances, the physicochemical properties of the monoclonal immunoglobulin lead to the formation of amyloid deposits or cryoglobulin precipitates, which are deleterious for the peripheral nerves. Finally, in a rare condition, that of POEMS syndrome, the immunoglobulin is not the pathogenic factor but probably an array of cytokines produced by the tumour.

Criteria for the diagnosis of paraneoplastic neurological syndromes have been proposed, which does not take into account neuropathies associated with malignant monoclonal gammopathies [13]. However, these criteria can easily be adapted for PNS disorders as a whole. Definite paraneoplastic PNS include three categories of disorders: first, those involving one of the aforementioned mechanisms, second cases of a well-established form of paraneoplastic neuropathy occurring with a tumour but no identified antibodies, which mainly corresponds to seronegative sensory neuronopathy, and third neuropathies that unequivocally improve with the sole treatment of the tumour. Conversely, any other form of neuropathy which occurs within 2 years of the diagnosis of cancer can only be provisionally considered as a possible paraneoplastic disorder.

**Paraneoplastic disorders of the PNS associated with antibodies toward intracellular antigens**

**Subacute sensory neuropathy (SSN) and other PNS disorders of the anti-Hu syndrome**

SSN depends on the destruction of sensory neurons in dorsal root ganglia by cytotoxic T-lymphocytes [14]. The onset is usually subacute or rapidly progressive with paraesthesia and pain. Sensory loss is mostly multifocal or asymmetrical, and the upper limbs are almost invariably involved [15,16]. The face, the chest, or the abdomen may also be concerned. Pain is frequent and sensory loss, affecting especially deep sensation, often leads to a severe sensory ataxia in the four limbs. Although if diagnosed late in the evolution, SSN can be a very disabling disorder, indolent and protracted courses have been reported [17]. CSF may show elevated protein concentration, pleocytosis or oligoclonal bands. The
electrophysiological hallmark of SSN is a severe and diffuse alteration of sensory nerve action potentials with frequently non-excitable sensory nerves. Motor conduction velocities are classically normal but are frequently mildly altered which may be confusing and lead to the inappropriate diagnosis of axonal sensory-motor neuropathy [18]. Although SSN occurs with different tumours including breast cancer and Hodgkin’s disease [19], small cell lung cancer (SCLC) represents 70–80% of cases. Most patients have anti-Hu antibodies, which have 99% specificity and 82% sensitivity for the diagnosis of cancer in patients suspected to have SSN [20]. If SSN is the most frequent and usually predominant manifestation of the anti-Hu syndrome, it is isolated in only 24% of patients, the others having various combinations of central and peripheral nervous system involvement [16].

Other PNS disorders may occur with anti-Hu antibodies [16]. The most frequent is dysautonomia which is frequently associated with SSN. It affects the cardiovascular and digestive systems. Orthostatic hypotension can be very severe and arrhythmia may explain cases of sudden death. Digestive pseudoobstruction is also a severe disease that results from the destruction of autonomic neurons in myenteric plexuses. Lesion of the lower motor neurons induces motor deficit, muscle atrophy and fasciculations. As in most cases, patients simultaneously have SSN, the resulting presentation is that of a sensory-motor polyneuropathy which since the evolution is usually rapid and the distribution asymmetrical, may be confused with a mononeuropathy multiplex. More symmetrical case with an extensive progression may also be misdiagnosed as Guillain-Barré syndrome. A predominant or pure motor neuron syndrome mimicking amyotrophic lateral sclerosis is quite exceptional [21]. Nerve vasculitis [22] and demyelinating neuropathy [23] have been reported but they are very unusual presentations of the anti-Hu syndrome.

Peripheral neuropathy with anti-CV2/CRMP5 and other onconeural antibodies
Periperal neuropathy occurs in 57% of patients with anti-CV2/CRMP5 antibodies and is frequently associated with cerebellar ataxia, limbic encephalitis or ocular involvement. The neuropathy [24] is different from that of patients with anti-Hu antibodies [25]. It is sensory or sensory-motor and predominates in the lower limbs. Pain is less frequent. Electroneuromyogram (ENMG) shows an axonal or mixed axonal and demyelinating pattern, but the slowing of motor conduction velocities does not reach the values usually observed in chronic inflammatory demyelinating polyneuropathies (CIDP) and conduction blocs are never seen. Nevertheless, when performed, nerve biopsy may show demyelinated fibers and onion bulb formations [24]. The association of anti-Hu and anti-CV2/CRMP5 antibodies is not rare. Patients with both antibodies may develop a neuropathy blending the characteristics of the two disorders, in particular with a mild demyelinating pattern on the ENMG.

SCLC and thymoma are the most frequent underlying tumours with anti-CV2/CRMP5 antibodies but the prognosis of SCLC is better with anti-CV2/CRMP5 antibodies than with anti-Hu antibodies [25]. PNS disorders occur only occasionally with anti-Yo, anti-Ma2, and anti-amphiphysin antibodies and the clinical pattern of the neuropathy in these cases has not been well established [26–28].

Paraneoplastic disorders of the PNS associated with antibodies directed toward cell surface antigens

The Lambert-Eaton myasthenic syndrome (LEMS)
LEMS is a presynaptic disorder of the cholinergic neuromuscular and autonomic synapses. It is paraneoplastic in 40 to 60% of cases usually in association with SCLC [29–31]. Other lung cancer is rare [29,32–34] and other organ tumour exceptional [30]. Muscle weakness predominates in the proximal lower limbs and can spread to other skeletal muscles including ocular muscles [29]. Conversely, respiratory failure is rare [35]. Tendon reflexes are depressed or abolished. Improvement of strength and tendon reflexes by exercise is reported in 40% of patients [36,37]. Autonomic dysfunction is characterized by mouth or eye dryness, blurred vision, impotence, constipation, impaired sweating, or orthostatic hypotension [29]. In a subgroup of patients, LEMS is associated with paraneoplastic cerebellar degeneration or with the anti-CV2/CRMP5 syndrome [38].

ENMG abnormalities in LEMS consist in the reduction of compound motor action potentials (CMAP), a decrement superior to 10% in case of low frequency repetitive stimulation (3–5 Hz) and increment superior to 100% after brief (20 to 60 s) maximum voluntary muscle contraction or high frequency repetitive stimulation (2–50 Hz) [39]. Presence of autoantibodies directed to voltage-gated calcium channels (VGCC) is a main point for the diagnosis of LEMS as these antibodies are present in 85 to 90% of patients and reach 100% in case of SCLC [40–42]. A direct role of anti-VGCC antibodies in the pathophysiology of LEMS through a presynaptic bloc of axonal signal has been demonstrated [39] as well as the transfer of the disease by the serum of the patients in case of pregnancy [43–45] or in animal models [41].

Neuromyotonia and peripheral nerve hyperexcitability (PNH)
Acquired neuromyotonia, PNH, and Isaacs’ syndrome encompass abnormal muscle activities generated in motor nerves like cramps, stiffness, twitching, spasms, or abnormal muscle relaxation [46]. In some patients, PNH is associated with motor weakness, paresthesias, hyperhidrosis and/or central nervous involvement including confusion, sleep disruption, mood changes, and hallucinations reaching in these particular cases the diagnosis of Morvan’s syndrome [47]. Diagnosis is based on...
ENMG recording of fibrillation potentials, fasciculation potentials, myokimia organized in doublet, triplet or multiplet, myokimic discharges, neuromyotonic discharges at rest, and post-effort or post-electric stimulus discharges [48]. Neuromyotonia is associated with thymoma in 15% of cases, less frequently with SCLC and occasionally with Hodgkin’s disease or plasmocytoma [47]. Dysimmune mechanisms suggesting a direct role of voltage-gate potassium channel antibodies have been supported by several experiments [49,50], but contactin-associated protein-2 (CASPR2) is now known to be the immune target even if numerous patients do not develop abnormal antibodies [12,46,51]. In Morvan’s syndrome, the central nervous system involvement is probably linked with LGI1 antibody which occurs more frequently with limbic encephalitis [52,53].

**Peripheral neuropathies in patients with malignant monoclonal gammopathies (MG)**

Monoclonal immunoglobulins associated with malignant clonal proliferations of B-lymphocytes represent 25–30% of all MG. IgM isotype is associated with lymphoplasmocytic lymphoma (Waldenström’s disease), IgG with lymphocytic leukaemia or lymphoma and IgA, or D with multiple myeloma. The overall risk of developing malignancy in patients with MG of unknown significance is about 1% per year but increases with age [54].

Amyloidosis occurs in 20–40% of patients with multiple myeloma. It is most frequent with λ light chains with a k/λ ratio of about 1/3. Peripheral neuropathy reveals amyloidosis in one fourth of the cases and usually presents as a painful sensory or sensory-motor neuropathy mainly affecting small fibers [55,56]. Carpal tunnel syndrome, macroglossia, purpura, nephrotic syndrome, renal insufficiency, congestive heart failure, and orthostatic hypotension are frequent [57]. About 70% of patients have at least two organ involvements at presentation [58]. Some atypical presentation of the neuropathy may occur including cases mimicking CIDP [59]. A rare presentation with monoclonal IgM and lymphoplasmocytic lymphoma is that of amyloidosis in roots and plexus [60,61]. Demonstration of amyloid deposits may be difficult and necessitate several biopsies. Cryoglobulins associated with lymphoma are mostly of type I (monoclonal IgG/IgM component only). Mononeuritis multiplex or sensory-motor neuropathy with vasculitis is the most frequent manifestation followed by Reynaud’s phenomenon, and skin and renal changes [62,63].

With Waldenström’s macroglobulinemia, the monoclonal IgM can behave as a peripheral nerve antibody. The neuropathy is similar to that which more frequently occurs with MGUS IgM. In 5 to 45% of patients, the reactivity is directed against MAG [64,65] and the light chain isotype is κ. The neuropathy is typically a chronic distal mostly sensory neuropathy. Pain, tremor and ataxia are frequent. Electrophysiology shows a predominantly distal demyelinating pattern demonstrated by a decreased terminal latency index under 0.3 [66,67]. Nerve biopsy when it is performed may show a typical widening of the most peripheral myelin lamellae and intra-myelin IgM deposits. Other reactivity is fairly rare in general and especially with lymphoma. IgM reacting with disialosyl gangliosides occur with a predominantly sensory neuropathy and ophthalmoplegia [68,69], and reactivity with GM1 with multifocal motor neuropathy [70,71].

POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes) syndrome is a rare multisystem disorder occurring with osteosclerotic myeloma [72,73]. A chronic sensorimotor predominantly distal axonal and demyelinating neuropathy and a monoclonal component are mandatory to establish the diagnosis [73]. The component is usually an IgG (more rarely an IgA) and the light chain of the λ isotype. Oedema including papilla oedema, ascites and ana-sarca, pulmonary hypertension, renal failure, thrombotic events, and congestive heart failure are part of the syndrome. Cytokines including IL-6, TNFα and especially VEGF are over-produced. Several studies have showed the great help provided by a dosage of plasma VEGF level for the diagnosis of POEMS syndrome when the presentation is incomplete [74–76]. Usually very high levels of VEGF are detected but some patients may present with mild or even low levels. Beside these well-characterized situations, there exist other neuropathies for which the link with the gammopathy is still unclear [77]. In Waldenström’s disease, a large spectrum of peripheral neuropathy may occur [78]. An unspecific distal predominantly sensory neuropathy may represent a majority of cases [64]. The pattern of the neuropathy is axonal or demyelinating. Observations of endoneural immunoglobulin deposits in nerve biopsies suggest that the MG may be deleterious for nerve fibers without the necessary formation of amyloid deposits [71,79]. Neuropathy with non-sclerotic myeloma that do not depend on amyloidosis are rare and most of the reported cases have an axonal pattern [80].

**Possible paraneoplastic peripheral neuropathies**

Since the concept of paraneoplasia has been fully developed in the first half of the 20th century, varieties of neuropathies other than those listed above have been reported as paraneoplastic. These include cases of Guillain-Barré syndrome, CIDP, mononeuritis multiplex, lower motor neuron diseases, brachial plexopathy and sensory or sensory-motor axonal polyneuropathy [81]. In a study, neuropathies occurring in a short delay with the discovery of cancer tended to be inflammatory including Guillain-Barré syndrome, CIDP, and neuropathies with vasculitis [82]. With lymphoma, demyelinating neuropathy is the most frequent pattern, but axonal neuropathy with microvasculitis
and lower motor neuron disease have also been reported \[83,84\]. None of these cases have one of the identified onconeural antibodies and a link between the neuropathy and the tumour has not been demonstrated. Improvement of a neuropathy following treatment of the tumour is a major criterion of the diagnosis of paraneoplastic disorders, but reported cases are few. They include lower motor neurone diseases \[85,86\], vasculitic neuropathies \[87\], and CIDP \[88\]. An epidemiological approach is another way to demonstrate a link between cancer and neuropathy. But studies are few and the published ones may not be free of statistical bias. For example, an Italian group found increased incidence of cancer in a cohort of patients with Guillain-Barré syndrome \[89\], but no specific tumour was observed. This is a general feature of neuropathies without onconeural antibodies, which strikingly contrasts with the overwhelming incidence of SCLC in patients with onconeural antibodies.

In rare cases, autoantibodies have been observed which suggests immune-mediated disorders. Thus, ganglionic acetylcholine receptor antibodies have been reported in patients with acute or subacute and sometimes chronic autonomic neuropathies \[90\] but these antibodies are not specific of cancer and at high titre rarely occur in patients with a known tumour although low or mild level of antibody may be present in several neurological conditions including with and without cancer and in patients with small cell lung tumour \[91\]. In a handful of cases, a mechanism similar to that of the well-identified paraneoplastic disorders may be suspected. Thus, a patient with breast cancer and lower motor neurone disease developed an antibody reacting with \(\beta\)IV spectrin \[92\]. Although low levels of anti-ganglioside antibodies can be found in patients with neuropathy and tumour probably as a consequence of a natural anti-cancer immunity \[93\], anti-ganglioside antibodies have been specifically linked with both the cancer and the neuropathy in a few patients with melanoma \[94,95\].

**Diagnostic strategy of paraneoplastic disorders**

**When and how to diagnose a paraneoplastic neuropathy?**

In more than 80% of cases, the paraneoplastic neurological disorder antedates the revelation of cancer by month or years and when the cancer is known, a relapse must be suspected. It is therefore important to identify those patients for whom an active search of an underlying tumour is needed. In this way, there are three main circumstances in which the clinical patterns of the neuropathy imply to consider the possibility of a paraneoplastic disorder.

The first is when a well-established paraneoplastic disorder is diagnosed. This includes SSN, LEMS, neuromyotonia and neuropathies with a well-characterized onconeural antibody. SSN depends on several etiologies including, genetic, toxic, dysimmune and paraneoplastic conditions while an important proportion remains idiopathic. In our personal series, an underlying tumour is present in no more than 6% of patients with definite SSN originating from a single population area (unpublished data). Distinguishing SSN from other sensory neuropathies is nevertheless important owing to its consequence. A set of criteria relying on easily obtainable clinical and electrophysiological items has good sensitivity and specificity to distinguish SSN from other neuropathies \[96\]. Following a recently proposed strategy for the etiological diagnosis of SSN \[97\], it is recommended to perform systematically a search for anti-Hu and CV2/CRMP5 antibodies in patients fulfilling the criteria of SSN. As paraneoplastic SSN can be seronegative, a search for a tumour must be performed if the evolution is acute or subacute and the CSF inflammatory. The question of a paraneoplastic origin may arise in a patient receiving platinum salts for the treatment of a small cell lung cancer and who develops subacute SSN. Some clinical features distinguish toxic from paraneoplastic SSN in particular platinum salt-induced SSN have a symmetrical distribution and almost spare small fibers \[98,99\]. A search for onconeural antibodies may help to distinguish the two disorders but only high antibody titers are indicative of a paraneoplastic origin since patients with SCLS may harbor low level of anti-Hu or anti-CV2/CRMP5 antibodies \[13\].

The main difficulty with LEMS is not to miss the diagnosis and perform a search for potentiation in a patient with peripheral motor deficit and low amplitude CMAP. As patients with anti-Hu and especially anti-CV2/CRMP5 antibodies may simultaneously have LEMS, it is recommended to systematically perform a search for potentiation when the CMAPs are abnormal. A clinical score, the DELTA-P score, has been proposed to predict the paraneoplastic origin of LEMS in a given patient according to the presence of bulbar weakness, erectile dysfunction, loss of weight, tobacco consumption, age and Karnosky’s score in the screened patients \[100\]. Anti-SOX1 antibodies which are specific of the tumour may also help to distinguish paraneoplastic from non-paraneoplastic LEMS \[101,102\].

The second circumstance which is highly suspect of a paraneoplastic neurological syndrome although not pathognomonic is when the peripheral neuropathy is associated with involvement of the central or autonomic nervous system. Such an association must therefore be carefully searched for in a patient with subacute peripheral neuropathy since central and autonomic nervous system manifestations may be almost asymptomatic. A subacute and severely deteriorating evolution is a common feature of paraneoplastic disorders. Therefore, peripheral neuropathies with an unusual, rapid and severe course should be considered as suspect of a paraneoplastic disorder inasmuch as the CSF shows cellular inflammatory reaction or local IgG
production. Patients in these circumstances may or may not have onconeural antibodies. Although there is no validated recommendation for the management of patients when onconeural antibodies are absent, it may be preferable to search for an underlying tumour when the neuropathy follows this pattern. As a rule, axonal distal polyneuropathy or CIDP do not deserve a specific search for a malignancy except when a monoclonal gammopathy is detected. The question is opened for nerve vasculitis for which there exist several case reports or small series mentioning association with lymphoma or carcinoma [84,103,104].

A search for monoclonal gammopathy is a common rule in the management of patients with peripheral neuropathy. A monoclonal IgG with λ light chain should prompt searching for amyloidosis or POEMS syndrome according to the clinical presentation while a κ light chain with a monoclonal IgM should orientate toward a possible autoantibody activity of the monoclonal component. Monoclonal cryoglobulins may be difficult to detect if they are precipitated in the serum sample. In this circumstance, a low blood complement level is very suggestive of cryoglobulinemia.

With lymphoma, the most important difficulty is to identify cases of neurolymphomatosis due to the infiltration of peripheral nerves by the tumour and distinguish them from paraneoplastic disorders. Pain and a presentation of radiculopathy are suggestive but the neuropathy may present in many other forms [105]. FDG-PET scanner may help to detect abnormal fixation along peripheral nerves, but nerve biopsy is the only way to ascertain a diagnosis, which is frequently a difficult decision since proximal nerve trunks, roots or plexus may have to be analyzed. Furthermore, a close phenotypic study of the mononuclear cells infiltrate is necessary to demonstrate monoclonality and distinguish lymphomatous infiltration from inflammatory reaction [84].

**Tumour diagnosis in patients with definite paraneoplastic PNS**

The strategy in search for the responsible cancer depends heavily on the nature of the paraneoplastic disorders and the associated antibodies [31]. In patients with SSN, LEMS, anti-Hu or anti-CV2/CRMP5, SCLC must be suspected first. The tumour is frequently limited to small metastatic lymph nodes that may escape detection by CT scan or lung fibroscopy. A FDG-PET scanner is then recommended but it should be kept in mind that if the method is highly sensitive it is not specific [106]. Mediastinal lymph nodes may be difficult to reach for biopsy and each case must be carefully discussed with a trained lung specialist or thoracic surgeon to adopt the safest strategy with the best chance of rapidly reaching the accurate diagnosis [107]. FDG-PET scanner has also the advantage of detecting extrapulmonary small cell tumours that may occur with the disorders listed above. When a first careful workup is negative, it is recommended to renew it after 3 to 6 months and then every 6 months for a period of at least 4 years [31]. With LEMS, 2 years are sufficient since most cancer appear within this delay [13]. When performing an extensive search for the underlying tumour, it is not rare to found a malignancy which is at odd with the expected cancer (e.g. a colon cancer with an anti-Hu antibody). If an expression of the onconeural antigen by the tumour is not demonstrated, a SCCL must still be suspected [16]. With neuromyotonia and CV2/CRMP5 antibodies, thymoma is an alternative possibility when other cancers are excluded.

With monoclonal gammopathy, the strategy of tumour diagnosis depends on the nature of the gammopathy. Waldenström’s disease and lymphocytic leukemia are usually diagnosed by blood cell analysis and bone marrow aspiration or biopsy. Lymphomas usually require FDG-PET scanner and lymph node biopsy. A search for a plasmocytic proliferation necessitates an extensive and careful bone radiographic screening since particularly with POEMS syndrome the tumour may present as solitary plasmocytoma. MRI is helpful for the detection of plasmocytomas in particular when they are located in the vertebrae. Plasmocytomas are usually not detected by bone scintigraphy with technecium tracers but may be showed by FDG-PET scanner [107].

**Treatment**

**Symptomatic treatments**

Pain is a frequent manifestation of paraneoplastic neuropathies and patients may greatly benefit from tricyclic antidepressants, antiepileptic and sometimes morphinic drugs [108].

The first-line treatment in LEMS is symptomatic and uses 3-4 diaminopyridine which is a validated strategy according to the 2011 Cochrane review [109]. Seizure is a dose-dependent serious side effect of 3-4 diaminopyridine and must be taken into account [110]. Perioral tingling, paresthesias, gastrointestinal symptoms, and in a few cases, QT interval prolongations can be encountered as well. With neuromyotonia, carbamazepine, phentoin, lamotrigine and sodium valproate can be used alone or in combination [111].

**Specific treatments**

**Paraneoplastic disorders with antibodies toward intracellular antigens**

Several studies have tried immunomodulatory or immunosuppressant treatments including high-dose steroids, intravenous immunoglobulins (IVig), plasma exchanges, cyclophosphamide, rituximab or a combination of them in patients with paraneoplastic disorders associated with intracellular antigen antibodies [112–115]. These studies are often uncontrolled or opened and include small numbers of patients with different paraneoplastic disorders and onconeural antibodies. Some of them suggest slight improvement or stabilization but as a
whole their results are inconclusive. In a retrospective study of a large number of patients with anti-Hu antibodies, an early treatment of the tumour was the only factor significantly associated with a stabilization of the neurological disorder [16].

**Paraneoplastic disorders with antibodies toward intracellular antigens**

The main treatment of paraneoplastic LEMS is, as in the princeps case, the tumour treatment which usually results in an improvement of the neuromuscular transmission failure [116]. In case of residual symptoms, prednisone or prednisone–azathioprine association is proposed on the basis of an old and small retrospective study [117]. Plasma exchanges, IgIV and rituximab may be selectively useful [117,118].

With PNH, tumour treatment sometimes permits disease control [119]. Clinical improvement and a decrease of autoantibody titer and ENMG abnormal activities had been shown after plasma exchanges [49,119]. In spite of absence of large trials, IVig, prednisolone, azathioprine and methotrexate are proposed as well [111].

**Paraneoplastic neuropathies with lymphoma**

As with carcinomas, an early treatment of the tumour is the most efficient way of improving or stabilizing the neurological disorder. Patients with POEMS or IgM monoclonal gammopathy with antibody activities usually do not or only poorly respond to steroids, IgIV or plasma exchanges which therefore are not recommended. With cryoglobulinemia or anti-MAG IgM, protocols incorporating anti-CD20 antibodies may be efficient to rapidly reduce the level of the gammopathy. In case of amyloidosis, the Mayo Clinic group has advocated high-dose chemotherapy and stem cell transplantation in selected patients [120] while a French collaborative study have showed the efficacy of conventional doses of melphalan plus prednisone [121]. With POEMS syndrome and systemic plasma cell proliferation, a treatment similar to that of amyloidosis is proposed while a local radiotherapy is recommended in patients with solitary or dominant osteosclerotic plasmacytoma [122]. Thalidomide, lenalidomide, and bortezomib are interesting drugs for both amyloidosis and POEMS syndrome but their neurotoxicity in patients with neurophathy should be taken into account. Anti-VEGF antibodies have been proposed [58] for the treatment of POEMS syndrome but gave conflicting results [122].

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