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98 Paraneoplastic Syndromes: Endocrinologic/Hematologic

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Paraneoplastic

Syndromes:

Endocrinologic/Hematologic Neoplastic cells can produce a variety of substances that can alter the physiology of hormonal, hematologic, dermatologic, rheumatologic, renal, and neurologic systems. Paraneoplastic syndromes refer to the disorders that accompany benign or malignant tumors but are not directly related to mass effects or invasion. Tumors of neuroendo crine origin, such as small-cell lung carcinoma (SCLC) and carci noids, are common causes of paraneoplastic syndromes, but these syndromes are associated with many types of tumors that produce peptide hormones, cytokines, and growth factors and induce the production of antibodies. Studies of the prevalence of paraneoplastic syndromes indicate that they are more common than is generally appreciated. The signs, symptoms, and metabolic alterations associ ated with paraneoplastic disorders are easily overlooked in the con text of a malignancy and its treatment. Consequently, atypical clinical manifestations in a patient with cancer should prompt consideration of a paraneoplastic syndrome. The most common hormonal and hematologic syndromes associated with underlying neoplasia will be discussed here.

ENDOCRINE PARANEOPLASTIC SYNDROMES Etiology Hormones can be produced from eutopic or ectopic sources. Eutopic refers to the expression of a hormone from its normal tissue of origin, whereas ectopic refers to hormone production from an atypical tissue source. For example, adrenocorticotropic hormone (ACTH) is expressed eutopically by the corticotrope cells of the anterior pituitary, but it can be expressed ectopically in SCLC. Many hormones are produced at low levels from tissues other than the clas sic endocrine source. Thus, ectopic expression is often a quantitative change rather than an absolute change in tissue expression. Neverthe less, the term ectopic expression is firmly entrenched and conveys the abnormal physiology associated with hormone production by neoplas tic cells. In addition to high levels of hormones, ectopic expression is often characterized by abnormal regulation of hormone production (e.g., defective feedback control in ectopic ACTH) and peptide pro cessing (resulting in large, unprocessed precursor peptide such as proopiomelanocortin [POMC]). Many different molecular mechanisms can cause ectopic hormone production. In rare instances, genetic rearrangements account for aberrant hormone expression. For example, translocation of the para thyroid hormone (PTH) gene can result in high levels of PTH expres sion in tissues other than the parathyroid gland because the genetic rearrangement brings the PTH gene under the control of atypical regulatory elements. A related phenomenon is well documented in many forms of leukemia and lymphoma, in which somatic genetic rear rangements confer a growth advantage and alter cellular differentiation and function. Although genetic rearrangements cause selected cases of ectopic hormone production, this mechanism is rare, as many tumors are associated with excessive production of numerous peptides. Cellu lar dedifferentiation probably underlies most cases of ectopic hormone production. Many cancers are poorly differentiated, and certain tumor products, such as human chorionic gonadotropin (hCG), PTH–related protein (PTHrP), and α-fetoprotein, are characteristic of gene expres sion at earlier developmental stages. In contrast, the propensity of certain cancers to produce particular hormones (e.g., squamous cell carcinomas produce PTHrP) suggests that dedifferentiation is partial or that selective pathways are derepressed. These expression profiles probably reflect epigenetic modifications that alter transcriptional repression, microRNA expression, and other pathways that govern cell differentiation. Ectopic hormone production might be considered merely epiphe nomenon associated with cancer if it did not cause clinical manifes tations. Excessive and unregulated production of hormones such as ACTH, PTHrP, and vasopressin can lead to substantial morbidity and complicate the cancer treatment plan. Moreover, the paraneoplastic endocrinopathies may be a presenting clinical feature of underlying malignancy and

prompt the search for an unrecognized tumor. General features that confirm cancer-associated ectopic hormone syndromes include: (1) excess hormone production from an atypical tissue source; (2) documentation of tumor hormone production based on immunostaining, mRNA production, or hormone secretion in vitro; (3) hormone gradient across the tumor vascular supply; and (4) resolution or decline of hormone levels after reduction of tumor mass. Imaging studies, including computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and octreotide scintigraphy also play an important role in the detection and characterization of tumors associated with paraneoplastic syndromes, particularly when endocrine clinical manifestations precede a cancer diagnosis (i.e., ectopic ACTH in lung cancer). Treatment of the under lying tumor is the mainstay of all paraneoplastic endocrine syndromes. Depending on the hormone produced, specific therapies can be used (see below) to ameliorate symptoms but rarely influence overall sur vival or cancer progression. A large number of paraneoplastic endocrine syndromes have been described, linking overproduction of particular hormones with specific types of tumors. However, certain recurring syndromes emerge from this group (Table 98-1). The most common paraneoplastic endocrine

TABLE 98-1 Paraneoplastic Syndromes Caused by Ectopic Hormone Production PARANEOPLASTIC SYNDROME ECTOPIC HORMONE TYPICAL TUMOR TYPESa Common Hypercalcemia of malignancy Parathyroid hormone–related protein (PTHrP) Squamous cell (head and neck, lung, skin), breast, genitourinary, gastrointestinal; osteolytic metastases 1,25-Dihydroxyvitamin D Lymphomas Parathyroid hormone (PTH) (rare) Lung, ovary Prostaglandin E2 (PGE2) (rare) Renal, lung Syndrome of inappropriate antidiuretic hormone secretion (SIADH) Vasopressin Lung (squamous, small cell), gastrointestinal, genitourinary, breast, ovary Cushing’s syndrome Adrenocorticotropic hormone (ACTH) Lung (small cell, bronchial carcinoid, adenocarcinoma, squamous), thymus, pancreatic islet, medullary thyroid carcinoma, pheochromocytoma Corticotropin-releasing hormone (CRH) (rare) Pancreatic islet, carcinoid, lung, prostate Ectopic expression of gastric inhibitory peptide (GIP), luteinizing hormone (LH)/human chorionic gonadotropin (hCG), other G protein–coupled receptors (rare) Less Common Non–islet cell hypoglycemia Insulin-like growth factor type II (IGF-II) Mesenchymal tumors, sarcomas, adrenal, hepatic, gastrointestinal, kidney, prostate Insulin (rare) Cervix (small-cell carcinoma) Male feminization hCGb Testis (embryonal, seminomas), germinomas, choriocarcinoma, lung, hepatic, pancreatic islet Diarrhea or intestinal hypermotility Calcitoninc Lung, colon, breast, medullary thyroid carcinoma Vasoactive intestinal peptide (VIP) Pancreas, pheochromocytoma, esophagus Rare Oncogenic osteomalacia Fibroblast growth factor 23 (FGF23) or phosphatonin Hemangiopericytomas, osteoblastomas, fibromas, sarcomas, giant cell tumors, prostate, lung Acromegaly Growth hormone–releasing hormone (GHRH) Pancreatic islet, bronchial, and other carcinoids Growth hormone (GH) Lung, pancreatic islet Hyperthyroidism Thyroid-stimulating hormone (TSH) Hydatidiform mole, embryonal tumors, struma ovarii Hypertension Renin Juxtaglomerular tumors, kidney, lung, pancreas, ovary Consumptive hypothyroidism Type 3 deiodinase Hepatic and other hemangiomas Cancer immunotherapy associated autoimmune diseases Autoimmune hormone deficiencies Thyroiditis, Graves’ disease aOnly the most common tumor types are listed. For most ectopic hormone syndromes, an extensive list of tumors has been reported to produce one or more hormones. bhCG is produced eutopically by trophoblastic tumors. Certain tumors produce disproportionate amounts of the hCG α or hCG β subunit. High levels of hCG rarely cause hyperthyroidism because of weak binding to the TSH receptor. cCalcitonin is produced eutopically by medullary thyroid carcinoma and is used as a tumor marker. Abbreviations: CTLA-4, cytotoxic T lymphocyte-associated protein-4; PD-1, programmed cell death

protein 1; PD-L1, programmed death ligand 1. syndromes include hypercalcemia from overproduction of PTHrP and other factors, hyponatremia from excess vasopressin, and Cushing's syndrome from ectopic ACTH. ■ ■HYPERCALCEMIA CAUSED BY ECTOPIC PRODUCTION OF PTHRP (See also Chap. 422). Etiology Humoral hypercalcemia of malignancy (HHM) occurs in up to 20% of patients with cancer. HHM is most common in cancers of the lung, head and neck, skin, esophagus, breast, and genitourinary tract and in multiple myeloma and lymphomas, as well as metastases associated with these, and other cancers. There are several distinct humoral causes of HHM, but it is caused most commonly by overpro duction of PTHrP. In addition to acting as a circulating humoral factor, bone metastases (e.g., breast, multiple myeloma) may produce PTHrP and other chemokines, leading to local osteolysis and hypercalcemia. PTHrP may also affect the initiation and progression of tumors by act ing through pro-survival and chemokine pathways. PTHrP is structurally related to PTH and binds to the PTH receptor, explaining the similar biochemical features of HHM and hyperpara thyroidism. PTHrP plays a key physiologic role in skeletal development and regulates cellular proliferation and differentiation in other tissues, including skin, bone marrow, breast, and hair follicles. The mecha nism of PTHrP induction in malignancy is incompletely understood;

Macronodular adrenal hyperplasia CHAPTER 98 Paraneoplastic Syndromes: Endocrinologic/Hematologic
Cancers treated with immunotherapy, particularly anti–CTLA-4, PD-1, PD-L1 however, tumor-bearing tissues commonly associated with HHM nor mally produce PTHrP during development or cell renewal. Hypometh ylation of the PTHLH locus, which encodes PTHrP, suggests a role for epigenetic factors in upregulating PTHrP production. PTHrP expres sion is stimulated by hedgehog pathways and Gli transcription factors that are active in many malignancies. Transforming growth factor β (TGF-β), which is produced by many tumors, also stimulates PTHrP. Mutations in certain oncogenes, such as Ras, also can activate PTHrP expression, as does loss of the tumor suppressor, p53. In addition to its role in HHM, the PTHrP pathway may also provide a potential target for therapeutic intervention to impede cancer growth. Another relatively common cause of HHM is excess production of 1,25-dihydroxyvitamin D. Like granulomatous disorders associated with hypercalcemia, lymphomas can produce an enzyme that converts 25-hydroxyvitamin D to the more active 1,25-dihydroxyvitamin D, leading to enhanced gastrointestinal calcium absorption. Other causes of HHM include tumor-mediated production of osteolytic cytokines and inflammatory mediators. Clinical Manifestations The typical presentation of HHM is a patient with a known malignancy who is found to be hypercalcemic on routine laboratory tests. Less often, hypercalcemia is the initial present ing feature of malignancy. Particularly when calcium levels are mark edly increased (>3.5 mmol/L [>14 mg/dL]), patients may experience fatigue, mental status changes, polyuria, dehydration, or symptoms of

nephrolithiasis. Hypercalcemia can shorten ST segments and QT inter vals, as well as bundle branch blocks and bradyarrhythmias.

Diagnosis Features that favor HHM, as opposed to primary hyper parathyroidism, include known malignancy, recent onset of hypercal cemia, and very high serum calcium levels. Like hyperparathyroidism, hypercalcemia caused by PTHrP is accompanied by hypercalciuria and hypophosphatemia. Patients with HHM typically have metabolic alkalosis rather than hyperchloremic acidosis, as is seen in hyperpara thyroidism. In contrast to PTH, PTHrP does not

appear to stimulate 1-α-hydroxylase and 1,25-dihydroxyvitamin D levels. Measurement of PTH is useful to exclude primary hyperparathyroidism; the PTH level should be suppressed in HHM. An elevated PTHrP level confirms the diagnosis, and it is increased in ~80% of hypercalcemic patients with cancer. 1,25-Dihydroxyvitamin D levels may be increased in patients with lymphoma. TREATMENT Humoral Hypercalcemia of Malignancy The management of HHM begins with removal of excess calcium in the diet, medications, or intravenous (IV) solutions. Saline rehydration (typically 200–500 mL/h) is used to dilute serum calcium and promote calciuresis; exercise caution in patients with cardiac, hepatic, or renal insufficiency. Forced diuresis with furo semide (20–80 mg IV in escalating doses) or other loop diuretics can enhance calcium excretion but provides relatively little value except in life-threatening hypercalcemia. When used, loop diuret ics should be administered only after complete rehydration and with careful monitoring of fluid balance. Oral phosphorus (e.g., 250 mg Neutra-Phos 3–4 times daily) should be given until serum phosphorus is >1 mmol/L (>3 mg/dL). Bisphosphonates such as zoledronate (4–8 mg IV), pamidronate (60–90 mg IV), and etidro nate (7.5 mg/kg per day orally [PO] for 3–7 consecutive days) can reduce serum calcium within 1–2 days and suppress calcium release for several weeks. Bisphosphonate infusions can be repeated, or oral bisphosphonates can be used for chronic treatment. Denosumab (120 mg subcutaneously [SC] weekly for 4 weeks and then monthly) can be used in patients who do not respond adequately to bisphos phonates. It acts as a decoy receptor for RANK ligand to mitigate stimulation of osteoclasts. Cinacalcet (30 mg PO bid to 90 mg PO qid) stimulates calcium-sensing receptors to suppress PTH secre tion and is therefore applicable in parathyroid carcinoma and rare cases of ectopic PTH-producing tumors. Hypercalcemia associated with lymphomas, multiple myeloma, or leukemia may respond to glucocorticoid treatment (e.g., prednisone 40–100 mg PO in four divided doses). Dialysis should be considered in severe hypercal cemia when saline hydration and bisphosphonate treatments are not possible or are too slow in onset. Previously used agents such as calcitonin and mithramycin have little utility now that bisphospho nates and other agents are available. PART 4 Oncology and Hematology ■ ■ECTOPIC VASOPRESSIN: TUMOR-ASSOCIATED SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE (See also Chap. 56). Etiology Vasopressin is an antidiuretic hormone normally pro duced by the posterior pituitary gland. Ectopic vasopressin production by tumors is a common cause of the syndrome of inappropriate antidi uretic hormone (SIADH), occurring in at least half of patients with SCLC. SIADH also can be caused by a number of nonneoplastic condi tions, including central nervous system (CNS) trauma, infections, and medications (Chap. 398). Compensatory responses to SIADH, such as decreased thirst, may mitigate the development of hyponatremia. How ever, with prolonged production of excessive vasopressin, the osmostat controlling thirst and hypothalamic vasopressin secretion may become reset. In addition, intake of free water, orally or intravenously, can quickly worsen hyponatremia because of reduced renal diuresis.

Tumors with neuroendocrine features, such as SCLC and carcinoids, are the most common sources of ectopic vasopressin production, but it also occurs in other forms of lung cancer and with CNS lesions, head and neck cancer, and genitourinary, gastrointestinal, and ovarian cancers. The mechanism of activation of the vasopressin gene in these tumors is unknown, but the frequent concomitant expression of the adjacent oxytocin gene suggests derepression of this locus. Clinical Manifestations Most patients with ectopic vasopressin secretion are asymptomatic and are identified because of the presence of hyponatremia on routine chemistry testing. Symptoms may include weakness, lethargy, nausea, confusion, depressed mental status, and seizures. The severity of symptoms reflects the rapidity of onset as well as the severity of hyponatremia.

Hyponatremia usually develops slowly but may be exacerbated by the administration of IV fluids or the insti tution of new medications. Diagnosis The diagnostic features of ectopic vasopressin produc tion are the same as those of other causes of SIADH (Chaps. 56 and 398). Hyponatremia and reduced serum osmolality occur in the set ting of an inappropriately normal or increased urine osmolality. Urine sodium excretion is normal or increased unless volume depletion is present. Other causes of hyponatremia should be excluded, including renal, adrenal, or thyroid insufficiency. Physiologic sources of vaso pressin stimulation (CNS lesions, pulmonary disease, nausea), adaptive circulatory mechanisms (hypotension, heart failure, hepatic cirrho sis), and medications, including many chemotherapeutic agents, also should be considered as possible causes of hyponatremia. Vasopressin measurements are not usually necessary to make the diagnosis. TREATMENT Ectopic Vasopressin: Tumor-Associated SIADH Most patients with ectopic vasopressin production develop hypo natremia over several weeks or months. The disorder should be corrected gradually unless mental status is altered or there is risk of seizures. Rapid correction can cause brain dehydration and central pontine myelinolysis. Treatment of the underlying malignancy may reduce ectopic vasopressin production, but this response is slow if it occurs at all. Fluid restriction to less than urine output, plus insensible losses, is often sufficient to correct hyponatremia partially. However, strict monitoring of the amount and types of liquids consumed or administered intravenously is required for fluid restriction to be effective. Salt tablets and saline are not helpful unless volume depletion is also present. Demeclocycline (150–300 mg orally 3–4 times daily) can be used to inhibit vasopressin action on the renal distal tubule, but its onset of action is relatively slow (1–2 weeks), and it has largely been supplanted by newer vasopres sin receptor antagonists. The vaptan class of drugs acts by inhibiting vasopressin receptors (V1A, V1B, V2) in the renal collecting ducts. Nonpeptide V2-receptor antagonists, tolvaptan (15 mg PO daily) or conivaptan (20–120 mg PO bid or 10–40 mg IV), are particu larly effective when used in combination with fluid restriction in euvolemic hyponatremia. Severe hyponatremia (Na <115 meq/L) or mental status changes may require treatment with hypertonic (3%) or normal saline infusion together with furosemide to enhance free water clearance. The rate of sodium correction should be slow (0.5–1 meq/L per hour) to prevent rapid fluid shifts and the possible development of central pontine myelinolysis. ■ ■CUSHING’S SYNDROME CAUSED BY ECTOPIC ACTH PRODUCTION (See also Chap. 398). Etiology Ectopic ACTH production accounts for 10–20% of cases of Cushing’s syndrome. The syndrome is particularly common in neuroendocrine tumors. SCLC is the most common cause of ectopic ACTH, followed by bronchial and thymic carcinoids, islet cell tumors, other carcinoids, and pheochromocytomas. Ectopic ACTH production

is caused by increased expression of the proopiomelanocortin (POMC) gene, which encodes ACTH, along with melanocyte-stimulating hormone (MSH), β-lipotropin, and several other peptides. In many tumors, there is abundant but aberrant expression of the POMC gene from an internal promoter, proximal to the third exon, which encodes ACTH. However, because this product lacks the signal sequence nec essary for protein processing, it is not secreted. Increased production of ACTH arises instead from less abundant, but unregulated, POMC expression from the same promoter site used in the pituitary. Because tumors lack many of the enzymes needed to process the POMC poly peptide, it is typically released as multiple large, biologically inactive fragments along with relatively small amounts of fully processed, active ACTH. Rarely, corticotropin-releasing hormone (CRH) is produced by pan creatic islet cell tumors, SCLC, medullary thyroid cancer, carcinoids, or prostate cancer. When levels are high enough, CRH can cause pituitary corticotrope hyperplasia and Cushing’s syndrome. Tumors that pro duce CRH sometimes also produce ACTH,

raising the possibility of a paracrine mechanism for ACTH production. A distinct mechanism for ACTH-independent Cushing's syndrome involves ectopic expression of various G protein–coupled receptors in adrenal nodules. Ectopic expression of the gastric inhibitory peptide (GIP) receptor is the best-characterized example of this mechanism. In this case, meals induce GIP secretion, which inappropriately stimulates adrenal growth and glucocorticoid production. Clinical Manifestations The clinical features of hypercorti solemia are detected in only a fraction of patients with documented ectopic ACTH production. Patients with ectopic ACTH syndrome gen erally exhibit less marked weight gain and centripetal fat redistribution, probably because the exposure to excess glucocorticoids is relatively brief and because cachexia reduces the propensity for weight gain and fat deposition. The ectopic ACTH syndrome is associated with several clinical features that distinguish it from other causes of Cush ing's syndrome (e.g., pituitary adenomas, adrenal adenomas, iatrogenic glucocorticoid excess). The metabolic manifestations of ectopic ACTH syndrome are dominated by fluid retention and hypertension, hypo kalemia, metabolic alkalosis, glucose intolerance, and occasionally steroid psychosis. The very high ACTH levels often cause increased pigmentation, reflecting increased activity of MSH derived from the POMC precursor peptide. The extraordinarily high glucocorticoid levels in patients with ectopic sources of ACTH can lead to marked skin fragility and easy bruising. In addition, the high cortisol levels often overwhelm the renal 11β-hydroxysteroid dehydrogenase type II enzyme, which normally inactivates cortisol and prevents it from binding to renal mineralocorticoid receptors. Consequently, in addi tion to the excess mineralocorticoids produced by ACTH stimulation of the adrenal gland, high levels of cortisol exert activity through the mineralocorticoid receptor, leading to severe hypokalemia. Diagnosis The diagnosis of ectopic ACTH syndrome is usually not difficult in the setting of a known malignancy. Urine-free cortisol levels fluctuate but are typically greater than two to four times normal, and the plasma ACTH level is usually >22 pmol/L (>100 pg/mL). A sup pressed ACTH level excludes this diagnosis and indicates an ACTHindependent cause of Cushing's syndrome (e.g., adrenal or exogenous glucocorticoid). In contrast to pituitary sources of ACTH, most ectopic sources of ACTH do not respond to glucocorticoid suppression. There fore, high-dose dexamethasone (8 mg PO) suppresses 8:00 a.m. serum cortisol (50% decrease from baseline) in ~80% of pituitary ACTHproducing adenomas but fails to suppress ectopic ACTH in ~90% of cases. Bronchial and other carcinoids are well-documented exceptions to these general guidelines, as these ectopic sources of ACTH may exhibit feedback regulation indistinguishable from pituitary adeno mas, including suppression by high-dose dexamethasone, and ACTH responsiveness to adrenal blockade with metyrapone. If necessary, petrosal sinus catheterization can be used to evaluate a patient with ACTH-dependent Cushing's syndrome when the source of ACTH is unclear. After CRH stimulation, a 3:1 petrosal sinus:peripheral ACTH ratio strongly suggests a pituitary ACTH source. Imaging studies (CT

or MRI) are also useful in the evaluation of suspected carcinoid lesions, allowing biopsy and characterization of hormone production using special stains. If available, PET scans or octreotide scintigraphy may identify some sources of ACTH production.

TREATMENT Cushing's Syndrome Caused by Ectopic ACTH Production The morbidity associated with the ectopic ACTH syndrome can be substantial. Patients may experience depression or personality changes because of extreme cortisol excess. Metabolic derange ments, including diabetes mellitus and hypokalemia, can worsen fatigue. Poor wound healing and predisposition to infections can complicate the surgical management of tumors, and opportunis tic infections caused

by organisms such as Pneumocystis carinii and mycoses are often the cause of death in patients with ectopic ACTH production. These patients have increased risk of venous thromboembolism, reflecting the combination of malignancy and altered coagulation factor profiles. Depending on prognosis and treatment plans for the underlying malignancy, measures to reduce cortisol levels are often indicated. Treatment of the underlying malignancy may reduce ACTH levels but is rarely sufficient to reduce cortisol levels to normal. Adrenalectomy is not practical for most of these patients but should be considered during surgery for the malignancy or if the underlying tumor is not resectable and the prognosis is otherwise favorable (e.g., carcinoid). Medical therapy with ketoconazole (300–600 mg PO bid), metyrapone (250–500 mg PO every 6 h), mitotane (3–6 g PO in four divided doses, tapered to maintain low cortisol production), etomidate (0.1–0.3 mg/kg/h IV), or other agents that block steroid synthesis or action is often the most practical strategy for managing the hypercorti solism associated with ectopic ACTH production. Glucocorticoid replacement should be provided to prevent adrenal insufficiency (Chap. 398). Unfortunately, many patients eventually progress despite medical blockade. Mifepristone (200–1000 mg PO qd) inhibits both glucocorticoid and progesterone receptors, has rapid onset of action, and improves glucose intolerance and hypertension in a subset of patients. ACTH-neutralizing antibodies and ACTH recep tor blockers are under investigation, as are selective inhibitors of the glucocorticoid receptor.
CHAPTER 98 Paraneoplastic Syndromes: Endocrinologic/Hematologic
■ ■TUMOR-INDUCED HYPOGLYCEMIA CAUSED BY EXCESS PRODUCTION OF INSULIN-LIKE GROWTH FACTOR TYPE II (See also Chap. 418) Mesenchymal tumors, hemangiopericytomas, hepatocellular tumors, adrenal carcinomas, and a variety of other large tumors have been reported to produce excessive amounts of insulinlike growth factor type II (IGF-II) precursor, which binds weakly to insulin receptors and more strongly to IGF-I receptors, leading to insulin-like actions. The gene encoding IGF-II resides on chromosome 11p15, a locus that is normally imprinted (that is, expression is exclu sively from a single parental allele). Biallelic expression of the IGF-II gene occurs in a subset of tumors, suggesting loss of methylation and loss of imprinting as a mechanism for gene induction. In addition to increased IGF-II production, IGF-II bioavailability is increased due to complex alterations in circulating binding proteins. Increased IGF-II suppresses growth hormone (GH) and insulin, resulting in reduced IGF binding protein 3 (IGFBP-3), IGF-I, and acid-labile subunit (ALS). The reduction in ALS and IGFBP-3, which normally sequester IGF-II, causes it to be displaced to a small circulating complex that has greater access to insulin target tissues. For this reason, circulating IGF-II levels may not be markedly increased despite causing hypoglycemia. In addi tion to IGF-II–mediated hypoglycemia, tumors may occupy enough of the liver to impair gluconeogenesis. In most cases, a tumor causing hypoglycemia is clinically apparent (usually >10 cm in size), and hypoglycemia develops in association with fasting. As with other causes of hypoglycemia, patients may

present with sweating, tremors, palpitations, confusion, seizures, or coma. The diagnosis is made by documenting low serum glucose and suppressed insulin levels in association with symptoms of hypoglyce mia. Serum IGF-II levels may not be increased (IGF-II assays may not detect IGF-II precursors), but an elevated IGF-II/IGF-I ratio greater than 10:1 is suggestive. Increased IGF-II mRNA expression is found in most of these tumors. Any medications associated with hypoglycemia should be eliminated. Treatment of the underlying malignancy, if pos sible, may reduce the predisposition to hypoglycemia. Frequent meals and IV glucose, especially during sleep or fasting, are often necessary to prevent hypoglycemia. Glucagon, recombinant GH, and glucocorti coids have also been used to enhance glucose production. Antibodies that inhibit IGF-II action are under

development.

■ ■HUMAN CHORIONIC GONADOTROPIN hCG is composed of α and β subunits and can be produced as intact hormone, which is biologically active, or as uncombined biologically inert subunits. Ectopic production of intact hCG occurs most often in association with testicular embryonal tumors, germ cell tumors, extragonadal germinomas, lung cancer, hepatoma, and pancreatic islet tumors. Eutopic production of hCG occurs with trophoblastic malignancies. hCG α subunit production is particularly common in lung cancer and pancreatic islet cancer. In men, high hCG levels stimulate steroidogenesis and aromatase activity in testicular Leydig cells, resulting in increased estrogen production and the development of gynecomastia. Precocious puberty in boys or gynecomastia in men should prompt measurement of hCG and consideration of a testicular tumor or another source of ectopic hCG production. Most women are asymptomatic. hCG is easily measured. Treatment should be directed at the underlying malignancy. PART 4 Oncology and Hematology ■ ■ONCOGENIC OSTEOMALACIA Hypophosphatemic oncogenic osteomalacia, also called tumor-induced osteomalacia (TIO), is caused by excessive production of fibroblast growth factor 23 (FGF23), previously referred to as phosphotonin. Oncogenic osteomalacia is characterized by markedly reduced serum phosphorus and renal phosphate wasting, leading to muscle weakness, bone pain, and osteomalacia. Serum calcium and PTH levels are normal. FGF23 inhibits the renal conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, resulting in low levels of 1,25-dihydroxyvitamin D. Oncogenic osteo malacia is usually caused by benign mesenchymal tumors, such as hemangiopericytomas, fibromas, and giant cell tumors, often of the skeletal extremities or head. It has also been described in sarcomas and in patients with prostate or lung cancer. Resection of the tumor reverses the disorder, confirming its humoral basis. FGF23 levels are increased in some, but not all, patients with osteogenic osteomalacia. FGF23 forms a ternary complex with the klotho protein and renal FGF receptors to reduce renal phosphate reabsorption. Treatment involves removal of the tumor, if possible, and supplementation with phosphate and vitamin D. Octreotide treatment reduces phosphate wasting in some patients with tumors that express somatostatin receptor subtype 2. Octreotide scans may also be useful in detecting these tumors. A human monoclonal antibody against FGF23, burosumab (0.5 mg/kg every

4 weeks) has been approved for the treatment of osteogenic osteomala cia. If needed, it can be increased to 2 mg/kg every 2 weeks. Burosumab improves metabolic features of the disease and may improve bone structure and fracture risk, but these outcomes are still being evaluated. The calcium-sensing receptor agonist cinacalcet has been effective in some patients, apparently by reducing PTH-mediated phosphaturia. FGF receptor inhibitors hold promise as future therapies targeted either to pathways that stimulate FGR23 production (e.g., FGFR1) or inhibit its action (e.g., FGF23 receptor). ■ ■CONSUMPTIVE HYPOTHYROIDISM Newborns with hepatic hemangiomas can develop a rare form of hypo thyroidism caused by overexpression of type 3 deiodinase (D3), an enzyme that degrades and inactivates thyroxine (T4) and triiodothyro nine (T3). The very high expression of D3 and consumption of thyroid hormones apparently outstrip the thyroid gland’s rate of hormone

production. The disorder is characterized by low T4, low T3, high TSH, and markedly elevated reverse T3 (rT3), reflecting the degradation of T4 to rT3. In addition to treating the underlying hemangioma (rarely other tumor types), patients are treated with l-thyroxine replacement, titrated to normalize TSH. Steroids and propranolol may provide ben efit, perhaps by inhibiting growth

factor pathways thought to stimulate D3 production. ■ ■CANCER IMMUNOTHERAPY-ASSOCIATED ENDOCRINOPATHIES (SEE ALSO CHAPS. 78, 401) Although not strictly a paraneoplastic endocrine syndrome, the intro duction of cancer immunotherapies, particularly immune checkpoint inhibitors (i.e., anti–CTLA-4, PD-1, PD-L1), is associated with a high incidence (~10%) of autoimmune endocrine disease. Hypophysitis and autoimmune thyroid diseases are most common, but autoimmune diabetes mellitus, adrenal insufficiency, hypoparathyroidism, and dia betes insipidus also occur. The mechanism of these autoimmune side effects remains unclear. CTLA-4 is expressed in the pituitary gland, likely explaining predisposition to anti–CTLA-4–associated hypophy sitis. Genetic predisposition and underlying endocrine autoimmunity likely play a role in thyroid and other endocrinopathies, becoming exacerbated following checkpoint inhibitor–induced immune activa tion. Autoimmune endocrine disease can emerge in the early weeks of immunotherapy but can also present after several months. At present, screening and prophylactic treatment are not routinely recommended. However, clinicians should be attuned to clinical or laboratory features of these disorders as they can be challenging to identify during can cer management. Treatment is similar to that of individual hormone deficiencies (Chaps. 391, 395, and 398). These endocrinopathies are generally irreversible and require lifelong hormone replacement. HEMATOLOGIC SYNDROMES The elevation of granulocyte, platelet, and eosinophil counts in most patients with myeloproliferative disorders is caused by the prolif eration of the myeloid elements due to the underlying disease rather than to a paraneoplastic syndrome. The paraneoplastic hematologic syndromes in patients with solid tumors are less well characterized than are the endocrine syndromes because the ectopic hormone(s) or cytokines responsible have not been identified in most of these tumors (Table 98-2). The extent of the paraneoplastic syndromes parallels the course of the cancer. With very rare exception, red cell, white cell, or platelet numbers are self-limited and not associated with symptomatic abnormalities. In some circumstances, elevations in platelet counts can be a marker that influences prognosis. By far, the most consequential hematologic abnormality in cancer patients is hypercoagulability. ■ ■ERYTHROCYTOSIS Ectopic production of erythropoietin by cancer cells causes most para neoplastic erythrocytosis. The ectopically produced erythropoietin TABLE 98-2 Paraneoplastic Hematologic Syndromes CANCERS TYPICALLY ASSOCIATED WITH SYNDROME SYNDROME PROTEINS Erythrocytosis Erythropoietin Renal cancers, hepatocarcinoma, cerebellar hemangioblastomas Granulocytosis G-CSF, GM-CSF, IL-6 Lung cancer, gastrointestinal cancer, ovarian cancer, genitourinary cancer, Hodgkin’s disease Thrombocytosis IL-6 Lung cancer, gastrointestinal cancer, breast cancer, ovarian cancer, lymphoma Eosinophilia IL-5 Lymphoma, leukemia, lung cancer Thrombophlebitis Unknown Lung cancer, pancreatic cancer, gastrointestinal cancer, breast cancer, genitourinary cancer, ovarian cancer, prostate cancer, lymphoma Abbreviations: G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocytemacrophage colony-stimulating factor; IL, interleukin.

stimulates the production of red blood cells (RBCs) in the bone mar row and raises the hematocrit. Other lymphokines and hormones produced by cancer cells may stimulate erythropoietin release but have not been proved to cause erythrocytosis. Most patients with erythrocytosis have an elevated hematocrit (>52% in men, >48% in women) that is detected on a routine blood count. Approximately 3% of patients with renal cell cancer, 10% of patients with hepatoma, and 15% of patients with cerebellar heman gioblastomas have erythrocytosis. In most cases, the erythrocytosis is asymptomatic. Patients with erythrocytosis due to a renal cell cancer, hepatoma, or CNS cancer should have measurement of red cell mass. If the red cell mass is elevated, the serum

erythropoietin level should be measured. Patients with a cancer that has been associated with erythrocytosis, ele vated erythropoietin levels, and no other explanation for erythrocytosis (e.g., hemoglobinopathy that causes increased O2 affinity; Chaps. 66 and 103) have the paraneoplastic syndrome. TREATMENT Erythrocytosis Successful resection of the cancer usually resolves the erythrocy tosis. If the tumor cannot be resected or treated effectively with radiation therapy or chemotherapy, phlebotomy may control any symptoms or risk related to erythrocytosis. ■ ■GRANULOCYTOSIS Approximately 30% of patients with solid tumors have granulocytosis (granulocyte count >8000/μL). In about half of patients with granu locytosis and cancer, the granulocytosis has an identifiable nonpara neoplastic etiology (e.g., infection, tumor necrosis, glucocorticoid administration). The other patients have proteins in urine and serum that stimulate the growth of bone marrow cells. Tumors and tumor cell lines from patients with lung, ovarian, and bladder cancers have been documented to produce granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GMCSF), and/or interleukin 6 (IL-6). However, the etiology of granulocy tosis has not been characterized in most patients. Patients with granulocytosis are nearly all asymptomatic, and the differential white blood cell count does not have a shift to immature forms of neutrophils. Granulocytosis occurs in 40% of patients with lung and gastrointestinal cancers, 20% of patients with breast cancer, 30% of patients with brain tumors and ovarian cancers, 20% of patients with Hodgkin’s disease, and 10% of patients with renal cell carcinoma. Patients with advanced-stage disease are more likely to have granulo cytosis than are those with early-stage disease. Paraneoplastic granulocytosis does not require treatment. The granulocytosis resolves when the underlying cancer is treated. ■ ■THROMBOCYTOSIS Some 35% of patients with thrombocytosis (platelet count >400,000/μL) have an underlying diagnosis of cancer. IL-6, a candidate molecule for the etiology of paraneoplastic thrombocytosis, stimulates the produc tion of platelets in vitro and in vivo. Some patients with cancer and thrombocytosis have elevated levels of IL-6 in plasma. Another can didate molecule is thrombopoietin, a peptide hormone that stimulates megakaryocyte proliferation and platelet production. The etiology of thrombocytosis has not been established in most cases. Patients with thrombocytosis are nearly all asymptomatic. Throm bocytosis is not clearly linked to thrombosis in patients with cancer. Thrombocytosis is present in 40% of patients with lung and gas trointestinal cancers; 20% of patients with breast, endometrial, and ovarian cancers; and 10% of patients with lymphoma. Patients with thrombocytosis are more likely to have advanced-stage disease and have a poorer prognosis than do patients without thrombocytosis. In ovarian cancer, IL-6 has been shown to directly promote tumor growth. Paraneoplastic thrombocytosis does not require treatment other than treatment of the underlying tumor.

■ ■EOSINOPHILIA Eosinophilia is present in ~1% of patients with cancer. Tumors and tumor cell lines from patients with lymphomas or leukemia may produce IL-5, which stimulates eosinophil growth. Activation of IL-5 transcription in lymphomas and leukemias may involve translocation of the long arm of chromosome 5, to which the genes for IL-5 and other cytokines map.

Patients with eosinophilia are typically asymptomatic. Eosinophilia is present in 10% of patients with lymphoma, 3% of patients with lung cancer, and occasional patients with cervical, gastrointestinal, renal, and breast cancer. Patients with markedly elevated eosinophil counts (>5000/μL) can develop shortness of breath and wheezing. A chest radiograph may reveal diffuse pulmonary infiltrates from eosinophil infiltration and activation in the lungs. TREATMENT Eosinophilia Definitive treatment is directed at the underlying malignancy. Tumors should be

resected or treated with radiation or chemo therapy. In most patients who develop shortness of breath related to eosinophilia, symptoms resolve with the use of oral or inhaled glucocorticoids. IL-5 antagonists exist but have not been evaluated in this clinical setting. CHAPTER 98 ■ ■THROMBOPHLEBITIS AND DEEP VENOUS THROMBOSIS Deep venous thrombosis and pulmonary embolism are the most common thrombotic conditions in patients with cancer. Migratory or recurrent thrombophlebitis may be the initial manifestation of cancer. Nearly 15% of patients who develop deep venous thrombosis or pulmonary embolism have a diagnosis of cancer (Chap. 122). The coexistence of peripheral venous thrombosis with visceral carcinoma, particularly pancreatic cancer, is called Trousseau's syndrome. Paraneoplastic Syndromes: Endocrinologic/Hematologic Pathogenesis Patients with cancer are predisposed to thromboem bolism because they are often at bed rest or immobilized, and tumors may obstruct or slow blood flow. Postoperative deep venous throm bosis is twice as common in cancer patients who undergo surgery. Chronic IV catheters also predispose to clotting. In addition, clotting may be promoted by release of procoagulants or cytokines from tumor cells or associated inflammatory cells or by platelet adhesion or aggre gation. The specific molecules that promote thromboembolism have not been identified. Chemotherapeutic agents, particularly those associated with endo thelial damage, can induce venous thrombosis. The annual risk of venous thrombosis in patients with cancer receiving chemotherapy is about 11%, sixfold higher than the risk in the general population. Bleomycin, l-asparaginase, nitrogen mustard, thalidomide analogues, cisplatin-based regimens, and high doses of busulfan and carmustine are all associated with an increased risk. In addition to cancer and its treatment causing secondary thrombo sis, primary thrombophilic diseases may be associated with cancer. For example, the antiphospholipid antibody syndrome is associated with a wide range of pathologic manifestations (Chap. 369). About 20% of patients with this syndrome have cancers. Among patients with cancer and antiphospholipid antibodies, 35–45% develop thrombosis. Clinical Manifestations Patients with cancer who develop deep venous thrombosis usually develop swelling or pain in the leg, and physical examination reveals tenderness, warmth, and redness. Patients who present with pulmonary embolism develop dyspnea, chest pain, and syncope, and physical examination shows tachycardia, cyanosis, and hypotension. Some 5% of patients with no history of cancer who have a diagnosis of deep venous thrombosis or pulmonary embolism will have a diagnosis of cancer within 1 year. The most common cancers associated with thromboembolic episodes include lung, pan creatic, gastrointestinal, breast, ovarian, and genitourinary cancers; lymphomas; and brain tumors. Patients with cancer who undergo

surgical procedures requiring general anesthesia have a 20–30% risk of deep venous thrombosis.

Diagnosis The diagnosis of deep venous thrombosis in patients with cancer is made by impedance plethysmography or bilateral compression ultrasonography of the leg veins. Patients with a noncom pressible venous segment have deep venous thrombosis. If compres sion ultrasonography is normal and there is a high clinical suspicion for deep venous thrombosis, venography should be done to look for a luminal filling defect. Elevation of d-dimer is not as predictive of deep venous thrombosis in patients with cancer as it is in patients without cancer; elevations are seen in people over age 65 years without concom itant evidence of thrombosis, probably as a consequence of increased thrombin deposition and turnover in aging. Patients with symptoms and signs suggesting a pulmonary embo lism should be evaluated with a chest radiograph, electrocardiogram, arterial blood gas analysis, and ventilation-perfusion scan. Patients with mismatched segmental perfusion defects have a pulmonary embolus. Patients with equivocal ventilation-perfusion findings should be

evaluated as described above for deep venous thrombosis in their legs. If deep venous thrombosis is detected, they should be antico agulated. If deep venous thrombosis is not detected, they should be considered for a pulmonary angiogram. Patients without a diagnosis of cancer who present with an initial episode of thrombophlebitis or pulmonary embolus need no additional tests for cancer other than a careful history and physical examination. In light of the many possible primary sites, diagnostic testing in asymp tomatic patients is wasteful. However, if the clot is refractory to standard treatment or is in an unusual site, or if the thrombophlebitis is migra tory or recurrent, efforts to find an underlying cancer are indicated. PART 4 Oncology and Hematology TREATMENT Thrombophlebitis and Deep Venous Thrombosis Patients with cancer and a diagnosis of deep venous thrombosis or pulmonary embolism should be treated initially with IV unfraction ated heparin or low-molecular-weight heparin for at least 5 days, and warfarin should be started within 1 or 2 days. The warfarin dose should be adjusted so that the international normalized ratio (INR) is 2–3. Patients with proximal deep venous thrombosis and a relative contraindication to heparin anticoagulation (hemorrhagic brain metastases or pericardial effusion) should be considered for placement of a filter in the inferior vena cava (Greenfield filter) to prevent pulmonary embolism. Warfarin should be administered for 3–6 months. An alternative approach is to use low-molecularweight heparin for 6 months. The new oral anticoagulants (factor Xa and thrombin inhibitors) are attractive because they do not require close monitoring of the prothrombin time and are not affected by dietary factors. Oral apixaban (10 mg bid for 7 days fol lowed by 5 mg bid for 6 months) is noninferior to dalteparin in the treatment of cancer patients who develop deep vein thrombosis or pulmonary embolism. Patients with cancer who undergo a major surgical procedure should be considered for heparin prophylaxis or pneumatic boots. Breast cancer patients undergoing chemotherapy and patients with implanted catheters should be considered for prophylaxis. Guidelines recommend that hospitalized patients with cancer and patients receiving a thalidomide analogue receive pro phylaxis with low-molecular-weight heparin or low-dose aspirin. Use of prophylaxis routinely during chemotherapy is controversial. Risk is affected by type of cancer, type of therapy, blood counts, and body mass index (all taken into account in the Khorana risk score; Table 98-3). Studies of Khorana high-risk patients with cancer using rivaroxaban and apixaban as clot prophylaxis have resulted in a 50% reduction in risk with a level of bleeding of about 5%. How ever, prophylaxis is not routinely recommended by the American Society of Clinical Oncology.

TABLE 98-3 Khorana Risk Score for Venous Thromboembolism in Cancer Patients PATIENT CHARACTERISTICS RISK SCORE POINTS Site of cancer Very high risk (stomach, pancreas)

High risk (lung, lymphoma, gynecologic,

genitourinary excluding prostate) Prechemotherapy platelet count ≥350,000/µL

Hemoglobin level <10 g/dL or use of red cell growth factors

Prechemotherapy leukocyte count >11,000/µL

BMI ≥35 kg/m2

RATES OF sVTE ACCORDING TO SCORES (%) RISK SCORE (POINTS) RISK CATEGORY

Low 0.3–0.8 1–2 Intermediate 1.8–2.0 ≥3 High 6.7–7.1 Abbreviations: BMI, body mass index; sVTE, symptomatic venous thromboembolism. Source: Reproduced from AJM Muñoz et al: Clinical guide SEOM on venous thromboembolism in cancer patients. Clin Transl Oncol 16:1079-1090, 2014. MISCELLANEOUS REMOTE EFFECTS OF CANCER Patients with cancer can develop paraneoplastic autoimmune disor ders (e.g., thrombocytopenia) and dysfunction of organs not directly invaded or involved with the cancer (rheumatologic and renal abnor malities are among the most frequent). The pathogenesis of these disorders is undefined, but often, the conditions reverse if the tumor is removed or successfully treated. Cutaneous paraneoplastic syndromes are discussed in Chap. 61. Neurologic paraneoplastic syndromes are discussed in Chap. 99. ■ ■FURTHER READING Agnelli G et al: Apixaban for the treatment of venous thromboembo lism associated with cancer. N Engl J Med 382:1599, 2020. Asonitis N et al: Diagnosis, pathophysiology and management of hypercalcemia in malignancy: A review of the literature. Horm Metab Res 51:770, 2019. Catani MV et al: The “Janus face” of platelets in cancer. Int J Mol Sci 21:788, 2020. Dynkevich Y et al: Tumors, IGF-2, and hypoglycemia: Insights from the clinic, the laboratory, and the historical archive. Endocr Rev 34:798, 2013. Feelders RA et al: Advances in the medical treatment of Cushing’s syndrome. Lancet Diabetes Endocrinol 7:300, 2019. Farge D et al: 2022 international clinical practice guidelines for the treatment and prophylaxis of thromboembolism in patients with cancer, including COVID19. Lancet Oncol 23:e334, 2022. Hattersley R et al: Endocrine complications of immunotherapies: A review. Clin Med 21:e212, 2021. Jan de Beur SM et al: Burosumab for the treatment of tumor-induced osteomalacia. J Bone Miner Res 36:627, 2021. Lin RJ et al: Paraneoplastic thrombocytosis: The secrets of tumor selfpromotion. Blood 124:184, 2014. Onyema MC et al: Endocrine abnormality in paraneoplas tic syndrome. Best Pract Res Clin Endocrinol Metab 36:101621,

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