INTERNAL MEDICINE

□ CASE REPORT □

Acute Tubulointerstitial Nephritis with Multiple Organ Involvement Including Fatal Adrenalitis: A Case Report with Autopsy Findings

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Abstract

A 68-year-old woman with Alzheimer's disease developed renal dysfunction after starting carbamazepine for epilepsy. Although Ga-67 citrate scintigraphy strongly suggested interstitial nephritis, renal biopsy was not possible due to her overall state. At 61 days after admission, she died of unexplained shock. At autopsy, severe infiltration of T lymphocytes was noted, not only in the renal interstitium but also in the liver, lungs, and adrenal glands. Adrenal failure was a possible cause of shock. In carbamazepine-induced interstitial nephritis, multiple organ involvement including fatal adrenalitis should be considered.

Key words: carbamazepine, tubulointerstitial nephritis, adrenal failure, autopsy

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Introduction

Acute tubulointerstitial nephritis is characterized by the infiltration of inflammatory cells into the renal interstitium. It is occasionally triggered by medications, such as antibiotics or non-steroidal anti-inflammatory drugs (1). Activated T cells and macrophages play pivotal roles in the development of interstitial nephritis (2, 3), and the involvement of endogenous nephritogenic antigens in this disease has recently been reported (4).

Carbamazepine is a classic anticonvulsant that is frequently used to control grand-mal seizures. Various adverse effects of carbamazepine have been recognized, including acute and chronic interstitial nephritis. Nicholls et al. reported a case of carbamazepine-induced acute renal failure with histological evidence of tubular damage in 1972 (5). Since then, only a few cases of carbamazepine-induced interstitial nephritis have been documented (6-13). In some of these reports, the involvement of other organs was also noted. To date, histological findings of multiple organ involvement in carbamazepine-induced interstitial nephritis have only rarely been described. We herein present the case of a patient with Alzheimer's disease who developed acute interstitial nephritis after starting carbamazepine therapy and died of shock attributable to adrenal failure. To our knowledge, this is the first autopsy report to present histological evidence of multiple organ involvement in carbamazepine-induced interstitial nephritis.

Case Report

A 68-year-old woman was admitted to our hospital with a chief complaint of dizziness. She had been diagnosed with paroxysmal atrial fibrillation six years earlier and had been treated with an antiarrhythmic agent (pilsicainide) for five years. Three years prior to the current hospitalization, she had been diagnosed with Alzheimer's disease. Approximately 90 days before admission, she experienced a grand-mal seizure and carbamazepine treatment was started. At the time of admission, her temperature was 36.2°C, her blood pressure was 98/61 mmHg and her pulse rate was irregular

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Table. Laboratory Data on Admission

■Urinalysis			■blood chemistry		
Specific gravity	1.012		T-bil	0.2	mg/dL
pH	7.5		AST	28	IU/L
Protein	(1+)		ALT	23	IU/L
Occult Blood	(3+)		LDH	306	IU/L
Sugar	(-)		ALP	295	IU/L
			γGT	84	IU/L
■Urine sediment			BUN	30.1	mg/dL
			Cre	2.89	mg/dL
Red blood cells	1-4	/HPF	UA	5.1	mg/dL
White blood cells	20-29	/HPF	Na	134	mEq/L
Eosinophils	(-)		K	5.0	mEq/L
Cast			Cl	96	mEq/L
squamous	(1+)		Ca	9.0	mg/dL
hyaline	(1+)		iP	3.6	mg/dL
			LDL-chol	148	mg/dL
■CBC			HDL-chol	51	mg/dL
			TG	76	mg/dL
White blood cells	3,600	/μL	CRP	3.6	mg/dL
Neutrophils	69.5	%	IgG	1,135	mg/dL
Eosinophils	5.3	%	IgA	233	mg/dL
Monocytes	11.2	%	IgM	78	mg/dL
Lymphocytes	13.4	%	C3	148	mg/dL
Red blood cells	279×10^4	/μL	C4	50.3	mg/dL
Hemoglobin	8.7	g/dL	CH50	53	U/mL
Hematocrit	25.3	%	MPO-ANCA	1.3	U/mL
Platelets	17.8×10^4	/μL	PR-3 ANCA	1.3	U/mL
			Cryoglobulin	(-)	
			■DLST	Not performed	

DLST: Drug-induced Lymphocyte Stimulating Test

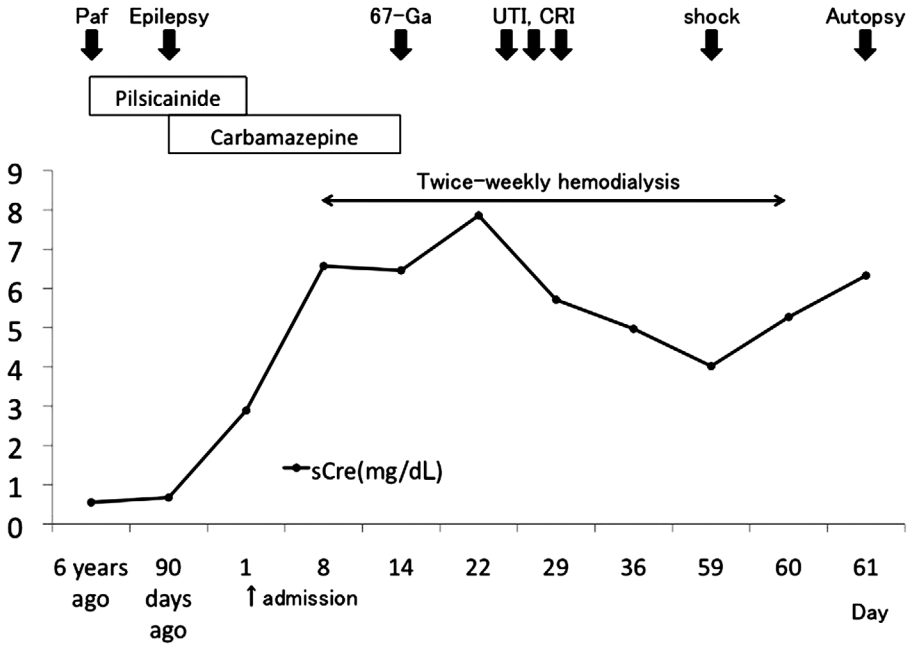

Figure 1. Clinical course. Paf: paroxysmal atrial fibrillation, UTI: urinary tract infection, CRI: catheter-related infection, HD: hemodialysis

at 30 beats per minute. The auscultation findings of the chest and lungs were normal. She exhibited no abdominal or back tenderness. Neither skin eruptions nor edema were noted. Performing a detailed neurological examination was not possible due to the patient's dementia. Blood examinations showed mild anemia, creatinine elevation to 2.89 mg/dL despite having been normal three months earlier and an elevated serum pilsicainide level of 1.66 μg/mL (normal range: 0.2 to 0.9 μg/mL). The levels of liver enzymes and electrolytes were normal. No serum M proteins were detected. A urine analysis showed hematuria (1+) and proteinuria (1+). The urinary protein to creatinine ratio was 0.5 g/gCre. Microscopic observation of the urinary sediments showed 1-4 erythrocytes and 20-29 leukocytes per high-

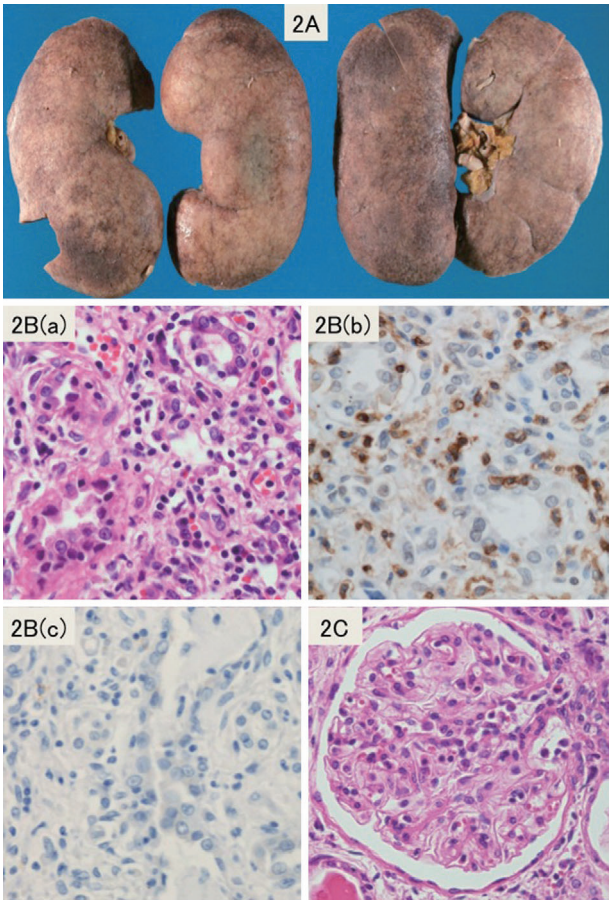

Figure 2. Pathological images of the kidneys. A: Macroscopically, both kidneys show severe swelling. Right kidney: 11.7 cm, 180 g. Left kidney: 12.2 cm, 220 g. B: Severe infiltration of mononuclear cells is noted in the renal interstitium. (a) Degenerated tubules show the invasion of lymphocytes into the tubular spaces. There is no granuloma formation. Mild infiltration of eosinophils is noted (×400). (b) The mononuclear cells are CD8-positive (×400). (c) CD20-positive cells are rare (×400). C: In contrast to the renal tubules, the glomeruli are essentially intact (×400).

power field. No urinary eosinophils were detected. Electrocardiography showed atrial fibrillation with a ventricular rate of 30 beats per minute. An impaired renal function appeared to be responsible for the increased serum pilsicainide concentration since this drug is primarily excreted through the kidneys. Pilsicainide was discontinued, and the patient underwent temporary pacemaker placement. Abdominal CT scanning revealed markedly enlarged kidneys with no detectable abnormalities in the urinary tracts. The sizes of the left and right kidneys were 11.2 cm and 12.1 cm, respectively. Bone marrow aspiration showed 0.4% plasma cells with normal morphology, thus making a diagnosis of renal myeloma unlikely. Both kidneys showed mild uptake on Ga-67 citrate scintigraphy. The serological findings of additional blood tests were unremarkable (the details are summarized in Table). Although the results of Ga-67 citrate scintigraphy strongly suggested a diagnosis of tubulointerstitial nephritis, a renal biopsy was not performed due to the patient's mental state. After performing Ga-67 scintigraphy, the patient's family told us not to administer any further tests, including the drug-induced lymphocyte stimulation test (DLST), considering the patient's medical condition. At the time of admission, the patient was nonoliguric (her urine output remained between 600 and 800 mL daily). Despite the discontinuation of carbamazepine and fluid replacement therapy, the patient's renal function deteriorated. A poor appetite and general malaise persisted after admission. A diagnosis of uremic gastroenteropathy was suspected. Hemodialysis was therefore initiated using a femoral catheter on the 8th hospital day. The patient experienced repeated urinary tract and catheter-related infections. Due to the uncertainty of the diagnosis and concern regarding exacerbation of infection, we did not initiate steroid therapy. The patient's renal function did not recover, and the urine volume remained below 300 mL daily. On the 59th hospital day, the patient's systolic blood pressure suddenly dropped below 80 mmHg and hypoglycemic episodes became frequent. Septic shock was initially suspected. Despite administering treatment with antibiotics and vasopressors, the patient died of shock on the 61 st hospital day. No elevations in liver enzymes were noted except on the date of death. The patient's clinical course is shown in Fig. 1. To elucidate the cause of the renal dysfunction, an autopsy was performed with the permission of the patient's family.

Macroscopically, both kidneys were edematous and enlarged (Fig. 2A). Microscopically, infiltration of T cells and macrophages into the interstitium was prominent (Fig. 2B(a)). The T cells were positive for CD8, and B cells were scarce (Fig. 2B(b), (c)). Inflammatory cells were seen invading the spaces among the tubules, and severe degeneration of the tubular epithelium was observed. Morphologically, the glomeruli were essentially intact (Fig. 2C). These findings were consistent with a diagnosis of acute tubulointerstitial nephritis. In the liver, severe infiltrations of T cells and macrophages with hepatocellular degeneration and focal pericentral necrosis were also noted (Fig. 3A). In the adrenal glands, degeneration of the cortex with prominent T cell infiltration was seen (Fig. 3B(a), (b)). The lungs showed mild fibrosis and infiltration of T cells into the walls of the alveoli (Fig. 3C). T lymphocytes in the liver, adrenal glands and lungs were also CD8-positive (data not shown). Apoptotic cells were detected among renal tubular epithelia, hepatocytes and adrenocortical cells using the Terminal Transferase dUTP Nick End Labeling (TUNEL) method (Fig. 4A, B). A diagnosis of multiple organ involvement in carbamazepine-induced tubulointerstitial nephritis was thus confirmed.

Discussion

Tubulointerstitial nephritis is characterized by the infiltration of inflammatory cells into the renal interstitium, often in association with interstitial edema and tubular degeneration. The majority of cases of interstitial nephritis are caused

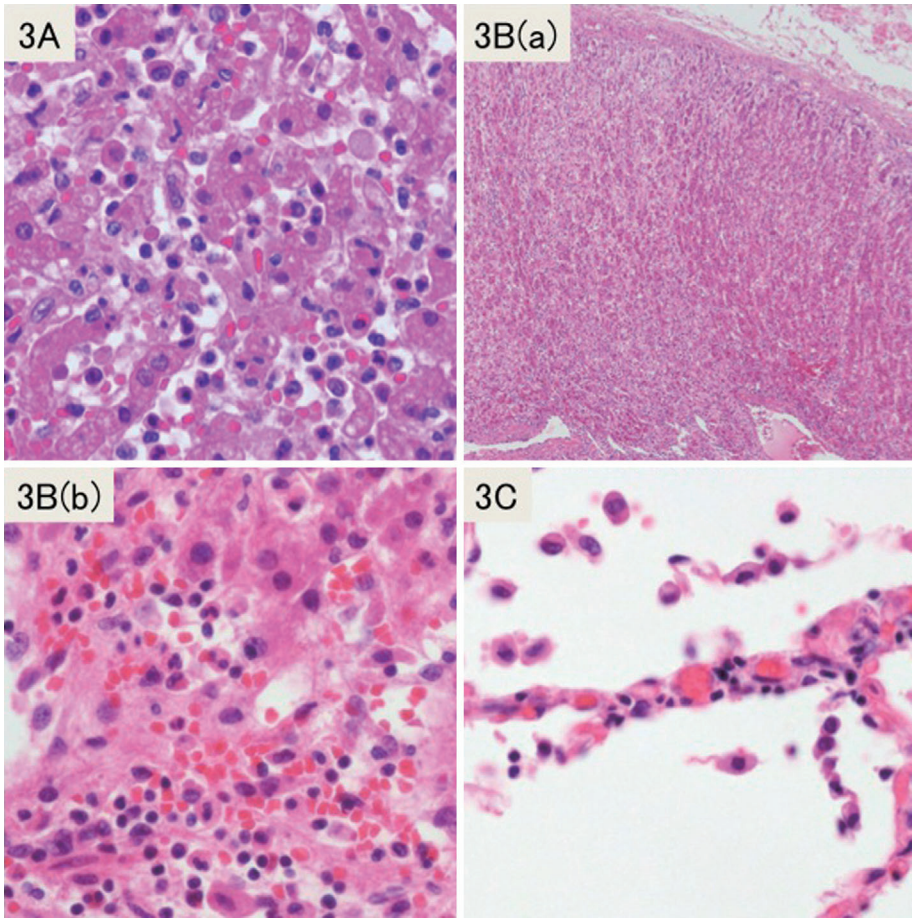

Figure 3. **Pathological images of other organs. A: Liver. T lymphocytes, macrophages and plasma cells are seen in association with diffuse hepatocellular degeneration and focal pericentral necrosis (×400). B: Adrenal glands. (a) T lymphocytes and cellular degeneration are prominent. The three-layer structure (Zona glomerulosa, Zona fasciculata, Zona reticularis) has deteriorated (×40). (b) Magnified view (×400). C: Lungs. Infiltration of mononuclear cells into the walls of the alveoli is shown (×400).**

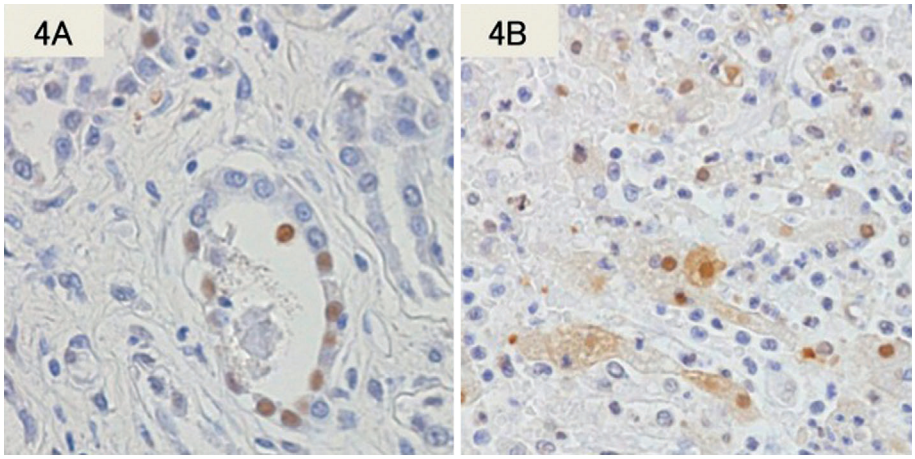

Figure 4. **TUNEL method. A: Kidney. Apoptotic cells are present in the tubular epithelia (×400). B: Liver. Some hepatocytes are apoptotic (×400).**

by medications, particularly beta-lactam antibiotics, although some cases are related to infection, sarcoidosis and autoimmune diseases such as tubulointerstitial nephritis and uveitis syndrome (1). Our present patient experienced no episodes of infection or serological abnormalities indicating autoimmune disease before admission. Except for carbamazepine,

she had not taken any medications or supplements before developing renal insufficiency. Taking these facts into account, carbamazepine is the most likely cause of acute tubulointerstitial nephritis in the present case. Carbamazepine-induced tubulointerstitial nephritis was initially reported in 1972 (5) and only a few cases have since been reported (6-13). To our knowledge, this is the first autopsy report to describe histological evidence of multiple organ involvement in carbamazepine-induced tubulointerstitial nephritis.

The precise mechanisms underlying the development of tubulointerstitial nephritis remain uncertain. Considering its dose-independence, reproducibility after re-administration of the suspected medication and similarities in extra-renal manifestations among reported patients, drug-induced interstitial nephritis most likely represents an allergic reaction to the offending agent (14). Recently, the expression of endogenous or exogenous antigens by renal tubular epithelial cells has been proposed to play an essential role in the development of tubulointerstitial nephritis (15). T lymphocytes and macrophages are frequently observed in the renal interstitial spaces, indicating that cell-mediated immunity is essential for the development of tubulointerstitial nephritis (1, 16, 17). In some exceptional cases, antibodies against components of the renal tubular basement membrane have been identified, suggesting the involvement of humoral-mediated immunity (18). In the present case, B cells were rarely seen in the renal interstitium, thus suggesting that cell-mediated immunity rather than humoral-mediated immunity plays a principal role in disease progression.

Carbamazepine has been widely used as an anticonvulsant for many years, and serious adverse effects of its use have been reported, including bone-marrow suppression, Stevens-Johnson syndrome (SJS), toxic epidermal necrosis (TEN), liver dysfunction, interstitial pneumonia and interstitial nephritis. Having the HLA-B*1502 allele reportedly increases the risk of developing carbamazepine-induced SJS and TEN in Asian populations (19). More recently, the presence of the HLA-A*3101 allele was shown to correlate with carbamazepine-induced hypersensitivity reactions in Europeans (20). Hence, it is conceivable that carbamazepine-induced tubulointerstitial nephritis is also associated with predisposing genetic factors. This issue needs to be clarified using genome-wide approaches in future research.

Information about the histological findings of extra-renal organ involvement in carbamazepine-induced interstitial nephritis is limited. Yamaki et al. reported a case of carbamazepine-induced tubulointerstitial nephritis with histologically-proven chronic hepatitis that was considered to be a consequence of carbamazepine-induced adverse reactions (10). In this case, we demonstrated the presence of severe infiltration of CD8-positive T lymphocytes and macrophages in the kidneys, liver, lungs and adrenal glands. Simultaneously, apoptotic cells were observed in these organs using the TUNEL method that detects apoptosis signal-induced DNA fragmentation. Since CD8-positive T lymphocytes recognize a specific antigen presented by the Class I major histocompatibility complex (MHC) expressed by almost all somatic cells that activates various kind of signaling pathways eventually resulting in apoptosis, these histological findings suggest the occurrence of antigen (i.e., carbamazepine) presentation by Class I MHC molecules and subsequent T cell-mediated apoptosis in affected organs.

Initially, sepsis was regarded as the cause of shock in the present case. However, the blood culture was negative for bacteria. Furthermore, no abscess formation was detected during the postmortem examination. Although we did not measure the adrenal hormone levels, the occurrence of frequent episodes of hypoglycemia plus the presence of severe structural degeneration and apoptotic cells in both adrenal glands suggested an impaired adrenal function. Hence, it is reasonable to assume that concomitant adrenal insufficiency also contributed to the shock state. To date, adrenalitis has not been reported as an adverse effect of carbamazepine. Despite the possibility of hemorrhagic necrotizing adrenalitis occurring in fatal multiple organ failure resulting from infection, a diagnosis of carbamazepine-induced adrenalitis should not be excluded in this case because there was no evidence of infection at the time of death.

In conclusion, we herein described an autopsy case of carbamazepine-induced tubulointerstitial nephritis. Multiple organ involvement with T cell-mediated cytotoxicity was demonstrated. Adrenalitis is therefore a potentially fatal complication of carbamazepine-related adverse effects.

The authors state that they have no Conflict of Interest (COI).

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