

Quinine-Induced Thrombocytopenia in a 64-Year-Old Man Who Consumed Tonic Water to Relieve Nocturnal Leg Cramps

To the Editor: The addition of quinine to seltzer water to create tonic water probably dates from the days of the British Raj in India. The bitter flavor of quinine is appealing to some,¹ and quinine is consumed in tonic water, bitter lemon, and other beverages, either alone or mixed with an alcoholic drink. The medicinal properties of quinine have been touted to prevent a number of ailments ranging from fevers and malaria to atrial fibrillation. One presumed beneficial use of quinine is the treatment of nocturnal leg muscle cramps.²⁻⁷ This therapeutic effect is a possible result of hyperpolarization of myofibrils by activation of Ca⁺⁺-dependent K⁺ channels.⁸ Among the serious adverse effects of quinine is thrombocytopenia induced by the formation of antibodies for platelet membrane glycoproteins.⁹⁻¹² The following case of quinine-induced thrombocytopenia presented as bright red blood per rectum.

Report of a Case.—A 64-year-old man went to the emergency department with a 2-day history of rectal bleeding of bright red blood. He complained of loose stools with bright red blood approximately twice daily for 2 days. He had a history of drinking 1.9 L of tonic water daily for leg cramps for 2 to 3 weeks before admission. On some days, he drank up to 5 L of tonic water. He reported easy bruising and gingival bleeding for 2 weeks. Three weeks before admission he had pneumonia treated with clarithromycin. He denied abdominal pain, nausea, vomiting, and hematemesis.

On examination he was a slightly pale obese man in no acute respiratory distress. Vital signs were normal except for a heart rate of 107 beats/min. Ecchymoses were present on his arms. Gingival mucosa was friable but not hemorrhagic. Rectal examination revealed dark brown-black stool, which was positive for occult blood.

The initial laboratory findings included hemoglobin level, 12.4 g/dL; hematocrit reading, 36.7%; leukocyte count, $6.9 \times 10^9/L$; platelet count, $3 \times 10^9/L$; prothrombin time, 11.6 seconds; international normalized ratio, 0.9; and partial thromboplastin time, 21.2 seconds.

On the second hospital day, evaluation for quinine-induced platelet antibody determined that he was negative for drug-dependent antibody (IgG and IgM) and positive for non-drug-dependent antibody (IgG and IgM).

He was initially treated with intravenous methylprednisolone sodium succinate and platelet transfusions. Due to lack of initial response, he also received intravenous immunoglobulin for 2 days. He was transfused with 2 U of packed red blood cells when his hemoglobin level reached 7.7 g/dL. Lower gastrointestinal tract endoscopy revealed a mass at 20 cm from the anal ring and identified by histology as a villous adenoma. On his ninth hospital day, he underwent lower anterior sigmoid resection. When the patient was discharged 13 days after admission, his platelet count was $169 \times 10^9/L$, and his hemoglobin level was 9 g/dL. A regimen of prednisone, 30 mg by mouth daily, and ferrous sulfate, 325 mg by mouth twice daily, was prescribed when he was discharged.

Comment.—This case of quinine-induced thrombocytopenia presenting as bright red blood per rectum in a 64-year-old man with villous adenoma was precipitated by the voluminous consumption of tonic water for leg cramps for 2 or 3 weeks before admission. The presence of non-drug-dependent quinine-induced platelet antibodies without drug-dependent quinine-induced platelet antibodies is likely explained by the sensitization of the patient to metabolites of quinine.⁹ The onset of symptoms led to coincidental diagnosis and successful removal of the colonic tumor. This case illustrates the need to consider quinine-induced thrombocytopenia in the differential diagnosis of bright red blood per rectum.

This occurrence of rectal bleeding associated with ingestion of tonic water by a man with villous adenoma of the rectum suggests also that health warnings may be needed on bottles of tonic water, bitter lemon, and other quinine-containing beverages to prevent the morbidity and mortality sustained by susceptible individuals who consume them, unaware of the medical risks.¹³ Residents of the United States currently may not purchase quinine in the form of over-the-counter preparations dispensed without prescription. Due to the uncertain efficacy of quinine for muscle cramps,¹⁴ in 1995 the Food and Drug Administration restricted nonprescription availability of quinine to protect the public from the risks of exposure, including rash, pruritus, generalized anaphylaxis, urticaria, erythema multiforme, photosensitivity,² hepatitis,¹⁵ thrombocytopenia,^{3,6} hemolytic-uremic syndrome,^{3,16} neutropenia,¹⁷ disseminated intravascular coagulation,^{3,4} and coma.¹⁸ Nevertheless, anyone may freely purchase quinine in the form of tonic water, bitter lemon, and other beverages and in other preparations, including herbal and alternative treatments,⁶ commonly available in health food stores, supermarkets, and on the Internet.⁶

The estimate of 26 cases of acute thrombocytopenic purpura due to quinine or quinidine per million users is likely low because of underreporting.⁹ The proliferation of reports from many locations to confirm the occurrence of thrombocytopenia secondary to ingestion of quinine in tonic water suggests that the incidence of the condition is increasing.⁷

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Primary Esophageal Motility Disorders

To the Editor: We read with interest the concise review by Adler and Romero,¹ in which they provided an informative and useful guide to the diagnosis and management of esophageal motility disorders.

While the review extensively contrasts the salient features of achalasia, diffuse esophageal spasm (DES), and nutcracker esophagus (NE), some additional comments concerning NE seem to be warranted. This condition has proved difficult to categorize, with some investigators regarding it as a nonspecific esophageal motility disorder,² others combining it with DES under the category of spastic disorders of the esophagus,¹ and others, in recognition of features unique to the condition, preferring to allocate it a separate category.^{3,4}

Although notable similarities exist between NE and DES, which Adler and Romero have emphasized, important practical differences exist between them from a manometric perspective. The simultaneous contractions that typify DES are rarely present

continuously and therefore may only be detected, if at all, by prolonged ambulatory manometry. In contrast, the high-amplitude peristalsis in NE is often continuous and readily detected by stationary manometry.²⁻⁴ In addition, while chest pain is more prevalent than dysphagia in patients with NE, chest pain and dysphagia display similar prevalence in patients with DES.^{4,5} Thus, on balance, we would argue that it is useful to regard NE and DES as separate entities. While Adler and Romero rightly point out that current management options for NE and DES are essentially the same, a conceptual separation of the 2 conditions may facilitate future advances in therapy.

The authors claim that an elevated lower esophageal sphincter (LES) baseline pressure higher than 40 mm Hg is a minor diagnostic criterion for NE.¹ We believe the literature does not support this statement.²⁻⁴ In a recent study, 54 consecutive NE patients with chest pain, dysphagia, or, rarely, heartburn displayed a mean \pm SD LES pressure of 26 \pm 10 mm Hg, which was not significantly different from that of 61 asymptomatic healthy volunteers (22 \pm 7 mm Hg).³ A retrospective audit of the last 350 patients referred to our unit for esophageal manometry included 16 NE patients, with the diagnosis of NE based on a mean distal esophageal contractile amplitude higher than 180 mm Hg. These NE patients displayed a mean LES pressure of 16 \pm 7 mm Hg. In only 4 cases was the LES pressure 25 mm Hg or higher; the highest value was 28 mm Hg. There was no apparent association between distal contractile amplitude and LES pressure. Moreover, of 10 NE patients who also underwent ambulatory esophageal pH monitoring, 5 had an abnormally high esophageal acid exposure time. Coexistent gastroesophageal reflux disease and NE, which Adler and Romero discussed, would seem at odds with the concept of a considerably elevated LES baseline pressure.

We trust that these comments will help to amplify an otherwise excellent review of these complex issues.

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In reply: We appreciate the insightful comments by Hansen et al. In a sense, DES and NE are different entities because they are defined by different manometric criteria. Unfortunately, clear

pathophysiologic processes do not delineate these disorders. For these reasons, the esophagologist and physiologist should consider NE and DES distinct entities as they explore pathophysiologic mechanisms. From the perspective of the clinical gastroenterologist or internist, NE and DES may not appear as discrete clinical entities: they cannot be distinguished by their clinical presentations, and their treatments, although often inadequate, are essentially the same. Therefore, how we think about these disorders depends largely on our perspective. Whether NE is a distinct clinical entity, a nonspecific esophageal motility disorder, a spastic motility disorder, or simply a manifestation of gastroesophageal reflux disease will be known only when we understand its pathogenesis.^{1,2} Some data support the hypothesis that DES results from dysfunction of the inhibitory neuromuscular mechanisms of the esophagus.³ Furthermore, most clinicians who deal with esophageal motility disorders on a regular basis have seen achalasia develop from previously diagnosed DES, suggesting that these diseases are related.

We agree that the elevated baseline LES pressure (>40 mm Hg) reported in association with NE is not absolutely required for its diagnosis. An elevated baseline LES pressure is reported in conjunction with NE by some investigators,^{4,5} while others,⁶ including those cited by Hansen et al, did not note this finding. It may be best to think of it as we do the elevated LES pressure associated with achalasia: frequently present, but not a required criterion for the diagnosis.

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Multiple Aortic Thrombi and Protein C and S Deficiency

To the Editor: In the case report describing multiple aortic thrombi associated with protein C and S deficiency, Onwuanyi et al¹ imply that the described patient had congenital combined deficiency of proteins C and S and attribute the patient's thrombotic complications to the combined deficiencies. Table 1 indi-

cates that protein C activity was 48% (reference range, 60%-138%) and protein S activity less than 3% (reference, >60%).

Combined deficiency of proteins C and S is common on an acquired basis, for example, in association with oral anticoagulation therapy (eg, warfarin), but rare on a hereditary basis. Although congenital deficiencies of proteins C and S are pathogenetically linked to venous thromboembolism, the data implicating congenital or acquired deficiencies of protein C or S in the pathogenesis or risk of arterial thrombosis are controversial.^{2,3} In addition, undetectably low protein S activity in the described patient suggests the possibility of an interfering substance or condition affecting the protein S activity assay, such as heparin or warfarin effects, activated protein C resistance, lupus anticoagulant, or elevated factor VIII.^{4,5}

In our opinion, the following questions seem to be addressed inadequately in the article: (1) What is the evidence that this patient has hereditary deficiencies of proteins C and S? (2) Were there further evaluations of the activities and antigen levels of proteins C and S, particularly with respect to the apparently undetectable protein S activity and the possibility of interfering substances or acquired conditions?

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In reply: As stated in our case report, the association of deficiency of protein C, protein S, or the combination of proteins C and S with arterial thrombosis is rare. This deficiency state may be either acquired or hereditary.^{1,2}

On presentation to the hospital, the patient had a prothrombin time (PT) of 12.4 seconds (international normalized ratio [INR], 1.17), activated partial thromboplastin time (aPTT) of 21.9 seconds, and normal liver function. Two sets of coagulation studies were performed approximately 12 weeks apart. The initial test was done while the patient was receiving intravenous heparin, about 3 weeks after the thromboembolic event. The PT and aPTT were elevated. The functional protein C activity was 48% and functional protein S activity was less than 3%. The factor V

activity level and the homocysteine level were normal. Lupus anticoagulant antibody was negative, and the antithrombin III activity level was marginally reduced. The second test, which was performed 5 weeks after hospital discharge and while the patient was receiving warfarin, revealed normal factor V (103%) and antithrombin III (134%) activity levels with functional protein C activity of 46% and functional protein S activity of 11%. The PT was 14.8 seconds (INR, 1.64).

The coagulation study results are consistent with a reduction of protein C and S activity levels, even when the patient was not receiving warfarin. Protein C and S activity assays are affected by warfarin therapy but not heparin therapy.² Furthermore, at the time of both coagulation studies, there was no clinical evidence of acute thromboembolism, inflammatory process, acute illness, or trauma, and the test for lupus anticoagulant was negative, thus excluding these potential causes of protein C and S deficiency. Also, the patient had no history of alcoholism. Thus, the cause of protein C and S deficiency is probably not acquired.

A more rigorous evaluation of the coagulation system is required to establish a hereditary basis for protein C and S deficiency. However, in a patient in whom coagulation cannot be interrupted, the assay for several other clotting factors, particularly vitamin K-dependent factors, would also be affected by anticoagulation therapy.

Diagnosis ideally would require the coagulation studies to be repeated 2 weeks after cessation of anticoagulation or that such

studies be performed in close family members.² The first option was untenable because of the risk for thromboembolism in our patient. The latter was not possible because the patient was subsequently lost to follow-up.

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CORRECTION

Incorrect Function Sign: In the article by Palumbo entitled "Glycemic Control, Mealtime Glucose Excursions, and Diabetic Complications in Type 2 Diabetes Mellitus," published in the June 2001 issue of *Mayo Clinic Proceedings* (*Mayo Clin Proc.* 2001;76:609-618), an incorrect function sign appeared in the first line of the text in Table 1. The line should read as follows: "Fasting plasma glucose level \geq 126 mg/dL *or.*"

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