

Paraneoplastic Syndromes: An Approach to Diagnosis and Treatment

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Recent medical advances have improved the understanding, diagnosis, and treatment of paraneoplastic syndromes. These disorders arise from tumor secretion of hormones, peptides, or cytokines or from immune cross-reactivity between malignant and normal tissues. Paraneoplastic syndromes may affect diverse organ systems, most notably the endocrine, neurologic, dermatologic, rheumatologic, and hematologic systems. The most commonly associated malignancies include small cell lung cancer, breast cancer, gynecologic tumors, and hematologic malignancies. In some instances, the timely diagnosis of these conditions may lead to detection of an otherwise clinically occult tumor at an early and highly treatable stage. Because paraneoplastic syndromes often cause considerable morbidity, effective treatment can improve patient quality of life, enhance the delivery of cancer therapy, and prolong survival. Treatments include addressing the underlying malignancy, immunosuppression (for neurologic, dermatologic, and rheumatologic paraneoplastic syndromes), and correction of electrolyte and hormonal derangements (for endocrine paraneoplastic syndromes). This review focuses on the diagnosis and treatment of paraneoplastic syndromes, with emphasis on those most frequently encountered clinically. Initial literature searches for this review were conducted using PubMed and the keyword *paraneoplastic* in conjunction with keywords such as *malignancy*, *SIADH*, and *limbic encephalitis*, depending on the particular topic. Date limitations typically were not used, but preference was given to recent articles when possible.

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ADH = antidiuretic hormone; CSF = cerebrospinal fluid; CT = computed tomography; IL = interleukin; IV = intravenous; IVIG = IV immunoglobulin; LEMS = Lambert-Eaton myasthenia syndrome; NICTH = non-islet cell tumor hypoglycemia; PNS = paraneoplastic neurologic syndrome; PTH = parathyroid hormone; PTHrP = PTH-related protein; SIADH = syndrome of inappropriate antidiuretic hormone secretion

More than 100 years ago, it was recognized that certain cancers cause various symptoms not attributable to direct tumor invasion or compression.¹ Labeled *paraneoplastic syndromes* in the 1940s,² these conditions remained poorly understood until recently. Currently, the best described paraneoplastic syndromes are attributed to tumor secretion of functional peptides and hormones (as in the case of endocrine paraneoplastic syndromes) or immune cross-reactivity between tumor and normal host tissues (as in the case of neurologic paraneoplastic syndromes). During the past several years, medical advances have not only improved the understanding of paraneoplastic syndrome pathogenesis but have also enhanced the diagnosis and treatment of these disorders.

Effective diagnosis and treatment of paraneoplastic syndromes may substantially affect overall clinical outcomes.

In some instances, paraneoplastic syndromes are manifest before a cancer diagnosis. Thus, their timely recognition may lead to detection of an otherwise clinically occult tumor at an early and highly treatable stage. Such a scenario occurs most commonly with neurologic paraneoplastic disorders. Although considerable clinical overlap with nonparaneoplastic disorders has long confounded the diagnosis of these conditions, numerous serologic and radiographic studies are currently available to aid in this process.

It is estimated that paraneoplastic syndromes affect up to 8% of patients with cancer.³ As patients with cancer live longer, and as diagnostic methods improve, this prevalence will likely increase. Yet, given the rarity of individual paraneoplastic syndromes, there are few prospective clinical trials to guide management. However, paraneoplastic syndromes frequently represent subtypes of conditions that also occur outside of a cancer association. This review incorporates clinical experience from case series of specific paraneoplastic disorders, as well as larger studies of clinically similar, nonparaneoplastic conditions, to provide an overview of the diagnosis and treatment of the most commonly encountered paraneoplastic syndromes.

PARANEOPLASTIC ENDOCRINE SYNDROMES

The paraneoplastic endocrine syndromes generally result from tumor production of hormones or peptides that lead to metabolic derangements. Thus, successful treatment of the underlying tumor often improves these conditions. Clinicians may also employ a number of medical therapies directed against the causative biologic process. Typically, paraneoplastic endocrine syndromes are detected in pa-

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A Glossary providing expansions of additional abbreviations appears at the end of this article.

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tients after a cancer diagnosis. The development of these disorders does not necessarily correlate with cancer stage or prognosis.⁴ The clinical features, associated malignancies, diagnostic studies, and treatment options of paraneoplastic endocrine syndromes are listed in Table 1.^{4,7-20}

SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION

The syndrome of inappropriate antidiuretic hormone secretion (SIADH), which is characterized by hypo-osmotic, euvolemic hyponatremia, affects 1% to 2% of all patients with cancer. Small cell lung cancer accounts for most of these cases, with approximately 10% to 45% of all patients with small cell lung cancer developing SIADH.⁵ Paraneoplastic SIADH arises from tumor cell production of antidiuretic hormone (ADH, also known as arginine vasopressin or vasopressin) and atrial natriuretic peptide. Antidiuretic hormone leads to increased free-water reabsorption; atrial natriuretic peptide has natriuretic and antidiuretic properties.⁵

Accurate assessment of volume status is a critical step in the diagnosis of SIADH because it affects the interpretation of laboratory data and directs therapy. In contrast to the hypovolemic hyponatremia caused by gastrointestinal losses, excessive diuresis, adrenal insufficiency, salt-wasting nephropathy, and cerebral salt wasting—all of which may be encountered in cancer patients—SIADH causes euvolemic hyponatremia.⁵ Both clinical and laboratory parameters may aid in the determination of volume status. A euvolemic state is supported by the absence of orthostatic vital sign changes or edema, normal central venous pressure, a serum uric acid concentration less than 4 mg/dL (to convert to $\mu\text{mol/L}$, multiply by 59.485), and a blood urea nitrogen level less than 10 mg/dL (to convert to mmol/L, multiply by 0.357). In the setting of euvolemic hyponatremia, a urinary sodium level greater than 40 mmol/L or a urine osmolality greater than 100 mOsm/kg of water (to convert to mmol/kg, multiply by 1) suggests the diagnosis of SIADH.⁶ By contrast, hyponatremia and elevated urinary sodium or osmolality occurring in a volume-depleted individual represent the *appropriate* secretion of ADH and respond to volume repletion.

The symptoms of SIADH depend on the degree and rapidity of onset of hyponatremia. Mild symptoms include headache, weakness, and memory difficulties. Serum sodium levels less than 125 mEq/L (to convert to mmol/L, multiply by 1), particularly if developing within 48 hours, can be marked by altered mental status, seizures, coma, respiratory collapse, and death.⁶ When hyponatremia develops during a longer time frame, neurologic complications may not occur.⁵

The time course of hyponatremia also affects the treatment of SIADH. In the setting of symptomatic hyponatremia developing within 48 hours, the serum sodium level

may be raised 1 to 2 mmol/L per hour and usually no more than 8 to 10 mmol/L during the first 24 hours of treatment.⁶ With chronic hyponatremia, the brain generates endogenous osmoles to minimize intracellular swelling. Rapid correction leads to water egress, brain dehydration, and central pontine and extrapontine myelinolysis, a condition characterized by lethargy, dysarthria, spastic quadriparesis, and pseudobulbar palsy—all of which can be permanent.^{5,6} Thus, a correction goal of 0.5 to 1.0 mmol/L per hour is generally recommended for these patients.⁶

The optimal therapy for paraneoplastic SIADH is treatment of the underlying tumor, which, if successful, can normalize the sodium level in a matter of weeks.⁵ In the short term, fluid restriction (usually <1000 mL/d, depending on the degree of hyponatremia and the extent of urinary excretion) may be implemented.⁶ When possible, offending medications (eg, opiates, certain antidepressants, vinca alkaloids, and cisplatin) should be discontinued.⁴

Administration of intravenous (IV) fluids for the treatment of SIADH requires an understanding of their composition. Normal (0.9%) saline has an osmolality of 308 mOsm/kg. If the urine osmolality is higher than 308 mOsm/kg, as is often the case in SIADH, normal saline infusion will result in retention of free water and further decline in the serum sodium level. Hypertonic (3%) saline has an osmolality of 1026 mOsm/kg, which often exceeds that of the urine. Its administration requires central venous access and carries a risk of overly rapid correction. Nevertheless, under the guidance of experienced clinicians and with frequent assessment of the serum sodium level, hypertonic saline offers a means of correcting severe, symptomatic hyponatremia within days. Adequate intake of dietary protein and sodium (with the use of salt tablets if necessary) is also a contributing factor in correcting hyponatremia and affects the degree of free water restriction that can be used.⁶

The primary pharmacologic treatments of SIADH are demeclocycline and vasopressin receptor antagonists. Demeclocycline interferes with the renal response to ADH and does not require simultaneous fluid restriction to achieve its effect. The time course of response ranges from days to weeks.⁵ Adverse effects of demeclocycline include nausea, anorexia, diarrhea, and renal toxicity (especially in the presence of baseline renal impairment). Long-term use can lead to diabetes insipidus (excretion of overly dilute urine resulting in hypernatremia). Because demeclocycline is an antibacterial agent, bacterial or yeast superinfection may also occur with prolonged use.⁵ In recent years, vasopressin receptor antagonists have become available for the treatment of hyponatremia. These agents, which block arginine vasopressin binding to receptors in the renal collecting ducts, result in the excretion of free water.^{5,7} In 2005, the US Food and Drug Administration approved conivaptan,

TABLE 1. Paraneoplastic Endocrine Syndromes^{a,b}

Syndrome	Clinical presentation	Laboratory findings	Associated cancers	Treatment options ^c	References
SIADH	Gait disturbances, falls, headache, nausea, fatigue, muscle cramps, anorexia, confusion, lethargy, seizures, respiratory depression, coma	Hyponatremia: mild, sodium 130-134 mEq/L; moderate, sodium, 125-129 mEq/L; severe, sodium <125 mEq/L Increased urine osmolality (>100 mOsm/kg in the context of euvolemic hyponatremia)	Small cell lung cancer, mesothelioma, bladder, ureteral, endometrial, prostate, oropharyngeal, thymoma, lymphoma, Ewing sarcoma, brain, GI, breast, adrenal	Restrict fluids (usually <1000 mL/d) and encourage adequate salt and protein intake Demeclocycline, 300-600 mg orally twice daily Conivaptan, 20-40 mg/d IV Tolvaptan, ~10-60 mg/d orally Hypertonic (3%) saline at <1-2 mL/kg/h	5-7
Hypercalcemia	Altered mental status, weakness, ataxia, lethargy, hypertonia, renal failure, nausea/vomiting, hypertension, bradycardia	Hypercalcemia: mild, calcium 10.5-11.9 mg/dL; moderate, calcium 12.0-13.9 mg/dL; severe, calcium ≥14.0 mg/dL Low to normal (<20 pg/mL) PTH level Elevated PTHrP level	Breast, multiple myeloma, renal cell, squamous cell cancers (especially lung), lymphoma (including HTLV-associated lymphoma), ovarian, endometrial	Normal saline, 200-500 mL/h Furosemide, 20-40 mg IV (use with caution and only after adequate fluid resuscitation) Pamidronate, 60-90 mg IV Zoledronate, 4 mg IV Prednisone, 40-100 mg/d orally (for lymphoma, myeloma) Calcitonin, 4-8 IU/kg SC or IM every 12 h Mithramycin, 25 µg/kg IV (often requires multiple doses) Gallium nitrate, 100-200 mg/m ² /d IV continuous infusion for 5 d Hemodialysis	4, 8, 9
Cushing syndrome	Muscle weakness, peripheral edema, hypertension, weight gain, centripetal fat distribution	Hypokalemia (usually <3.0 mmol/L), elevated baseline serum cortisol (>29.0 µg/dL), normal to elevated midnight serum ACTH (>100 ng/L) not suppressed with dexamethasone	Small cell lung cancer, bronchial carcinoid (neuroendocrine lung tumors account for ~50%-60% of cases of paraneoplastic Cushing syndrome), thymoma, medullary thyroid cancer, GI, pancreatic, adrenal, ovarian	Ketoconazole, 600-1200 mg/d orally Octreotide, 600-1500 µg/d SC or octreotide LAR, 20-30 mg IM monthly Aminoglutethimide, 0.5-2 g/d orally Metyrapone, ~1.0 g/d orally Mitotane, 0.5-8 g/d orally Etomidate, 0.3 mg/kg/h IV Mifepristone, 10-20 mg/kg/d orally Adrenalectomy	10-14
Hypoglycemia	Sweating, anxiety, tremors, palpitations, hunger, weakness, seizures, confusion, coma	For non-islet cell tumor hypoglycemia: low glucose, low insulin (often <1.44-3.60 µIU/mL), low C-peptide (often <0.3 ng/mL), elevated IGF-2:IGF-1 ratio (often >10:1) For insulinomas: low glucose, elevated insulin, elevated C-peptide, normal IGF-2:IGF-1 ratio	Mesothelioma, sarcomas, lung, GI	Glucose (oral and/or parenteral) Dexamethasone, 4 mg 2 or 3 times daily Prednisone, 10-15 mg/d Diazoxide, 3-8 mg/kg/d orally divided in 2 or 3 doses Glucagon infusion, 0.06-0.3 mg/h IV Octreotide, ~50-1500 µg/d SC or octreotide LAR, 20-30 mg IM monthly (often with corticosteroids) Human growth hormone, 2 U/d SC (often with corticosteroids)	4, 15-20

^a ACTH = adrenocorticotropic hormone; GI = gastrointestinal; HTLV = human T-lymphotropic virus; IM = intramuscular; IV = intravenous; LAR = long-acting release; PTH = parathyroid hormone; PTHrP = PTH-related protein; SC = subcutaneous; SIADH = syndrome of inappropriate antidiuretic hormone secretion. See Glossary at end of article for expansion of additional abbreviations.

^b SI conversion factors: To convert calcium values to mmol/L, multiply by 0.25; to convert cortisol values to nmol/L, multiply by 27.588; to convert C-peptide values to nmol/L, multiply by 0.331; to convert insulin values to pmol/L, multiply by 6.945; to convert osmolality values to mmol/kg, multiply by 1; to convert PTH values to ng/L, multiply by 1; and to convert sodium values to mmol/L, multiply by 1.

^c In addition to treating the underlying malignancy.

which is administered intravenously; in 2009, tolvaptan, an oral agent, was approved.^{21,22} It is important to note that much of the clinical experience with these agents comes from use in patients with more common causes of hyponatremia, such as chronic heart failure.⁷ Adverse effects of conivaptan include infusion site reactions, nausea and vomiting, and diarrhea. Adverse effects of tolvaptan include dry mouth, thirst, and constipation. Furthermore, it may be difficult to predict accurately the rate of serum sodium correction, which may occur rapidly in some instances. Vasopressin receptor antagonists are generally considered only after failure of fluid restriction. They should be initiated in a hospital setting, where rapid and repeated assessment of the serum sodium level is feasible.

HYPERCALCEMIA

Malignancy-associated hypercalcemia occurs in up to 10% of all patients with advanced cancer and generally conveys a poor prognosis.⁸ Indeed, the 30-day mortality rate for cancer patients with hypercalcemia is approximately 50%.²³ There are 4 principal mechanisms of hypercalcemia in cancer patients. Secretion of parathyroid hormone (PTH)-related protein (PTHrP) by tumor cells—known as *humoral hypercalcemia of malignancy*—accounts for 80% of cases and occurs most commonly with squamous cell tumors.⁹ On binding to PTH receptors in bone and kidney, PTHrP regulates bone resorption and renal handling of calcium and phosphate.⁸ Another 20% of cases arise directly from osteolytic activity at sites of skeletal metastases. Breast cancer, multiple myeloma, and lymphomas commonly cause hypercalcemia via this mechanism.⁹ Rarely, hypercalcemia may result from tumor secretion of vitamin D, which has been described in association with certain lymphomas, or from ectopic tumor secretion of PTH.⁹

The clinical features of hypercalcemia include nausea, vomiting, lethargy, renal failure, and coma. Symptom severity depends not only on the degree of hypercalcemia (calcium levels >14 mg/dL [to convert to mmol/L, multiply by 0.25]) are considered severe), but also on the rapidity of onset and the patient's baseline neurologic and renal function.⁹ The need for and nature of treatment should take all of these factors into account, as not all patients with hypercalcemia require aggressive therapy. The laboratory evaluation of hypercalcemia includes the following (reference ranges provided parenthetically): serum levels of ionized calcium (4.5-5.6 mg/dL), PTH (10-55 pg/mL [to convert to ng/L, multiply by 1]), and PTHrP (<2.0 pmol/L). In patients with malignancy-associated hypercalcemia, typical laboratory findings include an elevated calcium level, a low-to-normal PTH level, and often a high PTHrP level.⁸ In the absence of an ionized calcium level, total calcium, which represents both bound and unbound calcium, should

be corrected for the albumin concentration using the following formula: Corrected Ca (mg/dL) = Measured Ca (mg/dL) + [0.8 × (4.0 – Albumin (mg/dL))].

As with SIADH, the optimal approach to paraneoplastic hypercalcemia is treatment of the underlying tumor. When feasible, it is also important to discontinue medications that contribute to hypercalcemia (eg, calcium supplements, vitamin D, thiazide diuretics, calcium-containing antacids, and lithium) or that aggravate mental status changes.⁹ The first-line approach to persistent hypercalcemia is fluid repletion with normal saline, which increases the glomerular filtration rate and inhibits renal calcium reabsorption. Loop diuretics, which further inhibit renal calcium reabsorption, may be added after adequate volume resuscitation. However, because these agents may exacerbate dehydration and worsen hypercalcemia and renal function if used prematurely, they are not routinely recommended in all patients.⁹ Intravenous bisphosphonates, such as pamidronate and zoledronate, inhibit osteoclast bone resorption and are widely used because of their favorable efficacy and toxicity profiles. Generally, serum calcium levels will decline within 2 to 4 days, reach a nadir between 4 and 7 days after infusion, and remain suppressed for up to 3 weeks.⁹ Mild, asymptomatic hypocalcemia may follow bisphosphonate administration, and repletion is not recommended. The main adverse effects of bisphosphonate use are renal dysfunction and osteonecrosis of the jaw. Osteonecrosis of the jaw is caused by reduced local blood flow and leads to pain, swelling, loosened teeth, and exposed bone. It is mostly seen in patients with cancer (especially those with multiple myeloma) who have been treated with IV bisphosphonates for prolonged periods or in patients who have had recent invasive dental procedures.⁸ Corticosteroids may also be used in the management of hypercalcemia. Their main effect is via direct antitumor properties against lymphoma and myeloma cells, but they may also reduce gastrointestinal calcium absorption.⁸

Beyond bisphosphonates, few pharmacologic options for the long-term treatment of paraneoplastic hypercalcemia are available. Calcitonin, which inhibits bone resorption and increases renal calcium excretion, may be considered in patients with baseline renal disease for whom bisphosphonates may not be safe. Calcitonin's effects are typically short-lived and less robust than those of bisphosphonates.⁸ Mithramycin blocks bone resorption by inhibiting osteoclast RNA synthesis. However, it requires frequent dosing, is less effective than bisphosphonates, and has associated hepatic, renal, and hematologic toxicities.⁸ Gallium nitrate, which requires a continuous 5-day infusion, is usually reserved for cases refractory to bisphosphonate therapy. Its mechanism of action has been partially elucidated and includes inhibition of osteoclastic bone re-

sorption.^{8,24} Hemodialysis provides an effective strategy for patients with substantial renal or cardiac disease who cannot tolerate large fluid infusions or bisphosphonates.⁹

CUSHING SYNDROME

Approximately 5% to 10% of cases of Cushing syndrome (hypercortisolism) are paraneoplastic.¹⁰ Approximately 50% to 60% of these paraneoplastic cases are neuroendocrine lung tumors (small cell lung cancer and bronchial carcinoids).¹⁰⁻¹² In contrast to SIADH and hypercalcemia, patients often present with symptoms of paraneoplastic Cushing syndrome before a cancer diagnosis is made. Similarly, relapse of paraneoplastic Cushing syndrome may herald tumor recurrence.¹¹

Paraneoplastic Cushing syndrome arises from tumor secretion of adrenocorticotrophic hormone or corticotropin-releasing factor.^{10,12} These factors result in production and release of cortisol from the adrenal glands. Clinically, the condition features hypertension, hypokalemia, muscle weakness, and generalized edema.^{12,13} Weight gain with centripetal fat distribution is more common in nonparaneoplastic than in paraneoplastic Cushing syndrome.¹³ Associated laboratory findings include a baseline serum cortisol level greater than 29 µg/dL (to convert to nmol/L, multiply by 27.588), a urinary free cortisol level greater than 47 µg/24 h, and a midnight adrenocorticotrophic hormone level greater than 100 ng/L.¹³

Failure to respond to high-dose dexamethasone suppression distinguishes ectopic (ie, paraneoplastic) Cushing syndrome from a pituitary source.¹² For the high-dose dexamethasone suppression test, 2 mg of dexamethasone is given orally every 6 hours for 72 hours, and levels of urine 17-hydroxycorticosteroid (an inactive product resulting from cortisol breakdown) are measured at 9 AM and midnight of days 2 and 3 of the test. The suppression test is considered positive if 17-hydroxycorticosteroid levels are reduced by 50% or more.¹² Imaging studies, including computed tomography (CT), magnetic resonance imaging, and somatostatin receptor scintigraphy (ie, octreotide scan), are then used to locate the primary tumor. Given the distinct biochemical profile of paraneoplastic Cushing syndrome, inferior petrosal sinus sampling (to rule out a pituitary etiology) is generally not needed in the evaluation.¹³

Aside from treatment of the underlying tumor, first-line pharmacologic options for paraneoplastic Cushing syndrome are directed toward inhibition of steroid production. These drugs include ketoconazole, mitotane, metyrapone, and aminoglutethimide. Despite associated nausea and hepatotoxicity, ketoconazole is usually the best tolerated of these agents.¹⁴ Antihypertensive agents and diuretics, with careful monitoring of serum potassium, may also be used to control symptoms. Less commonly used options include

octreotide, which blocks the release of adrenocorticotrophic hormone,¹⁴ and etomidate, which inhibits aspects of steroid synthesis and has been used to decrease serum cortisol levels in patients who are unable to take oral medications.¹⁴ Mifepristone, which binds competitively to the glucocorticoid receptor, has recently been shown to improve clinical and biochemical parameters of Cushing syndrome.^{14,25} Although not currently approved by the US Food and Drug Administration for this indication, it may be obtained on compassionate grounds. When medical therapy is not successful, adrenalectomy may be considered.¹²

HYPOLYCEMIA

Tumor-associated hypoglycemia occurs rarely and can be caused by insulin-producing islet-cell tumors and (paraneoplastic) extrapancreatic tumors.¹⁵ The latter, termed *non-islet cell tumor hypoglycemia* (NICTH), presents as recurrent or constant hypoglycemic episodes with glucose levels as low as 20 mg/dL (to convert to mmol/L, multiply by 0.0555) and typically affects elderly patients with advanced cancer.¹⁶ Occasionally, these hypoglycemic episodes can predate the diagnosis of the underlying tumor.¹⁵

Non-islet cell tumor hypoglycemia is usually caused by tumor cell production of IGF-2 but may also arise from tumor cell production of insulin.¹⁵ In addition to low serum glucose levels during acute episodes, NICTH is characterized by low serum levels of insulin (often <1.44-3.60 µIU/mL [to convert to pmol/L, multiply by 6.945]) and C-peptide (often <0.3 ng/mL [to convert to nmol/L, multiply by 0.331]); low levels of growth hormone and IGF-1; normal or elevated levels of IGF-2; and an elevated IGF-2:IGF-1 ratio.^{15,16} In contrast, insulinomas cause elevated insulin and C-peptide levels, and the IGF-2:IGF-1 ratio is usually within the normal range.¹⁵

The optimal initial approach to NICTH is to treat (if possible, resect) the underlying tumor. When such an approach is not feasible, the goal of medical therapy is to maintain adequate blood glucose levels. In the acute setting, oral and/or parenteral dextrose are administered. An ampule of dextrose 50% IV fluid (D50) contains 25 g of dextrose in 50 mL of fluid and exerts an immediate effect on blood glucose. Oral glucose pastes and tablets raise blood glucose in 15 to 30 minutes. For recurrent or chronic hypoglycemic episodes, longer-term management includes corticosteroids, growth hormone, diazoxide, octreotide, or glucagon.¹⁵⁻¹⁷ Diazoxide, which inhibits insulin secretion by pancreatic β cells, has been used primarily in the management of islet cell tumor hypoglycemia.^{17,26} It is also approved for the treatment of hypoglycemia due to hyperinsulinism associated with extrapancreatic malignancies. Because octreotide has been associated with worsening hypoglycemia in some patients,¹⁵ a short-acting test dose

is recommended. Glucagon requires adequate hepatic glycogen stores, which may be assessed with a 1-mg IV glucagon challenge.¹⁷

PARANEOPLASTIC NEUROLOGIC SYNDROMES

Paraneoplastic neurologic syndromes (PNS) result from immune cross-reactivity between tumor cells and components of the nervous system.²⁷ In response to a developing cancer, a patient produces tumor-directed antibodies known as *onconeural antibodies*. Because of antigenic similarity, these onconeural antibodies and associated onconeural antigen-specific T lymphocytes²⁸ inadvertently attack components of the nervous system as well. In contrast to paraneoplastic endocrine syndromes, PNS are detected before cancer is diagnosed in 80% of cases.²⁹ Because tumor cells themselves do not directly produce the causative agents of PNS, and because onconeural antibodies may cause permanent damage, successful cancer treatment does not necessarily result in neurologic improvement. Immunosuppressive therapy is a mainstay of PNS treatment, but success is variable. Although PNS are rare, affecting less than 1% of cancer patients overall, certain malignancies have a substantially higher incidence of these conditions. For example, up to 5% of patients with small cell lung cancer³⁰ and up to 10% of patients with lymphoma or myeloma develop PNS.³⁰ Overrepresented cancers tend to produce neuroendocrine proteins (eg, small cell lung cancer and neuroblastoma), contain neuronal components (eg, teratomas), involve immunoregulatory organs (eg, thymomas), or affect immunoglobulin production (eg, lymphoma and myeloma).³⁰ The clinical features, associated malignancies, diagnostic studies, and treatment options of PNS are listed in Table 2.²⁷⁻⁷⁹

Depending on the affected nervous system compartment, PNS symptoms may include cognitive and personality changes, ataxia, cranial nerve deficits, weakness, or numbness. Paraneoplastic neurologic syndromes can affect the central nervous system (eg, limbic encephalitis and paraneoplastic cerebellar degeneration), the neuromuscular junction (eg, Lambert-Eaton myasthenia syndrome [LEMS] and myasthenia gravis), or the peripheral nervous system (eg, autonomic neuropathy and subacute sensory neuropathy). These conditions are not uniquely paraneoplastic. More than 70% of cases of limbic encephalitis and subacute sensory neuropathy occur without an associated malignancy.²⁹ Approximately 50% of cases of subacute cerebellar ataxia cases and 40% of LEMS cases are not paraneoplastic.²⁹ The broad differential diagnosis for many of these syndromes includes infectious, toxic, and metabolic etiologies. In patients with cancer, neurologic changes may also arise from brain metastases, leptomeningeal

disease, spinal cord and nerve root compression, and adverse effects of treatments, including radiation therapy and cytotoxic agents such as platinum, taxanes, and vinca alkaloids.³⁰

The diagnosis of PNS may incorporate imaging, serologies, electroencephalography, nerve conduction studies, electromyography, and cerebrospinal fluid (CSF) analysis for signs of inflammation.²⁷ Onconeural antibodies, which are usually detectable in the serum and rarely require CSF testing, may lack sensitivity and specificity. Approximately 30% of patients with presumed PNS do not have detectable antibodies in either serum or CSF.²⁹ Conversely, some well-defined onconeural antibodies may be detected in individuals with no neurologic illness. Given the overlapping clinical features with nonparaneoplastic disorders and the limitations of serologic testing, new diagnostic criteria have been proposed. These include the presence of cancer, the definition of classical syndromes, and the presence of onconeural antibodies. On the basis of these criteria, PNS have been classified as “definite” and “possible.”⁸⁰ Even in patients with detectable onconeural antibodies, it has been suggested that a diagnosis of PNS be made only after other possible causes of a particular neurologic syndrome have been excluded.

Because most patients diagnosed as having an apparent PNS will not have known cancer at the time, screening for an underlying tumor is indicated. This process includes complete history and physical examination, as well as imaging studies. If findings on CT of the chest, abdomen, and pelvis are negative, ¹⁸F-fluorodeoxyglucose–positron emission tomography or combined positron emission tomography and CT may identify the underlying tumor.^{27,81} In some instances, the PNS and associated antibodies may sufficiently suggest a particular cancer to prompt disease-specific imaging modalities such as mammography. If, despite these studies, no malignancy is identified, it has been recommended that clinical and radiographic surveillance be repeated every 3 to 6 months for 2 to 3 years.²⁷ Beyond that time, the likelihood of a subsequent cancer diagnosis decreases substantially.²⁹

Onconeural antibodies are classified according to 3 main categories: (1) those that are molecularly well characterized with a strong cancer association (anti-amphiphysin, anti-CV2 [CRMP5], anti-Hu [ANNA-1], anti-Ma2, anti-recoverin, anti-Ri [ANNA-2], anti-Yo [PCA-1]); (2) those that are partially characterized (ANNA-3, anti-mGluR1, anti-Tr, anti-Zic4, PCA-2); or (3) those occurring in both cancer- and non-cancer-associated syndromes (anti-acetylcholine receptor [AChR], anti-nicotinic AChR, anti-VGCC, anti-VGKC) (see Glossary at end of article for expansion of additional abbreviations).²⁷ For many PNS, the precise mechanism of antineuronal antibodies remains

TABLE 2. Paraneoplastic Neurologic Syndromes^a

Syndrome	Clinical presentation	Associated antibodies ^b	Diagnostic studies	Associated cancers	Treatment options ^b	References
Limbic encephalitis (LE)	Mood changes, hallucinations, memory loss, seizures, and less commonly hypothalamic symptoms (hyperthermia, somnolence, endocrine dysfunction); onset over days to months	anti-Hu (typically with small cell lung cancer) anti-Ma2 (typically testicular cancer) anti-CRMP5 (anti-CV2) anti-amphiphysin	EEG: epileptic foci in temporal lobe(s); focal or generalized slow activity FDG-PET: increased metabolism in temporal lobe(ss) MRI: hyperintensity in medial temporal lobe(s) CSF analysis: pleocytosis, elevated protein, elevated IgG, oligoclonal bands	SCLC (~40%-50% of LE patients), testicular germ-cell (~20% of LE patients), breast (~8% of LE patients), thymoma, teratoma, Hodgkin lymphoma	IVIG, 400-1000 mg/d to total 2-3 g Methylprednisolone, up to 1 g/d IV Prednisone, 1 mg/kg per day orally Plasma exchange Cyclophosphamide, ~2 mg/kg/d orally Rituximab, 375 mg/m ² IV per dose	27-44
Paraneoplastic cerebellar degeneration	Ataxia, diplopia, dysphagia, dysarthria; prodrome of dizziness, nausea, vomiting	anti-Yo anti-Hu anti-CRMP5 (anti-CV2) anti-Ma anti-Tr anti-Ri anti-VGCC anti-mGluR1	FDG-PET: increased metabolism (early stage) and then decreased metabolism (late stage) in cerebellum MRI: cerebellar atrophy (late stage)	SCLC, gynecologic, Hodgkin lymphoma, breast	IVIG, 400-1000 mg/d to total 2-3 g Methylprednisolone, up to 1 g/d IV Plasma exchange Cyclophosphamide, ~2 mg/kg/d orally Rituximab, 375 mg/m ² IV per dose	27, 28, 30, 33, 35, 36, 38-56
Lambert-Eaton myasthenia syndrome (LEMS)	Lower extremity proximal muscle weakness, fatigue, diaphragmatic weakness, bulbar symptoms (usually milder than in MG); later in course, autonomic symptoms (ptosis, impotence, dry mouth) in most patients	anti-VGCC (P/Q type)	EMG: low compound muscle action potential amplitude; decremental response with low-rate stimulation but incremental response with high-rate stimulation	SCLC (~3% of patients have LEMS), prostate, cervical, lymphomas, adenocarcinomas	3,4-DAP, maximum of 80 mg/d orally Guanidine, ~575 mg/d orally (with pyridostigmine) Pyridostigmine, ~240-360 mg/d orally (with guanidine) Prednisolone, 60-100 mg orally every other day Azathioprine, up to 2.5 mg/kg/d orally IVIG, 400-1000 mg/d to total 2-3 g Plasma exchange	27, 30, 44, 57-66
Myasthenia gravis (MG)	Fatigable weakness of voluntary muscles (ocular-bulbar and limbs), diaphragmatic weakness	anti-AchR	EMG: decremental response to repetitive nerve stimulation	Thymoma (in ~15% of MG patients)	Thymectomy Pyridostigmine, ~600 mg/d orally in divided doses Prednisone, ~1 mg/kg/d orally Azathioprine, up to 2.5 mg/kg/d orally (with corticosteroids) Cyclosporine A, ~3 mg/kg/d orally Tacrolimus, 3-4 mg/d orally Mycophenolate mofetil, 1-3 g/d orally Rituximab, 375 mg/m ² IV per dose Cyclophosphamide, 50 mg/kg/d IV for 4 d Plasma exchange IVIG, 400-1000 mg/d to total 2-3 g	27, 63, 67-72

(continued on next page)

TABLE 2. Continued.^a

Syndrome	Clinical presentation	Associated antibodies	Diagnostic studies	Associated cancers	Treatment options ^b	References
Autonomic neuropathy	Panautonomic neuropathy, often subacute onset (weeks), involving sympathetic, parasympathetic, and enteric systems; orthostatic hypotension; GI dysfunction; dry eyes/mouth; bowel/bladder dysfunction; altered pupillary light reflexes; loss of sinus arrhythmia CGP: constipation, nausea/vomiting, dysphagia, weight loss, abdominal distention	anti-Hu anti-CRMP5 (anti-CV2) anti-nAChR anti-amphiphysin	Abdominal radiography/barium studies/ CT: GI dilatation but no mechanical obstruction (for CGP) Esophageal manometry: achalasia or spasms (for CGP)	SCLC, thymoma	For orthostatic hypotension: Water, salt intake Fludrocortisone, 0.1-1.0 mg/d orally Midodrine, 2.5-10 mg orally 3 times daily Caffeine, ~200 mg/d orally For pseudo-obstruction: Neostigmine, 2 mg IV	27, 29, 37-41, 44, 73-77
Subacute (peripheral) sensory neuropathy	Parasthesias/pain (typically upper extremities before lower), followed by ataxia; multifocal/asymmetric distribution; all sensory modalities decreased but especially deep sensation/pseudoathetosis of hands; deep tendon reflexes decreased/absent; onset over weeks to months	anti-Hu anti-CRMP5 (anti-CV2) anti-amphiphysin	NCS: reduced/absent sensory nerve action potentials CSF analysis: pleocytosis, high IgG, oligoclonal bands	Lung (~70%-80%), usually SCLC; breast, ovarian; sarcomas; Hodgkin lymphoma	Methylprednisolone, up to 1 g/d IV Cyclophosphamide, ~3 mg/kg/d orally IVIg, 400-1000 mg/d, to total 2-3 g Plasma exchange	27, 29, 33 36-41, 44, 78, 79

^a CGP = chronic GI pseudo-obstruction; CSF = cerebrospinal fluid; CT= computed tomography; DAP = diaminiopyridine; EEG = electroencephalography; EMG = electromyography; FDG-PET = ¹⁸F-fluorodeoxyglucose-positron emission tomography; GI = gastrointestinal; IM = intramuscular; IV = intravenous; IVIG = IV immunoglobulin; LEMS = Lambert-Eaton myasthenia syndrome; MRI = magnetic resonance imaging; nAChR = nicotinic acetylcholine receptor; NCS = nerve conduction study; NMDA = *N*-methyl-D-aspartate; PET = positron emission tomography; PNS = paraneoplastic neurologic syndrome; SC = subcutaneous; SCLC = small cell lung cancer. See Glossary at end of this article for expansion of additional abbreviations.

^b In addition to treating the underlying malignancy.

unclear. Evidence supports a putative role in PNS pathogenesis for antibodies with extracellular targets (such as anti-AchR, anti-VGCC, anti-VGKC, anti-mGluR1, and anti-NMDA).^{27,44,82-84} For instance, anti-AchR and anti-VGCC antibodies interfere with acetylcholine binding and postsynaptic signal transduction, respectively, resulting in dysfunction of the neuromuscular junction. However, a number of antineuronal antibodies are directed against intracellular antigens, in which case *in vivo* antigen binding is unlikely to occur. In such cases, T-cell-mediated cellular immunity may contribute to pathogenesis.^{28,44} In general, conditions associated with unclear antineuronal antibody mechanisms respond less well to therapy and have a worse prognosis than other PNS.^{28,44,85}

Beyond treatment of the underlying tumor, immune modulation is a key component of PNS therapy. Specific modalities include corticosteroids, corticosteroid-sparing agents (eg, azathioprine, cyclophosphamide), the anti-CD20 monoclonal antibody rituximab, IV immunoglobulin (IVIg), and plasmapheresis (plasma exchange). The mechanism by which IVIG acts in the treatment of PNS and other autoimmune disorders is not completely understood but may include the following: (1) interacting with

Fc receptors on host effector cells (eg, neutrophils, natural killer cells), thereby “distracting” these cells from neural targets opsonized by PNS antibodies; (2) neutralizing the PNS autoantibody; (3) increasing the number and effect of the regulatory T cells that maintain immunologic self-tolerance; and (4) accelerating the fractional rate of catabolism of PNS antibodies by increasing the total immunoglobulin plasma concentration.⁸⁶⁻⁹³ Adverse effects of IVIG are commonly mild, related to the infusion rate, and include headache, chills, dizziness, and fluid retention. Up to 7% of patients develop IVIG-associated nephrotoxicity, and most of these cases occur with sucrose-containing preparations.⁹⁴ The risk can be decreased by using nonsucrose agents or by diluting the preparation and by decreasing the infusion rate.⁹⁵ Plasmapheresis directly removes antineuronal antibodies from the circulation, an effect that may be seen within days but typically lasts only 3 to 4 weeks. Concomitant administration of immune-modulating drugs appears to enhance the effect of plasmapheresis.⁹⁶ Depending on the timing of the procedure, consideration should be given to the possibility that plasmapheresis will increase drug clearance.⁹⁷ Whether through plasmapheresis or other means, reduction in onconeural antibody titers has

been associated with clinical benefit.^{27,82} If the underlying tumor is successfully treated, subsequent positive antibody titers may indicate tumor relapse.⁹⁸ For select PNS, therapies directed at the resulting neuropathophysiologic process provide substantial clinical benefit. Examples include pyridostigmine, an anticholinesterase agent, for myasthenia gravis, and 3,4-diaminopyridine, a potassium channel blocker, for LEMS.

The impact of PNS on overall prognosis is complex and reflects a number of factors. Development of a PNS may result in diagnosis and treatment of a cancer at an otherwise clinically occult—and highly treatable—stage. Conversely, independent of the underlying malignancy, the PNS itself can result in substantial morbidity. Because PNS may cause irreversible pathologic changes to the nervous system, treatment often results in symptom stability rather than improvement.²⁷ Finally, onconeural antibodies may indicate an antitumor immunologic effect. A 1997 study found that patients with small cell lung cancer who had anti-Hu antibodies were more likely to achieve a complete response after treatment than those patients without anti-Hu antibodies.⁹⁹ Such observations raise the possibility that treatment of the PNS with immune modulation may result in cancer progression. To date, however, this hypothetical concern has not been demonstrated clinically.

PARANEOPLASTIC DERMATOLOGIC AND RHEUMATOLOGIC SYNDROMES

Many of the dermatologic and rheumatologic paraneoplastic syndromes are conditions that occur most commonly without an associated malignancy. Nevertheless, the incidence of cancer is sufficient to warrant expedited age- and risk factor–appropriate screening studies in patients newly diagnosed as having these disorders. Management of dermatologic and rheumatologic paraneoplastic syndromes consists of cancer-directed therapy plus standard treatments of the nonparaneoplastic counterparts of these syndromes. In general, these syndromes are less responsive to therapy than are the nonparaneoplastic equivalents. Development of these disorders often precedes a diagnosis of cancer or recurrence of a previously treated malignancy.^{100,101} The clinical features, associated malignancies, diagnostic studies, and treatment of paraneoplastic dermatologic and rheumatologic syndromes are listed in Table 3.¹⁰⁰⁻¹³² A more detailed discussion of selected syndromes follows.

ACANTHOSIS NIGRICANS

Acanthosis nigricans is characterized by thickened hyperpigmented skin, predominantly in the axilla and neck regions. Most cases of acanthosis nigricans occur in persons with insulin resistance or other nonmalignant endocrine

disorders. Among paraneoplastic cases, gastric adenocarcinoma is the most commonly associated malignancy.¹⁰⁰ Up to 90% of cases of acanthosis nigricans of the palms, termed *tripe palms*, have been found to be cancer-associated.¹⁰² Paraneoplastic acanthosis tends to be more severe than the benign condition. Up to half of these patients have mucosal involvement.¹⁰³ Tumor production of transforming growth factor α and epidermal growth factor are proposed mechanisms for this disorder.¹⁰³ Symptomatic treatment, such as topical corticosteroids, has minimal benefit,¹⁰³ but successful treatment of the underlying malignancy may result in improvement and occasionally resolution of the condition.¹⁰²

DERMATOMYOSITIS

Dermatomyositis is an inflammatory myopathy featuring multiple skin changes before the onset of proximal muscle weakness.^{100,104} Classically, dermatologic findings include a heliotrope rash (so-named for the purplish color of the heliotrope plant) on the upper eyelids; an erythematous rash on the face, neck, back, chest, and shoulders; and Gottron papules, a scaly eruption over the phalangeal joints that may mimic psoriasis.¹⁰⁴ Approximately 10% to 25% of cases are paraneoplastic.^{100,105,133} Commonly associated malignancies include breast, ovarian, lung, and prostate cancer,¹⁰⁰ but it is not clear if this association merely reflects cancer prevalence in at-risk populations.¹⁰⁵

The diagnosis of dermatomyositis is suggested by an elevated level of creatine phosphokinase (which may be followed to monitor response to therapy), characteristic findings on electromyography, and muscle biopsy findings demonstrating a mixed B- and T-cell perivascular inflammatory infiltrate and perifascicular muscle fiber atrophy.¹⁰⁴ Because of the association between dermatomyositis and malignancy, expedited age-appropriate examinations and tests to screen for cancer are warranted in all patients with dermatomyositis.¹⁰⁴ Whether additional cancer screening is indicated remains unclear. In a series of 40 patients with dermatomyositis or polymyositis, the following clinical characteristics were significantly associated with malignancy: the presence of constitutional symptoms, the absence of Raynaud phenomena, rapid onset of myositis, higher mean erythrocyte sedimentation rate (48 vs 25 mm/h), and higher mean creatine kinase level (2840 vs 1346 U/L [to convert to μ kat/L, multiply by 0.0167]). The authors concluded that patients with these features may benefit from a more extensive search for malignancy, namely CT of the chest, abdomen, and pelvis.¹³⁴ Glucocorticoids are the mainstay of treatment for dermatomyositis, but paraneoplastic dermatomyositis often requires additional immune-modulating therapies.¹⁰⁰ In most cases, successful tumor-directed therapy will also ameliorate symptoms;

TABLE 3. Paraneoplastic Dermatologic and Rheumatologic Syndromes^a

Syndrome	Clinical presentation	Diagnostic studies/ laboratory findings	Associated cancers	Treatment options ^b	References
Acanthosis nigricans	Velvety, hyperpigmented skin (usually on flexural regions); papillomatous changes involving mucous membranes and mucocutaneous junctions; rugose changes on palms and dorsal surface of large joints (eg, tripe palms)	Skin biopsy: histology shows hyperkeratosis and papillomatosis	Adenocarcinoma of abdominal organs, especially gastric adenocarcinoma (~90% of malignancies in patients with acanthosis nigricans are abdominal); gynecologic	Topical corticosteroids	100,102, 103
Dermatomyositis (DM)	Heliotrope rash (violaceous, edematous rash on upper eyelids); Gottron papules (scaly papules on bony surfaces); erythematous rash on face, neck, chest, back, or shoulders (the last of which is known as <i>shawl sign</i>); rash may be photosensitive; proximal muscle weakness; swallowing difficulty; respiratory difficulty; muscle pain	Laboratory findings: elevated serum CK, AST, ALT, LDH, and aldolase; EMG: increased spontaneous activity with fibrillations, complex repetitive discharges, and positive sharp waves; Muscle biopsy: perivascular or interfascicular septal inflammation and perifascicular atrophy	Ovarian, breast, prostate, lung, colorectal, non-Hodgkin lymphoma, nasopharyngeal	Prednisone, 80-100 mg/d orally Methylprednisolone, up to 1 g/d IV Azathioprine, up to 2.5 mg/kg/d orally Methotrexate, up to 25 mg/wk orally Cyclosporine A, 100-150 mg orally twice daily Mycophenolate mofetil, 2 g/d orally Cyclophosphamide, 0.5-1.0 g/m ² IV IVIg, 400-1000 mg/d to total 2-3 g	100, 104-106
Erythroderma	Erythematous, exfoliating, diffuse rash (often pruritic)	Skin biopsy: histology shows dense perivascular lymphocytic infiltrate	Chronic lymphocytic leukemia, cutaneous T-cell lymphoma (including mycosis fungoides), GI (colorectal, gastric, esophageal, gallbladder), adult T-cell leukemia/lymphoma, myeloproliferative disorders	Topical corticosteroids Narrow-band UVB phototherapy	107-111
Hypertrophic osteoarthropathy	Subperiosteal new bone formation on phalangeal shafts ("clubbing"), synovial effusions (mainly large joints), pain, swelling along affected bones and joints	Plain radiography: periosteal reaction along long bones Nuclear bone scan: intense and symmetric uptake in long bones	Intrathoracic tumors, metastases to lung, metastases to bone, nasopharyngeal carcinoma, rhabdomyosarcoma	NSAIDs Opiate analgesics Pamidronate, 90 mg IV Zoledronate, 4 mg IV Localized radiation therapy	100, 112-114
Leukocytoclastic vasculitis	Ulceration, cyanosis, and pain over affected regions (especially digits); palpable purpura, often over lower extremities; renal impairment; peripheral neuropathy	Skin biopsy: histology shows fibrinoid necrosis, endothelial swelling, leukocytoclasia, and RBC extravasation	Leukemia/lymphoma, myelodysplastic syndromes, colon, lung, urologic, multiple myeloma, rhabdomyosarcoma	Methylprednisolone, up to 1 g/d IV Prednisone, 1.0-1.5 mg/kg/d orally Dapsone, ~25-50 mg/d orally Colchicine, ~0.5 mg orally 2 or 3 times daily Methotrexate, 5-20 mg/wk orally Azathioprine, 0.5-2.5 mg/kg/d orally IVIg, 400-1000 mg/d to total 2-3 g	100, 115-119

(continued on next page)

TABLE 3. Continued^a

Syndrome	Clinical presentation	Diagnostic studies/ laboratory findings	Associated cancers	Treatment options ^b	References
Paraneoplastic pemphigus (PNP)	Severe cutaneous blisters and erosions (predominantly on trunk, soles, palms); severe mucosal erosions, including stomatitis	Serum antibodies to epithelia (against plakins and desmogleins) Skin biopsy: histology shows keratinocyte necrosis, epidermal acantholysis, and IgG and complement deposition in epidermal and basement membrane zones	Non-Hodgkin lymphoma, chronic lymphocytic leukemia, thymoma, Castleman disease, follicular dendritic cell sarcoma	Prednisone, ~60-120 mg orally daily Azathioprine, ~1.5 mg/kg/d orally Cyclophosphamide, 100-150 mg/d orally Cyclosporine A (target plasma levels 100-150 ng/L) IVIg, 400-1000 mg/d to total 2-3 g Mycophenolate mofetil, 1-2 g/d orally Plasma exchange Rituximab, 375 mg/m ² IV per dose	100, 107, 120-125
Polymyalgia rheumatica (PMR)	Limb girdle pain and stiffness	Laboratory findings: elevated serum ESR (often not as high as in nonparaneoplastic PMR) and CRP	Leukemia/lymphoma; myelodysplastic syndromes; colon; lung; renal; prostate; breast	Prednisone, ~15 mg/d orally Methotrexate, ~10 mg/wk orally	126-128
Sweet syndrome (acute febrile neutrophilic dermatosis)	Acute onset of tender, erythematous nodules, papules, plaques, or pustules on extremities, face, or upper trunk; neutrophilia; fever; malaise	Skin biopsy: histology shows a polymorphonuclear cell dermal infiltrate	Leukemia (especially AML), non-Hodgkin lymphoma, myelodysplastic syndromes, genitourinary, breast, GI, multiple myeloma, gynecologic, testicular, melanoma	Clobetasol propionate, 0.05% topical Triamcinolone acetonide, 3-10 mg/mL intralesional injection(s) Methylprednisolone, up to 1 g/d IV Prednisone, 30-60 mg/d orally Potassium iodide, 300 mg orally 3 times daily (tablets) or 1050-1500 mg/d orally of saturated solution (Lugol solution) Colchicine, ~0.5 mg orally 3 times daily	100, 101, 129-132

^a ALT = alanine aminotransferase; AML = acute myeloid leukemia; AST = aspartate aminotransferase; CK = creatine kinase; CRP = C-reactive protein; EMG = electromyography; ESR = erythrocyte sedimentation rate; GI = gastrointestinal; IM = intramuscular; IV = intravenous; IVIG = IV immunoglobulin; LDH = lactate dehydrogenase; NSAID = nonsteroidal anti-inflammatory drug; RBC = red blood cell; SC = subcutaneous; UV = ultraviolet.

^b In addition to treating the underlying malignancy.

however, up to one-third of patients will have substantial residual motor impairment.^{100,104} In contrast to dermatomyositis, polymyositis—an inflammatory myopathy without associated dermatologic findings—is rarely associated with cancer.¹⁰⁴

HYPERTROPHIC OSTEOARTHROPATHY

Hypertrophic osteoarthropathy is characterized by periostosis and subperiosteal new bone formation along the shaft of long bones and the phalanges (“digital clubbing”), joint swelling, and pain.^{100,112} Vascular endothelial growth factor, platelet-derived growth factor, and prostaglandin E2 have all been identified as possible contributors to hypertrophic osteoarthropathy.^{112,135,136} Approximately 90% of cases are paraneoplastic, with the remaining cases found in association with conditions such as pulmonary fibrosis, endocarditis, Graves disease, and inflammatory bowel disease.¹¹³ Hypertrophic osteoarthropathy may also develop as a pri-

mary disorder, termed *pachydermoperiostosis*.¹¹² Clinical features of hypertrophic osteoarthropathy, particularly digital clubbing, are present in up to 10% of patients with lung tumors.¹⁰⁰ In patients with long bone involvement, nuclear bone scans will demonstrate symmetric and concentrated tracer uptake along these bones.¹¹² The symptoms of paraneoplastic hypertrophic osteoarthropathy may resolve with successful cancer therapy. Other treatment options include bisphosphonates, opiate analgesics, nonsteroidal anti-inflammatory drugs, and localized palliative radiation.^{112,113}

LEUKOCYTOCLASTIC VASCULITIS

Paraneoplastic leukocytoclastic vasculitis occurs most commonly with hematologic malignancies or with lung, gastrointestinal, or urinary tract tumors.^{115,116} Palpable purpura over the lower extremities accompanied by pain, burning, and pruritis is the characteristic skin presentation. Constitutional

symptoms, such as fever and malaise, are also common.¹¹⁷ Rarely, gastrointestinal and renal involvement may occur.¹¹⁷ Paraneoplastic leukocytoclastic vasculitis has been attributed to circulating tumor-associated antigens. These antigens lead to small vessel immune complex deposition, which triggers complement fixation and inflammation.¹⁰⁰ Paraneoplastic leukocytoclastic vasculitis often precedes a cancer diagnosis; however, because the overwhelming majority of cases of leukocytoclastic vasculitis are not paraneoplastic, cancer screening beyond general age-appropriate guidelines is not recommended.¹⁰⁰ Treatment of the malignancy has been shown to improve or resolve the disorder.¹¹⁶ In addition, colchicine, dapsone, and corticosteroids are options for mild to moderate disease. Methotrexate, azathioprine, or IVIG may be considered for resistant disease.¹¹⁷

PARANEOPLASTIC PEMPHIGUS

Paraneoplastic pemphigus is a severe blistering condition that affects the skin and mucous membranes. If not effectively treated, it can result in substantial morbidity (ie, secondary infection) and even death.¹²⁰ Paraneoplastic pemphigus is characterized by painful mucosal lesions as well as a polymorphic rash that is seen mainly on the palms, soles, and trunk.¹⁰⁷ The syndrome is thought to arise from antibodies directed against tumor antigens that exhibit cross-reactivity against various epidermal proteins.¹⁰⁰ Paraneoplastic pemphigus is typically seen in conjunction with B-cell lymphoproliferative disorders.¹⁰⁷ Treatment includes immune-modulating agents such as corticosteroids and rituximab, as well as cancer-directed therapy.¹⁰⁰

SWEET SYNDROME

Approximately 20% of patients with Sweet syndrome have an underlying cancer, most commonly acute myeloid leukemia or another hematologic malignancy.¹²⁹ The most commonly associated solid tumors are breast, genitourinary, and gastrointestinal cancers.¹⁰¹ The diagnosis of Sweet syndrome typically coincides with an initial cancer diagnosis or recurrence.¹⁰¹ Sweet syndrome is characterized by the sudden onset of painful, erythematous plaques, papules, and nodules on the face, trunk, and extremities as well as by neutrophilia and fever.¹⁰¹ First-line treatment includes systemic corticosteroids, colchicine, and Lugol solution.¹⁰¹ In general, paraneoplastic Sweet syndrome is less responsive to therapy than nonparaneoplastic cases, and treatment of the underlying tumor rarely improves symptoms.¹⁰¹

PARANEOPLASTIC HEMATOLOGIC SYNDROMES

Paraneoplastic hematologic syndromes are rarely symptomatic. These conditions are usually detected after a

cancer diagnosis, are typically seen in association with advanced disease, rarely require specific therapy, and may improve with successful treatment of the underlying malignancy.¹³⁷⁻¹⁴⁰ The clinical features, associated malignancies, diagnostic studies, and treatment of paraneoplastic hematologic syndromes are listed in Table 4.^{137,138,140-156}

EOSINOPHILIA

Paraneoplastic eosinophilia represents a subset of secondary eosinophilia that appears due to tumor production of the eosinophil growth factors interleukin (IL)-3, IL-5, and GM-CSF.^{137,157} By contrast, primary eosinophilia, a separate diagnosis encountered in hematology-oncology practices, often represents a clonal phenomenon caused directly by a hematologic neoplastic process.¹⁴¹ Clonal eosinophilia is associated with gene rearrangements involving *FIP1L1*, *PDGFR* α and β , and *FGFR1*.¹⁵⁸ Patients with paraneoplastic and other forms of secondary eosinophilia may have elevated serum levels of IL-3, IL-5, and GM-CSF, as well as elevated IL-2, an eosinophil chemoattractant.¹³⁷ Other causes of secondary eosinophilia include allergic reactions, parasitic infections, and collagen vascular diseases.¹⁴² The most commonly associated malignancies are lymphomas and leukemias, but paraneoplastic eosinophilia may also be seen with lung, gastrointestinal, and gynecologic tumors.¹⁴² Paraneoplastic eosinophilia is typically asymptomatic, but in certain cases it can cause wheezing and dyspnea, which usually respond to corticosteroid therapy.¹³⁸ The end-organ damage occasionally seen with clonal eosinophilia, such as an infiltrative cardiomyopathy, has not been seen with paraneoplastic eosinophilia. Agents such as hydroxyurea, imatinib, and interferon alfa, which are used in the treatment of clonal eosinophilia and the hypereosinophilic syndrome, are not typically used to treat paraneoplastic hypereosinophilia.^{141,143} After successful cancer treatment, return of eosinophilia may herald tumor recurrence.¹³⁷

GRANULOCYTOSIS

Paraneoplastic granulocytosis occurs in approximately 15% of patients with solid tumors.¹³⁸ The white blood cell count typically ranges from 12 to 30 $\times 10^9/L$ but in some cases exceeds 50 $\times 10^9/L$.¹⁵⁹ In patients with cancer, several factors may contribute to leukocytosis. In a recent series of greater than 750 cancer patients with white blood cell counts exceeding 40 $\times 10^9/L$, the following etiologies were identified: hematopoietic growth factors (69%), infection (15%), paraneoplastic (10%), glucocorticoids or vasopressors (5%), and newly diagnosed leukemia (1%).¹⁶⁰ Ancillary serum tests that may provide guidance if an etiology cannot be determined otherwise include erythrocyte sedimentation rate, C-reactive pro-

TABLE 4. Paraneoplastic Hematologic Syndromes^a

Syndrome	Clinical presentation	Laboratory findings	Associated cancers	Treatment options ^b	References
Eosinophilia	Dyspnea, wheezing	Hypereosinophilia (>0.5 × 10 ⁹ /L); elevated serum IL-5, IL-3, IL-2 and GM-CSF	Hodgkin lymphoma, non-Hodgkin lymphoma (B- and T-cell), chronic myeloid leukemia, acute lymphocytic leukemia, lung, thyroid, GI (pancreatic, colon, gastric, liver), renal, breast, gynecologic	Inhaled corticosteroids Prednisone, 1 mg/kg/d orally	137, 138, 141-146
Granulocytosis	Asymptomatic (no symptoms or signs of leukostasis such as neurologic deficits or dyspnea)	Granulocyte (neutrophil) count >8 × 10 ⁹ /L, typically without a shift to immature neutrophil forms; elevated LAP; elevated serum G-CSF	GI, lung, breast, gynecologic, GU, brain, Hodgkin lymphoma, sarcomas	Specific treatment not indicated	138, 147, 148
Pure red cell aplasia	Dyspnea, pallor, fatigue, syncope	Anemia (hematocrit, <20 not uncommon), low/absent reticulocytes, bone marrow with nearly absent erythroid precursors, platelet and white blood cell counts in normal ranges	Thymoma, leukemia/lymphoma, myelodysplastic syndrome	Blood transfusions Prednisone, 1 mg/kg/d orally Antithymocyte globulin, 500 mg daily IV (with corticosteroids and/or cyclophosphamide) Cyclosporine A, 100 mg orally twice daily Cyclophosphamide, 1-3 mg/kg/d orally Rituximab, 375 mg/m ² IV per dose Alemtuzumab, 30 mg IV per dose Plasma exchange Splenectomy	149-154
Thrombocytosis	Asymptomatic (no bleeding or clotting abnormalities)	Elevated platelet count, greater than ~400 × 10 ⁹ /L; elevated serum IL-6	GI, lung, breast, gynecologic, lymphoma, renal cell, prostate, mesothelioma, glioblastoma, head and neck	Specific treatment not indicated	138, 140, 155, 156

^a GI = gastrointestinal; GU = genitourinary; IL = interleukin; IM = intramuscular; IV = intravenous; LAP = leukocyte alkaline phosphatase. See Glossary at the end of this article for expansion of additional abbreviations.

^b In addition to treating the underlying malignancy.

tein (elevated in states of inflammation and infection), and leukocyte alkaline phosphatase (low in chronic myeloid leukemia).

Paraneoplastic granulocytosis is associated with lung cancer (particularly large cell lung cancer),¹⁶¹ as well as gastrointestinal, brain, breast, renal, and gynecologic cancers.¹⁴⁷ The mechanism is poorly understood. Some solid tumors have been shown to produce substances with colony-stimulating activity.¹⁴⁸ Alternatively, leukocytosis may result from bone marrow involvement by tumor. Once other etiologies are ruled out, paraneoplastic granulocytosis does not require specific therapy.¹³⁸ In contrast to leukemic blasts, which may cause hyperviscosity and vaso-occlusion at counts as low as 20 × 10⁹/L, the mature, deformable neutrophils that characterize paraneoplastic granulocytosis are unlikely to cause leukostasis below a count of 250 × 10⁹/L, and therefore do not require leukapheresis.

PURE RED CELL APLASIA

Paraneoplastic pure red cell aplasia is most commonly associated with thymoma.¹⁴⁹ Ineffective eradication of autoreactive T cells by neoplastic thymic tissue results in an autoimmune attack on red blood cell precursors.¹⁵⁰ Pure red cell aplasia can also be seen with other malignancies, such as lymphomas and leukemia. In these cases, a proposed mechanism is an increase in T-cell large granular lymphocytes causing autoimmune dysfunction of erythropoiesis.¹⁵⁰ Pure red cell aplasia may also arise from a stem-cell defect (myelodysplasia).¹⁶² Nonmalignant associations include infections with human immunodeficiency virus, herpes viruses, parvovirus B19, and hepatitis viruses. Bone marrow examination demonstrates the near absence of red blood cell precursors but preservation of megakaryocytes and granulocyte lineage. Treatment of paraneoplastic pure red cell aplasia is centered on cancer therapy and immunosuppression.¹⁵⁰ Corticosteroids, antithymocyte globulin, azathioprine, cy-

closporine A, cyclophosphamide, and the monoclonal antibodies alemtuzumab and rituximab have been used.^{150,151} Plasma exchange and androgen therapy have also been used.^{150,163} Caution is needed with immunosuppression for pure red cell aplasia associated with myelodysplasia and premalignant disorders, however, because accelerating malignant transformation has been reported.¹⁵² When due to thymoma, symptoms rarely resolve after thymectomy, and immunosuppression is usually required after surgery.¹⁴⁹ Erythropoietin-stimulating agents (eg, erythropoietin, darbopoietin) have been associated with the development of pure red cell aplasia¹⁶⁴ and are not recommended.

THROMBOCYTOSIS

Approximately 35% of patients with thrombocytosis, usually defined as a platelet count greater than $400 \times 10^9/L$, have a malignancy.¹³⁸ Other conditions commonly associated with reactive thrombocytosis include infection, post-splenectomy state, acute blood loss, and iron deficiency.^{165,166} Paraneoplastic thrombocytosis is thought to occur from tumor production of cytokines such as IL-6.^{140,155} Serum IL-6 levels have been used to distinguish paraneoplastic and other reactive thrombocytosis processes from clonal etiologies such as essential thrombocythemia, polycythemia vera, myelodysplasia, and acute and chronic leukemia.¹⁶⁵ The recently characterized JAK2 V617F mutation, present in 50% of cases of essential thrombocythemia but not present in cases of reactive thrombocytosis,¹⁶⁷ may also aid in the evaluation of an elevated platelet count. The vasomotor symptoms and thrombohemorrhagic complications that occur in up to half of patients with essential thrombocythemia rarely occur in patients with paraneoplastic thrombocytosis, and specific therapy is not indicated. Nevertheless, thrombocytosis is usually associated with advanced disease and worse clinical outcomes.^{138,140}

CONCLUSION

As the number of patients with cancer grows, and as these patients live longer, the incidence of paraneoplastic syndromes will likely increase. These conditions affect the presentation, clinical course, and treatment of cancer. As a result of recent diagnostic and therapeutic advances, many paraneoplastic syndromes are currently well defined, have a clear pathogenesis, and have effective treatment options. The ability to recognize and treat paraneoplastic syndromes may have a substantial effect on clinical outcomes, ranging from earlier cancer diagnosis, to improved quality of life, to increased delivery of tumor-directed therapy. Furthermore, ongoing research into these disorders may shed light on mechanisms of tumor development, maintenance, and proliferation.

Glossary

AchR = acetylcholine receptor
 ANNA = antineuronal nuclear antibody
 ANP = atrial natriuretic peptide
 CRMP = collapsin response mediator protein
 FGFR1 = fibroblast growth factor receptor 1
 FIP1L1 = factor interacting with PAP 1–like 1
 G-CSF = granulocyte colony-stimulating factor
 GM-CSF = granulocyte-macrophage CSF
 IGF = insulin-like growth factor
 JAK2 = Janus kinase 2
 mGluR1 = metabotropic glutamate receptor-subtype 1
 NMDA = *N*-methyl-D-aspartate
 PCA = Purkinje cell cytoplasmic autoantibody
 PDGFR = platelet-derived growth factor receptor
 VGCC = voltage-gated calcium channel
 VGKC = voltage-gated potassium channel

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