Keeping the Heart in Mind when Managing Hemolytic Uremic Syndrome

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**CASE COMMUNICATIONS**

Hemolytic uremic syndrome is a major cause of acute renal failure in childhood. The main clinical manifestations of HUS are microangiopathic hemolytic anemia, thrombocytopenia and acute renal failure. The kidneys and the gastrointestinal tract are the most commonly affected organs in HUS, but there may be central nervous system, pancreatic and myocardial involvement as well. Given the potential for mortality and morbidity among the patients who have cardiac involvement, early intervention and supportive treatment are crucial.

**PATIENT DESCRIPTION**

A 34 month old girl was referred to our pediatric intensive care unit due to disturbed consciousness, anemia, thrombocytopenia and renal failure following 3 days hospitalization for bloody diarrhea. She was afebrile and had been treated with ceftriaxone. Her heart rate was 125 beats/minute and her blood pressure 140/90 mmHg. Laboratory studies revealed a white blood cell count of 20,500 mm$^3$ with a left shift, hemoglobin 7.8 g/dl, platelets 60,000 mm$^3$, blood urea nitrogen 119 mg/dl, creatinine 3.5 mg/dl and electrolytes within normal limits. Liver enzymes were elevated (aspartate aminotransferase 201 u/L, alanine aminotransferase 139 u/L) with normal gamma glutamyltransferase and low albumin (2.9 g/dl). A peripheral blood smear revealed signs of intravascular hemolysis. HUS was diagnosed on the basis of microangiopathic hemolytic anemia, thrombocytopenia and oliguric renal failure. Peritoneal dialysis was performed. Stool cultures for *Escherichia coli*, Shigella, Salmonella and Campylobacter were negative.

On hospital day 5, a new systolic murmur, 2/6, best heard over the left sternal border, was detected on physical examination. Patient’s blood pressure was 120/90 and she was 2.5 kg above her basal body weight. Laboratory studies revealed urea levels of 136 mg/dl, creatinine 3.72 mg/dl, hemoglobin 9.78 g/dl, sodium 134 mEq/L and potassium 4.5 mEq/L. Creatine phosphokinase levels were 810 IU/L with 6.7% CPK-MB (total CPK-MB 54 IU/L). Troponin I level was 3.415 µg/L (normal < 0.07 µg/L). Electrocardiogram demonstrated low voltage QRS waves. Echocardiography revealed depressed function of the left ventricle with a left ventricular shortening fraction of 13%, and mild mitral and tricuspid regurgitation without dilatation of the left ventricle. No pericardial effusion was found. Despite such relatively extensive evidence of cardiac insufficiency on echocardiography, the child was respiratorily and hemodynamically stable and did not require either inotropic support or mechanical ventilation. Treatment consisting of supportive care, including blood transfusions, peritoneal dialysis and three courses of plasma pheresis led to gradual clinical and laboratory improvement. A second echocardiography was performed on hospital day 15 and showed normal left ventricular shortening fraction with no evidence of mitral or tricuspid regurgitation. Peritoneal dialysis was continued for a total of 30 days when renal function had recovered and there was adequate urine output. The patient was discharged home in satisfactory condition on hospital day 37. As of this publication, 3 years after admission to our institute, her plasma creatinine level is 0.55, her creatinine clearance 100 ml/min/1.73 m$^2$, and she has no hypertension.

**COMMENT**

Secondary cardiac involvement in HUS may be due to various aspects of the disease itself as well as to its treatment, such as volume overload in an anuric patient, electrolyte disturbances (mainly hyperkalemia) and persistent severe hypertension. Primary cardiac involvement has been reported before [1] and included thrombotic microangiopathy of the coronary vasculature resulting in myocardial ischemia, myocardial infarction, or depressed myocardial function, myocarditis, congestive heart failure with dilated cardiomyopathy, and pericardial effusion with tamponade. In our case, the clinical picture and imaging studies led to the diagnosis of myocarditis.
The incidence of primary cardiac involvement in HUS is unknown. Siegler [2] described a series of 230 patients with HUS among whom there was only one case of clinically apparent primary myocardial involvement. Nevertheless, reports of studies in which myocardial involvement in cases of HUS was tested by various diagnostic tools, such as echocardiography, showed a higher incidence than is clinically apparent. Poulton et al. [3] performed echocardiograms on 12 children who had HUS and no cardiac clinical signs: one of these children had evidence of transient dilatation and reduced contractility.

Clinical manifestations of myocardial involvement in HUS are diverse, but there are several that are common. Most patients develop myocardial involvement within 1–3 weeks of their initial presentation although late presentations have been reported as well [3]. The clinical picture may include signs and symptoms of myocardial dysfunction such as poor peripheral perfusion and pulmonary edema, yet, as in the case described here, there may be no clinical evidence of myocardial infarct. ECGs usually show non-specific ST-T wave changes with low voltage QRS waves. The echocardiogram may reveal a global cardiac dysfunction with sharp decrease in ejection fraction, and dilated cardiomyopathy has been reported in rare cases [3].

Askiti and co-authors [4] suggested the use of troponin I to detect cardiac involvement in severely ill HUS patients [4]. They followed troponin levels in a 22 month old girl who presented with typical HUS that induced severe myocardial dysfunction. cTnI levels were compatible with those associated with acute myocardial injury. There was significant elevation in cTnI 8 hours before the onset of acute myocardial failure and a peak elevation 24 hours later. It is important to emphasize that troponin I level is a marker for cardiac ischemia although it is measured in the presence of renal dysfunction.

In light of the risk of dire consequences, it might be prudent to routinely evaluate myocardial function in all patients who are diagnosed as having HUS. Having prior knowledge of concomitant cardiopathy and prompt provision of proper hemodynamic support during the acute phase of cardiac failure may save life. In many cases, mechanical ventilation and the use of inotropic agents on top of the standard treatment for HUS is enough to support the patient until cardiac function is restored. In severe cases, extracorporeal support has been used [5]. As in our case, cardiac injury is usually reversible, although there may be long-term cardiac damage.

**References**


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**Capsule**

**Tumor evolution inferred by single-cell sequencing**

Genomic analysis provides insights into the role of copy number variation in disease, but most methods are not designed to resolve mixed populations of cells. In tumors, where genetic heterogeneity is common, very important information may be lost that would be useful for reconstructing evolutionary history. Navin et al. show that with flow-sorted nuclei, whole genome amplification and next generation sequencing, they can accurately quantify genomic copy number within an individual nucleus. The authors applied single-nucleus sequencing to investigate tumor population structure and evolution in two human breast cancer cases. Analysis of 100 single cells from a polygenic breast revealed three distinct clonal subpopulations that probably represent sequential clonal expansions. Additional analysis of 100 single cells from a monogenic primary tumor and its liver metastasis indicated that a single clonal expansion formed the primary tumor and seeded the metastasis. In both primary tumors, we also identified an unexpectedly abundant subpopulation of genetically diverse ‘pseudodiploid’ cells that do not travel to the metastatic site. In contrast to gradual models of tumor progression, their data indicate that tumors grow by punctuated clonal expansions with few persistent intermediates.

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“Co-existence/or no existence”

Piet Hein (1905-1996), Danish scientist, mathematician, inventor, designer, author, and poet