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ABSTRACT

Introduction: Extra-gastro-intestinal tract manifestations associated with *Clostridium difficile* infection (CDI), including reactive arthritis (ReA), are uncommon.

Method: We report a case of ReA associated with a relapse of CDI in a 46-year-old woman. A toxigenic *C. difficile* strain was isolated from stools and characterized as PCR-ribotype 014/020/077. We conducted a comprehensive literature review of ReA associated with CDI (ReA-CDI). Diagnostic criteria for ReA-CDI were: (i) evidence of aseptic synovitis (confirmed by culture) developing during or immediately after colitis, (ii) presence of a toxigenic *C. difficile* strain in stool samples, and (iii) absence of other causes of colitis and arthritis.

Results: Forty-nine cases of ReA-CDI (excluding the present report) have already been described since 1976. Of these reports, Mean age of patients was 38 years (SD: 18.5), 46% were male, and 68% had HLA B27 genotype. Sixty-nine percent of patients received a β-lactamin treatment before CDI. ReA-CDI occurred a median 10 days (range 0-55 days) after CDI. Outcome was favorable in 90% of patients and oral non anti-inflammatory drugs were required for 55%.

Conclusion: ReA-CDI remains uncommon. Compared to the general population, it is more likely observed in younger patients with HLA B27-positive genotype.

INTRODUCTION

Clostridium difficile (CD) is a strict anaerobic, spore-forming, gram positive bacillus. Only toxigenic strains of CD are involved in gastro-intestinal tract infections. Clinical symptoms associated with CD infections (CDI) generally range from mild diarrhea to severe pseudomembranous colitis (PMC). CDI is defined by several signs and symptoms, presence of CD toxin and/or toxin-producing CD in stools, and no other causes of PMC after colonoscopic or histopathological evaluation [1]. The incidence of CDI is increasing in many countries worldwide and CD has a considerable burden on healthcare systems [2]. In particular, the United States Center for Disease Control and Prevention (CDC) recently placed CDI among bacterial infections posing the highest health risk due to antimicrobial resistance [3].

In Europe, the incidence of healthcare-associated CDI is 4.2 per 10,000 patient-days, with a case-fatality rate of 9% within three months after diagnosis [4]. In the United States, there was a total of 453,000 estimated number of CDIs in 2011 based on data from active population- and laboratory-based surveillance [2]. Antibiotic use, advanced age, and comorbidities (liver cirrhosis, heart disease, pulmonary disease, chronic dialysis, immunocompromised status) are the most common risk factors associated with CDI [4].

Extra-colonic CDI have been described in previous reports and include bacteremia [5], cellulitis [4], pancreatic [6] or splenic abscesses [7], pleural empyema [8], osteomyelitis [5], native or artificial joint [9,10], or appendicitis [10]. Extra-colonic manifestations have also been observed, such as uremic and hemolytic syndrome [11,12] and reactive arthritis (ReA), yet are probably unrelated to bacteria itself.

Birnbaum *et al.* proposed diagnostic criteria for ReA associated with CDI (ReA-CDI) [13], which include the following: i) evidence of aseptic synovitis (confirmed by culture) developing during or immediately after colitis, (ii) presence of toxins produced by *C. difficile* in stool samples, and (iii) absence of other causes of colitis and arthritis. The pathophysiology of Rea-CDI is poorly understood, while the underlying cause of its occurrence remains unknown.

We report herein a case of ReA-CDI observed in a 46-year-old woman and present a comprehensive review of previous cases in the literature.

CASE REPORT

A 46-year-old Caucasian woman was admitted to Saint-Antoine Hospital (Paris, France), for an acute episode of antibiotic-associated diarrhea.

She experienced iterative lower urinary tract infections (UTI) and chronic anemia due to iron deficiency. She reported no particular medication intake, no smoking, and no drug or alcohol use. She had no family history of or symptoms related to autoimmune disease.

Seven months before hospitalization, she had foot surgery as a result of hallux valgus. She reported large quantities of aqueous diarrhea that resolved after 10-day treatment with oral metronidazole. Stool testing was not performed at that time. Three weeks later, she developed oligoarthritis (both ankles and left knee), which lasted roughly 5 months and resolved during treatment with ketoprofene.

A few days prior to hospitalization, she was treated for a lower UTI with a two-day course of cefixim. She was admitted to the emergency room for severe diarrhea, vomiting and abdominal pain. Clinical examination revealed arterial pressure at 82/54mmHg (which was comparable to previous measures), tachycardia (110 bpm) and no other abnormalities. CD was detected in stool samples by enzyme immunoassay (GDH, Cdiff Quik Chek®, Alere) and confirmed by polymerase chain reaction (PCR) toxin B detection (GenXpert®, Cepheid) but not with a cell culture cytotoxicity assay. She underwent rehydration therapy and initiated a 10-day course of oral metronidazole. She had rapid clinical improvement and was discharged 2 days later.

She was readmitted 11 days after discharge for oligoarthritis (both ankles and left knee), fever (38. 1°C), myalgia, and recurrence of diarrhea. Upon examination, both of her ankles and left knee were slightly swollen and painful. Stool samples tested positive for toxinogenic CD again, while this time the cell culture cytotoxicity assay was positive. Strains from both the first and second episodes were genotyped as PCR-ribotype 014/020/077.

Joint X-ray was normal. Blood and urine culture were sterile. Complete blood count was normal except for lymphocyte count at 1326 cells/mm^3, hemoglobin at 11.3g/dL, and platelet count at 483,000/mm^3. There were no other ion (including calcium) or renal abnormalities. C-reactive protein level was 114.6mg/L, plasmatic protein electrophoresis demonstrated pro-inflammation (increase in α-1, α-2 and γ-globulins). An intra-articular puncture of the knee was performed and showed high degrees of inflammation with 10,000 elements/mm^3, including 7300/mm^3 polymorphic neutrophils, while no crystals were identified. Articular fluid was placed in bacteriological cultures, including incubation in anaerobic blood culture, which were negative.

Oral vancomycin 125mg was given four times daily for 10 days to treat CDI. Afterwards, paracetamol and tramadol were administered to treat probable ReA-CDI. Arthritis and diarrhea fully resolved within 3 weeks. At the one-year follow-up visit, no recurrence of diarrhea or arthritis was reported.

REVIEW

We performed a review of all ReA-CDI cases published in the literature. We searched for the combined terms "Reactive arthritis" and "*Clostridium difficile*" in PubMed and obtained 41 articles amounting to 51 cases of ReA-CDI. We excluded 2 patients who did not have toxin detected in stool samples, per definition of CDI [15]. In total, we summarize 39 articles including 49 cases of ReA-CDI, all of which were reported among adults and children since 1976 [14,16–49] (**Table 1**).

Patients had a mean age of 38 years (SD: 18.5) and were mostly females (54%). Patients were noticeably younger than those included in a European survey of 2011 but the proportion of females was similar (56%) [4]. HLA B27 genotype was observed in 28/41 patients (68%, 95%CI: 53.7 %-82.3 %).

First-line treatment of CDI was metronidazole in 13/24 (54.2%, 95%CI: 27.1-81.3%) and oral vancomycin in 11/24 cases (45.8%, 95%CI: 16.4-75.2%).

ReA occurred a median 10 days after CDI (range: 0-55 days). Of all 50 cases, initial presentation was monoarthritis in 9 (18%, 95%CI: 7.4-28.6%), oligoarthritis in 22 (44%, 95%CI: 30.2-57.8), and polyarthritis in 19 (38%, 95%CI: 24.5-51.5%). The two joints most frequently involved in ReA-CDI were ankles (63.6%, 95%CI: 45.8-81.4%) and knees (59.1%, 95%CI: 40.2-78%). ReA-CDI lasted from 5-800 days (median=42 days). Clinical outcome was favorable in 38/42 cases (90.5%, 95%CI: 81.6-99.4 %) as non steroid anti-inflammatory drugs were needed in 11/20 cases (55%, 95%CI: 33.2-76.8 %). No reoccurrence of CDI was described in the literature.

None of the 49 cases presented in this review reported the specific ribotype strain involved in CDI. The patient in our case report was infected with CD PCR-ribotype 014/020/077, one of the most frequent strains in France and Europe [50,51]. Further studies exploring a possible association between ReA and CD strain would be helpful in this context.

There are few data regarding the pathological mechanism involved in ReA-CDI. It could be hypothesized that immunologic tolerance is interrupted during antigenic presentation and contributes to ReA-CDI. Indeed, a major bacterial structure, lipopolysaccharide (LPS), is commonly found in the blood of patients with ReAs before the onset of arthritis, owing to other entero-invasive

pathogens such as *Salmonella* sp or *Chlamydia trachomatis* [52]. As CD is devoid of LPS, it remains to be demonstrated if other sources of circulating LPS or CD-antigen are present before the onset of ReA-CDI. CD-toxin A is known to increase permeability of the epithelial intestinal barrier [28]. As a result, CD-antigen and/or LPS from other gram-negative bacteria could reach blood circulation via the gut, driving an antigenic reaction and disrupting immunologic tolerance. Activated autoreactive T lymphocytes could then reach cartilage tissue and cause synovitis. Moreover, LPS from *Escherichia coli* is able to enhance the cytotoxicity activity of CD toxin A [54].

The hypothesis of antigenic presentation is also supported by the association between ReA-CDI and HLA B27 [54] and the high prevalence of HLA B27 patients in our review, compared to the general population, argues for a predisposition to ReA. Even patients without HLA B27 genotype were able to resolve ReA-CDI without any antibiotic treatment, providing corroborating evidence for non-septic arthritis. Unfortunately, we could not determine the HLA status of our patient.

Importantly, CD septic arthritis can only be excluded if there is no CD identified in the synovial fluid. In the literature, 28 negative articular liquid cultures were reported, on which only one CD-toxin PCR was performed [48]. In our opinion, the argument for a ReA-CDI diagnosis should require additional laboratory testing, such as specific culture for CD by toxin detection and 16S RNA analysis from articular liquid.

Even if the mechanisms underlying extra-colonic manifestations are unclear, some molecules like calprotectin (CP), interleukin (IL)-8 or IL-23 may play an important role in ReA-CDI [55]. CP is a calcium- and zinc-binding protein released from the cytosol after neutrophil activation [56]. CP has antibacterial, apoptosis-inducing, leukocyte-chemotactic properties and is a potential biomarker of inflammation [57], especially during inflammatory bowel disease's flare ups [59]. Fecal CP levels have also demonstrated strong correlation with neutrophil excretion in stool [60]. CP levels in the plasma and synovial fluid are also high during rheumatoid arthritis [61] and ReA [62]. CP has also been quantified in synovial tissue of rheumatoid arthritis patients, specifically in the lining adjacent to the cartilage-pannus junction, which is the primary site of cartilage destruction and bone erosion [61]. Of note, elevated levels of CP are also found in the feces of patients with CDI [58]. Further studies quantifying CP in plasma and synovial fluid from ReA-CDI patients would be worthwhile in order to elucidate its potential role.

CONCLUSION

We reported a case of ReA-CDI and analyzed 49 other cases of ReA-CDI published in the literature. Further studies are needed to determine the underlying pathophysiological mechanism behind ReA-CDI, while developing the role of specific ribotypes and CP.

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AUTHOR YEAR OF PUBLICATION	SEX	AGE (years)	HLA B27	REASON FOR PRESCRIBING ATB BEFORE CDI	ATB BEFORE CDI	ATB USED TO TREAT CDI	TUI (days)	LOCATION OF ARTHRITIS	OUTCOME	SYMPTOM DURATION (days)
Rollins *et al.* 1976	M	55	NA	ENT infection	β-lact	NA	35	Elbow, Wrist, Knee, Foot	NA, Resolution	5
Rothschild *et al.* 1977	F	23	NA	Genital infection	β-lact	NA	8	Knee	NA, Resolution	5
Fairweather *et* al. 1980	F	53	NA	Prophylaxis	Linc	NA	15	Wrist, Hip, Ankle, Foot	NSAID, Resolution	10
Bolton *et al.* 1981	F	45	-	Skin infection	Linc	IMDZ	21	Knee, Ankle	NSAID, Resolution	43
Abbott *et al.* 1982	F	27	-	NA	β-lact	NA	8	Elbow, Wrist, Knee	NA, Resolution	42
Puddey *et al.* 1982	M	48	+	Skin infection	β-lact	NA	16	Knee	NA, Resolution	56
McCluskey 1982	F	37	+	Skin infection	Linc	NA	14	Wrist, Knee, Ankle	NA, Resolution	29
Lofgren *et al.* 1984	M	61	+	Prophylaxis	β-lact	GLP	11	Hip, Knee	0, Resolution	14
Caroli *et al*. 1986	M	77	+	Respiratory infection	β-lact	NA	8	Knee	NA	NA
Paty *et al.* 1987	F	28	-	0	0	NA	28	Wrist, Hand, Knee, Ankle	NA, Resolution	21
Atkinson *et al.* 1988	M	22	-	Prophylaxis	β-lact	NA	0	Shoulder, Wrist, Ankle	NA, Resolution	200
Atkinson *et al.* 1988	M	44	+	Skin infection	β-lact	NA	16	Knee, Ankle	NA, Resolution	22
Hannonen *et al.* 1989	F	23	+	Other	Linc	NA	10	Wrist, Hand, Knee	NA, Resolution	60
Mermel *et al.* 1989	F	29	+	Genital infection	β-lact	NA	11	Hand, Knee, Ankle, Other	NA, Persistence	730
Hannonen *et al.* 1989	M	45	+	ENT infection	β-lact	NA	8	Wrist	NA, Resolution	210
Hannonen *et al.* 1989	F	36	-	ENT infection	Linc	NA	12	Wrist, Ankle	NA, Resolution	30
Limonta *et al.* 1989	F	24	NA	ENT infection	IMDZ	NA	3	Elbow, Hand, Ankle	NA, Resolution	21
Limonta *et al.* 1989	F	25	+	Other	0	NA	8	Elbow, Hand, Ankle	NA, Resolution	28
Cope *et al.* 1992	M	48	+	Skin infection	β-lact	NA	14	Wrist, Hand, Knee, Ankle	NA, Persistence	801
Putterman *et al.* 1993	F	61	-	Digestive infection	β-lact	NA	NA	Wrist, Hand, Knee, Ankle	NA	51
Sensini *et al.* 1993	M	39	-	Prophylaxis	β-lact	NA	18	Elbow, Hand, Ankle, Foot	NA	NA
Guillemin *et al.* 1994	F	999	+	NA	NA	NA	NA	Ankle	NA	NA
Keating *et al.* 1995	M	26	+	ENT infection	β-lact	IMDZ	3	Wrist, Hand, Ankle	LCS, Resolution	43
Rochet *et al.* 1995	F	68	+	NA	β-lact	NA	0	Elbow, Knee, Ankle, Foot	NA, Resolution	8
Wright *et al.* 1996	F	36	+	ENT infection	β-lact	GLP	5	Shoulder, Wrist, Knee	0, Resolution	42
Cron *et al.* 1997	M	3	NA	ENT infection	β-lact	GLP	20	Knee	NSAID, Resolution	90
Nikkari *et al.* 1997	F	34	+	Other infection	β-lact	IMDZ	7	Wrist, Ankle	NA, Persistence	366
Löffler *et al.* 1998	F	6	-	0	0	GLP	NA	Elbow, Shoulder, Wrist, Knee	NSAID, Resolution	7
Robert *et al.* 1998	M	70	NA	ENT infection	β-lact	NA	2	Hand, Ankle, Foot	NSAID, Resolution	120
Veillard *et al.* 1998	M	57	+	ENT infection	β-lact	NA	19	Elbow, Knee, Other	NSAID + LCS, Resolution	15
Kocar *et al.* 1998	M	20	-	NA	β-lact	GLP	10	NA	NA, Resolution	27
Kocar *et al.* 1998	M	20	-	NA	β-lact	GLP	30	NA	NA	NA
Kocar *et al*. 1998	M	21	-	NA	β-lact	GLP	20	NA	NA	NA
Kocar *et al*. 1998	M	23	+	NA	β-lact	GLP	10	NA	NA, Resolution	21
Kocar *et al*. 1998	F	25	+	NA	β-lact	GLP	7	NA	NA, Resolution	25
Kocar *et al*. 1998	F	25	+	NA	0	GLP	NA	NA	NA	NA
Soderlin *et al*. 1999	F	65	+	Digestive infection	β-lact	NA	4	Ankle	NA, Resolution	330
Vermeulen *et al*. 2000	F	22	+	ENT infection	β-lact	NA	7	Shoulder, Hand, Knee	NA	NA
Vermeulen *et al.* 2000	M	67	+	Respiratory infection	Linc	NA	28	Wrist, Ankle	NA, Resolution	140
Razavi *et al.* 2000	M	47	+	Digestive infection	β-lact	IMDZ	14	Hip, Ankle, Other	NSAID, Resolution	121
Jacobs A. *et al*. 2001	F	36	+	Other infection	β-lact	IMDZ	7	Knee	0, Resolution	14
Delegue P *et al*. 2001	F	28	+	Urinary infection	β-lact	IMDZ	5	Hand, Knee, Ankle	0, Resolution	90
Löffler *et al*. 2002	M	11	+	Prophylaxis	Linc	GLP	12	Shoulder, Wrist, Ankle	NSAID, Resolution	690
Miner *et al.* 2005	M	32	NA	Digestive infection	QLN	IMDZ + GLP	7	Elbow, Knee, Foot	0, Resolution	125
Ducroix *et al*. 2006	M	45	-	Digestive infection	β-lact	IMDZ + GLP	8	Hand, Knee, Ankle, Other	NSAID, Resolution	110
Durand *et al*. 2008	F	10	NA	ENT infection	β-lact	IMDZ	30	Hip	Surgery, Resolution	20
Prati *et al.* 2008	F	64	+	Respiratory infection	β-lact	IMDZ	17	Elbow, Ankle	0, Resolution	10
Birnbaum *et a*l. 2008	M	72	+	Respiratory infection	Linc	IMDZ	55	Shoulder, Knee, Ankle	NSAID + LCS, Resolution	110
Ben Abdelghani *et a*l. 2009	F	43	-	0	0	IMDZ	NA	Shoulder, Wrist, Ankle	SCS, Resolution	110

Table 1: Literature review of all cases of reactive arthritis associated with *Clostridium difficile* (N=49).

Notes : - : negative, + : positive, 0: no treatment, ATB : Antibiotic therapy, β-lact : beta-lactamin, CDI : *Clostridium difficile* infection, ENT : eye-nose-teeth, F: Female , GLP : glycopeptide, IMDZ : imidazole, LCS : local corticosteroids, Linc : lincosamide, M: male, NA : Not available, NSAID : oral non steroid anti-inflammatory drugs, QLN : quinolone, SCS : Systemic corticosteroids, TUI : time between CDI and reactive arthritis

HIGHLIGHTS

- *Clostridium difficile* associated reactive arthritis are uncommon.
- It is more likely observed in younger patients with HLA B27-positive genotype.
- Outcome was favorable in 90% of patients.