Paraneoplastic Disorders of Lower Motor Neuron

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Paraneoplastic Neurologic Disorders (PND) are remote neurologic effects of cancer that are caused neither by invasion of the tumour or its metastases nor by infection, ischemia, metabolic deficit, nutritional deficits, surgery, or other forms of tumour treatment.[1] Probably, the first report of PND dates back to 1890 when M. Auchè, a French physician, described peripheral nervous system involvement in cancer patients.[2] Cancers of lung, breast, ovary and lymphoreticular system are common causes of PND; Small Cell Lung Cancer (SCLC) being the commonest.[3]

As the incidence of cancers is increasing due to changes in lifestyle, the importance of knowing PND has increased. As there is lot of diversity in Paraneoplastic Disorders of Lower Motor Neuron, it is the topic for review in this article.

Pathogenesis

Antibodies generated as an immunological response to tumour onconeuronal antigens cross-react with cells of the nervous system causing neuronal damage. Multiple paraneoplastic anti-neuronal antibodies are discovered, since 1965 when Wilkinson and Zeromski first reported it in a case of carcinomatous neuropathy.[4] A particular PND may occur due to different types of anti-onconeuronal antibodies / cancers. However, some PNDs are classically associated with specific type of anti-neuronal antibodies and tumours. (Table 1) Multiple antibodies may be produced against different tumour antigens in same patient. Pittock SJ et al[5] noted that 56% of patients of PND (N=553) had more than one type of anti-neuronal antibody. These anti-onconeuronal antibodies have the capacity to suppress growth of the tumour against which they are produced.[6] Paraneoplastic antibodies to ion channels (VGCC, VGKC, AChR) on cell membrane, induce PND by themselves. While antibodies directed against intracellular antigens do not induce PND by themselves, but help in diagnosis as disease markers. T cell mediated cytotoxicity is the likely effector mechanism in them.[7]

The importance of PND lies in the fact that PND may be the first sign of an occult cancer. In one study, PND preceded cancer in 84% cases.[3] The immune response may make the tumour biologically relatively benign and therefore difficult to diagnose.[8] Identification of PND may lead to earlier treatment and improved outcomes in affected patients.[9] A PND may actually cause more disability than the cancer itself.[9] Also, recurrence of a PND may indicate recurrence of the causative tumour.[8]

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Table 1: Paraneoplastic Anti-neuronal antibodies, associated PND and cancer[10,11]

Antibody	Target	PND of LMN	Other PND that can occur	Associated Cancers
Anti-Hu	Proteins antigen HuD, HuC, Hel-N1, Hel-N2 in nucleus (not nucleolus) in Purkinje layer, Granule layer and peripheral nerve	Peripheral Neuropathy, Autonomic disturbance	PEM	SCLC
Anti-CV_2	Subpopulation of microglia	Peripheral Neuropathy	PEM, PCD, Chorea, Uveitis	SCLC, Thymoma
Anti-Yo	cdr2 (leucine zipper protein) in cytoplasm of Purkinje cells	Peripheral Neuropathy[12]	PCD	Ovaries, Breast
Anti-Amphiphysin	Amphiphysin located in perikarya of Purkinje cell, neuropil Molecular layer, Granule cell layer	Peripheral Neuropathy	PCD, PEM, Stiffperson syndrome	SCLC, Breast
Anti-NTCC	N-type calcium channels	Morvan's syndrome		Thymoma
Anti-VGCC	Pre-synaptic VGCC	LEMS	PCD	SCLC, Lymphoma
Anti-AChR	Post-synaptic AChR	MG		Thymoma
Anti-VGKC	VGKC	Neuromyotonia, Morvan's syndrome		Thymoma, SCLC

PEM: Paraneoplastic Encephalo-myelitis; PCD: Paraneoplastic Cerebellar Degeneration; LEMS: Lambert Eaton Myasthenic Syndrome; MG: Myasthenia Gravis; AChR: Acetyl Choline receptor; VGCC: Voltage Gated Calcium Channel; VGKC: Voltage Gated Potasium Channel; NTCC: N-type calcium channels; SCLC: Small Cell Lung Carcinoma.

Paraneoplastic Disorders affecting the Lower Motor Neuron:

Paraneoplastic Disorders affecting the Lower Motor Neuron include[12] :-

Motor or sensory neurons

* Anterior Horn Cell disease
* Subacute sensory neuronopathy Peripheral nerve
* Polyradiculopathy
* Brachial plexopathy
* Sensorimotor peripheral neuropathy
* Sensory neuropathy
* Motor neuropathy
* Vasculitic neuropathy
* Autonomic neuropathy
* Pandysautonomia
* Intestinal pseudo-obstruction
* Peripheral Nerve Hyperexcitability Syndrome (eg. Neuromyotonia, Morvan syndrome, Cramp-fasciculation Syndrome, Rippling Muscle disease)

Neuromuscular junction

* Lambert-Eaton Myasthenic syndrome (LEMS)
* Myasthenia Gravis Muscle
* Dermatomyositis
* Polymyositis
* Acute Necrotizing Myopathy
* Cachectic Myopathy

Anterior Horn Cell Disease

For a long time, it was debatable whether Anterior Horn Cell Disease is indeed paraneoplastic. Berghs S et al[13] reported a case Paraneoplastic Anterior Horn Cell Disease in a woman with breast cancer. Her serum contained autoantibodies directed against axon initial segments and nodes of Ranvier of myelinated axons, including the axons of motor neurons. The major targets of the autoantibodies in this patient were âIVÓ1 spectrin and âIV spectrin 140, the two isoforms of âIV spectrin gene. Partial improvement of the neurological symptoms followed cancer removal and there was a drastic reduction in the titre of the antibodies against âIV spectrin and nodal antigens, indicating its autoimmune nature.

Verma A et al[14] described a patient of SCLC with Anterior Horn Cell Disease having high Anti-Hu antibody titre. He did not respond to immune modulation and died. Loss of anterior horn cells was noticed at autopsy.

Shiva S et al[15] described a case of Paraneoplastic Anterior Horn Cell Disease in which occult small cell lung carcinoma was detected only after autopsy. The patient had presented with rapidly progressive pure motor paralysis, widespread wasting, fasciculation and respiratory failure. His initial X-ray and CT scan chest had appeared normal but his Anti-Hu titre was elevated.

Turk MH et al[16] described a patient who presented like Motor Neuron Disease (MND) with weakness and fasciculations in upper limbs. A growth was noticed in his right kidney. He underwent right radical nephrectomy and histology was suggestive of Renal Cell Carcinoma. His muscle weakness and fasciculations disappeared spontaneously 2 months after surgery. However, after another 5 years he developed similar complaints again in upper limbs and this time a growth was seen in lower part of his left kidney. A kidney saving surgery was done and his weakness improved in subsequent 3 months. This case also illustrates that a particular PND may reappear with tumour recurrence.

Thus, paraneoplastic Anterior Horn Cell Disease may be rare, but potentially treatable. However, routine analysis of anti-neuronal antibodies in patients with isolated Motor Neuron Disease (MND) is not warranted. Oliver S et al[17] did not find a single patient of pure MND (from amongst 145 patients of MND) to have anti-neuronal antibody directed against Hu, Yo, Ri, CV2/CRMP5, Ma2 and amphiphysin in significant titre. Very low reactivity against above antigens was detected

in 5/145 patients, but it probably represented background activity.

Guillian- Barré syndrome (GBS)

GBS has been reported in association with B-cell Acute Lymphoblastic Leukaemia[18], metastatic melanoma[19], lung cancer[20] and pancreatic cancer[21]. Miller-Fisher variant like presentation with IgG3 antibody to disialo-ganglioside in a patient with lung cancer has been described.[20]

In a large study by Vigliani MC et al[22], only 9/435 of GBS developed cancer in 6 months preceding or following GBS. In 7 of them, the diagnosis of cancer and GBS was concomitant. It was found that the mortality in GBS patients with cancer was higher than those without cancer.

Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)

CIDP, the stretched out form of GBS, results from continued antigenic challenge against the peripheral myelin. Paraneoplastic CIDP has been described in patients of hepatocellular carcinoma[23], EBV associated lymphoma[24], lung adenocarcinoma[25], transitional cell carcinoma[26] and gastric adenocarcinoma[27]. A patient of CIDP who went on to develop Lambert-Eaton Myasthenic Syndrome in the setting of SCLC with anti –Hu antibody and anti- VGCC is described in literature.[28]

Plexopathy

Brachial plexopathy is a rare PND. Lachance DH et al[29] have described a case of brachial plexopathy with mild sensorimotor neuropathy in a case of Hodgkin's disease who benefitted with corticosteroids. Coppens T et al[30] have described a case of brachial plexopathy along with sensorimotor neuropathy in a case of breast carcinoma with high anti-amphyphysin antibody. However, it should be remembered that brachial plexopathy can also occur due to radiotherapy in patients of cancer.

Neuropathy

Sensorimotor polyneuropathy is probably the most common of the paraneoplastic syndromes involving the nervous system and is more frequent in subjects with lung and breast cancers.

In one study of 422 consecutive patients with neuropathy, 26 had paraneoplastic neuropathy. In this study population, the incidence of carcinoma occurring with a short latency was 47% in sensory neuronopathy, 1.7% in Guillain Barré syndrome, 10% in mononeuritis multiplex and CIDP, and 4.5% in axonal polyneuropathy.[31]

Camdessanché JP et al[32] investigated the clinical and electrophysiological manifestations of neuropathies associated with anti-Hu antibodies in 20 patients. Peripheral neuropathy was the presenting symptom in 95% of patients. CNS and autonomic neuropathy were present in 40% and 30% of patients, respectively. The course of the neuropathy was acute, mimicking Guillain Barré syndrome in1 patient (5%), and subacute (55%) or progressive (40%) in the others. Clinically, the neuropathy was sensory (70%), sensorimotor (25%) or motor (5%). At onset, symptoms were symmetrical in 65% patients, asymmetrical in 25% or multifocal in 10%. Pain was a predominant manifestation (80%). Amyotrophy and fasciculations were rare. Electrophysiology revealed axonopathy to be the most frequent in 46.9% of nerves; an axonal/demyelinating or demyelinating pattern was seen in 18.3% and 4.9% of nerves, respectively. The axonal pattern was more frequent in sensory nerves while the mixed axonal/demyelinating pattern was more frequent in motor nerves ($P < 0.01$). Only 28.8% patients with a clinically pure sensory neuropathy had an electrophysiological pattern typical of sensory neuronopathy. The only statistical difference between sensory and sensorimotor neuropathies was that patients with sensorimotor neuropathy had more frequent motor nerve involvement ($P < 0.05$). This study concluded that motor nerve involvement is frequently seen in paraneoplastic neuropathy, even in the absence of a motor deficit.

Oki Y et al[33] categorized clinical features of paraneoplastic neuropathy into 'predominantly deep sensory disturbance' and 'predominantly superficial sensory disturbance' groups. The former group showed severe sensory ataxia and predominantly large myelinated fiber loss in the sural nerve. The latter group showed marked pain and severe hyperalgesia, and

predominantly small myelinated and unmyelinated fiber loss. Nerve conduction studies indicated an axonal neuropathy pattern in both groups with sensory action potentials more markedly diminished in the sensory ataxic form. Anti-Hu antibodies were detected in half of the patients in both groups. Immunotherapy was effective only for a short time; whereas treatment of the cancer was effective to improve or stabilize neuropathic symptoms in some cases from both groups.

Tschernatsch M et al[34] found anti-neuronal antibody in 47% and anti-nuclear antibody (ANA) without any anti-neuronal antibody in 25% patients with paraneoplastic neuropathy. Comparison of the ANA positive and ANA negative patients revealed that ANA positive paraneoplastic neuropathy was more frequently associated with breast cancer but was not associated with lung cancer ($P<0.05$). The main type of neuropathy in these patients was sensorimotor neuropathy. ANA negative patients had central nervous system involvement in addition. The functional outcome in ANA positive patients was better than in ANA negative patients ($P<0.05$).

Rijnders B et al[35] have described an unusual case of isolated bilateral diaphragmatic paralysis in patient with Renal Cell Carcinoma. Patient had partial recovery after curative resection of his Renal Cell Carcinoma was done.

Some new antibodies have been discovered in patients of paraneoplastic neuropathy in last few years. Tojo K et al[36] have described a case of paraneoplastic sensorimotor neuropathy along with encephalopathy associated with Anti-α-Enolase antibody in a case of Gastric Adenocarcinoma. Tschernatsch M et al[37] described antibody against a synaptic vesical protein (Synaptophysin) colocalised to cerebellum and myenteric plexus of the gut, in a case of SCLC with sensorimotor plus autonomic neuropathy.

However, some anti-cancer drugs can by themselves cause peripheral neuropathy leading to confusion as to whether neuropathy in a particular cancer patient is paraneoplastic or drug induced.[9] (Table 2)

Table 2: Anti-cancer drugs causing neuropathy

Syndrome	Causative Anti-cancer drugs
Predominantly sensory neuropathy	Cisplatin, Carboplatin, Thalidomide
Sensorimotor axonopathy	Cytarabine, Suramin, Vincristine, Paclitaxel, Docetaxel
Demyelinating neuropathy	Cytarabine, Suramin
Brachial plexopathy	Cytarabine
Lumbosacral radiculopathy	Intrathecal Methotrexate

Vasculitic Neuropathy

Paraneoplastic Vasculitic Neuropathy is characterized by non-systemic subacute vasculitic neuropathy. It occurs more frequently in SCLC and lymphoma.[38] Isolated cases in patients of carcinoma of common bile duct[39] and carcinoid tumour[40] have also been described. Neuropathy varies from mononeuritis multiplex to symmetrical polyneuropathy. Erythrocyte sedimentation rate and cerebrospinal fluid protein content are high. Electrophysiological studies reveal axonopathy. Nerve biopsy can document microvasculitis[38] and is probably due to T cell mediated immune response.[39] It is a potentially treatable condition. Anti-cancer chemotherapy and immunotherapy for vasculitis are both effective in its treatment.[38]

Autonomic Neuropathy

Autonomic Neuropathy presents as erectile dysfunction, postural hypotension, pupillary abnormalities and/or constipation. Paraneoplastic autonomic neuropathy is caused by ganglionic-receptor-binding and ganglionic-receptor-blocking antibodies. Levels of the binding antibodies correlate with severity of autonomic dysfunction in this condition.[41]

Paraneoplastic Gastrointestinal Motor Dysfunction

Paraneoplastic gastrointestinal motor

dysfunction presents as dysphagia or constipation. Lee HR et al[42] noted that it is more commonly associated with SCLC than other cancers. Gastric emptying was delayed in 89% of their patients and oesophageal dysmotility was present in 80%. One or more paraneoplastic autoantibodies were found in almost 90% patients. Anti-Hu antibody was most common antibody to be found. Other antibodies detected were anti-Yo and anti-NTCC antibodies. Autonomic reflex tests were abnormal in the 7/12 patients tested. This implies that in rest 5/12 patients, gastrointestinal motor dysfunction occurred without any other signs of autonomic neuropathy.

Viallard JF et al[43] have described a case of severe slow transit constipation with neuromyotonia and antibody to voltage gated potassium channel (VGKC). Patient's gastrointestinal symptoms responded well to plasmapharesis.

The paraneoplastic gastrointestinal motor dysfunction may be due to lymphocytes and plasma cells infiltration in gastrointestinal tract with loss of ganglion cells of myentric plexus[44] or interstitial cells of Cajal.[45]

Peripheral Nerve Hyperexcitability Syndromes

Peripheral Nerve Hyperexcitability Syndromes range from Cramp-fasciculation syndrome in its mild form to Neuromyotonia in its complete form. When central nervous system is also involved, it is called Morvan's syndrome. These Peripheral Nerve Hyperexcitability Syndromes are associated with antibodies to VGKC.[46]

Neuromyotonia is characterized by motor unit hyperactivity of peripheral origin leading to muscle cramps, fasciculation, muscle stiffness and persistent muscle contractions that may continue even during sleep. Neuromyotonic discharges are electrophysiologically characterised as bursts of motor unit potentials firing at more than 150 Hz for 0.5 to 2 seconds. The amplitude of the response typically wanes. Neuromyotonia has been described in patients of Hodgkin's Lymphoma[47], thymoma[48] and lung cancer.[48]Concomitant Anti-AChR antibody with or without Myasthenia may or may not be present. Neuromyotonia responds very well to anti-epileptic drugs like phenytoin and carbamazepine

Morvan's 'fibrillary chorea' or Morvan's syndrome is neuromyotonia associated with hallucinations, sleep disorders and behavioural abnormities. Morvan's fibrillary chorea is associated with antibodies to N-type calcium channel and voltage gated potassium channel.[11,49] Plasmapharesis and immunosuppression may be helpful in its treatment.[49]

Cramp-fasciculation syndrome is a condition characterised by muscle aches, cramps, stiffness, fasciculations associated with exercise intolerance. Fasciculations usually occur in the calf muscles. Electrodiagnostically it shows only fasciculations.[50] Cramps fasciculation syndrome in association with Myasthenia gravis with thymoma has been described.[51]

Rippling muscle disease is characterised by rippling waves of muscle contraction induced by mechanical stretch following strong muscular contraction. Patients also complain of muscle stiffness and slowness of movements at rest. Percussion of muscle in affected person leads to local painful mounding (myoedema) lasting several seconds. The rippling waves and mounding are all electrically silent during electromyographic recordings.[52] Rippling muscle disease may occur as a paraneoplastic manifestation in association with thymoma (with MG occasionally)[51] and lymphoma[53].

Myasthenia Gravis (MG)

About 50% of patients with thymoma have paraneoplastic myasthenia gravis[54] whereas only 10% patients of myasthenia gravis have thymoma. Myasthenia gravis is frequently associated with WHO type B1 and B2 thymomas.[55]

Mygland A et al[54] studied antibodies to Acetyl Choline Receptor (AChR), Titin, Ryanodine Receptor (RyR), and Voltage Gated Potasium Channel (VGKC) in 19 patients with thymoma-associated MG, of whom 5 had additional myositis and 6 had additional neuromyotonia. In the study, antibodies to AChR were present in all 19 patients. Anti-titin Ab was found in 17/19 patients. Anti-RyR Ab correlated with the

presence of myositis (P = 0.03). Patients with anti-RyR antibodies had high levels of anti-titin antibodies. Antibodies to VGKC were found in 4 patients with neuromyotonia and 1 of 3 patients of myositis. This study highlights the presence of antibodies to different skeletal muscles antigens and presence of other concomitant PND in patients of paraneoplastic MG.

Vernino et al[56] found that acetylcholine receptor (AChR) binding antibodies were present in all patients of paraneoplastic thymoma related MG. Muscle autoantibodies (AChR-binding, AChR-modulating, or striational) were also found in 59% of thymoma patients without any paraneoplastic neurological disorder. This shows that the presence of autoantibodies need not necessarily lead to paraneoplastic disorder.

It has been suggested that antibodies against non-acetylcholine receptor proteins of striated muscle are markers of the presence of a thymic epithelial tumor in patients with MG. These antibodies may be measured using an immunofluorescence assay against striated muscle (anti-STR) or an ELISA with a recombinant 30-kd titin fragment (anti-MGT30). When compared with anti-STR, anti-MGT30 showed a sensitivity of 69% (STR 77%), specificity of 100% (STR 56%, p = 0.026) for the identification of a thymic epithelial tumour versus thymic hyperplasia. It is therefore concluded that the anti-MGT30 ELISA is more specific than the anti-STR immunofluorescence assay for the diagnosis of paraneoplastic MG.[57]

Paraneoplastic MG and late-onset MG (age e" 50 years) both have a similar immunological profile with high titin and ryanodine receptor (RyR) antibody prevalence. MG severity is linked to the patient's immunological profile rather than presence of thymoma. When the diagnosis of paraneoplastic MG is established, the neoplasm should be removed surgically. Pre-thymectomy plasmapharesis or intravenous immunoglobulin should be considered in these patients to minimize post-thymectomy MG exacerbation risk. Paraneoplastic MG usually continues after thymectomy. The pharmacological treatment of paraneoplastic MG does not differ from non-paraneoplastic MG, except for tacrolimus that should be considered in difficult cases. Tacrolimus is immunosuppressant acting specifically in RyR antibody positive patients through enhancing RyR-related sarcoplasmic calcium release that in theory might be blocked by RyR antibodies, causing symptomatic relief in paraneoplastic MG.[58]

Though paraneoplastic MG is classically seen with thymoma, it has also been described to occur in Chronic Myeloid Leukaemia (responding to imatinib)[59] and SCLC[60]. Roohi F et al[61] have reported a patient presenting with acute respiratory failure and ultimately found to have overlap myasthenic syndrome (acquired myasthenia gravis with Lambert-Eaton myasthenic syndrome) in association with uterine leiomyosarcoma.

The myasthenia associated with antibodies to Muscle specific Kinase (MuSK) is usually not paraneoplastic.

Lambert-Eaton Myasthenic Syndrome (LEMS)

The autoimmune disorder of Lambert-Eaton Myasthenic Syndrome (LEMS) is associated with small cell lung carcinoma (SCLC) in 50-60% of cases.[62] LEMS patients have mild autonomic neuropathy presenting as dry mouth, papillary abnormality, constipation and/or impotence. Paraneoplastic LEMS can also lead to respiratory distress and requirement of ventilator support.[63]

Both human neuronal and SCLC cell lines express omega-conotoxin-sensitive voltage gated calcium channels (VGCCs), and antibodies directed against these channels interfere with pre-synaptic neurotransmitter release in LEMS. Pelucchi A et al[64] found that a positive result with anti-VGCC antibody radioimmunoassay is highly specific for LEMS, with or without SCLC, when the antibody titre is higher than 14.21 pM. However, Anti-VGCC antibodies were also present in about 40% of patients with SCLC without LEMS.

In a study by Maddison P et al[62], Anti-VGCC antibodies were detected in 10 out of 100 patients of SCLC screened. However, only 4 of them had clinical and electrophysiological features of LEMS. The median survival of the

four antibody positive LEMS patients (19.6 months) was considerably greater than that for the antibody negative (8.9 months) or antibody positive patients as a whole (10.5 months). These results suggest that there may be survival advantage due to functionally effective antibodies present in the sera of patients with LEMS.

There may be differences in autoimmune pathogenesis between LEMS without tumour and paraneoplastic LEMS. An antibody response to domain IV of alpha 1A subunit of P/Q-type VGCC is more common in LEMS without tumour (37.5%) than in paraneoplastic LEMS (4.6%, p=0.011).[65] This may have implications for diagnostic workup in LEMS patients without previously established diagnosis of a tumour.

Martin-Moutot N et al[66] found Anti-N type (125I-omega conotoxin GVIA) channel antibodies are present in 58% and anti-P/Q type (125I-omega conotoxin MVIIC) channel antibodies in 74% of patients with LEMS. About 16% patients in study group were seronegative for both tests. Thus, a combination of the two assays can detect autoantibodies in 84% patients.

The titres of anti-P/Q and anti-N antibodies may evolve independently and in an inverse relationship. Therefore, assays of both antibodies may provide more comprehensive information during follow-up of LEMS.[67]

The drug 3,4-diaminopyridine with anti-cholinesterase inhibitor is most effective in LEMS patients with or without SCLC. In LEMS with SCLC, specific tumour therapy will often improve the neurological disorder. In some cases plasmapheresis or intravenous immunoglobulin may be indicated.[68]

Dermatomyositis / Polymyositis

Sigurgeirsson B et al[69] found relatively less incidence of polymyositis as compared to dermatomyositis in patients of malignancy (9% and 15% respectively). In their study, the principal cause of death was malignancy in 14% of patients who had paraneoplastic polymyositis compared to 40% in those with dermatomyositis suggesting that neoplasm were more malignant in latter group.

Hill CL et al[70] identified 32.04% (198/618) patients of dermatomyositis who had cancer. 58.08% (115/198) patients had developed cancer after diagnosis of dermatomyositis was made. Dermatomyositis was strongly associated with malignant disease like ovarian, lung, pancreatic, stomach and colorectal cancers, and non-Hodgkin lymphoma. They also observed that 15% (137/914) patients of polymyositis had cancer, which developed after diagnosis of polymyositis in 69.34%. Polymyositis was associated with a raised risk of non-Hodgkin lymphoma, lung and bladder cancers. Thus, polymyositis may also be associated with cancer though not as much as dermatomyositis.

Dermatomyositis associated with malignancy does not respond as well to treatment as that without malignancy.[71]

Paraneoplastic Amyopathic Dermatomyositis responding well to IVIg has also been described.[72]

Acute Necrotizing Myopathy

Acute Necrotizing Myopathy presents as subacute symmetric proximal weakness in presence of malignancy. Levin MI et al[73] described it in patients with gastrointestinal adenocarcinoma, transitional cell carcinoma, prostatic carcinoma, and non-small cell lung carcinoma. Half of them improved after treatment with corticosteroids and tumour resection, whereas the rest died. Muscle pathology showed numerous necrotic fibres (8 to 100%) and intense alkaline phosphatase staining of the muscle connective tissue, but little inflammation.

Cachetic Myopathy

Cachetic Myopathy is characterized by generalised muscle wasting but relatively preserved muscle power along with occurrence of myoedema on tapping. Gomm SA et al[75] observed 18/100 patients with lung carcinoma had cachectic myopathy. Cachectic myopathy was more common in non-small cell lung cancer compared to small cell lung cancer. Additional feature noticed in the study was that, 99/100 patients had abnormal muscle histology and therefore were subclinically affected; 74 had type II atrophy, 12 had type I and II atrophy, one had type I atrophy and 12 had necrosis.

Treatment of Paraneoplastic Disorder

Treatment of underlying malignancy is best treatment for PND. However immunomodulation may be helpful. (Table 3)

Table 3: Response to treatment in cases of PND of Lower Motor Neuron[75]

Clinical syndrome	Response to Immunotherapy	Response to tumour therapy	Comments
Sensory Neuronopathy	No established effect. Rare partial responses	Stabilizes the patient in better condition.	Treatment of neuropathic pain with TCA and AED
Sensorimotor neuropathy	May improve	May improve	
Autonomic neuropathy	No established effect	No established effect	Symptomatic relief of orthostatic hypotension. neostigmine for pseudoobstruction
Vasculitic neuropathy	May improve	May improve	
Neuromyotonia	May respond	Not known	AED
Lambert Eaton Myasthenic Syndrome	Often responds	Often responds	2,3-Diaminopyridine, cholinesterase inhibitors may be tried.
Myasthenia gravis	Often responds	Often responds	Cholinesterase inhibitors
Dermatomyositis	Usually responds	May respond	

Conclusion:

A search for cancer should be made, if any typical paraneoplastic disorder (eg LEMS) comes to notice. If a new neurodeficit occurs in a patient of cancer, a possibility of paraneoplastic disorder should be kept after ruling out other causes for the same. Treatment of paraneoplastic disorder is treatment of underlying cancer itself; however immunosuppresion / immunomodulation may help.

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