Ulcerative Colitis-Primary Sclerosing Cholangitis in the Setting of Sickle-Cell Disease and Marfan's Syndrome: A Case Report

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ABSTRACT

A 32-year-old male with sickle-cell disease and Marfan's syndrome was diagnosed with ulcerative colitis and primary sclerosing cholangitis. He had clinical and endoscopic evidence of severe disease activity despite trials of anti-tumour necrosis factor agents, anti-interleukin therapy, and a Janus Kinase inhibitor. Eventually, he underwent a colectomy and ileo-anal anastomosis and remains well, with ongoing regular follow-up. This, to our knowledge based on the available literature, is the first reported case of ulcerative colitis coexisting with primary sclerosing cholangitis, Marfan's syndrome, and sickle-cell disease. The coexistence of these comorbidities complicated the patient's management course and required multidisciplinary team input. This case highlights the significance of multidisciplinary input in the management of such complex cases, particularly given the possibility of peri- and post-operative complications in cases of connective tissue disease and sickle-cell disease.

INTRODUCTION

CASE

We report the case of a 32-year-old Middle Eastern male, who was known to have sickle-cell disease and Marfan's syndrome, and was diagnosed simultaneously with ulcerative colitis (UC) and primary sclerosing cholangitis (PSC).

With regards to his ulcerative colitis, the patient had evidence of disease activity with 5 to 6 bloody stools per day with tenesmus and urgency. There was no abdominal pain. In terms of extraintestinal disease, he had primary sclerosing cholangitis as well as peripheral arthritis. He was a non-smoker and family history was only significant for sickle-cell disease in one of his parents. He was placed initially on Adalimumab with primary non-response, followed by rescue therapy with Infliximab after an admission with acute severe UC. He responded clinically and endoscopically for a period of five years, after which he had a secondary loss of response, despite adequate drug levels and absence of antibodies. Ustekinumab and Upadacitinib were trialed with primary non-response to the first, and a suboptimal response to the second.

Further evidence of disease activity was a colonoscopy showing marked erythema, ulcers, and an absent vascular pattern. Biopsies showed no evidence of dysplasia. Hemoglobin level was 8 g/dL, C-reactive protein was not markedly raised at 4 mg/L, but calprotectin was significantly elevated, being 1000 µg/g, reflecting significant disease activity. He had an unremarkable ultrasound at diagnosis despite cholestatic liver enzymes, but a subsequent Magnetic Resonance Cholangio-Pancreatography (MRCP) showed stricturing of the intra- and extra-hepatic bile ducts in multiple areas, consistent with a diagnosis of PSC.

The patient also had aortic regurgitation and recurrent palpitations, for which he was on Bisoprolol. His sickle-cell disease was complicated by one to two admissions a year with vaso-occlusive crises, and one admission for a hemolytic crisis. There were no previous admissions for acute chest syndrome or previous admissions to the intensive care unit, and he was on Hydroxyurea.

Physical examination showed Marfanoid features with tall stature, arachnodactyly, myopia, and a mitral regurgitation murmur. The patient was not jaundiced, and abdominal examination was unremarkable. There were no features of decompensated liver disease.

Given the uncontrolled nature of his bowel symptoms, and given the significantly raised risk of dysplasia and malignancy with the background of PSC, the decision was made after multidisciplinary team discussion to perform a colectomy. This included input from anesthetists, hematologists, gastroenterologists, and colorectal surgeons. The procedure was delayed because of an acute sickle-cell hemolytic crisis, but eventually the patient had a 2-step colectomy with ileo-anal anastomosis. He remains well and is undergoing regular pouch surveillance and regular surveillance with ultrasound and Magnetic Resonance Cholangio-Pancreatography (MRCP) for his PSC.

DISCUSSION

Ulcerative colitis (UC) is one of the subtypes of inflammatory bowel disease (IBD). It is characterized by inflammation affecting the colon, which can be limited to the rectum, or spread in a continuous manner throughout the large intestine. Diagnosis is made by colonoscopy showing erythema, erosions, ulceration, reduced or absent vascular pattern, friability, and in severe cases spontaneous bleeding. Management depends on disease severity, with 5-aminosalicylates being used to maintain remission in mild to moderate cases, while biologic therapy is employed in more severe ones. Anti-tumour necrosis factor agents are usually first-line in terms of advanced therapy. Anti-interleukins, and anti-integrins, as in this case, are also treatment options, as are

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Janus Kinase inhibitors. Indications for a colectomy, which is curative, include refractory disease, and the presence of complications such toxic megacolon, multifocal dysplasia, and malignancy. Primary sclerosing cholangitis (PSC) is one of the extra-intestinal manifestations of IBD. It results in bile duct stricturing and cholestasis, occurs more frequently in the setting of UC compared to Crohn's Disease, and requires close surveillance, as there is a significantly elevated risk of dysplasia and colorectal cancer as well as cholangiocarcinoma.

Sickle-cell disease (SCD) is an inherited hemoglobinopathy causing production of abnormal HbS, causing red blood cells to be sickle-shaped under oxidative stress. There is no direct association between sickle-cell disease and IBD, although there are several reported cases of concomitant disease[1,2,3]. IBD in the setting of SCD seems to have a preference for the colon, with most cases being UC[3]. Diagnosis may be delayed due to UC being mistaken for other gastrointestinal complications of SCD, including ischemic colitis, and this has been demonstrated in case reports[1]. A French retrospective study showed no difference in biologic-free or surgery-free survival, and no difference in complication rate between IBD patients with SCD and those without, and no specific safety issues with regards to prescribing biologics. A major difference noted, however, was that IBD patients with SCD were much more likely to have PSC, with about a third having concomitant PSC, compared to about 1% of IBD patients without SCD. All PSC patients observed in this study had an SS genotype[3]. The reason for PSC being more prevalent in SCD patients with IBD is unclear, as the literature on the area is scarce.

Marfan's syndrome is an autosomal dominant disorder due to a mutation in the gene encoding for fibrillin on chromosome 15. This leads to characteristic features including skeletal, chest wall, ocular, and cardiac issues. Gastrointestinal involvement is less often described although it is present. Symptoms can include abdominal pain, diarrhea, or constipation. Structural issues include hernias, volvulus, and diverticular disease, and there is also a propensity for functional bowel disorders[5]. Based on our literature review, there is only one reported case of IBD in a patient with Marfan's. This patient also had pyoderma gangrenosum[6].

Ulcerative colitis, PSC, sickle-cell disease, and Marfan's syndrome co-existing in the same patient has not so far been reported in the literature to our knowledge. This collection of comorbidities is rare, and together, complicate patient management, and require multidisciplinary input. Marfan's syndrome patients tend to be more complicated in terms of their anatomy, with colonoscopy being generally more complicated and technically difficult. Sickle-cell disease and its frequent crises means that timing of any surgeries for IBD needs to be well planned and involves close pre-, peri-, and post-operative management. PSC rates seem to be higher in IBD patients with sickle-cell disease based on the literature, and this is reflected in our patient's case.

CONCLUSION

This is the first reported case of IBD-PSC in a background of Marfan's syndrome and sickle-cell disease. Multidisciplinary input is crucial as these patients tend to have complex clinical courses, particularly in the setting of surgical intervention, and close monitoring is needed in view of the increased risk of complications.

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