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An Elderly Italian Nun with Presumed Vitamin K Deficiency Bleeding in a Rural Kenyan Hospital: A Narrative of the Potential Mechanisms

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Abstract: **Vitamin K deficiency is observed in 8% to 31% of healthy adults. The main diagnostic criteria for vitamin K deficiency bleeding (VKDB) is a prothrombin time (PT) that is ≥4 times elevated and which normalizes after administering vitamin K. This is in the context of risk factors for vitamin K deficiency (e.g., poor dietary intake, malabsorption syndromes, prolonged use of antibiotics, anticoagulants, etc.), bleeding diatheses, normal or increased platelets, and normal fibrinogen levels. In this report, an elderly Italian nun living in rural Kenya presented with a clinical picture in keeping with VKDB and was successfully managed with parenteral and oral vitamin K supplementation. A narrative on the potential etiology and mechanisms of her presentation has been put forward, including the contribution from her non-prescription topical medications.**

Keywords: **Vitamin K deficiency bleeding, VKDB, Vitamin K1, Vitamin K2, PIVKA-II, Kenya.**

1. INTRODUCTION

Vitamin K is a fat-soluble compound (together with vitamins A, D, and E) and belongs to a group of fat-soluble derivatives known as 2-methyl-1,4-naphthoquinones. It exists in 3 main isoforms: 2 primary forms, i.e., K1 (phylloquinone) and K2 (menaquinone), as well as a synthetic form, K3 (menadione), which is rarely in use due to associated toxicity in infants with glucose-6-phosphate dehydrogenase deficiency [1, 2]. K3 has since been replaced by a synthetic form of K1 called phytonadione. The primary source of K1 is green leafy vegetables, while K2 is found in fermented foods and is also synthesized by intestinal flora [1]. Vitamin K obtained from foodstuffs is absorbed in the jejunum and ileum, and in the presence of bile, pancreatic enzymes, and dietary fat, it is transported in chylomicrons into the circulation [3]. The recommended daily allowance for healthy adults of vitamin K is 120 µg/d for men and 90 µg/d for women [4]. Vitamin K is essential for the biosynthesis of prothrombin and clotting factors II, VII, IX, and X, as well as the activation of other proteins, e.g., anticoagulants C, S, and Z, osteocalcin, and matrix proteins. Vitamin K deficiency may lead to significant bleeding, osteomalacia, osteoporosis, and increased risks of cardiovascular disease [1]. Common causes of vitamin K deficiency include the consumption of insufficient vitamin K-rich foods (e.g., green leafy vegetables and fermented products), fat malabsorption states (e.g., inflammatory bowel diseases and celiac disease), prolonged use of antibiotics that disrupt the normal gut flora responsible for vitamin K synthesis, and medications that interfere with vitamin K metabolism (e.g., anticoagulants). Although vitamin K deficiency is observed in 8% to 31% of healthy adults, clinically significant

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bleeding occurs in persons with malabsorption syndromes, liver disease, or those receiving medications that interfere with vitamin K metabolism. Neonates have a deficiency of vitamin K at birth since vitamin K does not cross the placenta, hence the need for vitamin K injections within one hour after delivery to prevent vitamin K-deficient bleeding. The diagnosis of vitamin K deficiency in adults is established by a prolonged prothrombin time (PT) (and International Normalized Ratio, INR), which is corrected with vitamin K supplementation. See the diagnostic criteria in Table 1. The treatment of vitamin K deficiency in adults includes the administration of corrective oral (and parenteral) vitamin K at doses of 1 mg to a maximum of 25 mg. Several clinical society guidelines and protocols are available to this effect [4, 5].

Table 1: The diagnostic criteria for vitamin K deficiency bleeding: -

For a diagnosis of VKDB, you need these 2 criteria: -
1.PT that is ≥4 times the normal range and
2.The presence of 1 of the following conditions: ▪ Normal or increased platelet count. ▪ Normal fibrinogen and the absence of degradation products. ▪ PT returns to the normal range after administering vitamin K. ▪ Elevated levels of PIVKA-II.

Key: VKDB = vitamin K deficiency bleeding; PT = prothrombin time; PIVKA-II = protein induced by vitamin K absence; or antagonist-II.

2. CASE SUMMARY

A 76-year-old Italian nun who has lived in Kenya for the past 40 years first presented to us for evaluation of a 2-week history of prolonged bleeding after minor trauma. She had noticed excessive and prolonged bleeding after minor cuts on the fingers while gardening and working in the kitchen, despite applying direct pressure and using adhesive bandages (*Elastoplast*). She had no cardiovascular risk factors (apart from her age) and reportedly used "only paracetamol for pain, on and off." She denied using any other medications, e.g., warfarin, heparin, non-steroidal anti-inflammatory drugs, vitamin supplements, or any other prescription and non-prescription tablets or topical preparations. She had previous surgery for a right ovarian cyst and a cholecystectomy more than 30 years ago. Presently, she denied any recent acute illness, jaundice, dyspepsia, prior blood transfusions, tattoos, or any personal and family history of bleeding diatheses like hematemesis, melena stool, bleeding gums, hematuria, etc. She had no other clinical concerns. On physical examination, she was in good general health with normal vital signs. Her skin examination showed multiple bruises, petechiae, and ecchymoses distributed predominantly on both hands and arms, buttocks, and feet (on pressure points). There were two non-bleeding superficial lacerations on the left index finger with an adhesive bandage applied. The oral and buccal mucosae were normal. She had no stigmata of chronic liver disease. The systemic examination was unremarkable. Her important work-up showed a normal complete blood count with a hemoglobin of 12.4 g/dl and a platelet count of 436 $x10^3$/µL, a negative serology panel for hepatitis B and C, HIV, and syphilis, a normal blood sugar, and normal renal function tests. She had a negative blood slide for malaria parasites. Her liver panel showed normal transaminases, alkaline phosphatase, and bilirubin, but an elevated prothrombin test with an INR of 1.7 (a normal value is <1.1). An abdomino-pelvic ultrasound was normal. In light of her elevated INR and prolonged bleeding, we assessed her to most likely have some form of liver dysfunction leading to vitamin K deficiency-related bleeding. This was most likely caused by drugs that she had unknowingly used or was using presently, as well as a possible vitamin K deficient diet (she reported a vegetable and dairy product-deficient diet in the last 3-4 months) or malabsorption (even though she denied a history of bloating, diarrhea, or constipation). We therefore treated her with intravenous vitamin K 10 mg daily for 3 days as an outpatient (the vitamin K preparation available comes as 10 mg per vial). By the third day of treatment, the subcutaneous bleeding had completely subsided. She re-presented 5 days later with recurrent mild ecchymoses on both hands and a repeat INR of 1.8! In this second visit, her niece was called telephonically, who revealed that for several months the patient had been using some branded analgesics and ointments she obtained from Italy, which the patient brought to the clinic. These included *Aulin* tablets (containing nimesulide), *Eparina 1000* lotion (containing heparin), and *Ketoprofene* ointment (containing ketoprofen). These were assessed as directly contributing to the bleeding disorder and were immediately withdrawn. The patient also revealed that during a visit to Italy

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4 weeks prior, she had been treated for pneumonia with "strong antibiotics" for about 7 days. About a week later, she was also treated for severe watery diarrhea with another 5 or 6 days of antibiotics. She did not know the names of the antibiotics. We subsequently put her on oral vitamin K-containing capsules (dispensed as *Nature's Aid Vitamin K2 and Vitamin D3*), given as 1 capsule daily for 30 days. We reviewed her 2 weeks after starting the oral vitamin K, at which point all the ecchymoses had subsided and the repeat INR was normal at 0.8. At the end of the 30 days, the INR was still normal at 0.9 and has remained so in her subsequent follow-up visits. Presently, she's eagerly consuming a diet rich in green vegetables, fruits, and dairy products. She has since gotten a tooth extraction (long after the vitamin K supplements) without any bleeding complications.

3. DISCUSSION

Our patient most likely had a form of VKDB on the basis of a prolonged PT and INR (although her INR was not elevated to ≥4 times the normal range), a normal platelet count, and the normalization of the PT/INR following the administration of vitamin K, with the complete cessation of bleeding [1]. Her prolonged INR in the face of subcutaneous bleeding was in keeping with a vitamin K-deficient coagulation dysfunction. This was therapeutically proven with the cessation of such bleeding following the intravenous and oral administration of supplemental vitamin K and the full correction of the prolonged INR. Ideally, in VKDB, the PT/INR should correct within 30 minutes of intravenously administered vitamin K [1]. The direct measurement of vitamin K levels is often expensive, unreliable, and impractical for clinical use. Indirect measurements are employed, including the serum elevation of protein induced by vitamin K absence or antagonist-II (PIVKA-II) [6, 7]. In our low-resource setting, it was not logistically possible to test this. We propose the following possible etiologies and mechanisms for the VKDB in her:

Firstly, insufficient dietary intake of vitamin K-containing foodstuffs: The primary sources of natural vitamin K are green leafy vegetables and fermented dairy products. Due to a prevailing drought in the preceding 4-6 months in her area of current residence, our patient had largely been consuming cereals and legumes, e.g., rice, maize, beans, green grams, soya, etc. She reported very little consumption of green vegetables and no dairy products in the preceding 3-4 months. She had no history of lactose intolerance. This poor dietary intake may have contributed to the VKDB. Secondly, the use of antibiotics to treat her pneumonia and a diarrheal illness in Italy could have eliminated the commensal gut bacteria responsible for the synthesis of vitamin K. The occurrence of a watery diarrheal illness soon after a course of antibiotics in such an elderly person highly suggests an episode of antibiotic-associated diarrhea due to the iatrogenic elimination of normal gut flora by the antibiotics, whose gut flora would also be responsible for vitamin K2 synthesis. Thirdly, her use of nimesulide (*Aulin*) tablets and ketoprofen ointment (both NSAIDS) for osteoarthritis pains and heparin (*Eparina 1000*) lotion to treat her "dry skin" condition most likely worsened (rather than directly causing) the VKDB. Heparin is an anticoagulant. Heparin lotion is widely used to treat dry skin, thrombophlebitis, pain, and inflammatory diseases caused by vascular insufficiency, etc. Its main complication is varying degrees of bleeding, which could have worsened the VKDB [8]. Nimesulide has widely been reported to cause clinically significant hepatotoxicity, leading to its withdrawal from several countries [9]. In an Italian case-control study, nimesulide was associated with the highest risk, while high doses of systemic ketoprofen were associated with a modest risk of hepatotoxicity among various NSAIDS [10]. Nimesulide-associated hepatotoxicity is a form of drug-induced liver injury (DILI), predominantly affecting women, and presenting mainly with hepatocellular (with moderate to severely elevated transaminases), mixed, or cholestatic (only mild-moderately elevated alkaline phosphatase) patterns of liver dysfunction [11]. The mechanism of hepatotoxicity is most likely an idiosyncratic reaction to one of its intermediate metabolites, and patients may present with various degrees of bleeding [12, 13]. In her case, her transaminases, alkaline phosphatase, and bilirubin levels were normal. An important learning point to note is that elderly patients may be using multiple prescription and over-the-counter non-prescription oral and topical drugs (i.e., polypharmacy), which may contribute to their presenting clinical symptomatology [14]. These must be actively elicited during clinical encounters, including the use of collateral histories from family members and the physical inspection of all their prescription and non-prescription drugs during clinic visits.

4. CONCLUSION

A diagnosis of VKDB should be sought and managed in older adults presenting with risk factors for vitamin K deficiency, bleeding diatheses, and an elevated PT/INR, which can be corrected with vitamin K supplementation. Several mechanisms may explain the etiology of the vitamin K deficiency, including poor dietary intake, use of anticoagulants, etc. Due to a

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common tendency towards polypharmacy, older adults presenting with bleeding diatheses must have a comprehensive review of all prescription and non-prescription drugs, including topical preparations, as some of these could be contributing to the bleeding.

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INFORMED CONSENT

Informed consent was obtained from the patient to publish this case study.

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