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CASE REPORT

Anti-mitochondria antibody-related tubulointerstitial nephritis accompanied by severe hypokalemic paralysis

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Abstract
A 47-year-old man presented with severe hypokalemic paralysis and respiratory failure. A large amount of potassium was administered along with providing intensive care, and his condition improved. Hypokalemia was attributed to increased urinary potassium excretion. A kidney biopsy was performed to make a definitive histological diagnosis. It revealed acute tubulointerstitial nephritis (TIN). After the diagnosis, prednisolone was administered, and the TIN gradually improved. From the clinical course and laboratory findings, the TIN was presumed to be an autoimmune disorder. Further specific autoantibody tests were positive for anti-mitochondrial antibody (AMA), which has been gaining increasing attention in regard to TIN. In addition, all previous cases of TIN associated with AMA have affected females. The detailed pathogenetic mechanisms are as yet unclear and require further investigation.

Keywords Hypokalemia · Respiratory failure · Tubulitis

Introduction

Tubulointerstitial nephritis (TIN) is known to be induced by drugs, autoimmune and inflammatory diseases, infections, neoplasms, or electrolyte abnormalities. Adverse reaction to drugs is the most frequent cause of TIN followed by autoimmune and inflammatory diseases. Among autoimmune diseases, anti-Sjögren's syndrome-related antigen A and B antibodies are most frequently found in TIN [1]. Recently, an association between anti-mitochondrial antibody (AMA) and TIN has been gaining attention [2].

TIN sometimes complicates various electrolyte abnormalities such as hypokalemia. The degree of hypokalemia varies widely depending on the case, but potassium values so low as to cause severe hypokalemic paralysis are unusual.

Case report

We report the case of a 47-year-old man who had suffered from a cervical spinal injury, which manifested as numbness and a decline in grip strength of his left hand. He had been prescribed vitamin B and nonsteroidal anti-inflammatory agents for about 1 month. His condition initially improved. However, he experienced physical weariness and eventually suffered from paralysis of the extremities a week before admission to the hospital. He was unable to stand up when he was moved to the emergency department. His vital signs were as follows: blood pressure, 109/70 mmHg; pulse rate, 86 beats/min; body temperature, 37.2 °C; and oxygen saturation, 97% on room air. Neurological examinations indicated significant muscle weakness of his upper and lower extremities. He had no past history of a similar episode, nausea, vomiting, diarrhea, or weight loss. He had been prescribed nifedipine and pitavastatin for 10 years to control hypertension and hyperlipidemia, respectively. The

This article has previously been submitted to another academic medical journal written in Japanese (Rinshotaieki, 2015; 42: 37–41.). However, the main message of this article has changed, and the current figures and tables have not been replicated in the initial Japanese version, except for the table of laboratory examination results.

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results of the laboratory tests on admission are shown in Table 1. The results from additional examinations, carried out after admission, are shown in Table 2. Additionally, generalized aminoaciduria was observed (data not shown). Computed tomography and ultrasound scanning of the abdomen showed swollen bilateral kidneys, with a major axis of up to 150 mm in length. Electrocardiogram showed QT interval prolongation and flattening of the T wave. Based on the examinations and laboratory findings, his severe paralysis was thought to be caused by hypokalemia, and intravenous potassium administration was started immediately. However, serum potassium levels did not improve. Muscle strength continued to weaken, and he went into respiratory distress, possibly due to breathing muscle paralysis, which occurred within 1 day of his admission to the hospital. He

Table 1 Laboratory findings on admission

Peripheral blood	
White blood cells	15.6×10^9/L
Red blood cells	5.06×10^{12}/L
Hemoglobin	147 g/L
Platelets	316×10^9/L
Blood biochemistry	
Total protein	81 g/L
Albumin	39 g/L
Aspartate aminotransferase	0.5 μkat/L
Alanine aminotransferase	0.47 μkat/L
γ-glutamyltransferase	1.3 μkat/L
Urea nitrogen	6.78 mmol/L
Creatinine	141 μmol/L
Creatine phosphokinase	12.3 μkat/L
Creatine kinase—MB fraction	16.4 μg/L
C-reactive protein	15.4 nmol/L
Sodium	139 mmol/L
Chloride	103 mmol/L
Potassium	1.3 mmol/L
Calcium	2.1 mmol/L
Arterial blood gas	
pH	7.37
PaO_2	11.5 kPa
$PaCO_2$	4.3 kPa
Bicarbonate	18.3 mmol/L
Lactate	1.44 mmol/L
Anion gap (Sodium–bicarbonate–chloride)	17.7 mmol/L
Urinalysis	
pH	6.5
Specific gravity	1.015
Sugar	(1+)
Blood	(1+)
Protein	(2+)
Ketone bodies	(−)

Table 2 Additional laboratory examination after admission

Blood biochemistry	
Phosphorus	0.36 mmol/L
Magnesium	0.9 mmol/L
Uric acid	143 μmol/L
Thyroid-stimulating hormone	0.12 mIU/L
Free tri-iodothyronine	5.88 pmol/L
Free thyroxine	0.15 pmol/L
Plasma renin activity	6.8 μg/L/hr
Aldosterone	2.83 pmol/L
Adrenocorticotropic hormone	3.81 pmol/L
Cortisol	880 nmol/L
Antidiuretic hormone	6.68 pmol/L
Antinuclear antibodies	80 Times
Myeloperoxidase anti-neutrophil cytoplasmic antibody	Negative
Proteinase 3 anti-neutrophil cytoplasmic antibody	Negative
Anti-double stranded deoxyribonucleic acid antibody	Negative
Anti-Smith antibody	Negative
Anti-Sjögren's syndrome-related antigen A antibody	Negative
Anti-Sjögren's syndrome-related antigen B antibody	Negative
Antimitochondrial antibodies	80 times
Antimitochondrial M2 antibodies	835 times
Immunoglobulin G	9.75 g/L
Immunoglobulin G 4	0.37 g/L
Immunoglobulin G 4/immunoglobulin G	3.74%
Immunoglobulin M	5.17 g/L
Immunoglobulin A	2.64 g/L
Epstein–Barr virus immunoglobulin M	Negative
Epstein–Barr virus immunoglobulin G	Negative
Cytomegalovirus-pp65 antigen	Negative
Tuberculosis interferon-gamma release assays	Negative
Parvovirus immunoglobulin M	Negative
Parvovirus immunoglobulin G	Negative
Osmolality	284 mmol/kg
Protein fraction	Normal
Trans-tubular potassium gradient	3.6
Fractional potassium Excretion	13%
Percent tubular reabsorption of phosphate	70%
Fractional uric acid Excretion	40%
Urinalysis	
Urinary protein/Creatinine ratio	1.65 g/gCr
N-acetyl-β-D-glucosaminidase	38.5 U/L
β2-microglobulin	97.7 mg/L
Osmolality	378 mmol/kg
Sodium	118 mmol/L
Chloride	132 mmol/L
Potassium	35.3 mmol/L
Uric acid	5092 μmol/L
Creatinine	4410 μmol/L

was admitted into the intensive care unit (ICU) and intubated, and artificial breathing was started. The therapeutic process in the ICU is shown in Fig. 1. Because potassium levels were persistently low, mass administration of potassium (maximum dose: 480 mmol/day) into the central veins was initiated. Subsequently, hypophosphatemia and mild hypomagnesemia were also noted and were thus treated with their respective administration. The pathogenesis of these electrolyte disorders was likely due to increased urinary excretion.

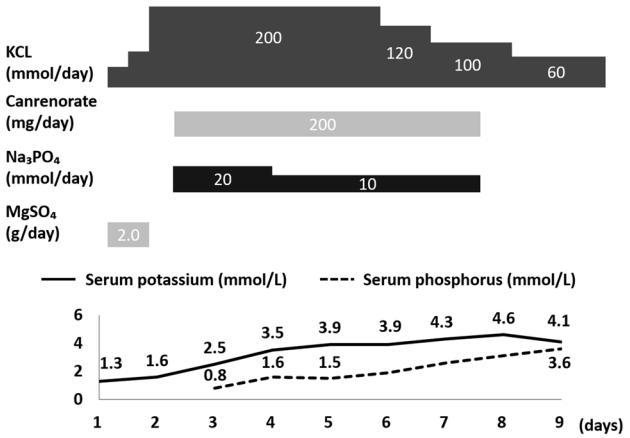

Fig. 1 The therapeutic process in the intensive care unit

Upon leaving the ICU, a kidney biopsy was performed to ensure a definite histological diagnosis. Fluorescent antibody staining of IgG, IgM, IgA, κ light chain, λ light chain, complement 3, complement 4, complement 1q, and fibrinogen showed no significant deposition in the glomeruli. Visualization of hematoxylin and eosin staining using light microscopy showed infiltration of diffuse inflammatory cells in the interstitial tissue. Acid fuchsin orange G-staining showed mild fibrosis and atrophy, but no deposition in the glomeruli (Fig. 2). Other noticeable changes in the glomeruli were not recognized. Nephritis was diagnosed as TIN. From the interview, we thought that vitamin B and nonsteroidal anti-inflammatory agents were responsible for the nephritis. Drug lymphocyte stimulation tests (DLST) were performed, and only vitamin B preparations tested positive. As it was considered unlikely that vitamin B supplements were the cause of the TIN, other possible etiologic factors were investigated.

During a subsequent interview, it was discovered that the patient's sister had primary biliary cirrhosis (PBC). Further autoantibody tests were performed, and all other specific autoantibody tests except AMA were negative during the investigation in this case. The patient's liver function was normal, and an abdominal ultrasound revealed no abnormalities.

The therapeutic process upon leaving the ICU is shown in Fig. 3. Prednisolone (50 mg/day) was started for nephritis, and his condition improved soon after therapy. The doses of prednisolone were reduced by 10 mg every 3 weeks until

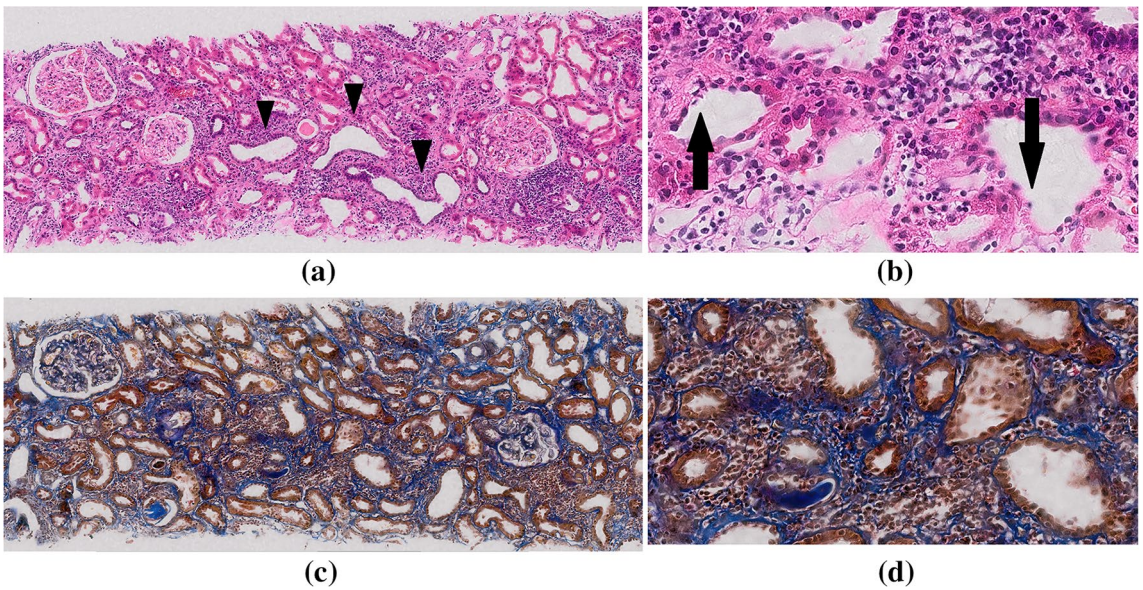

Fig. 2 Light microscopic findings of the renal biopsy specimen. **a** Hematoxylin and eosin (×100). **b** Hematoxylin and eosin (×400). A diffuse interstitial cellular infiltrate is present around the proximal and distal renal tubules, composed primarily of lymphocytes. Inflammatory cells are seen in the tubular epithelium in both proximal and distal renal tubules. The tubular epithelium is focally detached (arrows) and the tubular lumen focally expanded (arrowheads). **c** Acid fuchsin orange G (×100). **d** Acid fuchsin orange G (×400). Mild tubular atrophy and interstitial fibrosis is present

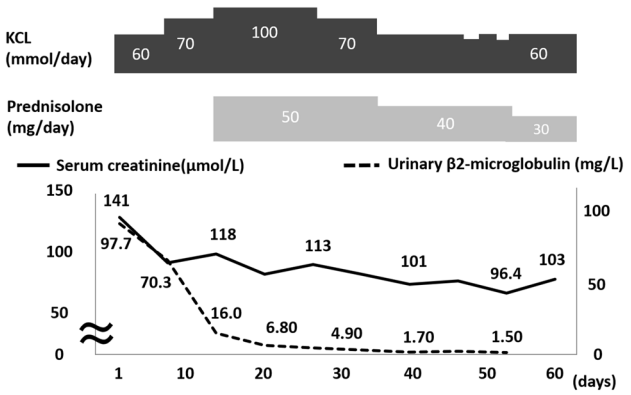

Fig. 3 The therapeutic process after leaving the intensive care unit

30 mg/day was reached. 1 month after the initiation of the therapy, the values of serum potassium, phosphate, and venous blood gas bicarbonate improved to normal range, and thus, oral intake of potassium preparation could be gradually reduced. The values of serum creatinine and UP/Cr decreased to 103 μmol/L and 0.07 g/gCr, respectively. In regard to tubulointerstitial markers, urinary β2-MG and NAG decreased to about 1.5 mg/L and 3.2 U/L.

Discussion

In this case, TIN presenting as fatal hypokalemia seemed to have some relationship with AMA. Generally, most cases of TIN in adults are caused by drugs, followed by infectious diseases and autoimmune disorders such as Sjögren's syndrome, IgG4-related disease (IgG4RD), or TIN with uveitis (TINU) syndrome [1, 3, 4]. The DLST of the vitamin B supplements the patient was taking was positive. However, false positives may occur when the drug itself has a lymphocyte-activating action [5]. Vitamin B is involved in the differentiation of B cells [6]. Therefore, the DLST results must be interpreted with caution. Vitamin B is consumed daily, and substances other than vitamin B such as cellulose or starch contained in the vitamin B pills are common in other preparations. We, therefore, considered that other causes should be sought to explain the pathophysiology of the TIN. In this case, the serum anti-Sjögren's syndrome-related antigen antibody was negative, and no obvious secretory gland dysfunction was observed. The increase in serum IgG or IgG4/IgG ratio was not observed, and renal histological findings typical of IgG4RD such as storiform fibrosis (bird's eye sign) were not found. The patient was introduced to ophthalmology before steroid therapy, but uveitis was not observed. Taken together, it is unlikely that TIN is caused by Sjögren's syndrome, IgG4RD, or TINU syndrome.

IgG-secreting plasma-cell infiltrates are a common finding in most cases of TIN [7], but TIN with plasma cells secreting IgM have also been reported [8]. In such cases, a high prevalence of elevated serum IgM levels, proximal and distal RTA, and AMA-positivity has been observed [2]. AMA is increasingly being considered as a cause of TIN [2, 8–21], but the details remain to be elucidated. In a few reports of TIN with AMA, patients have had subclinical PBC, indicating that the severity of PBC does not always correlate with that of the TIN [11–13].

A good response to treatment in laboratory findings such as electrolytes, acid–base, interstitial markers, renal function, and proteinuria indicated that TIN was the main pathogenesis, although AMA remains positive. Steroid therapy is often effective, as shown in previous cases in Table 3. However, it is not clear if AMA titer is reduced by steroid therapy. Interestingly, all the previous cases have been women. While it is interesting that our patient was a man, it is difficult to attribute much significance to a sex difference in TIN at the present time.

TIN with AMA is attracting recent attention but has not been comprehensively established as a new disease concept as of now. Therefore, there are no obvious diagnostic criteria for TIN with AMA. Nonetheless, TIN with AMA frequently accompanies both types of RTA, with high serum IgM value, and IgM-secreting plasma-cell infiltrating interstitial nephritis as shown in Table 3, which may be useful as diagnostic criteria.

At the beginning of hospitalization, the urinary potassium excretion was as high as 100 mmol/day, despite the presence of severe hypokalemia (data not shown). No other causes for the hypokalemia were apparent; the patient's dietary intake had been normal, and there was no history of diarrhea, vomiting, sweating, or polyuria. There was no evidence of alkalosis, insulin excess, β agonists, or thyroid dysfunction. On endocrine examination, the cortisol was mildly elevated, but there was no marked increase in aldosterone levels or a change in the renin/aldosterone ratio. Based on those findings, the major cause of hypokalemia was thought to be increased urinary potassium excretion.

This case merged metabolic acidosis, increased excretion of urinary phosphate, uric acid and sugar, and generalized aminoaciduria, suggesting dysfunction of proximal renal tubules. The arterial blood pH dropped to a minimum of 7.25, whereas the urine pH remained above 7.0 in ICU. These results are consistent with the disorder of distal renal tubules. Therefore, it follows that the renal tubules were broadly affected. AMA may translocate into renal tubule cells, probably through endocytosis, and interfere with the mitochondrial machinery by binding to the target enzyme, leading to RTA or TIN [22]. Hence, dysfunction within unknown transport systems of renal tubules, known as mitochondria-rich tissues, may be induced by AMA.

Table 3 Previously reported cases of tubulointerstitial nephritis with antimitochondrial antibodies or primary biliary cirrhosis

Author	Age/sex	Cr	K	IgM	M2-AMA	AMA	PBC	pro RTA	dis RTA	PSL	Dose	Efficacy	References
Takahashi	63/F	101	ND	8.6	24.4	320	(+)	(+)	(+)	(−)			[2]
Takahashi	38/F	163	ND	11.5	131	160	(−)	(+)	(+)	(+)	20 (ND)	(−)	[2]
Takahashi	53/F	99.9	ND	7.08	76.8	160	(−)	(+)	(+)	(+)	30 (ND)	(+)	[2]
Takahashi	55/F	101	ND	4.05	112	20	(−)	(+)	(+)	(−)			[2]
Takahashi	66/F	133	ND	6.63	178	80	(+)	(+)	(+)	(+)	30 (ND)	(+)	[2]
Takahashi	52/F	133	ND	6.65	157	320	(+)	(+)	(+)	(+)	30 (ND)	(+)	[2]
Takahashi	44/F	122	ND	12.8	562	ND	(+)	(+)	(+)	(+)	20 (ND)	(+)	[2]
Takahashi	56/F	240	ND	20.5	103	< 20	(+)	(+)	(+)	(+)	30 (ND)	(+)	[2]
Takahashi	38/F	75.1	3.6	10.4	31	160	(+)	(+)	(+)	(+)	30 (0.6)	(+)	[8]
Lino	51/F	156	3.9	ND	800	ND	(+)	(+)	ND	(+)	ND (0.5)	(+)	[9]
Lino	68/F	115	3.3	ND	640	ND	(+)	(+)	ND	(+)	ND (0.5)	(−)	[9]
Kodama	36/F	70.7	4.1	12.6	ND	640	(+)	(+)	ND	(−)			[10]
Bando	49/F	82.2	3.6	7.42	18.3	ND	ND	(+)	(+)	(−)			[11]
Hara	38/F	163	2.5	14.1	160	131	(−)	(+)	ND	(+)	20 (0.4)	(+)	[12]
Saeki	53/F	97.2	3.7	7.08	77.5	160	ND	(+)	(+)	(+)	40 (0.67)	(+)	[13]
MacDougall	50/F	174	2.6	6.3	800	ND	(+)	ND	ND	(+)	40 (0.73)	(+)	[14]
Kamouchi	58/F	177	2.9	ND	ND	ND	(+)	ND	ND	(+)	40 (ND)	(+)	[15]
Terrier	42/F	117	3.2	3.58	200	ND	(+)	(+)	ND	(+)	ND (1.0)	(+)	[16]
Komatsuda	36/F	70.7	4.1	12.6	(−)	640	(+)	(+)	(+)	(+)	25–30 (ND)	(+)	[17]
Komatsuda	66/F	133	3.3	6.63	178	80	(+)	(+)	(+)	(+)	25–30 (ND)	(+)	[17]
Komatsuda	77/F	124	4.2	0.74	40	20	(+)	(+)	(+)	(+)	25–30 (ND)	(+)	[17]
Komatsuda	52/F	133	3.4	6.65	157	320	(+)	(+)	(+)	(+)	25–30 (ND)	(+)	[17]
Bansal	46/F	207	ND	ND	ND	ND	(+)	ND	ND	(+)	40 (ND)	(+)	[18]
Iwakura	46/F	99.9	3.9	9.66	143	160	(+)	(−)	(−)	(−)			[19]
Rasolzadegan	28/F	177	ND	ND	19.5	ND	(+)	ND	ND	(+)	ND (ND)	(+)	[20]
Yamaguchi	49/F	124	2.8	10.8	10	ND	(+)	(+)	(+)	(+)	20 (0.3)	(+)	[21]
Present case	47/M	122	1.3	5.17	835	80	ND	(+)	(+)	(+)	50 (0.6)	(+)	

AMA antimitochondrial antibody (times), *Cr* creatinine (μmol/L), *dis RTA* distal renal tubular acidosis, *dose* dose of prednisolone (mg/day (mg/kg/day)), *efficacy* efficacy of prednisolone to interstitial nephritis, *F* female, *IgM* Immunoglobulin M (g/L), *K* potassium (mmol/L), *M* male, *M2-AMA* M2-antimitochondrial antibody (times), *ND* not determined or listed, *PBC* primary biliary cirrhosis, *pro RTA* proximal renal tubular acidosis, *PSL* prednisolone treatment

Clinically, this can result in tubular malfunction, as in the present case. However, whether this applies to this case remains a matter of debate.

In conclusion, we described a man with AMA-related TIN accompanied by severe hypokalemic paralysis. The pathogenesis is not completely clear and may require investigation of similar cases to explore possible underlying mechanisms.

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Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee at which the studies were conducted (IRB approval number 29–94) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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