Unusual manifestation of vitamin A deficiency presenting with generalized xerosis without night blindness

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Key Clinical Message
Vitamin A deficiency from malabsorption syndromes, including bariatric surgery, has become an emerging problem in developed countries. Early detection and prompt treatment lead to rapid and complete recovery. Nevertheless, it may result in irreversible blindness or death if left untreated. Health care personnel should be aware of this condition.

Keywords
Malnutrition, night blindness, protein-calories malnutrition, short bowel syndrome, vitamin A, vitamin A deficiency.

Introduction
A 32-year-old woman with a 1-year history of short bowel syndrome (SBS) presented with unusual manifestation of vitamin A deficiency. Four weeks prior to admission, she had generalized faint erythematous scaly patches mainly located on the proximal region of both arms, the shoulders and the upper back, but no typical ophthalmic manifestation of vitamin A deficiency. She had been suffering from SBS due to massive small bowel resection and had developed chronic diarrhea and significant weight loss during the prior 10 months. Unfortunately, total parenteral nutrition was not provided. Upon arrival, the patient had clinical signs of volume depletion and had multiple electrolyte abnormalities. Serum retinol level was extremely low; thus, a diagnosis of vitamin A deficiency due to fat malabsorption and inadequate treatment of SBS was made. After total parenteral nutrition and high-dose intravenous vitamin A was administered, all cutaneous lesions were dramatically resolved and complete recovery was achieved within a 1-week period.

Vitamin A is a fat-soluble vitamin, absorbed through the small intestine, which is required for the visual cycle, immune function, and cell and tissue differentiation. Vitamin A deficiency (VAD) has been recognized as one of the most important undernutrition problems worldwide. The problem is significant, particularly in children and pregnant women. Inadequate vitamin A intake is a major cause of vitamin A deficiency in the developing world, while fat malabsorption after intestinal resection
and intestinal bypass, particularly bariatric surgery, has become a rare but emerging cause of VAD in developed nations. Classic symptoms of VAD are ocular manifestations, including reversible night blindness, conjunctival and corneal xerosis, and keratomalacia, which can result in permanent blindness. Previous studies [1, 2] of VAD in patients with SBS reported classic ocular symptoms.

We here described an unusual manifestation of severe VAD presenting with generalized xerosis and desquamation without ophthalmic symptoms as a consequence of inadequate treatment of SBS. Fortunately, 1 week after vitamin A supplementation, all cutaneous lesions had dramatically resolved.

Case Presentation

A 32-year-old female patient with a 1-year history of SBS presented to the Home Parenteral Nutrition (HPN) Referral Center at Ramathibodi Hospital, Mahidol University (Bangkok, Thailand), with complaints of increased diarrhea, weight loss, and lethargy. She had been suffering with SBS following extensive small bowel resection 1 year previously and had then developed chronic diarrhea, steatorrhea, and significant weight loss during the prior 10 months as a consequence of severe malabsorption from SBS. Unfortunately, total parenteral nutrition was not available; thus, she developed severe malnutrition.

The patient had been in her usual state of health until 1 year earlier when she developed acute onset with worsening abdominal pain and then was diagnosed with superior mesenteric vein (SMV) thrombosis and massive small bowel infarction and gangrene. She also had splenic vein thrombosis and portal vein thrombosis with portal hypertension. Exploratory laparotomy with extensive small bowel resection with duodenal-ileal anastomosis was performed. The remaining small bowel was duodenum and only 10 cm of the terminal ileum, with intact ileocecal valve and colon continuity. The cause of SMV, splenic vein, and portal vein thrombosis was extensively investigated, revealing that the patient had a hypercoagulable state due to myeloproliferative neoplasms (positive for the JAK2 V617F mutation). Lifelong anticoagulant treatment was indicated, and the patient was prescribed enoxaparin subcutaneously. After surgery, her weight gradually decreased despite receiving oral nutrition support and multivitamin supplementation (including vitamin A, 5160 mcg retinol activity equivalent daily). Unfortunately, home parenteral nutrition was unavailable; therefore, malabsorptive symptoms, including chronic diarrhea and steatorrhea, gradually increased. The patient had experienced significant weight loss (from 65 kg to 33 kg) during the previous 6 months. Four weeks prior to admission she had developed generalized xerosis and faint erythematous scaly patches mainly located on the proximal region of both arms, the shoulders and the upper back (Fig. 1). Two weeks before admission the patient developed dehydration and fatigue and was admitted to a community hospital for 2 days. Intravenous (IV) glucose, vitamin B complex, and electrolyte infusion were administered in the hospital, after which she was referred to our HPN center for total parenteral nutrition support.

Upon arrival, she was cachexic and had clinical signs of volume depletion. Her temperature was 36.6°C, blood pressure 91/69 mm Hg, pulse 101 beats per min, and respiration 18 breaths per min. Her height and weight were 165 cm and 33.0 kg, respectively, with a body mass index of 12.0 kg/m². Dermatological examination revealed generalized xerosis with desquamation, especially on the shoulders, upper chest, and back. She had glossitis, severe subcutaneous fat depletion, and muscle wasting. She had no symptoms of night blindness, and an eye examination revealed the absence of xerophthalmia. She also had transverse white bands on all nails as well as sparse and dry hair, which were indicative of chronic protein-calories malnutrition. No palpable hyperkeratotic follicular papules were observed, and the remaining examinations were normal except for splenomegaly.

Investigations

Laboratory results revealed that the patient had multiple electrolyte abnormalities, including hypokalemia,
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hypocalcemia, hypophosphatemia, and hypomagnesemia. Her prothrombin time was prolonged, which was correctable with vitamin K supplementation, indicating that the patient had vitamin K deficiency. Her serum retinol level was 0.9 mcg/dL (reference range 20–50 mcg/dL) and vitamin D level was 16.3 ng/mL (reference range 20–100 ng/mL), indicating vitamin A and vitamin D deficiency. Serum vitamin E and serum triene/tetraene ratio, which are indicators of vitamin E level and essential fatty acid deficiency (EFAD), were within normal range. As she had received high-dose oral supplementation of water- and lipid-soluble vitamins prior to admission, the levels of serum thiamine, vitamin B-12, folate, and zinc were all normal.

Differential diagnosis

VAD was suspected to be the cause of generalized xerosis with desquamation, as the patient had chronic steatorrhea along with severe protein-calories malnutrition. Interestingly, she had no classic ocular symptom of night blindness, and an eye examination revealed no signs of xerophthalmia. Serum retinol level was extremely low, and vitamin A supplementation led to a dramatic response, which confirmed the diagnosis of VAD. The differential diagnosis of the cutaneous findings was essential fatty acid deficiency (EFAD). Her symptoms of generalized xerosis with desquamation and alopecia, along with a history of receiving parenteral glucose infusion without lipid emulsion in cachexic host, were compatible with EFAD. However, the serum triene/tetraene ratio was 0.14 (reference range <0.2); thus, we were able to exclude EFAD. There were no scaly erythematous patches on the perigenital and orogenital regions, so it was unlikely that this was a case of zinc deficiency. Additionally, serum zinc level was 115 mcg/dL (reference range 70–120 mcg/dL), which confirmed that the patient did not have zinc deficiency. Cutaneous findings included early features of exfoliative dermatitis, which can be caused by pre-existing skin diseases, drug allergy or cutaneous T-cell lymphoma. However, the complete resolution of generalized xerosis with desquamation after high-dose vitamin A infusion for 1 week supported a diagnosis of vitamin A deficiency-induced xerosis.

Treatment

After hospitalization, a central venous catheter was inserted. We provided empirical treatment of all suspected nutrient deficiencies on the day she was admitted, while all biochemistry tests were pending. Parenteral nutrition was provided, consisting of intravenous glucose, amino acids, lipid emulsion, multivitamin (Otsuka MV© injection), and trace elements (Addamel™ N, Halden, Norway). Calorie intake was gradually increased to avoid refeeding syndrome, and the caloric goal was achieved after 1 week. A vitamin A dose of 2000 mcg per day (the recommended parenteral vitamin A intake is 990 mcg/day [3]) was administered intravenously, resulting in dramatic improvement of skin signs over a 1-week period.

Results

A diagnosis of severe chronic disease-related malnutrition with VAD secondary to fat malabsorption was made. The patient’s skin rash resolved 1 week after receiving vitamin A supplementation.

Discussion

Our patient presented with isolated cutaneous manifestation of VAD, without classic ocular symptoms, as a consequence of inadequate treatment of SBS. Even though she received high-dose vitamin A supplementation orally, she developed VAD owing to fat malabsorption from SBS. The unusual manifestation of VAD, in this case, may be linked to the high-dose oral vitamin A supplementation, which probably alleviated the disease severity. She was treated with total parenteral nutrition and vitamin A supplementation at a dose of 2000 mcg per day. The patient’s recovery was dramatic; her skin lesions had completely disappeared 1 week after starting treatment.

Vitamin A is a fat-soluble vitamin which is important in retinal photoreceptor function, epithelial proliferation, and keratinization. Two important active metabolites are retinal, the active element of visual pigment, and retinoic acid, an intracellular messenger that modulates cell differentiation [4]. VAD can lead to serious systemic consequences, most commonly presenting with ophthalmic manifestations. Night blindness is considered one of the earliest and mildest symptoms of VAD. However, only a few studies have reported cases of VAD presenting with cutaneous manifestations [5, 6] without any ocular signs or symptoms. The cutaneous findings of VAD are the result of abnormal keratinization and can include follicular hyperkeratosis (phrynoderma), generalized xerosis, and sparse and/or dry hair [7]. Nevertheless, if vitamin A deficiency is suspected, the patients should be referred to an ophthalmologist for full ophthalmic evaluation to find out the evidence of xerophthalmia. Moreover, electroretinogram could provide additional valuable information to make appropriate diagnosis.

The most common cause of VAD in the developing world is insufficient nutrient intake due to malnutrition. However, in developed nations, VAD is commonly found in patients with a fat malabsorption state such as severe chronic liver disease, chronic pancreatitis, cystic fibrosis,
and SBS. In the modern era of bariatric surgery, malabsorptive procedures including intestinal bypass surgery have become an emerging cause of VAD [8–12] and other micronutrient deficiency syndromes. Interestingly, inappropriate intake, without any pathology, has been recently described as a cause of VAD in the developing country [13].

Earlier studies [1, 2] described cases of VAD in patients with SBS presenting with xerophthalmia. This is a reversible condition that responds promptly to vitamin A supplementation; however, if left untreated it may lead to permanent visual loss. A history of previous bowel resection, including cases of postbariatric surgery, should raise the possibility of inadequate absorption and storage of essential vitamins. Patients with fat malabsorption need to be screened regularly for micronutrient deficiency.

The recommended oral daily allowance (RDA) values for vitamin A in adults (at least 18 years of age) is 700 to 900 mcg retinol activity equivalent (RAE) for females and males, respectively [14]. Vitamin A is essential for prenatal and postnatal development; thus, pregnancy and lactation requirements are higher. However, vitamin A and other retinoids are teratogenic and can cause fetal malformation. The risk of birth defects is significantly higher in women who consume more than 3000 mcg per day [14]. Patients with any stage of xerophthalmia should receive treatment with 60 mg of vitamin A in oily solution orally; the same dose is repeated 1 and 14 days later. Doses should be reduced for patients <12 months of age. Pregnant women with night blindness or Bitot’s spots should be given vitamin A orally, but not exceeding 3000 mcg daily or 7500 mcg per week, for at least 4 weeks [15]. However, women of childbearing age who exhibit severe signs of xerophthalmia (e.g., acute corneal ulcer) should be treated with high-dose vitamin A supplementation [15]. It is necessary to balance the possible teratogenic effect against the serious consequences of VAD. Patients with malabsorptive diseases who have night blindness without other ocular changes should receive treatment for 1 month with 15 mg per day of a water-miscible preparation of vitamin A. This is followed by a lower maintenance dose, with the exact amount determined by monitoring serum retinol [16].

To the best of our knowledge, no dose recommendation has been made for treatment of vitamin A deficiency in patients with intestinal failure who require parenteral vitamin A administration. We treated the patient with total parenteral nutrition and vitamin A supplementation at a dose of 2000 mcg per day. Her skin lesions completely disappeared within 1 week after starting treatment.

The cause of VAD in this patient was a consequence of inadequate treatment of SBS. This refers to the malabsorptive state caused by physical or functional loss of significant portions of the small intestine [17], which results in malabsorption-induced diarrhea, dehydration, electrolyte disturbances, and malnutrition. The common causes in adults are physical losses usually resulting from extensive intestinal resection for a mesenteric vascular event, inflammatory bowel disease, trauma, malignancy, and complications from previous abdominal surgery [18]. Functional SBS is less common and may occur in cases when the intact small bowel is not adequately performing its digestive and absorptive function [19].

The normal small bowel length is estimated to be approximately 300–600 cm depending on how it was measured [20–22]. The duodenum length was around 25–30 cm and the length of the small intestine from ligament of Treitz to ileocecal junction is approximately 480 cm, with the proximal two-fifths being jejunum and the distal three-fifths being ileum [23]. It is generally accepted that to prevent dependence on total parenteral nutrition (TPN) the length of the remaining small intestine should be approximately 100 cm without colon continuity or 50 cm in the presence of a completely functional colon [24]. There have been a few reported cases of patients who were able to survive with TPN independence even though they had a small bowel remnant of less than 50 cm without an intact colon [25, 26]. In the case of our patient, home parenteral nutrition (HPN) was indicated, as she had undergone extensive small bowel resection and the remaining small bowel length was duodenum and 10 cm of the terminal ileum with intact ileocecal valve and colon continuity. Thus, she was discharged from the hospital with cyclic HPN (a total of 1630 kcal and 70 g protein per day intravenously over 16 h). Fortunately, after 6 months of HPN, we were able to wean the patient off parenteral nutrition after intensive nutritional counseling by a team of physicians, nurses, and dietitians. The patient has since performed well with her oral dietary intake, which consists of approximately 1800 kcal/day. The nutritional status of this patient returned completely to normal 6 months after her hospitalization at our center.

In conclusion, VAD is one of the most important undernutrition problems worldwide. Inadequate vitamin A intake is a major cause of VAD in the developing world, while fat malabsorption and bariatric surgery have become emerging causes of VAD in developed countries. The most common manifestations are nyctalopia (night blindness) and xerophthalmia, and it has been described in a number of patients with fat malabsorption. However, a patient can present with dermatological signs without ophthalmic manifestations. Early detection and prompt treatment of VAD leads to rapid and complete recovery. Nevertheless, VAD may result in irreversible blindness or death if left untreated. Hence, physicians, dietitians and
health care personnel should be aware of the possibility of fat-soluble vitamin deficiency, particularly vitamin A, in patients with fat malabsorption either from systemic diseases, SBS, or after bariatric surgery.

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Authorship

PP and PCS: conceived the study, treated the patient, and draft the manuscript. PC, PR, KJ, SK: treated the patient and revised the manuscript. DW: conceived the study, treated the patient, and revised the manuscript. All authors reviewed and approved the final manuscript before submission.

Conflict of Interests

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