Paraneoplastic Autonomic Neuropathy

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Background

Paraneoplastic syndromes (PNS) are a rare cause of autonomic neuropathy, which may manifest as disturbances in sympathetic and/or parasympathetic nervous system function. More often, autonomic problems in cancer patients are attributable to prolonged bed rest, neurotoxic chemotherapy, high-dose analgesics, and malnutrition. However, paraneoplastic autonomic neuropathy should be considered in all cancer patients who present with signs or symptoms of autonomic nervous system disease. Patients may develop autonomic disturbances at any time relative to the diagnosis of cancer. Often, the autonomic problems even precede the cancer diagnosis, and a high level of suspicion is required to identify the underlying neoplasm.

An international expert group established diagnostic criteria in 2004 that divide patients with a suspected paraneoplastic syndrome into "definite" and "probable" categories. These criteria are based on the presence or absence of cancer, the presence of well-characterized antibodies, and the type of clinical syndrome.

Patients with a definite PNS include those with the following:

- A classical syndrome (ie, encephalomyelitis, limbic encephalitis, subacute cerebellar degeneration, opsoclonus myoclonus, subacute sensory neuronopathy, chronic gastrointestinal pseudo-obstruction, LEMS, or dermatomyositis) and cancer that develops within 5 years of the diagnosis of the neurological disorder, regardless of the presence of paraneoplastic antibodies

- A nonclassical syndrome that objectively improves or resolves after cancer treatment, provided that the syndrome is not susceptible to spontaneous remission

- A nonclassical syndrome with paraneoplastic antibodies (well characterized or not) and cancer that develops within 5 years of the diagnosis of the neurological disorder
- A neurological syndrome (classical or not) with well-characterized paraneoplastic antibodies (ie, anti-Hu, anti-Yo, anti-Ri, antiamphiphysin, anti-CV2, anti-Ma2)

Patients with a possible PNS include those with the following:

- A classical syndrome without paraneoplastic antibodies and no cancer but at high risk to have an underlying tumor (eg, smoking history)
- A neurological syndrome (classical or not) without cancer but with partially characterized paraneoplastic antibodies
- A nonclassical neurological syndrome, no paraneoplastic antibodies, and cancer that presents within 2 years of the neurological syndrome

The main paraneoplastic syndromes associated with autonomic neuropathy include paraneoplastic peripheral neuropathies, paraneoplastic encephalomyeloneuropathies, and Lambert-Eaton myasthenic syndrome (LEMS). Each one of these may have other distinct symptoms and findings in addition to autonomic disturbances.

Pathophysiology

It has long been known that especially patients with small-cell lung cancer develop neurological signs and symptoms with greatly increased frequency; however, many other cancers including other lung tumors, thymoma, Hodgkin disease, testicular, and ovarian and breast carcinoma also cause paraneoplastic neurological syndromes.

Exactly how cancers result in paraneoplastic neurological symptoms is incompletely understood. Expression of onco-neuronal antigens by the cancer cells resulting in autoimmunity appears to be the mechanism. The known paraneoplastic antibodies may be directly pathogenic, or they may only be markers of T-lymphocyte activation. Passive transfer experiments have generally been unsuccessful.

Many antineuronal antibodies have been described to date, and new antibodies are described each year. Sometimes, more than one type of antibody is found in a single patient, and the same type of antibody may result in very different syndromes in different patients. It is also entirely possible that a patient who lacks identifiable autoantibodies and has a tumor known to express epitopes similar to neuronal structures (eg, small-cell lung cancer) may suffer from paraneoplastic autonomic failure due to an antibody that has not been identified.

Autonomic failure can occur when this autoimmune process produces sufficient damage the autonomic nervous system. Few data are available regarding immune attack on preganglionic neurons or central autonomic pathways, but Image 3 shows the typical CNS involvement in anti-Hu encephalomyeloneuropathy. Similar attacks on autonomic postganglionic and myenteric neurons can occur with other types of antineuronal antibodies.

The best understood syndromes involving paraneoplastic autonomic dysfunction are paraneoplastic sensory neuropathy, paraneoplastic encephalomyeloneuropathy, and Lambert-Eaton myasthenic syndrome.

Anti-Hu

Anti-Hu antibodies (which are also called antineuronal nuclear antibody type 1 [ANNA-1]) are the most pertinent to autonomic dysfunction and are often seen in the setting of small-cell lung cancer. The autoimmune response is directed to the Hu antigen, which is expressed by small-cell lung cancer cells and by all neurons. Antibodies to the Hu onconeuronal antigen can affect almost any portion of the central nervous system (CNS) or peripheral nervous system. The anti-Hu antibody is most often associated with a paraneoplastic sensory neuronopathy, which involves destruction of primary sensory neurons.

This antibody is diagnostically useful, but the exact role of humoral immunity in causing neural degeneration remains uncertain.

Anti VGCC

In Lambert-Eaton myasthenic syndrome (LEMS), antibodies against voltage-gated calcium channels are present. These antibodies lead to impaired presynaptic calcium release at the neuromuscular junction, resulting in predominantly proximal

muscle weakness. These antibodies not only block the voltage-gated calcium channels at theneuromuscular junction but also block them at parasympathetic and sympathetic nerve terminals, thus creating autonomic insufficiency and autonomic symptoms.

Autonomic dysfunction in LEMS is normally mild.

Other

Antibodies directed against ganglionic nicotinic acetylcholine receptors have been identified to cause autoimmune autonomic neuropathy; this type of antibody is rarely seen associated with malignancy.

Autonomic failure can also be seen in stiff person syndrome with antibodies directed against glutamic acid decarboxylase (GAD) or amphiphysin; this syndrome occasionally can be paraneoplastic in nature. Collapsin response-mediator protein (CRMP-5), also known as CV-2, is another paraneoplastic antibody associated with autonomic dysfunction. CRMP-5 is most often seen with small-cell lung cancer. Purkinje cell antibody-2 frequently causes cerebellar degeneration but can also be associated with autonomic failure.

The autoimmunity in paraneoplastic neurological syndromes does appear to confer some degree of antitumor effect. Inflammation similar to what is seen in the nervous system also affects the tumor.

Several cases have been reported in which a Hu antibody has occurred with classical paraneoplastic symptoms that spontaneously resolved without an underlying tumor being identified. This could be due to a spontaneous cure of the underlying cancer, possibly due to an antitumor effect of the paraneoplastic antibodies.

Frequency

United States

Precise incidence of paraneoplastic autonomic failure in patients with cancer is not known.

International

In the United Kingdom, a national screening program found 63 patients with paraneoplastic neurological symptoms (not including LEMS) from 2000-2001.

Mortality/Morbidity

Morbidity and death can result from severe failure of autonomic function. However, milder autonomic disturbances may be obscured by prominent symptoms of systemic cancer, anticancer therapy, or other peripheral nervous system (PNS) and CNS damage.

Race

No data suggests differences in frequency or outcomes based on race.

Sex

Conflicting evidence exists with many case series suggesting higher frequency in women but others suggesting higher frequency in men.

Age

PNS can occur at any age, many case series have recorded median age of onset in the seventh decade.

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History

Patients may present with autonomic neuropathy prior to diagnosis of cancer, at the time of cancer diagnosis, or after the treatment of cancer. Autonomic neuropathy often presents as orthostatic hypotension, which may be profound, keeping patients bedridden in spite of aggressive therapy to maintain blood pressure. However, careful evaluation may reveal more widespread disturbances. Abnormal gastrointestinal motility may cause a spectrum of problems from mild constipation and nausea to intestinal pseudo-obstruction due to autoimmune attack on myenteric neurons. Urinary incontinence, erectile dysfunction, and abnormalities of sweating are also common.

Concomitant somatic neuropathy is common and may cause pain and sensory loss, often in a length-dependent "stocking and glove" pattern but occasionally in a patchy distribution. Pain may be lightninglike or burning. When motor nerves are affected, patients may report weakness.

If the paraneoplastic process involves the CNS, symptoms can include reduced level of consciousness, seizures, memory or cognitive problems, personality change (ie, limbic encephalitis), ataxia, or even focal signs such as aphasia. CNS involvement may occur early or late; it often is responsible for profound morbidity and death.

Another symptom commonly seen in LEMS is an unpleasant metallic taste.

A patient may manifest a paraneoplastic syndrome with any combination of autonomic, peripheral, sensory, and CNS involvement. Cerebellar dysfunction, weakness, and encephalomyeloneuropathy also may occur.

As with any paraneoplastic neurological degeneration, autonomic dysfunction has been described with many types of cancer. These include particularly small-cell lung cancer and other lung tumors, thymoma, and ovarian and breast carcinoma. In some cases, paraneoplastic autonomic dysfunction occurs in the apparent absence of cancer. In patients without known cancer, any clinical history suggesting an underlying tumor (eg, unexplained weight loss) or high risk for particular cancers (eg, heavy smoking, personal or family history of cancer) can help suggest a link between autonomic symptoms and a paraneoplastic syndrome. Finding the primary tumor can prove very difficult in some patients.

The clinical course usually is subacutely progressive (lasting for weeks), leading to a bedridden condition if untreated, and often in spite of treatment.

Physical

Physical findings in patients with paraneoplastic autonomic failure resemble those of any patient with autonomic dysfunction and include the following:

- Orthostatic hypotension, often profound, in the absence of volume depletion
- Impaired pupillary light responses
- Absence of heart rate changes with respiration
- Abnormal Valsalva response
- Abnormal cold pressor response
- Impotence

Peripheral sensory neuronopathy often is evident as patchy superficial sensory loss and asymmetrically abnormal stretch reflexes.

Patchy asymmetric weakness and dyscoordination, or abnormal mental status, may occur in patients with CNS involvement.

Proximal muscle weakness is seen in LEMS.

Prior chemotherapy with vincristine typically causes areflexia that is diffuse and symmetric. Cisplatin can cause a sensory neuropathy and hearing loss, both of which are typically symmetric.

Carcinomatous meningitis can closely mimic the presentation of paraneoplastic encephalomyeloneuropathy.

Causes

Paraneoplastic autonomic dysfunction is a secondary effect of cancer. Small-cell lung cancer is particularly likely to cause paraneoplastic syndromes, but many types of malignancy can cause these types of syndromes.

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DIFFERENTIALS

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Other Problems to be Considered

Vincristine neurotoxicity
Cisplatin neurotoxicity
Carcinomatous meningitis
Scleroderma
Amyloid neuropathy

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WORKUP

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Lab Studies

- Autoimmune diagnosis
  - Serum analysis for the presence of antineuronal autoantibody using immunohistochemistry and immunoblotting is the key to diagnosis.
  - Lumbar puncture is often indicated, with ample volume of cerebrospinal fluid (CSF) sent for cytologic analysis in addition to the other usual tests. The spinal fluid often reveals a mononuclear pleocytosis, elevated protein, oligoclonal bands, and paraneoplastic antineuronal antibodies.

- Evidence of another process (eg, diabetes, scleroderma, amyloidosis) should be considered and ruled out by appropriate serologic tests and/or biopsies.
- Serological markers of malignancies (eg, CEA, PSA) can help to identify a cancer, which is not readily apparent by imaging.

Imaging Studies

- If the patient is not known to harbor a malignancy, then chest scanning (eg, high-resolution CT scan) definitely is indicated, since small-cell lung cancer is most often the associated tumor. If any abnormalities are seen, then biopsy usually is required, by either bronchoscopy or transthoracic needle.
- Imaging of the abdomen, pelvis, and brain is normally indicated looking for a primary tumor or metastasis. Mammography and gynecological ultrasound examinations are can be of value in females, and testicular ultrasound in men. PET scanning should be considered if no tumor is found. If no malignancy is found at presentation, repeating the workup every 3-6 months is advisable for the first few years.

Other Tests

- Electrophysiological studies: Electromyography (EMG)/nerve conduction velocity (NCV) studies can identify a neuropathy or defect of neuromuscular transmission if present. Pulse variability and autonomic skin responses can be performed in most laboratories. More extensive autonomic testing may be helpful to prove autonomic dysfunction in milder cases, though it usually it is not necessary.

Histologic Findings

Images 1-3 show typical histologic findings from a patient with small-cell lung cancer and autoimmune paraneoplastic autonomic failure. Loss of neurons is evident in autonomic ganglia and dorsal root ganglia, as well as within the CNS. Inflammatory infiltrates are also typical in the vicinity of neuron loss. Similar findings have been reported for autoimmune-mediated paraneoplastic autonomic dysfunction caused by other cancers.

The underlying tumor is often heavily infiltrated by inflammatory cells.

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TREATMENT

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Medical Care

Care of patients with paraneoplastic autonomic neuropathy depends on severity of autonomic failure and the status of the associated malignancy.

- Malignancy
  - The most important aspect of the medical care in a patient with paraneoplastic autonomic dysfunction is treatment of the underlying malignancy. If the malignancy can be cured, the progression of autonomic dysfunction may cease and potentially even reverse. If a cure is not possible and chemotherapy is a consideration, then a nonneurotoxic regimen that is immunosuppressive is theoretically appealing, such as cyclophosphamide and doxorubicin (Adriamycin) with minimal vincristine. However, no data show superiority of any particular regimen, as long as the tumor is controlled.
  - In exceptional cases, patients presenting with typical encephalomyeloneuropathy, including autonomic failure and positive antineuronal antibody titers, may be considered for chemotherapy even in the

absence of a tissue diagnosis. The risk of an occult malignancy in this specific situation is very high.

- Autoimmune process: In general, immunosuppressive treatments directed against the paraneoplastic antibodies (eg, plasmapheresis) have been disappointing. No therapy directed at suppressing the autoimmune response has been shown to be reliably effective; however, successful treatment of the associated malignancy by surgery and/or chemotherapy may slow or stop the progression of the neurological syndrome.

- Autonomic failure
    - Nonpharmacologic measures are useful for all patients with autonomic dysfunction:
        - Discontinue antihypertensive medications and other medications known to lower blood pressure, if feasible.
        - Increase fluid and salt intake.
        - Equipment aids may be helpful; these include tight support stockings, abdominal binders or antigravity suits for symptomatic hypotension, and bladder catheterization for urinary retention.
        - Dietary fiber and enemas may help improve bowel motility and decrease straining during defecation.
        - Patients with decreased sweating should limit their physical activity, particularly in hot weather. Sponging with water during activity may help prevent overheating.
        - Large meals may exacerbate hypotension and should be avoided.
        - Positional changes, such as standing, should be performed slowly and gradually.
        - Elevate the head of the bed and avoid prolonged recumbency.
    - Many pharmacological interventions directed against symptoms of autonomic failure are helpful; please see the article on Idiopathic Orthostatic Hypotension and Other Autonomic Failure Symptoms for a discussion.

Surgical Care

Biopsy is indicated to identify the associated malignancy, and surgical resection of the tumor should be undertaken when appropriate.

Consultations

If no known underlying cancer is present, consider seeking consultation from a pulmonary medicine specialist. A pulmonologist can help in finding small-cell lung cancer or other lung tumor through imaging and bronchoscopy.

A medical oncology specialist can be of diagnostic help, assisting in the treatment of the associated malignancy.

Gastroenterology and urology consultation may be needed if intestinal dysmotility and urinary incontinence are part of the clinical manifestations.

Diet

High fluid and salt intake is of potential value for orthostatic hypotension.

A fiber rich diet can help some gastric dysmotility symptoms.

Activity

Activity often is limited by the combination of orthostatic hypotension and neurological symptoms (eg, pain, numbness, dyscoordination, weakness, encephalopathy). However, no intrinsic limitations to safe activity (ie, fall prevention) exist.

Pulmonary embolus is a potentially fatal complication of the bedridden disabled patient; it may be less likely if the patient is active.

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MEDICATION

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No specific drug treatment is of proven value; however, cytotoxic chemotherapy for the associated malignancy is rational. For symptomatic management of autonomic failure, see article on Idiopathic Orthostatic Hypotension and Other Autonomic Failure Syndromes for details.

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FOLLOW-UP

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Further Inpatient Care

- Typically, the disorder is progressive, although stabilization with antineoplastic therapy has been reported. Consequently, follow-up is devoted to assessing adequacy of blood pressure support and bowel and bladder management.

Further Outpatient Care

- Custodial nursing home care often is needed if the autonomic failure is severe, because patients are bedridden and completely disabled.

In/Out Patient Meds

- Medications are the same as those used in inpatient care, except doses are adjusted with time and disease progression. See article Idiopathic Orthostatic Hypotension and other Autonomic Failure Syndromes for specific

suggestions.

Deterrence/Prevention

- No known method is effective in deterring or preventing occurrence of autonomic paraneoplastic failure, except to prevent exposure to known carcinogens such as tobacco smoke.

Complications

- Sudden death, presumably due to cardiac and/or vasomotor causes, can occur.
- Intestinal pseudo-obstruction and urinary tract infections from incomplete bladder emptying are possible. Overheating due to reduced sweat function can occur in hot temperatures or with physical exertion.

Prognosis

- Prognosis is poor. Prompt and effective treatment of the underlying malignancy may arrest progression of autonomic dysfunction, but in many cases, no improvement occurs. Survival is dependent on underlying cancer, patient age, and parts of the nervous system involved. The median survival of all patients with paraneoplastic syndromes has been estimated to be 1 year. The major exception is patients with Lambert-Eaton syndrome, in whom effective treatment may result in remission of the often mild autonomic symptoms, an underlying small-cell lung cancer may still be fatal.

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MISCELLANEOUS

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Medical/Legal Pitfalls

- One issue that can arise is failure to detect the associated malignancy at the time of presentation of autonomic failure. Repeated investigation for an underlying cancer is indicated. However, tumors can elude detection by all known diagnostic means for months or years in some patients, in spite of vigorous attempts at detecting the tumor.

Special Concerns

- Since the presumed pathogenesis is an idiosyncratic autoimmune response, these patients are not contagious and their management is directed primarily at the associated malignancy and management of autonomic symptoms.

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MULTIMEDIA

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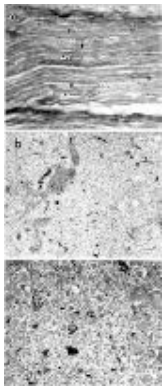
Media file 1: **Paraneoplastic autonomic neuropathy. Histopathology of peripheral nerve and sympathetic ganglion from a patient with autonomic failure, oat-cell carcinoma of the lung, and positive anti-HU antibody titer. (a) Peripheral nerve in longitudinal section stained with**

Luxol fast blue-periodic acid-Schiff (PAS) showing scattered wallerian degeneration (arrowheads). (b) Low-power view of a paravertebral sympathetic ganglion stained with hematoxylin and eosin (H&E). Arrowhead indicates perivascular mononuclear infiltrates. (c) High-power view of the same sympathetic ganglion showing degenerating neurons (single arrowheads) and mononuclear infiltrates (double arrowhead). Magnification bars in a and b indicate 100 mm; c is 50 mm.



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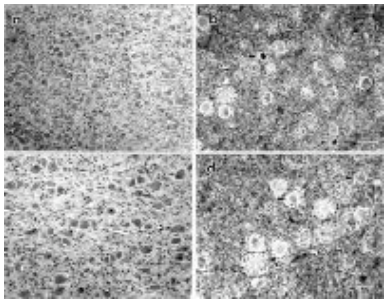
Media file 2: **Paraneoplastic autonomic neuropathy. Hematoxylin and eosin (H&E)–stained sections from dorsal root ganglion showing the hallmark histopathology of anti-HU disease; a and c are from a healthy patient; b and d are from a patient with autonomic failure, oat-cell carcinoma of the lung, and positive titer of anti-HU antibodies. The arrowheads in b and d indicate degenerating sensory neurons. Also note the interstitial hypercellularity and decreased numbers of neurons in b and d. Magnification bar in b indicates 100 mm and applies also to a. Similarly, the magnification bar in d indicates 50 mm, which also applies to c.**



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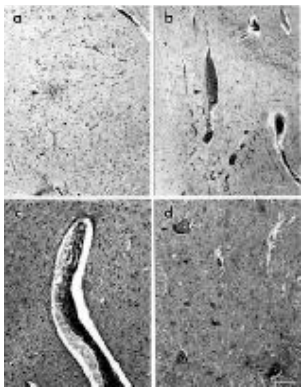
Media file 3: **Paraneoplastic autonomic neuropathy. Central nervous system sections from a patient with autonomic failure, oat-cell carcinoma of the lung, and positive titer of anti-HU antibodies stained with hematoxylin and eosin (H&E). (a) Inferior olive showing a cluster of mononuclear cells (arrowhead); (b) hippocampus showing perivascular mononuclear infiltrate (arrowhead); (c) midbrain section showing a vessel encased in a mononuclear infiltrate; (d) ventral horn of the thoracic spinal cord showing clusters of mononuclear cells around degenerating motor neurons (arrowheads). Magnification bars indicate 100 mm. The bar in b applies also to a and the bar in d also applies to c.**



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