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CASE REPORT

Metronidazole-induced encephalopathy during treatment for refractory diarrhea after cord blood transplantation

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Abstract
A 56-year-old man underwent cord blood transplantation for angioimmunoblastic T-cell lymphoma. He developed severe diarrhea and abdominal pain that persisted for more than 4 months. We suspected that he might have cord colitis syndrome (CCS), so metronidazole (MNZ) was administered. The patient's abdominal pain and diarrhea showed some improvement after the initiation of MNZ therapy, but they worsened on the cessation of MNZ, which prompted us to resume MNZ treatment. After the patient had taken MNZ (1500–2000 mg/day) for 78 days, he developed somnolence and dysarthria. We diagnosed him with metronidazole-induced encephalopathy (MIE) based on the characteristic magnetic resonance imaging findings and the clinical course. The patient's dysarthria and somnolence improved within a few days after the discontinuation of MNZ. CCS is a recently proposed clinical entity defined as a persistent diarrheal illness that is culture-negative, antibiotic-responsive, and not attributable to any known cause. Patients with CCS often have recurrent diarrhea after the discontinuation of MNZ and may require prolonged treatment for a median of 120 days. When treating CCS with MNZ, physicians should be alert for the development of MIE.

Keywords Metronidazole · Metronidazole-induced encephalopathy · Neurotoxicity · Cord blood transplantation

Introduction

Metronidazole-induced encephalopathy (MIE) is a rare adverse event in patients treated with metroniadzole (MNZ). The symptoms can include cerebellar dysfunction, altered mental states, and seizures. It usually recovers after the cessation of MNZ and the neurological prognosis is reasonably good. In rare cases, however, MIE can be irreversible. Thus, physicians must pay careful attention to detect the development of this condition [1]. Recently, the novel clinical entity CCS was proposed, and there have been some reports of patients with persistent diarrhea after cord blood transplantation (CBT) in which MNZ therapy was useful [2, 3]. We herein report a case of MIE during treatment for refractory diarrhea after CBT.

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Case report

A 56-year-old man underwent CBT for angioimmunoblastic T-cell lymphoma (Fig. 1). He developed severe diarrhea and abdominal pain on the 6th day after CBT, and stage 4 gastrointestinal graft-versus-host disease (GI-GVHD) was subsequently diagnosed. Following several administrations of high-dose steroids and intra-arterial steroid-injection therapy, the patient's GI-GVHD disappeared on pathological studies (Fig. 2). However, his abdominal pain and diarrhea persisted. The colonoscopy showed severe redness and swelling of terminal ileum. The inner pass of the terminal ileum constricted and the mucosal membrane easily bled. The mucosal membrane of the ascending and rectum was generally coarse and indistinct vascular pattern was seen on the endoscopy. The transverse and sigmoid colon had relatively mild inflammation. The histopathological study showed the formation of granulation tissue with noticeable infiltration of neutrophils inside the mucous membrane of the cecum and superficial monolayer sheet of regenerated epithelial cells. We found slight distortion of the gland ducts without infiltration of inflammatory cells in the ascending

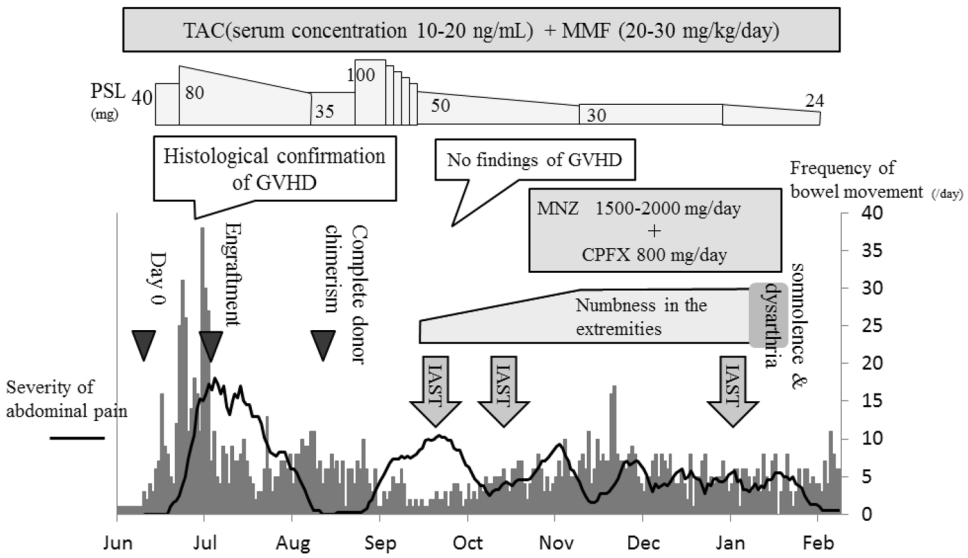

Fig. 1 *TAC* tacrolimus, *MMF* mycophenolate mofetil, *CPFX* ciprofloxacin, *MNZ* metronidazole, *PSL* prednisolone, *IAST* intra-arterial steroid-injection therapy. The severity of abdominal pain shows the effective doses of analgesic administered as needed per day

colon. There were distorted gland ducts and fibrosis of the interstitial tissue in the rectum but the inflammatory cells were unremarkable. We could not detect the evidence of GVHD such as increased apoptotic bodies in the all specimens. The esophagogastroduodenoscopy showed whitish and coarse mucous membrane of duodenum, mucosal erosion of stomach, and white patches on esophagus. The histopathological findings of endoscopic biopsy specimen were no evidence of GVHD and no evidence of involvement of inflammatory cells. The periodic acid-Schiff stain of the esophageal biopsy specimen was negative for fungal organisms. Neither Paneth-cell metaplasia nor granulomatous inflammation was observed in either the colonoscopic specimens or esophagogastroduodenoscopic specimens. The stool examinations were negative for *Clostridium difficile* toxin and pathogenic bacteria. The blood cultures on day 93 yielded *Enterococcus faecium*, but repeated cultures on day 100 were negative. An immunostaining study and quantitative polymerase chain reaction assay of the colonoscopic biopsy specimens for cytomegalovirus were both negative. We suspected that he might have CCS, so MNZ (1500–2000 mg/day) and ciprofloxacin were administered from day 139. The patient's abdominal pain and diarrhea showed some improvement after the initiation of MNZ therapy, but they worsened on the cessation of MNZ on days 163–168, which led us to resume MNZ treatment.

The patient developed somnolence and dysarthria on day 215. Brain MRI was performed on day 222. T2-weighted FLAIR MRI of the brain showed bilateral symmetric hyperintense lesions in the cerebellar dentate nuclei, medial longitudinal fasciculus and inferior colliculus (Fig. 3a, b). Hepatic encephalopathy and viral encephalitis were ruled out based on the laboratory findings and a cerebrospinal fluid examination (Table 1). Although we did not measure the serum vitamin B1 level, the patient had been taking thiamine with intravenous hyperalimentation. We diagnosed MIE based on the characteristic MRI findings and the clinical course, and immediately stopped MNZ. The patient's dysarthria and somnolence improved within a few days after the discontinuation of MNZ. The hyperintense lesions in the cerebellar dentate nuclei and the brainstem disappeared on day 237 (Fig. 3c, d). After we finished MNZ therapy, we administered meropenem, tazobactam/piperacillin, sulbactam/cefoperazone, teicoplanin, and gancicrovir. The diarrhea and abdominal pain subsided, and we finished antibiotics and anti-virus drugs 1 month after we ceased MNZ therapy. Thereafter we performed palliative therapy for the diarrhea and abdominal pain, and we administered antibiotics (sulbactam/ampicillin, cefazolin) or anti-viral drugs (gancicrovir, foscarnet) when he had a fever, pneumonia, CMV antigenemia or deteriorated inflammation on laboratory findings. The diarrhea and stomach pain recurrently deteriorated and improved. We slowly tapered steroid (prednisolone 12–26 mg/day). About 5 months after we ceased MNZ therapy, the diarrhea worsened. We confirmed the relapse of GI-GVHD on the colonoscopic biopsy. We treated GVHD with steroids, tacrolimus and mycophenolate mofetil, but we could not increase steroid because of the risk of infection. About 8 months after we ceased MNZ therapy, the diarrhea worsened with recurrent bloody stool. GI-GVHD worsened further on colonoscopic examination and histopathological study. About nine months after we ceased MNZ therapy, he died of pneumonia.

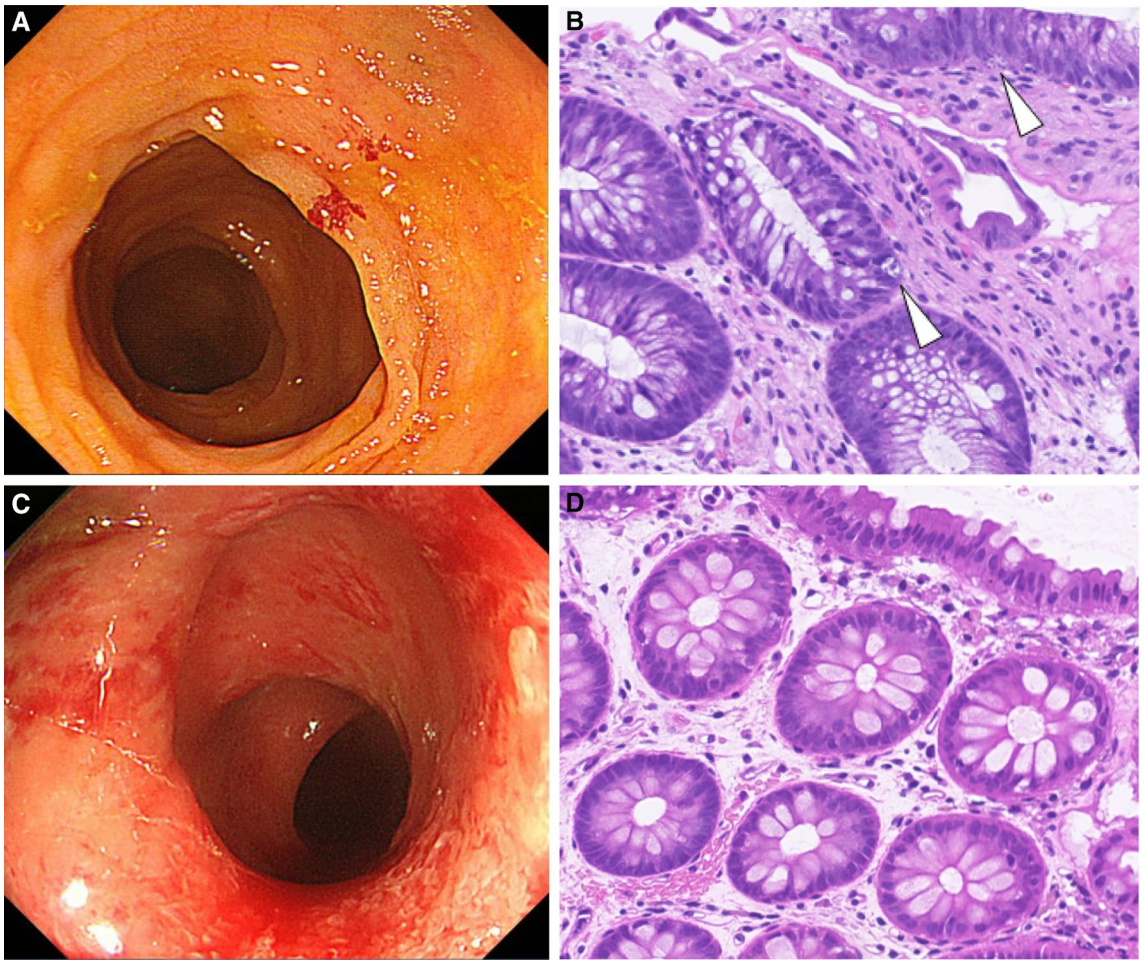

Fig. 2 Colonoscopy on day 16 showed an indistinct vascular pattern and edematous mucosal membrane in the transverse, descending, and sigmoid colon. Red spots were seen in the sigmoid colon and rectum. The figure shows the transverse colon (**a**). The histopathologic study of the colonoscopic biopsy specimens from the rectum revealed crypt distortion and loss, slight infiltration of inflammatory cells, and scattered apoptotic bodies (arrows) (**b**). A repeated colonoscopy was performed on day 112. The mucosal membrane of the terminal ileum was red and edematous and easily bled. The mucosal membrane of the ascending and rectum was generally coarse, and an indistinct vascular pattern was seen. The transverse and sigmoid colon had relatively mild inflammation. The figure shows the ascending colon (**c**). A colonoscopic biopsy from the rectum showed no evidence of GI-GVHD. Neither Paneth-cell metaplasia nor granulomatous inflammation, which are often present in CCS, were observed (**d**)

Discussion

MNZ is widely used for the treatment of anaerobic bacterial and protozoal infections. Refractory diarrhea after CBT can be caused by GI-GVHD, CMV colitis, and bacterial colitis. Recently, the novel clinical entity CCS was proposed [2]. CCS is defined as a persistent diarrheal illness that is culture-negative, antibiotic-responsive and not attributable to any known cause. In this study, 45% of the patients with CCS had recurrent diarrhea and were re-treated with fluoroquinolone and MNZ for a median of 120 days (range 14–730). Herrera et al. speculated a bacterial infection might cause the CCS because the CCS responded to antibacterial therapy. Bhatt et al. suggested that *Bradyrhizobium enterica* might be a pathogen of CCS [4], but this notion still remains controversial [5]. In our patient, a DNA sequence analysis of the biopsy specimen obtained by endoscopy on day 138 showed negative findings for *Bradyhizobium* (Tested by The Institute of Medical Science, The University of Tokyo, Tokyo, Japan). However, the chronic granulomatous colitis observed on the histopathological examination could represent an inflammatory colitis because the histopathological features are similar to those seen in Crohn's disease. Herrera et al. described that these histopathological features were not observed in GVHD or other diarrheal illness after allogeneic bone marrow transplantation (BMT) or peripheral blood stem cell transplantation (PBSCT) [2]. In contrast, Shimoji et al. reported that the chronic active colitis with granulomatous inflammation and Paneth cell metaplasia was frequently present in the GVHD and/or CMV colitis after

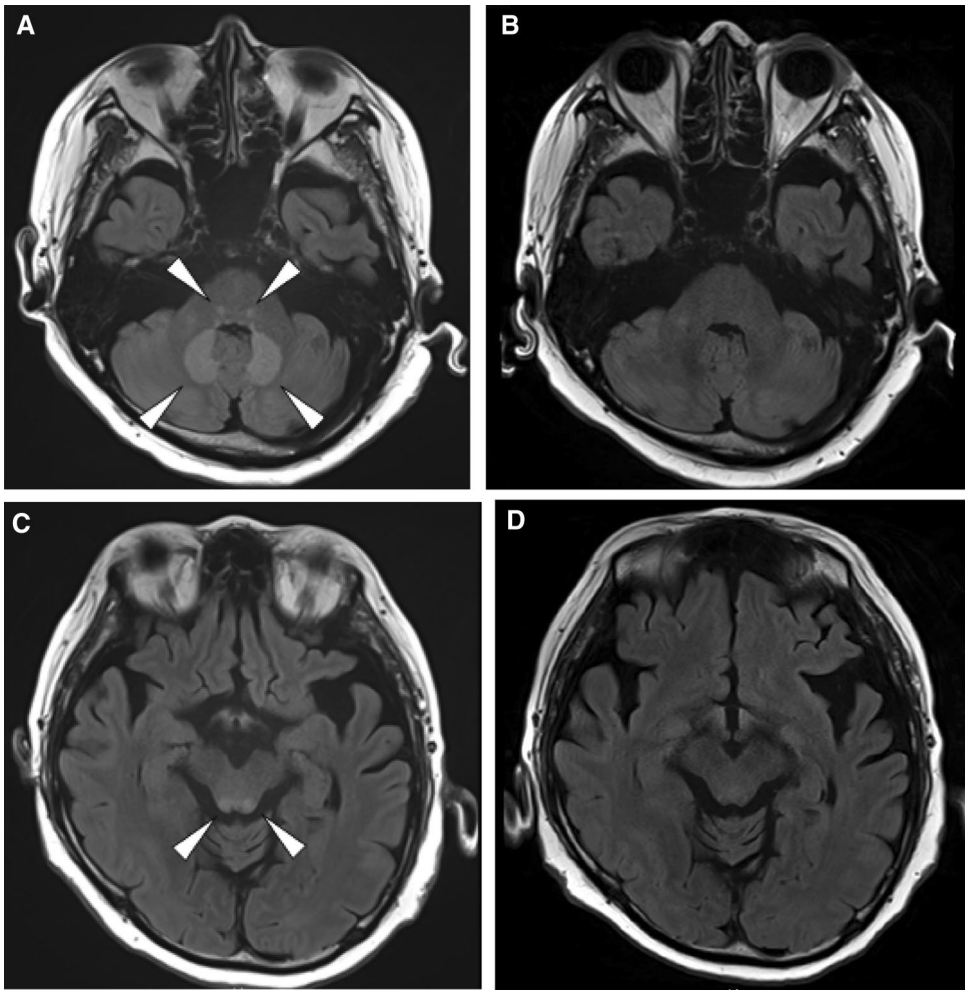

Fig. 3 T2-weighted FLAIR MRI of the brain at the onset of MIE demonstrated bilateral symmetric hyperintense lesions (arrows) in the cerebellar dentate nuclei, medial longitudinal fasciculus (**a**) and inferior colliculus (**b**). The lesions disappeared at 15 days after the discontinuation of MNZ (**c, d**)

Table 1 The laboratory findings on the development of MIE

WBC	7.74×10^9/L	AST	28 U/L	CSF-Glu	83 mg/dL
Neutrophils	77.7%	ALT	17 U/L	CSF-TP	72.5 mg/dL
Lymphocytes	7.5%	LDH	437 U/L	CSF-Alb	407.8 mg/L
Monocytes	14.1%	ALP	1896 U/L	CSF-LDH	29 IU/L
Eosinophils	0.6%	γ-GTP	1358 U/L	CSF-IgG	2.6 mg/dL
Basophils	0.1%	TP	4.1 g/dL	CSF-WBC	Negative
RBC	2.31×10^{12}/L	Alb	2.6 g/dL	CSF-RBC	Negative
Hb	7.9 g/dL	Ch-E	132 U/L	CSF-cytology	Negative
Ht	23.4%	T-Bil	1.6 mg/dL	CSF-CMV IgG)	Negative
MCV	101.3	D-Bil	0.9 mg/dL	CSF-CMV IgM	Negative
Plt	58×10^9/L	Cre	1.08 mg/dL	CSF-HSV IgG	Negative
Reti	4.16%	BUN	50 mg/dL	CSF-HSV IgM	Negative
		CK	15 U/L	CSF-sIL2R	< 50.0 U/ml
PT(INR)	0.91	Glu	104 mg/dL		
APTT	29.5 sec	AMY	40 U/L		
FIB	335 mg/dL	Na	142 mEq/L	Serum CMV-PCR	Negative
D-dimer	11.2 μg/mL	K	3.7 mEq/L	Serum HHV6-PCR	Negative
		Ca	8.4 mg/dL		
		CRP	0.5 mg/dL		
		NH_3	84 μg/dL		

BMT or PBSCT [6]. The histopathological findings are not specific to the CCS. In our case, the GI-GVHD disappeared on a pathological study after steroid therapy. The stool examinations were negative for *Clostridium difficile* toxin and pathogenic bacteria. Tests for cytomegalovirus were also negative. The blood cultures on day 93 yielded *Enterococcus faecium*, but repeated cultures on day 100 were negative. Since the patient's symptoms persisted despite the blood cultures being negative, *E. faecium* was not likely the cause of the persistent diarrhea. Neither Paneth-cell metaplasia nor granulomatous inflammation in the colonoscopic biopsy specimens were observed in our case (Fig. 2). These are often present but not mandatory in CCS [2]. Accordingly, we suspected that he was suffering from CCS. Indeed, the diagnosis of CCS was not definitive due to the fact that it is very difficult to make a definite diagnosis since its etiology still remains unestablished. His diarrhea and abdominal pain responded to MNZ therapy and recurred shortly after the discontinuation of MNZ, which led to the long-term administration of MNZ. Although marked improvement was not seen, we continued MNZ therapy since the previous study documented that the CCS often required a long-term treatment. We also used ciprofloxacin according to the previous report [2]. The alternative treatment was not proposed for the CCS.

The common adverse events of MNZ include indigestive symptoms such as nausea and diarrhea. While MNZ is usually well tolerated, in rare cases it can cause serious neurological adverse events, including central nervous system toxicity and peripheral neuropathy. Although the incidence of MIE is unknown, several reports have suggested that the use of higher doses of MNZ and the longer-term administration of MNZ is a risk factor for neurotoxicity [7–9]. According to a review of the previous 64 cases by Kuriyama et al. [1], the mean duration of MNZ therapy was 54 days (95% CI 21.2–87.9) and the mean cumulative dose of MNZ was 93.4 g (range 0.25–1095). In the present case, the patient took MNZ (1500–2000 mg/day) for 78 days, and the cumulative dose was 148 g.

MIE includes cerebellar dysfunctions such as dysarthria and ataxia, altered mental states, seizures, ototoxicity, and visual impairment [1]. T2-weighted MRI of the brain reveals bilateral symmetric hyperintense lesions. The lesions are typically located at the cerebellar dentate nuclei, the corpus callosum, the midbrain, the dorsal pons, and the medulla. The cerebellar dentate nuclei are most commonly involved on MRI [10]. MRI findings of bilateral symmetric involvement are highly characteristic of MIE and MRI is important in the diagnosis and follow-up. In most cases, the neurological symptoms resolve and the lesions on MRI disappear with the discontinuation of MNZ. In rare cases, however, the condition can be irreversible [1]. Although the pathophysiological mechanisms of metronidazole neurotoxicity remain to be elucidated, several causes have been proposed: axonal swelling with increased water content due to toxic injury; vascular spasm with mild reversible localized ischemia; the modulation of the gamma-aminobutyric acid receptors within cerebellar and vestibular systems; RNA binding with the inhibition of protein synthesis and axonal degeneration [11]. Wernicke encephalopathy is the most important disease in the differential diagnosis of MIE. MNZ is structurally similar to thiazole, a precursor of thiamine. Thus, it could lead to a reduction in thiamine absorption by acting as a thiamine analog [12]. The other differential diagnoses include methyl bromide intoxication, maple syrup urine disease, and enteroviral encephalomyelitis [10].

MNZ-induced peripheral neuropathy can also occur. Cação et al. reviewed 84 cases of MNZ-induced neurotoxicity [11]. According to this, 31% of the patients with MNZ-induced neurotoxicity had peripheral neuropathy (90.5% with CNS toxicity). The complete resolution of symptoms was observed in 36.7% of the patients with peripheral neuropathy after the discontinuation of MNZ; in contrast, 91.9% of the patients with CNS toxicity experienced the complete resolution of their symptoms. The mean time for recovery in patients with peripheral neuropathy and CNS toxicity was 72.4 days and 23.3 days, respectively. The recovery of the patients with peripheral neuropathy tended to be longer and the symptoms were more likely irreversible in comparison to the patients with CNS toxicity.

Our patient recovered rapidly after the discontinuation of MNZ, and lesions on MRI were completely resolved. The patient also had severe progressive peripheral polyneuropathy. We did not perform nerve conduction study. Only the position sense of the left foot improved after the discontinuation of MNZ; the senses of pain and touch in the lower legs did not improve. His peripheral neuropathy was possibly related to MNZ therapy to some extent, while conditioning chemotherapy or tacrolimus might be largely involved in it.

In conclusion, we herein reported the case of a patient who developed MIE during MNZ therapy for refractory diarrhea after CBT. Recently, the novel clinical entity CCS was proposed. CCS is often recurrent and requires the long-term administration of MNZ. We expect that more and more patients with refractory diarrhea after CBT will have a chance to receive MNZ. MNZ-induced neurotoxicity should be considered in any patients who present with neurological symptoms during MNZ therapy. Although the prognosis of MIE is reasonably good, the disability can be irreversible. Therefore, physicians should pay careful attention to patients who present with these symptoms in order to correctly diagnose such cases.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest in association with the present study.

Human rights All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from all patients for being included in the study.

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