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Vitamin C Deficiency in an Anticoagulated Patient

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A 64-year-old woman presented with a hemorrhagic perifollicular rash on her legs while taking warfarin. After biopsy, vitamin C deficiency was suggested as the diagnosis, which ascorbic acid assays later confirmed. Clinical resolution of the rash followed supplementation with vitamin C. Patients on a vitamin K limited diet may also be limiting their intake of vitamin C. Physicians should be aware of this possible correlation, and consider checking vitamin C levels in patients with a perifollicular hemorrhagic rash or other signs of vitamin C deficiency while on warfarin.

KEY WORDS: scurvy; vitamin C deficiency; warfarin; vitamin K.
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CASE REPORT

A 64-year-old white woman presented with a rash on both upper legs. There was no pain, itching or history of trauma. She denied contact with plants or new soaps or lotions. Her other medical problems included early stage adenocarcinoma of the breast, recurrent venous thromboembolism, papillary thyroid cancer, and bronchiectasis due to recurrent methicillin-resistant Staphylococcus aureus (MRSA) pneumonia. Her physical exam was significant for a perifollicular hemorrhagic rash, which was confluent in some areas, on both upper anterior legs from the thighs to her knees. (Fig. 1). She was taking warfarin and her INR (International Normalized Ratio) was therapeutic at 2.2. Her platelet count was normal at 177 K/uL. She was referred to the dermatologist for suspected vasculitis. Punch biopsy revealed nonspecific superficial to deep perivascular inflammatory infiltrate with extravasation of blood consistent with vitamin C deficiency. A serum vitamin C level was found to be 0.1 mg/dl (normal values greater than 0.2 mg/dl). She was treated with a diet high in vitamin C rich foods and oral supplementation (500 mg/day), and the rash improved over a period of 2–3 weeks (Fig. 2). However, her INR 1 month after increasing the foods rich in vitamin C in her diet was 1.8 mg/dl, subtherapeutic, and required an adjustment in her warfarin dose. She was continued on vitamin C supplements indefinitely.

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DISCUSSION

Vitamin C deficiency is a rare disease in the US population, with a point prevalence of 3.6 % according to National Health and Nutrition Examination Survey (NHANES), which measured vitamin C levels in a multistage stratified sample of the U.S. population aged 6 to 150 years.[1] Apparent vitamin C deficiency occurs after 60–90 days of eating a diet entirely lacking in vitamin C.[2,3] Although apparent vitamin C deficiency is rare, latent deficiency, vitamin C deficiency without overt physical findings is thought to be more common, but often goes undiagnosed because of its vague symptoms and signs.[4]

Warfarin exhibits its effect through inhibition of vitamin K epoxide reductase, an essential enzyme in vitamin K metabolism.[5] Patients on warfarin are instructed to limit the intake of foods that provide more than 60 % of the Daily Value for vitamin K. They are given charts of foods that fall in this category to maintain the INR in the desired range. This is fairly complicated advice. In 2011, the National Institute of Health changed their dietary advice to patients taking warfarin to simply maintain a consistent intake of vitamin K rich foods in their diet.[6] Prior to the new recommendations, some patients would avoid vitamin K containing foods entirely, which exposed them to the risk of multiple vitamin deficiencies, given the concomitant restriction of other nutrients present in vitamin K-rich foods. Table 1 contains a list of foods showing their content of both vitamin C and vitamin K.[7]

Our patient has several other risk factors for vitamin C deficiency, including her age, malignancy, and iron deficiency. The Recommended Dietary Allowance (RDA) for vitamin C in non-smoking, non-pregnant, and non-lactating females above 19 years old is 75 mg.[8]

NHANES 2007–2008 data shows that among American males over age 20, the mean vitamin C intake is 91.3 mg, whereas females over age 20 have lower mean levels of 77.9 mg, only 2.9 mg over the RDA.[9] Teenage females have the lowest mean average intake (73.8 mg), followed closely by preadolescent females (75.4 mg) and women in their sixties (75.6 mg). In a 10-year study in a group of healthy aging elderly people in Italy, vitamin C deficiency rose from 3 % to 6 % in men and from 2.3 to 4.5 % in

Figure 1. Hemorrhagic perifollicular rash resembling vasculitis in anticoagulated patient.

Figure 2. The rash improved after treatment with vitamin C rich foods and oral supplementation.

women. The authors conclude that in spite of an adequate appearance of health, good functional status and an adequate caloric intake, a considerable proportion of successfully aging elderly are deficient in several essential vitamins, including vitamin C. The authors now recommend multivitamin supplementation even in the healthy elderly to protect against nutritional deficiency.[10]

Low plasma concentrations of vitamin C are also common in people with cancer.[11–14] A study of 50 advanced cancer patients in hospice found 30 % to be vitamin C deficient, correlating with dietary vitamin C intake and markers of the inflammatory response.[13] Other studies corroborate the relationship of low plasma vitamin C concentrations with elevation in inflammatory markers such as C Reactive Protein (CRP).[14] Vitamin C is an electron donor with a high concentration inside leukocytes, where it scavenges reactive oxygen species in response to infectious and inflammatory insults.[3] Vitamin C is proposed to have an anti-inflammatory effect due to the correlation of the deficiency with elevation in inflammatory markers, but the exact mechanism is unclear.[15] Another study of 57 cancer patients with adequate daily intake, but low serum vitamin C levels, proposed increased utilization of vitamin C, for example, to scavenge lipid peroxides, as well as vitamin C sequestration by tumor cells as possible causes of the deficiency.[16] Although our patient's history of early adenocarcinoma of the breast and papillary thyroid cancer can be considered risk factors, her cancers were successfully treated 8 years ago, and unlikely contributors to her current vitamin C deficiency.

The final risk factor for vitamin C deficiency in our patient is iron deficiency. She has been diagnosed with iron deficiency anemia confirmed by bone marrow biopsy. Her gastrointestinal work up revealed only some benign colon

Table 1. Foods With Both High Vitamin C and Vitamin K Content*

Food	Common measure	Content per measure of vitamin C in milligrams	Content per measure of vitamin K in micrograms
Broccoli, cooked	1 cup	101.2	220.1
Brussels sprouts	1 cup	96.7	218.0
Kale	1 cup	53.3	1,062.1
Turnip greens	1 cup	39.5	529.3
Mustard greens	1 cup	35.4	419.3
Collards	1 cup	34.6	836.0
Spinach, fresh, boiled	1 cup	17.6	888.5
Lettuce, green leaf	1 cup	5.2	70.7

USDA National Nutrient Database for Standard Reference, Release 24[7]

polyps, hemorrhoids, and gastritis. The intestinal absorption of vitamin C is regulated by at least one specific dose-dependent, sodium-dependent active transporter.[3,8] A recent finding is that iron is important for the absorption of ascorbic acid, as iron increases the expression of sodium-dependent vitamin C transporter 1 (SVCT1) in human intestinal Caco-2 cells. Iron deficiency may lead to lower expression of SVCT1, and therefore may be a risk factor to developing vitamin C deficiency.[17]

CONCLUSION

Although our patient has other risk factors for vitamin C deficiency, such as her age, a history of cancer, and iron deficiency, it is likely that dietary factors are responsible, given the overlap in foods containing both vitamin K and vitamin C. To the best of our knowledge, there are no other cases reported in the literature of vitamin C deficiency in patients on warfarin. However, this phenomenon may be overlooked, due to the high prevalence of hemorrhagic rash in patients on warfarin and the lack of overt clinical findings in most cases of latent vitamin C deficiency. Physicians should be aware of this possible correlation, and consider checking vitamin C levels in patients with a perifollicular pattern of hemorrhagic rash or other signs of vitamin C deficiency while on warfarin. Future study can determine the prevalence of vitamin C deficiency in patients on warfarin. Better dietary education is needed in patients taking warfarin, to ensure that their diet contains a minimum amount of foods rich in essential vitamins such as vitamin C. The change in dietary recommendation for a consistent vitamin K intake while on warfarin, rather than limiting vitamin K rich foods, may reduce the occurrence of other vitamin deficiencies in patients taking warfarin.

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Conflict of Interest: *The authors declare that they do not have a conflict of interest.*

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