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CASE REPORT

Severe ileus and urinary retention in a patient with tuberculous meningitis

Shingo Konno, Tomomi Imamura, Masashi Inoue, Mayumi Murata, Hideki Sugimoto & Toshiki Fujioka

Department of Neurology, Toho University Ohashi Medical Center, Tokyo, Japan

Correspondence
Shingo Konno, Department of Neurology, Toho University Ohashi Medical Center, 2-17-6 Ohashi, Meguro-ku, Tokyo 153-8515, Japan.
Tel: +81-3-3468-1251; Fax: +81-3-3468-5082;
E-mail: d500372@oha.toho-u.ac.jp

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Key Clinical Message

An acute ileus and/or urinary retention are recognized as emergent complications requiring appropriate depressurizing treatments. Meningitis should be suspected as a cause of these autonomic disturbances.

Keywords

Autonomic disturbance, CNS demyelination, cranial nerve palsy, ileus, tuberculous meningitis, urinary retention.

Introduction

Tuberculous meningitis (TBM) occurs when tuberculosis bacteria (*Mycobacterium tuberculosis*) invade the membranes and fluid surrounding the brain and spinal cord. The complications of TBM are significant, and in some cases life-threatening, and include convulsions, hearing loss, increased intracranial pressure, hydrocephalus, brain infarction, and urinary retention [1–3]. Specifically, urinary retention is a type of autonomic disturbance that is common in patients with CNS inflammatory diseases and can usually be attributed to multiple sclerosis, acute disseminated encephalomyelitis (ADEM), myelitis, and meningitis-retention syndrome (MRS) [4–6]. However, acute colonic ileus, without any mechanical obstructions, is a relatively rare condition in meningitis patients [7, 8] and its mechanism remains unclear.

Here, we report a case of TBM accompanied by severe ileus and urinary retention, which were improved gradually after treating the meningitis.

Case History

A 42-year-old Japanese man was admitted to our hospital complaining of paroxysmal dull headaches, in the bilateral temporal regions, for 5 days before admission. He had no history of any recent vaccinations or common infections, nor had he come into contact with any source of tuberculosis. Apart from a 40°C fever, results of a general examination were normal. Neurological examination revealed mild neck stiffness and Kerning's sign of meningitis; however, other clinical signs were absent, including cranial nerve involvement, muscle weakness, brisk reflexes, pathological reflexes, and jolt accentuation of headache. The patient clinical course is shown in Figure 1.

Differential Diagnosis, Investigations, and Treatment

Hematological and blood chemical examinations showed a normal white blood cell (WBC) count and normal serum levels of the C-reactive protein. An initial cerebrospinal fluid (CSF) examination revealed an elevated pressure (175 mmH_2O) and the following concentration measurements: WBC count, 63 cells/μL (61 mononuclear cells); total protein, 151 mg/dL; glucose, 59 mg/dL (serum level 112 mg/dL); chloride, 119 mmol/L; and adenosine deaminase <2.0 U/L. Cytology was negative for malignant cells, and both Ziehl–Neelsen and Indian

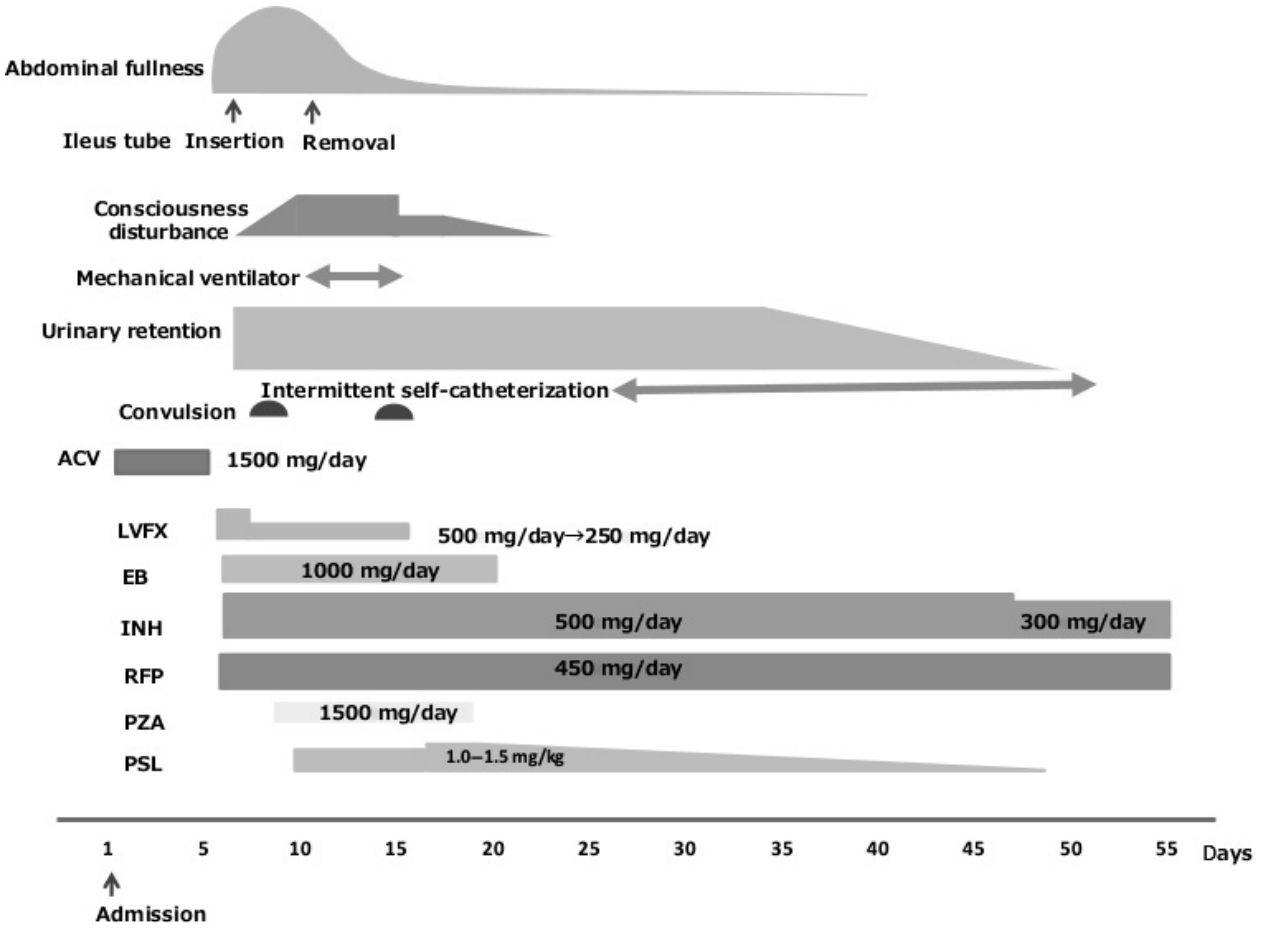

Figure 1. Patient clinical course. ACV, acyclovir; LVFX, levofloxacin; EB, ethambutol; INH, isoniazid; RFP, rifampicin; PZA, pyrazinamide; PSL, prednisolone.

staining were negative. A culture of the CSF tested negative for microorganisms, including *Mycobacterium tuberculosis*. Similar results were found using the polymerase chain reaction (PCR) on a CSF sample, and a tuberculin skin test was also negative. CSF pair values of IgG and IgM antibodies, with cytomegalovirus and herpes zoster virus, were within the normal range. The hospital laboratory data are presented in Table 1.

The patient was treated for possible herpes encephalitis with intravenous doses of acyclovir (1500 mg/day); however not only antibodies, but also direct PCR of the herpes simplex in the CSF were negative, and then acyclovir was discontinued. The patient continued to exhibit a high fever and developed a mildly stuporous mental state, with a Glasgow Coma Scale score of 14 (E4M4V6), 4 days after admission. Brain magnetic resonance imaging (MRI) with contrast enhancement showed no abnormal lesions on T1, T2, and diffusion-weighted images; however, gadolinium-enhanced T1-weighted images showed marked thickening of the leptomeninges, particularly around the medulla oblongata (Fig. 2). The patient complained of lower abdominal distension, and over 1000 mL of residual urine was removed via a Foley urinary catheter. Several hours later, he experienced acute whole abdominal fullness and pain, and an abdominal computed tomography (CT) scan showed marked total colonic dilatation, without volvulus or tumor mass (Fig. 3). An ileus tube was immediately inserted through the nose into the intestines, and the bowel contents were aspirated continuously. Additionally, the patient was placed on a mechanical ventilator due to aspiration of vomitus.

A second CSF analysis revealed an initial pressure of 200 mmH_2O, and the following concentration measurements: 100 WBCs/μL (95 mononuclear cells), 1035 mg/dL total protein, 25 mg/dL glucose (serum level 104 mg/dL), 114 mmol/L chloride, 18.7 U/L adenosine deaminase, and 864.1 pg/mL myelin basic protein (MBP). Additionally, the IgG index was 0.67 [(CSF IgG/serum IgG)/(CSF albumin/serum albumin)], without the presence of oligoclonal bands. Although the serum interferon-

Table 1. Hospital laboratory data in hospitalization.

Blood cell count			Cerebrospinal fluid analysis	First time	Second time	
WBC	7000	/μL				
RBC	460	x10^4/μL	Open pressure	175	200	mmH_2O
Hb	14.2	g/dL	Cell number	63	100	
Ht	40.5	%	M:P	61:2	95:5	
Plt	23.9	x10^4/μL	Pro	151	1035	g/dL
Biochemical examination			Glu	59	25	g/dL
TP	7.6	g/dL	Cl	119	114	mmol/L
ALB	4.8	g/dL	ADA	<2.0	18.7	U/L
T-Bil	1.0	mg/dL	MBP		864.1	pg/mL
AST	16	IU	IgG index		0.67	
ALT	21	IU	Virus antibody titers		Normal value	
LDH	370	IU/L	HSV IgG	0.30	<0.80	
BUN	17	mg/dL	HSV IgM	0.55	<0.80	
Cr	1.2	mg/dL	CMV IgG	0.43	<0.80	
Na	136	mM	CMV IgM	<0.20	<0.80	
K	4.1	mM	VZV IgG	0.22	<0.80	
Cl	101	mM	VZV IgM	0.11	<0.80	
CPK	80	IU	HSV-PCR	Negative		
CRP	0.02	mg/dL	TB-PCR	Negative		
Glu	112	g/dL	Ziehl–Neelsen and Indian staining		Negative	
HbA1c	5.5	%	Culture	Negative		
			Cytology	Class I		

M, mononuclear cell; P, polymorphonuclear cell; Pro, protein; ADA, adenosine deaminase; MBP, myelin basic protein; HSV, herpes simplex virus; CMV, cytomegalovirus; VZV, herpes zoster virus; TB-PCR, polymerase chain reaction for *Mycobacterium tuberculosis*.

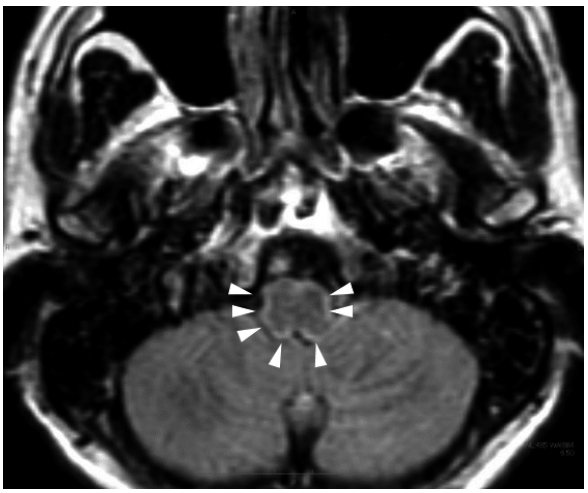

Figure 2. MRI findings at the level of the brain stem. A gadolinium-enhanced axial FLAIR image shows a diffuse leptomeningeal enhancement around the medulla oblongata (white arrow heads).

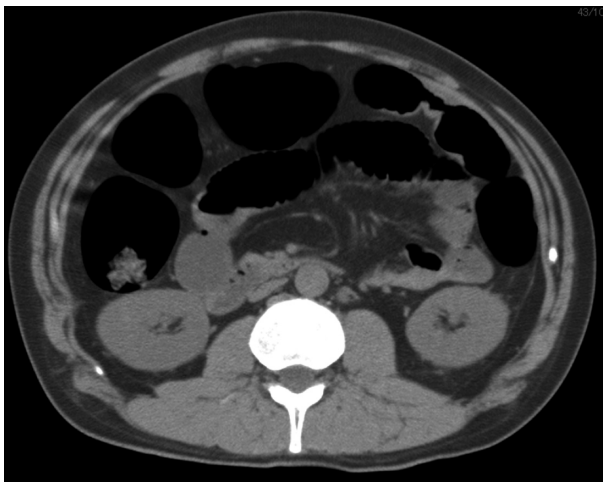

Figure 3. Abdominal CT findings. An computed tomography image without contrast medium-enhance shows dilatation along the full length of the colon, with partial niveaus, but without intestinal dilatation, volvulus, or a tumor mass.

gamma release assays and chest CT scans for pulmonary tuberculosis were negative, the CSF pattern, elevated adenosine deaminase levels, and clinical course prompted a diagnosis of TBM. Despite the ileus tube in the patient's gastrointestinal tract, daily oral administrations of antituberculosis medication (500 mg of isoniazid, 450 mg of rifampicin, 1000 mg of ethambutol, 1500 mg pyrazinamide) and intravenous treatment with 1.0–1.5 mg/kg prednisolone were begun. An MRI of the spinal cord, at the cervical, thoracic, and lumbar regions, with contrast enhancement did not detect abnormal intensity areas or lumbar spondylosis/herniation, except for a slight pachymeningeal enhancement. Even with the aid of a mechanical respirator, general convulsions

developed several times, which were controlled effectively with daily administration of 1000 mg levetiracetam.

Outcome and Follow-up

Within 1 week of treatment, abdominal fullness and aspiration pneumonia began to gradually improve. Consequently, having confirmed a clear sensorium, the patient was weaned from ventilatory support and the ileus tube was removed. Three weeks later, the patient had fully recovered from nausea and bowel movement disturbances and could return to his premorbid diet. Although prostate hypertrophy was not observed by urological ultrasound examination, the patient required intermittent self-catheterization for up to an additional month. Subsequently, spontaneous urination recovered without difficulty.

Discussion

Diagnosis of TBM is difficult and relies on the isolation of *Mycobacterium tuberculosis* from the CSF. In the case described herein, we did not detect this bacterium in the patient's CSF, even using culture and a direct PCR technique. However, a diagnosis of possible TBM was made based on previous work by Marais S and colleagues that proposed two categories of criteria as follows: (i) clinical criteria including symptom duration of more than 5 days and altered consciousness and (ii) CSF criteria including 10–500 cells/μL, lymphocytic predominance (>50%), a protein concentration greater than 1 g/L (100 mg/dL), and a CSF to plasma glucose ratio of <50% [9].

Tuberculous meningitis can sometimes present symptoms similar to those of other CNS inflammatory diseases, such as MRS and ADEM, which can further hinder the diagnosis process; however, we noted a number of differences between the clinical features of these diseases and those of our patient. MRS occurs without any obvious neurological abnormalities, except for a slightly brisk reflex, and typical symptoms include acute urinary retention along with headache, fever, and stiffness of the neck. Results of a CSF analysis are negative for viral titers; however, increased MBP, which is a CNS specific protein derived from the myelin sheath, and protein levels (up to 260 mg/dL) are observed. This finding is thought to be evidence of demyelination of the CNS, by autoimmune mechanisms triggered by the combined effects of infection and host factors. Therefore, although MRS appears similar to aseptic meningitis, it was proposed as a mild form of ADEM [4]. In comparison, along with urinary retention, our patient exhibited much higher protein levels in the CSF, disturbance of consciousness, and convulsions, which are a possible complication in TBM [1, 2]. Additionally, ADEM is recognized as an encephalopathy, which usually develops after a viral infection or vaccination, which is characterized by not only hemiparesis, hemiplegia, and epilepsy, but also lower urinary tract dysfunction [10]. Generally, a neuroimaging study, such as CT and/or MRI, can demonstrate the demyelinating lesions responsible for clinical symptoms.

There are limited data regarding tuberculosis infections as a cause of ADEM. Of the existing cases, many showed drastic demyelinated lesions on the cerebrum [11, 12] combined with extra CNS tuberculosis, such as pulmonary or miliary tuberculosis [13]. In these cases, antituberculosis medication and a high dose of intravenous corticosteroids (e.g., 1 g of methylprednisolone for 5 days) were effective [11, 12]. Previously, Udani et al. [13] postulated that sensitivity to tuberculoprotein, or to the brain itself, is the cause of the neurological manifestation of tuberculosis [13]. In the case described herein, the patient experienced headache and fever simultaneously; however, before onset he had not received any recent vaccinations nor contracted any obvious upper respiratory or digestive infections. Therefore, our case supports the opinion that CNS inflammation mainly results from a primary infection by *Mycobacterium tuberculosis*.

Interestingly, our examination findings included strikingly increased MBP levels in the CSF, without visible demyelinating lesions in the MRI study. It is surprising that the CNS was so dramatically affected given that the leptomeninges are strong barriers that protect the CNS parenchyma from bacterial invasion, although attacks by various inflammatory cells and mediators can generate a harmful effect on it. Despite this defensive membrane, some cases of meningitis are known to be associated with a number of physiological disturbances of the CNS, including auto-regulation [14], global [15] or regional cerebral blood flow reduction without structural lesions detectable by CT [16], electroencephalographic abnormality [17], increased intracranial pressure, metabolic alterations, and brain edema. Taken together, it is reasonable to conclude that MBP could be produced in damaged CNS parenchyma by disrupted intracranial homeostasis, rather than an autoimmunological reaction.

Additionally, our patient exhibited reversible severe ileus and urinary retention. The mechanism underlying these symptoms may be due to disturbances to the cranial nerves; TBM is commonly associated with palsies of the cranial nerves, with prevalence of vagus nerve palsy being lower than that of the oculomotor, abducens, and facial nerves [2]. While the vagus nerve provides innervation to the proximal colon, the majority of parasympathetic innervation to the distal colon originates from preganglionic neurons within the lumbosacral spinal cord, predominantly from the S1–S4 regions [18, 19]. In cases of

TBM, adhesion formation in or near the base of the brain results from a dense basal meningeal exudate that develops after inoculation of bacilli in the subarachnoid space [20], which interferes with CSF circulation and compresses the cranial nerves. Moreover, cranial nerve roots are exposed to such high levels of inflammatory mediators in the subarachnoid space that efferent excitation-conduction can be impaired. Therefore, both proximal and distal colonic paralysis must have been a result of inflammation and adhesion formation that spread from the cervical to the sacral nerve level of the subarachnoid space. If the patient had been awake and alert during his clinical course, we likely would have observed multiple cranial nerve palsies.

Acute dilation of the colon occurring in severely ill patients in the absence of any mechanical obstructions is called Ogilvie syndrome [21]. The pathogenesis of this syndrome results from an imbalance in the regulation of colonic motor activity by the autonomic nervous system [22], and its primary causes include surgical operations and anticholinergic medicines or opioids. There exist only a few reports regarding meningitis with colonic pseudo-obstruction [5, 6]; however, it is a particularly concerning complication given that acute megacolon can lead to ischemic necrosis in massively dilated intestinal segments, and the mortality rate can be over 20% [23, 24].

With regard to our patient's urinary retention, unfortunately, an urodynamic study was not performed; therefore, the details of his bladder function are unknown. However, it is reasonable to assume that both autonomic failures can be explained by a monogenetic etiology, because they developed around the same time as when the ileus manifested. The pelvic splanchnic nerves, including the parasympathetic nerve, arise from the anterior rami of the sacral spinal nerves S2–S4, and enter the sacral plexus. These nerves regulate the emptying of the bladder and control the opening and closing of the internal urethral sphincter [23]. In cases of MRS, lower urinary tract dysfunction has been shown to sometimes present with detrusor areflexia, or a nonrelaxing sphincter, by urodynamic studies [5]. Furthermore, Tateno et al. [6] reported that patients with MRS had slow detrusor activity over 4 months after detrusor areflexia, which suggest a disturbance of the upper motor neurons. Given that the MBP results suggested myelin damage, in our patient's case, a disturbance in neuronal conduction, extending from the superior urination control center in the pons to the lower center in the lumbosacral spinal cord, might also be involved in his urinary retention symptoms.

In conclusion, ileus and urinary retention are possible complication associated with CNS infection. These pathogenesis of this condition may involve of cranial nerve palsy and CNS demyelination.

Authorship

SK, MI, MM: contributed treatment of the patient. TI and HS: summarized the clinical data. SK and TF: wrote the paper.

Conflict of Interest

The authors state that they have no conflict of interests to disclose.

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