Severe sepsis as a cause of acute renal failure

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SUMMARY

Introduction: *The most common causes of acute renal failure in the intensive care units are severe sepsis and septic shock. Mortality reported in this kind of patients is about 70%. The pathophysiology of acute renal failure in severe sepsis includes systemic hypotension, direct renal vasoconstriction, infiltration of the kidney by inflammatory cells, renal ischemia, intraglomerular thrombosis and intratubular obstruction.*

Objective: *To show the incidence, mortality and histopathological etiology of acute renal failure in severe sepsis.*

Type study: *Retrospective, transversal and descriptive.*

Methods: *We study 332 cases of patients with severe sepsis, who were hospitalized in the Intensive Care Unit of Hospital General del Centro Médico Nacional, during five years.*

From these patients 107 developed acute renal failure due to severe sepsis. This group recived two differet kind of treatment, medical management (70%) and hemodyalisis (30%).

Renal biopsy was taken in 40 patients after six or seven days of the diagnosis of acute renal failure caused by severe sepsis.

Results: *In the group of 332 patients with severe sepsis 107 developed acute renal failure, this represents the 32.22%. The group of patients with renal biopsy presented the following results: 50% had acute tubular necrosis, 27.5% presented glomerular and tubular lesion, the rest 22.5% had glomerular and vascular lesion.*

The mortality for patients treated with medical management was of 69.3%, and for those treated with hemodyalisis was of 28.1%.

Discussion: *Nowadays, and due to the high incidence and mortality of this disease, is very important to generate more concise knowledge about the genesis and development of acute renal failure in the septic patient.*

Key words: ***Acute renal failure. Severe sepsis and lesion.***

SEPSIS SEVERA COMO CAUSA DE FALLA RENAL AGUDA

RESUMEN

Introducción: *Las causas más comunes de insuficiencia renal aguda en las unidades de cuidados intensivos son la sepsis severa y el choque séptico. La morta-*

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lidad reportada en los pacientes con sepsis severa e IRA es hasta del 70%. La fisiopatología propuesta para la falla renal en la sepsis grave incluye una combinación de factores como hipotensión sistémica, vasoconstricción renal, infiltración de células inflamatorias en el riñón, trombosis intraglomerular y obstrucción intratubular.

Objetivos: *Mostrar la incidencia, mortalidad y la histología de la insuficiencia renal aguda causada por sepsis severa.*

Diseño del estudio: *Retrospectivo, descriptivo y transversal.*

Metodología: *Se estudiaron retrospectivamente los casos de 332 pacientes con el diagnóstico de sepsis severa que fueron hospitalizados en la Unidad de Cuidados Intensivos del Hospital General del Centro Médico Nacional en el lapso de un lustro. De este total de pacientes 107 presentaron insuficiencia renal aguda secundaria a dicho proceso séptico. El diagnóstico se efectuó con base en las alteraciones de las pruebas funcionales renales (DCr, DmOms, DH20, U/PmOsm, FENA, FEK y IFR). Los pacientes fueron tratados de dos modos distintos, mediante manejo médico (70%) o con hemodiálisis (30%). A 40 de ellos se les tomó biopsia renal percutánea entre los seis y siete días posteriores a su diagnóstico. Todas las biopsias fueron estudiadas por microscopia óptica.*

Resultados: *Del grupo de 332 pacientes con sepsis severa 107 presentó insuficiencia renal aguda, lo que representa el 32,22% de la población en este grupo 40 pacientes (100%) a los que se les tomó biopsia renal; 20 pacientes (50%) tuvieron necrosis tubulointersticial, 11 pacientes (27,5%) desarrollaron lesión glomerular y tubular, y el resto 9 pacientes (22,5%) presentaron lesión glomerular y vascular.*

La mortalidad para el grupo tratado con manejo médico fue del 69,3%, mientras que la del grupo tratado con hemodiálisis fue del 28,1%.

Discusión: *Es necesario generar conocimientos más exactos sobre la génesis y desarrollo de la IRA en el paciente séptico, ya que la mortalidad en estos pacientes continua siendo elevada a pesar del inicio de diálisis temprana en cualquiera de sus modalidades, aun con las de reemplazo renal continuo.*

Palabras clave: ***Sepsis severa. Falla renal y Lesión renal.***

INTRODUCTION

According to the terminology proposed by the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) in 1992, the systemic inflammatory response syndrome (SIRS) is characterized by the presence of tachycardia, tachypnea, hypothermia, and leucocytosis or leucopoenia. SIRS may have an infectious or non-infectious origin. If a infectious cause is suspected, it is called sepsis. If sepsis leads to one or several organs dysfunction, lactic acidosis, oliguria, or mental status impairments, it is known as severe sepsis. Septic shock is present when sepsis leads to hypotension (systolic blood pressure < 90 mmHg) that cannot be corrected by fluid infusion[1,2] (Table I).

The pathophysiology of SIRS and of sepsis is not completely understood. However, one of the main factors in the pathogenesis is an exaggerated inflammatory response that follows the presence of

Table I.

Term	Definition
SIRS	Body temperature >38° C or <36° C; heart rate > 90/min; respiratory rate >20/min or $PaCO_2$ < 32 mmHg; and leucocytes count >12000 cells µL or < 4000 µL
Sepsis	SIRS with the presence or suspicion of infectious condition
Severe sepsis	One or several organs dysfunction, lactic acidosis, oliguria, or acute mental status impairment
Septic shock	Sepsis-induced hypotension (systolic BP < 90 mmHg) in spite of adequate fluid replacement. Patient on vasopressor or inotropic agents.

bacterial endotoxins and lipopolysaccharides (LPS), and which is characterized by an excessive production of proinflammatory agents such as tumoral necrosis factor alpha and some types of interleukines such as IL-1 and IL-6.[3,4] The increase in proinflammatory agents leads to fever, tachypnea, tachycardia, and leucocytosis, but also leads to activation of polymorphonuclear leucocytes that, together with the activation of the complement system, accounts for tissue damage.[5,6] Together with the development of an exaggerated inflammatory response, there is a decrease in substances that usually inhibit inflammation, such as IL-4, IL-10 and IL-13.[4-6]

SIRS and sepsis are associated with a pro-coagulation state induced by the effects of cascade activation of coagulation and fibrinolysis. This series of events may lead to disseminated intravascular coagulation (DIC), hemorrhage, or microvascular thrombosis.[6,7] The adrenal sympathetic system is also activated in sepsis, which increases plasma levels of norepinephrine and stimulates renin-angiotensin system, which in turn increases angiotensin II and vasopressin levels.[6-8] These mechanisms are in part responsible of the hemodynamic impairments such as vasodilation, hyperdynamic circulation, and microcirculatory changes.[7-9]

Severe sepsis is the consequence of the loss of auto-regulatory systems characterized by an unbalance between vasodilation and vasoconstriction, proinflammatory and anti-inflammatory cytokines, thrombosis and bleeding, oxidation and reduction reactions, and catabolic and anabolic activities, all of which contribute to organ dysfunction that characterizes this entity.[7,9,10] Besides, it is one of the most frequent causes of acute renal failure (ARF) that, according to data from worldwide literature, if affects about 20% of the patients admitted to intensive care units.[11,12] The incidence of ARF in patients with severe sepsis ranges from 20% to 25% and is increased to 50% if the patient presents with septic shock.[7,12] The reported mortality in patients with ARF secondary to severe sepsis is 70%, whereas the mortality rate in patients with ARF but no sepsis is 45%.[4,9,13,14]

The proposed pathophysiology for renal failure secondary to sepsis considers renal hypoperfusion as a main risk factor, which theoretically causes necrosis of the tubular epithelium, especially at the S3 segment of the proximal tubule. The death of these cells make them lose their adhesion properties to the tubular basal membrane and are shed to the tubular lumen producing urinary flow obstruction.[3,6,7] Apparently, this is not the only mechanism leading to renal failure, and other factors have been incriminated, such as the increase in afferent artery resistance, infiltration of the kidney by inflammatory cells, and intraglomerular thrombosis.[6-8]

The increase in afferent artery resistance increases vascular renal resistance, which leads to a decrease in renal flow.[8-9] The kidney infiltration by inflammatory cells produces local damage by the release of oxygen radicals, proteases, and cytokines. And the dysfunction of coagulation cascade and fibrinolytic system contributes to intraglomerular thrombosis.[8-10]

However, in spite of all the mechanisms previously described, the pathophysiology and the exact sequence of events leading to renal failure are poorly understood, in part because most of the knowledge generated in relation to the pathophysiology of ARF due to sepsis derives from animal studies. This led us to carry out, in the present study, histological confirmation from percutaneous renal biopsies of human beings with the diagnosis of ARF secondary to severe sepsis.

The main goal of the study is to demonstrate that acute renal failure in the septic patient is not necessarily due to tubular necrosis.

MATERIAL AND METHODS

We retrospectively studied 332 patients with the diagnosis of severe sepsis that were admitted to the Intensive Care Unit of the General Hospital of the National Medical Center, for the last five years. The inclusion criteria were:

1. Any patient that had developed severe sepsis secondary to peritonitis according to the 1992 consensus criteria of the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM).[1]
2. Independently of urinary volumes, patients had to have impaired renal function tests, mainly endogenous creatinine depuration and U/PmOsm.

Out of the 332 cases, 107 patients had acute renal failure secondary to the above-mentioned septic condition. The diagnosis of acute renal failure was confirmed by renal function tests impairments, which comprised: creatinine, osmolar, and free water depurations, U/PmOsm, and the renal failure index, and sodium and potassium excretion fractions. From this group of patients with ARF secondary to severe sepsis, percutaneous renal biopsy was done to 40 of them, after informed consent was obtained. All biopsies were histologically studied by light microscopy. Seventy percent (75 patients) of the patients with ARF received medical treatment with 600 mL of 50% hypertonic dextrose with one gram of furosemide for

24 hours. Forty milligrams of dipyridamole were intravenously administered q.i.d. to prevent platelet aggregation and decrease vascular damage. The remaining 30% (32 patients) of the patients were put on hemodialysis with the RSP kidney with acetate concentrate and a flow of 300 mL/min and positive pressure of 250 mmHg, each session lasting for 6 hours, 4-6 days/week. Medical treatment was started when endogenous creatinine clearance was below 15 mL/min and the U/PmOsm was below 1, independently of the other tests results, and was discontinued when diuresis was above 1000 mL in 24 hours, in the case of oliguric ARF, and hemodialysis was started when serum creatinine was above 5 mg/mL or urea was above 150 mg/dL and there was hypercalcemia and metabolic acidosis that could not be medically treated, and was discontinued when diuresis was above 1000 mL in 24 hours, or creatinine was below 5 mg/dL or urea was below 100 mg/dL, in case of high-output ARF. We would like to make clear that at the time these patients were treated, it was thought that hemodialysis decreased cardiac output and this increased the mortality in the severely septic patient, a situation that currently does not occur with bicarbonate kidneys and with continuous flow devices.

RESULTS

Out of the 40 patients (100%) in whom percutaneous biopsy was taken, 20 patients (50%) had tubulointerstitial necrosis (Figure 1), 11 (27.5%) had glomerular and tubular damage (Figure 2), and 9 (22.5%) had glomerular and vascular damage (Figure 3), see also Table II.

Out of the 75 patients receiving medical treatment, 52 (69.3%) died. Out of the remaining 32 patients treated with hemodialysis, 9 died (28.1%).

DISCUSSION

In most of medical literature relating t sepsis and ARF, the authors always conclude that necrosis tubular is the type of damage occurring, but they have not performed renal biopsies and this is inferred from the fact that the patient has oliguria and important azotaemia. However, in our cases there were tubular, glomerular and vascular lesions independently of the presence of oliguria or polyuria and of serum urea and creatinine levels, and on further progression to recovery or death, as it has been mentioned in the introduction and has been reported by our group on several occasions.[15,16]

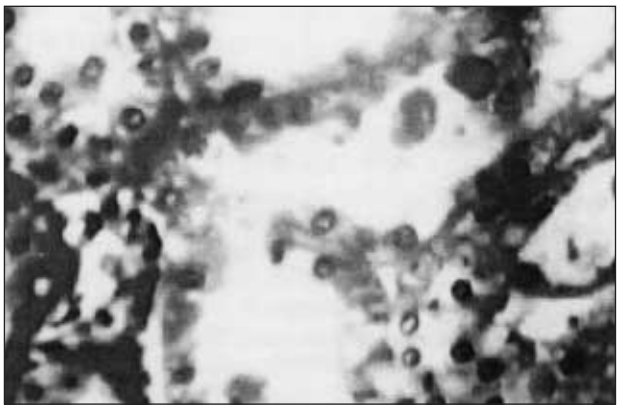

Fig. 1.—Microphotography showing tubular necrosis with basal membrane damage and cellular detritus within the lumen.

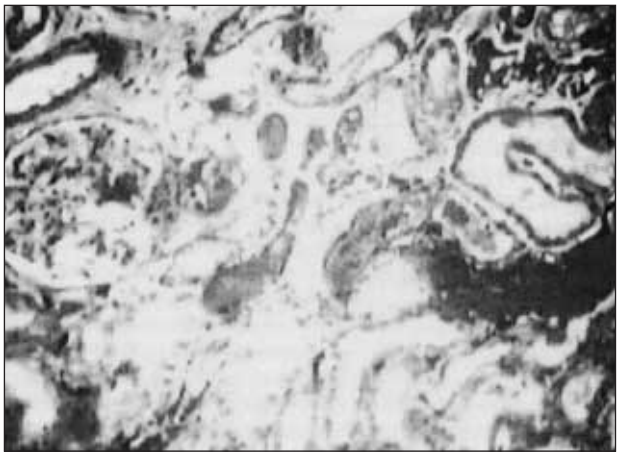

Fig. 2.—Microphotography showing glomerular lesion with microthrombi within the tubular lumen.

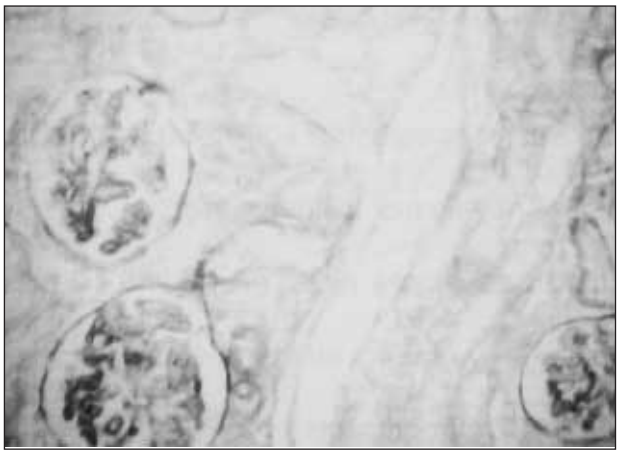

Fig. 3.—Glomerular and vascular lesion with bilateral cortical renal necrosis in a patient with sepsis.

Table II.

Num. of patients	Percentage	Histological result
20	50%	Damage with tubulointerstitial necrosis
11	27.5%	Glomerular and tubular damage
9	22.5%	Glomerular and vascular damage

In methods, we stated that independently of urinary volumes, treatment was started when creatinine depuration was lower than 15 mL/min and U/PmOsm lower than 1 in the first 75 patients meeting the inclusion criteria. Whether ARF was oliguric or polyuric was not taken into account in neither group since their ration was 1:1. Patients receiving medical treatment were switched to dialytic therapy if urea was above 150 mg/dL and creatinine above 5 mg/dL; we would like to mention that no patient received peritoneal dialysis since all these patients had peritonitis.

Patients in the second group was directly started on hemodialytic therapy, with the characteristics mentioned in material and methods, as soon as they met the inclusion criteria, independently of uremia level, and dialysis was discontinued when oliguric patients reached a diuresis > 1000 mL in 24 hours and urea and creatinine levels started to go down. This tended to occur between the fourth and sixth days after having started the therapy. This same criteria was also applied to those patients starting with medical treatment, although oliguric ARF tended to persist for more than 10 days, which made necessary to maintain dialysis for a longer time with a increased morbimortality risk.

The causes for sepsis were perforated appendicitis in 60% of the patients; 15% had pyogenous cholecystitis; 10% was suture dehiscence of hysterorrhaphy for post-cesarean section endometritis; 10% severe pancreatitis; and 5% colon perforation secondary to diverticulitis.

The severity of the patients was determined according to the classification that we use at the Intensive Care Unit of our Hospital, which is based on the determination of acute failures developed by the critically ill patient, which are the following: hemodynamic, gastrointestinal and hepatic, pulmonary, renal, metabolic-nutritional, and hematological. We did not use the APACHE systems since these classifications may varied with treatment and the score rapidly changes.[15,16]

We ought to stress that all patients dying in both groups was not because of ARF but to Multiple Organ Dysfunction Syndrome (MODS).

Forty patients had randomly done a percutaneous renal biopsy in lateral recumbent position, with no use of abdominal plane films or ultrasound since the anatomy was modified by the peritoneal condition and surgeries performed for treating the underlying cause. The kidney was located by means of anatomical reference points and a rachis needle. The specimen was further obtained with a Tru-cut needle, and light microscopy was performed.

CONCLUSIONS

Mortality of patients developing ARF due to severe sepsis still is high in spite of early initiation of dialysis and the development of continuous renal replacement therapies. The death in these patients is not only due to renal failure but also to sequential failure of other organs, leading to the multiple organ dysfunction syndrome caused by a systemic inflammatory response. According to the findings of light microscopy, we may see not only tubular necrosis develops in ARF, but there also may be interstitial, glomerular, and vascular damage, as shown in 40 of our cases.

A more profound knowledge on how exactly develop the events leading to renal damage and organ failure in severe sepsis is necessary since most of the knowledge comes from animal experimental studies, which not necessarily are a replica of what occurs in the human being. Once we will have all the answers to what generates the inflammatory response in all its varieties, and once we will have medications that will modify or modulate these changes, we will be able to prevent the occurrence of kidney and other vital organs failure, diminishing the morbimortality in the patient with severe sepsis.

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