CASE REPORT

Gastrointestinal bleeding secondary to trimethoprim-sulfamethoxazole-induced vitamin K deficiency

Azadeh Fotouhie, Hem Desai, Skye King, Nour Alhoda Parsa

SUMMARY

There is a well-known association between vitamin K deficiency and haemorrhagic events including gastrointestinal bleeding. There is also a well-known association between both poor dietary intake of vitamin K and chronic antibiotic use and the development of vitamin K deficiency. Although the medical literature notes that cephalosporin antibiotics have a propensity to cause vitamin K deficiency due to the molecular structure of the medications and their ability to suppress the synthesis of clotting factors, there are other antibiotics that have also been implicated in the development of vitamin K deficiency. There are very few reports of trimethoprim/sulfamethoxazole causing vitamin K deficiency and further leading to bleeding episodes. We present such a case and discuss the risk factors leading to such complications.

BACKGROUND

Among the spectrum of factors that can predispose a patient to developing gastrointestinal (GI) bleeding, vitamin K deficiency is a well-known culprit. Deficiency of this vitamin results in a decreased synthesis of essential clotting factors in the liver and hence creates a hypoprothrombinemic state, placing the affected patient at risk for developing haemorrhagic complications.1 2 A number of risk factors for vitamin K deficiency have been studied, including but not limited to poor dietary intake of the form of vitamin K known as phylloquinone and the disruption of the form of vitamin K produced by certain bacterial species in the GI tract, known as menaquinone, via chronic antibiotic use.3 5

There is a well-documented association between the chronic use of certain antibiotics and the development of haemorrhagic events secondary to vitamin K deficiency, specifically those from the cephalosporin class. Although the incidence of bleeding associated with the chronic use of different antibiotics has not been extensively documented, studies show that the incidence of bleeding associated with chronic cephalosporin use ranges from 2.2% to 19%, while the incidence of bleeding associated with other antibiotics ranges from 0% to 4%.3 6 This reports illustrates a rare case of a patient who developed GI bleeding secondary to vitamin K deficiency from chronic trimethoprim/sulfamethoxazole (TMP/SMX) use.

CASE PRESENTATION

A 52-year-old man with a history of B cell acute lymphoblastic leukaemia status postchemotherapy several years ago presented to the hospital because of a 1-day history of bright red blood that he noticed in his stool. On initial evaluation, he was found to be haemodynamically stable and his clinical examination was unremarkable, with a rectal examination negative for external haemorrhoids, anal fissures, or palpable masses. The rectal examination only revealed a small amount of bright red blood. Laboratory analyses showed normal haemoglobin, haematocrit and platelet counts, and normal liver function tests. Partial thromboplastin time was greater than 200 seconds, prothrombin time was 32.5 seconds, bleeding time was normal and an international normalised ratio (INR) was 3.2. Further history revealed no prior history of GI bleeds, a diet limited to cheeseburgers and fried chicken, with very little intake of green leafy vegetables and daily TMP/SMX prophylactically for the past several months in the setting of bacterial infections due to neutropenia. No invasive procedures, including a sigmoidoscopy and colonoscopy, were performed emergently after discussion with a gastroenterologist, as the patient had no further episodes of active bleeding and he remained haemodynamically stable. Laboratory studies were repeated and he continued to have an elevated INR level. Extensive infectious work up was negative for any pathogens.

DIFFERENTIAL DIAGNOSIS

Potential causes of GI bleeding in a patient without a prior history of bowel disease or chronic liver disease in conjunction with an elevated INR include:

▶ Vitamin K deficiency due to poor dietary intake;
▶ Vitamin K deficiency due to chronic antibiotic use.

OUTCOME AND FOLLOW-UP

The patient was treated empirically for a possible vitamin K deficiency. A 10 mg dose of vitamin K was given orally to the patient and over the next day his INR had improved to 1.0 and he did not have any episodes of melena or bright red blood per rectum for the remainder of the hospitalisation. A nutritionist was consulted and the patient was thus educated on improved dietary intake of foods rich in vitamin K, including green leafy vegetables. There was no further need for continued vitamin K
supplementation as his INR had normalised and remained within normal range for the remainder of the hospitalisation. Prior to discharge, the patient was having normal bowel movements. He was discharged in stable condition 2 days later and underwent a colonoscopy 2 months later, revealing normal colonic mucosa without any abnormal findings.

**DISCUSSION**

There are several risk factors and aetiological entities underlying GI bleeding. One such underlying aetiology is deficiency of vitamin K. The integral role of vitamin K in maintaining coagulation homeostasis is well known. Vitamin K is an essential component in the synthetic process of clotting factors II, VII, IX and X, and deficiency of this vitamin leads to a hypoprothrombinemic state. This, in turn, increases susceptibility to haemorrhagic events and renders the GI mucosa more prone to bleeding from minor insults.  

There are two types of vitamin K: phylloquinone, which is generally obtained through dietary intake of green leafy vegetables, and menaquinone, which is synthesised by certain bacterial species and serves as a constituent of the cell membrane in these species. Vitamin K deficiency can occur as a result of several risk factors including dietary deficiency of phylloquinone, a decrease in the synthesis of menaquinone through modification or eradication of normal gut flora via chronic antibiotics, malabsorption, or medications such as warfarin, which competitively inhibit the action of vitamin K.  

Several studies have been conducted to further elucidate the association between some of the risk factors for vitamin K deficiency, specifically poor dietary intake and chronic antibiotic use, and the incidence of developing a hypoprothrombinemic state and experiencing a bleeding event. These studies attempted to induce a hypoprothrombinemic state in participants by either strictly reducing dietary intake of phylloquinone or by essentially sterilizing or strictly altering bowel flora with the use of antibiotics known to destroy menaquinone-producing bacteria. None of these studies were successful in inducing hypoprothrombinemia by creating one of the two aforementioned risk factors. However, studies conducted on patients with already poor dietary intake of vitamin K or malabsorption leading to vitamin K deficiency showed that the use of antibiotics suppressing bowel flora placed them in a hypoprothrombinemic state and increased the incidence of haemorrhagic complications. This suggests that the patient’s underlying vitamin K status with concomitant risk factors determines the likelihood of coagulation abnormalities and bleeding.  

Interestingly, there appears to be a common and well-known association between the chronic use of cephalosporin antibiotics and vitamin K deficiency due to the N-methylthioisotetrazole (NMTT) ring structure found in cephalosporin antibiotics. This structure has the ability to directly inhibit the synthesis of vitamin K-dependent clotting factors. The incidence of bleeding associated with NMTT-containing antibiotics was shown to range from 2.2% to 19% while the incidence of bleeding associated with non-NMTT containing antibiotics such as TMP/SMX was shown to range from 0% to 4%.  

Our case illustrates a patient who most likely developed a vitamin K deficiency secondary to poor oral intake of dietary vitamin K or phylloquinone as evidenced by his history, compounded by decreased synthesis of menaquinone due to the chronic use of TMP/SMX, the only antibiotic he was using. Vitamin K deficiency is primarily known to cause ecchymosis and petechiae, however, it is also associated with spontaneous mucosal bleeding, as was present in our case. The diagnosis is supported by the normalisation of the INR after a single dose of vitamin K during his hospital course without any further episodes of active bleeding. The onset of action of vitamin K is ~12 hours; there are no clear guidelines on the treatment of vitamin K deficiency and studies focus on correction of the INR in warfarin-induced vitamin K deficiency. After a single oral dose of vitamin K, our patient’s INR normalised and remained within normal limits for the duration of the hospitalisation. Additionally, he planned to adhere strictly to the dietary advice given by the nutritionist. Close outpatient follow-up was arranged prior to discharge and on further visits he denied GI bleeding, bruising, or easy bleeding. He had significantly altered his diet as well. This case illustrates the importance of realising that although the epidemiology shows how rare it is, GI bleeding secondary to vitamin K deficiency caused by the chronic use of non-cephalosporin (non-NMTT-containing) antibiotics can happen in patients already at risk for developing this. It is important to assess dietary habits in addition to considering possible vitamin K supplementation for those at risk prior to initiating chronic antibiotic regimens.

**Learning points**

- **Treatment with antibiotics, including trimethoprim/sulfamethoxazole and cephalosporins, should be remembered as potential causes of vitamin K deficiency.**
- **Consideration should be given to monitoring the international normalised ratio in patients on antibiotics if there are other factors that may predispose to vitamin K deficiency, including poor dietary intake of green leafy vegetables, a history of malabsorption, or chronic liver disease.**

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**REFERENCES**

Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

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