Acute kidney failure due to varicella-zoster virus solved by early antiviral treatment based on brivudin

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ABSTRACT

A relation between acute kidney failure (AKF) and recent infection is well known in the medical community. Recent viral infections are rarer than bacterial infections in adults and patients. Here, we report a case of a 65-year-old woman who had a prolonged fever not responding to empiric antibiotic treatment and associated AKF characterized by oliguria, increased inflammatory markers, proteinuria, and swollen lower limbs. Tubulopathy with acute kidney injury (AKI) was diagnosed, and serial blood tests were performed together with an empiric treatment based on steroids and systemic antiviral drugs (*i.e.*, brivudin). An increased level of immunoglobulin M (IgM) anti-varicella-zoster virus was detected. Symptoms improved with combined steroidal and antiviral treatment since clinical resolution. AKI associated with tubulopathy is rarely associated with viral infection in adults or elderly patients. Yet when clinical pictures do not offer a clear diagnosis in the early phase, acute viral infection with the identification of viral DNA/RNA or serological IgM should also be taken into account.

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Introduction

A strong relation between acute kidney failure (AKF) and recent infection is well known in the medical community.[1,2] Post-infective glomerulonephritis is the most common clinical scenario with associated objective signs of hypertension, proteinuria, hematuria, and specific symptoms such as swollen limbs together with the increase of blood urea nitrogen (BUN) and serum creatinine with associated reduction of glomerular function (*i.e.*, glomerular filtration rate). Differential diagnosis with other clinical presentations of AKF in adults should be performed with any cause of dehydration and side effects of drugs.

Aging is an emerging and common risk factor for developing AKF because elderly patients may commonly suffer from recurrent infections and frequently suffer from dehydration for any cause, as far as taking an increased number of drugs to treat chronic diseases.[3,4] Furthermore, elderly patients are more likely to suffer from chronic and progressive kidney failure because of the presence of chronic underlying diseases such as heart failure or cancer.[3]

For these reasons, the clinical course of AKF in elderly patients seems to be more commonly associated with worse outcomes if compared with AKF in young people.

The most common sites of infection that precede AKF are skin (28% of cases), lung (16% of cases), and bladder (13% of cases), according to an epidemiological report;[5] bacterial infections of any district associated with *Staphylococcus* spp. are more frequent than those associated with *Streptococcus* spp. (*i.e.*, 46% *vs.* 16% respectively).[5]

Viral infection in adults or elder people seems to be rarer, but it may appear in immunocompromised patients (Table 1). Among common viral infections that may induce AKF, herpetic systemic infection is very rare.[4,6]

Here, we report an intriguing case of AKF due to viral infection by the herpes virus, with prompt clinical improvements after the right diagnosis and antiviral treatments.

Case Report

A 65-year-old woman was referred to the emergency department for fever associated with bladder pain and orange urine emission without any type of benefit with empiric antibiotic treatment with amoxicillin 1g twice daily. These symptoms began a few days prior.

Personal anamnesis revealed previous smoking habits and hypertension treated with perindopril. No antithrombotic drug was ongoing, nor was there nonsteroidal anti-inflammatory drug abuse in the last months. Previous laboratory tests (6 months ago) did not reveal any type of dysfunctions.

Physical examination revealed erythema with some vesicles and crusties on the abdomen and left conjunctivitis with any further objective clinical signs of acute diseases localized at the head, chest, or abdomen.

Hypertension and arrhythmia were not observed (*i.e.*, blood pressure 100/60 mmHg, 95 bpm) but there was a persistent fever (39°C).

Blood samples were performed and showed AKF with increased BUN (187 mg/dL) and creatinine (5.39 mg/dL) with associated decreased electrolytes (*i.e.*, Na^+ 130 mEq/L, K^+ 2.8 mEq/L); furthermore, biomarkers of recent infection were strongly increased with abnormal levels of fibrinogen (480 mg/dL), C-reactive protein (24.82 mg/dL), white blood cells (12700 mm^3), and procalcitonin (3.77 ng/mL).

A complete screen of all performed laboratory tests, including anti-inflammatory and autoimmune markers, is reported in Table 2. Furthermore, to exclude a cutaneous localization of systemic infection, serological markers im-

Table 1. Clinical conditions that may induce immunodepression in adults.

Age	Aging reduces the effectiveness of the immune system
Lifestyle	Lack of sleep, excessive alcohol and tobacco consumption
Malnutrition	Diet low in essential nutrients, vitamin deficiencies
Chronic disease	Chronic obstructive pulmonary disease, diabetes mellitus, obesity
Autoimmune diseases	Ulcerative colitis, Crohn's disease, rheumatoid arthritis, SLE and other
Drugs	Steroids, azathioprine, cyclosporin and other
Cancers	Solid and blood tumors
Anticancer	Chemo and radiotherapies

SLE, systemic lupus erythematosus.

Table 2. Laboratory tests ruled out for the described patient.

Test	Unit	11/10	12/10	13/10	14/10	15/10	30/10
BUN	mg/dL	187	187	167	120	69	43
Creatinine	mg/dL	5.59	5.2	2.75	1.8	0.94	0.87
Sodium	mEq/L	130	136	138	138	139	140
Potassium	mEq/L	2.8	3.1	3.3	3.4	3.9	4.0
Calcemia	mg/dL	9.6	9.5	9.2	9.6	9.5	9.6
AST	UI/L	134	112	100	85	58	35
ALT	UI/L	98	89	85	71	55	20
Uric acid	mg/dL	-	14.30	-	10.3	-	9.0
LDH	UI/L	418	400	390	350	350	280
C reactive protein	mg/dL	24.82	19.79	15.2	17.9	4.99	0.5
Fibrinogen	mg/dL	480					
D-DIMER	ng/mL	4759	3.545	2.800	950	250	150
Procalcitonin	ng/mL	2.99	2.0	0.70	0.35	0.12	0.15
Erytrosedimentation rate	mm/h	56	55	54	30	25	18
WBC	10^3/uL	12,700	11,000	12,000	11,000	10,000	9000
RBC	10^3/uL	3,970,000	3,890,000	3,890,000	3,780,000	3,800,000	4,000,000
Hemoglobin	g/dL	11.7	11.5	11.5	11.4	11.5	12.0
Platelet	10^3/uL	244,000	270,000	300,000	320,000	445,000	440,000
Serum iron	µg/L	27	25	35	38	38	42
C3 fraction	mg/dL	-	153	-	-	-	-
C4 fraction	mg/dL	-	9.8	-	-	-	-
ANA	-	-	Tested negative	No more tested	No more tested	No more tested	No more tested
ASMA	-	-	Tested negative	No more tested	No more tested	No more tested	No more tested
ENA	-	-	Tested negative	No more tested	No more tested	No more tested	No more tested

BUN, blood urea nitrogen; WBC, white blood cells; LDH, lactate dehydrogenase; RBC, red blood cells; ANA, antinuclear antibody; ASMA, anti-smooth muscle antibody; ENA, extractable nuclear antigen.

munoglobulin (Ig) M and IgG for several viral and bacterial agents were ruled out (Table 3). A pharmacological treatment based on intravenous (iv) pantoprazole 40 mg daily, iv amoxicillin 2 g twice daily, iv prednisone 40 mg daily, and enoxaparin 2000 u daily in off-label was started.

All blood samples were also tested after several days to have a progressive view of their trend and for this reason, we noted an increase after 3 days and then after 5 days of serum IgM against varicella-zoster virus (VZV) (*i.e.*, human herpes virus 3). Therefore, iv prednisone was reduced to 16 mg per os, and an antiviral treatment based on brivudin once daily for 7 days was started.[7,8]

The clinical scenario recorded a sudden improvement in fever and respiratory alkalosis, while laboratory data recorded an improvement after 10 days with a progressive reduction of kidney failure (*i.e.*, creatinine, BUN, and electrolyte impairment), as reported in Table 2. Furthermore, serological changes with a reduction of IgM anti-herpes virus and an increase in IgG anti-herpes virus were detected 15 days after the hospital admission; for this reason, our patient was dismissed from the hospital and planned for a follow-up visit on day 30 (serological trends of IgM and IgG against herpes virus were reported in Figure 1). Improvements in the daily report of signs and symptoms from the patients were reported with normalization of diuresis, and kidney function was confirmed after 30 days from hospital admission. The patient was finally discharged from the outpatient clinic of nephrology of our hospital.

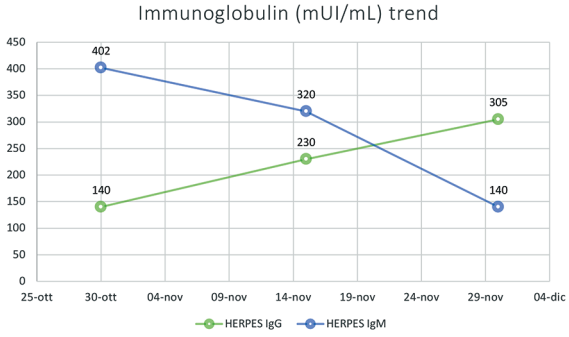

Figure 1. Serological evolution of anti-herpes immunoglobulin M and immunoglobulin G antibodies during the clinical management of the patient.

Discussion

Acute kidney injury (AKI) due to tubulopathies is usually characterized by a strong and quick increase of BUN associated with oliguria. Since oliguria is frequently associated with kidney hypoperfusion with local transient kidney ischemia,[9-11] transient or permanent hemodialysis may be considered one of the best urgent treatments. After the right treatment, kidney tubulopathy may also be completely restored with *restitutio ad integrum* of kidney function.[9-11] The case that we reported described AKF due to an acute viral infection of the herpes virus. Differential diagnosis with other infections or with chronic inflammatory and autoimmune diseases offered us the chance to suspect the herpes virus because associated dermatitis and skin infection are a common cause of AKI. Yet, because dermatitis showed clinical signs and symptoms typical of herpetic infection, a serological screening with IgM and IgG detection was planned, and after diagnostic confirmation, it was ruled out.

The choice of brivudin as the antiviral drug was on its easy bioavailability; moreover, it was shown to be effective

Table 3. Serological tests for infectious disease and their trend during the hospitalization of the patient.

Test	12/10	13/10	14/10	15/10	30/10
Brucella melitensis	Tested negative	No more tested	No more tested	No more tested	No more tested
Brucella Abortus	Tested negative	No more tested	No more tested	No more tested	No more tested
Salmonella Typhi Ant. H	Tested negative	No more tested	No more tested	No more tested	No more tested
Salmonella Paratyphi B Ant. H	Tested negative	No more tested	No more tested	No more tested	No more tested
Salmonella Paratyphi B Ant. O	Tested negative	No more tested	No more tested	No more tested	No more tested
Salmonella Paratyphi A Ant. H	Tested negative	No more tested	No more tested	No more tested	No more tested
Salmonella Paratyphi A Ant. O	Tested negative	No more tested	No more tested	No more tested	No more tested
Toxoplasma Gondii IgG	Tested negative	No more tested	No more tested	No more tested	No more tested
Toxoplasma Gondii IgM	Tested negative	No more tested	No more tested	No more tested	No more tested
Rubella virus IgG	Tested negative	No more tested	No more tested	No more tested	No more tested
Rubella virus IgM	Tested negative	No more tested	No more tested	No more tested	No more tested
Cytomegalovirus IgG	Tested negative	No more tested	No more tested	No more tested	No more tested
Cytomegalovirus IgM	Tested negative	No more tested	No more tested	No more tested	No more tested
Herpes IgG	Tested negative	Tested negative	Tested negative	Tested negative	Tested negative
Herpes IgM	Tested positive	Tested positive	Tested positive	Tested positive	Tested positive
HBsAg	Tested negative	No more tested	No more tested	No more tested	No more tested
HCV	Tested negative	No more tested	No more tested	No more tested	No more tested
Urine test	Sterile	No more tested	No more tested	No more tested	No more tested

IgG, immunoglobulin G; IgM, immunoglobulin M; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus.

in immunocompromised patients.[10-12] Specific follow-up was also planned with periodical serological tests. Furthermore, the fast improvement due to antiviral treatment with brivudin, an antiviral drug frequently used against herpes viruses, gave us a chance to evaluate the rate of recurrence of the herpetic infection in the following 24 months. This follow-up was suggested because herpetic infections have a high rate of systemic and local recurrences.[13]

Conclusions

This case gave us the chance to report an intriguing case of clinical and complete resolution of AKF for a herpetic infection. The usefulness of clinical case reports underlined one more time the chance to report unusual clinical approaches to common diseases such as AKI. In this case, the atypical postherpetic tubulopathies are associated with a complete remission of clinical damages and signs after the right treatment based on antiviral treatment, steroids, and hemodynamic support for damaged kidneys. Furthermore, our report facilitated a prompt clinical differential diagnosis for viral infections by highlighting the serological appearance of a specific IgM antiherpes virus and its subsequent serological disappearance when IgG anti-herpes virus levels increased. Of course, when the time to detect serological conversion from specific positivity of IgM to IgG disappears, the chance to perform AKF to post-viral infection drops out.

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