Paraneoplastic Syndromes of the Nervous System as Complications of Cancer

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Introduction

In patients with cancer the development of neurological symptoms usually represents metastatic involvement of the nervous system or complications secondary to coagulopathy, infection, metabolic and nutritional deficits, and toxic effects of cancer therapy [1]. A neurologic disorder is defined as paraneoplastic when none of the above causes are detected or when specific cancer-related immunological mechanisms are involved. Paraneoplastic neurologic disorders are important for several reasons. They may affect any part of the central and peripheral nervous system and mimic other neurologic complications of cancer. The paraneoplastic disorder usually develops before the presence of a cancer is known and its prompt recognition may help to uncover the neoplasm. The neurologic symptoms are often severe and can result in the patient's death. Early intervention with oncologic and immunotherapy may result in stabilization or improvement of neurologic symptoms although the potential for improvement depends on the type of syndrome and associated immune responses [2, 3].

Frequency and Pathogenesis

It is estimated that less than 1% of patients with cancer develop clinically symptomatic paraneoplastic neurologic syndromes, but the frequency varies with the type of cancer. For example, while 10–30% of patients with plasma cell dyscrasias or thymoma develop paraneoplastic neurologic symptoms, far less than 1% of patients with breast or ovarian cancer develop these disorders.

Most paraneoplastic neurologic disorders appear to be mediated by immunological mechanisms. The occurrence of serum and cerebrospinal (CSF) antibodies that target proteins selectively expressed by the tumor and nervous system has suggested a mechanism whereby the tumor expression of neuronal proteins triggers an anti-tumor immune response that cross-reacts with the nervous system. In general, the efficacy of the immune response against the tumor is limited or not sustained enough to control its growth, but the effects on the nervous system are prominent.

In some antibody-associated paraneoplastic syndromes, the accompanying cytotoxic T-cell mechanisms appear to be the main pathogenic effectors [4, 5]. The autoantigens of these disorders are usually intracellular, and the associated antibodies are detectable in serum and CSF of the patients. Although not directly pathogenic, these antibodies may play an ancillary role in enhancing the immune response [6]. The detection of these antibodies, also known as paraneoplastic or onconeuronal antibodies (Table 13.1), forms part of the diagnostic tests that confirm the paraneoplastic nature of the neurologic disorder and directs the search of the underlying tumor. In contrast, there are antibody-associated paraneoplastic syndromes in which the humoral immune response plays a dominant pathogenic role [7, 8]. These include the autoimmune encephalitis syndromes and some disorders of the neuromuscular junction and peripheral nerves that associate with antibodies to proteins of the neuronal cell surface, the synapse or the neuromuscular junction (further referred to as cell surface antibodies). In general these syndromes are more responsive to immunotherapies and for some syndromes, patients can have complete or near complete recoveries with treatment [9].

Several other paraneoplastic disorders, including inflammatory neuropathies or myopathies, are likely immune

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Table 13.1 Paraneoplastic antibodies*

Antibody	Associated cancer	Syndrome
Anti-Hu	SCLC, other	Encephalomyelitis, sensory neuronopathy
Anti-Yo	Gynecological, breast	Cerebellar degeneration
Anti-Ri	Breast, gynecological, SCLC	Cerebellar ataxia, opsoclonus, brainstem encephalitis
Anti-Tr/DNER	Hodgkin's lymphoma	Cerebellar degeneration
Anti-CV2/CRMP5	SCLC, thymoma, other	Encephalomyelitis, striatal encephalitis (chorea), cerebellar degeneration, uveitis, peripheral neuropathy
Anti-Ma proteins[a]	Testicular germ-cell tumors and other neoplasms	Limbic, diencephalic (hypothalamic) and upper brainstem encephalitis; rarely cerebellar degeneration
Anti-amphiphysin	Breast, SCLC	Stiff-man syndrome, encephalomyelitis
Anti-recoverin	Retinopathy	SCLC
Anti-bipolar cells of the retina[b]	Retinopathy	Melanoma

*The detection of these antibodies confirms the paraneoplastic nature of the neurologic disorder
[a]Antibodies limited to Ma2 (also called anti-Ta antibodies) usually associate with limbic and brainstem encephalitis and germ-cell tumors. Antibodies directed at Ma1 and Ma2 usually associate with brainstem encephalitis, cerebellar degeneration and several types of cancer (lung, breast, ovary, among others)
[b]Antibodies to other retinal proteins such as transducin-β, rhodopsin, and arrestin among others have also been described in some patients with melanoma and retinopathy. The diagnostic value of these antibodies is unclear

mediated and associate with infiltrates of mononuclear cells, cytotoxic T-cells, or deposits of IgG and complement in the involved nerve or muscle [10, 11]. Patients with these disorders have a variety of antibodies that when present support the diagnosis of the inflammatory process. In general these antibodies do not serve as surrogate markers of paraneoplasia. However, recent reports show that patients with dermatomyositis and antibodies to TF1γ are more likely to have an associated cancer compared to patients without these antibodies suggest that the immune classification of these disorders is evolving [12].

In addition to immune-mediated mechanisms, there are other paraneoplastic causes of neurologic dysfunction, including competition between the tumor and nervous system for substrates (e.g., glucose), inappropriate secretion of hormones or cytokines by tumor cells (e.g., anti-diuretic hormone), among others. This chapter focuses on the syndromes that occur in association with immune-mediated mechanisms.

Diagnosis of Paraneoplastic Neurologic Disorders: General Concepts

There are four clinical features that complicate the diagnosis of most paraneoplastic neurologic disorders, (1) the frequent presentation of neurologic symptoms before the diagnosis of the cancer, (2) the occurrence of similar syndromes without a cancer association, (3) the absence of well characterized antibodies in a variable proportion of patients, and (4) the small size of the associated tumors, which are usually difficult to demonstrate at the time of neurologic symptom presentation [13].

Presentation of Symptoms

The majority of paraneoplastic neurologic syndromes develop rapidly in a matter of days or weeks. Patients who develop syndromes of the central nervous system often describe prodromic gastrointestinal or upper respiratory tract symptoms resembling a viral illness that is followed by the neurologic symptoms. Most patients with syndromes affecting the central nervous system have CSF abnormalities such as pleocytosis, increased protein concentration, oligoclonal bands, and elevated IgG index that suggest an inflammatory or immune-mediated process.

In about 60% of patients, the paraneoplastic neurologic disorder develops before the presence of a tumor is known. There are a few exceptions such as the paraneoplastic retinopathy that affects patients with melanoma ("melanoma-associated retinopathy"); patients with this disorder usually have a history of metastatic melanoma [14].

Syndromes Similar to Paraneoplastic Disorders May Occur Without a Cancer Association

Although some syndromes are more frequently associated with cancer than others, all paraneoplastic syndromes have a counterpart that may occur without a cancer association. The disorders that are frequent paraneoplastic manifestations of cancer include limbic encephalitis, opsoclonus-myoclonus, subacute cerebellar degeneration of the elderly, Lambert-Eaton myasthenic syndrome (LEMS), encephalomyelitis, sensory neuronopathy, cancer-associated retinopathy, and melanoma-associated retinopathy [13]. A patient presenting

with any of these syndromes should raise suspicion of a paraneoplastic etiology. For some syndromes the age of the patient can be an important clue to whether the disorder is likely paraneoplastic. For example, acute or subacute cerebellar symptoms in an adult are more likely to be paraneoplastic than in children, in whom other etiologies are much more frequent. Young women with anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis are much more likely to have an associated tumor than children or older patients with this disorder [9].

Antibodies and Paraneoplastic Neurologic Disorders

The antibodies that are associated with paraneoplastic neurologic disorders can be divided into two broad categories. There are the paraneoplastic (or onconeuronal) antibodies that when detected almost always indicate that the neurologic disorder is a paraneoplastic manifestation of cancer (Table 13.1). The other category comprises the cell surface antibodies. These antibodies associate with neurologic syndromes that occur with or without a cancer association, such as the antibodies against voltage-gated calcium channels (VGCC) in the Lambert-Eaton myasthenic syndrome.

The probability of detecting an antibody characteristic of a paraneoplastic syndrome depends on the type of cancer association. For example, older women with cerebellar degeneration associated with breast or gynecologic cancers almost always harbor anti-Yo antibodies, but if another tumor is involved other antibodies or no antibodies will be identified. Most paraneoplastic syndromes of the peripheral nervous system do not associate with paraneoplastic antibodies. Only a few sensorimotor neuropathies develop in association with anti-CV2/CRMP5 antibodies or anti-Hu, the latter suggesting a neuronopathy caused by dorsal root ganglia dysfunction, rather than a peripheral neuropathy [15, 16].

When testing for antibodies it is important to be aware that some antibodies may be detected at low titers in the serum of patients with or without cancer or neurologic findings [17]. These low titer serum antibodies have not been shown to have clinical relevance and should not mislead the differential diagnosis away from other non-paraneoplastic causes of the patients' complaints. Additionally, for the paraneoplastic syndromes that affect the central nervous system and dorsal root ganglia, antibody titers are higher in the CSF than the serum and in some cases, serum may be negative; therefore, evaluation of the CSF should be undertaken when making the initial diagnosis [18].

Tumors Associated with Paraneoplastic Disorders

At the time of neurologic symptom presentation the tumors of many patients are usually small and confined to a single organ or to the regional lymph nodes. The combined use of CT and PET imaging uncovers occult tumors in approximately 80% of cases; the remaining 20% require close follow-up with repeat studies [19–22]. Ultimately, 90% of all tumors associated with paraneoplastic disorders are diagnosed within the first year of neurologic symptom development.

The detection of specific antibodies often helps in the selection of diagnostic tests, directing the search of the tumor to a few organs. For some syndromes, such as anti-Ma2 encephalitis associated with germ-cell neoplasms of the testis, CT and PET studies can be negative, but ultrasound often reveals the neoplasm or abnormalities that associate with the neoplasm (e.g., microcalcifications). In men younger than 50 with anti-Ma2-associated encephalitis but without a clinically detectable tumor, studies have shown that in most instances a microscopic tumor was present at orchiectomy [23, 24]. The tumors involved in paraneoplastic neurologic syndromes are most commonly malignant, either carcinomas or less frequently lymphoma or leukemia. However, some disorders are associated with benign tumors such as mature cystic teratomas (dermoid cysts) [25]. In these cases PET studies are often negative and other studies such as CT, MRI, and pelvic or vaginal ultrasound for detecting ovarian teratoma should be pursued [26].

Specific Paraneoplastic Neurologic Disorders

Paraneoplastic Limbic Encephalitis

This disorder is characterized by mood disturbances, seizures, and short-term memory loss [27]. The outcome is variable; the disorder may stabilize leaving the patient with severe anterograde memory deficits, may progress causing profound deficits of behavior and cognition leading to frank dementia, or may resolve. In two thirds of the patients, the CSF shows mild pleocytosis, increased proteins, intrathecal synthesis of IgG, and oligoclonal bands. The typical MRI findings include uni- or bilateral mesial temporal lobe abnormalities that are best seen on T2-weighted images, and infrequently contrast enhance (Fig. 13.1a, b) [28]. However, the MRI may be normal despite evidence of temporal lobe dysfunction demonstrated by EEG or hypermetabolism sometimes detected by PET [29]. The EEG may reveal that patients with unexplained low level of consciousness are in status epilepticus. Neurological symptoms usually precede

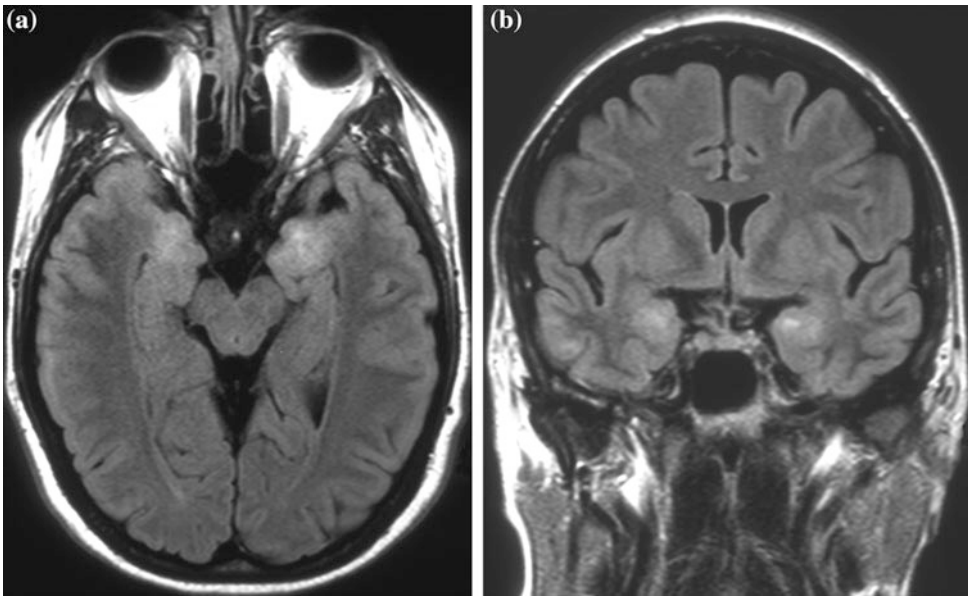

Fig. 13.1 **a**, **b** MRI findings in limbic encephalitis. Axial (**a**) and coronal (**b**) MRI fluid-attenuated inversion recovery (FLAIR) sequences from a patient with anti-Hu associated limbic encephalitis. Note the bilateral medial temporal lobe hyperintensities that are considered characteristic of most cases of limbic encephalitis. Similar findings occur with other immune-mediated limbic encephalitis, paraneoplastic or not, and with some viral encephalitis

the diagnosis of the tumor. The tumors most frequently involved are lung cancer, usually small-cell lung cancer (SCLC) and tumors of the testes and breast [27].

The pathological findings in most paraneoplastic limbic encephalitis associated to paraneoplastic (onconeuronal) antibodies include perivascular and interstitial inflammatory infiltrates, neuronal loss, and microglial proliferation that predominate in the limbic system (hippocampus, amygdala, hypothalamus, and insular and cingulate cortex). In addition, the majority of patients have variable involvement of other areas of the nervous system, mainly the brainstem [30].

There are several immune responses that may associate with limbic encephalitis. Patients with anti-Hu antibodies often have limbic encephalitis as part of a multifocal encephalomyelitis [31, 32]. Similarly the limbic encephalitis associated with CV2/CRMP5 antibodies rarely stays confined to the limbic system and these patients often have additional sensorimotor neuropathy, cerebellar ataxia, chorea, uveitis, and optic neuritis [15]. Anti-Ma2 antibodies are most commonly found in young men who develop limbic encephalitis in association with hypothalamic and brainstem dysfunction and a tumor of the testis [23]. A classic syndrome of limbic encephalitis is uncommonly found in association with antibodies to amphiphysin.

Several of the autoimmune encephalitis syndromes associated with cell surface antibodies manifest primarily as limbic encephalitis. These include anti-alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), gamma-amino-butyric acid B receptor [(GABA (B)], leucine-rich, glioma-inactivated 1 (LGI1), and metabotropic glutamate receptor 5 (mGluR5) antibody associated disorders. These antibodies are markers of the neurologic disorder and the suspicion that the disorder is paraneoplastic should be based on the presence of cancer risk factors and the specific immune response. For example, AMPAR encephalitis (discussed further later in this chapter) is paraneoplastic in about 70% of cases (usually cancer of the lung, breast, or thymus) while less than 10% of LGI1 encephalitis cases are paraneoplastic (usually thymoma).

Detection of antibodies to VGKC had been considered as a characteristic marker of limbic encephalitis but these antibodies are not specific and have been reported in patients with a variety of syndromes including neurodegenerative and nonimmune diseases [33, 34]. Most patients reported with VGKC antibodies and typical limbic encephalitis were likely cases of LGI1 encephalitis [35].

When associated with antibodies to intracellular antigens limbic encephalitis is usually poorly responsive to treatment. The exception is the encephalitis associated with Ma2 antibodies for which treatment of the tumor and immunotherapy results in improvement in about one third of cases. The limbic encephalitis associated with the autoimmune encephalitis syndromes and antibodies to the neuronal cell surface are much more treatment responsive (tumor directed and immunotherapy) [36].

Paraneoplastic Cerebellar Degeneration

The presenting symptoms of this disorder are dizziness, nausea, blurry or double vision, oscillopsia, and gait difficulties. Associated with these symptoms, or occurring after a few days, the patient develops truncal and limb ataxia, dysarthria, and dysphagia. At examination, patients usually have down-beating nystagmus [37]. This clinical picture is similar for most types of paraneoplastic cerebellar

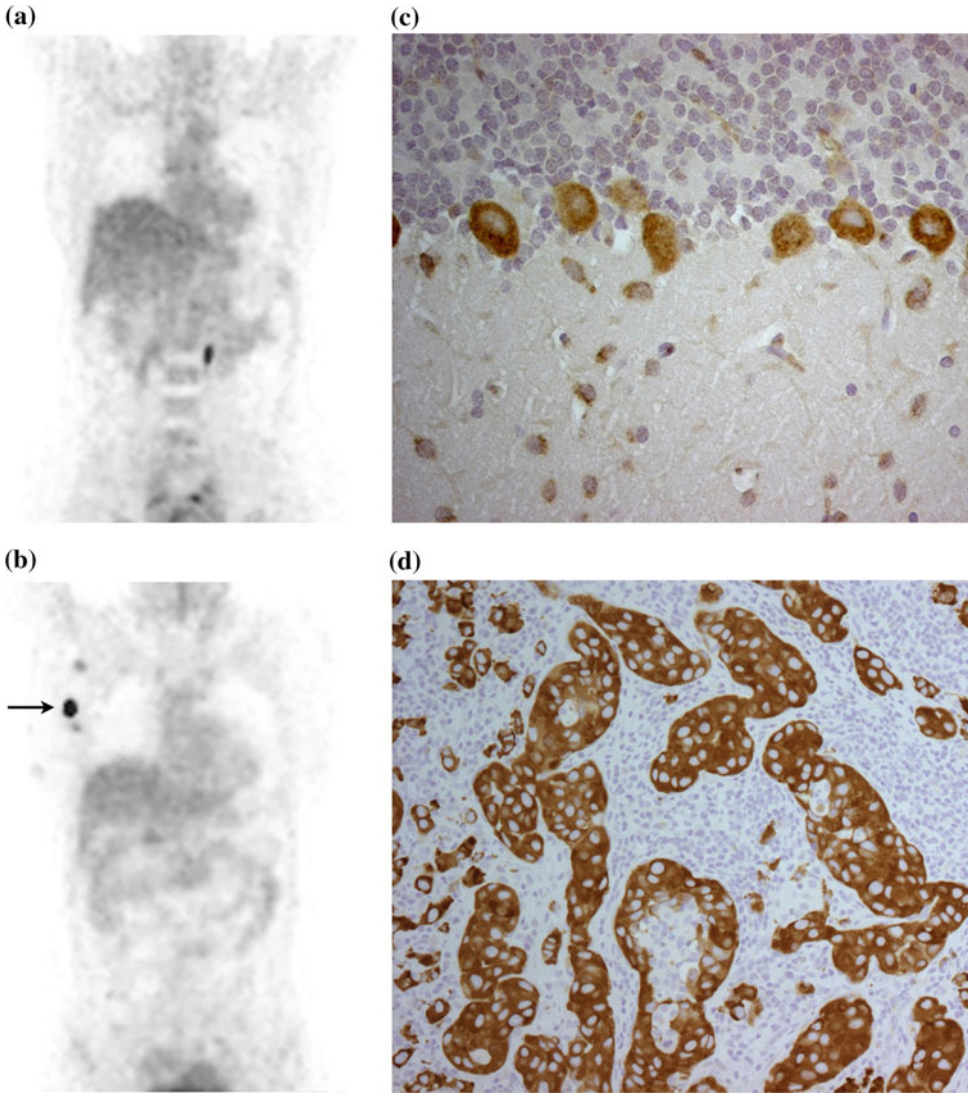

Fig. 13.2 **a–d** Studies in a patient with anti-Yo associated cerebellar degeneration. **a** corresponds to a normal FDG-PET obtained when the patient had anti-Yo associated cerebellar degeneration for 2 years. **b** is an FDG-PET obtained 3 years later (5 years after neurologic symptom presentation) showing a hypermetabolic abnormality in the right axillary lymph nodes (*arrow*). **c** shows the patient's anti-Yo antibodies immunolabeling a section of rat cerebellum (note the characteristic Purkinje cell reactivity of the anti-Yo antibodies). **d** shows that the neoplastic cells from the lymph node (identified by PET) react with the anti-Yo antibodies of the patient (*brown cells*). **c** and **d** Avidin-biotin-peroxidase, ×400

degeneration, irrespective of the type of cancer or antibody association, although the course of the disease may be different depending upon the associated immune response [38]. In general, neurologic symptoms precede the tumor diagnosis. The CSF usually shows pleocytosis, increased proteins, intrathecal synthesis of IgG, and oligoclonal bands. In the early stages of the disease, brain MRI is usually normal, but after several months may show global cerebellar atrophy.

There is a strong association between the development of specific anti-neuronal antibodies and the type of tumor associated with the paraneoplastic cerebellar disorder (Fig. 13.2a–d). These include SCLC and anti-Hu antibodies [32, 39], ovarian or breast cancer and anti-Yo antibodies [40], Hodgkin's lymphoma and anti-Tr/DNER antibodies [41], and breast, ovarian, or SCLC cancer and anti-Ri antibodies (Table 13.1) [42, 43]. Furthermore, the presence of anti-Hu antibodies is usually associated with symptoms indicating involvement of other areas of the nervous system (i.e., encephalomyelitis and sensory neuronopathy) [31]. The presence of anti-Ri antibodies is associated with opsoclonus or other abnormalities of ocular motility, including nystagmus, abnormal visual tracking, and abnormal vestibulo–ocular reflexes in 70% of the patients; these patients may also develop laryngeal spasms.

Symptoms of paraneoplastic cerebellar dysfunction may occur without the presence of anti-neuronal antibodies. In this case, the tumors more frequently involved are non-Hodgkin's lymphoma and lung cancer (non-SCLC and SCLC) [39, 44]. A subset of patients with SCLC without anti-Hu antibodies develops antibodies against VGCC [45]. These antibodies are similar to those associated with LEMS and some patients develop symptoms of both cerebellar dysfunction and LEMS.

Pathological studies show diffuse loss of Purkinje cells accompanied by degeneration of the dentate and olivary nuclei, and long tracts of the spinal cord. These findings can be

associated with mild or prominent lymphocytic infiltrates [46, 47]. When present, the inflammatory infiltrates usually involve the deep cerebellar nuclei in addition to the brainstem and other areas of the nervous system, suggesting that the cerebellum is the main target of a multifocal encephalomyelitis.

Treatment of the tumor and immunosuppressants do not usually affect the course of the cerebellar disorder although there are a few reports of responses to tumor treatment and immunotherapies [48–50].

Paraneoplastic Encephalomyelitis

This disorder describes patients with cancer who develop multifocal neurological deficits and signs of inflammation involving two or more areas of the nervous system, including brain, cerebellum, brainstem, spinal cord, dorsal root ganglia, and autonomic ganglia [46]. This gives rise to a mixture of symptoms derived from limbic encephalitis, cerebellar degeneration, brainstem encephalitis, and myelitis along with sensory deficits and autonomic dysfunction.

Symptoms of paraneoplastic brainstem encephalitis can include diplopia, dysarthria, dysphagia, internuclear or supranuclear gaze abnormalities, facial numbness, and subacute hearing loss. The spinal cord symptoms usually result from an inflammatory degeneration of the lower motor neurons [51]. Symptoms of autonomic dysfunction may include gastrointestinal paresis and pseudo-obstruction, orthostatic hypotension, cardiac arrhythmias among others (see discussion later in this chapter).

Several paraneoplastic immunities can associate with encephalomyelitis or multifocal encephalitis including the ones discussed next.

Anti-Hu

Patients with anti-Hu antibodies frequently develop encephalomyelitis in association with sensory neuronopathy secondary to dorsal root ganglia involvement; the tumor most frequently involved is SCLC [31, 32, 52, 53]. Other antineuronal antibodies that occur less frequently (sometimes in combination with anti-Hu) include, anti-CV2/CRMP5 and anti-amphiphysin [54, 55].

Anti-CV2/CRMP5

The encephalomyelitis associated with anti-CV2/CRMP5 antibodies may affect any of the areas indicated above along with the striatum (chorea), uvea (uveitis), and peripheral nerves, resulting in a mixed axonal demyelinating sensorimotor neuropathy [15, 56, 57]. The tumors more frequently associated are SCLC and thymoma.

Paraneoplastic disorders associated with anti-CV2/CRMP5 or anti-Hu are in general poorly responsive to treatment of the tumor or immunotherapies, including plasma exchange, intravenous immunoglobulins (IVIg) or cyclophosphamide. However, successful treatment of the tumor and prompt immunotherapy directed at the cytotoxic T-cell response (e.g., IVIg and cyclophosphamide) may result in stabilization or partial improvement of symptoms [3].

Anti-Ma Proteins

The encephalitis of patients with immunity to Ma proteins is more restricted to the limbic system, hypothalamus, brainstem, and cerebellum than the encephalomyelitis associated with other antibodies [58]. These patients may present with classical limbic encephalitis or severe hypokinesis and hypophonesis (pseudomutism) with relative preservation of cognitive functions [59]. Supranuclear ocular paresis is common, usually affecting vertical gaze more than horizontal gaze leading some patients to be incorrectly diagnosed with progressive supranuclear palsy. The tumors more frequently associated are germ-cell neoplasms of the testis and non-SCLC [23]. About 35% of patients with anti-Ma2 associated encephalitis respond to treatment; the neurological improvement is usually partial and predominantly occurs in young men with successfully treated testicular neoplasms [2].

Autoimmune Encephalitis with Cell Surface Antibodies

This group of encephalitic disorders occurs in association with antibodies located on the neuronal cell surface or related to the synaptic junction. The syndromes vary according to the associated immune response and include a variety of complex neuropsychiatric symptoms such as deficits of memory, behavior, cognition, psychosis, seizures, movement disorders, or coma. As the antibodies are pathogenic their removal often results in improvement although relapses occur at a variable rate based on the syndrome. The autoimmune encephalitis syndromes in which a paraneoplastic etiology is relatively frequent are discussed next; other syndromes are rarely or not known to be associated with cancer.

NMDAR Encephalitis

This disorder usually affects young women and children ($\sim$80% of patients), but can also affect male and older individuals [9]. Many patients have a viral-like prodrome followed by the development of prominent psychiatric symptoms (bizarre behavior, hallucinations), seizures, orofacial and limb dyskinesias, dystonia, and decreased level of consciousness that within days or weeks progresses to include autonomic or breathing instability requiring intensive care and ventilator support. Partial syndromes such as patients with predominant psychiatric symptoms or abnormal movements, and less severe phenotypes can occur, although virtually all patients develop several elements of the syndrome.

All patients have IgG antibodies against the GluN1 subunit of the NMDAR (Fig. 13.3a–c) [60]. At presentation these antibodies are always present in the CSF but were shown to be absent in the serum of 13% of patients, supporting the importance of CSF analyses at initial diagnosis [18]. These antibodies should not be confused with other IgG antibodies that target other subunits of the NMDAR or those of the IgM or IgA subtypes that are unrelated to NMDAR encephalitis. Other CSF findings often include a lymphocytic pleocytosis sometimes with increased proteins and/or oligoclonal bands. About one third of patients have increased signal on MRI T2 or fluid-attenuated inversion recovery (FLAIR) sequences involving the cortical or subcortical brain regions, and at times the cerebellar cortex [60].

The likelihood of an underlying tumor, most commonly a teratoma of the ovary, is age-dependent (~40% in patients ≥14 years; <10% in patients <14 years) while tumors in children and men are uncommon [9].

The treatment for all of the autoimmune encephalitis is based on experience with NMDAR encephalitis that is the most frequent of these disorders and centers on immunosuppression. This includes corticosteroids, IVIg, or plasmapheresis, either alone or in combination as first-line treatments and rituximab and/or cyclophosphamide as second-line agents. Identification and treatment of an accompanying tumor is important as it appears to associate with better outcome and decreased risk of relapses [9].

AMPAR Encephalitis

This disorder primarily affects middle-aged women. Some patients present with the subacute onset of confusion, memory loss, seizures, and psychiatric symptoms consistent with limbic encephalitis that may be associated with prominent psychiatric features, whereas other cases present with rapidly progressive abnormal behaviors similar to acute psychosis [61–63]. About 70% of cases are paraneoplastic with tumors of the thymus, lung, and breast more commonly associated [62]. Interestingly, patients with AMPAR antibody associated encephalitis as with other autoimmune encephalitis often have other autoantibodies such as thyroid peroxide or ANA antibodies suggesting an underlying propensity to develop autoimmunity. The CSF findings are similar to NMDAR encephalitis and there are cases in which antibodies are only present in CSF [62]. MRI findings are seen in many but not all patients and in about half are limited to increased T2 or FLAIR signal in the medial temporal lobes; in other patients the MRI may show increased signal in cortical regions [63].

GABA(B)R Encephalitis

Patients with antibodies to GABA(B)R develop symptoms of limbic encephalitis including memory loss, confusion, and hallucinations with seizures that can be difficult to control [64]. A few patients have been reported with additional findings including ataxia, opsoclonus-myoclonus,

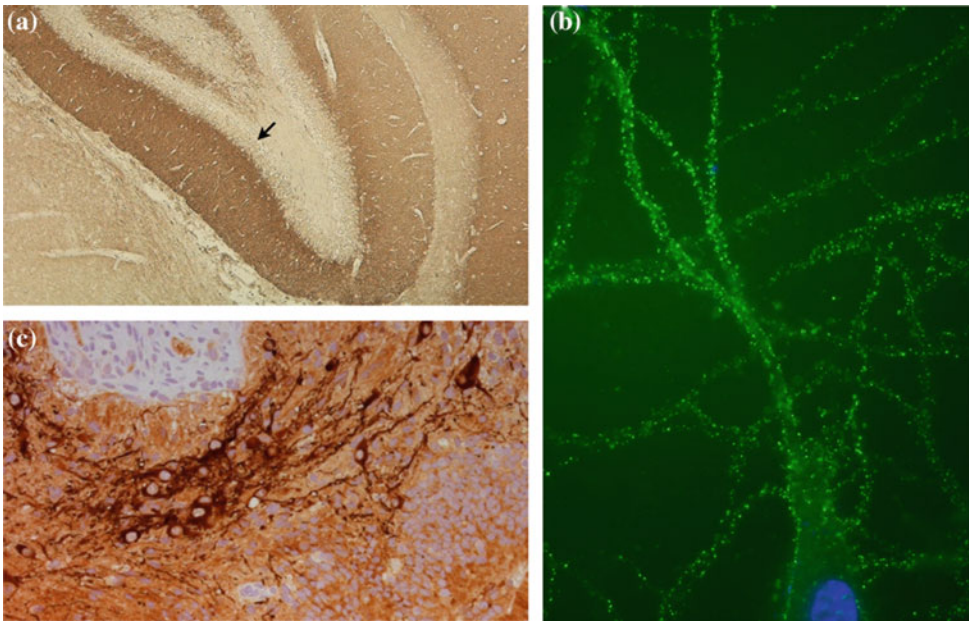

Fig. 13.3 **a–c** Studies in a patient with paraneoplastic NMDAR encephalitis and ovarian teratoma. **a** shows the CSF reactivity of a patient with anti-NMDAR antibodies with a sagittal section of rat hippocampus; the immunolabeling is mainly concentrated in the inner aspect of the molecular layer adjacent to the dentate gyrus (*arrow*). **b** shows that the antibody reactivity is with the cell surface and dendrites of neurons (the picture corresponds to a culture of rat hippocampal neurons immunolabeled with the patient's antibodies). **c** shows that the teratoma of the patient contains immature neurons; these are demonstrated with MAP2 labeling, a specific marker of neurons and dendrites. **a** avidin-biotin-peroxidase, ×50; **b** immunofluorescence ×800; **c** avidin-biotin-peroxidase, ×400

autonomic dysfunction and hypoventilation, and prominent psychiatric symptoms [65].

The disorder equally affects men and women and about half of the cases are paraneoplastic with SCLC or other neuroendocrine lung tumors most common. Patients with an associated cancer are older than those without a tumor (median age of 67.7 vs. 39 years) and in these cases the neurologic symptoms usually predate the cancer diagnosis [65].

Paraneoplastic Sensory Neuronopathy

This disorder is characterized by progressive sensory loss involving lower and upper extremities, trunk, and face. The sensory deficits are frequently accompanied by painful paresthesias and dysesthesias. This and the frequent asymmetric presentation of symptoms may lead to the diagnosis of radiculopathy or multineuropathy [66, 67]. At presentation, vibration and joint position sensations may be more affected than nociceptive sensation. The sensory loss causes disorganization of movement resulting in sensory ataxia and pseudoathetoid movements. Some patients develop sensorineural hearing loss. Paraneoplastic sensory neuronopathy frequently develops in association with encephalomyelitis and autonomic dysfunction (see paraneoplastic encephalomyelitis). In more than 80% of the patients, the sensory neuronopathy precedes the diagnosis of the tumor, usually a SCLC [31].

Nerve conduction studies demonstrate small amplitude or absent sensory nerve action potentials. Motor nerve and F-wave studies are usually normal, with no signs of denervation unless there is involvement of the spinal motor neurons in the setting of encephalomyelitis. Some patients develop motor conduction abnormalities as a result of a mixed axonal and demyelinating neuropathy that accompanies the degeneration of dorsal root ganglia neurons [68, 69].

Pathological studies show an inflammatory, probably immune-mediated degeneration of the neurons of the dorsal root ganglia, and equivalent ganglia of cranial nerves (e.g., Gasserian ganglia) [70]. Other findings include atrophy of the posterior nerve roots, axonal degeneration, and secondary degeneration of the posterior columns of the spinal cord. Mild inflammatory infiltrates can be found in peripheral nerves and sometimes muscle [66].

Paraneoplastic sensory neuronopathy rarely responds to immunotherapies, including plasma exchange, IVIg, and immunosuppressants [32]. In some patients the use of steroids may result in partial improvement of symptoms [71]. Efforts should be directed toward prompt identification and treatment of the tumor.

Paraneoplastic Opsoclonus-Myoclonus (POM)

POM usually affects infants younger than 4 years of age (median age, 18 months) and often presents with staggering and falling along with body jerks, ataxia, refusal to walk or sit, opsoclonus, irritability, and sleep problems that may contribute to episodes of rage [72, 73]. Nearly 50% of children with POM have neuroblastoma, and about 2% of children with this tumor develop opsoclonus. Neurologic symptoms may precede or develop after the diagnosis of neuroblastoma.

POM frequently responds to treatment of the tumor and immunotherapy that may include corticosteroids, adrenocorticotrophic hormone, IVIg, cyclophosphamide, and rituximab [74]. The sleep disturbances and episodes of rage often respond to trazodone; however, residual psychomotor deficits, behavioral and sleep disturbances are common [72, 73, 75]. Patients with POM have a better tumor prognosis than patients without paraneoplastic symptoms.

In adults, POM develops in association with truncal ataxia resulting in gait difficulty and frequent falls. In more than half of the patients, POM precedes the diagnosis of the tumor, usually a SCLC [76]. Patients with breast cancer may harbor anti-Ri antibodies (see paraneoplastic cerebellar degeneration) although most patients are antibody negative [42, 77]. The clinical course of paraneoplastic opsoclonus is worse than that of idiopathic opsoclonus. Paraneoplastic opsoclonus may respond to immunotherapy or IVIg, but symptom improvement depends on successful treatment of the tumor [78]. If the tumor is not treated, neurologic symptoms often progress to a severe encephalopathy resulting in the patients' death. In addition to treatment of the tumor and IVIg, there are reported clinical responses to depletion of serum IgG using protein-A columns, clonazepam, valproic acid, and thiamine [79].

There is a recent description of a POM syndrome occurring in a subgroup of young women within the context of a brainstem-cerebellar syndrome associated with ovarian teratoma [80]. The majority of these patients had full recovery with tumor treatment and immunotherapy; one patient who did not have tumor treatment improved with immunotherapy. Antibodies to intracellular or cell surface neuronal proteins were not detected in these patients.

Paraneoplastic Stiff-Person Syndrome

This disorder is characterized by fluctuating rigidity of the axial musculature with superimposed spasms. Rigidity primarily affects the lower trunk and legs, but it can extend to the shoulders, upper limbs, neck, and less frequently muscles of the face. Symptoms may be limited to one extremity (stiff-limb

syndrome). Spasms are often precipitated by voluntary movement, emotional upset, and auditory and somesthetic stimuli. Typically, the rigidity disappears during sleep or following general anesthesia, suggesting dysfunction at the spinal or supraspinal level [81]. Electrophysiologic studies show continuous activity of motor units in the stiffened muscles that considerably improve after treatment with diazepam.

The disorder can occur as a paraneoplastic manifestation of cancer (usually breast or SCLC) but about 85% of cases are idiopathic [82]. Patients with paraneoplastic stiff-person syndrome tend to be older than non-paraneoplastic cases and to have asymmetric and distal distribution of symptoms often with cervical involvement, spinal myoclonus, and pruritus [83, 84].

The serum and CSF of patients with paraneoplastic stiff-person syndrome may contain antibodies to amphiphysin and these patients usually have breast or SCLC [83–85]. Amphiphysin antibodies are not syndrome specific and have been described in encephalitis, neuropathy, and myelopathy [83]. In patients without cancer the major autoantigen is glutamic acid decarboxylase 65 (GAD65) sometimes found in association with antibodies to GABA (A) receptor; 70% of these patients develop type I diabetes and other autoimmune diseases [83, 86, 87].

In addition to stiff-person syndrome, paraneoplastic rigidity and spasms can occur in patients with extensive encephalomyelitis or focal myelitis [88]. Some of these patients harbor anti-Ri antibodies [89]. Patients with progressive encephalomyelitis, rigidity and myoclonus (PERM) often have antibodies to the alpha 1 subunit of the glycine receptor (GlyR) [90–92]. These cases are rarely associated with cancer (Hodgkin's lymphoma, thymoma). Serum GlyR antibodies are not specific to PERM as they have been described in patient with SPS without features of PERM as well as in patients with various disorders, including optic neuritis or multiple sclerosis [92, 93].

Histopathological abnormalities found in stiff-person syndrome ranges from normal to include mild perivascular lymphocyte infiltration and loss of motor neurons and interneurons in the anterior horns of the spinal cord [94–96].

Improvement of stiff-person syndrome can be obtained with IVIg and GABA-enhancing drugs, such as diazepam, clonazepam, gabapentin, or baclofen, but sustained improvement usually requires treatment of the tumor and steroids [97, 98]. Patients with PERM and glycine receptor antibodies can respond with good outcome to immunotherapy [99].

Motor Neuron Dysfunction

The occurrence of motor neuron disease as a paraneoplastic syndrome is controversial. Two systematic reviews of the literature concluded that there was not an increased incidence of cancer among patients with amyotrophic lateral sclerosis (ALS) while a recent report using data from 16 population-based cancer registries found an elevated risk of death from ALS in survivors of melanoma and tongue cancer [100–102]. About 20% of patients with anti-Hu antibody associated encephalomyelitis and sensory neuronopathy develop symptoms resembling ALS due to predominant involvement of the spinal cord (Fig. 13.4) [31, 51]. Patients with lymphoma rarely develop subacute, progressive, painless, and often asymmetrical lower motor neuron dysfunction. Upper motor signs are absent, fasciculations are rare and the bulbar muscles are usually spared contrasting this syndrome with typical ALS [103, 104].

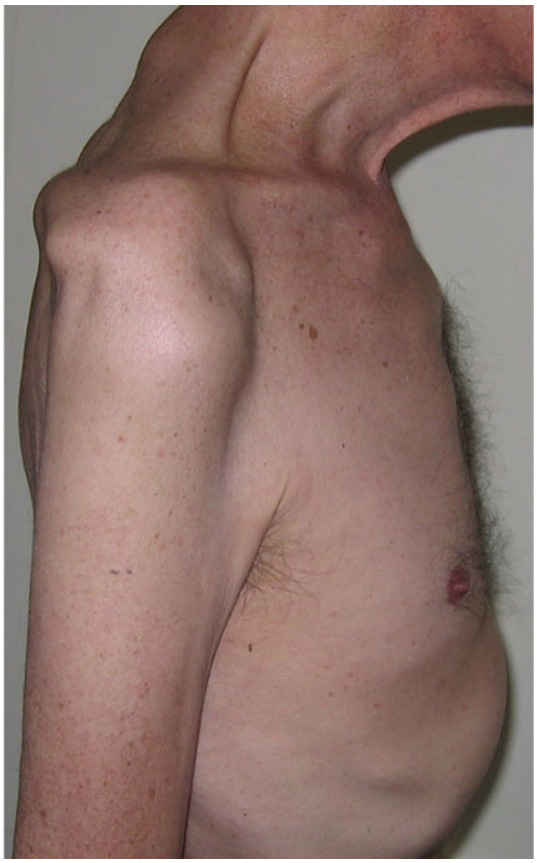

Fig. 13.4 Severe neurogenic muscle atrophy in a patient with SCLC and anti-Hu-associated myelitis. The initial neurologic symptom of this patient was flaccid motor weakness selectively involving the upper extremities and neck extension. After eight weeks he was unable to move the upper extremities. These symptoms associated with fasciculations and loss of reflexes in the arms. Cranial nerves, strength and reflexes in the lower extremities were normal. The picture demonstrates widespread atrophy of the muscles of the neck and shoulder

Paraneoplastic Sensorimotor Neuropathy

Many patients with advanced malignancy develop a peripheral neuropathy that is usually mild, with little impact

on quality of life [105]. The cause of these neuropathies is multifactorial, including metabolic abnormalities, nutritional deficits, and toxic effects of chemotherapy and biologic therapies (e.g., cisplatin, paclitaxel, docetaxel, vinca alkaloids, thalidomide, and bortezomib, among others) [106].

There is a group of sensorimotor neuropathies that develop a few months before or by the time a malignancy is discovered. Symptoms may present in a subacute or acute fashion and are usually progressive. In most cases the neuropathy is part of other processes such as encephalomyelitis, mononeuritis multiplex, or acute or chronic inflammatory demyelinating polyneuropathy [107]. Antibody studies are negative except for patients with SCLC who may have CV2/CRMP5 antibodies and less commonly Hu antibodies [108]. Pathological studies usually show axonal degeneration with frequent inflammatory infiltrates, although some patients have predominant demyelinating findings. The latter are more likely to respond to corticosteroids and IVIg than the axonal neuropathies.

Paraneoplastic Vasculitis of Nerve and Muscle

This disorder is a nonsystemic vasculitic neuropathy that involves nerve, muscle, or both and has been reported in association with solid tumors and lymphoma [109–111]. The onset is usually subacute with the development of a painful symmetric or asymmetric sensorimotor polyneuropathy, or less frequently mononeuritis multiplex. The course is progressive. The erythrocyte sedimentation rate is usually elevated and the CSF shows a high protein content. Electrophysiological studies show a diffuse asymmetric axonal polyneuropathy or multifocal mononeuropathy [112]. Nerve biopsy studies show intramural and perivascular inflammatory infiltrates, usually without necrotizing vasculitis. The inflammatory infiltrates are mainly composed of CD8+ T-cells [113].

Paraneoplastic vasculitis of nerve and muscle often responds to treatment of the tumor, corticosteroids, and cyclophosphamide [109].

Sensorimotor Polyneuropathy Associated with Malignant Monoclonal Gammopathies

The malignancies that are associated with monoclonal gammopathies or M proteins include multiple myeloma and osteosclerotic myeloma, which are typically associated with IgG or IgA M proteins, and Waldenström's macroglobulinemia, B-cell lymphoma, and chronic B-cell lymphocytic leukemia, which are associated with IgM M proteins.

Multiple Myeloma

The current leading cause of peripheral neuropathy in multiple myeloma is iatrogenic and due to direct nerve toxicity of the drugs used for tumor treatment (e.g., vincristine, thalidomide, bortezomib, among others). Paraneoplastic neuropathies do occur in about 10% of patients with neurologic symptoms usually preceding the myeloma diagnosis. The neuropathy is most often sensorimotor and slowly progressive. Treatment of the myeloma rarely improves the neuropathy. Amyloid deposition is a cause of neuropathy in some patients [114, 115]. In patients with amyloid-associated neuropathy, symptoms are similar to those with distal axonal sensorimotor neuropathy, but frequently include atypical features, such as pain, carpal tunnel syndrome, a clinical picture of multiple mononeuropathy, and autonomic dysfunction. Treatment is aimed at the myeloma but even when successful, the neuropathy often persists [116].

Osteosclerotic Myeloma/POEMS Syndrome

This is an unusual form of myeloma characterized by single or multiple plasmacytomas that manifest as sclerotic bone lesions. These lesions involve ribs, vertebrae, pelvic bones, and proximal long bones, and usually spare skull and distal extremities [117]. All or some features of the POEMS syndrome (*p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *M* component, and *s*kin changes) may be present and it is under debate if there is a true distinction between osteosclerotic myeloma and POEMS [118]. More than 50% of patients with sclerotic myeloma develop a peripheral neuropathy, often before the tumor diagnosis that resembles a chronic demyelinating polyradiculoneuropathy with motor predominance and high CSF protein content [119]. However, compared to CIDP, there is no macrophage-associated demyelination, and levels of vascular endothelial growth factor (VEGF) in serum are commonly quite elevated [120]. Focal treatment of the sclerotic lesions with resection or radiation therapy, the use of prednisone alone or in combination with melphalan, or lenalidomide with or without dexamethasone often results in neurologic improvement [121, 122]. Patients with widespread lesions or rapidly progressive neuropathy may respond to peripheral blood stem cell transplant [123].

Waldenström's Macroglobulinemia

Symptoms of peripheral neuropathy occur in about 45% of these patients, and in approximately 10% the deficits are severe [124]. The cause of the neuropathy are heterogeneous and include axonal neuropathies related to amyloid, cryoglobulinemia, tumor infiltration, and vasculitis and demyelinating neuropathies related to antibodies against

myelin-associated glycoprotein (MAG), sulphatide or various gangliosides [125, 126]. The neuropathy associated with IgM anti-MAG is characterized by progressive distal sensorimotor deficits, with predominant involvement of vibration sense, sometimes with postural tremor, pseudoathetosis, and progressive gait dysfunction.

Electrophysiologic studies demonstrate slow conduction velocities and prolonged distal motor and sensory latencies, compatible with a demyelinating neuropathy. Pathology studies show widening between lamellae of myelin sheaths due to intercalation of anti-MAG antibodies [127]. The neuropathy associated with anti-sulphatide antibodies is predominantly axonal.

Treatment should be directed at the Waldenström's macroglobulinemia. Patients with demyelinating neuropathy and IgM anti-MAG M proteins may respond to plasma exchange, IVIg, or rituximab [128]. However, most patients require aggressive treatment with chemotherapeutic agents such as chlorambucil, cyclophosphamide, or fludarabine [129, 130]. Responses to rituximab with or without fludarabine or cyclophosphamide have been reported [131, 132].

Paraneoplastic Autonomic Dysfunction

This disorder usually develops in association with other paraneoplastic syndromes, such as encephalomyelitis or LEMS. Symptoms often precede the detection of the tumor, usually a SCLC. The autonomic dysfunction may result from adrenergic or cholinergic nerve dysfunction at the pre- or, most frequently, postganglionic level [133, 134]. There are three disorders that can be life threatening: esophageal and gastrointestinal dysmotility with intestinal pseudoobstruction, cardiac dysrhythmias, and orthostatic hypotension. Other accompanying symptoms may include dry mouth, erectile, and sphincter dysfunction. Because autonomic dysfunction can be the presentation of encephalomyelitis, testing for anti-Hu antibodies should be considered in some patients [135, 136]. About one third of patients with anti-CV2/CRMP5 will have manifestations of autonomic neuropathy [56]. There is another subgroup of patients with autonomic neuropathy who develop antibodies to the ganglionic acetylcholine receptor [137]; these antibodies may occur in patients with or without cancer, and their detection suggests that symptoms may improve with immunotherapy [138].

Lambert–Eaton Myasthenic Syndrome

LEMS is a disorder of the neuromuscular junction characterized by impaired acetylcholine release from the presynaptic motor terminal [139]. Symptoms include fatigue, leg weakness, muscle aches, and vague parasthesias. Dry mouth and other symptoms of autonomic dysfunction are common [140]. Cranial nerve involvement tends to be mild and transient, usually described as transient diplopia. Neurologic examination shows proximal weakness in the legs more than the arms and depressed reflexes, sometimes accompanied by eyelid ptosis and sluggishly reactive pupils. After brief muscle contraction, reflexes may potentiate. Similarly, after brief exercise strength may improve.

Routine nerve conduction studies show small amplitude compound muscle action potentials (CMAP) [141]. At slow rates of repetitive nerve stimulation (2–5 Hz), a decremental response of greater than 10% is seen; at fast rates (20 Hz or greater) or after maximal voluntary muscle contraction, facilitation occurs and there is an incremental response of at least 100%.

LEMS is associated with cancer in 50–70% of patients, most commonly SCLC. LEMS can also occur in conjunction with other paraneoplastic syndromes, such as paraneoplastic cerebellar degeneration or encephalomyelitis [39, 142]. Patients with paraneoplastic LEMS tend to be men older than 50 years of age while non-paraneoplastic LEMS occurs over a much wider age group with a slight female predominance [143]. Neurologic symptoms typically precede or coincide with the diagnosis of the tumor. In one study 91% of SCLCs were detected within 3 months of LEMS onset and 96% within 1 year [144]. Patients diagnosed with SCLC beyond 2 years of the LEMS diagnosis often had inadequate initial cancer screening. The Dutch-English LEMS Tumor Association Prediction (DELTA-P) score can be used at initial diagnosis to predict those patients with a high risk of having an associated SCLC [143]. Additionally, about 65% of patients with LEMS and SCLC have serum antibodies to SOX1 [145].

LEMS results from an antibody mediated attack against the presynaptic VGCC which results in decreased release of acetylcholine vesicles during depolarization. The detection of antibodies to P/Q-type VGCC is used as a serologic test for LEMS [146]. About 90% of LEMS patients have these antibodies regardless of whether the disorder is paraneoplastic or not [146].

Therapies for LEMS include treatment of the associated cancer, medication to increase the release of acetylcholine, and immunotherapy with the majority of patients having neurological improvement. The drug of choice is 3,4-diaminopyridine which is well tolerated and results in improvement of 80% of patients [147]. Long-term immunosuppression with prednisone alone or combined with azathioprine or cyclosporine should be considered in patients who remain symptomatic after controlling the tumor [148–150]. Immunomodulation with IVIg or plasma exchange is usually effective but the benefits are short lasting [148, 151, 152].

Paraneoplastic Peripheral Nerve Hyperexcitability

Paraneoplastic peripheral nerve hyperexcitability (PNH), also known as paraneoplastic neuromyotonia or Isaacs syndrome, is characterized by spontaneous and continuous muscle fiber activity of peripheral nerve origin [153]. Symptoms include muscle cramps, weakness, difficulty in muscle relaxation, carpopedal spasms, and sometimes excessive sweating. The involved muscles show undulating myokymia and may be hypertrophic [154]. EMG shows fibrillation, fasciculation, and doublet, triplet or multiplet single unit discharges that have a high intraburst frequency [155]. This abnormal activity continues during sleep and general anesthesia, is abolished by curare, and may be reduced or abolished by peripheral nerve block [153, 156].

Approximately 25% of patients with PNH develop central nervous system dysfunction characterized by changes in mood, hallucinations, and sleep dysfunction or in some cases typical limbic encephalitis. The combination of PNH and central nervous system involvement is called Morvan's syndrome. About 30–50% of cases of Morvan's syndrome are paraneoplastic with thymoma the most commonly associated tumor; patients with thymoma may have additional symptoms of myasthenia gravis [157].

About 80% of patients with Morvan's have antibodies that were previously identified as targeting the voltage-gated potassium channel (called anti-VGKC antibodies) [158]. It is now known that these antibodies do not target the VGKC but rather another protein in the VGKC-complex called contactin-associated protein-2 (Caspr2) [159, 160]. In contrast, isolated PNH rarely associates with Caspr2 or other antibodies [161]. Antibodies to other unidentified targets in the VGKC-complex have been found in some patients and are of unclear clinical significance.

Neuromyotonia often improves with sodium channel-blocking agents such as phenytoin, carbamazepine and lamotrigine. Plasma exchange can provide transient benefit for patients with severe symptoms although immunosuppression (corticosteroids, azathioprine) may be required for prolonged responses [162]. There are reports of marked improvement with oncologic treatment [163, 164].

Dermatomyositis

Dermatomyositis (DM) is a multi-system inflammatory myopathy. The classic skin manifestations include purplish discoloration of the eyelids (heliotrope rash) with edema, and erythematous, scaly lesions over the knuckles. The presence of necrotic skin ulcerations and pruritus appears to occur more frequently when the DM is paraneoplastic than without a cancer association [165].

DM occurs more often in women at a 2:1 ratio and about 30% of cases are paraneoplastic [166]. The risk of developing cancer is highest within the first 3 years of DM onset although the cancer diagnosis may precede or be concurrent with the DM diagnosis [167, 168]. In women the most common tumors are ovarian and breast cancer, and in men, lung and gastrointestinal cancer. In an Asian population there was an over-representation of nasopharyngeal carcinoma [169]. An association with cancer has not been demonstrated in childhood DM.

Clinical, electromyographic, and pathological findings of DM are similar in patients with and without cancer. Patients typically present with proximal muscle weakness of subacute onset and elevated levels of muscle enzymes. Electromyographic features include short, small, polyphasic motor unit potentials, fibrillations, sharp waves, insertional irritability, and high-frequency repetitive discharges [170]. The muscle biopsy shows degeneration, regeneration, necrosis, phagocytosis, and an interstitial mononuclear infiltrate [171, 172]. Neck flexors and pharyngeal and respiratory muscles are commonly involved; their dysfunction may result in aspiration and hypoventilation and contribute to death. Reflexes and sensory exam are normal. There is a subset of DM patients who develop cutaneous involvement without clinically evident myopathy (amyopathic dermatomyositis); MRI studies may show subclinical muscle involvement [173].

A variety of autoantibodies have been described in patients with DM. Studies suggest that antibodies to transcription intermediary factor 1γ (TIFγ) and/or nuclear matrix protein (NXP2) are useful markers of a paraneoplastic origin of the DM [174–176]. In one study, at least one of these two antibodies was present in 83% of patients with cancer-associated DM, compared with 51% of patients without cancer [177].

Other than treatment of the underlying cancer, the general approach to treatment of DM is the same whether paraneoplastic or not. Corticosteroids and methotrexate are the most commonly used medications while IVIg and/or cyclosporine are used in refractory or intolerant patients [11]. Other immunomodulatory treatments reported as useful in severe, refractory cases include mycophenolate mofetil, tacrolimus, and rituximab [178, 179].

Patients with graft versus host disease (GVHD) may develop symptoms that resemble those associated with DM. Treatment with cyclosporine or tacrolimus in association with corticosteroids often results in improvement [180, 181].

Acute Necrotizing Myopathy

Patients with this disorder develop subacute or less commonly acute muscle pain and symmetric proximal weakness,

associated with high levels of serum creatine kinase. The disorder evolves rapidly to generalized weakness, which involves pharyngeal and respiratory muscles, often leading to death in a few weeks. Several types of tumors are involved including SCLC, cancer of the gastrointestinal tract (stomach, colon, gall bladder, pancreas), breast, kidney and prostate [182]. Muscle biopsy shows prominent necrosis with little or absent inflammation and macrophages that are seen around the necrotic fibers [183, 184]. In cancer patients, the differential diagnosis should include chemotherapy and cytokine-induced (IL-2, interferon-α) rhabdomyolysis [185]. In one series of eight patients, three who had cancer, all patients improved with prolonged immunotherapy, mostly high-dose prednisone and IVIg [184]. One patient with SCLC and severe weakness from biopsy proven necrotizing myopathy had marked improvement over 3 months with tumor treatment (chemoradiation) in the absence of immunotherapy [186].

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