Herbal Medicine-induced Meningitis-retention Syndrome

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Abstract

A 73-year-old woman developed subacute meningitis-retention syndrome (MRS), dermatitis, and latent pneumonitis likely due to the herbal medicines Shinbu-Tou and Rikkunshi-Tou. The responsible site of lesions for urinary retention seemed to be the spinal micturition pathways and, to a lesser extent, the sacral spinal cord. All of her clinical manifestations were successfully ameliorated within three weeks of discontinuation of the herbal remedies.

Key words: herbal medicine, meningitis-retention syndrome, drug-induced meningitis, urinary retention

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Introduction

It is generally believed that herbal medicine is safe and time tested. However, it can cause some adverse events: e.g., pseudoaldosteronism due to *Licorice* (*Glycyrrhiza*, Kan-zou) (1) or hepatitis/pneumonitis due to *Bupleurum* (Saiko) (2), etc. Here, we report for the first time a case in which herbal medicines (Shinbu-Tou and Rikkunshi-Tou) induced meningitis-retention syndrome (MRS) (3, 4), dermatitis, and latent pneumonitis in an elderly woman.

Case Report

A 73-year-old woman was referred by a general physician because of a combination of acute urinary retention, fever and nuchal pain. In April she had been administered herbal medicine (7.5 g/day Shinbu-Tou and 7.5 g/day Rikkunshi-Tou) to treat diarrhea. However, in December, she had developed generalized skin eruptions, without prior infections. Allergic dermatitis was the tentative diagnosis. The herbal medicine was terminated, and 20 mg/day oral prednisolone was administered. Her skin eruptions were ameliorated immediately and the steroid was tapered off. But in January,

the skin eruptions became exacerbated again in the abdomen. She also developed 38.0°C fever, nuchal pain, voiding difficulty and abdominal distention. She had no diseases history nor was taking any other drugs previously. Upon referral to our hospital, transurethral catheterization revealed 800 mL of urine left behind, and a balloon catheter was inserted in the urethra. The patient had constipation. Neurological examination showed mild stiffness in the neck and a positive Kernig sign. She had no muscle weakness. The deep tendon reflexes of her extremities were slightly decreased. Sensations of superficial and deep modalities were normal including the perineal area, and no perineal pain or skin eruptions were noted. Laboratory examination showed mildly increased C-reactive protein of 2.84 mg/dL (normal<0.3 mg/dL), eosinophilia (17.5%, normal<6%, among white blood cell count of 7,010/mm³), and increased IgE of 360 IU/mL (normal<173 IU/mL). She was also found to have a mild reticular shadow in the right lower lung by a chest X-ray. Results of screening for collagen disease and anti-tumor antigens were normal (hemolytic unit of complement 36.8 U/mL [normal range, 30-40], C3 83 mg/dL [86-160], C4 24 mg/dL [17-45], circulating immune complex C1q<1.5 microg/mL [<3.0], negative anti-Sm, RNP, Scl-70, SS-A, SS-B, RAHA, cardiolipin, P-ANCA, C-ANCA, DNA antibodies),

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Figure 1. Urodynamic recording of the patient's bladder on the 6th hospital day. In the storage phase (bladder filling), the urodynamic study showed normal volumes of 276 mL at the first sensation and 460 mL at bladder capacity, and there was no detrusor overactivity. In the voiding phase (voiding), the patient could not contract her bladder voluntarily at all, indicating an acontractile detrusor (arrowheads) without urinary flow. The sphincter EMG sound was unchanged, indicating a non-relaxing sphincter. Note that the paper speed in the voiding phase was four times faster than in the bladder-filling phase. Flow: urinary flow, Pves: vesical (bladder) pressure, Pabd: abdominal (rectal) pressure, Pdiff: differential detrusor pressure = Pves - Pabd, EMG: electromyography

as were blood coagulation tests, except for a positive speckled-type anti-nuclear antibody titer of 320 (normal < 40). Urinalysis showed no evidence of infection. Results of the drug-induced lymphocyte stimulation test (DLST) for both Shinbu-Tou and Rikkunshi-Tou were positive. The cerebrospinal fluid (CSF) examination on admission day showed leukocytosis of $170/\text{mm}^3$ (mononuclear : polymorphonuclear=51:119, no eosinophils), xanthochromia, increased protein content of 95 mg/dL, and a decreased glucose level of 30 mg/dL (24% of serum glucose). Bacterial smears and cultures, including tuberculosis and cryptococcus, were negative. The CSF assay showed no increase in adenosine deaminase, oligoclonal bands or myelin basic protein. Magnetic resonance imaging scans of the brain and the spinal cord were normal, and no arteriovenous fistula or spinal cord compression were noted, except for a small extraspinal, intradural spot (at the T2 level, presumably microbleeding) that disappeared completely in the follow-up MRI scan. Results of the nerve conduction study were normal. The above neurological and laboratory findings strongly suggested drug-induced meningitis (5), neurogenic

urinary retention, dermatitis, and latent pneumonitis, likely due to the herbal medicine.

Her nuchal pain and fever were gradually ameliorated without treatment. However, after removal of the balloon catheter, the patient was still unable to urinate. Therefore, she was taught clean, intermittent self-catheterization (CISC) four times a day. We performed a urodynamic study on the 6th hospital day. She could not urinate and no uroflowmetrogram was obtained. A double-lumen 8F catheter (for use with saline infusion and intra-vesical pressure measurements) was inserted into the bladder. We performed a medium-fill (50 mL/min) electromyography (EMG)-cystometry with a urodynamic computer (Urovision; Lifetech Inc., Houston, TX, USA) and an electromyographic computer (Neuropack M2; Nihon Kohden Inc., Tokyo, Japan), simultaneously recording the detrusor pressure, which is the difference in the intra-vesical and intra-abdominal (rectal) pressures, sphincter EMG via a concentric needle electrode in the external anal sphincter muscle, and urinary flow via a uroflowmeter. The methods and definitions used for the urodynamic study conformed to the standards proposed by the International Continence Society (6). Sphincter EMG revealed normal voluntary contraction of the sphincter. During bladder filling, she had the first sensation at 276 mL (100 mL < normal < 300 mL) and a bladder capacity of 460 mL (200 mL < normal < 600 mL); we then stopped infusing saline into the bladder. She did not show detrusor overactivity during filling even after the provoking maneuver by coughing. When we asked her to void, however, she was unable to contract her bladder at all (underactive detrusor). The sphincter EMG activity persisted on voiding (unrelaxing sphincter), which normally disappears completely (Fig. 1). Analysis of external sphincter EMG (7) revealed long duration (mean duration 10.43 ms, normal < 10.0 ms; number of units with duration more than 10.0 ms, 5, normal < 2) neurogenic motor unit potentials. No decelerating bursts ('whale noises') were observed. On the 10th day, the repeated CSF findings returned to normal without treatment. Follow-up chest X-ray and blood tests returned to normal, except for increased IgE. On the 18th day, her residual urine volume became less than 30 mL and she was discharged from hospital.

Discussion

The present patient was unique in that she developed MRS, dermatitis, and latent pneumonitis likely due to the herbal medicines Shinbu-Tou and Rikkunshi-Tou. Since this condition was associated with positive anti-nuclear antibodies, drug-induced lupus reaction might also have occurred together. To the best of our knowledge, no such cases have been reported to date. Therefore, we did not know the exact pathomechanism of the clinical manifestation in our patient, although eosinophilia, increased IgE in the serum, and the positive DLST for Shinbu-Tou and Rikkunshi-Tou strongly suggested an allergic/autoimmune reaction. Shinbu-Tou and

Table 1. Meningitis-retention Syndrome and Related Disorders (cited from Ref. 4)

	neurological symptoms/signs					urodynamics	cerebrospinal fluid (CSF)		MRI	viral titers
disease	headache fever	stiff neck Kernig	DOC convulsion	LE reflexes	sensory	bladder function	increased cells,protein	MBP,OCB		
ADEM with conus lesion	+	+	+	N or brisk or decreased	sensory level or saddle	DHIC	+	+	WML+ spinal cord	no
ADEM	+	+	+	brisk	sensory level	DHIC	+	+	WML+ spinal cord	no
meningitis- retention syndrome	+	+	-	N or brisk	N	DA	+	+-	-	no
myelitis (a part of ADEM)	++	++	-	brisk	sensory level	DHIC	+	+-	spinal cord	no
sacral herpes (sacral radiculitis)	-	-	-	N or decreased	unilateral saddle, skin eruption	DA	+	-	-	HSV,VZV
retention with CSF abnormality alone	-	-	-	N	N	DA	+	?	-	HSV2 or no

ADEM: acute disseminated encephalomyelitis

DOC: disturbance of consciousness

LE: lower extremities

N: normal

Sensory level: sensory disturbance below the cervical/thoracic level

Saddle: sensory disturbance in the saddle/sacral area

DHIC: detrusor hyperreflexia with impaired contractile function

DA: detrusor areflexia

MBP: myelin basic protein

OCB: oligoclonal band

WML: white matter lesion

HSV: herpes simplex virus

VZV: varicella zoster virus

Rikkunshi-Tou share herbal ingredients *Poriacocos Wolf* (a mushroom, Bukuryou; its active components include eburicoic acid, pachymic acid, etc.), *Alancea Japonica* (a plant, Soujutsu; its active components include beta-eudesmol, hinesol, etc), and ginger (a plant, Shoga; its active components include shogaol, etc.). Therefore, these components might account for the clinical manifestation in our patient.

MRS is a combination of aseptic meningitis and acute urinary retention that both neurologists and urologists may potentially encounter (12). Patients with MRS exhibit no other neurological abnormalities except for mild pyramidal involvement, e.g., a slightly brisk reflex in the lower extremities (Table 1) (3, 4). For this reason, and increased myelin basic protein in the cerebrospinal fluid (3, 4), MRS is considered to be a very mild form of acute disseminated encephalomyelitis (ADEM). The responsible site of lesions for urinary retention in MRS is thought to be the spinal cord. The acontractile detrusor in such patients is regarded as the result of spinal shock. Our patient also revealed neurogenic changes in the sphincter EMG, suggesting that lesions in the sacral Onuf's nucleus might also have contributed to the occurrence of urinary retention in the present case (6). As for the diagnosis, the present patient lacked the following: apparent encephalitic signs such as disturbance of consciousness, epilepsy or aphasia; and myelitic signs such as gait abnormalities, sensory-level abnormalities or saddle dysesthesia. Therefore, the clinical manifestations of our pa-

tient differ markedly from those of typical ADEM (8). The uro-neurological examination excluded diseases that may cause urinary retention, e.g., diabetic neuropathy, lumbar spondylosis, spina bifida occulta, Fowler's syndrome (9), sacral herpes (10), typical myelitis, or herpetic brainstem encephalitis (11). Since MRS has a benign and self-remitting course (3, 4), we primarily chose conservative treatment in the present case. With careful observation and CISC, which was started in order to avoid over-distension bladder injury, all of her clinical manifestations were successfully ameliorated within three weeks.

In conclusion, an elderly woman acutely developed MRS, dermatitis, and pneumonitis likely due to the herbal medicines Shinbu-Tou and Rikkunshi-Tou. The responsible sites of lesions for urinary retention seemed to be the spinal micturition pathways and, to a lesser extent, the sacral spinal cord. All of her clinical manifestation were successfully ameliorated within three weeks of discontinuing medication.

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