



Spontaneous bilateral avascular necrosis of knees and hip leading to early bilateral total hip arthroplasty: a case report of an 18-year-old man recently diagnosed with Crohn's disease

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Abstract

Avascular necrosis (AVN) is linked to considerable morbidity, resulting in severe pain and functional impairment. Herein, for the first time, we reported an 18-year-old patient with Crohn's disease during the remission phase under Azathioprine therapy who presented with articular pain. Although no underlying risk factors, the patient was diagnosed with severe AVN of the bilateral femoral head and both knees simultaneously following pain in involved areas. This case highlights the importance of demand multidisciplinary approach to chronic disease. Moreover, clinicians should be aware of articular manifestations in IBD patients to diagnose and treat these conditions as soon as possible. Patients should be evaluated for their psychologic, gastrointestinal, and extra-gastrointestinal comorbidities during each follow-up visit.

Keywords Crohn's disease · Osteonecrosis · Avascular necrosis · Inflammatory bowel disease · Lower back pain

Introduction

Crohn's disease (CD) is a chronic gastrointestinal inflammatory disease that can affect each part of the gastrointestinal tract from the mouth to the anus. The CD is a multifactorial disease that genetic predisposition, infection as well as immunological, and environmental factors in addition to diet, influence its spread [1]. People between the ages of 15

and 30 and also 40 and 60 years had more frequently shown CD among developed countries [2]. Common manifestations are both systemic and gastrointestinal such as abdominal pain, diarrhea, hematochezia, nausea, and vomiting, as well as fever and chills [3]. Moreover, skin, vertebrae, eyes, liver, bones, bile ducts, and joints are scarcely involved [4]. The most common extra-gastrointestinal complication is musculoskeletal disorders such as axial arthritis (ankylosing spondylitis and sacroiliitis), enthesopathy, dactylitis, or endplate sclerosis [5].

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Avascular necrosis (AVN) or osteonecrosis is characterized by infarction of cellular components of bone which is commonly found in the femoral head [6]. The unexpected loss of blood supply followed by vascular insufficiency, is mostly a result of an underlying disease such as hematologic disorders, hemoglobinopathies, and systemic lupus erythematosus [7]. Although non-union results, a study comparing to the healthy group, showed that CD patients mostly develop AVN after about twelve years of disease recognition in their forties [8]. Long-term high-dose corticosteroid consumption, smoking history, and disease severity were all associated with increased risk of hip AVN in CD patients [9]. Although rare, however, it has been suggested that patients with inflammatory bowel disease (IBD) are predisposed to AVN even though without corticosteroid regimens [10]. Herein, for the first time, we report an 18-year-old man, with a history of CD for the past year, presenting with spontaneous bilateral femoral head and knees AVN, who had no potential underlying risk factors.

Case report

An 18-year-old man, diagnosed with CD about 3 years ago (Fig. 1) and successfully achieved both endoscopic and clinical remission with Azathioprine, was presented with symptoms of stiffness and pain in his hips, predominantly on the right side. His first presentation of CD was abdominal pain, diarrhea, and significant weight loss. He was diagnosed with CD according to c-reactive protein (CRP) of 37 (up to 30), erythrocyte sedimentation rate (ESR) of 59 (up to

20), fecal calprotectin of 390 $\mu\text{g}/\text{mg}$ (up to 200), ferritin of 29 ng/mL , along with hemoglobin of 14.3 g/L . Regarding his medical records, ileocolonoscopy had revealed normal vasculature, deep and superficial ulcerations with significant skip areas. To confirm the diagnosis, he had undergone computed tomography (CT) enterography which showed bilaminar segmental mural hyperenhancement, wall thickening, as well as strictures with/without mild upstream dilatation, and ulcerations with restricted diffusion of ileum. In the first months, he was prescribed tapering low-dose corticosteroid and azathioprine. He had significantly responded to this therapy and the disease remained silent with only azathioprine since then. In his follow-up records to date, according to his gastroenterologist, his inflammatory markers and fecal calprotectin, in addition to endoscopic remission.

Currently, he began experiencing pain for the past 6 months, initially presenting with mild symptoms in activity and then gradually increasing severity over time to the point that at his first visit, he not only complained of severe pain at rest but also according to his impaired gait, he decided to quit school. During 6 months of the gradual increase of the pain, he lost the potential of weight-bearing in addition to the groin pain. A noticeable reduction in the range of motion was also observed, resulting in claudication. Alongside this pain, there has been a slight lower back discomfort, without any associated constitutional symptoms such as fever, weight loss, or night sweats. He also declined unpasteurized dairy food intake. The patient had no history of alcohol or tobacco use and had not experienced any previous trauma. Furthermore, there was no documented history of corticosteroid consumption for the underlying CD. He claimed no history

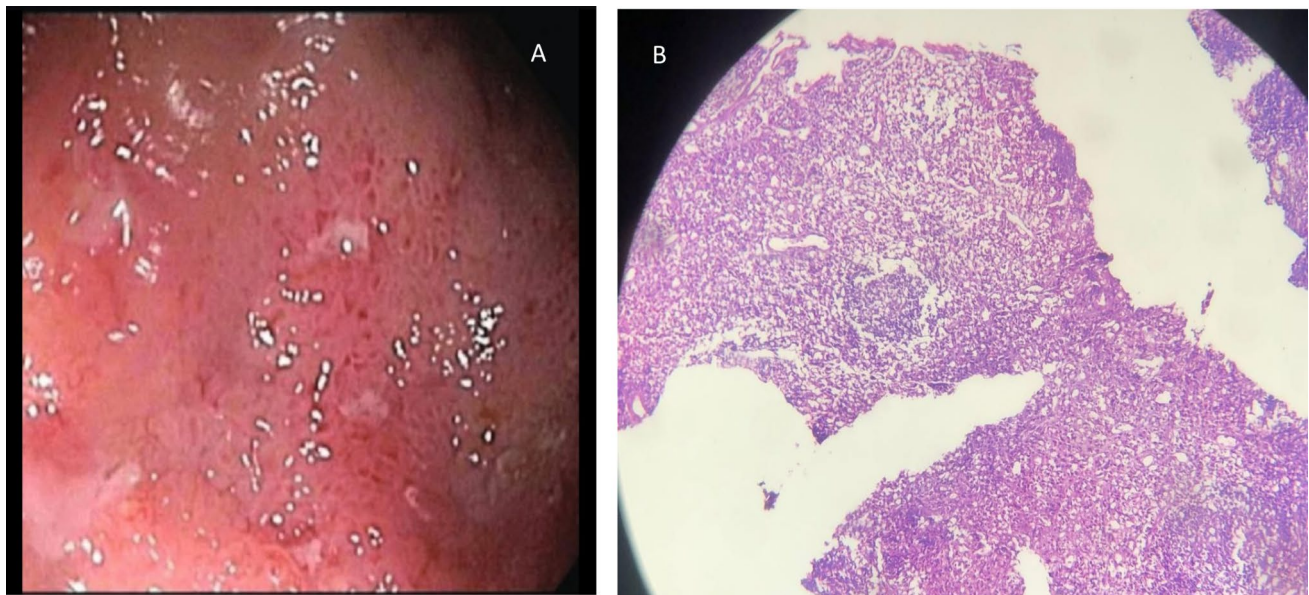


Fig. 1 **A** Multiple ileal aphthous lesions seen in colonoscopy; **B**: biopsy showed aphthous and deep fissuring ulcers

of hematological or rheumatological disease in his family. Moreover, he was not a past, present, or passive smoker. He had no other pain or inflammation in other joints. The history of morning stiffness and articular inflammatory pain was negative. The physical examinations highlighted significant shortness in the length of the right lower limb. A considerable reduction was found in assessing the range of motion of the right hip, accompanied by pain during internal rotation with a positive Patrick test.

Considering possible hematological or rheumatologic diseases as the cause of pain, we performed laboratory tests (Table 1). Endoscopic and laboratory examinations showed a remission phase of CD. IBD-associated spondyloarthropathy would be the first diagnosis according to bilateral osteonecrosis, however, he had no other history similar to spondyloarthropathies and more importantly, his laboratory results were negative for c- and p-ANCA as well as further inflammatory markers. All results were negative and fell within the normal range. The patient also tested seronegative for HLA-B27, HLA-B5, and HLA-B51 (Table 1). Considering infectious causes, the results of the viral serology tests for human immunodeficiency virus (HIV), Hepatitis B, and Hepatitis C were all negative. Additionally, the Purified protein derivative (PPD) test yielded a result of 0 mm. Further diagnostic tests including wright, 2-mercaptoethanol (2-ME), and Coombs wright were conducted, all showing negative results. Magnetic resonance imaging (MRI) was performed. The MRI of the hips revealed bilateral femoral head AVN accompanied by head collapse (Fig. 2). According to the fact that our patient had no potential risk factor for AVN such as age, CD length and severity, smoking, alcohol consumption, and most importantly, corticosteroid use, he was diagnosed with AVN, as a complication of CD with no underlying risk factor.

The Association Research Circulation Osseous (ARCO), is credited with developing the widely recognized classification system for staging osteonecrosis of four distinct stages. The initial stage, referred to as stage 0, is characterized by histological alterations in the absence of any accompanying clinical manifestations. Conversely, the final stage, stage 4, is marked by clear indications of advancement towards osteoarthritis [11]. In our case, bilateral femoral head AVN is accompanied by head collapse. The condition was classified as stage 3 according to the ARCO staging system. The orthopedic consultation was sought to determine suitable therapeutic options, resulting in the patient undergoing bilateral total hip arthroplasty (THA) surgery. While the patient was being followed, a noticeable reduction in hip pain was observed, resulting in a complete return to his normal daily activities after the surgery.

After a few months, in follow-up sessions, the patient presented with a complaint of swelling, crepitation, and intolerable pain in both knees. Following his THA surgery

decreasing his hip pain, he began to notice the increasing pain in both knees. He had mild discomfort in both knees, which has progressively worsened over the past months. These symptoms have been significantly impacting the patient's quality of life and sleep. He was woken up at night suffering the pain to the extent that during the last month, analgesics lost their alleviating effects. Upon physical examination, swelling and tenderness in the left knee were observed. Laboratory results showed positive (2+) rheumatoid factor (RF), while the anti-nuclear antibodies, anti-dsDNA test, and anti-CCP Ab tests all yielded negative results (Table 2). The total complement levels were determined to be within the normal range. Additionally, the inflammatory factors were also found to be within the normal range (Table 2). MRI examination of both knees revealed the presence of mild joint effusion and osteonecrosis in the subchondral region of the posterior aspect of the femoral condyle in both knees (Fig. 3). The patient was referred to orthopedic section, fortunately, surgical intervention was deemed unnecessary. Instead, conservative therapy including rest and non-steroidal anti-inflammatory drugs was started to relieve pain and maintain joint congruency, and range of motion was recommended, resulting in significant improvement of knee pain within 3 months.

Discussion

We reported bilateral femoral head and knees AVN concomitantly for the first time in a young man with only a year of CD diagnosis, with no associated risk factors, episodes of disease activation for the past year, history of high dose corticosteroid use or corticosteroid use in 2 years and a half (Fig. 4).

The causative factors and underlying mechanisms of osteonecrosis in individuals with IBD have yet to be fully understood. However, disease activity and corticosteroid therapy had led to AVN as an extra-intestinal manifestation of IBD [12]. AVN is a medical condition associated with considerable morbidity, often leading to severe pain and functional impairment. It has been observed that individuals with IBD exhibit a higher incidence of AVN when compared to the general population [13]. Rolston et al. have provided evidence indicating that around 2% of individuals with IBD may be susceptible to AVN. A significant proportion of patients who presented with incidental findings of AVN had previously reported hip or low back pain to their gastroenterologist. They reached the determination that individuals diagnosed with IBD exhibited a significantly greater incidence of AVN compared to those without IBD [7]. Vakil and Sparberg conducted a study involving 204 patients with IBD, in which they observed that 4.3% of these patients developed osteonecrosis due to corticosteroid therapy [10].

Table 1 Laboratory study at first visit

	Test, unit	Result	Reference range
Biochemistry	AST, U/L	18	Up to 35
	ALT, U/L	18	Up to 45
	ALP, U/L	134	64–306
	Albumin, g/dL	5.3	3.5–5
	Total cholesterol, mg/dL	124	Desirable <200
	HDL, mg/dL	45	36–60
	LDL, mg/dL	60	High >160
	Calcium, mg/dL	10.2	8.5–10.5
	Phosphorus, mg/dL	4.3	2.6–4.5
	TSH, mIU/L	4.36	0.5–8.5
	PTH, pg/mL	40.6	15–65
	VIT D, ng/dL	34.6	30–100
	Uric acid, mg/dL	4.3	Male 3.4–7 female 2.4–5.7
	Hematology	WBC, μ L	4.35
RBC, $10^6/\mu$ L		5.61	4.2–6.3
Hb, g/dL		16.8	12–16
Hematocrit %		49.2	30–45
MCV, fL		87.7	80–100
MCH, pg		29.9	27–32
MCHC, g/dL		31.11	33–38
Platelet, μ L		201,000	150,000–450,000
PT		17.5	
PTT		34.5	
Serology	INR	1.83	
	ESR 1 h	14	Positive: > 30
	CRP quantitative	Negative	–
	Wright	Negative	–
	Coombs wright	1/20	–
	2ME	Negative	–
	Anti B2-GLP1 antibody (IgG)	1.1	–
	Anti B2-GLP1 antibody (IgM)	1	Positive: > 20
	Anti cardiolipin antibody (IgM)	3.3	Negative < 12
	Anti cardiolipin antibody (IgG)	2	Negative < 12
	Anti-ds DNA	31.4	Positive: > = 100
	C3	107	90–180
	C4	21	10–40
	CH50	50	Positive: > = 90
	FANA	Negative	Up to 1/100
	C-ANCA	Negative	Up to 1/10
	P-ANCA	Negative	Up to 1/10
	RF	2+	–
	Anti-CCP-Ab	1.1	Negative < 5
	HLA-B27	Negative	–
	HLA-B5	Negative	–
	HLA-B51	Negative	–
HIV-Ab	Negative	–	
HCV-Ab	Negative	–	
HBS-Ag	Negative	–	
Tuberculin test mm	0	–	
Feces	Calprotectin, μ g/mg	33	Up to 200

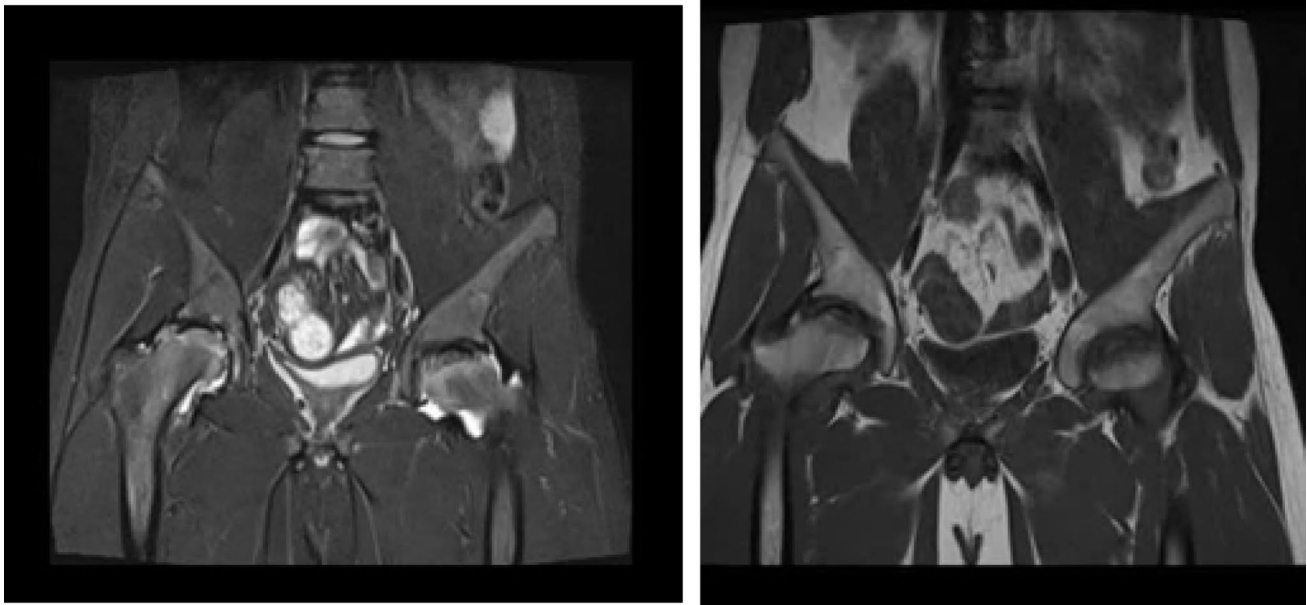


Fig. 2 MRI of hip joints (the video is also accessible in supplementary file)

Table 2 Laboratory study, few months later after hip surgery

	Test, unit	Result	Reference range
Serology	ESR 1 h	12	Positive: > 30
	CRP quantitative	Negative	–
	Wright	Negative	–
	Coombs wright	1/40	–
	2ME	Negative	–
	Anti B2-GLP1 antibody (IgG)	1.8	–
	Anti B2-GLP1 antibody (IgM)	2.5	Positive: > 20
	Anti cardiolipin antibody (IgM)	2.1	Negative < 12
	Anti cardiolipin antibody (IgG)	4	Negative < 12
	Anti-ds DNA	24.7	Positive: > = 100
	C3	120	90–180
	C4	38	10–40
	CH50	30	Positive: > = 90
	FANA	Negative	Up to 1/100
	C-ANCA	Negative	Up to 1/10
	P-ANCA	Negative	Up to 1/10
	RF	2+	–
	Anti-CCP-Ab	1.1	Negative < 5
	HLA-B27	Negative	–
	HLA-B5	Negative	–
HLA-B51	Negative	–	
HIV-Ab	Negative	–	
HCV-Ab	Negative	–	
HBS-Ag	Negative	–	

Additionally, the researchers put forth a hypothesis suggesting that individuals with CD and ulcerative colitis may be more susceptible to steroid-induced osteonecrosis even at lower doses of steroids. A study represented a 39-year-old woman suffering CD, under prednisolone therapy with bilateral knee AVN [13]. The authors also demonstrated that in contrast to hip, knee involvement is unilateral. A previous report released the case of a 22 year-old woman with bilateral knee AVN and CD at the same time [14]. In our case, the patient did not claim any history of previous steroid use in 2 years and a half, as confirmed by his gastroenterologist. He only underwent 6 months of tapering low-dose corticosteroid therapy along with azathioprine. In contrast, according to Freeman and colleagues evaluating 877 patients with CD, the overall incidence of AVN was found to be as low as 0.5%. They also reported four male patients with CD and osteonecrosis, of which, similar to our case, two had no steroid therapy. Based on their findings, the authors concluded that there is no correlation between steroid therapy and the risk of this extra-intestinal manifestation [15]. Importantly, active IBD is commonly associated with hypercoagulability [16], small-vessel vasculitis, and immunologic mechanisms. It is worth noting that the presence of inflammatory cytokines, such as interleukin (IL)-1 and Tumor necrosis factor (TNF)-alpha, may suppress bone formation and modeling [17]. IBD has been linked to the occurrence of disseminated intravascular coagulation (DIC), which is triggered by elevated levels of factors V and VIII, von Willebrand factor, and concurrent reductions in protein S, and protein C antithrombin III [18]. The observed propensity towards thrombosis provides support for the hypothesis

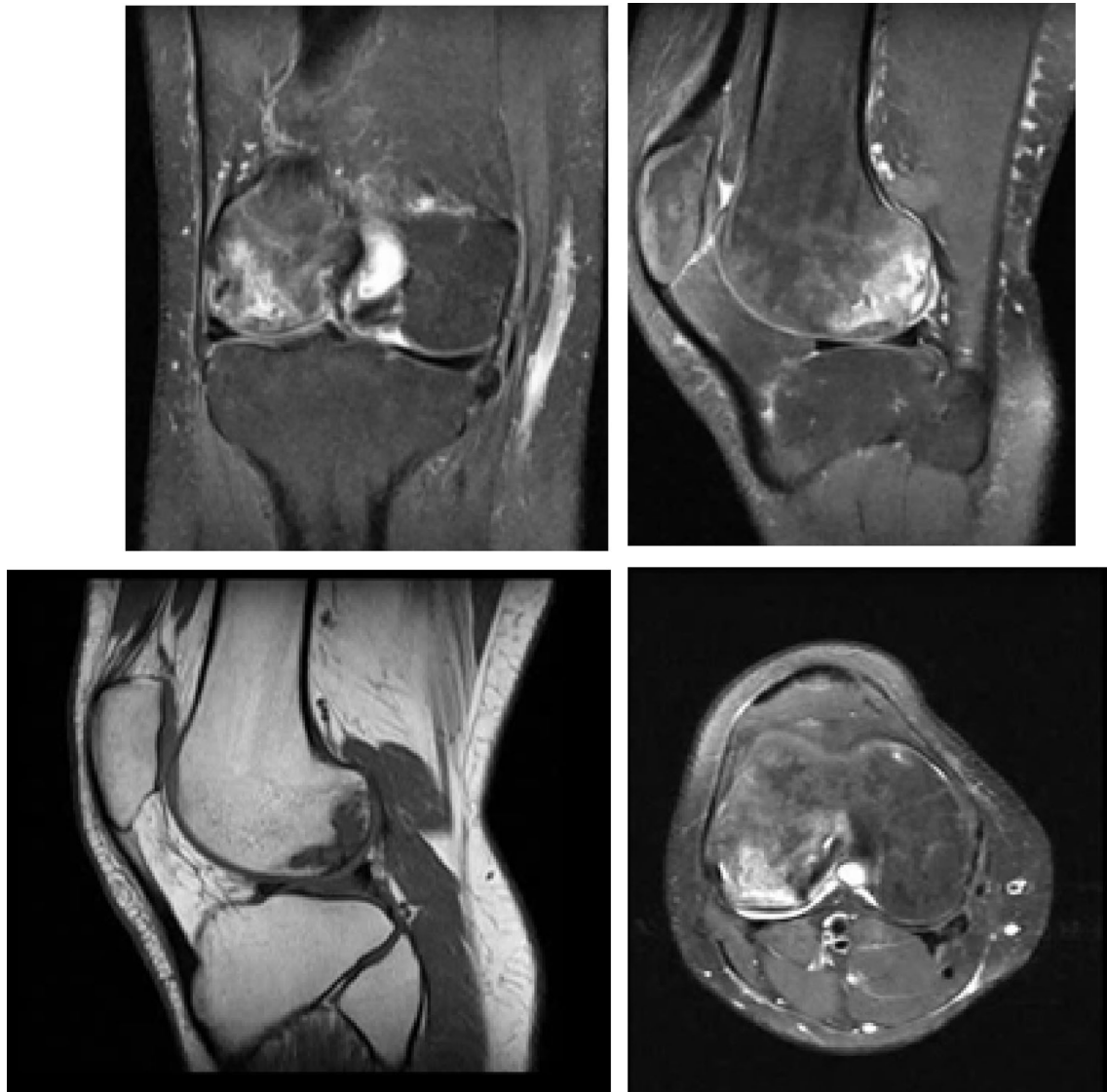


Fig. 3 MRI of knee joints (the video is also accessible in supplementary file)

that osteonecrosis may be a rheumatological condition associated with IBD, rather than a consequence of its treatment. Although so young with only a year of CD duration, our patient seems to show the same pattern. He had no other previously reported risk factors such as smoking or bone damage or the same familial pattern. More importantly, he had no periods of disease activity for the past year, which lower the possibility of vasculitis or hypercoagulopathies. Further, his age did not match previous studies on joint complications of BD patients. This case magnifies the importance of cohorts and longitudinal studies to reveal possible risk factors of CD-associated AVN and how to prevent it. We suggest that lifestyle and symbiotic risk factors could also alter the possibility of such rare complications. Future studies are deemed necessary to help clinicians apply lifestyle

changes, prognostic evaluations, and pharmaceutical therapies for such chronic diseases to prevent early or late comorbid complications.

It is worth mentioning, that our patient had a positive rheumatoid factor (RF) in his serologic investigation. This factor could be positive in the normal population and rheumatoid arthritis (RA) [19]. Positive RF without RA-associated manifestations such as articular inflammatory pain and morning stiffness, is not of clinical significance, not only in this patient but in any patient presenting.

Finally, one of the most important aspects of approaching our patient was his psychological status. He had to deal with such horrible pain at the age of youth, more importantly, he quit school, could not enter university and studied while suffering from this pain and all the treatment and surgery.

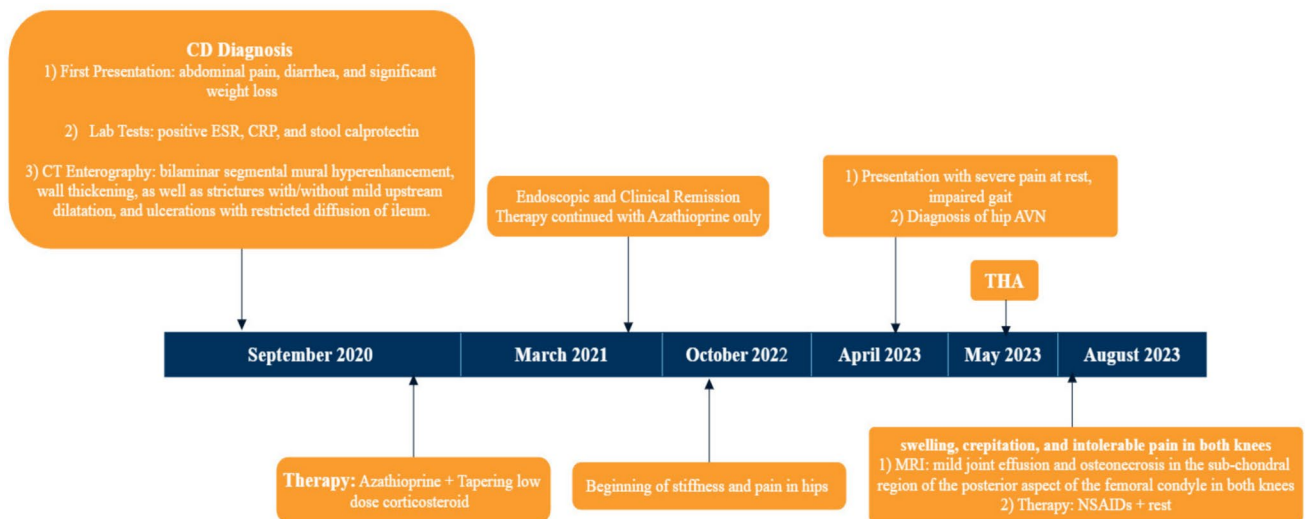


Fig. 4 Clinical course of the disease; from CD diagnosis to knee involvement

We consulted a psychologist and referred our patient for routine programmed therapeutical sessions to maintain his life stability across all these damages. Thereafter, he showed improved compliance and response to the alleviative therapy. We suggest that clinicians facing patients with chronic diseases, specifically rare conditions that alter their lifetime status, always consider a psychiatric consultation on the case. This brings about not only better response to the therapy but also augments patients' quality of life.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s12328-024-01987-y>.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Written informed consent was given from the patient to publish anonymously his medical records and history.

References

1. Ranasinghe IR, Hsu R. Crohn Disease 2023.
2. Ghersin I, Khteeb N, Katz LH, et al. Trends in the epidemiology of inflammatory bowel disease among Jewish Israeli adolescents: a population-based study. *Aliment Pharmacol Ther.* 2019;49:556–63.
3. Fabián O, Kamaradová K. Morphology of inflammatory bowel diseases (IBD). *Cesk Patol.* 2022;58:27–37.
4. Klamt J, de Laffolie J, Wirthgen E, et al. Predicting complications in pediatric Crohn's disease patients followed in CEDATA-GPGE registry. *Front Pediatr.* 2023;11:1043067.
5. Tavassoli S, Shahabinasab I, Norouzi A, et al. From bowel inflammation to the bone and joints: musculoskeletal examination in inflammatory bowel disease (IBD). *BMC Musculoskelet Disord.* 2021;22:1019.
6. Mont MA, Hungerford DS. Non-traumatic avascular necrosis of the femoral head. *JBJS.* 1995;77:459–74.
7. Rolston VS, Patel AV, Learch TJ, et al. Prevalence and associations of avascular necrosis of the hip in a large well-characterized cohort of patients with inflammatory bowel disease. *J Clin Rheumatol.* 2019;25:45–9.
8. Bakhshi Z, Yadav S, Harmsen WS, et al. Osteonecrosis in inflammatory bowel disease: clinical features, risk factor analysis, and outcomes. *Inflamm Bowel Dis.* 2023;29:1223–30.
9. Yadav S, Harmsen S, Jithinraj EV, et al. Analysis of risk factors for avascular necrosis in inflammatory bowel disease: 1667. *Off J Am Coll Gastroenterol | ACG.* 2014;109–494.
10. Vakil N, Sparberg M. Steroid-related osteonecrosis in inflammatory bowel disease. *Gastroenterology.* 1989;96:62–7.
11. Choi HR, Steinberg ME, YCheng E. Osteonecrosis of the femoral head: diagnosis and classification systems. *Curr Rev Musculoskel Med.* 2015;8:210–20.
12. Hauzeur JP, Malaise M, Gangji V. Osteonecrosis in inflammatory bowel diseases: a review of the literature. *Acta Gastro-Enterol Belg.* 2009;72:327–34.
13. Klingenstein G, Levy RN, Kornbluth A, et al. Inflammatory bowel disease related osteonecrosis: report of a large series with a review of the literature. *Aliment Pharmacol Ther.* 2005;21:243–9.
14. Barbosa M, Cotter J. Osteonecrosis of both knees in a woman with Crohn's disease. *World J Gastrointest Pharmacol Ther.* 2016;7:579–83.
15. Freeman HJ, Freeman KJ. Prevalence rates and an evaluation of reported risk factors for osteonecrosis (avascular necrosis) in Crohn's disease. *Canadian J Gastroenterol Hepatol.* 2000;14:138–43.
16. Seamon J, Keller T, Saleh J, et al. The pathogenesis of nontraumatic osteonecrosis. *Arthritis.* 2012;2012: 601763.

17. Amarasekara DS, Yu J, Rho J. Bone loss triggered by the cytokine network in inflammatory autoimmune diseases. *J Immunol Res.* 2015;2015: 832127.
18. Souto JC, Martínez E, Roca M, et al. Prothrombotic state and signs of endothelial lesion in plasma of patients with inflammatory bowel disease. *Dig Dis Sci.* 1995;40:1883–9.
19. Tiwari V, Jandu JS, Bergman MJ. Rheumatoid factor. *StatPearls [Internet]: StatPearls Publishing; 2022.*

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