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CASE BASED REVIEW

A case of cryopyrin-associated periodic fever syndrome during canakinumab administration complicated by inflammatory bowel disease

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Abstract

Cryopyrin-associated periodic fever syndrome (CAPS) is a highly debilitating disorder, which is characterized by unregulated interleukin-1β production driven by autosomal dominantly inherited mutations in the *NLRP3* gene. Patients with CAPS often present with early-onset episodes of fever and rash. These patients also present with variable systemic signs and symptoms, such as arthritis, sensorineural hearing loss, chronic aseptic meningitis, and skeletal abnormalities, but minimal gastrointestinal symptoms. Recently, effective therapies for CAPS targeted against interleukin-1 have become available. We report a case of a young Japanese woman with CAPS who developed inflammatory bowel disease during canakinumab therapy. The patient had colostomy after intestinal perforation and changed canakinumab to infliximab. To the best of our knowledge, this is the first report of a case of inflammatory bowel disease secondary to CAPS complicated by gastrointestinal symptoms and arthritis which canakinumab could not control. Patients with CAPS who have symptoms that cannot be controlled by canakinumab should be considered for possible co-morbidities.

Keywords Canakinumab · Cryopyrin-associated periodic fever syndrome · Inflammatory bowel disease · Infliximab

Cryopyrin-associated periodic fever syndrome (CAPS) is an autosomal dominantly inherited autoinflammatory disorder associated with mutations in the NLRP3 gene, which ultimately lead to excessive production of interleukin-1β (IL-1β) and systemic inflammation. The treatment for CAPS is an anti-IL-1β inhibitor. This is the first report of a case of inflammatory bowel disease secondary to CAPS complicated by gastrointestinal symptoms and arthritis which anti-IL-1β inhibitor could not control.

A female patient showed an urticarial-like rash on the trunk and extremities from early childhood. From approximately 4 years old, arthritis of both knee joints and intermittent fever appeared. She was diagnosed with oligoarticular type juvenile idiopathic arthritis and started taking oral medication of methotrexate and nonsteroidal anti-inflammatory drugs. After treatment, arthralgia was reduced, but joint swelling and high C-reactive protein (CRP) levels of 6–7 mg/dl (normal < 0.14 mg/dl) persisted. She started taking prednisolone (PSL) for arthralgia and arthritis. After induction of PSL, arthralgia was reduced, but remission was not achieved. PSL was continued at 10 mg/day because a large dose could cause side effects and a small dose could cause more pain. At the age of 15 years, she was suspected of having CAPS due to recurrent fever, an urticarial-like rash, and persistent arthritis. An *NLRP3* genetic test was performed. This test showed a mosaic mutation (*E567K*) and she was diagnosed with CAPS. After introduction of canakinumab, the fever and rash disappeared immediately. We gradually increased the dose of canakinumab (150 → 300 → 450 → 600 mg/dose) and shortened the dosing interval (8 → 6 → 4 weeks), but arthritis and CRP levels did not return to normal.

At the age of 20 years (4 years after canakinumab induction), she underwent gastrointestinal endoscopy for diarrhea of approximately 10 times a day and intermittent fever. A longitudinal ulcer without granuloma was observed. Diagnosis of Epstein–Barr virus enteritis was made because of a small number of Epstein–Barr virus encoded small ribonucleic acid cells, and diarrhea was alleviated by valganciclovir. However, the arthritis

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persisted and was not dependent on the amount of canakinumab. Therefore, the dose of canakinumab was reduced to 300 mg from 600 mg.

At the ages of 21 and 23 years, she had bloody stool in addition to diarrhea. Gastrointestinal endoscopy revealed multiple longitudinal ulcers (Fig. 1) and a stricture of the terminal ileum (Fig. 2); however, the pathology indicated that "there was atrophic mucosa with erosive inflammation. There was no loss of goblet cells or a disordered or twisted gland duct arrangement. Lymphocytes, plasma cells, and neutrophilic infiltration were found in the lamina propria, and the stroma was edematous. Mild cryptitis was also observed. No epithelioid granuloma had formed and no amyloid was deposited. The above pathological images showed non-specific inflammation. There were no malignant findings and no obvious virus-infected cells". Therefore, Crohn's disease or ulcerative colitis could not be confirmed. Because of intestinal perforation, small bowel stenosis, a high CRP level of 30 mg/dl, and intraperitoneal abscess, fasting management, and antimicrobial therapy were started after colostomy. We considered that the arthritis was attributed to inflammatory bowel disease (IBD), rather than to CAPS, because long-term fasting reduces joint swelling. We changed canakinumab to infliximab to prioritize control of intestinal inflammation, which may cause intestinal perforation and severe arthritis. After switching from canakinumab to infliximab, the arthritis, diarrhea, and quality of life were improved, but an intermittent urticarial-like rash (Fig. 3) emerged with afebrile condition. However, CRP levels remained of approximately 2 mg/dl were observed.

CAPS is a rare inherited autoinflammatory disorder, which is characterized by systemic, cutaneous, musculoskeletal, and central nervous system inflammation. Gain-of-function mutations in *NLRP3* in patients with CAPS lead to activation of the NLRP3 inflammasome, resulting in inappropriate release of inflammatory cytokines, IL-1β [1, 2]. CAPS includes three clinical entities: familial cold-induced autoinflammatory syndrome, Muckle–Wells syndrome (MWS), and chronic inflammatory neurological cutaneous articular syndrome/neonatal-onset multisystem inflammatory disease. These syndromes share several overlapping clinical features. All of the subtypes have fever, rash, and musculoskeletal, ocular, and central nervous system involvement to varying degrees. Some patients have clinical features that overlap with more than one subtype [3], which is consistent with the concept of a single disease spectrum (Table 1) [4, 5]. To date, there are many different sequence variants of the *NLRP3* gene and approximately 100 heterozygous *NLRP3* mutations associated with a CAPS phenotype [6–8]. The presence of multiple mutations coding the same amino acid suggests mutational hotspots [4]. Our patient with the *E567K* mutation was considered to have MWS on the basis of clinical symptoms [4].

Because IL-1 plays a central role in the pathogenesis of CAPS, blocking of IL-1 is the main therapeutic approach. Early and aggressive treatment for patients with CAPS is crucial for avoiding end-organ damage. Most CAPS-specific

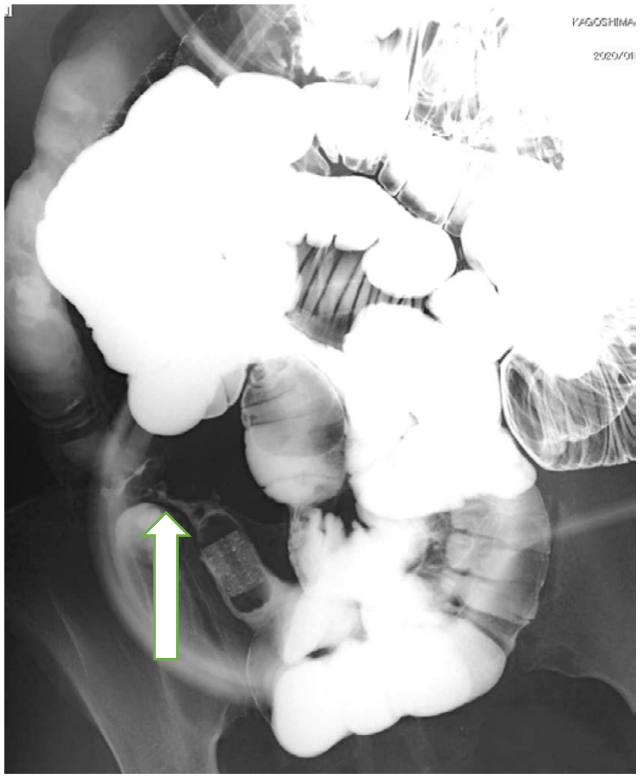

Fig. 2 Gastrointestinal contrast examination in a 23-year-old female patient with CAPS. The arrow indicates stenosis of the terminal ileum

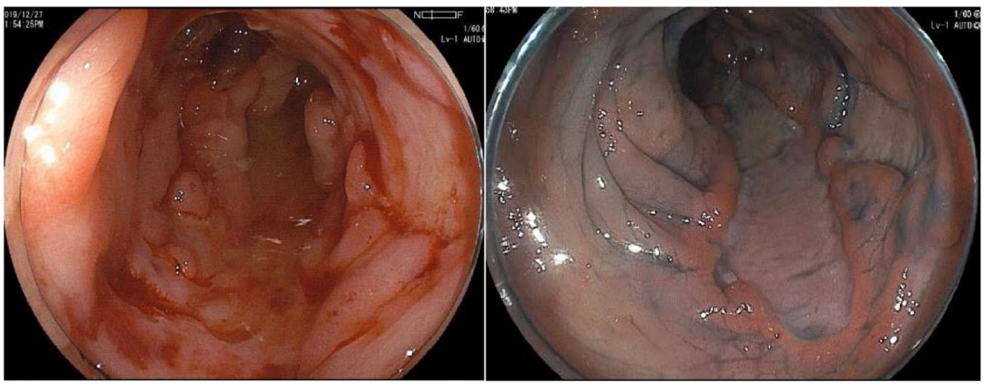

Fig. 1 Endoscopic findings in a 23-year-old female CAPS patient with newly developed bloody stools. Photographs showing many longitudinal ulcers in the sigmoid colon. A tissue biopsy showed no granulomas

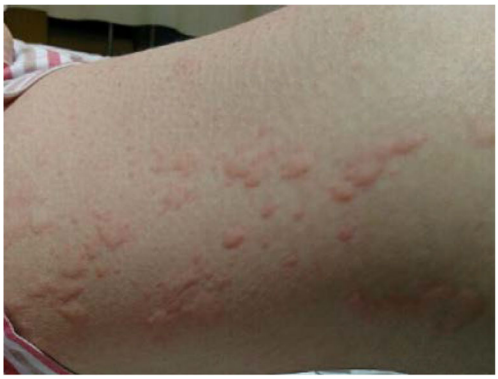

Fig. 3 Urticarial-like rash on the thigh in a 23-year-old female patient with CAPS. Similar rashes also appeared and disappeared on the trunk and upper limbs. There was no itching, such as urticaria

symptoms are reversible if treatment is provided early. Currently, three IL-1 inhibitors, anakinra, rilonacept, and canakinumab, are available. Their safety and effectiveness have been examined and documented in numerous studies [9–13]. Of these, only canakinumab is available in Japan. Canakinumab is a human anti-IL-1β monoclonal antibody that does not react with other members of the IL-1 family. Subcutaneous administration of canakinumab to 35 patients with CAPS resulted in a complete response in 34 patients [10]. Gene mutations of *NLRP3* include *R260W*, *T348M*, *D303*N, and *E311K* [10]. Lachmann et al. showed that treatment with subcutaneous canakinumab once every 8 weeks was associated with a rapid remission of symptoms in most patients with CAPS, especially those with MWS [10]. However, in our female patient with MWS, fever and rash rapidly improved after canakinumab administration, but arthritis did not achieve remission, despite the increase in canakinumab.

Kuemmerle Deschener JB et al. reported that gastrointestinal symptoms such as abdominal pain, diarrhea, and constipation were more common in CAPS patients with low-penetrance NLRP3 variants (*Q703K*, *V198M*, and *R488K*) (73%) than patients with pathogenetic NLRP3 variants (54%) [14]. However, there are no reports of CAPS complicated with IBD regardless of NLRP3 variants as well as *E567K* pathogenic mutation like this patient.

Specific single-nucleotide polymorphism mutations or polymorphisms related to NLRP3 inflammasome genes contribute to IBD susceptibility in various ways [15]. It has been reported that an aberrant activity of NLRP3 inflammasome in IBD may be due to a specific single-nucleotide polymorphism mutations [16, 17]. However, the role of NLRP3 in IBD is not yet fully elucidated as it seems to demonstrate both pathogenic and protective effects [15]. We could not find any reports of patients with CAPS who had concomitant IBD. In addition, there are no reports that canakinumab induced IBD.

Table 1 Clinical spectrum and features of CAPS

	FCAS	MWS	CINCA/NOMID
spectrum			
mild	←	→	severe
symptoms			
	rash	rash	rash
	fever/fatigue	fever/fatigue	fever/fatigue
	arthralgia/myalgia	arthralgia/myalgia	arthralgia/myalgia
			/arthropathy/distal femur overgrowth
	conjunctivitis/keratitis	conjunctivitis/keratitis	conjunctivitis/keratitis
		/uveitis	/uveitis/papilledema
		hearing loss	hearing loss
	headache	headache	headache/sterile meningitis
			/elevated intracranial pressure
Morbidity			
	amyloidosis (rare)	amyloidosis	amyloidosis, developmental delay

CAPS cryopyrin-associated periodic syndrome, *FCAS* familial cold autoinflammatory syndrome, *MWS* Muckle–Wells syndrome, *CINCA* chronic infantile neurological cutaneous articular syndrome, *NOMID* neonatal-onset multisystemic inflammatory disease

Gastrointestinal symptoms not currently included in standard CAPS outcome measures, often resistant to anti-IL-1β therapy, persisted in more than half of the children and adults reassessed at 1-year follow-up [14]. We set a therapeutic goal to reduce intestinal and joint inflammation, rather than fever and rash, for our patient's quality of life. Although intermittent urticarial-like rash (Fig. 2) and CRP levels of approximately 2 mg/dl continued, we achieved improvement of arthritis and diarrhea by switching from canakinumab to infliximab.

Symptoms vary from mild arthralgia to severe arthritis with painful swelling of joints in approximately 5–10% of patients with ulcerative colitis and in 10–20% of patients with Crohn's disease. According to available data, most patients with active IBD and concomitant arthritis benefit from infliximab therapy [18]. Infliximab, which is an important treatment for IBD with or without concomitant arthropathy [19], rapidly improves peripheral arthritis in patients with IBD. Some authors reported in open-label studies that there was improvement in peripheral arthritis in patients with IBD who were treated with infliximab at 5 mg/kg; these patients had previously been refractory to PSL or methotrexate [20, 21]. There have been no reports of the effectiveness of infliximab on CAPS. Although there have been several case reports of CAPS [22–36], no reports were associated with IBD. We considered that our patient's arthritis was only caused by IBD-related CAPS or both IBD and CAPS. Even now, the CRP of this patient is around 2 mg/dl; we must be cautious about the onset of amyloidosis in the future. A combination of canakinumab and infliximab may be able to ameliorate all symptoms of IBD secondary to CAPS, but this combination therapy is difficult to recommend in practice because of the rare experience and unpredictable adverse events.

This is the first case of IBD secondary to CAPS complicated by gastrointestinal symptoms and arthritis during canakinumab administration. We intend to follow progress of our patient's disease carefully.

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Authors' contributions All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.

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Compliance with ethical standards

Disclosures None.

Ethics approval All ethical considerations are taken into account to protect patient rights.

Consent to participate and consent for publication We obtained consent from this patient for report and publication.

Code availability Not applicable.

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