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JSM Renal Medicine

Case Report

Cyclosporine Induced Acute Kidney Injury in Hemophagocytic Lymphohistiocytosis

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Submitted: 13 December 2016

Accepted: 03 January 2017

Published: 05 January 2017

Keywords

- Haemophaocyticlymphohistiocytosis
- Cyclosporine
- Acute kidney injury
- Recovery

Abstract

We describe a female patient in her 70s with haemophagocytic lymphohistiocytosis who developed an acute kidney injury secondary to cyclosporine use. Haemophagocytic lymphohistiocytosis (HLH) is a rare and severe immunologic disorder characterized by multiorgan system involvement, fever, rash, hepatosplenomegaly, cytopenias, and a range of neurologic manifestations. It is usually present in a paediatric population.

The patient was treated according to the 2004 HLH protocol which included cyclosporine. The patient had been established on a stable on a dose of 125mg PO BD, with target trough levels of between 100 - 200 ng/L within range for the preceding four weeks. Her weight had plummeted due to HLH, losing up to 40% of her body weight from symptom onset. Her baseline serum creatinine was low at 46 μ mol/l, decreasing throughout her hospitalisation. As we had not checked her body weight on a regular basis, dose adjustments of cyclosporine had not been made periodically.

She developed AKI, in conjunction with a doubling of her cyclosporine level. Her creatinine had tended to increase but there was a delay in the diagnosis of AKI because the significant rise in her serum creatinine level was masked due to excessively low level of serum creatinine. After cyclosporine was withheld, and the dose adjusted, the patient recovered fully.

This case highlights the importance of appreciating the absolute rise in creatinine as a marker of the severity of renal impairment, especially in patients with low baseline serum creatinine and the importance of regular monitoring of weight in conditions where patients have a propensity to rapid weight loss.

ABBREVIATIONS

HLH: Haemophagocytic Lymphohistiocytosis; AKI: Acute Kidney Injury; AKIN: Acute Kidney Injury Network

INTRODUCTION

Haemophagocyticlymphohistiocytosis is a rare and severe immunologic disorder characterized by multiorgan system involvement, fever, rash, hepatosplenomegaly, cytopenias, and a range of neurologic manifestations. It is usually present in a paediatric population. The diagnosis of any form of HLH is based on a number of clinical signs and laboratory findings that often overlap with other illnesses resulting in delayed diagnosis [1].

The incidence is estimated to be 1.2 cases per million per year [2]. It is classified as primary (familial, underlying genetic abnormality) or secondary to an underlying condition such as infection, autoimmune/rheumatologic disease, malignancy, or metabolic disorder.

Regardless of cause, HLH results from excessive release of interferon-gamma from activated T cells, which leads to continual expansion and activation of the cytotoxic CD8+ T cell, histiocyte, and macrophage population [3]. Activated CD8+ T lymphocytes and macrophages infiltrate multiple organs, including the bone marrow, lymph nodes, spleen, liver, brain, and kidney, and secrete high levels of inflammatory cytokinesleading to tissue damage and multiple organ failure [3]. Cyclosporine is part of the treatment protocol for HLH. It has potent immunosuppressive properties, reflecting its ability to block the transcription of cytokine genes in activated T cells [4]. The inhibition of T cell activation is of use in the treatment of HLH.

CASE PRESENTATION

We describe the case of a 76 year old Caucasian woman with a diagnosis of haemophagocytic lymphohistiocytosis. She had presented with a one month history of spiking temperatures up to 39.5 degrees Celsius, weight loss, fatigue and cognitive decline. She had been transferred from another institute to be admitted under the infectious diseases team initially to help establish a

diagnosis. A broad infectious work-up, including blood and urine cultures was negative.

At presentation in our institution on the 15th October 2016 she had a serum creatinine of 46μmol/l. Her height was 156cm and weight was 43.4kg. It had been 62 μ mol/l a month previously at the start of her illness. Her weight had been 55kg prior to the start of her illness, and she had lost 20% of her body weight at point of diagnosis. Physical examination showed a decreased level of consciousness. She was hypotonic, had downgoingplantars, constricted pupils, responded to painful stimuli. GCS was 9/15 (V2 E2, M5). She had a normal cardiovascular, respiratory and abdominal examination with no evidence of hepatosplenomegaly.

Bone marrow biopsy and aspirate helped establish the diagnosis. Bone marrow biopsy was done on 18th October. It showed a cellularity of 35%, trilinear haematopoiesis with maturation and increased haemophage activity with haemophagocytosis. She had a markedly raised ferritin up to a maximum of 44418 ng/L, and cytopenias with haemoglobin of 7.6 g/100ml, platelets persistently less than 100x 10^3/ml. Her fibrinogen was low at 50 mg/100ml. She did not have hypertriglyceridemia. From these results, we diagnosed this patient with a rare case of adult-onset HLH and applied comparative paediatric protocols. Viral studies showed that she had a high EBV titre and it was presumed that this was secondary HLH driven by EBV infection.

Diagnosis was made six weeks after symptom onset. Prompt treatment was initiated with the 8 week initial HLH-2004 immunochemotherpay protocol. Therapy included corticosteroids, etoposide, and cyclosporine A, with intrathecal methotrexate given because of progressive neurologic symptoms.

Day 1 of treatment was 21/10/16, six days after transfer to our institution. This included Etoposide 150mg/m2 day 1 and day 4, then 75mg/m2 day 8 and day 11 followed by weekly Etoposide after this at 75mg/m2. Dexamethasone 10mg/m2 for the first two weeks was given, followed by 5mg/m2 for two weeks, and then 2.5mg/m2. Intrathecal methotrexate 12.5mg was given four times, once a week from week three to week six because of neurological symptoms.

Despite treatment she continued to lose weight, with her weight decreasing to 38.8kg four weeks after starting treatment. Her serum creatinine also tracked downwards, plateauing at 26 μ mol/l, three weeks after starting treatment. She was on a stable dose of cyclosporine of 125mg PO BD. and her blood cyclosporine level had been stable (Table 1) for five weeks.

Over the course of a week her serum creatinine gradually started to increase, up to 40 μmol/l on 1/12/16, five weeks post start of treatment. This value demonstrated a 153% increase from her lowest level (26 umol/L). Therefore, she was diagnosed as AKI Network (AKIN) stage 1 [5]. The value of serum cyclosporine elevated to 393 ng/L. The patient had not received any drugs that are related to the worsening of kidney function. Medications included cotrimoxazole prophylaxis 960mg PO Monday/Wed/Friday,

Valacyclovir prophylaxis 500mg PO BD, levetiracetam 500mg PO BD, Cubitan nutritional supplement 200mls PO BD, Forticreme nutritional supplement 200mls PO TDS, cyclosporine 125mg PO BD. Clinical pharmacology along with nephrology were consulted with the review of her medications. She had not been septic at the time and was not dehydrated.

After we recognized her renal impairment, we discontinued cyclosporine. Then the serum creatinine level went back to the current baseline over the following days. The recognition of her renal impairment the cyclosporine level was immediately put on hold, and her renal function was monitored closely and it improved back to the current baseline over the following days.

DISCUSSION

In HLH, renal involvement, particularly AKI, is seen in up to 50% of pediatric patients [6-8]. It tends to occur in association with disease presentation. Clinical manifestations include oliguria, azotemia, and nephrotic syndrome [7]. The spectrum of AKI is similar in patients with primary and secondary HLH [9]. It is considered a strong predictor of increased mortality and has been attributed to multiorgan failure or the use of nephrotoxic drugs.

Acute cyclosporine nephrotoxicity is characterized by a reversible, dose-dependent reduction of the glomerular filtration rate (GFR) and the renal plasma flow, caused by direct toxic effects on the renal vasculature and systemic effects of cyclosporine [10]. It has been demonstrated experimentally

Table 1: Serum Creatinine and corresponding Cyclosporine level

	25/10/16	3/11/16	17/11/16	24/11/16	01/12/16	08/12/16
Serum Creatinine μmol/l	34	32	26	26	40	25
Cyclosporine Level ng/L	121	154	152	162	393	172
Body Weight	43.6kg		40.7kg		38.8kg	

Table 2: Target Cyclosporine level 100 to 200 ng/L.

	25/10/16	3/11/16	17/11/16	24/11/16	01/12/16	08/12/16
Serum Creatinineμmol/l	34	32	26	26	40	25
Serum Creatinine mg/dl	0.38	0.36	0.29	0.29	0.45	0.28
Ciclosporin Level ng/L	121	154	152	162	393	172
Body Weight	43.6kg		40.7kg		38.8kg	

thatcyclosproine can induce a strong vasoconstriction in the afferent preglomerular arteriole [11]. Concomitantly, the sympathetic and renin-angiotensin system may be activated, which enhances impaired intrarenal hemodynamics. As occurred in this case acute cyclosproine nephrotoxicity occurs early after initiation of therapy and presents clinically with a transient elevation of the serum creatinine which normalises shortly after reduction or discontinuation of cyclosporine [12].

In this case the patient had experienced a marked weight loss. At point of diagnosis she had lost 20% of her weight. When she developed renal impairment, her weight had plummeted even further. In a condition where a patient experiences marked weight loss it is important to appreciate that the serum creatinine will decrease due to muscular atrophy. This patient was critically ill and mostly bed bound because of her concomitant cognitive impairment. Therefore, this patient would have experienced massive skeletal muscle wasting, resulting in decreased value of serum creatinine.

Appropriate diagnosis is critical, because irreversible kidney damage can be prevented. The patient recovered fully after the cyclosporine was held. She finished the eight week initial cycle, and started on maintenance therapy. Her eight week repeat bone marrow was normal and her bloods had stabilized and her ferritin continued to trend downwards. She recovered some of her neurological capacity, though not to the point of independent functioning. She was discharged home, to be looked after by family members, two of which were nurses.

This case highlights the importance of appreciating the absolute rise in creatinine as a marker of the severity of renal impairment, especially in patients with low baseline serum creatinine. The trend in creatinine is important, especially in the acute setting. Appropriate diagnosis is critical, because irreversible kidney damage can be averted.

Acute kidney injury in HLH can occur secondary to dysregulated immune responses and direct overwhelming inflammation mediated by activated macrophages within the kidney. Renal involvement has been frequently reported; however precise descriptions of the renal manifestations are lacking. A search of the literature did not reveal any case reports on cyclosporine toxicity resulting in aki while treating HLH in the initial phase. This case report is the first one to specifically focus on AKI with cyclosporine in initial management phase. To our knowledge only one other case report has reported on cyclosporine induced renal failure while on maintenance therapy [13]. This was part of a short review on different obstacles a clinician had encountered in managing HLH and it did not elaborate on the specifics on what happened to the patient in question. However it was noted it occurred during maintenance therapy on cyclosporine.

A high index of suspicion is crucial. With conditions such as HLH the dose of cyclosporin may need to be adjusted on a regular basis based on the patient's weight so regular monitoring and adjusting of doses is vital.

ACKNOWLEDGEMENTS

The authors wish to thank the Pharmacy department in University Hosptial Galway.

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Cite this article

Murphy R, Murphy E, Krawczyk J (2017) Cyclosporine Induced Acute Kidney Injury in Hemophagocytic Lymphohistiocytosis. JSM Renal Med 2(1): 1007.