ACG CASE REPORTS JOURNAL

CASE REPORT | INFLAMMATORY BOWEL DISEASE

Crohn's Disease in a Patient With Fibrodysplasia Ossificans Progressiva

Daniel Havlichek III, MD[1], Daniela Guerrero Vinsard, MD[2], Robert J. Pignolo, MD, PhD[3], and Sunanda Kane, MD, MSPH[2]

[1]*Department of Internal Medicine, Mayo Clinic, Rochester, MN*
[2]*Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN*
[3]*Division of Geriatric Medicine and Gerontology, Department of Medicine, Hospital Internal Medicine, and Endocrinology, Mayo Clinic, Rochester, MN*

ABSTRACT

Fibrodysplasia ossificans progressiva (FOP) is a rare disease characterized by inflammatory flares of soft tissues, leading to heterotopic ossification and significant cumulative morbidity and early mortality. FOP minor trauma, including intramuscular medication administration, can induce ossification and should be avoided. We present a case of known FOP in a patient who presented with fevers of unknown origin and was found to have biopsy-proven ileal Crohn's disease. Crohn's disease management was complicated by concerns that intramuscular therapies would induce ossification, and oral monotherapy with methotrexate was initiated with excellent results.

INTRODUCTION

Fibrodysplasia ossificans progressiva (FOP) is a rare disease with approximately 800 cases known to the scientific community worldwide.[1] The disease is characterized by inflammatory flares of soft tissues, resulting in heterotopic ossification in skeletal muscles, fascia, and tendons with gradual restriction of movement because of joint ankyloses.[2] Flares are precipitated by minor trauma, overexertion, intramuscular injections, and viral illness.[3] Flares are typically treated with a 4-day course of steroids and/or nonsteroidal anti-inflammatory drugs. However, current clinical trials are underway to determine optimal therapy.[4,5] The overall prognosis is poor with median lifespan of about 40 years with most deaths resulting from thoracic insufficiency syndrome from progressive ossification, costovertebral malformations, and severe spinal deformities.[2]

In contrast to FOP, inflammatory bowel disease (IBD) is a relatively common condition with as many as 1.3 million persons living in the United States and Canada with the diagnosis.[6] In addition to acute disease, Crohn's disease (CD) can present indolently with nonspecific symptoms including fever and weight loss and can go undiagnosed for years before a formal diagnosis is made.[7,8] To the best of our knowledge, there are no previous cases of coexisting CD and FOP reported in the literature.

CASE REPORT

A 22-year-old man with history of FOP presented with intermittent fevers of several months' duration and a 20-pound weight loss over the preceding 6 months. He was previously hospitalized for treatment of a left upper extremity abscess which was believed to be the source of his fevers. At that time, workup was remarkable for a normal white blood cell count of 7.7, anemia with hemoglobin of 8.4 g/dL without evidence of iron deficiency, platelet count of 454, sedimentation rate elevated to 65 mm/h, and C-reactive protein (CRP) elevated to 119 mg/L. Magnetic resonance imaging of the upper extremity was negative for abscess, and he was discharged on antibiotics.

One month later, the patient presented to the hospital with continued intermittent fevers. He had no localizing symptoms other than mild cough and 2–4 loose stools daily without frank blood. The patient had completed his antibiotic course, and there was no evidence of ongoing infection. He was febrile on presentation to 38°C, and laboratory test results were remarkable for normal white blood cell count of 6.3 and ongoing anemia with hemoglobin of 9.9 g/dL, sedimentation rate elevated to 46 mm/h, and CRP elevated

ACG Case Rep J 2022;9:e00737. doi:10.14309/crj.0000000000000737. Published online: January 25, 2022

Correspondence: Daniel Havlichek III, MD (Havlichek.daniel@mayo.edu).

to 82 mg/L. Abdominal computed tomography and pelvic computed tomography with intravenous (IV) contrast revealed loops of a thickened distal small bowel in the pelvis with trace free fluid. Magnetic resonance enterography showed diffuse wall thickening and mural hyperenhancement involving a long segment of the distal ileum (Figure 1). Extensive evaluation for an infectious etiology including *Blastomyces*, *Histoplasma*, human immunodeficiency virus, *Campylobacter*, *Yersinia*, *Cryptosporidium*, and tuberculosis was negative. Fecal calprotectin was substantially elevated at $>$ 1,000 μg/g (normal $<$50 μg/g). Given the location of enhancement on magnetic resonance enterography, colonoscopy was performed which demonstrated areas of abnormal ileal mucosa with erythema and serpiginous ulcerations 10 cm from the ileocecal valve (Figure 2). Biopsies from these areas revealed mixed inflammatory infiltrate in the lamina propria with neutrophilic infiltrate in the epithelium and crypts with surface epithelial injury and ulceration. The history, radiography, and histology were all consistent with probable CD.

Out of an abundance of caution and the desire to avoid parenteral CD therapies in the context of his FOP, the patient was initiated on oral methotrexate at 5 mg daily 5 times per week. Since starting therapy, the diarrhea and fevers have resolved, and the patient has gained weight.

DISCUSSION

To the best of our knowledge, this is the first case report of a patient with coexisting FOP and IBD. FOP raises significant challenges in IBD management because many available therapies require IV or injectable administration. Although subcutaneous and IV therapies can be administered to patients with FOP, care should be taken to avoid accidental intramuscular (IM) administration or repeated misplaced IV lines because this may result in heterotopic ossification. Although there is robust evidence on treatment regimens for CD, optimal comanagement of CD and FOP is unknown. Given the rarity of co-occurrence of CD and FOP in the literature, it is likely that these diseases arose independently in this patient.

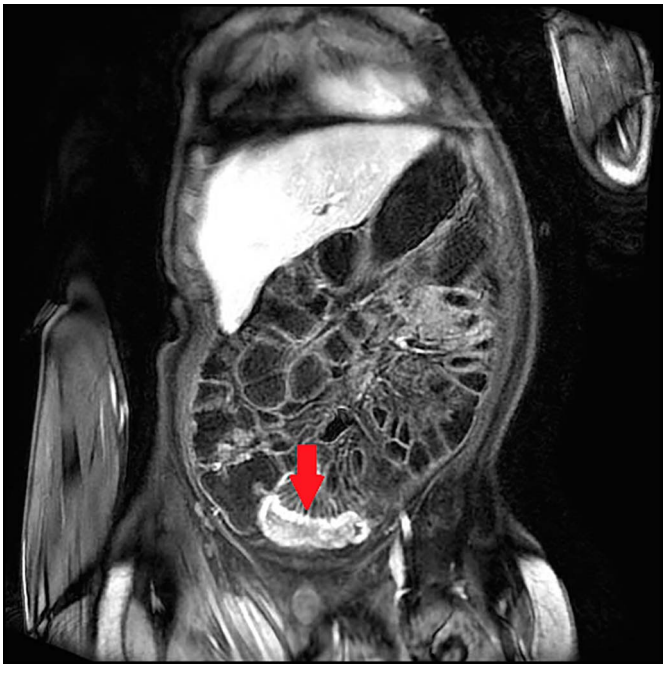

Figure 1. Ileal wall thickening (red arrow) and hyperenhancement on magnetic resonance enterography.

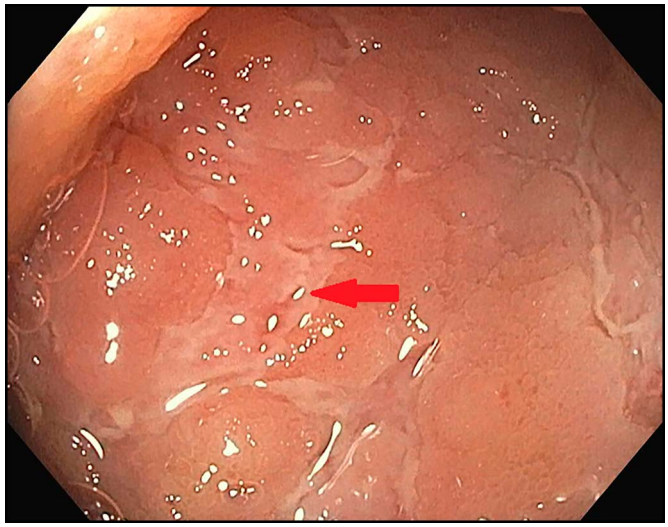

Figure 2. Superficial erosions (red arrow) of the terminal ileum on colonoscopy.

In terms of CD management, oral therapy with methotrexate was selected to avoid the risks of heterotopic ossification that poorly placed IV lines and IM drug administration entail. Budesonide was not chosen because of cost constraints, and azathioprine was not chosen because of the need for frequent laboratory monitoring and the patient's concern that long-term use can increase risk of hepatosplenic T-cell lymphoma. If methotrexate fails, either of these agents or off-label upadacitinib are alternative oral therapies to be considered. If those are not effective, infliximab, anti–tumor necrosis factor therapy, or vedolizumab (anti $\alpha_4\beta_7$ integrin) would be the suggested next step, given the longer 8-week interval for IV maintenance dosing. It is also reasonable to consider subcutaneous therapies such as injectable anti–tumor necrosis factor or ustekinumab (anti-interleukin-12/23) with care taken to avoid accidental intramuscular administration.

Best practice for monitoring endoscopic disease activity also remains unclear in a case of FOP. Colonoscopy in FOP is challenging because of airway limitations; patients often have thoracic insufficiency syndrome, ossification of the neck, and temporomandibular joint ossification precluding traditional intubation. Ideally, an experienced anesthesiology team with the ability to perform nasotracheal fiberoptic intubation should be available during the case if complications arise. Given these limitations, we plan to follow hemoglobin and CRP at 3-month

intervals. If flare arises, fecal calprotectin and either capsule endoscopy or magnetic resonance enterography will be performed to avoid the risks associated with repeat colonoscopy. It remains to be seen how the inflammatory milieu of CD impacts the course of FOP or if CD treatments could reduce the risk of future FOP flares in the patient.

DISCLOSURES

Author contributions: D. Havlichek III drafted the manuscript and acquired the data and images. D. Guerrero Vinsard, RJ Pignolo, and S. Kane designed and critically reviewed the manuscript. S. Kane is the article guarantor.

Financial disclosures: None to report.

Informed consent was obtained for this case report.

Received May 2, 2021; Accepted October 6, 2021

REFERENCES

1. Mantick N, Bachman E, Baujat G, et al. The FOP Connection Registry: Design of an international patient-sponsored registry for fibrodysplasia ossificans progressiva. *Bone*. 2018;109:285–90.
2. Pignolo RJ, Shore EM, Kaplan FS. Fibrodysplasia ossificans progressiva: Clinical and genetic aspects. *Orphanet J Rare Dis*. 2011;6:80.
3. Hsiao EC, Di Rocco M, Cali A, et al. Special considerations for clinical trials in fibrodysplasia ossificans progressiva (FOP). *Br J Clin Pharmacol*. 2019; 85(6):1199–207.
4. Pignolo RJ, Kaplan FS. Druggable targets, clinical trial design and proposed pharmacological management in fibrodysplasia ossificans progressiva. *Expert Opin Orphan Drugs*. 2020;8(4):101–9.
5. Kaplan FS, Al Mukaddam M, Beujat G, et al. *The Medical Management of Fibrodysplasia Ossificans Progressiva: Current Treatment Considerations*. Proc Intl Clin Council FOP 2019;1:1–111. (https://d3n8a8pro7vhmx.cloudfront.net/ifopa/pages/212/attachments/original/1584543455/FOP_TREATMENT_GUIDELINES_March2020.pdf?1584543455). Accessed February 21, 2021.
6. Loftus EV Jr. Update on the incidence and prevalence of inflammatory bowel disease in the United States. *Gastroenterol Hepatol (N Y)*. 2016; 12(11):704–7.
7. Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG clinical guideline: Management of Crohn's disease in adults. *Am J Gastroenterol*. 2018;113(4):481–517.
8. Burgmann T, Clara I, Graff L, et al. The Manitoba Inflammatory Bowel Disease Cohort Study: Prolonged symptoms before diagnosis—How much is irritable bowel syndrome? *Clin Gastroenterol Hepatol*. 2006;4(5):614–20.