A 48-year-old homeless man, who has smoked 1 1/2 packs of cigarettes per day for 30 years, presented to our hospital for the first time with fever, chills, night sweats, and abdominal pain. He gave a history of left nephroureterectomy for transitional cell carcinoma nearly six years ago. Four months before admission here, a transurethral resection of bladder tumors revealed high-grade multifocal transitional cell carcinoma invading the bladder muscle. Ten weeks ago, urinary obstruction and urosepsis required placement of a right-sided nephrostomy tube. Six weeks before admission, he underwent a robotic-assisted laparoscopic radical cystoprostatectomy with bilateral pelvic lymph node dissections and creation of an ileal conduit urinary diversion. He also reported a 30-pound weight loss over the past several months and recent lumbar back pain, cough, and dyspnea. Exam revealed a temperature of 102° F, a pulse of 110 beats/minute, a soft abdomen with bilateral lower quadrant tenderness, normal breath and heart sounds, and a normal appearing ileal conduit stoma and right nephrostomy stent. Chest radiograph showed multiple bilateral subcentimeter pulmonary nodules suspicious for metastatic disease. Computed tomogram of the abdomen and pelvis demonstrated omental and peritoneal deposits, a large mass of pelvic lymph nodes, and multiple L3-L4 lytic bone lesions. Urinalysis was positive for nitrites and numerous white blood cells. Hematocrit was 19%, and white blood cell count was 21,000/mm³ of blood. The patient was admitted for treatment of urosepsis, transfusion, and further assessment of his presumed metastatic disease. An electrocardiogram was recorded (Figure below).

Figure: Electrocardiogram recorded on admission.

What is your diagnosis?
Explication is on page 98.
ECG of the Month
Presentation is on p. 97.

DIAGNOSIS: Sinus tachycardia at 110 beats/minute. Short QT interval – 0.25 seconds; 0.33 seconds when corrected for heart rate (QTc) – suggesting hypercalcemia. Otherwise, the ECG is normal.

Although long QTc intervals are common, are read by virtually all computer programs, and have multiple causes, short QTc intervals are uncommon, are rarely recognized, and have a limited differential diagnosis. The QTc is inversely related to the level of ionized serum calcium, which constitutes approximately 47% of total serum calcium. It is the ST segment, rather than the T wave, that is altered, and hypercalcemia causes shortening or virtual disappearance of the ST segment (Figure). Digitalis also shortens the QT interval, but, unlike hypercalcemia, the drug has other characteristic effects on the electrocardiogram, such as h hammock-like ST-segment sagging that also pulls the T wave down, diminishing its height, an increase in U wave amplitude, prolongation of the PR interval, and, in toxic doses, a wide variety of arrhythmias. Congenital long QT interval syndromes associated with potentially lethal ventricular tachyarrhythmias have been recognized for decades, and recently, short QT interval syndromes linked to such rhythm disturbances have been described. There are no data in humans to indicate an increased risk of sudden death in patients with hypercalcemia.

This patient’s electrocardiogram is typical of hypercalcemia, and a serum calcium level within hours of the electrocardiogram was 13.6 mg/dL (reference range, 8.4 to 10.3). His serum albumin level was 1.9 g/dL (reference range, 3.4 to 5.0). Because an increase in serum albumin concentration of 1 g/dL increases protein-bound serum calcium by 0.8 mg/dL, his ionized calcium level was equivalent to that of a patient with an albumin level of 3.9 g/dL and a total serum calcium level of 12.8 mg/dL.

Hypercalcemia has many causes, and a malignant neoplasm is the single most common one, followed by primary hyperparathyroidism. Some 20% to 30% of patients with cancer are estimated to develop hypercalcemia. The malignancies most often associated with hypercalcemia are tumors of lung, breast, kidney, ovary, and multiple myeloma and other hematologic malignancies. A wide variety of other malignancies have been associated with hypercalcemia, and in our patient, transitional cell carcinoma of the bladder was the culprit.

In patients with hypercalcemia of malignancy, production of humoral factors by the primary tumor - often parathyroid hormone-related protein and rarely parathyroid hormone itself or 1, 25-dihydroxyvitamin D - is thought to be the mechanism in 80% of patients and skeletal metastases with bone osteolysis in 20% of patients. In those with bone metastases, the tumor cells release a variety of cytokines that activate osteoclasts, thus inducing bone resorption and release of calcium into the circulation.

Hypercalcemia in a patient with malignancy is an ominous prognostic sign. In this patient, intravenous saline and bisphosphonates, standard treatment for hypercalcemia of malignancy, lowered the serum calcium, and antibiotics and removal of the stent temporarily controlled the urosepsis. However, widespread tumor, progressive renal failure, and recurrent urosepsis led to his death four weeks after admission.

Currently, virtually no computer program attempts to diagnose electrolyte abnormalities. Thus, the physician needs to recognize the characteristic features of hypercalcemia, hypocalcemia, hyperkalemia, and hypokalemia.

REFERENCES
2. Ibid. 516-539.
9. Bjerregaard P, Nallapaneni H, Gussak I. Short QT interval syndromes linked to such rhythm disturbances have been described. There are no data in humans to indicate an increased risk of sudden death in patients with hypercalcemia.

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