CASE REPORTS/CLINICAL VIGNETTES

Coagulopathy Due to Celiac Disease Presenting as Intramuscular Hemorrhage

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INTRODUCTION: Celiac sprue most commonly presents with steatorrhea, abdominal pain, and weight loss. Celiac disease is now becoming more recognized for its atypical presentations. Anemia, osteoporosis, and childhood failure to thrive have been widely discussed.

OBJECTIVE: In this paper, we present a case of nontraumatic intramuscular hemorrhage associated with prolongation of both prothrombin time and activated partial thromboplastin time.

MAIN RESULTS: Coagulopathy, unmasked by the use of a nonsteroidal anti-inflammatory drug, was found to be attributable to vitamin K deficiency associated with malabsorption of multiple fat soluble vitamins. Celiac sprue was confirmed by small bowel biopsy. A review of the literature finds that, whereas asymptomatic prolongation of coagulation is relatively common in celiac sprue, clinical bleeding is a rare but described presentation.

CONCLUSION: This case emphasizes the importance of recognizing hemorrhage as an atypical manifestation of celiac disease and offers the opportunity to review the clinical and laboratory evaluation of a patient who presents with unexplained hemorrhage.

KEY WORDS: celiac disease; prothrombin time; vitamin K; blood coagulation disorders; hemorrhage.

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INTRODUCTION

Celiac disease is a common immune disorder that typically presents with gastrointestinal complaints including abdominal pain, diarrhea, and weight loss. It is estimated to have a prevalence in the United States and Europe of 1%.^{1,2} Recently, attention has been focused on the atypical presentations of celiac disease such as isolated anemia, osteoporosis, short stature, and peripheral neuropathy.³ Whereas these associated

findings of celiac disease have become more recognized, hemorrhagic presentations of celiac disease owing to coagulopathy are quite rare. This is a case report of severe intramuscular hemorrhage caused by vitamin K deficiency caused by previously undiagnosed celiac disease.

CASE REPORT

A 64-year-old White male with a history of chronic diarrhea but no prior bleeding problems presented to the emergency department for evaluation of multiple bruises and pain and swelling of his left arm over the last 24 hours. He had been prescribed naproxen for joint pain 2 days before presentation, and 1 day later he had spontaneous bleeding including epistaxis, periorbital ecchymosis, and left arm pain with progressive bruising and swelling. He took no other medicines. Significant prior history included bowel movements 5 to 6 times a day for 9 years. Colonoscopy done to evaluate this in the first year of symptoms was negative. At that time, he was also found to have anemia and hypocalcemia and was prescribed iron and calcium supplements. He also had a pruritic and vesicular rash on his abdomen for 1 year. Otherwise, personal and family histories were negative for hematologic, malabsorptive, or endocrinologic disorders.

On initial examination, the left forearm had superficial ecchymosis, which extended from the index finger to the mid upper arm. Repeat examination 4 hours later revealed diffuse tenseness to the left forearm compartments. At that time, the patient reported left forearm pain, but denied numbness, paresthesias, or inability to move the fingers. Temperature of the arm was noted to be normal. The left radial pulse was strong. Repeat examination also revealed ballotable fluid at the right elbow, ecchymosis under the right eye and at the right popliteal region, and petechiae on the right foot. Vital signs at that time were: temperature 96.5, blood pressure 97/63, heart rate 91, respiratory rate 18, and oxygen saturation 97% on room air. Computed tomography (CT) scan of the left arm revealed diffuse hemorrhage into the muscles of the upper arm and forearm (Fig. 1). Laboratory results yielded a prothrombin time (PT) of >200 seconds (normal 10–13) and an activated partial thromboplastin time (PTT) of 143 seconds (normal 23–32). Platelets were normal. Hemoglobin of 11.0 dropped to 8.4 g/dL over 20 hours. Quantitative warfarin level was zero. Salicylate level was normal. Fibrinogen level was 428 mg/dL (normal 204–493). PT and PTT inhibitor assays were normal.

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Figure 1. CT scan of arm hemorrhage. Findings: There is diffuse swelling of the soft tissues obliterating the normal muscle planes over the medial aspect of the arm, proximal to the elbow, extending to the forearm, along the anterior aspect, down to the wrist. Because of the patient’s inability to move this extremity, the precise anatomical location is difficult to establish. It appears to be a diffuse soft tissue inflammatory process, which obscures muscle borders, although it appears to predominantly spare the subcutaneous fat and may actually be within the muscles. Given the patient’s clinical history, this likely represents diffuse hemorrhage.

Bleeding time was normal. Given this patient’s worsening intramuscular hemorrhage and coagulopathy, he was treated with vitamin K 5 mg orally, FFP 6 units, and cryoprecipitate 4 units which led to resolution of bleeding. Clinical concern for the development of compartment syndrome was addressed in this case by correcting the underlying coagulopathy combined with serial examinations to monitor limb function. Interventional diagnosis or surgical treatment was averted. In further workup, ionized calcium was 0.85 mmol/L (normal 1.09–1.33). Albumin was 2.4 g/dL (normal 3.4–5.0). Transferrin was 154 mg/dL (normal 202–364). Parathyroid hormone was elevated at 444 pg/mL (normal 70–270). Vitamin D level returned <5 ng/mL (normal 20–100). Anti-transglutaminase IgA antibody was >105 U/mL (normal <5), anti gliadin IgG was >100 U/mL (normal <11), and IgA was 54 U/mL (normal <11). Interestingly, the patient also presented with a rash on his anterior abdomen that was composed of vesicles and papules, some of which contained small areas of hemorrhage. After correction of coagulopathy and hypocalcemia, the patient was discharged with normal coagulation studies and in good condition with a gluten-free diet, vitamin K, calcium, and vitamin-D supplementation. His vesicular dermatitis resolved in 1 week.

Table 1. Diseases Associated with Celiac Sprue

Diseases associated with celiac sprue
Dermatitis herpetiformis
Diabetes mellitus Type I
Autoimmune thyroiditis
Addison’s disease
Primary biliary cirrhosis
Autoimmune hepatitis
Sclerosing cholangitis
Sjogren’s syndrome
Hyposplenism
IgA nephropathy
Cerebellar ataxia
Migraine headaches
GI lymphoma or carcinoma
Turner’s/Down’s syndrome

Table 2. Manifestations of Celiac Sprue

Usual manifestations	Unusual presentations (described as “atypical” if gastrointestinal symptoms are silent)
Diarrhea	Recurrent abdominal pain without evidence of malabsorption
Steatorrhea	Elevated transaminases
Abdominal pain	Infertility
Iron deficiency anemia	Clinically significant bleeding caused by coagulopathy
Positive fecal occult blood test	Edema caused by low albumin
Weight loss (or failure to thrive in infants)	Peripheral neuropathy
Asymptomatic hypoproteinemias	Tetany
Hypoproteinemia	Fractures caused by osteomalacia
Folate deficiency	Neuropsychiatric symptoms
B12 deficiency	Seizures
Asymptomatic vitamin-D deficiency or hypocalcemia	

Outpatient esophagogastroduodenoscopy with duodenal biopsy was done 2 weeks after starting the gluten-free diet. It revealed paucity and scalloping of duodenal folds and a mosaic pattern and fissures of the mucosa. The histopathologic evaluation of distal duodenal biopsies showed near total villous atrophy with crypt hyperplasia and chronic inflammation with increased intraepithelial lymphocytes. These endoscopic and histologic findings are consistent with celiac disease.

Small bowel series almost 2 months into a gluten-free diet showed only slight irregularity of the mucosal pattern. At 4 months after starting the gluten-free diet, the patient’s bruising had resolved; stools also normalized in consistency and frequency. The patient gained 25 lbs. This patient’s malabsorption manifested as hemorrhage caused by vitamin-K deficiency, and his vesicular rash was clinically consistent with dermatitis herpetiformis. Both features are consistent with his biopsy-proven celiac sprue.

DISCUSSION

This case represents celiac disease presenting as frank hemorrhage from previously occult coagulopathy that was unmasked by the use of nonsteroidal anti-inflammatory medication. It reflects a rare manifestation of the disease.

The first challenge in this case was to identify the etiology of the bleeding diathesis. Bleeding can be seen from dysfunction of any part of the hemostatic balance including platelet plug formation, vascular integrity, coagulation factors, and fibrin deposition. The history and physical provide clues to the type of dysfunction. For instance, mucosal bleeding is more often seen in problems with the primary platelet plug in contrast to the joint and muscle bleeding seen in coagulation factor deficiencies. A prior personal or family history of bleeding with Surgery or dental work may suggest an underlying heritable cause. In our patient, the new onset of spontaneous bleeding as an adult suggested an acquired defect in the hemostatic pathway, and the deep muscle hemorrhage pointed toward dysfunction of coagulation factors.

Appropriate initial tests to guide evaluation include comprehensive blood count (CBC) with peripheral blood smear, prothrombin time (PT), partial thromboplastin time (PTT), and

Table 3. Manifestations of Coagulopathy in Patients with Biopsy-proven Celiac Disease

Manifestation of coagulopathy		Patient(s)	Relevant findings	Publication
Hematoma	Spontaneous bruising at venipuncture sites	9-mo-old female	Loose stools and vomiting 1.1-kg weight loss × 3 mo PT >5 min	Jones, 1973 ¹¹
	Hematomas at intravenous needle puncture sites	57-y-old female	Diarrhea × 2 mo Weight loss PT > 3× normal Hypocalcemia	Gerson, 1973 ¹²
	Bruising and large subcutaneous hematomas	9-mo-old female	Failure to thrive Greasy stools Decreased iron level PT prolonged	Rodesch, 1976 ⁸
	Spontaneous bruising of limbs and hematomas on legs	27-y-old female	Pale bulky stool 9.5-lb weight loss × 3 mo PT 120 Low concentration of Factors II, VII, and X Hypocalcemia	Graham, 1982 ¹³
	Multiple bruising on arms and legs and hematoma of foot	21-y-old female	PT 180 Low concentration of factors II, VII, and X Osteomalacia Increased fecal fat excretion Impaired xylose absorption	Graham, 1982 ¹³
	Ecchymotic lesions on extremities	68-y-old female	4-lb weight loss × 2 mo Hypocalcemia Deficiency of vitamin K-dependent clotting factors	Avery, 1996 ¹⁴
	Generalized bruising	32-y-old female	Diarrhea aPTT 94 s PT 86 s Vitamin A and E deficiency	Hussaini, 1999 ⁹
	Multiple hematomas and easy bruising	41-y-old male	3-4 lb wt loss × 3 mo Light color fatty stools 2-3 per day PT unclottable AptT 106 s Low concentrations of factors II, VII, IX, and X	Vaynshtein, 2004 ¹⁵
Hematuria	Gross hematuria	48-y-old female and 62-y-old female	Increased fecal fat Diarrhea with 5-6 light color, malodorous stools per day 23-lb wt loss × 1 y Hypocalcemia Increased fecal fat Decreased xylose absorption	Ross, 1966 ⁴
	Gross hematuria	57-y-old female	Diarrhea × 2 mo Weight loss PT >3× normal Hypocalcemia	Gerson, 1973 ¹²
	Hematuria	65-y-old female	INR>10 Subnormal fat absorption	Battacharyya, 1999 ¹⁶
	Macrohematuria	28-y-old male	Diarrhea × 15 d PT undetectable Hypocholesterolemia	Moussa, 2003 ¹⁷
Hemarthrosis	Hemarthrosis of the knee	21-y-old female	PT 180 Low concentration of factors II, VII, and X Osteomalacia Increased fecal fat excretion Impaired xylose absorption	Graham, 1982 ¹³
Intestinal bleed	Intramural intestinal bleed on laparotomy	57-y-old female	Diarrhea × 2 mo Weight loss PT >3× normal Hypocalcemia	Gerson, 1973 ¹²
	Free intraperitoneal blood and left mesocolonic hematoma on laparotomy	42-y-old male	INR 1.8 Abnormal xylose absorption	Cameron, 1998 ¹⁸
	Melena, ecchymoses, and hematomas	26-y-old male	PT 103 s aPTT 110vs Low concentration of factor V, slowly normalizing with gluten-free diet	Shanahan, 1983 ¹⁹

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Table 3. (continued)

Manifestation of coagulopathy		Patient(s)	Relevant findings	Publication
Retroperitoneal hemorrhage	Retroperitoneal hemorrhage on laparotomy	57-y-old female	Diarrhea × 2 mo Weight loss PT >3× normal Hypocalcemia	Gerson, 1973 ¹²
Intracranial hemorrhage	Cerebral intraparenchymal hemorrhage	4-y-old male	4–5 stools per day Less than 3% for height and weight PT 85 s aPTT 45 s	Rath, 2003 ²⁰

a bleeding time. A low platelet count will be present if there is a quantitative deficiency in this key mediator of the primary thrombus plug, whereas a prolonged bleeding time will suggest an impairment in platelet function. Either result would prompt further evaluation of the cause of the platelet abnormality. In the case of our patient, mild functional platelet impairment was suspected as a predictable consequence of the nonsteroidal anti-inflammatory drug's reversible inhibition of thromboxane A₂ production, but the severity of bleeding, normal bleeding time, and the presence of normal platelet count suggested dysfunction in another component of the hemostatic process.

Disseminated intravascular coagulation (DIC) results in imbalance between fibrin production and fibrinolysis. Typically such patients appear clinically ill, and testing reveals schistocytes, low fibrinogen level, and elevated fibrinogen degradation products. In this patient, the absence of systemic illness and normal fibrinogen level made DIC or vasculitis unlikely, and the prolongations of the PT and PTT quickly led to a diagnosis of coagulopathy.

Coagulopathy occurs when there is a deficiency in 1 or more of the coagulation factors or the presence of acquired inhibitors. A mixing study can be done to distinguish between factor deficiency and inhibitor presence. If an inhibitor is present, mixing plasma with the patient's blood does not result in correction of PT or PTT; as our patient's coagulopathy corrected with plasma, an inhibitor was not suspected. The prolongation of the PT indicates disorder of the extrinsic pathway of coagulation involving factor VII, whereas prolongation of the PTT suggests disorder of the intrinsic pathway, most commonly factor VIII or IX, and uncommonly deficiency in factor XI or XII. The abnormality of both the PT and PTT, as seen in our patient, leads to consideration of either abnormalities of multiple coagulation factors or less commonly a deficiency or inhibitor of the common pathway factors II, V, X, or fibrinogen. Multiple coagulation factor defects are seen in cases of vitamin-K deficiency, anticoagulant use, "super-warfarin" rodenticide ingestion, or liver disease. In all of these cases, the hepatic synthesis of factors II, VII, IX, and X from vitamin K is impaired.

In this patient's case, the elevation of both PT and PTT implied dysfunction of multiple coagulation factors, and the associated hypocalcemia suggested that the possible mechanism was via combined malabsorption of fat soluble vitamins K and D. This was consistent with his history of chronic diarrhea. Subsequent laboratory evaluation confirmed the vitamin deficiency, and this led to an evaluation for malabsorption, ultimately discovering celiac sprue.

Celiac disease presents in a multitude of ways reflecting the specific malabsorption of nutrients that becomes most deficient in each patient. This occurs because of an immune reaction to gliadin that is catalyzed by tissue transglutaminase. This

reaction attracts T cells to the intestinal mucosa, which causes villous atrophy and crypt hyperplasia. It is theorized that celiac disease may have an autoimmune component similar to other diseases such as type I diabetes mellitus or autoimmune thyroiditis (Table 1). These immune-mediated changes lead to malabsorption that can manifest in many organ systems.

Gastrointestinal manifestations comprise the majority of symptoms of celiac disease. The most common symptom is diarrhea, seen in 85% of patients with a diagnosis of sprue.⁴ Weight loss is also commonly seen with 57% of patients reporting a weight loss of 10 pounds or more.⁴ In children this may present as failure to thrive measured by weight or height.^{4,5} In some cases, the enteropathy can induce hypoalbuminemia sufficient to cause edema.^{4,6}

Endocrine effects may occur as a result of malabsorption of fat-soluble vitamins. Vitamin-D deficiency can induce hypocalcemia severe enough to create clinical signs and symptoms such as paresthesias, Chvostek and Trousseau's signs and, in some cases, even tetany.⁶ Some degree of hypocalcemia has been reported in 48% of patients with celiac disease, which in extreme cases can lead to secondary hyperparathyroidism and osteomalacia.^{4,5}

Hematologic effects include the common finding of anemia and the rare finding of symptomatic coagulopathy. Anemia is found in 43% of patients and may occur as a result of inadequate uptake of iron, folic acid, and more rarely vitamin B12.⁴ A second mechanism for anemia is occult gastrointestinal blood loss, which has been found in more than 50% of patients with total villous atrophy.⁷ Coagulopathy in celiac disease is thought to be caused by malabsorption of vitamin K. Phylloquinone, a form of vitamin K derived from green vegetables or vegetable oils, is normally absorbed in the small intestine.⁸ Deficiency may occur from inadequate intake, depletion of colonic flora, or malabsorption.⁹ In a study by Cavalloro, 18.5% of patients with celiac disease had an international normalized ratio (INR) greater than 1.4.¹⁰ Although gastrointestinal, endocrine, and hematologic abnormalities are most common in celiac disease, there are a myriad of other presentations, some well described and some newly reported (Table 2).

Vitamin K malabsorption leading to hemorrhage is an unusual presentation of celiac disease. However, varieties of coagulopathy have been detailed in the literature as early as 1960. Ecchymosis, hematoma, hematuria, intestinal bleed, retroperitoneal hemorrhage, cerebral intraparenchymal hemorrhage, and hemarthrosis are the current descriptions of bleeding seen with celiac disease (Table 3). The most common manifestation of bleeding from hypoprothrombinemia is ecchymosis.

Intramuscular bleeding severe enough to cause concern for compartment syndrome has not been previously described.

This patient's bleeding may have presented acutely because the coagulation defect was unmasked by the antiplatelet effect of the nonsteroidal anti-inflammatory drug. The chronic diarrhea that had not been diagnosed until this episode also assisted in narrowing the diagnosis. The clinical significance of this case lies in the consideration of celiac disease in patients who present with unexplained coagulopathy. The presence of abnormal tests of coagulation should prompt the clinician to consider any signs of malabsorption. This, along with an awareness of the associated diseases and protean manifestations of celiac sprue, can lead to earlier recognition of the diagnosis.

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CONFLICT OF INTEREST: Ethan Cumbler, M.D., served on a clinical advisory panel for ESP pharma in 2004 for antihypertensive therapy after stroke. The other authors reported no conflicts.

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