

28 year-old man with thrombophilia and hypercalcemia

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A 28 year-old Hawaiian Chinese man was admitted for abdominal discomfort. The patient had a six-month history of recurrent venous thromboembolic disease including multiple bilateral lower extremity DVTs and pulmonary emboli. His abdominal pain had increased in intensity over the week prior to admission and was associated with an increase in abdominal girth and constipation. He also noticed swelling of his right calf similar to his past DVTs, and worsening shortness of breath.

The patient's past medical history was significant for recurrent lower extremity DVTs and pulmonary emboli over the six months prior to admission, despite being adequately anticoagulated with warfarin. His past work up for hereditary causes of thrombophilia had been negative, and he was currently being treated with subcutaneous low molecular weight heparin, enoxaparin 1 mg/kg twice daily. The patient had no family history of thrombophilia. He smoked cigarettes one pack per day, used marijuana, but did not drink alcohol nor travel outside of the United States. He worked as a forklift operator and had no significant occupational exposures.

Physical examination revealed an obese man with mild dyspnea, a temperature of 99.2 degrees, blood pressure 122/78 mm Hg, pulse 113 beats/min, and respiratory rate 20 breaths/min with an oxygen saturation of 99% on room air by pulse oximetry. His exam demonstrated scleral icterus and jaundiced skin. Cardiovascular exam was significant for tachycardia and lung fields were clear. His abdomen was slightly distended with hepatosplenomegaly and ascites. Bilateral calf tenderness and swelling to 48 cm circumference were also present. Laboratory studies were significant for bilirubin 2.3mg/dL (0.1-1.0 mg/dL), AST 179 U/l (0-40 U/l), ALT 52 U/l (0-45 U/l), albumin 2.1g/dL (3.5-5.0 g/dL), and alkaline phosphatase 25 U/l (25-125 U/l). His calcium was 14.5mg/dL (8.6-10.7 mg/dL) and his PTH was 3 pg/mL (10-65 pg/mL). Perfusion-ventilation nuclear medicine scan demonstrated left femoral and left iliac vein thrombosis extending to the inferior vena cava, and high probability of bilateral pulmonary emboli.

His hypercalcemia was treated with hydration and furosemide as well as pamidronate. On admission, he was also anticoagulated with continuous infusion of unfractionated heparin.

Further work up revealed normal PSA, AFP and hCG, but an elevated CEA 58ng/mL (normal 0-5 ng/mL) and CA 19-9 1,022,000 U/mL (normal <40 U/mL). CT scan displayed large, hypodense areas of the right lobe of the liver and evidence of right hepatic vein thrombosis (Figure 1). A subsequent biopsy of the liver was consistent with cholangiocarcinoma (Figure 2). The patient chose to undergo chemotherapy, and was treated with one course of 5-fluorouracil. He later developed hepatorenal failure with hypotension and died.

Figure 1.— CT scan of abdomen revealing multiple dilated ducts and a large hypodense region in the liver.

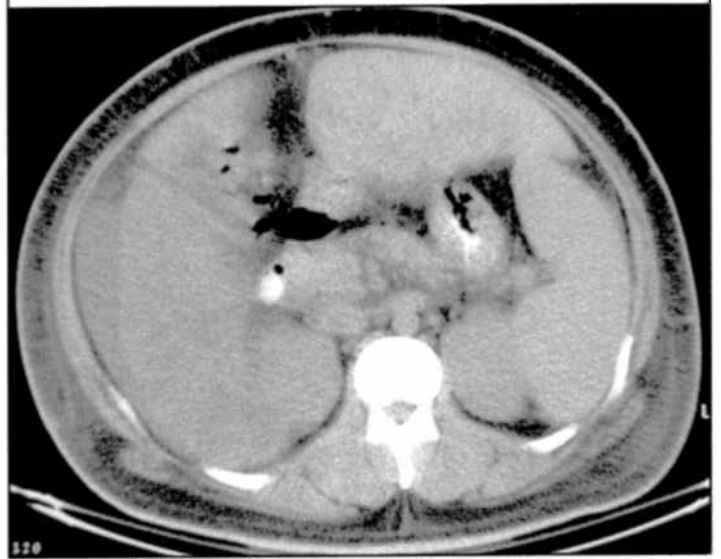
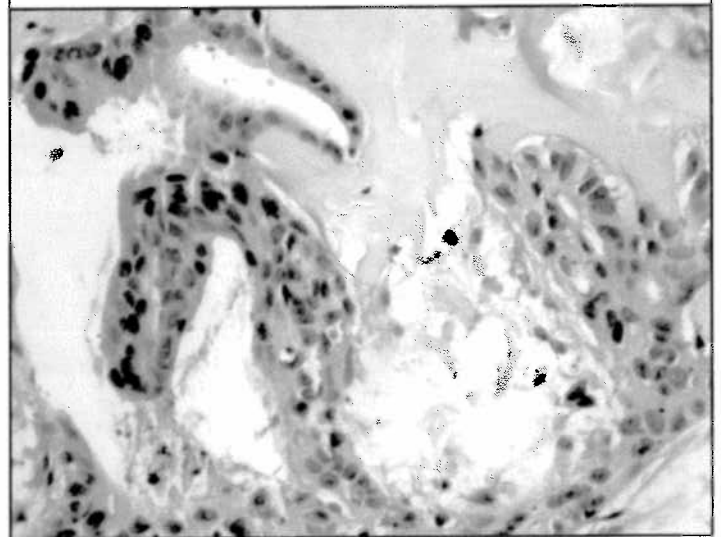


Figure 2.— Biopsy of tumor demonstrating atypical ducts consistent with an adenocarcinoma, anisokaryosis and an increased nuclear to cytoplasmic ratio.



Discussion

This patient presented with hypercalcemia and thrombophilia, complications often seen in malignancy. The following discussion addresses the various etiologies of hypercalcemia, mechanisms specific to hypercalcemia in malignancy, and treatment of the condition. Thrombophilia and its hereditary and acquired causes are also described. The article focuses on the epidemiology of VTE in cancer patients, and the efficacy and practicality of screening for tumors in patients presenting with thrombophilia.

Hypercalcemia

Hypercalcemia results when calcium is absorbed from the intestine and resorbed from bone faster than it is excreted in the urine and deposited in bone. In the diagnostic workup, it is helpful to think of diseases that can alter these processes. (Table 1)

Table 1.— Differential Diagnosis of Hypercalcemia

Increased intestinal absorption

milk-alkali syndrome
renal failure (phosphate binders)
hypervitaminosis D
exogenous vitamin D
chronic granulomatous diseases
malignant lymphoma
acromegaly

Decreased renal excretion

familial hypocalciuric hypercalcemia
thiazide diuretics

Increased bone resorption/ Decreased bone deposition

hyperparathyroidism
malignancy
hyperthyroidism
immobilization
hypervitaminosis A
lithium (via PTH-related protein)
pheochromocytoma (via PTH-related protein)

Hyperparathyroidism is the most common cause of hypercalcemia in the ambulatory setting, accounting for over 90% of cases. Among hospitalized patients however, 60% of hypercalcemic states are due to cancer. Hypercalcemia occurs in 10 to 20% of cancer patients, and is most prevalent in those with breast cancer, lung cancer and multiple myeloma.¹ Three mechanisms have been discussed: osteolytic metastases with local cytokine mediators, secretion of PTH-related protein (PTHrP), and tumor production of calcitriol (1,25 (OH)₂-vitamin D₃). The laboratory evaluation of hypercalcemia in this group should include a PTH level because there is also a higher incidence of primary hyperparathyroidism among cancer patients than in the general population.

Breast and non-small cell lung cancers and other solid tumors that metastasize to the bone produce tumor necrosis factor, interleukin-1 and other cytokines that stimulate osteoclastic activity. This local induction of bone resorption increases serum calcium levels. PTHrP mediated hypercalcemia, also called humoral hypercalcemia of malignancy, is the most common cause of hypercalcemia in nonmetastatic tumors and non-Hodgkins lymphomas. PTHrP acts in a manner similar to PTH increasing bone resorption and calcium reabsorption in the kidneys. The diagnosis may be made by measuring serum PTHrP levels, but currently no treatment is available to inhibit its release. Tumor cell production of calcitriol is responsible for hypercalcemia in almost all cases of Hodgkin's lymphoma and about a third of the cases of non-Hodgkin's lymphoma. High calcitriol titers increase intestinal absorption of calcium and bone resorption.

The hypercalcemic patient often presents with nonspecific complaints of fatigue, anorexia, nausea, vomiting, abdominal pain, constipation, polydipsia and polyuria. Neurological manifestations may range from weakness and lethargy to altered mental status and coma. Nephrogenic diabetes insipidus and renal failure secondary to volume contraction and direct parenchymal damage also may occur. The severity of the signs and symptoms depend on both the degree and rate of increase in calcium levels.

First-line treatment for hypercalcemia in cancer patients is appropriate treatment of the malignancy. Unfortunately, most patients

presenting with high serum calcium are in advanced stages of disease, and must be treated by other modalities. Normal saline infusion is often helpful because patients will present with hypovolemia secondary to vomiting and polyuria. Loop diuretics like furosemide have a limited effect on increasing calcium excretion. Bisphosphonates are effective in inhibiting osteoclastic activity and thus resorption from the bone. Pamidronate or zoledronate are the preferred bisphosphonates available in the US and are dosed every two to four weeks. Gallium nitrate also inhibits bone resorption, but its use is limited by its nephrotoxicity. It should not be given with other potential nephrotoxic agents. Calcitonin treats hypercalcemia by both inhibiting bone resorption and through increasing calcium excretion via the kidney. Calcitonin therapy is usually limited to two to three days due to tachyphylaxis. Plicamycin is another osteoclast inhibitor, but with severe adverse effects including nephrotoxicity, hepatotoxicity, thrombocytopenia, and coagulopathy. Severe manifestations of hypercalcemia, such as coma, may require hemodialysis.

Thrombophilia

Thrombophilia leading to venous thromboembolism (VTE) is responsible for 250,000 hospitalizations per year. It is a major risk factor for pulmonary embolism, which in turn accounts for 50,000 deaths a year. The most common hereditary etiologies of thrombophilia are factor V Leiden, prothrombin G20210A, antithrombin III (ATIII), protein C, and protein S mutations. Together they are responsible for 30 to 50% of all VTE cases.² Acquired thrombophilic defects include trauma, pregnancy, surgery, prolonged immobilization, nephrotic syndrome, antiphospholipid syndrome, and malignancy.³ Hyperhomocysteinemia is another common etiology, and can be either hereditary or acquired.

Factor V Leiden

In the coagulation pathway, factor Va and factor Xa convert prothrombin to thrombin. During fibrinolysis, activated protein C cleaves factor Va, rendering it inactive. The factor V Leiden mutation involves a replacement of glutamine for arginine at position 506 during the synthesis of factor V. This substitution slows the rate of inactivation of factor Va, leading to increased levels of the clotting factor. Two pathophysiologic mechanisms have been proposed to explain the thrombophilic risk in these patients: first, by converting more prothrombin to thrombin, and second, through slowing fibrinolysis by decreasing the activity of protein C. Factor V Leiden is the most common hereditary prothrombotic disorder. The ethnic variation among factor V Leiden patients is significant for a high prevalence among Caucasians (5.27%), compared to Asian (0.45%) and African (1.23%) populations.³ In contrast to its high prevalence, the factor V Leiden carries a low risk for VTE relative to other hereditary mutations. Heterozygotes (relative risk 5-10) have a lower risk than homozygotes (relative risk 80) and compound heterozygotes for other thrombophilic mutations.^{3,4}

Prothrombin G20210A

Prothrombin G20210A is a substitution of alanine for guanine in the untranslated 3 region of the prothrombin mRNA. Heterozygotes with this mutation have been shown to have 30% higher prothrom-

bin levels. This is believed to be the mechanism for the procoagulant activity.⁵

The G20210A mutation, with a prevalence of 2%, is the second most common hereditary cause of thrombophilia.³ Similar to the factor V Leiden defect, this trait is more common in Caucasian populations. The G20210A heterozygotes have a lower risk of VTE (RR 2-5) compared to AT III, protein C or S carriers or compound heterozygotes.⁴

Antithrombin III, Protein C, Protein S

AT III, protein C and protein S are enzymes required for fibrinolysis. Deficiencies in their amount or function can lead to a thrombophilic state. Homozygous or compound heterozygous protein C and S patients develop a usually fatal condition called purpura fulminans. Thus, adult patients are heterozygous or compound heterozygotes with the factor V Leiden defect.

AT III is an irreversible inhibitor of thrombin and other clotting factors. Protein C interacts with protein S to inactivate factors Va and VIIa and to induce fibrinolysis. Mutations in the genes of these enzymes lead to either reduced synthesis of the protein or decreased enzymatic function. AT III, protein C, and protein S defects account for 5-15% of VTE events.⁵ A study comparing hereditary defects of coagulation revealed the following relative risks of thrombosis compared to individuals with no defects: antithrombin III 8.1, Protein C 7.3, Protein S 8.5, and factor V Leiden 2.2.⁶ In establishing a laboratory diagnosis, it is important to remember that AT III, protein C and S may be falsely low in an acute episode of thrombosis.⁷ Also, heparin may decrease levels of AT III, and warfarin may reduce levels of protein C and S.⁵ Screening for these defects should be delayed until two weeks after anticoagulation medications have been stopped.

Antiphospholipid Syndrome

Antiphospholipid antibodies (APLAs) are autoantibodies including the lupus anticoagulant and anticardiolipin antibody. These antibodies are more prevalent in the elderly, people with autoimmune diseases or HIV, and patients on medications such as procainamide, quinidine, and chlorpromazine. Similar to hyperhomocysteinemia, APLAs are responsible for both arterial and venous thrombi. Proposed mechanisms for the thrombotic activity of APLAs include inducing increased adherence of platelets and monocytes to the endothelial wall, alteration of the thromboxane/prostacyclin balance, and functional impairment of antithrombin III, protein C, protein S, and other coagulation inhibitors.

The prevalence of APLAs ranges from two to 5% among healthy blood donors, while for patients with systemic lupus erythematosus it can be as high as 60%. The lupus anticoagulant has been associated with a higher thrombotic risk than the anticardiolipin antibody.

Hyperhomocysteinemia

Homocysteine is an amino acid formed by the metabolism of methionine. Elevations in homocysteine level can be caused by genetic defects, nutritional deficiencies (vitamin B6, vitamin B12, and folate), medications (cholestyramine, carbamazepine, phenytoin, niacin, and theophylline), and liver or renal failure.

While there are numerous case-control and cross-sectional stud-

ies reporting a strong association between hyperhomocysteinemia and atherosclerotic events, there is some controversy surrounding the relationship. Possible prothrombotic mechanisms of homocysteine include endothelial dysfunction due to free radical formation during the reduction of homocysteine, direct inhibition of endothelial cell growth, direct platelet proaggregatory effects, and promotion of leukocyte recruitment. It is still unclear whether hyperhomocysteinemia is a cause of thrombophilia or a marker of thrombosis, and larger prospective studies are needed to elucidate this issue.⁸

Studies directed specifically at VTE have found an odds ratio of 2.5 to 2.95 among patients with homocysteine levels greater than two standard deviations above the mean value of the control group.^{3,4}

Malignancy

The association of malignancy and VTE is well documented in the literature. In our patient without thrombotic risk factors who presented with hypercalcemia and recurrent VTE, there was a high suspicion of cancer. Cancer increases the risk for thrombotic events through activation of clotting by tumor cells, endothelial injury, and stasis. Upon pooling the results of multiple retrospective studies, the odds ratio for newly diagnosed malignancy in patients with VTE as compared to those without VTE is 2.09 (95% CI 1.72-2.54).⁹ The odds ratio for newly diagnosed malignancy in idiopathic VTE compared with secondary VTE is even higher, OR 4.81 (95% CI 3.45 to 6.72).⁹ The greatest risk for cancer is seen in those with recurrent VTE such as this patient.

Large retrospective studies have determined that cancers of the pancreas, liver, ovary, and brain are most strongly associated with VTE. These tumors lack obvious early presenting signs, and are often discovered at later stages. This patient with cholangiocarcinoma presented at an advanced stage with VTE being one of his presenting signs.

Although a relationship between VTE and cancer has been clearly demonstrated, deciding whether to screen for cancer in a patient who presents with DVT remains a controversial issue. Studies show that most patients presenting with DVT who are eventually diagnosed with cancer, had occult tumors at the time of presentation.⁹ Thus, thorough screening could potentially lead to earlier detection and outcomes that are more favorable.

An optimal cancer screening protocol in thrombophilia patients should include three principles. First, the examination should avoid causing further harm, discomfort or psychological stress. Invasive tests should be postponed in the acute setting while patients are anticoagulated to avoid bleeding complications. Second, screening tests should yield results that could potentially change the natural history of the disease. Unfortunately, for some of the common cancers associated with VTE including tumors of the pancreas and liver, early detection does not necessarily change prognosis. In addition, in one large cohort study with over 26,000 patients with VTE, 40% of patients who were also found to have a malignancy had distant metastases and 25% had regional spread.¹⁰ Therefore, a majority of the study patients presented with advanced disease, and diagnosis at time of VTE event was unlikely to alter prognosis. Third, the screening protocol should be cost-effective. Because malignancy is a relatively rare cause of thrombophilia, it may not be cost-effective to perform an extensive cancer screening on each

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(benzoyl peroxide)

Rx Only

DESCRIPTION: TRIAZ[®] (benzoyl peroxide) 9% Gel and TRIAZ[®] (benzoyl peroxide) 9% Cleanser are topical, gel-based, benzoyl peroxide containing preparations for use in the treatment of acne vulgaris. Benzoyl peroxide is an oxidizing agent that possesses antibacterial properties and is classified as a keratolytic. Benzoyl peroxide (C₁₄H₁₀O₂) is represented by the following chemical structure:



TRIAZ 9% Gel contains Benzoyl Peroxide 9% as the active ingredient in a gel-based formulation consisting of: Purified Water USP, C12-15 Alkyl Benzoate, Glycerin USP, Cetyl Stearyl Alcohol, Glycolic Acid, Polyacrylamide (and) C13-14 Isoparaffin (and) Laureth-7, Glyceryl Stearate (and) PEG-100 Stearate, Steareth S-2, Sodium Hydroxide, Steareth S-20, Dimethicone 200, Zinc Lactate, Disodium EDTA.

TRIAZ 9% Cleanser contains Benzoyl Peroxide 9% as the active ingredient in a vehicle consisting of: Glycerin USP, White Petrolatum USP, C12-15 Alkyl Benzoate, Sodium Cocoyl Isethionate, Purified Water USP, Special Petrolatum Fraction, Sodium C14-16 Olefin Sulfonate, Zinc Lactate, Carboner, Potassium Polyphosphate, NF, Titanium Dioxide USP, Triethanolamine, NF, Glycolic Acid, Lavender Extract, Menthol Crystals USP.

CLINICAL PHARMACOLOGY: The mechanism of action of benzoyl peroxide is not totally understood but its antibacterial activity against *Propionibacterium acnes* is thought to be a major mode of action. In addition, patients treated with benzoyl peroxide show a reduction in lipids and free fatty acids, and mild desquamation (drying and peeling activity) with simultaneous reduction in comedones and acne lesions. Little is known about the percutaneous penetration, metabolism, and excretion of benzoyl peroxide, although it has been shown that benzoyl peroxide absorbed by the skin is metabolized to benzoic acid and then excreted as benzoate in the urine. There is no evidence of systemic toxicity caused by benzoyl peroxide in humans.

INDICATIONS AND USAGE: TRIAZ 9% Gel and TRIAZ 9% Cleanser are indicated for the topical treatment of acne vulgaris.

CONTRAINDICATIONS: These preparations are contraindicated in patients with a history of hypersensitivity to any of their components.

WARNINGS: When using this product, avoid unnecessary sun exposure and use a sunscreen.

PRECAUTIONS: General: For external use only. If severe irritation develops, discontinue use and institute appropriate therapy. After reaction clears, treatment may often be resumed with less frequent application. These preparations should not be used in or near the eyes or on mucous membranes.

Information for Patients: Avoid contact with eyes, eyelids, lips and mucous membranes. If accidental contact occurs, rinse with water. Contact with any colored material (including hair and fabric) may result in bleaching or discoloration. If excessive irritation develops, discontinue use and consult your physician.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Data from several studies employing a strain of mice that are highly susceptible to developing cancer suggest that benzoyl peroxide acts as a tumor promoter. The clinical significance of these findings to humans is unknown. Benzoyl peroxide has not been found to be mutagenic (Ames Test) and there are no published data indicating it impairs fertility.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with benzoyl peroxide. It is not known whether benzoyl peroxide can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Benzoyl peroxide should be used by a pregnant woman only if clearly needed. There are no available data on the effect of benzoyl peroxide on the later growth, development and functional maturation of the unborn child.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when benzoyl peroxide is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Allergic contact dermatitis and dryness have been reported with topical benzoyl peroxide therapy.

OVERDOSAGE: If excessive scaling, erythema or edema occurs, the use of these preparations should be discontinued. To hasten resolution of the adverse effects, cool compresses may be used. After symptoms and signs subside, a reduced dosage schedule may be cautiously tried if the reaction is judged to be due to excessive use and not allergenicity.

DOSAGE AND ADMINISTRATION: TRIAZ 9% Gel: Apply once or twice daily to cover affected areas, or as directed by your dermatologist. Use after washing with a mild cleanser, such as one of the TRIAZ Cleansers, and water.

TRIAZ 9% Cleanser: Wash affected areas once or twice daily, or as directed by your dermatologist. Avoid contact with eyes or mucous membranes. Wet skin and liberally apply to areas to be cleansed, massage gently into skin for 10-20 seconds working into a full lather, rinse thoroughly and pat dry. If drying occurs, it may be controlled by rinsing cleanser off sooner or using less often.

HOW SUPPLIED: TRIAZ 9% Gel - 1.5 oz. (42.5 g) tube, NDC 99207-207-01. **TRIAZ 9% Cleanser** - 6 oz. (170.3 g) tube, NDC 99207-208-12. **TRIAZ 9% Cleanser** - 12 oz. (340.2 g) bottle, NDC 99207-208-09.

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patient who presents with primary VTE. Thus, there are many obstacles to designing an ideal cancer screening program, and at this time, there is insufficient evidence to support screening all patients diagnosed with idiopathic VTEs. Further research involving prospective studies may help to resolve this controversy.

Conclusion

In conclusion, malignancy is part of the differential diagnosis of both hypercalcemia and thrombophilia. Cancer is the most common etiology of hypercalcemia among inpatients. It is important to recognize the nonspecific presenting complaints of a hypercalcemic patient, and to be familiar with the various treatments. Thrombophilia is also a complication of malignancy, and may be the presenting sign. However, screening all VTE patients for cancer remains controversial. Patients presenting with idiopathic VTE, recurrent VTE, or other signs of malignancy (such as hypercalcemia) are at higher risk for having an occult neoplasm. Further evaluation may be warranted in these patients.

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