ACG CASE REPORTS JOURNAL

CASE REPORT | COLON

Gastrointestinal Manifestations of CLOVES Syndrome

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ABSTRACT

Congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and scoliosis/skeletal/spinal anomalies (CLOVES) is a recently recognized syndrome. It is caused by somatic mutations in the PIK3CA gene that regulates cell growth and division. Although gastrointestinal manifestations of other PIK3CA-associated disorders have been described, they have not been well-characterized in CLOVES syndrome. We present a case report of a 34-year-old man with an established diagnosis of CLOVES syndrome who underwent a diagnostic colonoscopy for hematochezia and colonic wall thickening on imaging. Colonoscopy revealed widespread variceal-like submucosal lesions. Computed tomography/angiography showed the absence of the inferior mesenteric vein, impairing venous drainage.

KEYWORDS: CLOVES; colonoscopy; bleeding

INTRODUCTION

The PIK3CA-related overgrowth spectrum (PROS) encompasses 13 distinct disorders characterized by somatic, noninherited mutations in the PIK3CA gene, which regulates cell growth and division.[1–3] Congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and scoliosis/skeletal/spinal anomalies (CLOVES) is a PROS-related syndrome first described in 2007.[4] The diagnosis of CLOVES is made clinically and supported by characteristic imaging findings. Genetic testing of affected tissue can confirm the diagnosis; however, a negative test cannot exclude the diagnosis given frequent mosaicism in expression of the mutation. Typical findings in patients with CLOVES include fatty truncal masses, lymphovascular anomalies, abnormal extremities, skin abnormalities, and other issues ranging from small or absent kidneys to abnormal joints or scoliosis.[4,5] Complications can arise including consumptive coagulopathy, thrombophlebitis, thromboembolic disease, and lymphatic malformations. Although gastrointestinal involvement has been documented in other PROS-related syndromes,[6–11] endoscopic findings and vascular abnormalities have not been reported in CLOVES.

CASE REPORT

A 34-year-old man was referred for hematochezia with abdominal discomfort, tenesmus, and urgency. His symptoms started years before, with gradual progression to daily bleeding. He did not report any nocturnal stooling, weight loss, infectious symptoms, or extraintestinal symptoms. His family and social histories were noncontributory. Outpatient magnetic resonance imaging (MRI) showed diffuse mural thickening and mucosal hyperenhancement involving the distal colon and rectum. His laboratory investigations showed mild normocytic anemia with a hemoglobin of 13.6 g/dL and mild thrombocytopenia with platelets 140×10^9/L. The remainder of his investigations, including electrolytes, creatinine, ferritin, liver enzymes, celiac screen, and C-reactive protein, were normal. His physical examination was notable for limb size discrepancy, ectatic veins on his upper limbs, and port wine lesions. His abdomen was soft and nontender, with no organomegaly. A digital rectal examination was normal.

Two years earlier, a medical geneticist had confirmed a diagnosis of CLOVES syndrome based on the presence of limb overgrowth, skin abnormalities (including port wine stains and superficial vascular malformations), macrodactyly, and numerous vascular abnormalities seen on imaging. MRI confirmed the congenital absence of multiple deep venous structures, including bilateral

ACG Case Rep J 2023;10:e01050. doi:10.14309/crj.0000000000001050. Published online: May 10, 2023

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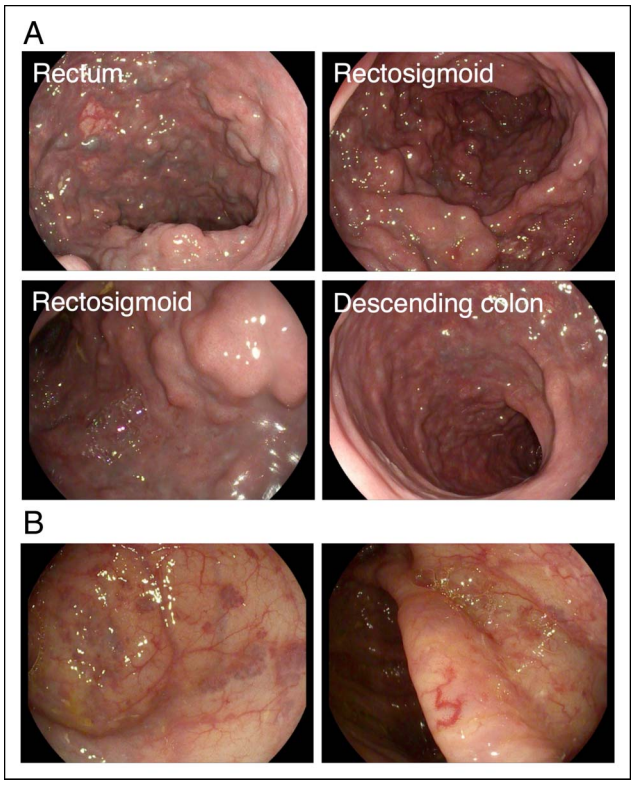

Figure 1. Colonic mucosa of patients with CLOVES syndrome. (A) Submucosal lesions seen throughout the descending colon, sigmoid, and rectum. (B) Superficial angiodysplastic lesions seen throughout the colon.

tibial and left basilic veins, with associated venous varices throughout his upper and lower extremities, chest wall, and paraspinal muscles. No abdominal abnormalities were noted at that time.

A diagnostic colonoscopy was performed. Examination of the rectum, sigmoid, and descending colon revealed diffusely raised, nodular mucosa overlying bluish dilated vessels, similar to varices (Figure 1). There were no signs of inflammation or ischemia. Biopsies were not obtained given the predicted risk of bleeding. In the transverse and ascending colon, there were numerous arteriovenous malformations (Figure 1) on a background of normal-appearing mucosa. The appearance of the terminal ileum was normal. There was no evidence of active or recent bleeding throughout.

Dedicated abdominal vascular imaging was obtained to further characterize the lymphatic and venous vasculature given the patient's known diagnosis. The MRI completed before the referral was reviewed and demonstrated thickening of the descending colon and rectum (Figure 2), corresponding to the colonoscopic distribution. A new computed tomography/angiography study demonstrated dysplastic venous drainage and an absence of the normal inferior mesenteric vein (Figure 2). Multiple pericolic and intramural phleboliths were also noted (Figure 2). Descending and rectal wall thickening was redemonstrated. The differential diagnosis included colonic and rectal complications of portal hypertension; however, this was ruled out by imaging and laboratory investigations.

Management to date has been supportive, given the low volume of hematochezia and mild anemia. Blood work is being monitored regularly; bowel routine was optimized to avoid constipation and straining; and signs and symptoms of large-volume blood loss prompting urgent care were discussed. The patient's hematochezia has since subsided, and hemoglobin levels have normalized.

DISCUSSION

This is the first report documenting the endoscopic and vascular malformations of the gastrointestinal tract in CLOVES syndrome. Both upper[12] and lower gastrointestinal bleeding[4] have been reported in patients with CLOVES; however, the degree and appearance of endoscopic and vascular abnormalities have not been well-characterized. In our case, the hematochezia most likely originated from either varicosities in the distal colon or superficial vascular malformations in the proximal colon, with the latter potentially also contributing to occult bleeding and/or anemia.

Gastrointestinal involvement has been well-documented in Klippel-Trenaunay syndrome (KTS), a relatively prevalent PROS-related syndrome. A study of children with KTS reported

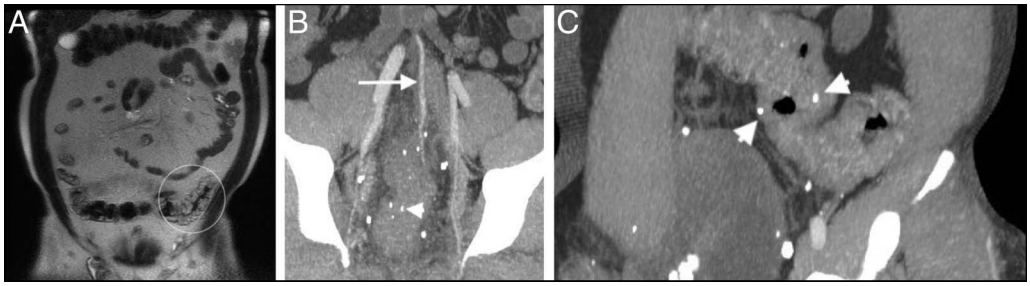

Figure 2. (A) Magnetic resonance image showing descending colonic and rectal wall thickening. (B) CT images showing dysplastic venous drainage and the absence of a normal inferior mesenteric vein (long arrow). (C) CT imaging showing multiple pericolic and intramural phleboliths, as indicated by short arrows. Descending and rectal wall thickening is again demonstrated. CT, computed tomography.

gastrointestinal bleeding in 1% of patients, albeit with one dying from complications of lower gastrointestinal bleeding.[8] Bleeding from the distal colon has been commonly reported in patients with KTS.[6–11]

The workup for gastrointestinal manifestations of CLOVES should include screening for anemia and ordering inflammatory markers, celiac disease, and abdominal imaging. The main differential diagnoses would include inflammatory bowel disease or other colitides, depending on the history. Although there are no reports of ischemic colitis in PROS-related syndromes, given the increased risk of thrombotic disease, it should also be ruled out.[13,14] Ultimately, colonoscopy may be appropriate to endoscopically map mucosal abnormalities and to rule out other causes. Although the risk of procedure-associated bleeding is unknown, it should be emphasized at the time of consent.

The crucial role of imaging in PROS-related syndromes has previously been delineated.[15] Characterization of low-flow and high-flow vascular malformations by magnetic resonance angiography can help distinguish between PROS-related syndromes, map the vasculature, and assess risk associated with surgery. In the current case, magnetic resonance angiography allowed us to identify malformations in the gastrointestinal vasculature. Mapping the gastrointestinal vasculature should be strongly considered in the case of gastrointestinal manifestations of PROS-related syndromes to allow for optimal planning should the need for surgical resection arise.

No guidelines exist on the management of PROS-related gastrointestinal manifestations. However, management of bleeding in KTS is wide-ranging, from conservative management[7] to endoscopic laser ablation,[9,10] embolization,[11] and surgery[6,10] with variable success. The acuity of presentation, presence of vascular malformations, and risks associated with interventions should be carefully considered. In our case, given the mild gastrointestinal symptoms, a conservative approach was taken and has been successful to date.

Medical options for the management of CLOVES-related sequelae are emerging. Alpelisib (BYL719), a selective inhibitor of the p110a subunit of PI3K, was approved in 2022 for the treatment of PI3K-related overgrowth syndromes after its compassionate use in 19 patients.[16] Patients treated with BYL719 showed a decrease in target lesions and skin capillary abnormalities. Correction of disseminated intravascular coagulation causing chronic gastrointestinal bleeding was achieved in 3 patients. It has also been used successfully to treat vaginal bleeding from vascular malformations in a patient with CLOVES.[17] An ongoing international multicenter randomized clinical trial (EPIK P2) will provide further information on the efficacy and adverse effects of this treatment in patients with CLOVES. Sirolimus, an mTORC1 inhibitor targeting downstream signaling of PI3K, has also been studied in CLOVES. It has been shown to modestly decrease areas of lymphatic overgrowth[18] and lesion-associated bleeding in pediatric patients with PI3K-related overgrowth syndromes.[19] The efficacy of these inhibitors in the prevention or treatment of acute bleeding from gastrointestinal lesions has yet to be determined.

To conclude, although vascular malformation as a cause of gastrointestinal bleeding remains rare, it should be suspected in patients with suspected or established PROS-related syndromes such as CLOVES. Awareness of these syndromes by gastroenterologists is critical in the appropriate workup, management, and follow-up of these patients.

DISCLOSURES

Author contributions: J. St-Pierre and N. Forbes conceived and designed the study. J. St-Pierre drafted the manuscript. All authors analyzed and interpreted the data. All authors critically revised the manuscript for intellectual content. All authors approved the final version of the manuscript. N. Forbes is the article guarantor.

Financial disclosure: None to report.

Informed consent was obtained for this case report.

Received January 4, 2023; Accepted April 7, 2023

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