Sailing the ship of life: scurvy and autoimmunity . . .

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***Abstract*:** Celiac disease (CD) is a multisystem disorder known to manifest in a multitude of ways to include diarrhea, anemia, and nutritional deficiencies. The malabsorptive state can present as certain classical conditions such as autoimmune gastritis and osteopenia/osteoporosis but scurvy is less recognized within the literature. In this case, we present a unique presentation of scurvy as a result of an undiagnosed CD.

Keywords: celiac disease, malabsorption, rheumatoid arthritis, scurvy, vitamin C deficiency

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Introduction

Consequences of nutritional deficiencies secondary to celiac disease (CD) are anemia, neurologic disorders, and osteopenia. Vitamin C deficiency (scurvy) secondary to CD is less well described. In the United States, ascorbic acid deficiency typically occurs in severely malnourished individuals with diets devoid of fruits and vegetables.[1] We report the challenge of diagnosing scurvy in a patient presenting with nonspecific constitutional symptoms, oral ulcers, and later perifollicular hemorrhage and easy bruising.

Case description

A 74-year-old Caucasian female presented with a history of acid reflux and irritable bowel syndrome who presented with a 3-month history of persistent, painful oral ulcers, and recurrent episodes of nonspecific arthralgias. Biopsies of the ulcers demonstrated ulcerated squamous mucosa with lichenoid inflammation. She had minimal relief with multiple recurrent oral and topical therapies. Given persistence of her oral ulcers she was referred to Rheumatology. An extensive rheumatologic workup demonstrated a positive 14.3.3 ETA protein suggesting rheumatoid arthritis (RA). Medrol dose pack with Certolizumab gave modest improvement, although her oral lesions persisted. Additional autoimmune testing demonstrated a positive anti-Gliadin and anti-tissue transglutaminase IgG after IgA antibodies were negative without any evidence of IgA deficiency. Multiple biopsies of the gastric antrum, small bowel, and colon demonstrated benign small bowel mucosa with normal architecture and were negative for changes of CD, *Helicobacter pylori*, and microscopic colitis. Genotyping demonstrated HLA DQ2/DQ8 positivity. She was initiated on a gluten-free diet with only modest improvement although her anti-tTG IgG antibodies became undetectable. She requested evaluated by Hematology/Oncology as part of her workup. Vitamin C level, along with other vitamin levels, was ordered. Vitamin C levels were undetectable. The diagnosis of scurvy was made and oral ascorbic acid was prescribed. Her levels remained persistently low and transitioned to intravenous (IV) vitamin C. Eventually the patient did respond to IV vitamin C, with a level back in the normal range about 2 months after the initial vitamin deficiency was identified in mid to late 2020. Clinical response was also noted with improvement in her oral ulcers, resolution of her petechiae, and modestly improved joint pain. She was able to eventually transition to oral high-dose vitamin C once more compliant with a gluten-free diet.

Discussion

CD is a common genetic disease which is becoming increasingly recognized within the literature due to more advanced diagnostic methods and awareness within the general population. It is a

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systemic disorder characterized by a hyperactive immune response against gluten in genetically susceptible individuals.[1] More than 95% of genetically susceptible individuals have an association with the major histocompatibility haplotypes HLA-DQ2 and DQ8 as seen in our patient.[1] The prevalence of CD is estimated to be 0.5–1% in certain areas of the world.[1,2] The pathogenesis of the disease is the trigger of the adaptive and innate immune systems resulting in both intestinal and extracellular manifestations.[2] According to international guidelines, the disease is typically diagnosed by a combination of serological tests for tissue transglutaminase or anti-endomysial antibodies along with histopathological findings of villous atrophy/crypt hyperplasia primarily in the duodenum and jejunum.[1–3] There is also the 'four out of five rule' whereby the presence of ⩾4 of the following may be sufficient for the diagnosis of CD: typical signs and symptoms such as diarrhea or malabsorption, CD-specific antibody positivity, HLA-DQ2 and/or HLA-DQ8 positivity, intestinal damage such as villous atrophy or clinical response to a gluten-free diet.[4] The most common clinical presentation of the disease is a malabsorptive clinical state but other nonspecific symptoms such as anemia, extreme fatigue, folate deficiency, or macrocytic anemia are also common.[2] However, over the last few decades, there have been documented cases of other nonclassical and unique presentations. Ciecierega *et al.*[5] documented a rare co-existence of Hartnup disease in the setting of CD secondary to combined deficiencies in amino acids and proteins. Mansueto *et al.*[6] reported a case of severe vitamin b12 deficiency resulting in multiple sclerosis like presentation secondary to underlying CD. A similar case of myelopathy was reported by Cavallieri *et al.*[7] when severe copper deficiency resulted in a subacute combined degeneration presentation. Ultimately histologic diagnosis combined with gluten-free diet and copper replacement resulted in cessation. Patel *et al.*[8] reported a possible link between celiac-linked anemia and dilated cardiomyopathy. Certain epidemiological studies have noted an increased risk of CD and heart disease with pathogenesis unknown at this time. However, a possible link may be nutritional deficiencies such as chronic anemia resulting in a hyperdynamic state and progression to cardiac failure. Hence, due to the chronic inflammatory state of the disease along with the malabsorptive component, it can be seen then how our patient was able to develop scurvy, a disease forgotten to the developed world.

Scurvy is one of the oldest documented disorders frequently seen with pirates and sailors due to the paucity of fresh fruits aboard their voyages.[9] After extensive trial and error by James Lind, it came to light that the underlying pathogenesis was that of reduced bioavailability of vitamin C[10] and he was able to identify citrus fruits as an effective therapy. Humans, unlike most mammals, do not have the ability to store or synthesize vitamin C; therefore, we are dependent on proper intake from fruits and vegetables.[9,10] Upon ingestion and proper breakdown, it is absorbed in the ileum and transported to the rest of the body to be utilized in collagen synthesis and elastic fiber stabilization.[10] Hence, this disease has since been almost unknown within the developed world. However, this disease remains frequent within the developing world.[11,12] The most common presentations are easy bruising and bleeding secondary to collagen degradation but other manifestations include normocytic normochromic anemia, pancytopenia, dermatologic manifestation with perifollicular petechiae, hemorrhagic nodules, and the classic 'corkscrew' hair follicles.[11,12] The diagnosis remains challenging due to the numerous manifestations of the disease but when suspected includes a thorough history and physical exam, followed by vitamin C measurement. Vitamin C measurement in either serum or urine can be used with accuracy, with a level below 0.25 mg/dL suggestive of scurvy.[13] Treatment consists of high doses of vitamin C up to 1 g initially followed by a maintenance dose.[13]

Our patient's symptoms presented us with many diagnostic challenges over the 9 months that she had her oral ulcers and other nonspecific symptoms, before her easy bruising and perifollicular hemorrhage occurred. Systemic autoimmunity was suspected early on, and when her 14.3.3 ETA protein test returned positive it was not completely clear that RA was responsible for all of her symptoms, although oral ulcers may occur from this illness. Her diagnosis of CD was also hindered by negative intestinal biopsies. The patient also had a notable psychiatric history with prior diagnoses of depression, anxiety, and recurrent panic attacks which may have served as a risk factor for vitamin C deficiency. It is likely that her CD and RA were largely responsible for her early symptoms, whereas later symptoms, to include easy bruising, were due to scurvy. Scurvy can mimic rheumatological disease especially when arthralgias, synovitis, or manifestations imitating

cutaneous vasculitis occur.[14] The overlap of CD, RA, and scurvy made this a very challenging case to diagnose and treat.

Conclusion

Scurvy is a relatively uncommon disease in the developed world but remains a crucial diagnosis to consider in the appropriate patient. It is essential for the practicing clinician to have a basic knowledge of the clinical signs and symptoms of the disease. Increasing cognizance of the disease will ultimately ameliorate and shorten the duration from diagnosis to treatment.

Authors' note

The views expressed are those of the authors and do not reflect the official policy or position of the US government, the Department of Defense, or the Department of the Air Force.

Author contributions

Essien Francis: Conceptualization; Data curation; Formal analysis; Investigation; Visualization; Writing – original draft; Writing – review & editing.
Jacocks Charles: Data curation; Investigation; Project administration; Writing – original draft; Writing – review & editing.
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Conflict of interest statement

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Ethical approval

Our study did not require formal approval from an IRB board because this was a case report.

Informed consent

Informed consent and consent to publish was obtained from the patient for this report.

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