CASE REPORT

A case of acute kidney injury and disseminated intravascular coagulation associated with influenza B viral infection

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Abstract There are few reports of acute kidney injury (AKI) associated with influenza viral infection. We treated a case of AKI that developed after an influenza B viral infection. A 35-year-old man visited a local physician for a fever and was diagnosed with influenza B. He was prescribed laninamivir, then returned to the physician 5 days later with dyspnea and was referred to Hospital A. Upon admission, respiratory arrest developed, for which he received tracheal intubation and mechanical ventilation. AKI was noted after admission and the patient was transferred to our hospital the next day. AKI and disseminated intravascular coagulation (DIC) were present at the time of transfer, thus a transfusion and continuous hemodiafiltration (CHDF) were performed, and administrations of thrombomodulin alpha and antithrombin III were initiated. Although the patient had DIC, AKI, and disturbance of consciousness, and was in a clinical state resembling influenza-associated encephalopathy, there was no clear abnormality shown in CT scans of the head. Urine output, renal function, and respiratory condition gradually improved, thus CHDF was stopped and extubation performed. The patient had no complications and was discharged on hospital day 22. Some reports have been presented regarding cases of AKI due to rhabdomyolysis associated with influenza viral infection, whereas our patient developed AKI as a complication of an influenza B viral infection without rhabdomyolysis or hemolytic

uremic syndrome. Influenza B may cause AKI and DIC, and affected patients can be in a serious condition requiring immediate attention.

Keywords Influenza B · AKI · DIC · PMMA · CHDF

Introduction

Although the influenza virus is transmitted throughout the year, the incidence is highest during the winter months. Influenza viral infections are characterized by a sudden onset of high fever and respiratory symptoms. They usually pass with few after-effects, though some cases show complications such as kidney injury leading to kidney failure due to rhabdomyolysis. This report describes a patient with acute kidney injury (AKI) and disseminated intravascular coagulation (DIC) associated with an influenza viral infection, but without rhabdomyolysis, who showed a good clinical course.

Case report

A 30-year-old male with a past medical history of chronic gastritis went to a local physician complaining of fever and general malaise on March 7, 2013. A rapid diagnostic test was positive for influenza type B, and he was prescribed laninamivir and sent home. However, the symptoms worsened and he returned March 11 to the same physician, who noted a pale facial color and coarse crackles on auscultation of the chest, and immediately referred the patient to Hospital A. Upon admission there, the patient exhibited wheezing, decreased SpO₂, and cyanosis, and eventually developed respiratory failure, necessitating the use of tracheal intubation and mechanical ventilation. Decreased

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urine output, elevated serum creatinine (10.9 mg/dL), and acute kidney injury (AKI) were also observed, thus the patient was transferred to our hospital on March 12.

Results of our initial physical examination showed BT at 37.4 °C, HR at 112 beats/min, BP at 102/68 mm Hg, SpO₂ 100 % (FiO₂ 0.40, PC 15 cm H₂O, RR 10/min, PEEP 3 cm H₂O, PS 10 cm H₂O), coarse crackles upon auscultation of the right lung field, and intraoral and intranasal bleeding. A rapid diagnostic test was positive for influenza type B. Urinalysis (Table 1) and blood tests (Tables 2, 3) showed AKI and DIC, though no indication of acute nephrotic syndrome or acute glomerulonephritis. In addition, there were no signs of rhabdomyolysis or hemolytic uremic syndrome (HUS). Sputum, urine, and blood culture results were negative, as were CT scan images for signs of encephalitis (Fig. 1). Pneumonia was present,

predominantly on the right side, which was a probable secondary bacterial infection associated with the influenza B viral infection (Fig. 2). There was also marked bilateral renal enlargement associated with AKI but no dilation of the renal pelvis.

Figure 3 shows the clinical course of the infection. Since laninamivir is an inhalant, the effect depends on the certainty of the inhalation. There was a possibility that the patient was unable to sufficiently inhale, thus the drug may not have been effective. Therefore, 50 mg of peramivir was administered once on the day of admission. A high level of procalcitonin (60.0 ng/mL) indicated that bacterial infection could not be ruled out. Therefore, administration of the following regimen was initiated as empiric therapy: MEPM at 0.5 g × 2/day and CPFX at 200 mg × 1. The patient exhibited consciousness disturbance and we suspected influenza-associated encephalopathy. It was difficult to perform an MRI examination while the patient was on a ventilator and CHDF, thus we employed head CT, which did not reveal findings indicative of encephalitis (Fig. 1). However, other findings included stab ports in the abdomen from mites or chiggers. Because thrombocytopenia was observed, the possibility remained that the patient had a severe fever with thrombocytopenia syndrome (SFTS). In addition, rickettsia infection due to scrub typhus or a tick bite could not be ruled out, thus we gave MINO at 100 mg × 2/day. An SFTS viral test and assay for antibodies against Rickettsia tsutsugamushi were negative.

Next, we considered the possibility that folliculitis was the cause of the red spots on the body of the patient and MINO was discontinued on hospital day. For AKI, the

Table 1 Urinalysis

Urinalysis		Urinary chemistry		
Specific gravity	1.010	Na	64	mEq/L
pH	6.0	K	32.2	mEq/L
Blood	3+	Cl	57	mEq/L
Protein	2+	NAG	18.2	IU/L
Keton	–	UN	302.4	mg/dL
Bil	–	Crea	42.2	mg/dL
RBC	>100 /HPF	P/C	3.38	g/g cr
WBC	5 ~ 9 /HPF	FENa	12.5	%
		FEUN	45.8	%

Table 2 Blood examination

Peripheral blood			Biochemistry			γGTP	395	IU/L	Anti CL β2GP-Ab	<1.2	U/mL
WBC	9700	/μL	TP	4.9	g/dL	T-Bil	0.3	mg/dL	Anti CL-Ab	<8	
Ne	79.2	%	Alb	1.9	g/dL	Amy	204	IU/L	Anti sm-Ab	(–)	U/mL
Mo	1.1	%	Na	129	mEq/L	CPK	152	IU/L	Anti Scl-Ab	(–)	
Ly	18.7	%	K	6.7	mEq/L	Glu	69	mg/dL	Anti Jo-1-Ab	(–)	
Eo	0.8	%	Cl	99	mEq/L	Hp	380	mg/dL	PR3-ANCA	<1.0	
Ba	0.2	%	Ca	7.2	mg/dL	Serology			MPO-ANCA	<1.0	
RBC	432	×10 ² /μL	Pi	11.3	mg/dL	CRP	13.29	mg/dL	Anti GBM-Ab	<2	
Hb	8.6	g/dL	Mg	2.9	mg/dL	PCT	60.0	ng/mL	Coagulation		
Ht	25.0	%	BUN	172.4	mg/dL	CH50	47.4	/mL	PT-INR	1.10	
Plt	1.2	×10 ⁴ /μL	Crea	11.02	mg/dL	C3	83	mg/dL	APTT	42.7	s
			eGFR	5.1	mL/min/BSA	C4	20	mg/dL	FIB	467	mg/dL
			AST	31	IU/L	RF	2	IU/L	AT-III	67	%
			ALT	31	IU/L	ASO	197	IU/mL	FDP	47.0	μg/mL
			LDH	421	IU/L	ANA	<40		D-dimer	18.1	μg/mL
			Ch-E	147	IU/L	ds-DNA	<10				
			Alp	410	IU/L	LA	17.6	s			

Table 3 Blood gas analysis

pH	7.349		Na ⁺	131	mEq/L
pCO ₂	35.3	mmHg	K ⁺	4.7	mEq/L
pO ₂	198.0	mmHg	Cl ⁻	105	mEq/L
HCO ₃ ⁻	19.0	mmol/L	Ca ²⁺	1.90	mEq/L
BE	-5.5	mmol/L	GLU	156	mg/dL
SAT	98.8	%	Lac	9.0	mg/dL
Hb	8.5	g/dL			
COHb	1.0	%

Fig. 1 Head CT. No findings indicating encephalitis were observed in CT scan images

previous local physician had deduced prerenal and renal failure due to dehydration, and used a fluid loading regimen. We also used fluid loading, but the patient responded poorly. Blood pressure and IVC pressure were maintained, and FENa of 12.5 % and FEUN of 45.8 % indicated increased renal AKI. We considered it difficult to deny drug-induced AKI because there are no reports of renal injury associated with L-carbocysteine and Laninamivir, and he had taken famotidine for a long period.

On the day of admission to our hospital, the patient began receiving PMMA-CHDF (BG-1.3U[®], D 700 mL/h, F 300 mL/h) using nafamostat mesilate. Thrombomodulin alfa and lyophilized human antithrombin III concentrate were also administered for DIC, and urine output gradually improved. PMMA-CHDF was terminated on hospital day 7. Renal function continued to improve after withdrawal of CHDF. Because his respiratory condition also stabilized, extubation was performed on day 9. The general condition and inflammatory reactions in the patient also improved,

Fig. 2 Chest CT. Findings indicating pneumonia were predominant on the right side, which was likely secondary to bacterial pneumonia associated with influenza B viral infection

and antibiotic therapy was ended on day 10. Subsequently, the patient underwent rehabilitation therapy and was discharged on day 22.

Discussion

Influenza viral infections are prevalent in the winter and related symptoms include high fever, general malaise, cough, and joint pain. In addition, various complications are caused by an influenza viral infection, such as respiratory complications, neuropsychiatric disorders, muscular disorders, cardiac dysfunction, ocular disorders, hepatic dysfunction, hematologic disorders, dysgeusia, and renal dysfunction, with the latter most often reported as a complication in pediatric cases, while adult cases are rare.

There are few reports detailing influenza B virus infection cases, thus we examined reports about influenza A viral infections. The suggested causes of renal dysfunction include a prerenal cause due to rhabdomyolysis or dehydration, acute tubular necrosis associated with HUS and DIC, and the influenza virus itself causing direct interstitial renal injury [1]. We have summarized reported cases of AKI associated with adult influenza, which is possible with both A and B, in Table 4. Many of those cases were complicated with rhabdomyolysis. Although the present patient did not have rhabdomyolysis or HUS, he was in critical condition due to DIC. Some cases of DIC

Fig. 3 Developments after hospital admission

Table 4 Summary of reported cases of adult influenza associated with acute kidney injury

Author	Age	Sex	Type of influenza virus	Crea (mg/dL)	Cause of Acute kidney injury	Therapy	Outcome
Eugene et al. [6]	28	F	n.d.	20.5	Rhabdomyolysis	PD	Recovery
	53	F	n.d.	9.0	Rhabdomyolysis	PD	Death
	76	F	n.d.	13.0	Rhabdomyolysis	HD	Recovery
Myking et al. [7]	45	M	A	12.0	Unknown	PD	Recovery
Lynn et al. [8]	65	M	A	13.6	Rhabdomyolysis	HD	Recovery
Annerstedt et al. [8]	69	M	A	10.7	Rhabdomyolysis	HD	Recovery
	37	M	A	9.59	Rhabdomyolysis	HD	Recovery
Abe et al. [9]	40	M	B	13.37	Rhabdomyolysis	HF, HD	Recovery
	57	M	A	5.61	Rhabdomyolysis	Conservative therapy only	Recovery
	67	M	A	3.72	Rhabdomyolysis	Conservative therapy only	Recovery
	53	M	A	6.82	Rhabdomyolysis	CHF, HD	Recovery
	54	M	A	8.96	Rhabdomyolysis	CHF, HD	Recovery
Pradère et al. [10]	82	M	A	8.9	Rhabdomyolysis	HD	Recovery
SAID et al. [11]	44	M	B	9.6	Rhabdomyolysis	HD	Recovery
Sato et al. [12]	41	M	A	9.37	Rhabdomyolysis	Oseltamiir + PE + HD	Recovery
Fearnley et al. [13]	21	F	A	1.45	Rhabdomyolysis	HF	Recovery

nd not described, PD peritoneal dialysis, HD hemodialysis, CHF continuous hemofiltration, PE plasma exchange

Table 5 Summary of reported cases of disseminated intravascular coagulation associated with influenza

Author	Age	Sex	Type of influenza virus	Platelet ($\times 10^4/\mu\text{L}$)	Crea (mg/dL)	Therapy	Outcome
Whitaker et al. [14]	43	F	A	n.d.	12.8	Heparin, HD	Death
	23	F	A	n.d.	11.7	Conservative therapy only	Recovery
	33	F	A	n.d.	12.3	HD	Lost to follow up
	40	F	A	n.d.	11.2	HD	Lost to follow up
	56	M	A	n.d.	11.7	HD	Death
	75	F	A	n.d.	4.7	Heparin	Recovery
Shenouda et al. [15]	33	F	A	5.4	0.8	Heparin, HD	Death
Luksza et al. [16]	14	M	B	4.5	n.d.	Conservative therapy only	Recovery

nd not described, *PD* peritoneal dialysis, *HD* hemodialysis

due to influenza have been reported (Table 5), though it is not clear why influenza causes DIC.

Increased vasopermeability is thought to be the basis for increased severity of influenza viral infections. Inflammatory cytokines (TNF- α , IL-6, IL-1 β) are induced by a viral infection, which in turn induce protease expression, such as matrix metalloprotease-9 and trypsin. Those proteases then promote viral replication, resulting in an influenza virus-cytokine-protease cycle [2, 3]. Occurrence of the influenza virus-cytokine-protease cycle in vascular endothelial cells results in cellular injury, and increased vascular membrane permeability is thought to lead to multiple organ failure. When our patient was being treated at Hospital A, a bacterial infection was not evident, while he already exhibited DIC. Therefore, the influenza virus-cytokine-protease cycle is thought to have occurred in our patient, causing DIC, and improvement likely occurred because of cytokine adsorption.

There are no known reports of cytokine adsorption in relation to the influenza virus-cytokine-protease cycle. In some sepsis patients, cytokine adsorption has been performed in hopes of improving prognosis (non-renal indication) by addressing the cytokine storm [4]. Polymyxin-B direct hemoperfusion (PMX-DHP) is widely used in Japan, while high volume hemofiltration (HVHF) is employed in the US and Europe. In some cases, a polymethylmethacrylate (PMMA) hemofilter is utilized, which has excellent capability to adsorb cytokines. One study compared the outcomes of sepsis patients treated by PMMA-CHDF, PMX-DHP, or HVHF, and the results suggested that PMMA-CHDF yields a non-inferior outcome as compared with the other two [5]. We administered PMMA-CHDF for non-renal indications in our patient to improve his condition, and noted prompt improvement of renal function and systemic condition. Antibiotics might have helped improve bacterial pneumonia, though our findings suggest that

improvement occurred due to cessation of the influenza virus-cytokine-protease cycle from cytokine adsorption via a PMMA membrane.

The influenza B viral infection may cause AKI and DIC. When DIC is complicated with an influenza B viral infection, it is more likely to become fatal. Therefore, scrupulous attention is necessary for affected patients.

Conclusions

AKI can develop as a complication of an influenza viral infection without HUS or rhabdomyolysis. When an influenza B viral infection induces AKI and DIC, the patient is more likely to be in a serious condition and attention is necessary.

Conflict of interest None of the authors have competing or conflicts of interest to declare.

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