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Emergencies in Oncology

Current Management

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Malignant neoplasms may cause life-threatening complications requiring prompt diagnosis and emergency therapy. Whether or not the underlying neoplasm is potentially curable, the physician can often provide worthwhile prolongation of life and dramatic symptomatic relief. Among the serious complications of neoplasia are superior vena cava obstruction, airway obstruction, pericardial tamponade, spinal cord compression, brain metastasis, meningeal involvement by cancer, hyperuricemia, hypercalcemia and hyperkalemia.

THE PRESENCE of a malignant neoplasm, especially one not potentially curable, sometimes evokes in a physician a feeling of nihilism and lack of urgency in diagnosis or therapy. This review is intended to focus attention on the major life-threatening complications of neoplasia that can be alleviated by prompt diagnosis and therapy. Space does not permit the inclusion of all the serious complications of neoplasia. Among those omitted are the complications due to increase or decrease of the cellular elements of the blood, hemorrhagic disorders, hyperviscosity, and such metabolic disturbances as hypernatremia and hyponatremia, hypoglycemia and lactic acidosis. By the same token, physicians must remain alert to the nononcologic complications that may occur in patients with cancer.[1]

Superior Vena Cava Obstruction

The superior vena cava is formed by the confluence of the innominate veins, which in turn arise from the confluence of the internal jugular and subclavian veins. The last major tributary of the superior vena cava is the azygos vein, which receives blood from the chest wall. If the superior vena cava is blocked above the entrance of the azygos, blood can bypass the obstruction through chest wall collaterals and reenter the superior vena cava via the azygos. If the obstruction is below the entrance of the azygos, blood must pass in a retrograde manner down the azygos and other chest wall veins to reach the drainage area of the inferior vena cava. Hence an obstruction below the level of the azygos is more poorly tolerated.[2]

A primary thoracic neoplasm is the cause in most patients. About 80 percent are due to lung cancer, more commonly on the right and more commonly in small cell carcinoma. About 15 percent of right upper lobe malignant lesions will result in superior vena cava obstruction.[2] Other neoplastic causes include lymphoma, thymoma and, rarely, metastatic tumors.[2,3] Although the syndrome was first described in 1757 in a patient with a luetic aortic aneurysm, benign causes are now very rare, making up less than 5 percent of cases.[2,3] Other benign causes are goiter, tuberculosis, sarcoid, mediastinitis, thrombosis,[2,3] and sternocostoclavicular hyperostosis.[4]

The clinical features are characterized by venous hypertension in the area normally drained

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by the superior vena cava.[2,3] Rapidly growing lesions are tolerated poorly; collaterals have insufficient time to develop.[5] One sees the rapid or insidious onset of facial and neck edema, accompanied by upper extremity edema (which may begin on one side). Distended neck veins are seen unless neck edema is severe enough to obscure them. Tortuous collateral veins are visible on the chest and upper abdomen in most patients,[2,3,5] Dyspnea may be caused by tracheobronchial obstruction. The increased intracranial pressure can result in headache, stupor, coma, seizures, cerebral hemorrhage, engorgement of the retinal veins and papilledema.[2,3] Esophageal obstruction may coexist.[2] Death may result from cerebral edema, airway obstruction or cardiac complications. At autopsy 70 percent of patients are found to have cardiac or pericardial metastases.[2]

Diagnosis should be easy, except in mild, early cases. Venous manometry adds little.[3] Infrared photographs[2] show the collateral veins nicely but are unnecessary. A venogram of the superior vena cava will localize the lesion and aid in evaluating collaterals.[2] However, a venogram is not necessary before starting therapy. Indeed, any venipunctures in the upper extremities should be avoided to prevent hemorrhage.[3] The risk of hemorrhage should make one reluctant to carry out a biopsy, whether scalene, bronchoscopic or mediastinal.[3] The risk of obtaining a tissue diagnosis, plus the overwhelming probability that the lesion is malignant, allow one to break the usual rule and begin therapy at once. Especially in a severe case, one should not delay therapy even one day to obtain unnecessary studies. Once therapy has reduced the venous pressure, a biopsy can be done more safely.

Irradiation is the mainstay of therapy.[2,3,6,7] Response occurs in greater than 80 percent of patients at doses of at least 4,000 rads.[2,6,7] If collaterals are well developed, minimal tumor shrinkage will bring clinical relief.[2] Giving 400 rads per day produces no more side effects than giving 200 rads per day.[2] The recurrence rate is only about 10 percent following a response.[2,3,6,7] Apparently even if the superior vena cava is again obstructed, collaterals have time to develop, so that the syndrome may not recur. Corticoids may be of transient benefit, even though radiation edema has not been shown to exist in this situation.[2] Nevertheless, many oncologists recommend their use before and during irradiation. Of course, in lymphoma corticoids can have a direct antitumor effect. Similarly, some experienced oncologists use emergency chemotherapy before starting irradiation. They point to the occasional patients whose conditions deteriorate rapidly during the first few days of irradiation. However, in randomized trials, nitrogen mustard (mechlorethamine) added nothing to irradiation.[2,6]

In most patients, chemotherapy is used after irradiation. In small cell lung cancer, and possibly in other very responsive tumors, it may be permissible to use combination chemotherapy without irradiation.[8] Further data should clarify this point. Chemotherapeutic agents should not be injected into high-pressure arm veins.[3] Ancillary measures may be of transient benefit.[3] Elevation of the head of the bed may partially alleviate brain edema. Diuretics may be of some use but are not free of side effects. Anticoagulant therapy and fibrinolytic therapy are of unproved value.[9] Surgical bypass of the obstruction may rarely be possible[10] but would play no role in most patients. About 10 percent of patients with lung cancer and 45 percent of those with lymphoma survive at least 30 months after the onset of the obstruction.

Airway Obstruction

Obstruction of the airway may result from fungating head and neck malignant lesions.[11,12] Extrinsic compression may be caused by neoplasms of the thyroid, lung or mediastinum—for example, thymoma. Uncommon causes include involvement of the Waldeyer ring by leukemia, lymphoma or heavy chain disease.[13-15] The clinical features are characterized by stridor, retraction and use of accessory muscles.[12] Superior vena cava obstruction may coexist.[3] Soft tissue x-ray films of the neck, an air bronchogram or tomography may show the obstruction.[11,12] Emergency tracheostomy or intubation may be necessary, if one can get below the level of obstruction.[11,12] Emergency surgical operation, irradiation or chemotherapy may be used, depending on the nature of the tumor. Corticoids may be tried, but they are of uncertain value except in lymphoid neoplasia.

Pericardial Tamponade

Neoplasms of the lung or breast, lymphomas, melanoma, leukemia and, rarely, other tumors may cause pericardial metastases, effusion and tamponade.[16,17] Irradiation to the mediastinum can cause pericarditis as an early or late compli-

cation,[18,19] and subsequent bleomycin therapy can bring it on as a "recall" phenomenon. Infection must always be ruled out. The clinical features include a reduced pulse pressure, paradoxical pulse, distended neck veins, the Kussmaul sign, quiet heart sounds and often a friction rub.[16,17] An enlarged, globular heart shadow may or may not be present on a chest radiograph. An electrocardiogram frequently shows low voltage, with or without ST abnormalities. Electrical alternans may occur. A clinically significant effusion is usually shown by echocardiography.

Prompt pericardiocentesis under electrocardiographic and perhaps echocardiographic control[21] can be life-saving. Some advise leaving a small catheter in place for several days. If the fluid contains malignant cells and the effusion recurs, intrapericardial injection of a chemotherapeutic agent may be tried[17] in responsive tumors. Fluorouracil has been used in doses of 500 to 1,000 mg or thiophosphoramide (THIOTEPA®) in doses of 15 to 30 mg. Data are insufficient to suggest which agent is preferable. It would seem wise to avoid extreme irritants such as nitrogen mustard (mechlorethamine) or quinacrine (atabrine) which might produce fibrosis and constriction, but there are no data on this point. Irradiation, either external or by intrapericardial injection of radioactive chromic phosphate, can be effective for neoplastic effusions.[17] Creation of a pericardial "window" may be carried out under local anesthesia[16] and should be considered if nonsurgical methods do not bring prompt relief. Pericardiectomy may be necessary for severe postirradiation changes in a patient with a good prognosis.

Therapy with corticoids can alleviate radiation-induced pericarditis.[18-20] On the other hand, in patients who have had mediastinal irradiation in the past, pericarditis may develop (for the first time) when administration of corticoids is stopped —such as in combination therapy of lymphomas.[20] For this reason, corticoids are being omitted from these patients' regimens.[20] Paradoxically, therefore, irradiation can cause pericarditis but is used to treat neoplastic pericardial involvement. Corticoids may precipitate radiation pericarditis by their withdrawal, but they are used to treat radiation pericarditis once it occurs.

Spinal Cord Compression

A metastatic tumor compressing the spinal cord is almost always extramedullary.[22-28] This complication may be seen with neoplasms of the lung, breast, prostate, kidney and thyroid, as well as in myelomas, lymphomas, leukemias, sarcomas and carcinomas of unknown primary.[22-28] Metastases may reach the cord via arteries, paravertebral veins, direct extension from an involved vertebra or through a foramen from a retroperitoneal tumor.[22]

The clinical features[22] include pain, either local or radicular, in 90 percent of patients. Paresthesias may be present. Early weakness may go undetected in a bedridden patient or one ill for other reasons. Later, gait disturbances, spastic paraparesis, extensor plantar responses and hyperreflexia supervene. A sensory level may not involve all sensory modalities initially. Sphincter loss is a late finding. Early diagnosis is of prime importance in avoiding paraplegia.[22-28] On the other hand, initial delay does not always mean hope is lost. Occasionally a patient may walk again although therapy was not begun until 27 days after the onset of weakness.[23] Hence one must strive for early diagnosis but should not abandon a patient in whom diagnosis was missed initially.

X-ray films or radionuclide bone scans show vertebral involvement in about 80 percent of patients.[22,24] Lumbar puncture should usually be done in conjunction with a myelogram;[22] the neurologic situation worsens after the tap in 8 percent of patients. Fluid should be collected for cytologic and chemical examination before contrast material is injected.[22] A myelogram shows the extent of the lesion and may show a second level of compression besides the obvious one. If the block is complete, cisternal or cervical puncture may be needed to delineate the lesion.

Laminectomy is usually the treatment of choice if the cord compression is due to vertebral collapse or to a radioresistant tumor.[22,24] Operative mortality is about 8 percent in these patients.[22,24] Up to half of all patients will be able to walk, but only 5 to 7 percent of paraplegic patients will be able to do so.[22] Surgical operation is followed by irradiation.[22] If the tumor is radiosensitive (for example, lymphomas, Ewing sarcoma, neuroblastoma or small cell lung cancer) *and* if there is no vertebral collapse, irradiation may be used without operation.[22,23,25,27] However, if the neurologic signs worsen, laminectomy will still be needed. Irradiation is also used in patients who would not tolerate surgical operation. There is no randomized trial of surgical treatment versus irradiation for metastatic tumors compressing the

cord. Chemotherapy may be used as an emergency measure before operation or irradiation, especially in responsive tumors.[22,27] Corticoids should be used as an emergency measure before definitive therapy; their use is supported by studies in animals.[22,23,25-28] The usual dosage of dexamethasone is 4 mg every six hours. Corticoids are often given during irradiation, but radiation edema has not been proved to exist in this setting.[22] It is obviously preferable to treat threatening lesions of the cervical, thoracic or lumbar vertebrae with irradiation and bracing than to await the appearance of a neurologic deficit. Back or neck pain is an important warning which should be investigated.

Brain Metastasis

The most frequent cause of brain metastasis is lung cancer; others include melanoma, breast, thyroid, stomach and testicular cancer, as well as trophoblastic cancer.[22,29] Lymphomas rarely occur in the brain as space-occupying lesions, except in immunosuppressed transplant patients.[28] The clinical picture[22] includes headache in 53 percent of patients. Seizures, either focal or generalized, occur in about 15 percent. Obtundation is apparent in 33 percent, but careful testing will show confusion in greater than 50 percent. Papilledema is seen initially in 25 percent of patients. Depending on the site of the lesion or lesions, one may find visual field cuts, hemiparesis, aphasia or reflex changes. It is of note that about 10 percent of "strokes" prove to be brain metastases.[22]

The computerized tomographic (CT) scan is probably the most useful diagnostic aid, especially when it is used with contrast injection.[22] The CT scan helps differentiate tumor, vascular accident, abcess, subdural hematoma and hydrocephalus, each of which may occur in a patient with cancer.[22] Radiographs of the skull may show calcification, pineal shift or bony lesions; the last can confuse the interpretation of radionuclide brain scans. Lumbar puncture should not be done unless it is necessary to rule out meningeal infection or metastases.[22] Brain stem herniation may occur, especially in the presence of papilledema or a posterior fossa lesion.

Radionuclide brain scans are useful but require careful interpretation. Gallium scans are often falsely normalized by corticoid therapy, while technetium scans are not.[30] Technetium scans are often positive in a vascular accident; gallium scans may also be. Either type of scan may be positive with skull or scalp lesions, either infectious or neoplastic; here the CT scan is most useful. Angiography is usually diagnostic but is less needed with the use of CT scans. An electroencephalogram is often abnormal but may contribute little clinically. Pneumoencephalography has little use since CT scans have become available. Echoencephalography may detect a midline shift or dilated ventricles, but it is less sensitive than a CT scan.

Therapy includes emergency use of corticoids; their effects may be transient but dramatic.[22,29] Dexamethasone, 4 mg every six hours, is usually effective, but much higher doses are occasionally needed. Hypertonic solutions have some role in the acute reduction of brain edema, but the effect is temporary. They should be used with caution in the presence of marginal cardiac or renal function.[29] Mannitol, 20 percent solution, as an intravenous infusion may be used in doses up to 100 grams in 24 hours. It equilibrates slowly, so there is less rebound effect than with urea.[29] Glycerol, 1 gram per kg of body weight by mouth every four to six hours, has much less activity. It is used for maintenance therapy by some authorities, not at all by others.[29] It can be given intravenously. Anticonvulsants are used for seizure control. They are not necessary prophylactically in a patient who has never had a seizure, unless the patient has had a craniotomy.[22] Irradiation of the whole brain at 2,000 to 4,000 rads, depending on the tumor type, is the treatment of choice. Corticoids are given before and during irradiation by most authorities, although the existence of radiation edema is not universally accepted.[22,29] Some cytotoxic agents enter the central nervous system in varying degrees (such as the nitrosoureas, hydroxyurea, procarbazine), but none substitutes for irradiation in the therapy of brain metastases. Craniotomy may very rarely be indicated for potentially curable disease, such as a patient in a complete remission of testicular cancer in whom an isolated brain metastatic lesion develops. In addition, in a patient cured of cancer a resectable brain tumor, such as a meningioma, may rarely develop. A statistical association of breast cancer and meningioma has been reported.

Meningeal Involvement by Cancer

Meningeal involvement is present at autopsy in 4 percent of all cancer patients[22] but is less common as an antemortem diagnosis. The more com-

mon causes include breast cancer, non-Hodgkin lymphoma (mainly histiocytic), and the acute leukemias, as well as cancer of the lung, stomach, pancreas, prostate, Hodgkin disease and melanoma.[22,28,31-35] For unknown reasons this complication is very rare in squamous cancers. In 8 percent of patients with meningeal involvement, this represents the first sign of a neoplasm.

The clinical features may include increased intracranial pressure from obstructive hydrocephalus, scattered focal signs such as cranial nerve and upper or lower extremity deficits, back pain, seizures and confusion.[22,28,31-35] Neck stiffness occurs in 16 percent to 25 percent of patients. The spinal fluid shows increased pressure in 64 percent, increased protein in 85 percent, and decreased glucose in 55 percent to 76 percent of patients. However, both protein and glucose values may be normal in 10 percent. A positive spinal fluid cytology is present by definition, but to show it one may need repeated taps and careful fluid examination after concentration by cytocentrifuge or nucleopore filter.[22,28] Bacterial and fungal infection must be ruled out. In leukemia cranial nerve palsies may occur in the absence of spinal fluid pleocytosis and require prompt irradiation.[22] Eosinophilia in the spinal fluid is a rare finding.[33]

Therapy may include irradiation, intrathecal chemotherapy, or both.[22] Irradiation to the vertebral column reduces marrow tolerance to future systemic chemotherapy, so that cranial irradiation may be combined with lumbar intrathecal chemotherapy, as is done in meningeal leukemia.[22] It should be noted that if spinal irradiation is used, it should extend to the inferior limit of the dural sac, not merely to the cord itself. The most commonly used intrathecal agent is methotrexate at a dose of 6.25 to 10 mg per sq meter given twice a week until the fluid is clear.[22] It is probably safer not to exceed 12 mg as a single weekly dose in adults. Alternate agents are cytarabine (Ara-C) at a dose of 30 mg per sq meter[22,28] or thiophosphoramide (THIOTEPA),[36] each given on a similar schedule. After the spinal fluid has cleared, monthly maintenance intrathecal chemotherapy is used by some authorities. If cranial irradiation is not used, intrathecal chemotherapy should be given via an Ommaya reservoir to assure adequate intracranial dosage.[22] Intrathecal agents should be diluted in preservative-free solutions such as normal saline or Elliot's B solution in an attempt to reduce the incidence of side effects.[28] About 58 percent of patients respond to therapy.[22,28] Response is probably better in cases of lymphoma, leukemia and breast cancer than in other neoplasms. Of those who respond, about half do not have clinical meningeal recurrence, but many still have meningeal tumor at autopsy. Either irradiation or intrathecal chemotherapy can produce neurologic side effects ranging from confusion and neck stiffness to severe encephalopathy or paraplegia.[22,28,36] The incidence of side effects is probably higher if both irradiation and intrathecal chemotherapy are given to the same region.[28] It may be difficult to distinguish these neurologic side effects from recurrent tumor or infection. Cultures, cytologic studies, and a CT scan are helpful.

For purposes of discussion, one may separate meningeal tumor involvement from cord compression. In practice this distinction may be difficult. One may see a discrete mass on myelography in a patient whose spinal fluid contains malignant cells.[22] In such a case, irradiation is probably preferable, although there is no definitive study on this point. Intrathecal agents may destroy free-floating cells or tiny tumor seedlings, but it is unreasonable to expect them to diffuse into a 1-cm mass in adequate concentration.

Hyperuricemia

Uric acid is the end product of purine metabolism. Its major source is cell breakdown and its major excretory pathway is renal. Hyperuricemia may occur as a result of increased production, decreased excretion or both.[37-40] Increased production occurs during rapid cellular proliferation, such as in hematologic neoplasia, or during sudden cell lysis as a result of chemotherapy or of irradiation. Decreased plasma uricolysis may also play a role.[41] Urates may precipitate in the renal tubules or ureters, causing ureteral colic, azotemia, oliguria and decreasing urate excretion, leading to a vicious cycle.

Prophylactic allopurinol should be given before chemotherapy or irradiation of sensitive tumors, especially with bulky disease or if the serum uric acid level is borderline or elevated before therapy.[37-40,42-44] Allopurinol inhibits xanthine oxidase, which converts hypoxanthine and xanthine to uric acid. Note that this enzyme also inactivates 6-mercaptopurine and azathioprine (Imuran®), so that when either of these agents is given with allopurinol, the dose of these agents should be cut to 25 percent to 33 percent of the

usual dose.[37] The dose of 6-thioguanine need not be cut. Allopurinol in doses of 300 to 600 mg per day will usually cause a fall in the serum uric acid level in about three days, so that its administration should be started two or three days before cytolytic therapy, if time permits. In an occasional patient higher doses of allopurinol will be required, but they act no faster. Secondary gout is rare, so prophylactic colchicine need not be added.[40] Uricosuric agents such as benemid are contraindicated; the object is to decrease renal urate excretion, not increase it. An investigational intravenously given solution of allopurinol has been used for patients unable to retain oral medication, but it acts no faster than the oral form.

Maintenance of urine output above 2 liters a day is important. Keeping the urine pH above 7.0 will greatly increase urate solubility. Sodium bicarbonate, 9 to 12 grams a day, may be required to do this. If large amounts of sodium cannot be used, such as in congestive failure, acetazolamide (Diamox®) in doses of 1 gm a day will usually alkalinize the urine temporarily until allopurinol becomes effective. Acetazolamide will aggravate metabolic (for example, lactic) acidosis and should be avoided in this circumstance. The urine should be observed for crystals in the presence of hyperuricemia. If oliguria occurs, therapy with mannitol may be tried. One may start with 12.5 grams of a 20 percent solution given intravenously over three minutes. If urine output increases to 40 ml per hour, a 20 percent solution may be infused at a rate sufficient to keep urine flow about 250 ml per hour until the serum uric acid falls to safe levels. The dose of mannitol is limited to 100 grams per 24 hours to avoid clinical features resembling water intoxication.[37,44] If these measures fail, peritoneal dialysis or hemodialysis[39,45] or flushing the ureters via retrograde catheters[46] may be considered. Clearly, prevention of this complication is far better than treatment.

Hypercalcemia

Hypercalcemia occurs in about 20 percent of patients with cancer. The most frequent mechanism is "direct" lysis of bone by osseous metastases. This mechanism is incompletely understood; prostaglandins may be involved.[47,48] In addition, hypercalcemia without detectable bony metastases may develop. Ectopic parathormone production has been reported in squamous carcinoma of the lung or head and neck, and also in renal cell, ovarian and other types of cancer. Only one or two cases of ectopic parathormone production by breast cancer have been reported; here a coexistent parathyroid adenoma is more likely.[49-55] Non-vitamin D sterols have been reported in breast cancer[56] but not confirmed.[57] Prostaglandins have been reported in renal cell cancer, and also in sarcomas, melanoma, and breast, ovary, and other types of cancer.[47,48] Osteoclast-activating factor has been reported in myeloma[58] and similar bone-resorbing factors in acute lymphocytic leukemia.[59] Estrogens, antiestrogens, androgens or progestins may cause hypercalcemia in breast cancer within one to three weeks after starting therapy.[60] This effect is not due to release of hypercalcemic factors by dying cancer cells, because it can occur in the absence of tumor shrinkage. The differential diagnosis of hypercalcemia includes vitamin D excess, the milk-alkali syndrome, adrenal insufficiency, hyperthyroidism, tuberculosis and sarcoid. Whatever the underlying disease, hypercalcemia may be brought on by dehydration or immobilization in bed; the former decreases excretion of calcium, the latter increases its removal from bone. Thiazides may also aggravate hypercalcemia.

The early clinical signs of hypercalcemia include nocturia, polyuria and polydipsia. Later findings include nausea and vomiting with dehydration, weakness, lethargy, constipation, hyporeflexia, oliguria and coma. Digitalis toxicity may be precipitated. Ectopic calcification is unusual, probably because of the short duration of malignant hypercalcemia.

General principles of therapy include treating the cancer when possible, encouraging ambulation, correcting dehydration, increasing calcium excretion, decreasing calcium removal from bone, reducing calcium intake and interruption of hormone therapy in cases of breast cancer.[50,61-65] For patients with serum calcium levels below 14 mg per dl, oral rehydration and ambulation may suffice. Normal saline solution should be given intravenously if oral intake is inadequate. Oral phosphate may be used if the serum phosphate level is not elevated.[64] If prostaglandin production is suspected, such as in renal cancer, one may try indomethacin or aspirin.[47,48] Prednisone, 60 to 80 mg per day, or other corticoids, may be effective within a few days to a week, making it more useful for chronic than for acute control of hypercalcemia.

For patients with dangerous elevations of

serum calcium (over 14 mg per dl) a more vigorous regimen is necessary.[63-65] Dehydration should be corrected within two hours, as cardiac and renal function allow. When urine flow reaches 100 ml per hour, furosemide, 40 to 200 mg, may be given intravenously every one to two hours. The saline infusion should be matched to the preceding hourly urine output; one may need 8 to 12 liters in the first 24 hours. The serum potassium level should be monitored every four hours and potassium, 20 to 40 mEq, added to each liter as necessary to prevent severe hypokalemia. Up to 50 mEq of magnesium per day may be needed, but it is less important because the effects of hypomagnesemia are counteracted by hypercalcemia. The careful monitoring this regimen requires is best done in an intensive care unit. Aggressive therapy is stopped when the serum calcium level falls below 14 mg per dl. One must keep in mind that about half of patients with hypercalcemia and cancer will have hypokalemia even before therapy.

Chemotherapeutic agents are especially useful when sodium intake must be limited. Their action does not depend on renal excretion and can occur in the presence of oliguria. Mithramycin at a dose of 25 μg per kg of body weight is given as a 30 to 60 minute infusion.[65-67] It is often effective in lowering serum calcium levels within 12 to 48 hours. A single dose usually has little toxicity except nausea. Repeated doses every three to seven days may be needed; here one may see thrombocytopenia, a bleeding tendency, leukopenia, liver enzyme elevations, renal damage, and occasionally hypocalcemia or hypokalemia.[65-67] Some authorities prefer mithramycin to forced diuresis even when oliguria is not present.

Actinomycin D and methotrexate also have calcium-lowering effects, but their toxic effects make them less useful. Intravenously given sodium phosphate is, in my opinion, rarely needed, although some authorities feel it has a role, especially in hypophosphatemic patients.[63-65] Complications include widespread calcifications, shock and renal failure. If intravenous phosphate is used, no more than 1 gram of elemental phosphorus should be given within eight hours.[64] Neither intravenously given nor orally given phosphate should be used if the serum phosphate level exceeds 4 mg per dl. Phosphate should also be avoided in the presence of significant renal insufficiency.[64] Chelating agents can cause a transient drop in serum calcium level but are nephrotoxic.[65] Calcitonin has been effective in doses of 3 to 6 MRC (Medical Research Council) units per kg of body weight per day and deserves further trial.[65,68] Hemodialysis may be effective in severe cases.

Hypocalcemia is an uncommon complication of cancer.[64,69,70] Calcitonin production by the tumor, sepsis, malabsorption, azotemia, hypomagnesemia, hyperphosphatemia, anticancer agents, hypoparathyroidism due to destruction of the glands by cancer or surgical operation, and increased calcium uptake by osteoblastic metastases may each play a role.[64,66,67,69-72]

Hyperkalemia and Hypokalemia

"True" hyperkalemia occasionally results from successful therapy of exquisitely sensitive tumors such as Burkitt lymphoma or acute lymphocytic leukemia.[71-73] Massive cell lysis releases life-threatening amounts of potassium, as well as phosphate and other electrolytes. Anticipation of this complication allows careful monitoring of serum electrolyte levels and renal function. Ion exchange resins and dialysis may be required. Hyperuricemia and hypocalcemia may coexist and should be watched for.

"False" hyperkalemia may occur with patients in whom platelet or leukocyte counts are elevated to a pronounced degree.[72,74] The cells lyse in the tube before the serum is separated for analysis, releasing intracellular potassium. A rapidly separated, heparinized specimen may show a normal (or at least less elevated) plasma potassium level. No therapy is required. Normal findings on an electrocardiogram help to allay anxiety.

Hypokalemia may occasionally be caused by a renal tubular defect, perhaps due to muramidase (lysozyme), in acute nonlymphocytic leukemia.[75] Other causes include severe diarrheal states caused by the Zollinger-Ellison syndrome, vasoactive-intestinal-polypeptide-producing islet cell tumors, colorectal villous adenoma, or intestinal lymphoma.[76] Hypokalemia, sometimes severe, may be seen in 52 percent of cancer patients who have hypercalcemia.[77] This fact must be kept in mind, especially when intensive diuretic therapy is begun.

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