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CYCLOSPORINE: SEPSIS AND ACUTE KIDNEY INJURY

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ABSTRACT

A 60 year male with adult onset nephrotic syndrome with focal segmental glomerulosclerosis was on steroids for 4 months and cyclosporine for one month. He came with complains of cough and breathlessness. Chest x-ray showed middle right zone consolidation. He had anemia, leukocytosis and thrombocytopenia. His urea and creatinine levels were elevated at the time of admission. He was diagnosed of sepsis and was started on antibiotics. Cyclosporine was immediately withdrawn but corticosteroid was continued due to his primary condition. His urine output dropped and creatinine increased leading to acute kidney injury. It was diagnosed as cyclosporine induced sepsis leading to kidney injury. He was advised renal biopsy and hemodialysis for which he did not give his consent.

KEYWORDS: acute kidney injury, cyclosporine, sepsis.

CASE PRESENTATION

A 60 year male with adult onset of nephrotic syndrome with focal segmental glomerulosclerosis (on renal biopsy) was on steroids for 4 months and cyclosporine for one month. He presented with cough and breathlessness (grade 4) since 1 week. On physical examination, pedal edema, facial puffiness and right sided lung crepitations were present. Laboratory parameters showed urine protein (+2), anemia, leukocytosis, thrombocytopenia, hypokalemia and hypoalbuminemia. Chest X-ray showed middle right zone consolidation. D-dimer levels were 1.7mcg/ml and echocardiogram reported ejection fraction- 69%, concentric LVH, severe pulmonary arterial hypertension, moderate tricuspid regurgitation and dilated right atrium and right ventricle. He was started on piperacillin+tazobactum and azithromycin

in view of sepsis on day 1 of admission. Cyclosporine was stopped but corticosteroid 60mg/day was continued for the primary disease. Furosemide was given for treating volume overload. However, during the next week urine output decreased and serum urea and creatinine increased as shown in following table.

Post admission	input (ml)	Urine Output (ml)	Weight (kg)	Sodium (mEq/l)	Potassium (mEq/l)	Urea (mg/dl)	Creatinine (mg/dl)
DAY 1	500	600		134	3.0	40	1.7
DAY 2	650	250	68.1	134	3.1	52	3.2
DAY 3	700	0	70.4	131	3.8	64	4.5
DAY4	1800	0	72.6	131	3.7	74	5.9
DAY5	650	250	74.0		3.9		7.0
DAY6	650	150	74.5	130	3.8	102	8.1
DAY7	700	400	74.9	133	3.8	111	9.1

The dose of piperacillin+tazobactum was reduced to half on 5th day of admission. Platelet levels improved after transfusion. His cough was relieved on the 7th day post admission. But creatinine levels were very high and he remained oliguric on 7th day of post admission. He was advised dialysis and renal biopsy for which he did not give his consent. Post discharge he was continued on furosemide, prednisolone and ranitidine.

DISCUSSION

Cyclosporine causes immunosuppression and is nephrotoxic. In this patient, immunosuppression secondary to cyclosporine could have manifested as sepsis in turn leading to acute kidney injury (AKI). Corticosteroids can also cause immunosuppression but were continued as a treatment for primary disease.

Cyclosporine suppresses humoral immunity but is more effective against T-cell dependent immune mechanism. It inhibits antigen triggered signal transduction in T lymphocytes, blunting expression of many lymphokines, including IL-2 and expression of anti-apoptotic proteins[1]. The molecular mechanism of action the drug is associated with nephrotoxicity. Histological changes post nephrotoxicity appear as obliterative vasculopathy of the afferent arteriole and tubulointerstitial fibrosis in advanced cases. The underlying mechanisms involves release of vasoactive substances are angiotensin II, endothelin, prostaglandins and nitric oxide as well as the stimulation of proliferative genes such as transforming growth factor-beta, osteopontin, and collagen I & IV.[2]

Due to the immunosuppression of cyclosporine, patient's immune system is low and is vulnerable to many infections. The above patient developed sepsis from a presumed or known site of infection. Severe sepsis is associated with organ failure. In sepsis, clinical signs include fever or hypothermia, unexplained tachycardia, tachypnea, shock and changes in mental status and peripheral vasodilation. Hemodynamic measurements that suggest septic shock are an increased cardiac output, with a low systemic vascular resistance. Laboratory indicators of sepsis are leukocytosis/leukopenia, thrombocytosis/thrombocytopenia, protein C deficiency, antithrombin deficiency, elevated D-dimer level, prolonged PT/PTT, elevated creatinine, elevated liver enzymes, elevated C-reactive protein, elevated procalcitonine levels.[3] Many of the clinical symptoms and laboratory indicators were seen in our patient.

A sepsis-induced renal failure is indicated by the following criteria: urine output less than 0.5 mL/kg/hr for 2 hours in the presence of adequate intravascular volume or after an adequate fluid challenge or doubling of the serum creatinine level.[3] The patient had very less urine output and nearly six times rise in creatinine. Sepsis causing acute kidney injury is quite well known in critically ill patients. Initially decreased cardiac output was considered to be main reason causing hypoperfusion to kidney. However in hyperdynamic circulation, kidney has increased renal blood flow and renal vascular resistance plays a key role in organ failure. Sepsis-induced renal micro vascular alterations like vasoconstriction, capillary leak syndrome with tissue edema, leukocytes and platelet adhesion with endothelial dysfunction, micro thrombosis, intra-abdominal pressure cause an increase in renal vascular resisitance.[4] Recent retrospective studies done in emergency departments showed that development of AKI was associated with older age, pre-existing chronic kidney disease, use of angiotensin converting enzyme inhibitor or angiotensin receptor blocker, presence of shock, positive blood culture, and low white blood cell and platelet counts.[5] Some of risk factors were seen in our patient. In such cases nephrotoxic drugs should be avoided.

CONCLUSION

Cyclosporine cause immunosuppression and nephrotoxicity but it is very important to identify sepsis secondary to immunosuppressive drugs. It is very difficult to find out the correct cause of injury to kidney with few parameters like physical examination and laboratory values. Biopsy is the ultimate answer to it. The above patient did not give consent for biopsy and his examination findings, signs, symptoms and laboratory values were in favor of sepsis. So, we conclude that patient developed sepsis due to immunosuppression by cyclosporine causing acute kidney injury.

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