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Case Report

Efficiency of antifungal drugs in patient with p22^{phox}-deficient chronic granulomatous disease accompanied by Crohn's-like colitis

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Abstract

Here, we present a case of p22^{phox}-deficient chronic granulomatous disease (CGD) accompanied by pathologically Crohn's-like colitis. Treatment with antifungal drugs and 5-aminosalicylic acid yielded a drastic improvement in the intestinal manifestations of the disease, suggesting a similar pathophysiology between CGD and Crohn's disease.

Introduction

Gastrointestinal tract involvement in chronic granulomatous disease (CGD) is present in most such patients (colitis, perianal sepsis, gastric outlet obstruction, and liver abscess). A history of recurrent infections during childhood is common. Crohn's-like inflammatory bowel disease in CGD has been reported. On the other hand, there is evidence that release of pro-inflammatory cytokines is reduced and acute inflammatory response impaired in Crohn's disease, suggesting that it might be an immunodeficiency rather than an excessive inflammatory reaction[1].

Here we describe a case of p22^{phox}-deficient chronic CGD accompanied by pathologically Crohn's-like colitis. Treatment with antifungal drugs and 5-aminosalicylic acid (5ASA) yielded a drastic improvement in the intestinal manifestations of the disease.

Case

An 11-year-old boy was admitted to our hospital due to periproctodynia and painful bowel movement. His family history was unremarkable. Immunological and genomic studies at 14 months of age had resulted in a diagnosis of CGD. Flow cytometric evaluation of H_2O_2 production in neutrophils as detected by dihydrorhodamine 123 was less than 1% of that seen in normal neutrophils. Genomic analysis revealed compound heterozygous mutations of the p22-phox coding gene (*CYBA* ; a 4-base deletion on the 3′ end of exon 1 and a missense mutation (24GGG>AGG) in exon 2). After treatment with sulfamethoxazole/trimethoprim and interferon gamma (IFN-γ : 25X10k JRU/m^2 subcutaneously three times per week) together with isonicotinic acid, hydrazide, and rifampicin, his fever, lymphadenopathy, and granulomatous lesions on the chest improved rapidly. The following 10 years were uneventful, although symptoms such as lymphadenopathy and perianal abscess remained slightly during the period when IFN-γ was administered only once a week. Two weeks before admission to our hospital, the patient began to complain of lymphadenopathy and pain in the right inguinal region. Periproctodynia and painful bowel movement also appeared together with akathisia.

On admission, his height and weight were 129.3 cm (−2 SD) and 27 kg (−1.2 SD), respectively, and tem-

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perature 36.6°C. His heart rate, breathing rate, and blood pressure were 94/min, 18/min, and 98/52 mmHg, respectively. He showed aphthous, bilateral inguinal lymphadenopathy (right, 1.5 cm × 1.5 cm ; left, 0.5 cm × 0.5 cm) with tenderness and impetigo on the trunk.

Although Meropenem (60 mg/kg/d) was given intravenously after admission, his symptoms did not improve. His laboratory findings revealed no inflammatory reaction and a high level of β-D glucan, at 30.3 pg/ml (normal range : below 20), as shown in Table 1. A stool culture tested positive for *Candida albicans*. A colonoscopy revealed erosion, redness, and mild edema from the rectum to the sigmoid region (Fig. 1). The results of pathological investigations revealed mucosal inflammation (granulomas, aggregates of macrophages, the formation of lymphoid aggregates in transmural inflammation, crypt abscess, and metaplasia), as shown in Fig. 2. These findings were compatible with those of Crohn's disease. Upper gastrointestinal endoscopy revealed mild erosion. Although no pathogen could be confirmed by histopathological examination or blood culture, candidiasis was suspected based on the high levels of β-D glucan and mucosal inflammation. Therefore, combination treatment with 5ASA, micafungin (MCFG), and fluconazole (FLCZ) was administered together with subcutaneous injection of IFN-γ 30X10k JRU/m^2 every other day. Fluconazole interferes with fungal cytochrome P450 activity and decreases ergosterol synthesis, while MCFG is a concentration-dependent inhibitor of 1,3-β-D glucan synthase. Therefore, their antifungal mechanisms are entirely different, and their combination is considered to be effective. The patient's periproctodynia, painful bowel movement, and lymph nodes subsequently showed a gradual improvement and the impetigo disappeared. The levels of β-D glucan decreased and the results of a second colonoscopy appeared normal on the 50th day. The patient was finally discharged on day 65 after admission. The intestinal manifestations of the disease did not reappear under treatment with IFN-γ every other day together with 5ASA and FLCZ for more than 1 year on an outpatient

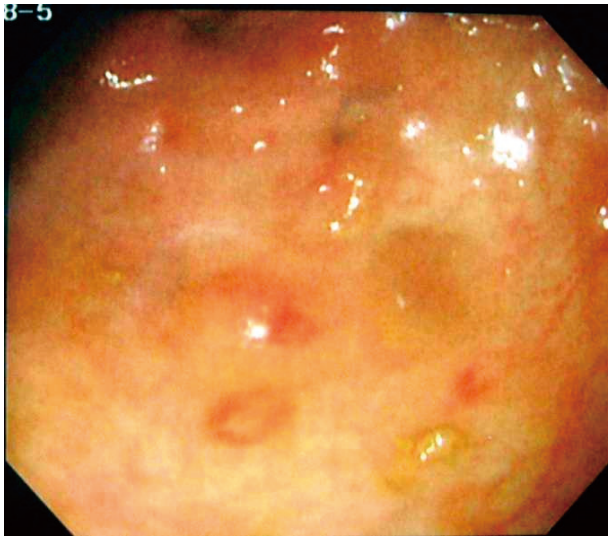
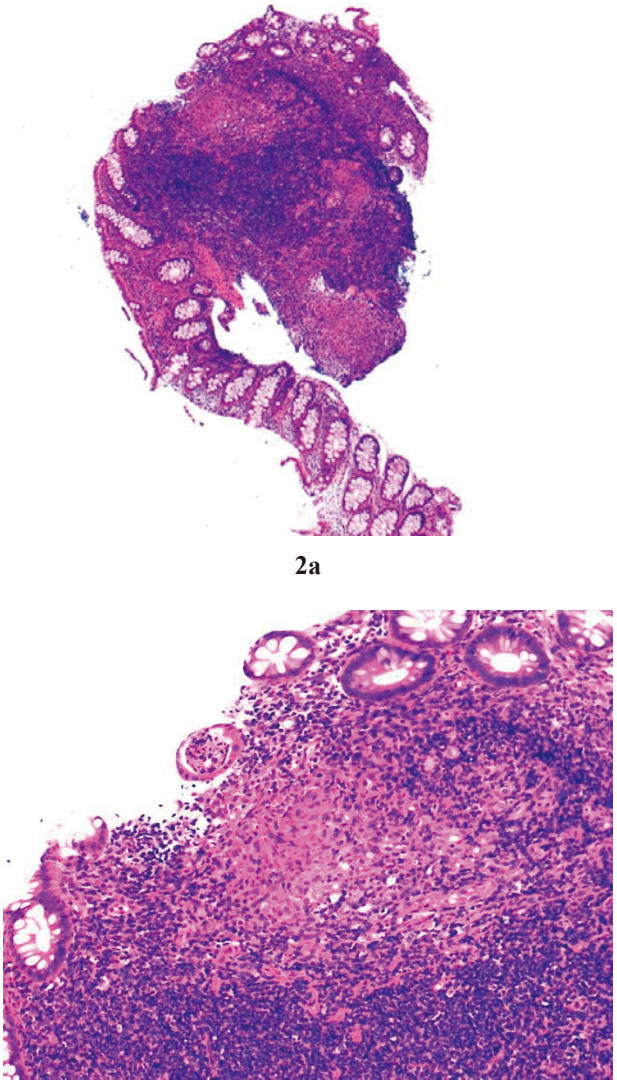


Fig. 1 Endoscopy revealed erosion, redness, and mild edema from rectum to sigmoid region.

Table 1. Laboratory findings

WBC	20.6	k/μl	T/B ratio	78%/16%		Nitroblue tetrazolium test	<1%
neut	59.5	%	CD3	50.30%		neutrophil	
eosin	1.2	%	CD4	30.40%		phagocytic capacity	55.90%
baso	0.1	%	CD8	18.70%		bacteriocidal capacity	22.00%
lymph	25.0	%	CD4/CD8	1.63			
mono	14.2	%	HLA-DR	39.7%		Chemiluminescence	
RBC	4.13	M/μl				(H_2O_2 production)	0.25%
Hb	9.0	g/dl	blastogenesis			DHR-123	decreased
Ht	28.3	%	PHA	59034	CPM	cytochrome b (7D5MoAb)	(-)
PLT	37.7	10 k/μl	CON-A	50201	CPM		
			PWM	16240	CPM	β D-glucan	30.3 pg/ml
IgG	1,200	mg/dl				serum Candida antigen	(-)
IgA	45.5	mg/dl	ADCC activity	67%		serum Aspergillus antigen	(-)
IgM	116	mg/dl	NK cell activity	21%		stool *Candida albicans*	1+
IgD	10	mg/dl	serum G6PDH	1.1	IU/1/98.6F	stool *Clostridium difficile*	(-)
IgE	55.1	IU/ml	MPO staining	normal		blood culture	(-)
IgG subclass normal range for age							
C3	128	mg/dl					
C4	32	mg/dl					
CH50	51.7	mg/dl					



2a

2b

Fig. 2 Colonoscopy revealed granulomas, aggregates of macrophages, formation of lymphoid aggregates in transmural inflammation, crypt abscess, and metaplasia. a (×20), b (×100)

basis.

Discussion

Small and large intestinal manifestations in CGD were first reported by Ament in 1973. Since then, a number of such cases have been reported with large intestinal involvement (non-caseating granulomas)[2], and deep geographic and serpiginous ulcers, findings very similar to those of Crohn's disease[3-5]. Beatriz et al. investigated 156 patients with CGD and found gastrointestinal involvement in 46. Crohn's-like inflammatory bowel disease was diagnosed in 5 of these patients (11%), with 2 requiring diverting colostomy and repair of a rectovesical fistula[6]. Crohn's disease and gastrointestinal involvement in CGD share many common characteristics. In general, most such changes occur in the colon and are mild. In contrast to the poorly formed granulomata typical of Crohn's disease, granulomata in gastrointestinal involvement in CGD were sharply defined aggregates of epithelioid histiocytes surrounded by dense lymphocytic inflammation[6]. The granulomata in the present case comprised sharply defined aggregates of epithelioid histiocytes together with lymphocytic inflammation. The high tendency for such features to appear in the colon suggests that over-stimulation of the inflammatory response plays a role in the development of gastrointestinal involvement in CGD. Some case reports on colitis associated with CGD have suggested that persistence of viable bacteria within phagocytes located in the colonic mucosa might cause excessive stimulation of the inflammatory process and subsequent mucosa damage[7]. All the patients in previously reported cases have been treated with steroids. Sulfasalazine, infliximab, and granulocyte-colony stimulating factor were also used in some cases.

In two similar cases with inflammatory complications, hematopoietic stem cell transplantation was necessary[8]. However, to our knowledge, there have been no reports to date of patients with CGD being treated with antifungal drugs and 5ASA. In the present case, the patient's condition improved markedly without steroids. Some studies have investigated the relationship between fungus and Crohn's disease[9][10]. Interestingly cytochrome b content and toxic oxygen metabolite production in circulating neutrophils from patients with Crohn's disease is diminished[11], and superoxide anion production by mitogen is significantly lower than by normal neutrophils[12]. These characteristics have also been identified in CGD. Therefore, in some cases, Crohn's disease may be due to the same or a similar hereditary pathophysiology as that in CGD. This suggests that antifungal drugs or/and antibiotics would be effective in treating such intestinal involvement.

In conclusion, the present case suggests a similar pathology between CGD and Crohn's disease. In addition to endoscopic examination, fungal infection should also be considered in treating such cases of intestinal involvement.

Conflict of interest

This work was not supported by any grant and the authors would like to report no conflict of interest.

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抗真菌薬が有効であったクローン病類似大腸炎をきたした p22^{phox} 欠損慢性肉芽腫症の一例

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【要旨】 病理学的にクローン病に類似した大腸炎を伴った p22^{phox} 欠損慢性肉芽腫（CGD）の 1 例を経験した。大腸炎の所見は抗真菌薬および 5-アミノサリチル酸製剤の治療によって劇的に改善した。CGD とクローン病との間での病態の共通性を示唆された。

〈キーワード〉 慢性肉芽腫症、クローン病、INF-γ、真菌、β-D グルカン