

Meena Thayu · Wayne L. Chandler · Srdjan Jelacic
Carrie A. Gordon · Geoffrey L. Rosenthal
Phillip I. Tarr

Cardiac ischemia during hemolytic uremic syndrome

Received: 5 June 2002 / Revised: 14 October 2002 / Accepted: 15 October 2002 / Published online: 7 February 2003
© IPNA 2003

Abstract Increased thrombin generation and impaired fibrinolysis during *Escherichia coli* O157:H7-associated hemolytic uremic syndrome (HUS) plausibly diminish myocardial blood flow, but the frequency of cardiac ischemia during HUS is unknown. We identified a 9-year-old boy with HUS in whom myocardial diastolic dysfunction was demonstrated by echocardiography, who also had elevated serum troponin-I and creatine

kinase MB mass. However, eight additional patients with HUS did not have elevated markers of cardiac injury. When present, elevated troponin-I should be considered to represent myocardial injury, and not attributed simply to renal insufficiency. It is possible that myocardial ischemia and secondary arrhythmias account for some sudden deaths that occur during acute HUS.

Keywords Creatine kinase MB mass · *Escherichia coli* O157:H7 · Hemolytic uremic syndrome · Myocardial ischemia · Troponin-I

M. Thayu · S. Jelacic · C. A. Gordon · P. I. Tarr
Department of Pediatrics,
University of Washington School of Medicine,
Seattle, Washington, USA

M. Thayu
Division of Gastroenterology and Nutrition,
Children's Hospital of Philadelphia,
Philadelphia, Pennsylvania, USA

W. L. Chandler
Department of Laboratory Medicine,
University of Washington School of Medicine,
Seattle, Washington, USA

S. Jelacic · P. I. Tarr
Division of Gastroenterology,
Children's Hospital and Regional Medical Center,
Seattle, Washington, USA

C. A. Gordon
Division of Nephrology,
Children's Hospital and Regional Medical Center,
Seattle, Washington, USA

G. L. Rosenthal
The Children's Heart Center,
Children's Hospital and Regional Medical Center,
Seattle, Washington, USA

G. L. Rosenthal
Center for Pediatric and Congenital Heart Diseases,
The Cleveland Clinic Foundation,
Cleveland, Ohio, USA

P. I. Tarr (✉)
Division of Gastroenterology, CH-24,
Children's Hospital and Regional Medical Center,
4800 Sand Point Way NE, Seattle, WA 98105 USA
e-mail: tarr@kids.wush.edu
Tel.: +1-206-9874150 or +1-314-4546173
Fax: +1-206-9872221 or +1-314-4542412

Introduction

The hemolytic uremic syndrome (HUS) is a thrombotic microangiopathic sequel to gastrointestinal infection with *Escherichia coli* O157:H7. HUS occurs in approximately 15% of children under 10 years who are symptomatically infected with this pathogen [1], is diagnosed approximately 1 week after the onset of diarrhea, and is characterized by thrombi in small vessels of multiple organs [2, 3]. Additional coagulation lesions include profound prothrombotic and anti-fibrinolytic abnormalities [4, 5, 6, 7, 8] and elevation of circulating platelet-activating factor [9]. It is plausible that these prothrombotic abnormalities lead to the vascular lesions in the multiple organs that are affected during HUS.

Some patients with HUS have overt myocardial dysfunction [10]. We recently treated a patient with *E. coli* O157:H7-associated HUS in whom serum markers suggested myocardial injury. This observation prompted us to investigate the sera of additional infected children for evidence of myocardial insult during HUS caused by *E. coli* O157:H7.

Case report

The patient is a 9-year-old previously healthy boy who presented after 4 days of abdominal pain, diarrhea, and emesis. Loperamide was administered for symptomatic relief. Later that day, bloody

Table 1 Left ventricular wall thickness (and Z score) in the primary case study patient

Days of illness	Posterior wall		Interventricular septum	
	Diastole	Systole	Diastole	Systole
13	9 mm (0.38)	15 mm	8 mm (-0.53)	11 mm
16	11 mm (1.94)	17 mm	12 mm (2.62)	17 mm

Table 2 Characteristics of primary case study patient

Day of illness serum sample obtained	Creatinine (mg/dl) ^a	Platelet count (x10 ³ /mm ³)	Hematocrit (%)	Carbon dioxide, total (mEq/l)	Troponin-I (ng/ml) ^b	CK total (IU/l) ^c	CK-MB mass (ng/ml) ^d
6	0.5	286	44	22	–	–	–
7	0.5	210	43	24	0.1	–	0.1
8	1.4	30	43	19	–	–	–
9	2.3	28	40	19	–	–	–
10	5.1	32	28	18	0	65	3
11	4.9	29	22	20	–	131	–
12	5.5	33	19	19	–	173	–
13	5.6	36	24	–	28.7	–	–
14	6.0	122	21	23	15.7	586	–
15	5.6	221	20	22	21.0	720	–
16	4.3	198	32	28	23.4	–	34
17	4.3	281	28	29	23.6	84	–
18	4.2	225	30	23	–	–	–
19	2.9	117	36	23	–	–	–
20	2.8	150	36	22	–	–	–
21	2.7	166	33	27	–	–	–
22	2.7	254	33	29	–	–	–
23	2.7	342	33	25	–	–	–
24	2.8	419	36	22	0	–	–

^aTo convert values for serum creatinine to micromoles per liter, multiply by 88.4

^bTroponin-I adult normal <2 ng/ml

^cCK total adult female normal range 30–231 IU/l, adult male normal range 30–285 IU/l

^dCK-MB mass adult normal <5 ng/ml

diarrhea ensued. He was admitted to his local hospital the next day, at which time a stool culture was obtained that 2 days later yielded *E. coli* O157:H7. Admission complete blood count (CBC), blood urea nitrogen (BUN), electrolyte, and creatinine concentrations were normal. On day 8 of illness, the patient was transferred to the Children's Hospital and Regional Medical Center because of a falling platelet count, diminishing urine output, and rising serum creatinine.

On transfer, the patient had an oral temperature of 38.1°C, a pulse of 104/min, a respiratory rate of 44/min, and a blood pressure of 147/93 mmHg. He was irritable but responsive. He had edematous eyelids and extremities, clear lungs, a normal cardiovascular examination, and diffuse abdominal tenderness. Bowel sounds were present, and there were no masses, organomegaly, or peritoneal signs. His initial CBC in our institution had a white cell count of 28,500/mm³ (42% polymorphonuclear cells, 25% band forms, 1% metamyelocytes, 14% lymphocytes, and 18% monocytes), hemoglobin concentration of 14.5 g/dl, hematocrit of 43%, and platelet count of 30,000/mm³. His initial blood biochemical analysis demonstrated a sodium concentration of 124 mEq/l, a potassium concentration of 3.8 mEq/l, a chloride concentration of 102 mEq/l, and a bicarbonate concentration of 19 mEq/l. The BUN and creatinine concentrations were 27 and 1.4 mg/dl, respectively. The chest radiograph demonstrated small bilateral subpulmonic effusions, and abdominal films demonstrated a diminished luminal diameter in the distal colon with wall thickening. Urine output ceased on day 9 of illness. By day 10 of illness, his hemoglobin had fallen to 10.1 g/dl, fragmented erythrocytes were observed on peripheral blood smear, the BUN and creatinine concentrations had risen to 97 and 6.0 mg/dl, respectively, and hemodialysis was initiated.

On days 11 and 12 of illness, the patient developed respiratory distress and required nasally administered oxygen for optimal

blood saturation; a chest radiograph demonstrated bilateral pulmonary opacities. His systolic and diastolic blood pressures ranged between 111 and 140, and 61 and 98 mmHg, respectively. An electrocardiogram performed to exclude the possibility that cardiac ischemia caused the respiratory abnormalities demonstrated sinus tachycardia with non-specific ST and T wave abnormalities. An echocardiogram performed on day 13 of illness demonstrated a structurally normal heart (Table 1). The ventricular muscle thickness was normal, and a small apical pericardial effusion was seen. Right ventricular and left ventricular systolic functions were good. However, the left ventricular filling pattern suggested mildly decreased left ventricular compliance. Bilateral pleural effusions were also seen.

The troponin-I level was 28.7 ng/ml (normal in adults is <2 ng/ml) on day 13 of illness (Table 2). The troponin-I levels remained elevated on days 14 through 17, and returned to normal by day 24. The venous blood pH ranged between 7.31 and 7.45 between days 13 and 16 of illness. The maximum total creatine kinase (CK) activity was 720 IU/l on day 15 and returned to normal by day 17. CK-MB mass, the CK isoform released into the circulation following injury to myocardium, was elevated to 34 ng/ml on day 16. Additional cardiac markers were not sought because there was insufficient saved serum. A subsequent echocardiogram performed on day 16 of illness demonstrated persistently poor left ventricular compliance, small pericardial and pleural effusions, and normal systolic function. The ventricular wall and septal thicknesses were increased, perhaps because of myocardial edema (Table 1).

On day 18 of illness, a laparotomy was performed because of blood pressure instability and severe metabolic acidosis. During surgery, a necrotic, perforated, left colon was identified, and a partial colectomy and colostomy were performed. An intraoperative

Table 3 Characteristics of additional study patients

Patient	Day of illness serum sample obtained	Creatinine (mg/dl) ^a	Platelet count (x10 ³ /mm ³)	Hematocrit (%)	Carbon dioxide, total (mEq/l)	Days of oligoanuria	Troponin-I (ng/ml) ^b	CK total (IU/l) ^c	CK-MB mass (ng/ml) ^d
A	6	1.1	47	30	30	0	0	722	3
B	7	1.6	51	24	22	0	0	75	2
C	8	4.2	11	10	15	0	0.1	111	2
D	10	4.9	24	18	19	0	0.2	80	1
E	12	1.1	54	26	31	0	0	82	<1
F	8	5.2	36	25	15	2	0.2	247	2
G	9	5.9	59	20	14	3	0	328 ^b	4
H	6	1.6	24	26	20	7	0	98	2

^aTo convert values for serum creatinine to micromoles per liter, multiply by 88.4

^bTroponin-I adult normal <2 ng/ml

^cCK total adult female normal range 30–231 IU/l, adult male normal range 30–285 IU/l

^dCK-MB mass adult normal <5 ng/ml

transesophageal echocardiogram demonstrated persistently increased left ventricular wall thickness and hyperdynamic systolic function. Additional complications during illness included pancreatitis, hypotension treated with dopamine and epinephrine, *Staphylococcus aureus* bacteremia, and respiratory failure necessitating intubation. The patient was extubated on day 32 of illness and urine output resumed on day 33; dialysis was continued for a total of 57 days. The patient was discharged after 59 hospital days, and the colostomy was closed 4 months after placement.

To assess the extent of his residual renal disease, an open kidney biopsy was performed at the time of colonic reanastomosis. Histopathological evaluation demonstrated an area of subcapsular scar formation containing globally sclerosed glomeruli. The deeper cortex exhibited patchy interstitial fibrosis. Several of the 28 glomeruli examined contained focal segmental sclerosis and mesangial proliferation; thrombi were absent. As of this writing, 11 months after admission to our institution, the patient's creatinine is 1.3 mg/dl and he has no hypertension.

Laboratory investigation of patients with *E. coli* O157:H7-associated HUS

To determine if troponin-I levels are elevated in children with *E. coli* O157:H7-associated HUS, either because of myocardial injury or renal insufficiency, we assayed sera from infected patients who developed HUS. These sera were collected when HUS developed, as part of a regional prospective study of the pathophysiology of childhood HUS in children infected with *E. coli* O157:H7 [1, 2, 4]. Briefly, families of children with HUS whose stool cultures yielded *E. coli* O157:H7 were approached, and, if informed consent was granted, extra blood was obtained for research at clinically indicated phlebotomies. Sera from eight of these patients, which had been frozen at –70°C since separation from whole blood, were thawed and assayed for total CK activity (Beckman LX20), troponin-I (Abbott, AxSYM), and CK-MB mass (Abbott, AxSYM). Neither freezing [11] nor dialysis [12] affects these markers. A day of oligoanuria was defined as a 24-h period during which the urine output was less than 0.5 ml/kg of body weight per hour.

Results

Clinical and laboratory details, and troponin-I, total CK, and CK-MB mass of additional patients studied are displayed in Table 3. None of the patients was hypotensive on the days during which sera were obtained (data not shown). Several patients had metabolic acidosis, as demonstrated by reduction of the serum bicarbonate concentrations. Except for the child described in detail above, blood gas values were not determined on any patient. All patients had normal concentrations of troponin-I. Only one patient (patient F) had an elevated total CK, but the CK-MB mass was normal.

Discussion

Myocardial injury during HUS is usually manifest as cardiomyopathy, with ischemia or infarction being only rarely documented [13]. Furthermore, the assessment of cardiac injury using modern assays such as troponin-I in combination with MB fractionation has not been performed systematically. One study assessing ischemic myocardial injury in a group of children with HUS utilized determinations of CK and its isoenzymes, and concluded that elevations were most likely attributable to injury to skeletal muscle, and not to myocardium [14]. Troponin-I was not measured in that study, and the microbial precipitant of the HUS in those patients was not established.

Our inability to document myocardial ischemia in any of eight additional children with *E. coli* O157:H7-associated HUS warrants discussion. It is possible that yet to be determined mechanisms, such as recruitment of microvascular collateral vessels, attenuate cardiac damage despite the demonstrated generation of thrombin and impairment of fibrinolysis that accompany HUS. Alternatively, myocardial injury might occur in a higher proportion of children than we were able to document, but at other times in their course. It is also possible that arrhythmias, hypoxemia, and ion and fluid shifts, during

or following dialysis, contribute to myocardial ischemia by decreasing coronary perfusion pressure or otherwise decreasing myocardial oxygen delivery. Ischemia in the patient described above was noted following the institution of dialysis [15] and during a period of anemia. As demonstrated in our patient, myocardial ischemia can occur during HUS, and it is plausible that such ischemia underlies at least some of the sudden deaths that comprise a subset of fatalities in childhood HUS [16].

Our findings also have practical implications. In children with HUS, elevated levels of troponin-I should be considered to reflect myocardial injury and not be simply attributed to azotemia, because most patients studied by us had normal values despite renal insufficiency. Several studies focusing on the prognostic value of cardiac troponins during renal replacement therapy in adult patients undergoing chronic dialysis [12, 17, 18, 19] have, in general, found that elevations of cardiac troponins have prognostic value, even in asymptomatic patients. One study in particular demonstrated that hemodialysis did not alter serum levels of troponin-I or CK-MB [16]. Also, the patient presented above suggests that an echocardiogram might not be sufficiently sensitive to exclude cardiac ischemia in HUS when systolic function alone is considered. It is important to consider that myocardial edema and diastolic dysfunction are contributing factors when cardiopulmonary insufficiency is present in patients with HUS.

HUS patients with elevated troponin-I should be monitored closely for signs of cardiopulmonary compromise or arrhythmias, but our data do not permit us to propose that myocardial ischemia be investigated in all children with HUS. However, we certainly recommend seeking evidence of myocardial ischemia and diastolic dysfunction if there is cardiopulmonary compromise. We would also consider investigation of myocardial ischemia in children with HUS who have severe multivisceral organ injury, as observed in the patient described above. Future attempts to address the frequency and timing of cardiac injury during HUS should prospectively and systematically collect sera from patients with HUS from well-defined causes, and include patients with a spectrum of HUS severity, and during different phases of their illness.

Acknowledgements This research was funded by National Institute of Diabetes and Digestive and Kidney Diseases grant 1RO1DK52081. We would like to thank the nurses and staff of the Pediatric Intensive Care Unit of the Children's Hospital and Regional Medical Center for their care and monitoring of the patient, and Jennifer Falkenhagen McKenzie for expert assistance in the preparation of this manuscript.

References

1. Wong CS, Jelacic S, Habeeb RL, Watkins SL, Tarr PI (2000) The risk of the hemolytic-uremic syndrome after antibiotic treatment of *Escherichia coli* O157:H7 infections. *N Engl J Med* 342:1930–1936
2. Tsai HM, Chandler WL, Sarode R, Hoffman R, Jelacic S, Habeeb R, Watkins SL, Wong CS, Williams GD, Tarr PI (2001) von Willebrand factor and von Willebrand factor-cleaving metalloprotease activity in *Escherichia coli* O157:H7-associated hemolytic uremic syndrome. *Pediatr Res* 49:653–659
3. Habib R (1992) Pathology of the hemolytic uremic syndrome. In: Kaplan BS, Trompeter RS, Moake JL (eds) *Hemolytic uremic syndrome and thrombotic thrombocytopenic purpura*. Dekker, New York, pp 315–353
4. Chandler WL, Jelacic S, Boster DR, Ciol MA, Williams GD, Watkins SL, Igarashi T, Tarr PI (2002) Prothrombotic coagulation abnormalities associated with *Escherichia coli* O157:H7 infections. *N Engl J Med* 346:23–32
5. Bergstein JM, Riley BS, Bang NU (1992) Role of plasminogen-activator inhibitor type 1 in the pathogenesis and outcome of the hemolytic uremic syndrome. *N Engl J Med* 327:755–759
6. Kar NC van de, Hinsbergh VW van, Brommer EJ, Monnens LA (1994) The fibrinolytic system in the hemolytic uremic syndrome: in vivo and in vitro studies. *Pediatr Res* 36:257–264
7. Nevard CH, Jurd KM, Lane DA, Philippou H, Haycock GB, Hunt BJ (1997) Activation of coagulation and fibrinolysis in childhood diarrhoea-associated haemolytic uraemic syndrome. *Thromb Haemost* 78:1450–1455
8. Chant ID, Milford DV, Rose PE (1994) Plasminogen activator inhibitor activity in diarrhoea-associated haemolytic uraemic syndrome. *QJM* 87:737–740
9. Smith JM, Jones F, Ciol MA, Jelacic S, Boster DR, Watkins SL, Tarr PI, Henderson WR Jr (2003) Platelet-activating factor and *Escherichia coli* O157:H7 infections. *Pediatr Nephrol* (in press)
10. Brandt JR, Fouser LS, Watkins SL, Zelikovic I, Tarr PI, Nazar-Stewart V, Avner ED (1994) *Escherichia coli* O 157:H7-associated hemolytic-uremic syndrome after ingestion of contaminated hamburgers. *J Pediatr* 125:519–526
11. Collinson PO, Wiggins N, Gaze DC (2001) Clinical evaluation of the ACS:180 cardiac troponin I assay. *Ann Clin Biochem* 38:509–519
12. Tun A, Khan IA, Win MT, Hussain A, Hla TA, Wattanasuwan N, Vasavada BC, Sacchi TJ (1998) Specificity of cardiac troponin I and creatine kinase-MB isoenzyme in asymptomatic long-term hemodialysis patients and effect of hemodialysis on these cardiac markers. *Cardiology* 90:280–285
13. Eckart P, Guillot M, Jokic M, Maragnes P, Boudailliez B, Palcoux JB, Desvignes V (1999) Cardiac involvement during classic hemolytic uremic syndrome. *Fr Arch Pediatr* 6:430–433
14. Ramirez J, Zgaib S, Miguel R de, Ferraris J, Persico R, Graca IZ da, Gianantonio C (1989) Activity of creatine kinase and its isoenzymes in hemolytic uremic syndrome. *Medicina (B Aires)* 49:285–292
15. Munger MA, Ateshkadi A, Cheung AK, Flaharty KK, Stoddard GJ, Marshall EH (2000) Cardiopulmonary events during hemodialysis: effects of dialysis membranes and dialysate buffers. *Am J Kidney Dis* 36:130–139
16. Robson WL, Leung AK, Montgomery MD (1991) Causes of death in hemolytic uremic syndrome. *Child Nephrol Urol* 11:228–233
17. Deegan PB, Lafferty ME, Blumshon A, Henderson IA, McGregor E (2001) Prognostic value of troponin T in hemodialysis patients is independent of comorbidity. *Kidney Int* 60:2399–2405
18. Apple FS (1997) Prognostic value of serum cardiac troponin I and T in chronic dialysis patients: a 1-year outcomes analysis. *Am J Kidney Dis* 29:399–403
19. Iliou M, Fumeron C, Benoit MO, Tuppin P, Le Courvoisier C, Calogne VM, Moatti N, Buisson D, Jacquot C (2001) Factors associated with increased serum levels of cardiac troponins T and I in chronic haemodialysis patients: Chronic Haemodialysis and New Cardiac Markers Evaluation (CHANCE) study. *Nephrol Dial Transplant* 16:1452–1458